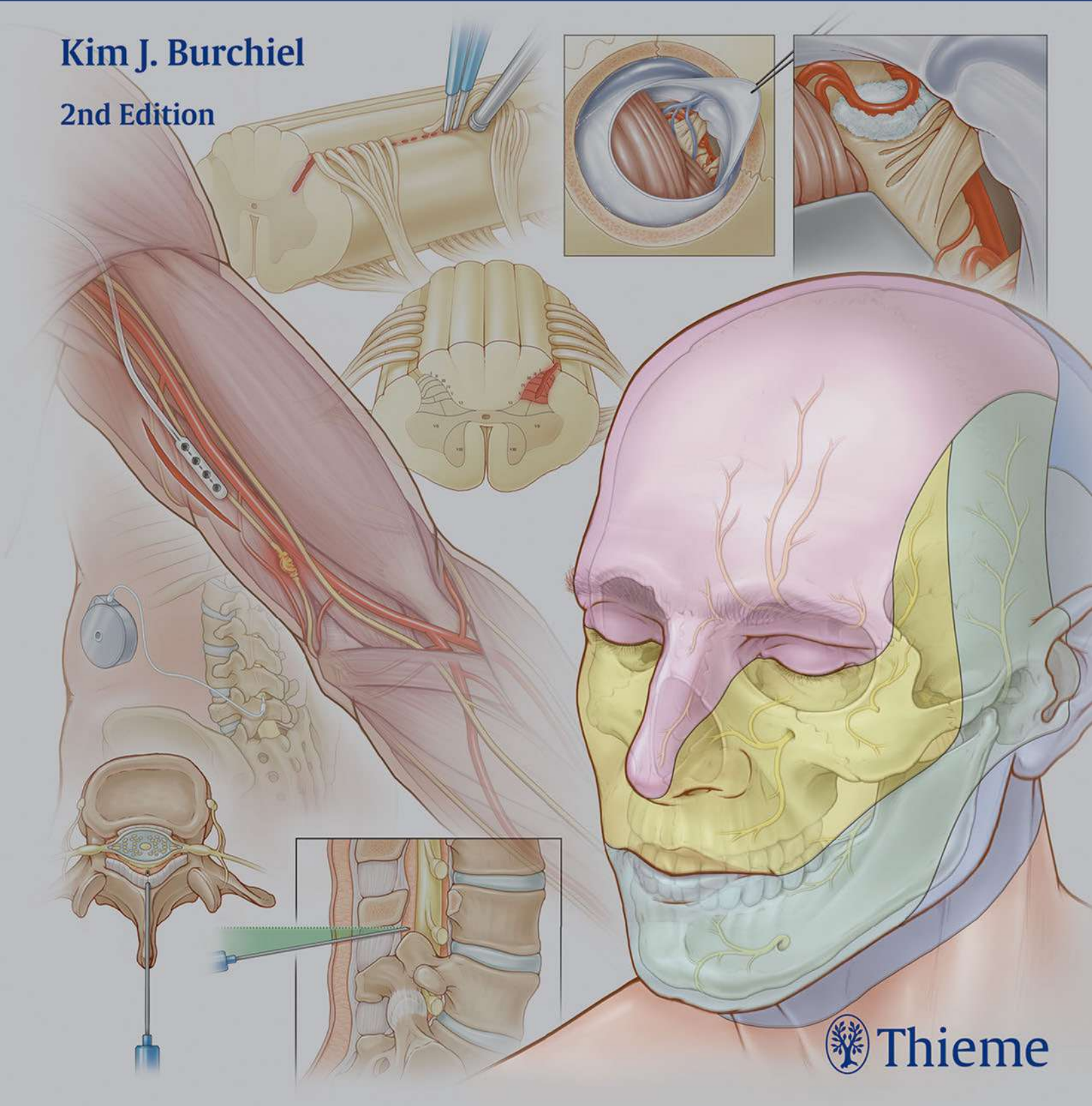
Surgical Management of Pain

Kim J. Burchiel

2nd Edition



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This book is dedicated to my resident and fellow trainees, past, present, and future.
Only by your efforts will this field progress and flourish.

Kim J. Burchiel, MD, FACS

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Foreword

Over the past several decades, neuroscience has gained society's attention as never before. Technological advances of neuroimaging, understanding in the basic sciences, and increasingly sophisticated therapeutic interfaces are endowing functional neurosurgery with unprecedented capabilities. The application of these powers to relieve the suffering of our fellow man is a responsibility all of us share. Few aspects of neurosurgery are as difficult or challenging as that of treating the patient with medically intractable pain. There are many far more straightforward—and far less frustrating—areas in surgery. And yet, helping the patient in pain is one of the most fundamental and important things a physician can do. That intractable pain syndromes are among the most prevalent conditions only heightens the critical importance of this endeavor.

The ability to help the patient in pain requires a fund of knowledge, experience, and competence that is very much in demand. Basic understanding of pain and its anatomic and physiologic substrate remains incomplete, and while some interventions have been highly successful, many others have had only mixed results. Our training programs, with their diversity of subspecialty areas and operative offerings to distract all of us from potentially more refractory problems, often struggle to educate tomorrow's healers in this crucial domain. Experience and, ultimately, competence cannot be gleaned from textbooks alone, but much of the requisite fund of knowledge can be transmitted and attained through the best of such works. This edition is one of these.

There are few neurosurgeons as qualified as Kim Burchiel to have conceived, organized, and edited this reference work. His experience and expertise in this field are recognized and respected by all in neurosurgery. This text takes on the breadth of the surgical management of pain with consistency and lucidity and is geared to the practicing physician. The Editor's Comments at the close of each chapter are especially valuable: in addition to summarizing key points and contributing his own experience, Dr. Burchiel shares the wisdom of one who sees the big picture and can place the condition and the surgical considerations in proper perspective. His commentaries successfully strike a balance between realistic appreciation of present limitations and constructive insight into where we've been and where we need to go. Burchiel's *Surgical Management of Pain* conveys both the science and the art of the field to guide us forward in this challenging and most important discipline of helping patients.

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Preface

The concept of a textbook dedicated to the surgical treatment of various pain syndromes was born more than a dozen years ago, from what I felt was, at that time, a lack of definition of the field. My goal was a compilation of historic and contemporary procedures that would at least frame the subject. The first edition of this textbook was well received and became a reference point for clinicians. I felt that we had achieved the goal of definition to a large degree.

With the perspective of time, it is clear that certain procedures have either proven ineffective, have been supplanted by more modern techniques, or have been updated by new knowledge. This new edition attempts to winnow the field by devoting content to conditions and operative procedures that continue to have an important and active role in the area of surgical pain management. We have striven to make the text clear to the reader and to bolster opinions with the highest quality outcome data available.

The text is supported by illustrations that communicate the principles of the discussion, or the relevant surgical procedures. I think the reader will find that this effort has made the book more understandable and informative.

The treatment of chronic pain is daunting and imperfect. Surgeons understandably shrink from the challenge. What we do is invasive, some would say brutal, and in many cases irreversible. Often, prudent surgeons avoid a surgical approach to pain in consideration of the dictum *primum non nocere*: "first, do no harm." It is certainly a driving principle that governs my day-to-day practice. The antidote to responsible reluctance is knowledge, experience, and, ultimately, competence in knowing when we can reasonably help and when we cannot.

My hope is that this textbook will perpetuate the discipline of surgical pain management. Only by continuing this discussion can we ever hope to make further progress in this area. I have been impressed during my career, and in watching the progress of other colleagues, that a surgeon dedicated to the relief of pain can make an enormous impact on patients' lives. This is not something to be forgotten or abandoned. In fact, I believe that our finest contributions to the surgical treatment of pain are yet to come.

Kim J. Burchiel, MD, FACS

Acknowledgments

I would like to recognize the support of Thieme in bringing this edition to fruition. Judith Tomat and Kay Connerly were the prime movers, and Timothy Hiscock has ably brought the project home. Every person I have worked with in the production of this textbook has been an exemplar of professionalism and collegiality. I am indebted to you all.

I would also express my deepest thanks to our illustrator, Andy Rekito. He has devoted his efforts to make this book both attractive and informative. By his example, he has taught me much about the value of medical illustration and the content that is sometimes subliminally imbedded in a figure. I think he is the current role model in this field.

Finally, I would like to convey my sincere gratitude to the chapter authors. You are all very busy people and have put up with endless questions and revisions. I know for you that this is a labor of love, as it is for me. I hope the final product justifies your commitment to this textbook.

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Section I

Anatomic and Physiologic Foundations for Nociceptive and Neuropathic Pain

1 Physiologic Anatomy of Nociception

Susan Ingram

Pain is an important protective mechanism in detecting the presence of tissue damage.[1] Tissue damage is detected by nociceptive afferents that respond to high-intensity stimulation and relay the information to the central nervous system (CNS). Inflammatory pain caused by activation of nociceptors by immune mediators following tissue damage is also protective. However, pain can also be pathological, persisting long after the initial insult or even occurring in the absence of any observed tissue or nerve damage. Indeed, pain is not a direct reflection of injury or tissue pathology but rather the perception of damage and includes cognitive and emotional processing by the brain.[2] This distinction is important because it accepts the role of the brain in defining our perception of pain. The distinction becomes particularly relevant when considering the etiology of chronic pain. This chapter summarizes components of the pain system, mechanisms of activation of the pain system, and current understanding of pain pathways and connections to the brain.

Anatomy and Physiology

Nociceptive Primary Afferents

First-order sensory neurons, called primary afferents, are neurons whose cell bodies are localized to peripheral ganglia. Dorsal root ganglia lie outside the spinal cord and innervate the periphery while trigeminal ganglia are located at the base of the skull and innervate the head, neck, and face. These primary afferent neurons send bipolar axons out to peripheral target areas and in to the spinal cord. They are differentiated by specific stimuli that are transduced to elicit action potentials and by their conduction velocities. Large diameter primary afferents ("Aβ") are myelinated, fast-conducting axons and respond to light mechanical or touch stimuli. Nociceptive neurons are activated by high-intensity stimuli and are generally split into two categories: medium-diameter, lightly myelinated "Aδ" neurons, and unmyelinated, slowly conducting "C" fibers that respond primarily to chemical stimuli. Activation of Aδ neurons correlates well with the first aspect of noxious damage (fast pain), and C fiber activation is associated with the second (slow pain) aspect of a noxious stimulus. Both Aδ and C fibers are heterogeneous, or polymodal, with respect to the types of noxious stimuli that they respond to, as well as the neurotransmitters, channels, and receptors that they express.[3,4]

Central Projections

Primary afferents extend axons and axon collaterals, which may extend into multiple levels of the dorsal horn of the spinal cord (**Fig. 1.1**). These terminals release glutamate in addition to various other neurotransmitters and neuropeptides. C-type nociceptors can be divided into two separate populations: those that contain neuropeptides (such as substance P and calcitonin-gene-related peptide [CGRP]) and the tyrosine kinase A (TrkA) receptor for nerve growth factor (NGF), and those that do not. Nonpeptidergic nociceptors respond to glial-derived neurotrophic factors and bind isolectin *Griffonia simplicifolia* IB4 (IB4). These nociceptors innervate the central region of lamina II. Peptide-containing nociceptors terminate in lamina I, the outer portion of lamina II, and in deeper layers of the dorsal horn.

The dorsal horn consists of projection neurons and interneurons that can contain gamma-aminobutyric acid (GABA), glycine, or glutamate. The complex circuitry of the dorsal horn and its incredible neuron heterogeneity are still under investigation. Some spinal nociceptive neurons respond specifically to nociceptive stimuli; these are termed "nociceptive-specific" and are primarily found in lamina I. These neurons respond to nociceptive stimuli via Aδ and C fiber inputs, have small receptive fields, and provide information as to the local-

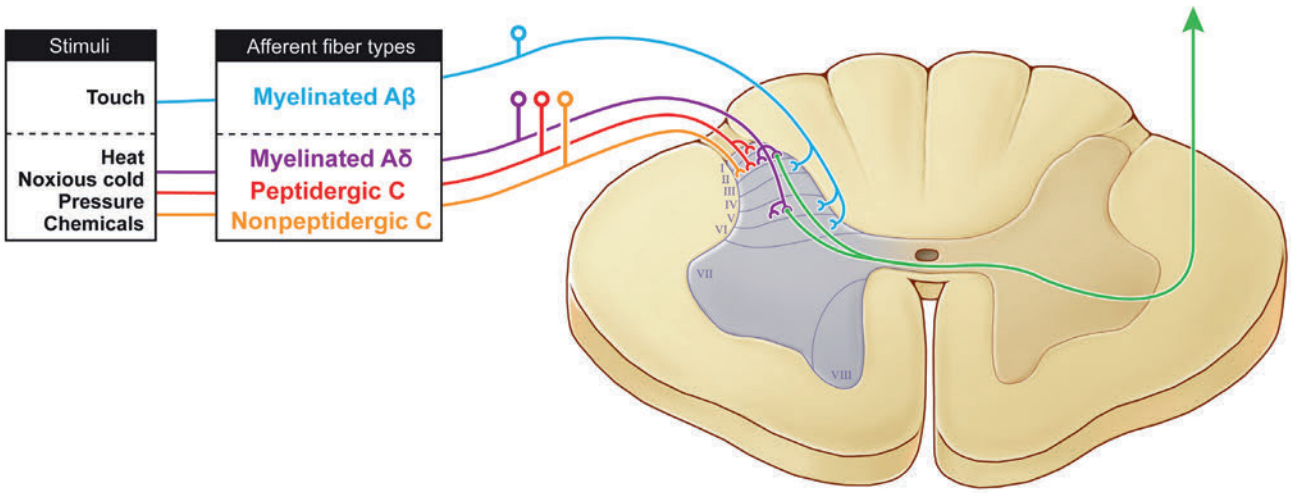

Fig. 1.1 Primary afferent projections. Free nerve endings of nociceptive Aδ and C fibers are activated by a host of noxious stimuli in the periphery and project through the dorsal root fibers in to the dorsal horn of the spinal cord. They are generally classified into lightly myelinated Aδ fibers (*purple*) that terminate in lamina II and V; peptidergic unmyelinated C fibers (*red*) that terminate in lamina I and II; and nonpeptidergic, unmyelinated C fibers (*orange*) that terminate in lamina II of the dorsal horn. Nonnociceptive afferents that transmit touch information are myelinated Aβ fibers (*blue*) that project to the dorsal horn through the dorsal column and terminate in lamina III, V, and VI. Nociceptive secondary neurons (*green*) cross the midline and project laterally through the spinal cord to the brain.

ization of the stimuli. Other cells in lamina I are polymodal nociceptive neurons. The dorsal layer of lamina II receives peptidergic C fibers, while non-peptidergic C fibers innervate the mid-layer of lamina II. Inner lamina II receives thinly myelinated and unmyelinated fibers that sense innocuous touch while lamina III and IV neurons primarily respond to innocuous touch information carried by Aβ fibers. Neurons in lamina V receive inputs from nociceptive primary afferents, as well as convergent innocuous information from other sensory modalities. These neurons are known as wide-dynamic-range (WDR) neurons and have large, complex receptive fields. The axons from second-order nociceptive neurons cross the midline and ascend contralaterally.

Lamina I and V nociceptive neurons project to many brainstem and thalamic targets[5] via the lateral spinothalamic tract (STT), the spinoreticular tract, and the spinomesencephalic tract (**Fig. 1.2**). Spinothalamic projection neurons primarily project to the ventroposterior (VP) thalamic nucleus, which in turn sends projections to the somatosensory cortex. This projection is responsible for the sensory discrimination aspects of the pain stimulus. A smaller number of STT neurons project to the medial thalamus/intralaminar nuclei. This medial pathway innervates cortical and subcortical regions involved in emotional and motor responses to pain.

The brainstem targets of the spinoreticular tract include the caudal portion of the ventrolateral medulla (CVLM), dorsal reticular nucleus, nucleus tractus solitarius, lateral parabrachial area (PB), and periaqueductal gray (PAG). This pathway has received a lot of attention recently due to the direct projection from the parabrachial area to the amygdala, an area involved in mediating the aversive properties of pain.[6] The fibers in the spinomesencephalic tract terminate in subnuclei of the reticular formation, including the nucleus cuneiformis, superior colliculus, and the Edinger-Westphal nucleus, as well as the ventrobasal thalamus, medial thalamus, and the limbic system.

Functional imaging studies have altered our understanding of cortical pain processing.[7] A "pain matrix" of brain areas activated by noxious stimuli includes primary and secondary somatosensory cortices (S1 and S2), the anterior cingulate cortex (ACC), and the insular cortex (IC). The rostral agranular IC has both afferent and efferent connections with nociceptive pain processing areas.[8] Recent work has demonstrated an important role of the habenula in integrating information from the sensory discrimination areas of the pain matrix with the affective and motivational areas.[9] The idea of a "pain matrix" is useful in the context of acute pain but cortical processing appears to be altered by chronic pain. For example, lesions of S1, S2, ACC, or IC areas may reduce chronic pain initially but pain usually returns over time, reflecting plasticity within the brain and pain networks.[7]

Descending Control of Pain

Nociceptive impulses can be modulated at the level of the spinal cord by descending information from the brain.[10] This is an important evolutionary benefit as an organism can ignore pain in a fight-or-flight

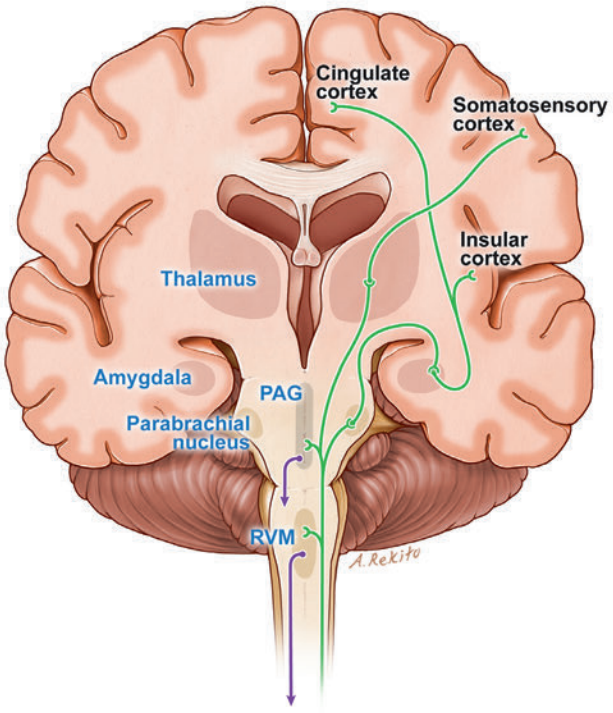

Fig. 1.2 Ascending pain pathways. Nociceptive dorsal horn projection neurons in the spinothalamic tract (STT) transmit information to the somatosensory cortex via the thalamus. Other nociceptive projection neurons project to brainstem nuclei and relay to target limbic brain areas, including the insular cortex and cingulate cortex. The ascending information (*green pathways*) engages descending systems (*purple pathways*) that regulate nociceptive afferents in the spinal cord.

situation. The descending antinociception pathway includes PAG and rostral ventromedial medulla (RVM) projections to the dorsal horn and is described in detail in *Central Nervous System Mechanisms in Pain Modulation* (see Chapter 2).

Transduction Mechanisms

The high-threshold C and Aδ fibers terminate as free nerve endings in the skin while Aβ fibers innervate Pacinian corpuscles and Merkel cells to detect vibration and light pressure. Pain transduction begins with activation of channels and receptors that are activated by high-threshold heat, cold, mechanical stimuli, or the myriad of chemicals released with tissue damage.

Heat

Human psychophysical studies have shown that the typical pain threshold for heat is around 43°C. After an intense search for a heat "sensor," a channel that was activated with heat stimuli was identified.[11] This channel is also pharmacologically activated by capsaicin, the active ingredient in hot peppers and other related compounds. Cloning of the capsaicin receptor or vanilloid receptor 1 (TRPV1), a member of the transient receptor potential (TRP) ion channel family, opened the door to the incredible heterogeneity of proteins expressed in nociceptors. Recent studies have defined an important role of TRPV1 in heat transduction and heat hypersensitivity. Nonetheless, studies with TRPV1-deficient mice show intact heat sensitivity,[12] suggesting that TRPV1 is not the only molecule involved in heat transduction. Other potential candidates are listed in **Table 1.1**.

Cold

As with heat, cold (~ 25°C) can also elicit pain. Primary afferent neurons that respond to cold have been identified with natural cooling chemicals, such as menthol or eucalyptol, and fall into the Aδ class of primary afferent fibers.

Mechanical Stimuli

An insult to the skin first activates high-threshold nociceptors via mechanical pressure to the free nerve endings. The consensus of many studies is that mechanical stimuli activate nonselective cation channels that induce action potentials in the primary afferent.[4] Although there are several candidate proteins (**Table 1.1**), it has been difficult to show in genetic knockdown experiments that any of these proteins are necessary for mechanotransduction.

Role of Channels Involved in Excitability

Following transduction of painful stimuli, activation of voltage-gated sodium, potassium, and calcium channels conduct these signals to release neurotransmitters into the spinal cord. Intensity of stimulation is encoded by increasing frequency of action potentials. Recently, many of these channels have been targeted as possible therapies for pain and hyperalgesia.[13] Both tetrodotoxin (TTX)-sensitive voltage-gated sodium channels (Nav 1.1, 1.6, and 1.7) and TTX-insensitive channels (Nav 1.8 and 1.9) are expressed in primary afferent neurons. The voltage-gated sodium channel Nav 1.7 has been implicated in a variety of human pain disorders.[14,15] Both loss-of-function mutations and gain-of-function mutations cause pain disorders. Nav 1.7 is upregulated in inflammatory pain models, suggesting that it contributes to inflammatory hyperalgesia,[16] but it does not appear to be altered following nerve injury.[17] Nav 1.8 is highly expressed in C nociceptors.[18] Voltage-gated calcium channels are also modulated in inflammatory or pain states,

Table 1.1 Primary afferent transduction proteins and stimuli

Transduction mechanism	Stimuli
Heat receptors	
TRPV1	Capsaicin and vanilloid compounds; heat > 43°C; enhanced by inflammatory mediators
TRPV2	Heat > 52°C (expressed in Aδ)
TRPV3/TRPV 4	Found in epithelia rather than sensory neurons and respond to 25–35°C; may be heat detectors
Cold receptors	
TRPM8	Cold 10–30°C; menthol sensor
TRPA1	Cold < 15°C
KCNK2 (TREK-1)	Expressed in C nociceptors; can be modulated by heat and pressure
KCNK4 (TRAAK)	Expressed in C nociceptors; can be modulated by heat and pressure
Mechanoreceptors (candidates)	
DEG/ENavC channels	Members of the degenerin/epithelial Nav channel family, including mec-4 and mec-10 in *C. elegans* and ASIC 1, 2, 3; but knockouts of ASIC channels have few deficits in mechanotransduction
TRPV2	Responds to osmotic stretch as well as noxious heat
TRPA1	May be a detector of mechanical stimuli
KCNK channels	KCNK2, 4 and KCNK18 (target of hydroxy-α-sanshool, Szechuan pepper)
Chemoreceptors	
Receptor tyrosine kinases	NGF (TrkA receptor),
GPCRs	Serotonin, histamine, bradykinin, glutamate, CGRP, prostaglandins, eicosanoids, endocannabinoids, leukotrienes
KCNK channels	Two-pore potassium channels
Protease-activated receptor (PARS)	Extracellular proteases cleave and activate PARs
ASICs	Protons
P2X	Adenosine triphosphate (ATP)
TRP channels	Capsaicin and vanilloid compounds (TRPV2), menthol (TRPM8)

Source: Data derived from Basbaum and Julius, Cellular and molecular mechanisms of pain. Cell 2009;139:267–284.

Abbreviations: ASIC, acid-sensing ion channels; DEG/ENav, degenerin/epithelial Nav channel; GPCR, G protein–coupled receptors; KCNK, 2 P-domain potassium channels; P2X, purinergic receptor channels; TRP, transient receptor potential channels.

suggesting that they may be useful therapeutic targets. Gabapentin, an anticonvulsant drug that targets the α2δ subunit of calcium channels, has been used to treat neuropathic pain.[19] Finally, KCNQ channels have been explored as potential therapeutics. KCNQ channels are low-threshold, voltage-activated potassium channels that do not inactivate. These channels help to stabilize membrane potential and dampen excitability. They are also negatively regulated by G protein–coupled receptors (GPCRs), such as bradykinin, leading to increased excitability of nociceptors.[20] Activators of the KCNQ channels (such as flupirtine and retigabine) have been useful as analgesics.[21]

Pathophysiology

Peripheral Sensitization

Persistent pain is often due to direct and long-lasting damage to peripheral nerve fibers, through either injury or disease states. Sensitization results in allodynia (nociception triggered by normally innocuous stimuli) and hyperalgesia (increased responsiveness to pain stimuli). There are multiple mechanisms underlying these plastic changes at both peripheral and central sites (**Fig. 1.3**).[4,22] Release of inflammatory

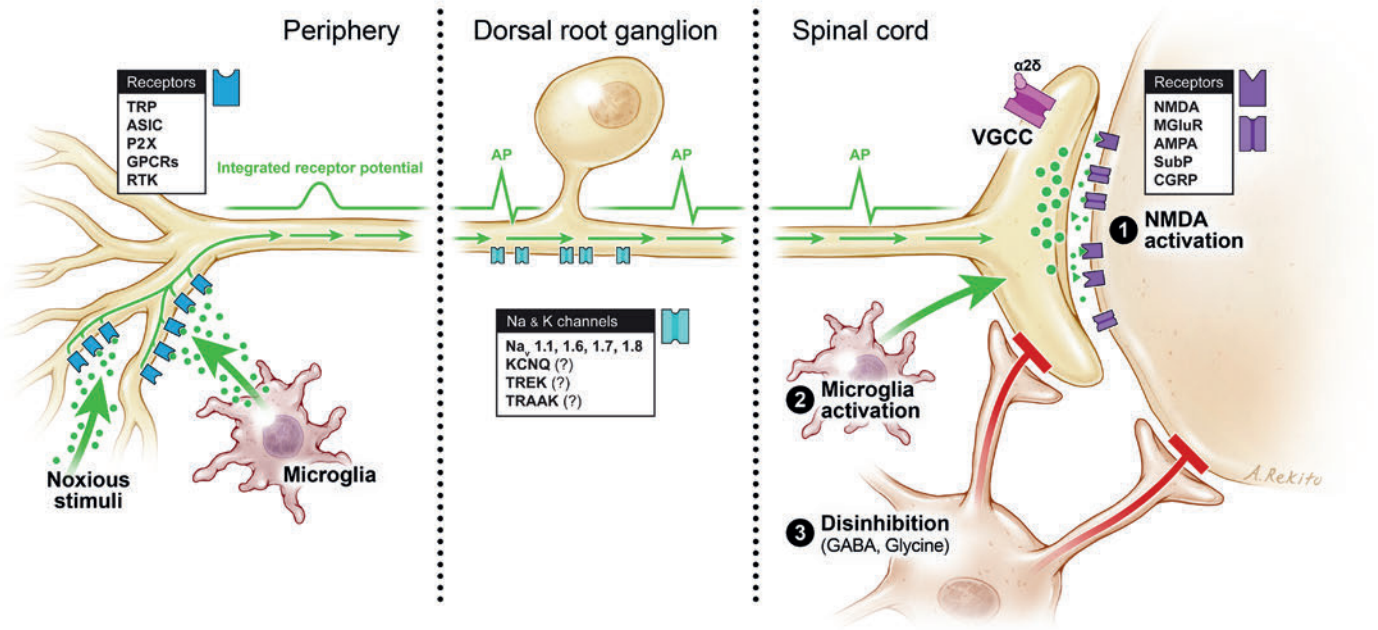

Fig. 1.3 Mechanisms of sensitization. Nociceptive information can be altered at multiple points along the transmission pathway. In the periphery, free nerve endings are poised to be activated with tissue damage. Inflammatory mediators and noxious stimuli activate transduction molecules on free nerve endings. Prolonged exposure to these mediators can induce changes in receptor proteins that enhance their ability to detect and transduce innocuous stimuli. Once action potentials have been elicited in primary afferent terminals, they are actively transmitted to the spinal cord. Alteration of sodium and potassium channels involved in propagation of action potentials can modulate primary afferent excitability and contribute to sensitization. In central terminals, prolonged excitation promotes neurotransmitter release and enhanced activation of spinal projection neurons. Persistent injury can modulate presynaptic release of neurotransmitters, sensitivity of postsynaptic receptors, and activity of inhibitory interneurons in the dorsal horn. Some specific mechanisms of sensitization in the spinal cord include (1) activation of postsynaptic "silent" NMDA receptors, (2) microglia activation and release of inflammatory mediators, and (3) disinhibition of dorsal horn projection neurons by altering activity of inhibitory interneurons or postsynaptic $GABA_A$ and glycine receptors.

mediators ("inflammatory soup") following tissue damage alters the gating and kinetics of transduction molecules (see **Table 1.1**) through direct binding of the chemicals to the receptor proteins or via intracellular second messenger signaling. This "inflammatory soup" contains neurotransmitters and peptides (substance P, CGRP, bradykinin), prostaglandins, leukotrienes, neurotrophins, cytokines, chemokines, extracellular proteases, and protons. Nociceptors express heterogeneous populations of receptors for these inflammatory mediators and activation of these receptors results in increased excitability of the nociceptors.[23,24] To date, common therapeutics target cyclooxygenases (COX-1 and COX-2) to reduce the synthesis of prostaglandins.

More recently, work on NGF highlights several other peripheral mechanisms of persistent pain. In the adult, NGF is released following tissue injury and is a component of the inflammatory soup.[25] NGF activates TrkA receptors that are selectively expressed by C nociceptors.[26] Activation of TrkA receptors can potentiate TRPV1 responses at peripheral terminals,[27] as well as signal the cell nucleus to increase expression of several pronociceptive proteins, including substance P, TRPV1, and Nav 1.8 channels.[26,28] The fact that NGF acts as an inflammatory mediator in adults (as opposed to its neurotrophic effects during early development) made it a promising target candidate for pain therapies. In clinical trials, efficacy of anti-NGF antibodies for some chronic pain conditions has been shown; however, many of these trials have been halted due to safety concerns.[29,30] Other potential therapeutics currently being developed are antagonists of TRPV1 and TRPA1 receptors.[31]

Central Sensitization

Intense stimulation or persistent injury can cause plasticity in the CNS such that normally innocuous stimuli lead to the perception of pain.[32] For example, in neuropathic pain syndromes, abnormal ectopic excitability of myelinated Aβ sensory fibers leads to paresthesias and dysesthesias while increased discharge in Aδ and C fibers leads to stabbing, burning pain.[33]

This central sensitization can be mediated by several different mechanisms,[22] including changes in glutamate receptor activation, loss of inhibitory control, glial mechanisms, and descending pain facilitation. These mechanisms may contribute to observed dendritic remodeling in the periphery and dorsal horn.[34]

Glutamate/NMDA-Dependent Sensitization

Prolonged stimulation of nociceptive primary afferents results in "wind-up"[35] or increased excitation of secondary neurons in the dorsal horn. This excitation is due to increased presynaptic release of glutamate elicited by the action potential barrage and more efficient presynaptic release from primary afferents, as well as to changes in postsynaptic sensitivity of glutamate receptors. Normally, glutamate released from nociceptive primary afferents activates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors. The increased release of glutamate with inflammation activates metabotropic glutamate receptors and previously silent *N*-methyl-D-aspartic acid (NMDA) receptors.[36] Activation of NMDA receptors enhances intracellular calcium, which has been implicated in the hypersensitivity or hyperalgesia induced by inflammatory processes. This process has been compared to long-term potentiation (LTP) processes in the brain.[37] NMDA receptors have been targeted as potential therapies for pain; however, results from clinical trials have been disappointing to date. They have a narrow therapeutic window due to serious CNS side effects, and their therapeutic usefulness may be limited to patients with complex regional pain syndrome and painful diabetic neuropathy.[38]

Loss of Inhibitory Control

Dorsal horn neurons are under the inhibitory control of descending inhibitory serotonergic, noradrenergic, and dopaminergic pathways from the PAG, RVM, locus coeruleus, and raphe nuclei, as well as by local GABA and glycine-containing interneurons.[39] Tricyclic antidepressants may target these descending circuits when used for neuropathic pain. The balance of inhibitory/facilitatory control of pain by the descending inhibitory pathways may be shifted in states of neuropathic or chronic pain.[40,41]

Inhibitory spinal interneurons provide control over dorsal horn neuron excitability via the release of GABA and glycine, and they also release opioid peptides that modulate nociception. Opioids act in the spinal cord both presynaptically to inhibit the release of pronociceptive neurotransmitters (substance P and CGRP) and postsynaptically to inhibit lamina I and V neurons.[42] Inhibitory neurotransmission by these spinal interneurons decreases neuropathic pain,[43] but the mechanism is not understood. Changes in the number and excitability of the interneurons and alterations in postsynaptic $GABA_A$ receptors on spinal projection neurons have been proposed.[44]

Glial Mechanisms

Microglia and astrocytes, activated after nerve injury, release inflammatory mediators, such as adenosine-5′-triphosphate (ATP), cytokines, proteases, and growth factors that enhance persistent pain.[45] Microglia may be activated by the release of ATP from injured primary afferents. The ATP receptors P2X and P2Y localized to microglia detect the released ATP and initiate release of brain-derived neurotrophic factors (BDNFs), leading to disinhibition of lamina I neurons and increased responses to pain.[46] Other receptors of glial-derived factors, such as the fractalkine receptor (CX3CR1) and toll-like receptors (TLRs), have also been implicated in nerve injury.[4] The interactions between neurons and glia are of intense interest in the pain field, and future studies hold the potential of providing an understanding of how to modulate these interactions for pain therapies.

Functional and Structural Imaging in Chronic Pain

Ongoing noxious stimuli induce synaptic plasticity in the CNS (**Fig. 1.4**).[47,48] Neuroimaging studies using positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and magnetoencephalography (MEG) have shown that there are widespread changes in brain activation and information processing between acute pain[49] and chronic pain stimuli.[7,50] Studies using acute nociceptive stimuli highlight the typical "pain matrix," where activation of the posterior insula and somatosensory cortical areas S1 and S2 are involved in the sensory-discriminatory aspects of the pain while activation of the ACC, prefrontal cortex (PFC), and insula are important for the emotional and motivational aspects of the pain.[48,51] Both peripheral and central sensitization cause neuroplastic changes in the "pain matrix."[52–54] The changes are not simply a shift in the stimulus-response curves reflecting an increase in activity in the pain-related areas of the brain, but changes in activity of the brain during rest,[55] and changes in network connectivity[56,57] and pain processing[58,59] have been noted in chronic pain patients.

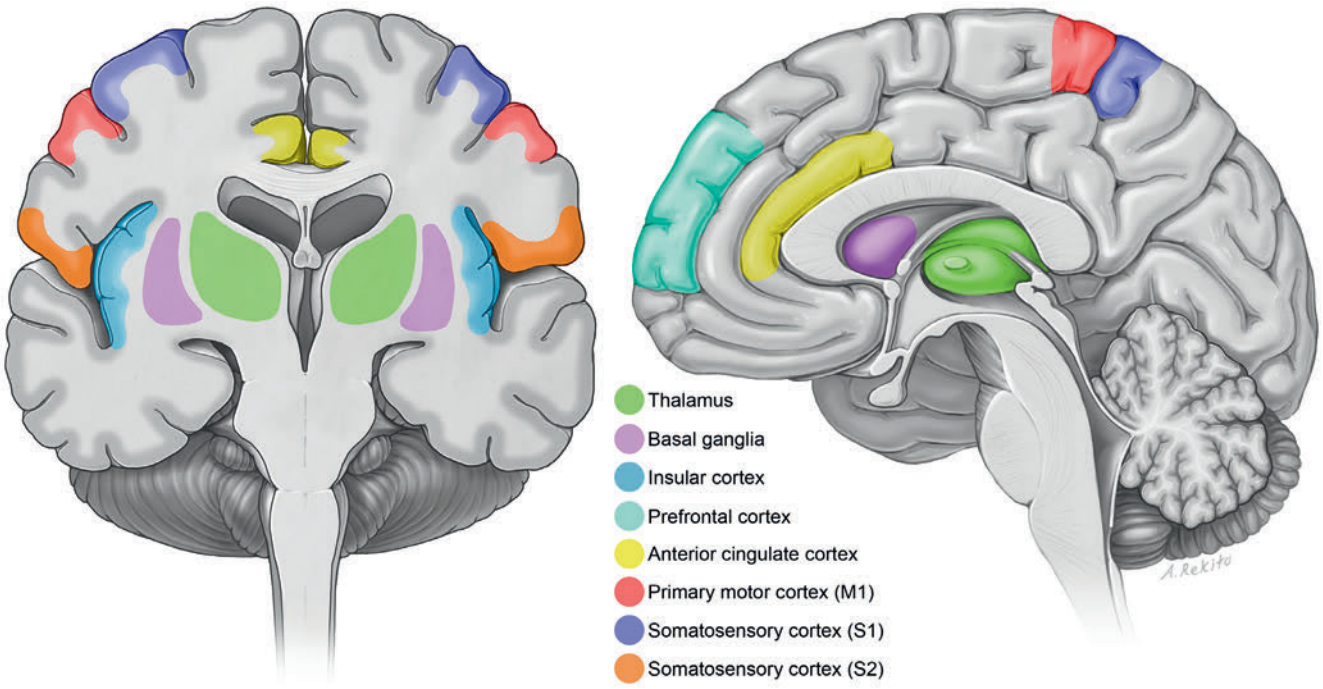

Fig. 1.4 The "pain matrix." Schematic showing major brain areas that are activated by pain.

Summary

Understanding how the brain exerts such a profound influence on an individual's perception of pain is fundamental to understanding different chronic pain states and key to the development of new-generation pain therapies. Further development of brain imaging techniques and studies of individual differences in pain processing will be crucial to advance our knowledge, as will further studies of mechanisms of neural plasticity in the transition from acute to chronic pain.

Editor's Comments

Nociception is technically defined as the activation of peripheral nociceptors (Aδ and C fibers). As is illuminated in this chapter, the process is a bit more complex than that. This chapter deals with the process of nociception from the periphery to central perception.

In 1644, René Descartes theorized that pain was a disturbance that passed along specific nerve fibers from the periphery to the brain. This theory was transformative, since it replaced the notion that the perception of pain was somehow a spiritual or mystical experience, with the concept that pain sensation was an internal, physical, and mechanical process. Descartes's work, along with Avicenna's, were the harbingers of later theories of specificity.

Despite these insights, to a degree Descartes had it wrong. There is no specific wiring for pain perception from the periphery to the brain. It is a highly integrated system that incorporates nearly all systems of the central nervous system, including detection, inhibition, facilitation, and mobilization of homeostatic mechanisms, emotional responses, and memory. The key point of this chapter is that beyond the primary afferent, the concept of the "labeled line" for detection of impending, or actual, tissue injury becomes progressively naïve as we ascend from the spinal cord segment to brainstem, thalamus, basal ganglia, and neocortex.

Dr. Ingram refers to the "pain matrix." This is a useful device to begin to understand the complexity of nociceptive processing. Although she uses the term "matrix" with respect to cortical processing, it may be best to think of this matrix as extending from the spinal segment to the neocortex, with progressive processing and integration of nociceptive information. It is this process that has been so extensively studied over the past few decades, and to a degree, it is the aspect of the system that we understand best. How this system changes as pain becomes more "chronic" is the challenge that will occupy neuroscientists over the next several decades.

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2 Central Nervous System Mechanisms in Pain Modulation

Mary M. Heinricher

It has long been appreciated that the relationship between pain sensation and stimulus intensity is neither simple nor constant.[1] The magnitude of the response to a given damaging or potentially damaging (i.e., noxious) stimulus is known to vary widely between individuals and to depend on a host of cognitive, emotional, and social factors. The work of Beecher, who noted that soldiers wounded in World War II reported much less pain than would have been expected from their injuries, is widely cited.[2] Arousal, attention, learning, fear, and stress all have been shown in psychophysical studies to influence pain sensation in humans. For example, subjects report increases in pain when their attention is directed to a noxious stimulus but, when distracted, show decreases in both the ability to discriminate pain intensity and the perceived unpleasantness of the painful stimulus.[3,4] Parallel changes in nociceptive responses have been reported in animals. Examples include monkeys performing vigilance tasks,[3] hungry cats or rats given access to food,[5] and rats exposed to a mild stress[6] and to biologically relevant fear stimuli, such as predator odor.[7]

The recognition that this puzzling variation in pain responses has an understandable neural basis and that it can be accounted for, at least in part, by the actions of endogenous pain-modulating systems is much more recent and grew from two observations. First was the report that electric stimulation within the midbrain periaqueductal gray region of rats produced potent analgesia.[8] This phenomenon came to be called *stimulation-produced analgesia* (SPA) when subsequent work confirmed the initial findings using more quantitative tests of nociception and extended it to additional species, including humans.[9] Second was the characterization of endogenous opioid peptides,[10] since it was evident that endogenous neurochemicals that bound the same receptor as opiate drugs could modify pain responses if released under physiological conditions. These two findings motivated an intensive research effort directed toward understanding central pain-modulating systems. The purpose of this chapter is to review current knowledge concerning these systems. The emphasis is on evidence demonstrating that these are truly pain-modulating systems that have the ability to enhance as well as suppress pain, and that, under physiologic conditions, pain modulation is integrated with autonomic, neuroendocrine, and behavioral adjustments to provide a coordinated response to environmental challenges.

Opioid-Activated Descending Control: The Periaqueductal Gray–Rostral Ventromedial Medulla System

The best-studied and probably functionally most significant system contributing to pain modulation is a network having critical links in the brainstem, in the periaqueductal gray (PAG), and in the rostral ventromedial medulla (RVM) (**Fig. 2.1**).[11] The PAG is a cell-rich region surrounding the cerebral aqueduct in the midbrain. The RVM is defined functionally rather than cytoarchitecturally and includes the nucleus raphe magnus and adjacent reticular formation. Numerous behavioral studies demonstrate that nonselective activation of neurons within the PAG or RVM has a potent antinociceptive effect.

Antinociception is largely, although not exclusively, the result of interference with nociceptive processing at the level of the spinal cord. This follows from the fact that PAG or RVM stimulation inhibits not only integrated, supraspinally organized responses to noxious stimuli, but also noxious-evoked activity of dorsal horn neurons and spinally organized nociensor reflexes.[12] The anatomic substrate for descending modulation is a projection to spinal and trigeminal dorsal horns from the RVM.[9] This large, diffuse projection travels through the dorsolateral funiculus and terminates at all levels in the superficial layers and

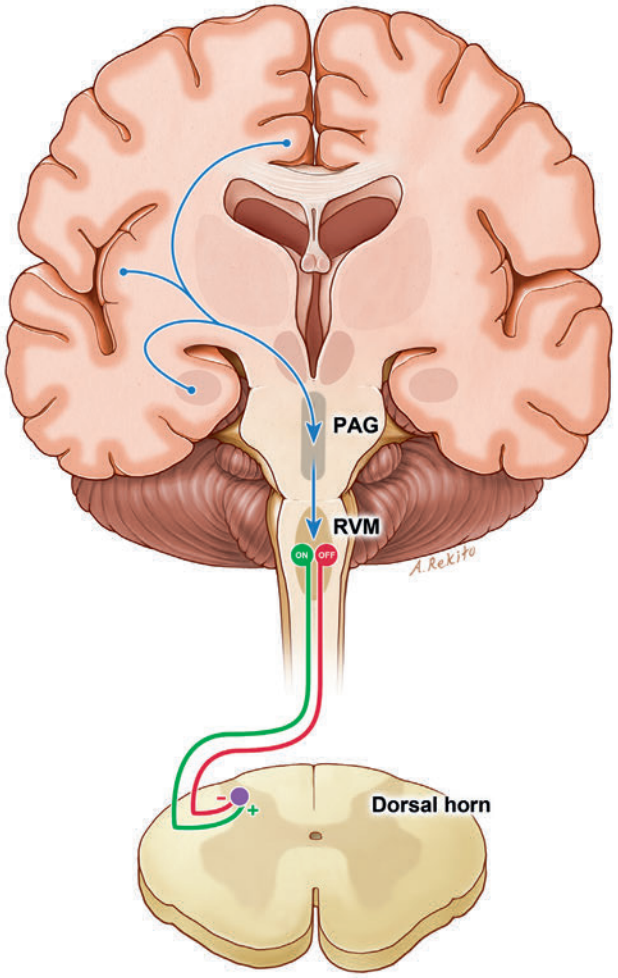

Fig. 2.1 Brainstem nociceptive modulatory network has links in the midbrain periaqueductal gray (PAG) and rostral ventromedial medulla (RVM). The RVM, which includes the nucleus raphe magnus and adjacent reticular formation, receives a large input from the PAG. The RVM in turn projects to the dorsal horn, primarily to the superficial layers and lamina V, where it can influence processing of nociceptive information. Note that processes organized in limbic forebrain structures, most notably the amygdala, can influence the PAG-RVM system via dense reciprocal connections with the PAG.

lamina V. The PAG itself has only a sparse projection to the spinal cord, and its influence on the dorsal horn is relayed through the RVM. Information thus flows through the PAG to the RVM, which in turn influences the activity of nociceptive neurons in the dorsal horn.

This system is also an important substrate for opioid analgesia, as discussed in more detail below. It has become clear, moreover, that the system has the potential to *enhance* pain as well as *inhibit* it. Although the net effect of electric stimulation within the RVM is generally antinociceptive, low-intensity stimulation at some sites leads to an increase in dorsal horn nociceptive responses and nociceptive reflexes. Electrophysiologic and behavioral studies have demonstrated a significant contribution of descending facilitatory influences from the RVM. Paradigms include the increased nociceptive responding associated with acute narcotic withdrawal, inflammation, and peripheral nerve injury, as well as top-down influences such as mild stress.[11] The PAG-RVM system thus exerts a bidirectional control over nociceptive processing (see Fields and Heinricher[9] and Heinricher et al[11] for reviews).

The neural basis for bidirectional control of nociception can be traced to a heterogeneous cell population within the RVM. Neurons in this region fall into three physiologically, pharmacologically, and functionally distinct classes.[13,14] Cells of one class, *off-cells,* are characterized by a cessation of firing during nociceptive reflexes **(Fig. 2.2)**. Cells of a second class, *on-cells,* are defined by a burst of activity during nociceptive reflexes. Recent work using selective pharmacological manipulation of these two classes has shown that on-cells facilitate nociception, whereas off-cells inhibit nociception.[11,15] The pause in firing that defines off-cells permits nociceptive responses to occur, and drugs that eliminate this pause produce analgesia.[16] Abnormal activation of on-cells contributes to a number of chronic or pathological pain states.[9,11] As would be expected from the circuit diagram in **Fig. 2.1**, both cell classes are excited by electrical stimulation within the PAG, and at least some cells of each class project to the dorsal horn.

A third class of RVM neurons, *neutral cells,* show no change in activity associated with nociceptive responding, and no role in pain modulation has been

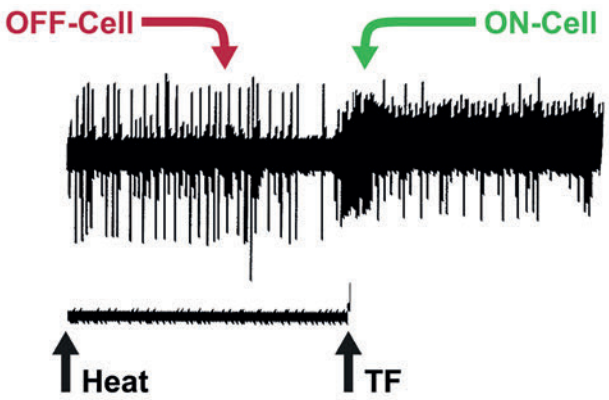

Fig. 2.2 Activity of an off-cell (*large spikes*) and on-cell (*smaller spikes*) recorded during a single tail-flick trial. Cell activity is in upper trace, output of tail position monitor in lower trace. Sweep is 10 seconds, and heat was turned on at the beginning of the trace. The tail flick occurred approximately 5 seconds later, when tail temperature reached approximately 42 °C (*arrow*). Note the characteristic pause in firing of the off-cell, which was followed less than half a second later by activation of the on-cell and then the tail flick (TF).

identified.[9] Some neutral cells project to the spinal cord, and presumably contribute to other aspects of brainstem function, such as autonomic control.

Our understanding of the neuronal populations and circuitry within the PAG is not as advanced as that within the RVM. However, there is some recent evidence to suggest that the PAG, like the RVM, can facilitate pain. More important, the PAG is involved in a variety of functions in addition to pain modulation—among them reproductive behavior, vocalization, and integration of defense responses—and has been considered a midbrain extension of the "limbic system."[17] In an elegant series of anatomic and stimulation studies, Bandler and colleagues showed that the PAG is organized into rostrocaudally organized columns with distinct connectivity and function. Stimulation throughout the PAG produces behavioral antinociception and inhibition of dorsal horn nociceptive neurons, but this antinociception is accompanied by a complex of behavioral and autonomic responses that depend on which column is stimulated. It is now recognized that the antinociception produced by stimulation in the PAG represents an aspect of integrated defense responses.[18–20] These observations linking PAG-mediated analgesia with defense also accord well with the effects of PAG stimulation in humans, described as "fearful" or evoking feelings of apprehension, which could represent an emotional correlate of defense.[21,22]

Although animal work provides strong support for the role of the PAG-RVM system in pain modulation, clinical application of this information has not been entirely successful, and both the effectiveness and reliability of "deep-brain stimulation" (DBS) for intractable pain have been questioned.[23–26] Several factors may contribute, but it is of note that targets for DBS in humans have not generally been within the PAG itself, at least not in the caudal ventrolateral aspect, which is the region usually targeted in animals. Rather, extreme rostral PAG and periventricular structures are more commonly used. The neural elements activated by stimulation at these sites have not been identified. Further, massive ascending and descending tracts connecting brainstem structures with more rostral regions run adjacent to the third ventricle in periventricular fiber systems. These axons traveling to and from the brainstem include, but are not limited to, monoaminergic systems. A range of systems is thus activated by electrical stimulation at these sites, and which of these is responsible for the analgesic effects has not been determined. Extensive rostral projections from the PAG itself take a periventricular course, with targets in both diencephalic and telencephalic regions implicated in nociception. The RVM also has ascending projections, with targets including the medial thalamus. These anatomic findings buttress behavioral demonstrations that higher stages of nociceptive processing are, like the dorsal horn, subject to control by the PAG-RVM system.[27] This raises the possibility that stimulation as typically used clinically activates an *ascending* PAG outflow, which may bypass some of the emotional and autonomic effects of stimulating in the PAG itself.

Interestingly, the parafascicular nucleus (Pf) in the medial thalamus receives ascending projections from the PAG. In animal studies, neurons in Pf respond to noxious cutaneous or visceral stimulation over large receptive fields, and electrical stimulation or morphine microinjection in this area produces antinociception, preferentially suppressing the "emotional" component of pain.[28,29]

Neurochemistry of the PAG-RVM Pain-Modulating System

The early focus on the PAG-RVM system as an "analgesia system" has clearly proved to be incomplete. The physiological and functional heterogeneity of the RVM and the complex intertwining of antinociception with other aspects of defense within the PAG mean that electric stimulation will not be the ideal way to investigate this system or to manipulate it for therapeutic purposes. However, both PAG and RVM contain a large number of neurotransmitters and neuromodulators. Substances demonstrated within the PAG using anatomical approaches include catecholamines, serotonin, substance P, γ-aminobutyric acid (GABA), glutamate, aspartate, enkephalin, somatostatin, neurotensin, galanin, vasoactive intestinal polypeptide, neuropeptide Y, calcitonin gene-related peptide, and cholecystokinin. The RVM displays a similar wealth of neuroactive substances, including enkephalin, serotonin, GABA, somatostatin, vasoactive inhibitory peptide, and substance P, with some neurons coexpressing one or more neuropeptides with serotonin.[9] Functional studies that would pinpoint the roles of these different neurotransmitters and neuropeptides lag considerably. Only a few have been studied in detail, but at this point, it is clear that there are unlikely to be specific neurochemical signatures for pain-inhibiting and pain-facilitating neurons. Nevertheless, continuing advances in our understanding of the functions of different neuroregulators in controlling PAG and RVM neurons should provide better pharmacologic tools to manipulate more specifically those neural systems relevant to pain control.

Opioids

Microinjection mapping studies reveal only a limited number of specific brain regions that support opioid analgesia, among them the PAG and RVM. Endogenous opioid peptides and opioid receptors, μ, δ, and

κ, are found within both structures.[15] The focus has been on the μ receptor as having the primary role in the analgesic actions of opioids in the brainstem. Activation of δ receptors has only modest behavioral effects under normal conditions, but effects are enhanced during prolonged inflammation.[30,31] Activation of the κ receptor by infusion of selective agonists into either the PAG or RVM does not produce potent analgesia and, in fact, can interfere with μ-mediated analgesia.

Opioids applied within either PAG or RVM thus produce a net behavioral effect (*antinociception*) equivalent to that produced by electric stimulation at the same site. In contrast, inactivation of these structures does not produce analgesia and even attenuates the analgesic effects of opioids applied at the same site. Thus, opioids must produce analgesia by activating an outflow that inhibits nociceptive processing. In both PAG and RVM, however, the direct cellular effect of opioids is to produce a hyperpolarization, and only a subset of neurons in either region are responsive. Another subset of neurons are activated by opioids, but this is an indirect effect, mediated by inhibition of GABA-containing inhibitory interneurons **(Fig. 2.3)**.[15,32] As might be predicted from this disinhibitory model and the proposed roles for RVM on- and off-cells, opioids disinhibit RVM off-cells and inhibit RVM on-cells. The activation of off-cells is necessary for the analgesic actions of systemically administered morphine.[16]

Opioid inhibition of on-cells is a direct effect and, although not necessary or sufficient for analgesia, presumably contributes. Interestingly, suppression of on-cell firing may play a role in the respiratory depressant effect of opioids.[33] This suggests that a focus on the presynaptic actions of opioids, which lead to off-cell activation, is likely to lead to analgesic drugs with a better therapeutic index.

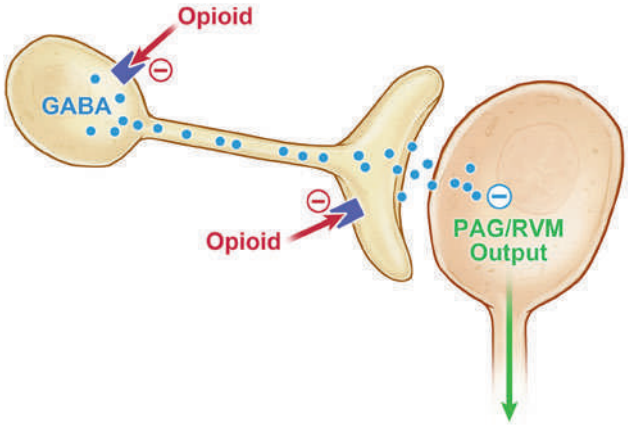

Fig. 2.3 Opioids activate output neurons from periaqueductal gray (PAG) and rostral ventromedial medulla (RVM) indirectly, by inhibiting GABA-ergic inhibition. This can be mediated postsynaptically, that is, by an action on GABA-containing interneurons, or presynaptically, by depressing release of GABA from the terminal.

Serotonin

Spinally projecting neurons within the RVM manufacture a number of neurotransmitters and neuropeptides, among them substance P, enkephalin, thyrotropin-releasing hormone, somatostatin, cholecystokinin (CCK), excitatory amino acids, GABA, and serotonin. For some reason, serotonin has dominated the thinking of many investigators. This is despite the fact that serotonergic neurons make up less than 20% of RVM neurons, and evidence that serotonin contributes to descending facilitation as well as inhibition.[34,35] Certainly, a primary role for this neurotransmitter in inhibiting nociception now seems unlikely. Current evidence is more consistent with the idea that serotonin released at spinal levels gates both pronociceptive and antinociceptive effects mediated by release of other, as yet unidentified, neurotransmitters.[36]

Norepinephrine

The antinociception resulting from activation of the PAG-RVM system is diminished by intrathecal application of α-adrenergic antagonists.[37] Catecholamine-containing cell bodies are not found within the RVM, so this must be mediated, in part, by activation of pontospinal noradrenergic pathways. Proudfit and colleagues have provided evidence for a model in which substance P neurons in RVM project to and activate A7 noradrenergic neurons to produce an antinociception mediated by a spinal α_2 receptor. Opioid inputs to A7 produce not analgesia, but hyperalgesia, which is mediated by a spinal α_1 receptor. Thus, under the influence of substance P or opioid inputs from the PAG-RVM system, pontospinal noradrenergic cell groups mediate analgesia or hyperalgesia, respectively.[38–40] These opposing behavioral effects involve different α-adrenergic receptors, again providing a potential starting point for selective manipulation.

■ Conditioned Pain Modulation and "Diffuse Noxious Inhibitory Controls"

The principle of counterirritation, in which "pain inhibits pain," is the basis for pain therapies in which application of a controlled pain-inducing stimulus is used to relieve existing, generally chronic, pain. Counterirritation therapies have been used for centuries, and the role for counterirritation mechanisms in reducing pain is supported by quantitative

psychophysical studies demonstrating an extrasegmental reduction in perceived pain intensity, an increase in pain threshold in humans, and attenuation of nociceptive reflexes in animals consequent to delivery of a second noxious stimulus.[41–43] The inhibition is preferential for so-called second pain, which is mediated by unmyelinated nociceptors. "First pain," mediated by small-diameter myelinated fibers, is much less reduced.[44] Tactile threshold is not elevated. This phenomenon is now referred to as "conditioned pain modulation," referring to the fact that the response to a probe stimulus is altered by addition of a "conditioning" stimulus (the remote stimulus). Impairment of conditioned pain modulation has been documented in a host of chronic pain conditions, and has been shown to predict development of chronic postoperative pain.[45,46]

Attempts to outline neurophysiologic mechanisms for counterirritation have focused on the fact that nociceptive, especially multireceptive or "wide-dynamic-range," dorsal horn neurons are inhibited by noxious stimuli applied to almost any area of the body outside its own relatively small excitatory receptive field. Innocuous stimuli are ineffective, and this phenomenon has thus been termed *diffuse noxious inhibitory control* (DNIC).[47] The conditioning stimulus can be in the area immediately surrounding the excitatory receptive field or on a remote body part so that intense stimulation of the nose, either forepaw, or even visceral structures will inhibit the response of a dorsal horn neuron with an excitatory receptive field on the right hindpaw. DNIC is thus presumed to represent the neurophysiologic correlate of conditioned pain modulation in humans, although this has not been proven. DNIC is mediated via supraspinal loop, not through the PAG-RVM system but through the subnucleus reticularis dorsalis, located more caudally and laterally in the medulla.[48]

Dorsal Column Stimulation: Segmental and Supraspinal Mechanisms

The gate control theory proposed by Melzack and Wall in 1965[49] was an early attempt to explain the lack of a simple correlation between noxious stimulus intensity and pain sensation. Based on knowledge of dorsal horn projection neurons that responded to both noxious and innocuous peripheral stimuli and of descending inhibitory control of dorsal horn processing, the theory postulated a gate, comprising neurons in the substantia gelatinosa, that controlled throughput of somatosensory information to higher centers. This gate would be opened by input from small-caliber primary afferent fibers but would be shut by input from large-diameter fibers. Although the gate could be influenced by systems descending from the brain, the emphasis was on the balance of small- and large-fiber input arriving in the dorsal horn as the critical factor controlling the state of the gate. When opened, the gate would allow a signal giving rise to a sensation of pain to be transmitted by projection neurons.

The gate control theory would predict that electric stimulation of the dorsal columns could relieve pain by activating ascending branches of low-threshold myelinated tactile afferents. Indeed, stimulation of the dorsal columns is now a well-established intervention for some forms of chronic pain, and has been shown to suppress activity of nociceptive dorsal horn neurons. The link between segmental mechanisms envisioned in the gate control theory and the clinical efficacy of dorsal column stimulation remains to be proved, however. In fact, there is evidence that the analgesic effect of dorsal column stimulation is via an extrasegmental or even supraspinal loop.[50,51] In sum, although dorsal column stimulation may be an effective treatment in some pain conditions, the underlying mechanism is as yet unclear.

Conclusion

A number of brainstem systems have been shown to modulate the responsiveness of nociceptive processing circuits at spinal and supraspinal levels. The best-studied and probably functionally most significant is the PAG-RVM system, known to be an important substrate for opioid analgesia. Other brainstem systems, notably pontine noradrenergic cell groups and subnucleus reticularis dorsalis in the caudal medullary reticular formation, have been shown also to modulate nociception. These systems are not strictly independent and are connected, often directly but also indirectly, through their reentrant relationships with dorsal horn nociceptive processing **(Fig. 2.4)**. Their function is to integrate the processing of nociceptive information with other physiological and behavioral demands. Thus, whereas the PAG-RVM axis is critically involved in defense, the caudal medullary system mediating feedback inhibition (i.e., DNIC) is more likely concerned with coordinating motor adjustments when multiple stimuli demand a response. Thus, understanding the contribution of these systems to different pain states should add to our ability to control pain, and manipulation of these systems, particularly using pharmacologic tools to access pain-inhibiting outflows more precisely, should prove clinically useful.

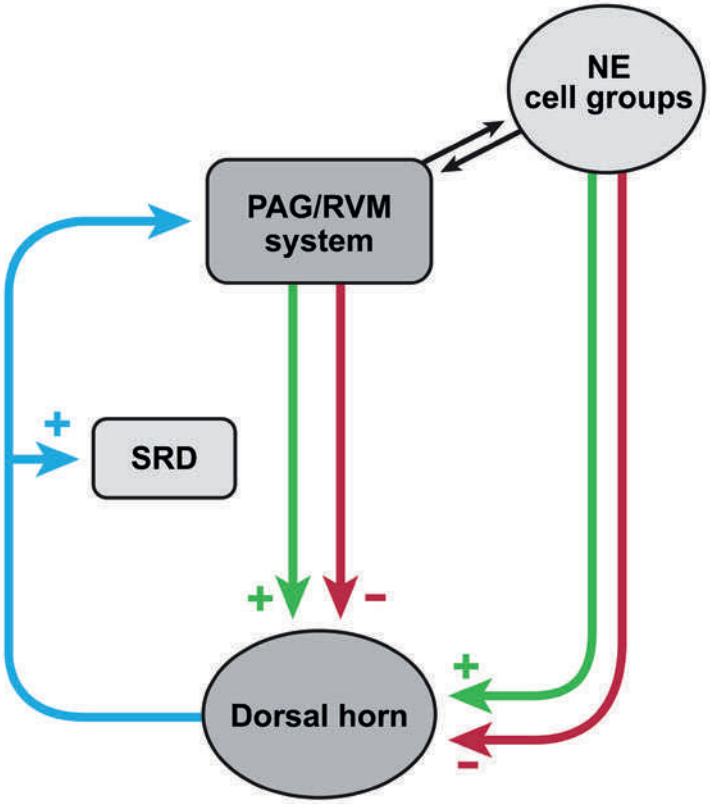

Fig. 2.4 Parallel, interconnected brainstem pain-modulating systems. The periaqueductal gray–rostral ventromedial medulla (PAG-RVM) system has a primary but not an exclusive role in controlling spinal nociceptive processing. It is reciprocally connected with pontine noradrenergic cell groups, and both groups can exert a positive or negative influence over spinal pain mechanisms. Feedback inhibition of wide-dynamic-range neurons, likely mediated through subnucleus reticularis dorsalis (SRD), appears not to be directly dependent on the PAG-RVM system, but all three are linked by their reentrant relationships with the dorsal horn.

Editor's Comments

The discovery of the role of the periaqueductal gray (PAG) and rostral ventromedial medulla (RVM) in pain modulation has been one of the most important findings in the recent history of nociception. This finding demonstrated that variability in pain perception is more than "psychological" and that it has a clear and understandable basis in physiology. The relationship of these areas to the earliest findings of stimulation-produced analgesia (SPA) formed the basis of the attempt to control chronic pain by deep-brain stimulation (DBS) in the PAG and, later, periventricular gray (PVG). Dr. Heinricher makes a good case for why the latter may not have worked so well. She also points out that electrical stimulation of PAG is almost guaranteed to produce a variety of effects, not all of which support antinociception.

In the 1970s and early 1980s, DBS for pain control was, in fact, the first widespread application of this technology, although small-scale application of brain stimulation had been used for several decades prior in the treatment of pain, epilepsy, and behavioral disorders. In retrospect, the application of DBS to chronic pain in that era failed, due in part to the naivety of the concept but largely due to the failure to obtain the evidence that the procedure was unequivocally effective.

As we now know, the PAG is part of a duplex system of nociceptive control, in that it has both inhibitory and excitatory effects. As one of the few currently practicing neurosurgeons with direct experience in this procedure, I can attest to the overwhelming fear that many patients experienced when the PAG was stimulated, in concert with the "emotional" and " autonomic" effects of PAG physiology described in this chapter. In fact, the PVG target was adopted largely to avoid the undesirable effects of PAG stimulation. Unfortunately, and again as Dr. Heinricher points out, the PVG area is a truly "mixed" collection of afferent and efferent pathways, all of which can be recruited by stimulation, and many of which may be countervailing.

This leads to the potential conclusion that "electric stimulation will not be the ideal way to investigate this system or to manipulate it for therapeutic purposes." Although this may be true, as we come to better understand the effects of DBS, there may be an opportunity to reexplore DBS for pain control. Perhaps the use of an area less prone to produce emotional response when stimulated might represent an inroad. My hope is that at some point in the future, we will reexplore the issue in light of the substantial knowledge we continue to accrue relating to the regulation of nociception at the level of the brainstem.

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3 Pathophysiology of Chronic Neuropathic Pain

Marshall Devor

The term *neuropathic pain* covers a broad range of clinical diagnoses that are united by a common etiology (neuropathy, due to any of a variety of agents) and probably a common constellation of pathophysiological mechanisms. Neuropathic pain conditions are frequently refractory to current medical treatment, and in some cases neurosurgical approaches may be considered as a means of providing pain relief. Persistent neuropathic pain is also a frequent *complication* of surgical interventions, including neurosurgical ones. An understanding of the underlying physiology and pathophysiology can guide treatment and reduce the risk of iatrogenic harm.

The International Association for the Study of Pain (IASP) defines neuropathic pain as pain caused by a lesion or disease of the somatosensory nervous system (http://www.iasp-pain.org, education/taxonomy, 2011 update). If the lesion or disease impacts the peripheral nervous system (PNS), the result is peripheral neuropathic pain; if the central nervous system (CNS) is impacted, it is central pain. This chapter deals with the former. For a discussion of central pain, see Boivie (2006).[1] Chronic pain caused by peripheral nerve injury is paradoxical. Damage to a nerve, like damage to a telephone cable, is expected to reduce signal transmission, causing negative symptoms like hypoesthesia and numbness. But it frequently causes positive symptoms as well, notably chronic pain. This chapter will focus primarily on the pathophysiological mechanisms responsible for such positive symptoms. The main take-home message is that nerves are biological structures. They do not behave like copper wires. Trauma, disease, and the indiscriminant cutting or crushing of nerves can handicap patients with serious chronic pain.

Anatomy and Physiology

Signal Generation in the PNS

Primary sensory neurons mostly reside in the dorsal root ganglia (DRGs) and in several cranial nerve ganglia, notably the trigeminal ganglion (TRG). Each has a single peripheral process with one or a cluster of sensory endings (transducers) in innervated tissue and a profusion of central synaptic terminals. Electrical impulses (action potentials, "spikes") are generated in the sensory ending and propagate directly to the spinal cord (or brainstem). They also invade the sensory cell soma en passage, although this invasion can be blocked without acutely affecting sensory signaling from the periphery to the CNS.[2] There are virtually no synapses in sensory ganglia.

Sensation is normally perceived at the *location* of the sensory endings of the activated neurons. This is so whether the neurons are activated by a sensory stimulus, or whether the underlying impulses are generated ectopically elsewhere along the sensory transmission pathway (e.g., as a result of electrical nerve stimulation). The *quality* of sensation normally depends on the specific sensory endings activated by a stimulus (touch, thermal, nociceptive). *Intensity* depends on the number of afferents recruited and their firing rate. Natural stimuli typically activate a variety of sensory ending types at a given location, giving rise to complex sensory experience. Developmental processes in the embryo create a match between sensory endings in the periphery and the corresponding processing networks in the CNS. This sets the framework for adaptive reflex action and for congruence between conscious percepts and applied stimuli. Although set developmentally, the match needs to be maintained throughout life by feedback mechanisms. These remain poorly understood.

In the event of pathology the match between periphery and center can be disrupted. Following amputation, for example, pain is frequently felt in the absent limb (phantom limb pain). The impulses that cause the phantom pain are generated not in sensory endings, which are no longer present, but further proximally in the signaling pathway. Mismatch is usually less dramatic than this. Mild burns, for example, frequently cause nociceptive endings to become "peripherally sensitized." As a result gentle, nonnoxious warming of the skin now activates heat nociceptors, causing pain to be felt (heat

allodynia). Sensory localization remains normal, but there is a mismatch in intensity coding. If thermal response threshold falls below the ambient temperature, afferent firing and burning pain appear to be spontaneous. Sensitized nociceptors also show an exaggerated response to suprathreshold heat and mechanical stimuli, resulting in heat and mechanical "hyperalgesia." Sensitization may even result in de novo responses in previously insensitive ("silent") mechanoreceptors.[3,4]

Peripheral sensitization reflects a transient increase in the responsiveness of transducer molecules and ion channels in the axonal membrane of nociceptive sensory endings, usually due to protein phosphorylation by inflammatory mediator molecules, or exogenous irritants such as capsaicin. The mediators, such as tumor necrosing factor (TNF)-α, IL-1β, and other cytokines, act either directly on target proteins or indirectly via intracellular signaling pathways. The result is direct activation of the nociceptor and/or its sensitization to applied stimuli.[3] The source of the immune mediators can be local resident cells (e.g., glia, mast cells, keratinocytes), circulating precursors (e.g., bradykininogen) or immune cells recruited by cytokine signaling. A very different kind of sensitization, central sensitization, also occurs after injury disease. This plays out in the CNS (below).

Pain amplification by peripheral and central sensitization is a normal adaptive process. It is an integral aspect of the immune system response to injury and is mediated by familiar immune cells and chemical mediators. The resulting pain is typically transient, adaptive, and self-limiting. By amplifying pain, peripheral and central sensitization contribute to wound healing by reducing use of the injured body part. But things can go wrong. In the event of nerve injury and chronic inflammatory disease these processes can result in chronic intractable pain.

Signal Processing in the CNS

Spinal Cord and the Trigeminal Brainstem

Central synaptic endings of the various types of primary afferents converge on neurons in the spinal cord dorsal horn and the trigeminal brainstem. Some of these postsynaptic neurons are driven primarily by nociceptors ("nociceptive-selective neurons"). Others are driven exclusively by low-threshold mechanoreceptive input ("touch-selective neurons"), whereas still others receive convergent input from a mix of afferent types ("wide-dynamic-range" [WDR] or "multireceptive" neurons). These cell types are distributed differentially in the laminae of Rexed. The nociceptive-selective neurons are located superficially mostly in the substantia gelatinosa. Then come the low-threshold-selective neurons and deepest, the convergent neurons. Transmission neurons in all laminae send an ascending axon to the brain. Primary afferents that are sensitive to touch and vibration, in addition to terminating in the intermediate and deep laminae of the dorsal horn, also send an ascending axon in the dorsal column directly to the gracile and cuneate nuclei of the lower medulla. From here information on touch and vibration is relayed directly to the ventrobasal thalamus (via the medial lemniscus), and thence to the primary somatosensory cortex (S1).

Ascending Pathways

The ascending axons of spinal cord projection neurons terminate in various brainstem and thalamic nuclei where information is processed and relayed to the subcortical forebrain and the cerebral cortex. Most of these axons ascend in the contralateral anterolateral column system (spinobulbar tract ["paleo"] and spinothalamic tract ["neo"]). Somatosensory, including nociceptive, information distributes broadly in the brain, contributing to areas involved in motor control, autonomic regulation, affect, cognition, and of course sensory perception. Some of the ascending pathways have fairly specific anatomical projections. Examples are the spinocerebellar tracts, the dorsal column–medial lemniscus system, and projections of the nociceptive-selective neurons in dorsal horn lamina I to the brainstem parabrachial complex and the posterior thalamus. With respect to pain signaling, some investigators place single-minded stress on projections of lamina neurons.[5] Most, however, believe that nociceptive information is conveyed by the anterolateral column system from deep dorsal horn neurons as well as superficial ones.

Central Sensitization

Peripheral sensitization of nociceptive sensory endings largely accounts for heat allodynia and both heat and mechanical hyperalgesia. However, it does not explain "tactile allodynia" (i.e., pain evoked by light touch). Tactile allodynia is an everyday event after minor abrasions or sunburn, and also a common feature of neuropathic pain. The pain response upon skin contact is immediate, much too fast for C-fibers, where a delay of a second or more would be expected between stimulus and response. Aδ-nociceptors might account for the short latency. However, touching tender skin does not evoke the double sensation, first then second pain, expected from dual activation of Aδ- and C-fibers. Moreover, electrophysiological recordings show that mechanical response thresholds of Aδ- and C-nociceptors rarely drop into the nonnoxious range in animal models of tactile allo-

dynia, whether the allodynia is caused by inflammation or neuropathy.[6–10] These and other lines of evidence indicate that tenderness to the touch is signaled by low-threshold Aβ touch afferents, not sensitized nociceptors.[3,11–13] It is "Aβ pain" and is due to CNS "amplification." Note, however, that central sensitization does not simply amplify; it changes sensory modality. Touching allodynic skin does not evoke strong touch, it evokes pain. Correspondingly, it activates the cortical areas normally activated by noxious stimuli.[14,15]

A large number of cellular and molecular mechanisms have been put forward to account for central sensitization.[16,17] Some examples are activation of previously blocked *N*-methyl-D-aspartic acid (NMDA)-type glutamate receptors, imbalance of chloride ion equilibrium, glial activation, and altered descending control. With the exception of one popular hypothesis (the loss of inhibitory interneurons), most proposed processes are transient and reversible.

The radical idea that pain can be signaled by nonnociceptive, rapidly conducting, thickly myelinated, Aβ low-threshold mechanoreceptive touch afferents constitutes a revolution in our understanding of both inflammatory and neuropathic pain. Indeed, since tactile allodynia is arguably the most common cause of suffering and disability in neuropathic pain patients, pain signaled by Aβ touch afferents would appear to be as important as pain signaled by nociceptors! Like wakefulness versus sleep, central sensitization reflects transient switching of the CNS to an alternative mode of pain processing. It is induced and dynamically maintained over time by afferent drive from the periphery, usually carried by nociceptors. That is, tissue injury or inflammation drives central sensitization. Blocking the peripheral drive eliminates the allodynia, usually within minutes or hours.[18–20] For example, the tactile allodynia evoked by a mild burn is maintained by ongoing discharge from heat nociceptors in the skin. When this maintaining drive is reduced by cooling the skin, central sensitization and tactile allodynia rapidly disappear.[21] In the event of neuropathy, altered ("phenotypically switched") low-threshold Aβ afferents may also become capable of inducing and maintaining central sensitization.[20,22–24]

The Pain Matrix

Noninvasive brain imaging reveals a consistent set of cortical areas that become activated during noxious stimulation.[25] These constitute the "pain matrix." The pain matrix includes, among other cortical areas, the anterior cingulate gyrus, the prefrontal cortex, the insula, and the postcentral gyrus (S1). In some of these areas the degree of activation correlates with the perceived intensity, or alternatively the perceived aversiveness, of the stimulus.[26] It is generally presumed that pain matrix activations are the neural correlate of conscious pain perception. However, although information about noxious events obviously reaches these cortical areas and is presumably used in the processing functions executed there, a role in pain perception should not be taken for granted. These same cortical areas also respond to nonpainful alerting stimuli.[27] Moreover, lesions in pain matrix areas, localized or extensive, do not cause analgesia. Indeed, such lesions frequently cause pain (e.g., poststroke pain). Likewise, direct stimulation of the cortex does not evoke a pain percept (except at a small proportion of posterior insular sites[28]) and seizures are rarely preceded by a painful aura.[29] There is no known area that justifies the moniker "primary pain cortex (P1)."[30] Perhaps the "raw feel" of pain is represented subcortically.[31]

Endogenous ("Top-Down") Pain Control

The bottom-up transmission of pain signals is subject to constant modulatory control from the brain via pathways that suppress or facilitate pain experience. The best-known pathways are the descending bulbospinal modulatory systems that originate in the rostro-ventromedial medulla (RVM), the locus coeruleus, the brainstem raphe nuclei, and the dorsal reticular nucleus (DRt). These nuclei establish a dynamic balance between pain inhibition and facilitation at the level of the dorsal horn[32] (see Chapter 2). Activity in the descending bulbospinal nuclei, in turn, is affected both by nociceptive signals ascending from the spinal cord (in a pain-inhibits-pain feedback loop) and by control from above, notably by the mesopontine periaqueductal gray (PAG) and mesopontine tegmental anesthesia (MPTA) area nuclei and various forebrain regions.[33,34] In addition to these descending systems that gate spinal cord pain processing, it is presumed that there also exist modulatory networks that operate entirely within the forebrain. Neuromodulatory approaches to pain control, including deep-brain stimulation (DBS), cortical surface stimulation (with implanted electrodes and repetitive transcranial magnetic stimulation [rTMS]), and perhaps dorsal column/spinal cord stimulation, are aimed at exploiting the endogenous modulatory processes.

Interindividual differences in pain perception and moment-to-moment variations due to distraction, stress, placebo, hypervigilance, counterirritation, and other sensory, cognitive, and emotional states, are mediated by the endogenous brainstem and forebrain modulatory circuitry. In this context it is important to stress that these "psychological" modes of pain control cannot be dismissed as "just in the mind." Their effect is contingent on the specific neurological substrates just reviewed. Moreover, major classes of drugs, including opiates and

antidepressants, used in the treatment of chronic pain act by recruiting one or another of the endogenous modulatory pathways. There is even evidence that chronic pain conditions, both inflammatory and neuropathic, can be exacerbated, and perhaps even caused, by abnormalities in endogenous pain inhibition or facilitation.[35,36] Correspondingly, in animal models, neuropathic pain symptoms can be eliminated by surgically reducing descending facilitation.[37]

Pathophysiology

Symptoms, Signs, and Their Variability

Peripheral neuropathic pain can result from trauma, infection, inflammation, metabolic abnormalities, malnutrition, vascular abnormalities, neurotoxins (including chemotherapeutics), radiation, autoimmune attack, iatrogenic causes, or inherited mutations affecting the PNS. All induce the same fundamental pathological changes in axons and associated glial cells in peripheral nerves (neuropathy), sensory or autonomic ganglia (ganglionopathy), or dorsal roots (radiculopathy). These changes often lead to positive sensory abnormalities: spontaneous dysesthesias and pain, allodynia, hyperalgesia, pain on weight bearing, and sensory peculiarities such as electric shock–like paroxysms and hyperpathia. As described below, research advances can now account for these symptoms and signs, at least for the most part, with known pathophysiological mechanisms.[38] The new knowledge has not yet been translated into more effective treatment modalities. However, numerous promising targets and strategies have been identified that will inevitably be exploited in the development of better therapeutic options in the future.

One characteristic of neuropathic pain that still lacks a comprehensive explanation, however, is its notorious variability from patient to patient, even when the precipitating injury or disease is essentially the same. Individual differences can be quite extreme. Following limb amputation, for example, about one third of individuals report frequent and often severe pain in the stump and/or phantom limb, and another one third report little or no pain.[39] Likewise, whereas everyday cuts, bruises, and needlesticks damage small cutaneous nerve branches with no long-term consequences, occasionally the minor acute pain cascades into a catastrophic condition such as chronic regional pain syndrome (CRPS).

Pain variability has traditionally been attributed to environmental factors such as ongoing distractions, cultural norms, and personality. Evidence accumulated in recent years, however, points to genetic predisposition as being responsible for at least half of the overall variability.[40] A search for genetic polymorphisms that affect pain susceptibility is currently under way. Good progress has already been made at defining rare mutations that cause painful peripheral neuropathies,[41,42] and in some cases gene identity has proved highly informative as to mechanism. Remarkable examples are familial erythromelalgia, paroxysmal extreme pain disorder, and a congenital insensitivity to pain, conditions that appear to be due to gain- and loss-of-function mutations in the voltage sensitive Na^+ channel Nav 1.7.[42] Other examples are congenital insensitivity to pain with anhydrosis (CIPA) due to mutations in the nerve growth factor (NGF) pathway, and type 2 Charcot-Marie-Tooth neuropathy (CMT-2) due to myelin damage. A start has also been made at defining polymorphisms that predispose one to more common neurological diseases that may be painful[43] (http://www.painresearchforum.org/resources/pain-gene-resource). This includes both disease susceptibility genes and genes whose alleles determine the amount of pain different individuals will suffer given the same disease or injury ("pain susceptibility genes").[44]

Neuropathic Pain Mechanisms

Nerve Injury and Disease Alter the Phenotype of Sensory Neurons

Depending on its nature and severity, neuronal injury and disease cause the distal part of the axon, including the sensory ending, to retract from the tissue it innervates ("dying back") or to undergo anterograde (Wallerian) degeneration. Cutting axons, or the whole nerve, always leads to axonal degeneration distal to the lesion. But the residual proximal axon, the DRG cell soma, and sensory connections with the CNS usually survive for a long time.[45] The properties of these proximal segments change, however. In particular, they can become abnormal pain generators. The primary cause of the change is disruption of the signaling processes that regulate neuronal excitability in the normal nervous system. Understanding neuropathic pain requires an understanding of these processes.

Neural signaling takes two forms: rapid electrical impulse traffic (measured in meters/second) and the relatively slow axoplasmic transport of molecules (measured in centimeters/day). Electrical impulses convey moment-to-moment sensory information to the CNS by driving synaptic neurotransmitter release. Axoplasmic transport carries signals independent of impulse traffic and plays a mostly trophic role. The two interact, however, when sensory signaling is considered over longer periods of time. For example, spike activity integrated over minutes, hours, or days affects the incorporation of transported molecules

into the axon membrane (at peripheral sensory endings and central synaptic terminals). It also affects the release of trophic signaling molecules from axon terminals into peripheral tissues and the CNS. Nerve injury and disease have consequences for impulse traffic and trophic regulation. The most important consequence is the emergence of electrical hyperexcitability and abnormal firing in injured sensory axons. This is the first step in the generation of neuropathic paresthesias, dysesthesias, and pain. Nerve injury also has consequences for CNS processing of afferent nerve signals by inducing central sensitization and altering endogenous pain modulation.

The cascade of events appears to be as follows.[38,46] Axonal transection blocks the normal flow of neurotrophic signaling molecules between the periphery and the sensory cell body. This triggers a change in the quantity of many of the proteins synthesized ("expressed") by the cell body in the DRG and exported to both peripheral and central axon endings. Some proteins become expressed in excess ("up-regulation of gene expression") while others are down-regulated. Several thousand genes are regulated in this way following nerve injury, a significant fraction of all of the genes expressed in sensory neurons.[47–49] Among other things, this alters the excitability of primary afferents and PNS-to-CNS signaling. A major challenge is to determine which of the numerous changes in gene expression are responsible for neural hyperexcitability and pain, and which are responsible for other consequences of nerve injury (e.g., regeneration).

In addition to changes in gene expression, the delivery ("trafficking") of transported molecules is disrupted. Probably the most significant type of disruption is the accumulation of ion channel and receptor proteins at sites of injury. This includes neuromas, zones of demyelination, retraction bulbs (e.g., in axons that are dying back), and outgrowing sprouts. Channels may accumulate at such hot spots even if there has been overall downregulation of channel synthesis. The best-documented example is the accumulation of Na^+ channels in neuroma endings. Although the synthesis of most types of Na^+ channels is downregulated, the exception being Nav 1.3, there is nonetheless significant channel accumulation in neuromas (**Fig. 3.1**).[50,51] In the case of demyelination, Na^+ channels accumulate locally in patches of axonal membrane that have been denuded by the stripping off of myelin. The ectopic accumulation of Na^+ channels in neuroma endings and patches of demyelination gives rise to local electrical hyperexcitability, ectopic impulse discharge, and positive sensory symptoms.[38]

Finally, neuropathy may induce changes in the kinetics or current-carrying ability of ion channels and receptors, enhancing electrical excitability. This can result from alternative splicing of channel subunits, altered stoichiometry in the assembled protein complex, and postassembly modifications. Postassembly changes were noted above in the context of peripheral sensitization. Specifically, following nerve injury, proinflammatory mediators, trophic factors, and even coneurotransmitters can phosphorylate channels and receptors, typically by activating protein kinases (PKA, PKC).[52–54]

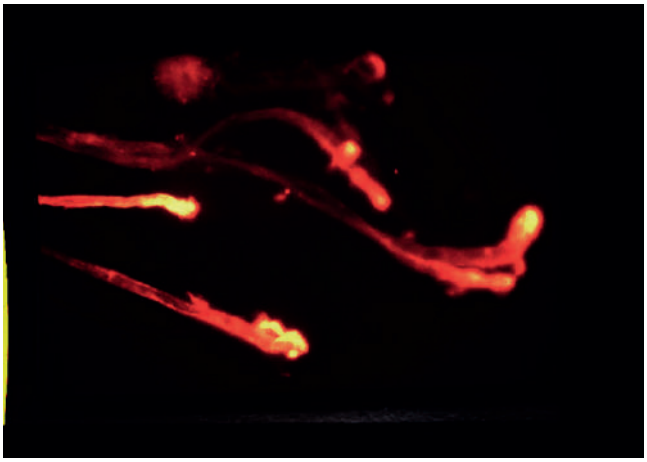

Fig. 3.1 Immunolabeling shows the accumulation of Na^+ channels at the chronic cut end of injured axons. (For details see Devor M, Keller CH, Deerinck TJ, Levinson SR, Ellisman MH. Na+ channel accumulation on axolemma of afferent endings in nerve end neuromas in Apteronotus. Neurosci Lett 1989;102(2–3):149–154.)

Ectopic Discharge (Ectopia): Spontaneous and Stimulus-Evoked

Neuromas, sprouts, and patches of dysmyelination that form following nerve injury are structural entities. They are not necessarily pain sources. They contribute to pain only to the extent that they become abnormal sources of impulse generation (electrogenesis). Ectopia was first reported in classical electrophysiological studies in which recordings were made from sensory axons that terminate in an experimental nerve-end neuroma (**Fig. 3.2**). The electrogenic source was identified as the neuroma on the grounds that it was eliminated by acute neuroma resection and by local anesthetic block of the nerve end. Likewise it was enhanced by mechanically probing the neuroma, the presumed basis of the Tinel sign.[55–57] As expected, activity generated ectopically drives spinal and higher order neurons in the CNS in the normal way.[19,25,58,59]

In subsequent research ectopic electrogenesis, both spontaneous and stimulus-evoked, was shown to occur also at midnerve pacemaker locations, as is seen in entrapment neuropathies and malignant disease, including neuromas-in-continuity, disseminated microneuromas, and patches of demyelination.[60–62]

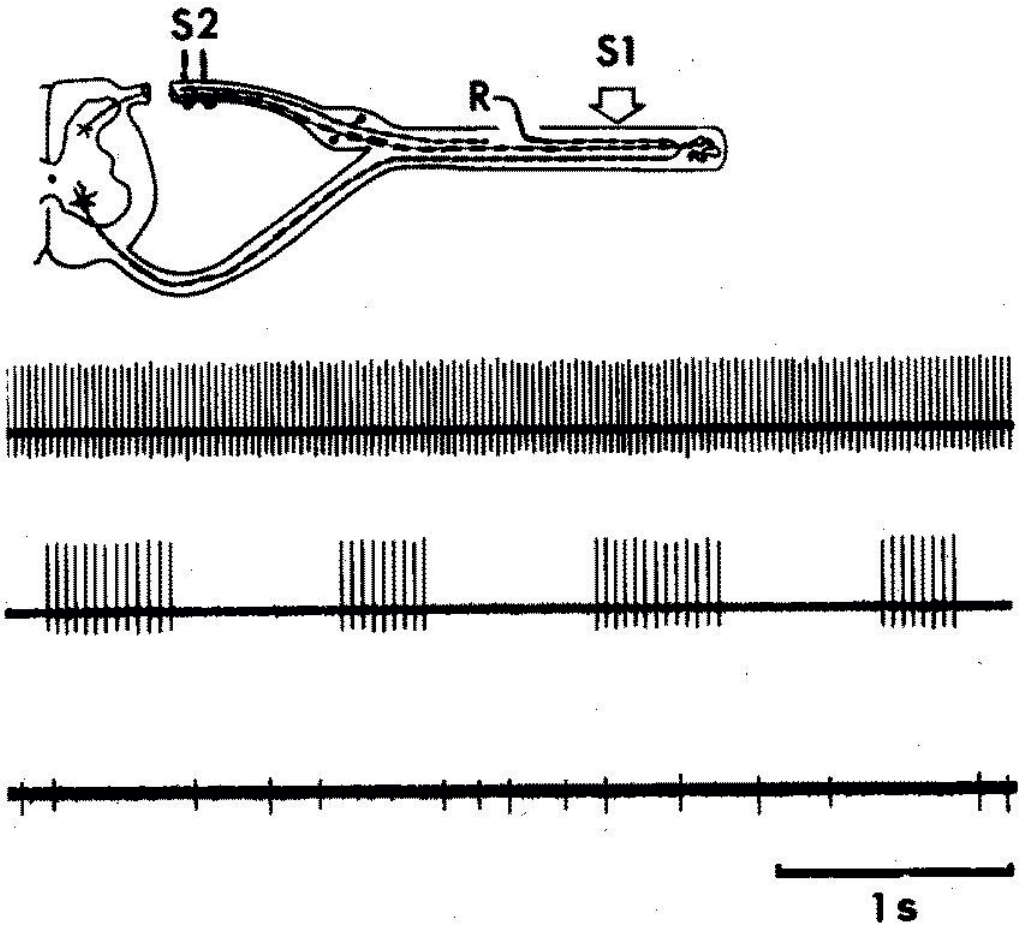

Fig 3.2 Recordings (R) from afferent axons associated with an injured nerve frequently show abnormal ongoing tonic, bursting, or slow irregular discharge that originates ectopically at the nerve injury site and associated DRGs. In the example illustrated, the ectopia originates in an experimental nerve-end neuroma.

Ectopia also occurs in regenerating sprouts[63,64]; at sites of nerve inflammation (neuritis)[65,66]; in experimental diabetic polyneuropathy[67,68]; after viral infections[69,70]; after vincristine, taxol, and mercury intoxication[71,72]; and in hereditary demyelinating polyneuropathies.[73] Note that the specific agent that causes the neuropathy may have an effect. For example, ectopia may predominate in A- or C-fiber afferents. Likewise, when the neuropathy is disseminated such as in diabetic and toxic polyneuropathy, ectopic pacemaker activity has disseminated sources rather than a focal source. The principles, however, are common to all.[38]

In addition to mechanical force, ectopic pacemaker sites also develop abnormal sensitivity to depolarizing chemical, thermal, and metabolic factors. These include cytokines and other inflammatory mediators (e.g., TNFα, IL-1β, NGF), prostaglandins, temperature changes, ischemia, hypoxia, and hypoglycemia.[38,74] Notable among these are responses to circulating catecholamines and noradrenalin released from sympathetic efferent endings. The resulting sympathetic-sensory coupling, which is manifest in neuromas and DRGs, is an important substrate of sympathetically maintained chronic pain states (SMP).[75,76] All of these factors contribute to spontaneous neuropathic pain and exacerbate stimulus-evoked pain. Ectopia may also arise in residual neighboring "uninjured" afferent neurons even though these neurons have not been damaged directly.[77] The electrogenic source(s) in this case is still uncertain, but likely possibilities are sensory endings and reactive collateral sprouts that become exposed to inflammatory mediators, catecholamines, or metabolic disruption in the skin or other innervated tissue.

DRGs Are Also a Source of Spontaneous and Evoked Ectopia

Cutting the spinal nerve just peripheral to the DRG evokes ectopia, recorded in the dorsal root near its entry into the spinal cord, although no activity is

observed when the same axons are cut just centrally to the DRG.[78] This observation led to the discovery that the DRG soma is also a key ectopic generator.[79–81] In fact, in head-to-head comparisons in neuropathy models, about 75% of the overall spontaneous discharge generated in injured nerves proved to originate in the DRG compared with only 25% in the neuroma.[82–84]

In addition to spontaneous firing, activity in DRG neurons is also initiated or exacerbated by the same chemicals and forces that drive ectopia at sites of axonal injury. Despite being protected from direct stimulation by the rigid walls of the intervertebral foramen, and despite the fact that DRG neurons receive (almost) no synaptic inputs, there are many factors capable of exciting them. For example, DRG neurons can be activated by mechanical stimulation during movement or straight-leg raising, which applies traction to the sciatic nerve,[85] by agents in the systemic circulation, by temperature, and by sympathetic efferent activity.[38,76] The de novo ability of the neurons to respond to such slow-onset (ramp) stimuli has been traced to the development of subthreshold oscillations in the cell membrane (**Fig. 3.3**).[86,87]

Ectopia in both the DRG and nerve injury sites is also subject to a variety of electrophysiological processes that can amplify it. For example, momentary

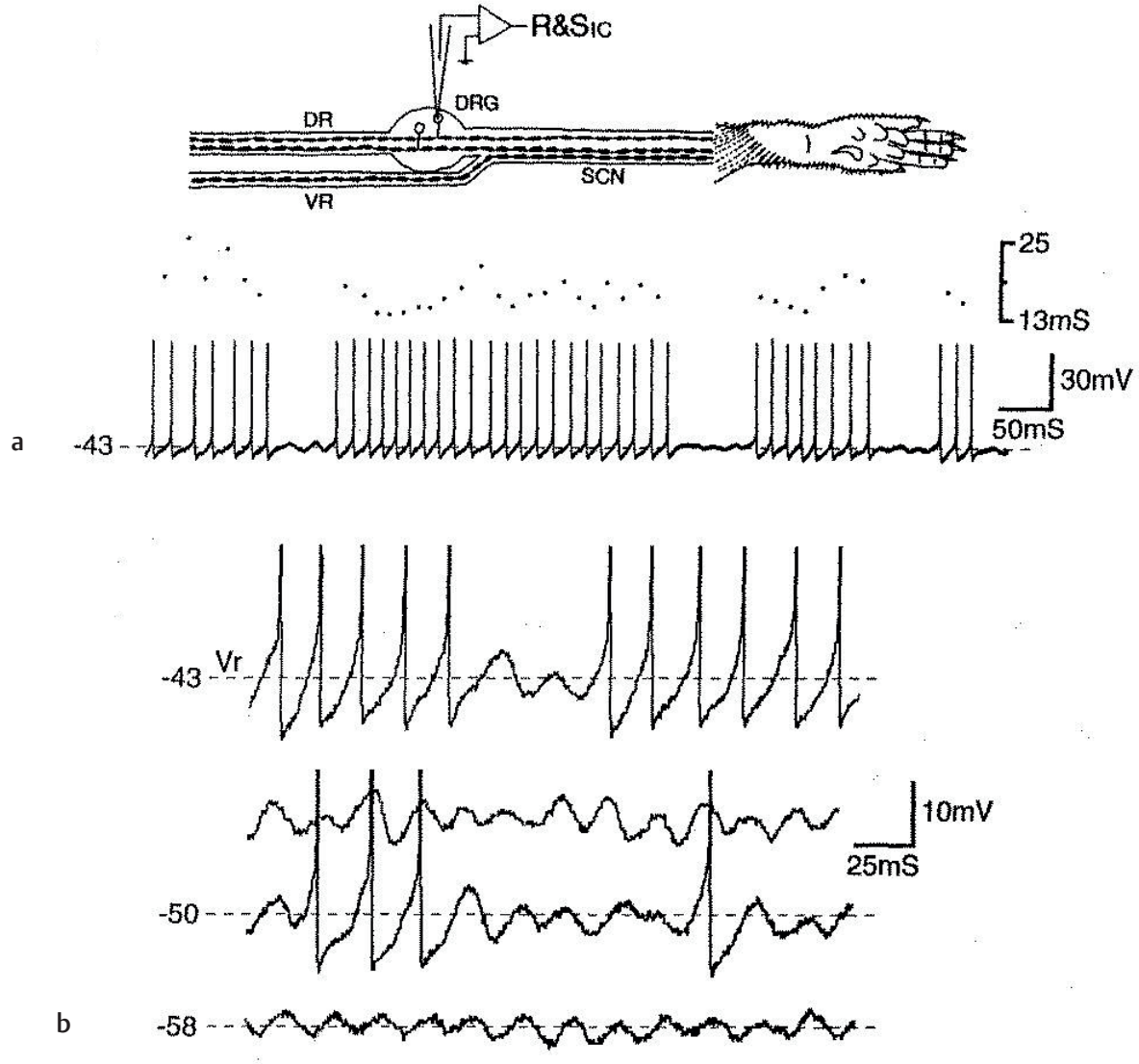

Fig 3.3 In DRG neurons, and perhaps also at other ectopic pacemaker sites, subthreshold oscillations trigger repetitive burst firing. (**a**) The recording setup is shown above. Interspike intervals during each of the four bursts shown are fairly stable as demonstrated in the dot display (above the spikes). This rhythmic discharge is interrupted by pauses of variable duration. (**b**) This DRG neuron had subthreshold oscillations at –58 mV, but did not fire action potentials. When the membrane potential was depolarized to –50 mV and –43 mV, simulating natural excitatory stimulation, the oscillation sinusoids increased in amplitude and the larger ones began to trigger single spikes and spike bursts. (Data from Amir et al.[86,87])

mechanical probing of ectopic pacemaker sites frequently evokes "afterdischarge," firing that long outlasts the stimulus itself. On repeated stimulation this may build up incrementally ("wind-up"). Injured sensory neurons also interact abnormally through ephaptic (electrical) coupling and, more importantly, through a nonsynaptic neurotransmitter-mediated (paracrine) mechanism, axonal and DRG "crossed afterdischarge."[80,88,89] These processes likely underlie neuropathic pain paroxysms and the hyperpathic intensification and spread of sensation beyond the stimulation site.[90]

A striking example is trigeminal neuralgia (TN). According to the "ignition hypothesis of TN,"[91] pain paroxysms begin with discharge in a small cluster of trigeminal nerve afferents that are activated by cutaneous trigger point stimulation, or spontaneously at the ectopic pacemaker zone established by neurovascular compression (NVC) of the trigeminal root. Crossed afterdischarge in the TRG or at the NVC site then "ignites" ectopic activity in previously passive neighboring afferents. This activity ignites additional passive neighbors, and these ignite still more. The resulting positive-feedback "chain-reaction" builds up rapidly to an intense, explosive peak. Since neurons of all types become active simultaneously, an event that otherwise occurs only with electrical shocks, the felt sensation is like an electric shock. Surgical microvascular decompression (MVD) of the trigeminal root immediately reduces the ectopic drive caused by the repeated mechanical impact of the pulsating blood vessel at the NVC site. Over the longer term it also fosters remyelination, permanently removing ectopic pacemaker capability along the trigeminal root (see Chapter 43).

Association of Ectopic Hyperexcitability with Neuropathic Pain in Humans

The method of percutaneous microneurography has extended observations on ectopia to awake humans, including neuropathic pain patients. Microneurography remains a research, rather than a diagnostic, tool because of its technical difficulty and its intrinsic risk. Practitioners are justifiably reluctant to insert sharp electrodes into already problematic nerves. Nonetheless, enough studies have appeared to make it clear that ectopic hyperexcitability occurs in patients as in nerve-injured animals, and that it is a fundamental contributor to many clinical neuropathic pain conditions.

Not long after the first observations in animals, Nystrom and Hagbarth (1981)[56] carried out a pioneering study in which they documented ongoing firing in the peroneal nerve in a lower extremity amputee who had ongoing phantom foot pain. Percussion of the neuroma evoked stabbing pain (the Tinel sign) and an intense burst of spike activity. The evoked bursts, and the evoked pain, were eliminated by local anesthetic block of the neuroma. But interestingly, much of the ongoing discharge persisted, hinting at an origin in the DRG. Additional electrophysiological evidence of sensory ganglia as a pain source in humans includes the observation of trigger point–induced spike bursting in TRG recordings in patients with TN[92] and of antidromic discharge in the sural nerve upon painful straight-leg raising in a patient with radiculopathic low back pain (sciatica) (Lasegue's sign).[93]

The early studies recorded multiunit spike activity mostly in A-fibers. A recent innovation, the "marking method," permits resolution of ongoing activity also in individual C-fibers. Results have provided evidence that the ongoing burning pain that is so common in peripheral neuropathies is associated with intense spontaneous discharge in C-fiber nociceptors, mostly of the mechano-insensitive type.[94] Burst firing, afterdischarge, and other interesting peculiarities of ectopia first described in animal models have also been seen in the patients, further strengthening the clinical relevance of the experimental models. At present there is direct evidence of a relation between C-fiber ectopia and pain in a variety of neuropathic conditions, including small-fiber neuropathies, erythromelalgia, diabetic polyneuropathy, and even fibromyalgia.[95–98]

Other Evidence Linking Ectopia to Neuropathic Pain

The ectopic pacemaker hypothesis is supported by various observations in addition to electrophysiology. For example, pain is evoked in humans by applying to neuromas substances known from animal preparations to excite ectopic pacemaker sites, including K^+ channel blockers and adrenergic agonists.[99] Correspondingly, if a trigger point can be identified (e.g., by deep palpation), associated pain is uniformly stopped by local infiltration or more proximal nerve block. Even the most severe pains, such as CRPS, are reliably stopped by peripheral nerve or brachial plexus block. This speaks to the peripheral origin of the pain-causing discharge in most, and perhaps all, chronic pain conditions caused by nerve injury or disease affecting nerves. Blocks, of course, cannot be counted on to provide pain relief beyond the duration of action of the agent injected, although they apparently sometimes do.

There are anecdotal reports that diagnostic nerve or plexus block does not always stop phantom limb pain.[100] This has given rise to the widely held belief that phantom pain originates in the dysfunctional cortical plasticity.[101] However, even if these nerve blocks had been shown to be technically complete, a peripheral driver cannot be ruled out until ectopic impulse generation in the associated DRGs has been considered.

In addition to the electrophysiological observations noted above, specific evidence that ectopia originating in DRG neurons may contribute to neuropathic pain is available from model systems and pain patients. In animal models increasing or decreasing spontaneous ectopia by delivery of chemical agents directly to the ganglion increases or decreases DRG ectopia and pain behavior accordingly.[102–108] Because tensile forces are applied to the DRG during movement and leg raising, mechanosensitivity of DRGs plays a particularly important role in disorders of the vertebral column. Kuslich et al[109] exposed the spinal nerves and DRGs in patients with radiculopathy using a local anesthetic technique that permitted them to talk to the patient during the procedure. Mechanical stimulation on the spinal nerve and DRG capsule consistently provoked the patients' characteristic shooting sciatica pain, whereas probing the local fascia, annulus fibrosus, periosteum, and similar sites produced only local sensations in the back.

Therapeutic Implications of Ectopic Hyperexcitability in Peripheral Neuropathic Pain

From the evidence just reviewed it is clear that in many peripheral neuropathies, and perhaps all, the primary driver of neuropathic pain is abnormal impulse discharge originating in the PNS. But this is not the only role of ectopia. In addition it induces and maintains central sensitization, and affects endogenous modulatory networks. These central effects, in turn, amplify the sensory consequences of PNS ectopia and also amplify input from residual intact afferents, giving rise to tactile allodynia and exacerbating hyperalgesia. Thus, whereas CNS targets associated with central sensitization and endogenous pain control are rational targets for arresting pain signals that have already been generated, the primary therapeutic targets for suppressing the generation of neuropathic pain are in the PNS. Suppressing peripheral ectopia has the dual effects of stopping the primary pain-provoking drive and of reversing central sensitization and hence tactile allodynia. It kills two birds with one stone. Peripheral drivers also tend to be more accessible and less subject to unanticipated side effects and pain recurrence due to neuroplasticity. Nonetheless, given our limited ability to realize suppression of PNS generators at present, CNS targets play an important therapeutic role.

Nerve Block, Focal Suppression of Ectopia, and Ablative Procedures

Trigger point, nerve and regional blocks using local anesthetics and other membrane stabilizers reliably stop local ectopia and associated pain.[110,111] But the effect is short lasting. The longest-acting membrane stabilizers currently available, depot steroids, act for a few weeks at best, have limited efficacy, and have systemic side effects. Slow infusion of membrane stabilizers at pacemaker locations (neuromas, DRGs) using implantable pumps is a solution that could be implemented today. This approach has not really taken hold, however, partly because of technical challenges related to today's pumps (e.g., the anchoring of catheters and the need to constantly refill drug reservoirs). Emerging biopump technologies based on engineered cells or tissues, and gene therapy based on viral vectors, are also potential solutions for the future. Topical application of membrane-stabilizing drugs such as lidocaine has a role in cases where the problematic electrogenesis is localized and very superficial.

On the face of it, ablative approaches seem a natural alternative. After all, traumatic and surgical transection of nerves, especially small nerves, does not usually cause chronic pain. Unfortunately, however, excision of painful neuromas, transection of nerves proximal to ectopic pacemaker sites, and reamputation of limbs usually fail to eliminate pain for long and often exacerbates it (see Chapter 53). The presumed reason is that the pathophysiological processes that caused peripheral ectopia and pain in the first place simply recur, this time more proximally. A particular patient with a nerve injury that has already proved to cause neuropathic pain is a priori susceptible, and at high risk of pain recurrence following resection.[112,113] The reason may be genetic as noted above. Thus, while surgical ablation may be relatively benign under some circumstances, it is not a practical approach for treating neuropathic pain patients. An exception is when pain is not spontaneous, but evoked by mechanical forces such as weight bearing. Mobilization of mechanosensitive neuromas to locations where they are less likely to be compressed can provide pain relief.[112] In the future genotyping, or use of nongenetic biomarkers, might allow prediction of whether or not a particular individual is susceptible and likely to develop pain after nerve injury.[44] Interestingly, some nerves only rarely evoke pain after transection even in susceptible individuals. These include dental pulps and the intrinsic innervation of long bones. For still unknown reasons, root canal treatment and total hip replacement are rarely followed by neuropathic pain, whereas crushing or cutting other nerves (e.g., intercostals) frequently is.

Percutaneous partial ablation of DRGs is an alternative to neurectomy for treating regional neuropathic pain conditions of the limbs, spine, and head. Directed at the TRG in the treatment of TN, this is a by-and-large successful interventional approach, often used for older or frail patients where MVD is not an option (see Chapters 46–49). Ablation is usually accomplished using radiofrequency (RF) thermocoagulation or, particularly for TN, using glycerol

injection, balloon inflation, or gamma knife. The aim is to reduce abnormal afferent input whether it originates in the ganglion itself or in the periphery. A significant risk of these procedures, however, is destruction of too large a fraction of the afferent input to a particular segment. This may lead to dense numbness and sometimes to dysesthesias and "anesthesia dolorosa." This is a severe and often intractable neuropathic pain condition that is generated within the CNS (central pain) due to deafferentation. With some exceptions, open surgical rhizotomy and ganglionectomy have largely been abandoned for this reason. Pulsed RF treatment (pRF), in which brief heat pulses are delivered to nerves or ganglia, mitigates the danger by minimizing the tissue heating, but probably at the cost of reduced efficacy.

In the context of anesthesia dolorosa, the frequently confused terms *denervation* and *deafferentation* should be distinguished. Nerve injury denervates peripheral tissue. But when this occurs in adults, most DRG cell somata survive for a long time, and impulses generated in neuromas and DRGs continue to bombard the CNS and to evoke sensory experience (e.g., Tinel sign). Nerve injury does not cause deafferentation. Rather, deafferentation results from plexus avulsion, dorsal rhizotomy, or ganglionectomy. These cause rapid degeneration of the central terminals of sensory neurons so that electrical activity in the corresponding nerves and DRGs can no longer activate the dorsal horn. The CNS is deafferented. Like central pain in general, the mechanism(s) of deafferentation pain is almost entirely unknown. Commonly offered explanations are "denervation supersensitivity" and release from inhibition. Since the pain generator is in the CNS, therapeutic approaches need to be directed at the CNS with all that this implies (e.g., the dorsal root entry zone (DREZ) procedure; see Chapter 56).

Systemic Drugs

Systemic administration of drugs with the aim of reducing ectopic pacemaker activity generated focally (e.g., in TN) or in a disseminated manner (e.g., in polyneuropathy) can be effective. This is best exemplified by dosing with membrane-stabilizing drugs. These agents are selective; they suppress ectopia and neuropathic pain at serum concentrations many orders of magnitude lower than is required to block axonal conduction.[38] For example, whereas lidocaine at blood levels of ~ 10 µM (3 mg/kg IV) reliably stop ectopia and pain,[114,115] nerve block requires about 2% lidocaine (~ 100 mM), a concentration 10,000 times higher. Systemic administration of nerve-blocking concentrations would be lethal.

Local anesthetics are not available in per os form. But most of the orally available drugs currently used in the medical treatment of neuropathic pain are, in fact, membrane stabilizers and selectively suppress ectopia. This is despite the fact that their generic names and commercial promoters typically highlight some other aspect of the drug's pharmacology.[38,116] The antidepressant analgesics are a prime example. Although tricyclics (e.g., amitriptyline) and SNRIs (e.g., duloxetine) are widely presumed to act by suppressing catecholamine reuptake at inhibitory synapses in the CNS, they are also efficient membrane stabilizers with a clear local anesthetic action in the PNS.[117–119] Likewise for anticonvulsants. Carbamazepine and gabapentin, which have an analgesic action in neuropathic pain, are membrane stabilizers and effectively suppress ectopia in the PNS.[120,121] Anticonvulsants that have no analgesic effect, such as barbiturates, do not suppress ectopia. To this list can be added the analgesic antiarrhythmic mexiletine, the NMDA-R antagonist ketamine,[122] and even derivatives of the nonsteroidal anti-inflammatory drug (NSAID) diclofenac.[123] Some of these drugs appear to be more effective for lancinating pain and others for constant burning pain. This may be due to relative selectivity for A- versus C-fibers, for mechanical versus heat sensors, or for subtly different electrogenic processes.[124] Unfortunately, and not by chance, these drugs tend to have a common set of dose-limiting adverse side effects, including somnolence and sedation. This is likely due to suppression of neuronal activity in the CNS. Developing peripheralized versions of these drugs, which do not cross the blood-brain barrier, may be a way forward.

Summary and Perspective

Chronic neuropathic pain constitutes a significant burden for the sufferer, his or her family, caregivers, employers, and society at large. Whereas a generation ago very little was known about its underlying causes, this is no longer the case. A biological framework is now in place for understanding the problem at the systems, cellular, and molecular levels. The key concept is that axon bundles are not telephone cables. In health, regulatory mechanisms ensure that electrical impulses are generated only at appropriate locations and in response to appropriate stimuli. Healthy afferents are largely *incapable* of generating sustained impulse discharge at midnerve or within sensory ganglia, even in the presence of strong or sustained depolarizing stimuli. Rather, beyond the sensory ending, axons are designed exclusively to conduct impulses and to synaptically drive CNS networks. But in the event of injury or disease in the pain signaling system, afferents undergo a qualitative change in behavior. They acquire de novo ectopic pacemaker capability. This results in abnormal

impulse discharge and hyperexcitability. The ectopic activity, and the central changes that it induces and maintains, form the foundations for neuropathic pain.

There remains a debate in the literature concerning diversity. Some authors argue that each neuropathic pain diagnosis has its own pain mechanism on the grounds that they are triggered by different precipitating events and present with different clinical pictures and natural histories. I have attempted to make the case that (peripheral) neuropathic pain is basically a single diagnostic category. It is largely a disease of faulty regulation of afferent excitability caused by a limited number of fundamental pathophysiological processes. Clinical diversity reflects differences in the manifestation of these processes (e.g., focal vs. systemic and cutaneous vs. deep). The situation is not unlike infectious disease, where a single pathogen can produce different symptoms depending on the tissue infected, and different pathogens cause a diversity of clinical presentations via a limited set of pathogenic mechanisms. It is for this reason that diverse neuropathic pain diagnoses can be captured in diagnostic questionnaires with only a handful of questions[125] and why most effective medicines have a common therapeutic characteristic, membrane stabilization.

Increasing realization of the risk of iatrogenic harm has reduced the use of ablative techniques in the neurosurgical treatment of pain in recent decades. Unfortunately, only a limited range of non-ablative options are currently available. Remaining options include mobilizing neuromas; partial TRG lesions and microvascular decompression for TN; release of nerve entrapments; implantable pumps; and neuromodulation with nerve, DRG, spinal cord, and brain stimulation. However, a wide range of neurosurgical strategies lie open for future development based on prolonged suppression of localized ectopic pacemakers. Ideas include improved methods for focal delivery of membrane-stabilizing drugs, biopumps, and optogenetic approaches using hyperpolarizing opsins. Finally, improved methods of identifying individuals at high risk of developing intense ectopia, perhaps using genetic markers, may permit re-introduction of ablative approaches in patients with a low risk of developing chronic pain.

In the medical community there is a widely held belief that unrelieved pain can "burn" itself into the CNS just as over eons a torrential river can gouge a canyon in solid rock. This is called "pain centralization" or "transition to chronicity." The presumption is that persistent pain per se induces biological changes in the brain that render treatment by conventional modalities ineffective.[126] Although sustained noxious input from the periphery can maintain central sensitization, and has consequences visible in the highest levels of the CNS,[127] the pessimistic belief that this can lead to irrevocable changes should be regarded with skepticism. In clinical practice, whenever an obvious peripheral source of pain is present and can be blocked or removed, pain vanishes without a trace no matter how intense it was or how long it was present. Examples include labor pain, pain from passage of a kidney stone, and the pain of an arthritic hip. The way in which pain per se can cause permanent harm is by inducing a downward spiral of psychosocial deterioration and financial distress in the chronic pain sufferer. However, it is unlikely that the potential for identifying and eliminating ectopic sources of neuropathic pain has an expiry date.

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Editor's Comments

I am grateful to Professor Devor for providing us with a brilliant but readable summary of the nature, and pathophysiology, of neuropathic pain. He is *the* world authority on the subject, and I believe that this paper should be required reading for every caregiver who treats patients with neuropathic pain.

The search for agents that can improve neuropathic pain has been the "holy grail" of pain research over the last several decades. In that time, we have learned a lot about the mechanisms of chronic pain. However, that knowledge has not yet yielded a major breakthrough in its pharmacologic treatment, either medical or surgical. In practice we continue to "borrow" pharmacology from other disciplines. The membrane-stabilizing agents that are so effective in trigeminal neuralgia (TN) are, in fact, *anticonvulsants*. Generally these agents work well in cases where pain is described as episodic, shocking, electrical, or lancinating. More commonly, neuropathic pain is described as constant, burning, aching, tearing, or painful pressure. Some success has been achieved with gabapentin, or pregabalin, for these constant pains, but not to the same degree that we can reliably alleviate TN. Anticonvulsants do not work well for these constant pains, which tells us their mechanisms must be different. *Antidepressants* are another class of agents that can allow patients to cope with chronic pain,

but they rarely completely alleviate the pain. *Opioid analgesics* are notoriously ineffective in treating neuropathic pains, and *anti-inflammatory agents* also have limited indications.

With respect to surgery, Dr. Devor discusses the theoretical limitations of ablative surgery for neuropathic pain, as well as the unintended harm it can produce. As an exception to the general rule that neuropathic pain is usually not relieved by the *intentional* production of further damage to the nervous system, he rightfully cites the exception of trigeminal destructive procedures (nerve, ganglion, posterior sensory root) and provides an explanation for their success. In fact, as he discusses, Devor developed the "ignition" hypothesis of TN, which maintains that otherwise innocuous stimulation (touch) can trigger abnormal discharges from areas of trigeminal dysmyelination, which in turn produces a cascading series of depolarizations of cell bodies in the ganglion. This wave of depolarizations is felt as extreme electrical shock, stabbing, or burning pain in the face. Reduction of sensation in the trigger area would diminish triggering stimuli, and thereby be predicted to diminish pain episodes.

Dr. Devor briefly alludes to another destructive approach, the dorsal root entry zone (DREZ) procedure of Sindou. This is the other major exception to the general rule regarding ablative surgery for neuropathic pain, since given proper patient selection, DREZ is usually predictably effective in cases of limb pain after plexus avulsion. DREZ will be covered in Chapter 58, but it is instructive to consider this surgery, and what it and the aforementioned trigeminal destructive procedures tell us about the nature of some forms of central neuropathic pain.

The likelihood that genetic factors play a role in the incidence, phenotype, and severity of chronic pain conditions is a focal point of this paper. When we consider the diversity of chronic pain states, and even what appears to be their somewhat unpredictable manifestation, it is odd that we have only recently begun to consider the genetic and epigenetic influences on chronic pain states. I believe this will be an area of rapid advancement within the coming decade. One cannot read this chapter without forming the impression that we are on the threshold of discovery of much more effective medical and surgical pain treatment.

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Section II

Pain Medicine

4 Approach to the Patient with Chronic Pain

Joshua M. Rosenow

Evaluating patients with chronic pain can be a challenging exercise for even the experienced clinician. These patients have often traveled a long road through the health care system and have experienced many frustrations. Moreover, they frequently present with expectations that may be difficult to meet. This chapter is intended to serve as an overview for neurosurgeons of some of the considerations that need to be taken into account when treating these patients. This process may be time-consuming, but it is time well spent because a hasty encounter will leave many things unresolved on both sides of the physician–patient relationship.

Prior to Arrival

A letter from the patient's referring physician may provide valuable insight into the patient's state of mind as well as his or her pain complaint. In addition, this helps to focus the encounter because these patients may have numerous somatic complaints. Moreover, it establishes a line of communication with the referring physician and aids in the coordination of care.

The physicians should obtain as complete a record of prior treatments and outcomes as possible, including operative reports, psychological reports, imaging, diagnostic testing (electromyography, discography, etc.) reports, imaging studies and reports (preprocedure and postprocedure for each surgery), specialist consultations, physical therapy summaries, and relevant office notes. It is also helpful to know if there have already been applications for long-term worker's compensation disability or social security disability, as well as if litigation is involved.

It may be helpful to send a set of clinic policies and procedures to patients prior to the visit to help establish ground rules on such items as missed appointments, medication prescribing and refills, general time frame for routine return phone calls, and paperwork completion.

The Initial Visit

It is crucial to understand the patient's goals not just for the initial encounter, but for the physician–patient relationship as well. Conversely, patients need to understand the capabilities and limits of the relationship (which parts of care the evaluating physician may or may not be willing to assume responsibility for) to avoid misunderstandings down the road that can erode the patient's trust in the physician. For example, a patient may expect the evaluating physician to assume prescribing responsibility for chronic narcotics or to aid in the patient's quest for disability benefits.

Patients with chronic pain have already undergone numerous evaluations and explained their story ad nauseum, and may become disenchanted or angry at the thought of having to go through it again. They should be reassured that this is a key part of determining both why their prior treatments have not succeeded and if there are any further surgical treatments that may provide them with their desired outcome. Also, the patient should understand that it may require more than a single visit for a full evaluation and to determine a therapeutic course of action. This may also require further diagnostic testing or other consultative evaluations, such as psychological testing.

The failure of previous medical or surgical attempts to relieve pain may be due to the failure of the treatment itself, but it might also be related to a variety of underlying psychosocial issues. Pain relief that is judged as adequate by a previous physician may not have been helpful enough for the patient.

Possible reasons for prior treatment failure are:

- Incorrect diagnosis
- Incorrect choice of therapy (medical or surgical)
- Incorrect application of therapy (wrong level, wrong site)
- Failure to apply the therapy to the full extent necessary for symptomatic relief (e.g., declaring a medication to have failed prior to increasing

the dose to a sufficient amount or not sufficiently decompressing a stenotic spine)
- Side effects limiting full application of a treatment
- Treatment-related side effect (adjacent segment degeneration, etc.)
- Patient factors (health, anatomy, allergies) that prevent full application of a treatment
- Intraprocedural complication
- Technical failure of procedure (e.g., nonunion)
- Incorrect expectations of outcome (either on the part of the patient or the result of poor expectation management on the part of the physician)
- Medicolegal factors
- Occupational factors
- Psychological and social factors

History

General Aspects

A detailed history may be the most helpful factor in establishing a diagnosis and forming a treatment plan. The history provides important information not only about the possible mechanisms and pathophysiology of the patient's pain, but also about the emotional and psychological status of the patient. It often requires a combination of a firm hand to guide the interview and prevent excessive wandering by the patient, along with allowing enough flexibility to allow the patient to volunteer valuable information. Keeping each of these sometimes complex patient histories chronologically organized is a good way to stay on track.

Pain History and Onset

Once the current baseline is established, including standard factors such as location, quality, radiation, duration, and exacerbating and alleviating factors, this pain may be analyzed in relation to the patient history.

Determining the relationship of the current pain to the original pain enables the physician to determine if this pain represents new pain or a continuation/progression of a previous pain complaint. What prior treatments were used? What effect on the pain did they have? This helps determine if prior therapies were inappropriate (perhaps guided by wrong diagnosis) or just not used to their full extent.

If the current pain is substantially different from the original pain, this may imply that a different process may be responsible for the current pain or that the current pain is the result of a treatment side effect. Patients often undergo misguided treatments for pain syndromes. These treatments can themselves cause further pain. As previously stated, procedural complications can also result in pain that is unlike the presenting pain. The physician should be cautious of those patients whose pain changes significantly in location and character after a treatment.

Was there an obvious inciting incident associated with the pain? Was this mechanism consistent with the patient's original complaints? The location, distribution, quality, intensity or severity, and duration of the first pain should be ascertained. Were there any other, associated neurologic symptoms at the time and did any of these develop in a subacute fashion? Was any treatment applied immediately?

Pain that is the result of an activity on the job presents a special situation due to the issue of worker's compensation claims. This type of history needs to be even more fastidiously documented, including the exact time and date of the injury. Other information should be obtained, such as whether the patient continued to work after the injury, when and to whom the injury was reported, and the response of the patient's employer to the injury as regards the patient's work status.

Neuropathic pain syndromes, such as complex regional pain syndrome (CRPS 1 and 2), most often have an antecedent injury that sets the syndrome in motion (with trigeminal neuralgia—Burchiel TN 1—being an exception), unlike nociceptive pain, such as degenerative spinal disease, which is often slowly progressive.

The physician should also ascertain the impact of the pain on the patient's daily life. This is accomplished by asking the patient to provide the timeline of an average day. This provides important insight into the psychological effects of the pain on the patient's life and the level of disability the patient is experiencing.

Pain Characteristics

The patient should be asked to describe in detail the current quality, site, radiation, severity, and alleviating/exacerbating characteristics of the pain at the time of evaluation and to indicate whether any of these factors has changed since the onset or during the interval. Those factors that have no effect on the pain are important as well. Such factors include stress and other emotional disturbances, movement, pressure, heat or cold, coughing, sneezing, straining, and deep breathing. The 0 to 10 visual analogue scale (VAS) is the most commonly used pain rating scale, even if it is not the most robust measure. It is often more useful to administer the visual analogue scale by asking the patient to mark the level of pain on an unlabeled 10-cm line. Physicians should be wary of

those patients whose pain either never varies from 10 or is rated as "11" on a scale of 0 to 10.

Pain may be classified as localized, radiating, or referred. Localized pain continues at the same location as its origination. This pain may be associated with other anatomic and sensory changes at the site of pain, such as hyperalgesia, wind-up hyperpathia, color change, and trophic changes of the skin. Pain may also be described as radiating along the distribution of a nerve root's dermatome or the innervation of a peripheral nerve. This is distinct from pain that is referred from a deep visceral structure to a separate distinct anatomic location. Classic examples of this are back pain or superficial abdominal pain from chronic pancreatitis and scapular pain from cholecystitis.

Pain Treatment History

Obtaining a recounting of past medical and interventional treatments and the response to each is an invaluable part of the evaluation. A thorough analysis of this part of the history prevents the clinician from repeating past failures. Which classes of medications have been tried? Were the medication trials adequate? Were interventional techniques used appropriately? Did each subsequent treatment follow logically based on past information? Has *every* treatment failed to provide any relief? Moreover, this history helps to ascertain patient compliance and assess for etiologies of past treatment failures. The clinician needs to take a very critical view of this section of the history, always asking *why* a treatment failed and if there is anything else for the neurosurgeon to offer the patient.

Past Medical and Surgical History

Concomitant medical conditions can adversely impact both medical and surgical treatments. Factors such as obesity, diabetes, hypertension, hypothyroidism, chronic obstructive pulmonary disease, and inflammatory arthritis are common and each has the ability to complicate therapy. Patients frequently will omit conditions they do not consider important or will omit conditions they consider treated. For completeness, the inquiry should proceed through a comprehensive list of organ systems.

If the patient has failed multiple surgical procedures for the pain syndrome, were there surgical failures for other conditions as well? If so, is this due to an intrinsic patient medical factor, poor surgical techniques, unrealistic expectations, the patient seeking unnecessary surgical treatments, or just bad fortune? Does the patient appear compliant with the physician instructions for other ailments?

Family History

Patterns may be recognized from a family history. Have multiple family members undergone spinal surgery? Are they all employed in high-impact professions? Is there a family tendency toward spinal degeneration or stenosis? Are multiple family members receiving disability insurance? Chronic pain behavior may be a learned trait within families.[1] There is level III evidence through cohort studies that a history of child abuse may increase pain and pain behaviors.[1–4]

Social and Psychological History

A complete psychological and psychosocial assessment is crucial for the overall management of the patient with chronic pain. There is substantial class III and IV literature on this subject that is well covered in other sources.[5–9] The psychological and psychosocial part of the history helps to determine the contribution of affective or environmental factors to the patient's pain syndrome. Referral to a psychologist with special expertise in the evaluation and treatment of patients with chronic pain is an essential part of the total care of these patients. At the minimum this part of the history should include a listing of current and prior psychological and psychiatric illnesses. Special attention should be paid to depression, a common condition in patients with chronic pain. The astute neurosurgeon will delve deeper into this issue than simply inquiring about the patient's mood. The patient's daily schedule provides important data about his or her depression. Other clues are irritability, insomnia, abulia, weight gain or loss, and suicidal ideation. The patient's family can provide important perspective as well.

The neurosurgeon should also explore the patient's vocational status and vocational stressors, including compensation and litigation issues. These can impact the patient's motivation and outcome from treatment as demonstrated by level III and IV evidence.[10–13]

Whereas the history should include current prescription drugs, an appropriately thorough history should also include over-the-counter and alternative (e.g., herbal) medicines. Illicit pharmaceutical use (both current and past) should be elicited by direct questioning, including specifically asking about the most commonly abused pharmaceuticals. It is important to determine not only what patients are using, but also if they are using it appropriately. Be alert for patients using others' prescription medications for their own benefit or using medications up earlier than prescribed and obtaining substitutes illicitly. A history of tobacco smoking and alcohol use, including the type and frequency of use of each,

should be included as well. Physical and psychological dependence on drugs and alcohol is a common impediment to treatment.

A useful exercise is to conceptualize the patient's pain syndrome as separate components of pain and suffering. Pain is the purely physical and physiologic component of the syndrome, whereas suffering includes the individual's reaction to the pain as well the pain's effect on the rest of the person's psychological and emotional environment. Suffering includes depression, anxiety, loss of self-esteem, failed relationships, past emotional and physical abuses that shape the pain response, poor coping strategies, and withdrawal from friends and family. Surgical interventions may be an excellent method for dealing with the pain, but they are inadequate at handling an impressive suffering component. Again, a skilled pain psychologist is adept at determining the balance between the pain and suffering components along with identifying maladaptive coping strategies and other pitfalls of which the surgeon should be aware prior to embarking on a therapeutic relationship with the patient.

Although it is true that there is a small population of individuals entirely without a physical basis for their pain complaints,[14] the majority of patients with chronic pain show a complex interplay between psychological and physical components of their pain syndrome in varying proportions. Among the neurosurgeon's challenges in evaluating and managing patients with chronic pain are first determining the relative balance between these factors and then using that estimation to drive the selection of an individualized combination of medical, interventional, surgical, and psychological treatments for each patient.

Physical and Neurologic Examinations

The examination of the patient with chronic pain is essentially no different from that of a patient presenting for any other type of neurosurgical evaluation. The neurosurgeon must be vigilant for signs such as weakness and pathologic reflexes that may indicate conditions such as nerve root or spinal cord compression that could warrant urgent further evaluation or treatment. These findings should not be discounted or neglected just because the patient may have already seen other physicians or have had other surgical procedures.

The central sensitization that occurs in many patients with chronic pain can result in certain characteristic exam findings. Central sensitization affects the wide-dynamic-range (WDR) neurons in the dorsal horn of the spinal cord that receive input from both Ab and C fibers. In neuropathic pain states, Ab fiber depolarization also results in stimulation of these other fibers, resulting in allodynia, the perception of pain from light touch. Patients with chronic pain may exhibit generalized hyperpathia, exaggerated and prolonged reactions to painful stimuli. For example, this may manifest itself as the patient reporting that a pin prick is intensely painful over the entire body. Repetitive stimulation of C fibers may result in an augmented response to each subsequent stimulus, a process known as wind-up. Repetitive light stroking of the painful area is interpreted by the patient as increasingly painful with each iteration.

Red flags on examination should engender skepticism in the examiner. These may include Waddell's signs[15–17] for nonphysiologic back pain (mostly level IV evidence) and other inconsistencies on physical and neurologic examination. For instance, does a patient with apparent ankle dorsiflexor weakness when seated have the ability to heel-walk without much difficulty? Do the findings fail to conform to a peripheral or spinal nerve distribution? Importantly, Fishbain[18] published a structured review (level III evidence) of the medical literature on the validity of Waddell's signs and noted that Waddell's signs are not reliable as a discriminator of physiologic from nonphysiologic pain.

Formulating a Treatment Plan

The patient with chronic pain requires an individualized treatment plan. First, the treatment team should be able to work in a cohesive manner and present a united front to the patient. Representative members of a pain team are chosen from the following clinical areas:

- Surgical specialist(s)
- Anesthesia
- Neurology
- Medical specialists (internal medicine, oncology, etc.)
- Physiatry
- Pain psychology
- Psychiatry
- Nursing
- Physical therapy
- Occupational/vocational therapy
- Social work
- Addiction medicine

The clinicians involved should have clear and open lines of communication between them. The best method for achieving this is to set up a regularly scheduled patient management meeting attended by the pain team. A team consensus may be reached and be discussed with the patient and his or her family.

Next, in defining a plan, it is important to outline the plan in as much specificity as possible and then stick to it. The plan should have steps included for dealing with medication-related side effects and procedural failures. This gives the patient a clear

understanding of what steps will be taken and in what order. Moreover, the patient will understand what the expected outcomes are for each step and what will be done if the actual result does not meet the expected outcome at each step. Part of outlining this plan may include the signing of a treatment contract on the part of the patient and clinician.[19–21] If a contract is signed, the patient should have a copy to keep. Contracts should denote the obligations of both parties as well as the consequences for violations.

Setting expectations of treatment is a crucial part of the overall plan. Often the patient's expectations have not been met by past medical and surgical treatments either because the treatments have not delivered anticipated results or because the patient's expectations were not realistic. Substantial time should be spent discussing realistic outcomes for each care step, as well as for the overall plan of care. For instance, it may or may not be realistic for a patient to return to the same line of work following treatment, but it is critical to understand if the patient believes that he or she will do so. The clinician's and patient's ideas of a "good" outcome may be divergent, and this disparity needs to be understood and managed.

Goal and expectation setting should include lifestyle modification as needed. Smoking and obesity are negative determinants of outcome[22–24] (level IV evidence), and the willingness to work on resolving these problems is a good determinant of the patient's level of motivation. Return visits may need to be scheduled to evaluate progress on certain goals or to discuss

Editor's Comments

It is difficult to communicate how a clinician should approach a chronic pain patient. Experience clearly matters. What Dr. Rosenow has outlined here is an excellent summary that hits most of the important points. From my standpoint, there are a couple of other aspects of the assessment of a patient with chronic pain that are worth mentioning.

First, although a comprehensive review of the patient's history is vital, many patients with chronic pain appear for evaluation with literally reams of data: prior evaluations, treatments, diagnostic testing, imaging, and so on. The clinician must use the record and not be a victim of it. Only experience can teach which aspects of the record merit initial close scrutiny, and the record should be available indefinitely for re-review. However, in some cases a page-by-page reading of the records is simply not practical. It is important that the evaluating clinician take a fresh look at the problem, working from the present backward, and use the record to answer directed questions.

Next, remember that the patient has come to you for assistance. At the initial encounter, patients often bring anger, expectations, and demands, which may or may not be appropriate for the first minutes of your acquaintance. It is imperative for the patient to know you are there to try to help and to render an opinion, and perhaps therapy. You are not there as a fiduciary for whatever trauma the patient may or may not have sustained from dealing with the health care system, worker's compensation, or the legal process. I often have to remind patients that we have just met, and that I am there solely to try to alleviate their pain problems. This message can be conveyed, if necessary, in a forthright and nonthreatening manner. I find that this helps to establish the "ground rules," and in most cases, further cement the patient–physician bond.

One of the most important statements to make during the initial encounter with a patient with chronic pain is that you *believe* him or her. None of us has the capability to feel what the patient is experiencing. The patient may appear to have more pain than the diagnosis can explain, but we are only observers of the outermost shell of the nested layers of suffering, pain, and nociception in a given patient. Our job is to determine if we can help the patient by surgical or nonsurgical means, *not* to act in judgment over the patient's behavior. It is vital that the patient know this, and this statement, more than almost any other comment you can make to the patient, calms what may be a stressful situation, and establishes the roles of patient and caregiver.

When a patient comes to a surgeon, or at least, an interventionalist, the underlying question will be: "Would a surgical procedure help?" The surgeon should quickly assess whether either a neuromodulatory or destructive procedure would be indicated. In most cases, nondestructive neuromodulation is best. However, destructive procedures for trigeminal neuralgia, or brachial plexus avulsion pain are very effective. On the other hand, a negative answer to the question of surgery should not be equated with failure. Many times eliminating that option focuses therapeutic strategy and energy on nonsurgical therapies. It is an important negative, and it may deflect the patient from yet another attempt at pain relief from what is a passive therapy.

The main challenge to the treatment of a patient with chronic pain is the willingness of the caregiver to engage. It is not an easy venture, as Dr. Rosenow points out, but it is one that can be fulfilling for the patient and clinician. Reading this chapter will set the clinician up to engage successfully in the care of these patients, an experience that will be seasoned over time.

consultation or imaging results prior to the physician's agreeing to embark on a therapeutic relationship. Return visits also allow the physician to assess the amount of information internalized by the patient from previous visits. Written materials given to the patient to read at home may aid in increasing retention of information discussed during the office visit.

Some patients may not be accepted for care. A true pain team is not just a dumping ground for all patients that other specialists do not want to manage. Patients with a significant ongoing pattern of pharmaceutical misuse, whether legal or illegal, need to first have these issues resolved. Moreover, severe overwhelming emotional and psychological problems also need to be brought under control, especially prior to nonurgent surgical procedures.

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5 Psychological Assessment

Kari A. Stephens and Aaron Vederman

The Nature of Chronic Pain

Although assessment and treatment of chronic noncancer pain constitutes an important part of most routine clinical care settings, comprehensive and specialized assessment of chronic pain is particularly important when considering surgical treatment options. The assessment and treatment of chronic pain is challenging due to its inherently subjective nature as well as the panoply of medical, psychological, and social factors related to course and treatment outcome. The experience of chronic pain varies from patient to patient, influenced by physiologic factors ranging from the integrity of the nervous system and comorbidities such as peripheral neuropathies to psychological and social factors. Psychological and social factors are particularly complex because they may encompass a range of phenomena extending from internal processes such as basic patterns of learning and behaviors and subjective beliefs and appraisals of pain as well as external factors that include complex situational factors (job loss, labor and industry involvement, etc.). Just as specific comorbid medical diagnoses may affect the experience of chronic pain, so too may psychological comorbidities (anxiety, depression, histrionic personality traits, etc.). Given that chronic pain is multidimensional and multifactorial,[1] an understanding of the meaning and function of pain to a patient is key to assessing for the best patient selection for surgical procedures.

Perspectives

The assessment and conceptualization of chronic pain varies across treatment modalities. Not surprisingly, the medical model typically emphasizes aspects of chronic pain stemming from sensory or neurologic factors whereas behavioral medicine and health psychology focus on emotional, cognitive, and behavioral components of the pain experience. Either of these broad approaches in isolation may confer an overly compartmentalized perspective, and the corpus of published literature and clinical experience reinforce the need for an integrated approach to assessing and treating chronic pain. Such integration is usually best achieved via the modern multidisciplinary model employed by many pain centers. Multidisciplinary models of care (i.e., structured pain programs, integrated multidisciplinary care teams) incorporate a biopsychosocial model of care, which has been well established as superior to the traditional biomedical model of care for chronic pain.[2] Although chronic pain usually begins as a biological process, psychological and social factors often play key roles in the process.

Beyond a broad conceptualization of chronic pain, comprehensive pain programs typically involve a biopsychosocial approach to pain treatment and interventions.[3] Most comprehensive pain programs involve team coordination in care between physicians, psychologists, counselors, physical therapists, case managers, occupational therapists, psychiatrists, and nursing staff, with a focus on mood and functional restoration. These interdisciplinary programs often involve physical and occupational therapy, exercise, medical management, pain psychology, relaxation training, and vocational rehabilitation. These programs have a strong evidence base for reducing disability from chronic pain.[3,4] However, sustainability and accessibility of these comprehensive programs are difficult due to financial costs to the individual patients, the lengthy time commitment, and the limited dissemination of these programs, making it difficult for patients to access care in these settings. Disparities in care with surgical interventions for chronic pain have not been well examined, but given the complicated patient populations suffering from chronic pain, it is likely disparities in service exist. Given that access to psychological experts for presurgical evaluations is also scarce, it is likely many patients who are underinsured, and often the most vulnerable, lack access to these

presurgical assessments. A recent study has examined disparities in service for spinal cord stimulators (SCSs), given their increased use and evidence suggesting that only about 50% of patients benefit from this treatment and specific risk factors limiting SCS treatment efficacy have not been well established.[5] Disparities in service delivery of SCSs in a retrospective study of 4,843 patients across four states in the United States found that in high-volume hospital settings, the SCS was more commonly used among Caucasian patients, male patients, patients with private insurance, and patients with fewer comorbidities.[6] Psychological assessments have the potential to help mitigate service disparities.

Patients being considered for surgical procedures are often naïve with respect to treatment in interdisciplinary pain programs and are often also naïve toward the idea of a biopsychosocial approach to pain treatment. However, psychological and social factors not only influence the development of chronic pain, they also predict poor outcomes to surgical treatments. Given this complicated set of risk factors, surgeons are using psychological evaluations as part of the evaluation process to select the best candidates for procedures. Psychological assessments may also provide a gateway to helping patients engage a more comprehensive model, by offering some psychoeducation and specific recommendations for treatment during the evaluation, as well as improving the selection of surgical candidates.

The aim of this chapter is to provide a broad overview of the rationale for psychological assessment in surgical management of chronic pain, the major nonmedical factors associated with chronic pain, the constituent elements recommended for most psychological assessments, a review of the major clinical assessment tools, and outcome prediction and treatment planning. Ultimately, there continues to be no uniform consensus on the composition or use of the psychological assessment for surgical management of chronic pain. Some of the factors contributing to this lack of consensus will be touched on in the body of the chapter as well. Nevertheless, it is hoped that this chapter will provide a foundation and compass by which individual clinicians and surgical centers may incorporate psychological assessment and treatment planning in the manner most efficacious to their needs.

Rationale for Psychological Assessment

History

Psychological assessment has a long and broad history. Some of the earliest applications of clinical assessment were employed by the psychiatrist Emil Kraepelin (1856–1926) and neurologist Jean-Martin Charcot (1825–1893) to evaluate traits of mental functioning associated with psychopathology.[7] Assessment methods began to diverge into distinct "qualitative" and "quantitative" foci early in the 20th century. As with many other stark theoretical dichotomies, the effectiveness of such "clinical" versus "statistical" approaches to assessment was fiercely debated for decades, although today most clinicians are willing to employ a range of these methods in conducting a clinical assessment. Nevertheless, the general trend suggests that objective and quantifiable methods (such as the Minnesota Multiphasic Personality Inventory (MMPI)) are more often requested by referral in medical settings over projective assessment methods (Rorschach, Thematic Apperception Test, etc.).

One of the driving forces in the development of both quantitative and qualitative assessment was the need to make predictions pertaining to employment success, military placement, and treatment planning in the mentally ill. Today psychological assessment is also commonly employed in schools, medical settings, businesses, and forensic arenas. Naturally, the referral questions generated by these different settings determine the content and purpose of the assessment, and variation in assessment tools, content, and tone is the rule rather than the exception. More germane to this chapter, psychological assessment was first employed in medical settings to determine which patients may have psychiatric comorbidities. Indeed, psychological assessment continues to be commonly used in considering any medical procedure in which lifestyle, behavior, compliance, or mood may impact candidate selection and outcomes. These include organ transplants, bariatric surgery, and SCSs, to name only a few. In particular, psychological assessment is often undertaken to identify the presence of cognitive dysfunction meeting criteria for dementia or intellectual disabilities, either of which may suggest that an individual may struggle with decisional capacity, communicating changes in pain, or independent compliance with aftercare requirements.[7,8] Furthermore, psychological assessment often focuses on substance use disorders, psychosis, or Axis I or II pathology that may interfere with treatment or outcomes.[9,10] The above conditions are typically diagnosed in a binary fashion: either diagnostic criteria are met or they are not. However, aside from merely detecting psychological illness in a diagnostically binary fashion, with the development of behavioral medicine and health psychology, a more nuanced consideration of psychological assessment in medical settings has evolved. Within these clinical disciplines is the understanding that psychological factors need not necessarily reach the *DSM* diagnostic threshold in order to play a significant role in the onset, course,

and treatment of medical illness. Thus, the aim of assessment in behavioral medicine is not necessarily to diagnose a mental disorder, but rather to provide shade, texture, and nuance to complicated clinical phenomena such as chronic pain. The clinician conducting a psychological assessment for surgical pain management often must maintain a fine balance. On one hand, whereas a nuanced assessment of a patient is often overtly requested, busy medical providers may also tacitly prefer binary diagnoses and firm predictions for outcome in keeping with a general medical model. The balance between these two competing needs has led to more direct collaboration between the physician and psychologist to make the final determination for the appropriateness of candidacy for surgical intervention for chronic pain.

Rationale for Presurgical Psychological Assessment

Presurgical psychological assessment can improve patient selection, promote preparation for surgical interventions for patients in need of these treatments, and facilitate treatment for psychological and social issues related to chronic pain. Some evidence has been found to support the notion that enhancing a patient's confidence and knowledge about surgical procedures may increase self-efficacy and improve treatment outcome, particularly for SCSs.[11] Presurgical psychological assessments can facilitate patients' engagement in appropriate psychological interventions that could help reduce risk factors and increase success from these procedures, consistent with multidisciplinary pain programs. In addition, these assessments can help identify alternative treatments that may be more likely to be effective for the patient. Finally, these assessments can help prevent pitfalls for physicians who may have patient selection biases due to rapport, clinician intuition, or pressure by patients to recommend the procedure.[12] Collaboration with the psychologist can help ameliorate difficult patient interactions and add objectivity to the patient selection decision. Psychological interviews themselves offer an opportunity for psychologists to be therapeutic and can be used to provide psychoeducation, help clarify questions of concern about the procedure, and address treatment recommendations for previously unidentified psychological and social issues. Surgeons play a critical role in explaining this process to patients and can promote patient-centeredness by explaining the utility of the psychological assessment toward improving surgical outcomes and expanding and enhancing the treatment modality.

Psychological and Social Risk Factors for Spinal Surgery and Spinal Cord Stimulator Outcomes

Meta-analyses have continued to push forward and advance our understanding of postsurgical predictions of successes in outcomes. Several categories of psychological risk factors specifically for failed back surgery were noted in a recent review: psychopathology (*DSM-IV* Axis I and Axis II disorders), emotions (depression, anxiety/fear, anger), pain sensitivity/somatization (excessive pain focus), cognitions (passive coping strategies, perceived lack of control), opioid and substance abuse and misuse, and interpersonal issues (reinforcement of pain behavior, abuse, and abandonment history).[13] Although depression is common in clinical samples experiencing chronic pain, depression with associated self-harm or active suicidal behaviors is a contraindication.[14] Furthermore, because surgical interventions often represent last resorts, psychological screening should determine whether disappointing complications or outcomes are likely to result in hopelessness, which in turn has been related to medical noncompliance.[15] Several reviews specific to lumbar surgery and SCSs agree on the following well-established psychosocial risk factors: presurgical somatization, depression, anxiety, job dissatisfaction, low education, poor coping (i.e., passive coping), litigation, anger, neuroticism, psychological trauma in childhood, chemical dependency, spousal reinforcement of pain behaviors, lack of or limited partner/spousal support, self-perception of presurgical good health, fear of movement or re-injury, negative outcome expectancy, lack of optimism, maladaptive beliefs about pain, history of maladjustment, and lack of English proficiency.[16–18] Other reviews have noted the additional risk factors of pain chronicity, poor social support, and significant cognitive deficits.[19,20] Some research suggests that psychosocial risk factors are better predictors of pain and disability compared with magnetic resonance imaging (MRI) and discography.[21]

Celestin and colleagues[16] conducted one of the most comprehensive meta-analyses to date. They reported that with regard to lumbar surgery, higher levels of depression, somatization, and hypochondriasis were predictive of poorer outcomes in a majority of studies. Passive coping styles were also associated with poorer outcomes in some studies. This finding was quite robust, even when studies used different measures to assess for these domains of psychological functioning. They reported that variables related to physical functioning were less consistently related to treatment outcomes. For example,

baseline activity interference and disability were associated with treatment outcomes in only about half of their included studies, and pretreatment disability was related to poor treatment outcomes in only a minority of studies. Furthermore, demographic factors were of limited importance in predicting treatment outcomes, with older age and female gender moderately associated with poorer outcomes. Of note, pain duration was negatively associated with treatment outcomes in each of the studies examining that variable. With regard to SCSs, they included only four studies that met the entry criteria in their meta-analyses. They reported that psychological factors (including depression and anxiety) were the most predictive of treatment outcome (three out of four studies) whereas baseline disability level and pain ratings were not predictive of outcome. Similar to the results for lumbar surgery, they found that older age was predictive of outcomes in some, but not all, studies. Across all studies they did not find consistent associations between gender, worker's compensation status, employment status, previous surgeries, and treatment outcome.

Ultimately, psychological factors were more useful as predictors of outcome than variables related to pain and activity level. Why, then, does hesitancy often characterize the tone of the literature with respect to firm statements regarding the utility of psychological prescreening? This is likely due to the fact that rigorous randomized controlled trials (RCTs) focusing on psychological predictors have not been conducted thus far. Thus, as was the case in 2002, when the previous edition of this text was published, current recommendations for psychological assessment are largely based on prospective cohort studies. Although the state of the literature allows us to make assumptions about the importance of psychological and social variables, predictive data regarding the efficacy of specific assessment tools are generally lacking. Nevertheless, whereas RCTs may be the gold standard by which eventual consensus is reached on the makeup of psychological screening batteries, the existing data of large cohort studies likely provide a great deal of direction to clinicians involved in multidisciplinary settings. For instance, although it is true that the exact proportions of risk for poor outcomes associated with various levels of depression are unknown, such data would be of utility for treating individual patients in the clinic, who often present with psychosocial profiles more complex than typical study populations. Indeed, it may be enough to know that clinically significant levels of depression are associated with poorer response to treatment, such that concomitant therapy or psychotropic treatment may be offered. Thus, psychological assessments put these risk factors in the context of the individual patient's complexities to help clarify surgical candidacy.

Psychological and Social Risk Factor Assessment Methods and Tools

Standard Methods for Psychological Assessment

A study based on a national survey of surgeons in the Netherlands recommends a multidisciplinary approach to patient selection because of the lack of uniformity in both the use and appreciation of predictive tests by surgeons in patient selection for chronic pain–related surgical procedures.[22] Whereas attempts have been made to standardize presurgical psychological assessment methods and tools, no consensus for which method is best has yet emerged.[23,24] A review of 25 studies found 20 different screening questionnaires were used for prescreening patients before surgeries to address back pain, illustrating the lack of any standard set of screening measures.[16] Nevertheless, in current practice, standardized methods for conducting psychological assessment include the use of some set of validated measures of risk factors and a clinical interview by a trained expert in mental health, typically a clinical psychologist.

Given the purported importance of affective, personality, and attitudinal factors in chronic pain, it might be predicted that objective assessment tools such as the MMPI would be a highly efficacious addition to the assessment battery. However, at least one study found that patients with mildly abnormal MMPI-2 profiles actually reported higher percentages of improvement in pain after 4 years of intrathecal therapy, compared with patients with more conventionally "normal" profiles.[25] Use of the MMPI and the MMPI-2 Restructured Form (MMPI-2-RF) have been most studied as standardized presurgical psychological assessment tools, with MMPI elevations on depression (Scale 2), hysteria (Scale 1), and hypochondriasis (Scale 3) being most predictive for surgical failure.[16,19,26] Nevertheless, self-report inventories such as the MMPI-2 likely have utility in screening for surgical pain candidates because its validity scales permit an assessment of malingering and psychoses that well-defended patients may obscure during clinical interviewing.[27] Although the utility of the MMPI has been called into question,[25] several other studies have found that at least the hysteria and hypochondriasis clinical subscales can predict those who are most likely to respond to treatment for low back pain.[20,28] Ultimately, the MMPI and MMPI-2-RF have been the most widely studied self-report assessment measures for presurgical psychological assessments and have been shown to help predict poor outcome from surgical procedures. As for potential drawbacks, clinical interpretation of test

results is required, the MMPI is lengthy to deliver, literacy requirements are high, and the test is not free.

Many assessment tools developed and tested for presurgical psychological assessments require fees, are lengthy, rely on self-report and high levels of literacy, and do not stand alone given that they require expert and context-specific psychological interpretation. In practice, using standardized tools to assess risk factors has many advantages, and selecting self-reported scale measures with good validity and reliability can be quite useful in augmenting the standard psychological clinical interview. Finding scales that are easily accessible and free (e.g., Patient Health Questionnaire [PHQ-9] for depression and generalized anxiety disorder [GAD-7] for anxiety), have low literacy requirements, and have been translated into multiple languages can be of great utility.

It is worth reiterating that data are typically lacking to support any single assessment tool or cluster of tools that should be used across all clinical settings and in all patient populations. One reason for the heterogeneous findings on the specific predictive power for individual assessment tools may relate to variability in clinical conditions themselves. As Deer and colleagues[10] note, presuming a set of ideal "predictors" assumes an established constellation of outcomes and goals for all patients. However, these authors note that goals are likely to vary for cancer versus noncancer patients or for chronic pain versus spasticity, and treatment approaches may vary widely by specific condition. Furthermore, it appears likely that it will be easier to identify characteristics associated with poor rather than good outcomes.[16,29] Although any number of outcomes may be measured, successful outcome generally focuses on decreased medical treatment, decreased pain, return to work, and increased functioning in activities of daily living.

Many evaluation tools utilized in the clinical assessment of pain are self-report and frequently completed by the patient. Generally, such instruments have strong face validity, but their predictive power for appropriate surgical candidates is not as well established because normative samples in developing these measures were not exhaustive. Thus, use of any given tool often must be extrapolated to the specific population of interest. Moreover, many individuals completing self-report inventories are often able to detect the underlying purpose of specific questions, including those aimed at establishing positive and negative response biases. Moreover, clinicians should be aware of social desirability bias, which involves the tendency to answer questions in a manner that will be viewed favorably by others. Such a bias may be increased in scenarios in which there is a strong investment in obtaining certain outcomes, such as proving to be a good candidate for surgical pain management.

These issues belie the importance of specialized training for administering and interpreting psychological test data. This becomes especially important when one considers the nuanced skill of assigning relative importance to certain measures over others when integrating these data with clinical data from the diagnostic interview. Nevertheless, skilled doctoral-level clinicians are not always available to conduct presurgical evaluations. Because a template or process approach seems more important than administration of any particular assessment tool, other types of clinicians, including generalist clinical psychologists and social workers, may be sufficiently adept at identifying areas of concern prior to surgical interventions. Moreover, as Bruns and Disorbio[18] note, it seems unlikely that it would be possible to construct a single set of psychological criteria or measurements that could serve as an optimal set of predictors for all medical procedures. The reason for this is that different variables will carry various degrees of importance from patient to patient. For instance, addictive behaviors and past history of substance dependence would be of primary importance if a treatment is attempted with the hope of reducing a patient's use of opioid pain relievers. Similarly, assessing job dissatisfaction and motivation to return to work might be particularly relevant if the aim of medical treatment is to help a patient return to work. With that in mind, the clinician conducting presurgical assessments should be familiar with a broad range of important factors within the biopsychosocial model and select assessment tools that they feel will help to address the clinical data of interest. As noted, there is not likely to be any broad consensus across sites with regard to specific assessment tools in the near future. Instead, clinicians will likely benefit from reviewing systematic reviews of biopsychosocial risks for poor surgical outcome.[18,30,31]

A patient's attitudes and beliefs about pain are an important aspect of the clinical interview and overall assessment, so clinicians may wish to include specific objective measures within this psychological domain. Assessment of pain attitudes and beliefs may be especially important if it is apparent from the patient's history that more conservative treatment options have not been given adequate attention. The Pain Beliefs and Perceptions Inventory (PBPI) may be a good measure to include as a brief screen; it consists of only 16 items and is easily completed by most patients. Although there are a variety of interpretive methods available for the PBPI, one system allows tabulation of scores within a four-factor structure: Pain as Mystery, Pain as Constant, Pain as Permanent, and Self-Blame. Although data are lacking for the use of the PBPI for specifically predicting surgical outcomes in chronic pain patients, a clinician may nevertheless use these data as part of an overall qualitative evaluation of the patient. For instance, the

Pain as Mystery and Pain as Constant subscales have shown significant associations with trait anxiety (State-Trait Anxiety Inventory) and catastrophizing (Pain-Related Self-Statements Scale) cognitions.[32,33]

The Survey of Pain Attitudes (SOPA) is another assessment tool available to clinicians to assess attitudinal components of chronic pain, and may have an advantage over the PBPI in that it generates a larger number of subdomains. The SOPA comes in 57-, 35-, and 30-item formats, with strengths and weaknesses associated with each. Ultimately, the clinician should select which version will confer the greatest advantage depending on the particular assessment needs. If time or assessment burden is of greatest concern, the two shortest versions of the SOPA would be preferable; if repeated assessment over a longitudinal course is planned, the 57-item version may be indicated due to its higher retest reliability.[34] Ultimately, due to alterations in their psychometric properties, the short forms of the SOPA are not interchangeable with the long version.

Regardless of the specific assessment tools used, the clinical interview will typically serve as one of the most critical components of assessment. Specifically, it is important to directly ascertain a patient's expectations of the likely benefits and potential difficulties associated with surgical interventions for pain. One of the largest multicenter studies of intrathecal therapy for cancer and noncancer chronic pain found a mean symptom relief of 61%. This suggests that education regarding expectations will be required for many, and that intrathecal therapy is contraindicated for the rare patient with a fixed and unalterable expectation that treatment will result in total or near-complete pain relief.[27,35]

Although any single assessment tool cannot be recommended for all assessment and across all patient populations, general assessment protocols or algorithms have been posited as one approach. Bruns and Disorbio as well as Block and colleagues have developed methods for screening to address potential use of standardized risk assessment algorithms specific for presurgical psychological assessment for chronic pain.[18,32,36] Block and colleagues' method worked best when assessing patients without severe or unusual forms of psychopathology and when weighing the effects of numerous mild to moderate risk factors. Their method was based on tallying the number of risks present and listing risk factors based on empirical findings, with a clinical algorithm to quantify risk and required clinical judgment to interpret and determine a recommendation for patient selection.[32,36] The utility of this method for SCS candidates remains somewhat limited given that these patients typically have longer durations of pain and severe psychopathology compared with cohorts of patients being considered for other surgical interventions for chronic pain. A practical recommendation for use of this tool is to exclude candidates with severe psychopathology, and then apply the scoring system.

Bruns and Disorbio's model proposes a biopsychosocial vortex, or a "downward spiral" of chronic pain, used to create a set of four categories or risk factors to synthesize predictors associated specifically with poor SCS outcome.[37,38] They developed and proposed the use of the Battery for Health Improvement 2 (BHI-2) scale as a tool to support patient selection for SCS. Groupings of factors within the 217 items include validity and symptom magnification, physical symptoms, affect, character disorders, and social environment. Their goal was to create one psychological test using 18 scales to represent their groupings, anchored in evidenced-based findings of psychological and social risk factors. The BHI-2 is comprehensive and can augment standard psychological clinical interviews as an assessment tool measuring psychosocial risk factors particular to SCS. They also developed the BBHI-2, which has some validity as a shortened version of the BHI-2 and which may be more practical in clinical use. Furthermore, Bruns and Disorbio offer three vignettes to address how to select patients at low, moderate, and high risk for poor outcome using their proposed biopsychosocial vortex paradigm.[38] The BHI-2 and BBHI-2 scales are the only known scales specifically designed to address SCS patient selection and may be a useful adjunct to the standard psychological interview. Unfortunately, the BHI-2 is lengthy, is not universally adopted among psychologists performing presurgical psychological assessments, provides no guidance on weighting of risk factors assessed, and does not account for variances in the referral question(s) for the assessment.

Best Practices for Standardized Presurgical Psychological Assessments

The consensus is that a collaborative biopsychosocial assessment performed by a skilled psychologist and a physician is needed for optimal patient selection, preferably with the inclusion of standardized tools that measure the relevant risk factors associated with poor surgical outcomes. The results of the psychological assessment alone should not exclude a patient from a surgical procedure; rather, both the psychologist and the physician must understand each other's role and ideally consult directly with one another.

The psychologist and physician must determine how to weigh risk factors in relation to the goals for the surgical procedure (e.g., the goal to get back to work versus reduce reliance on pain medications

may imply different weighting of risk factors). A psychologist's clinical assessment and judgment is necessary to determine risk and to contribute to the recommendation for or against the surgical procedure. In general, three main dimensions should be assessed during a presurgical psychological assessment: (1) psychosocial risk factors; (2) assessment of the patient's overall understanding of the treatment procedure (e.g., does the patient have a good understanding of what to expect from the procedure and what is required for postsurgery?); and (3) assessment of the patient's expectations for pain relief and general outcome of the procedure. The three dimensions must be assessed in the context of a standardized psychological interview by a psychologist with chronic pain expertise. Standardized measures for established risk factors for poor outcome with surgical procedures should be incorporated, when feasible, to augment the clinical interview. The psychologist should convey clinical impressions and provide recommendations for mitigating any factors that might lessen the appropriateness of the patient for the surgical procedure.

Presurgical psychological assessment can improve patient selection, promote preparation for surgery for patients in need of these treatments, and

Editor's Comments

Drs. Vederman and Stephens have reviewed the current status of psychological assessment prior to pain surgery, in particular. There should be no doubt that the challenges of this assessment are substantial and that there is, as yet, no consensus on either the value of such assessment or the instruments by which this should be accomplished.

It should be self-evident that the evaluation of a patient with chronic pain should involve psychological testing and structured interview. There is no evidence that this inhibits patient care, and ample evidence that this helps in patient selection, patient education, and appropriate expectation setting for the surgeon and patient. An integrated approach to psychological assessment and surgical treatment, if appropriate, is the ideal. Unfortunately, I think it is the exception.

Why is psychological assessment not uniformly practiced in the world of pain surgery? The possible answers are numerous. First, it costs time and money. As this chapter points out, psychologists capable of performing such an inventory are not uniformly available, particularly outside of an academic environment. That is, access is limited. Securing funds to perform these assessments represents another layer of difficulty and bureaucracy, and in some instances the payer represents a barrier (e.g., Medicare). Almost as important, patients who seek out invasive care are often intent on a "surgical solution" to their pain. Whether this is due to a legitimate history of multiple failures of conservative management or to "passive coping strategies," the patient often sees the psychological assessment at worst as a potential barrier to treatment or, only slightly better, as a requisite rite of passage. In either instance the patient is usually not terrifically motivated to be subjected to testing and interview.

For the surgeon, psychological assessment of the patient can also be viewed as a burdensome barrier. Several factors might be in play: The surgeon may not have ready access to a psychologist for the reasons noted above, obtaining authorization for such an assessment requires both staff time and attention, and a "negative" evaluation may convert a potentially preoperative patient into a customer who has effectively, and unhappily, been "turned away" from what many view as their "last hope." In effect, psychological assessment can often result in the chagrin of both the referred patient and the referring physician. Surgeon dyspepsia may also be a by-product, since the surgeon has been thwarted from performing his or her art, and all of the attendant effort has ultimately not resulted in a (billable) procedure.

That there is a lack of consensus on the method by which patients should be assessed psychologically, and on the necessity for such testing, simply reinforces the potential liabilities of such measures. As pointed out in this chapter, it is unlikely that a valid, objective, quantitative, easily administered screening test for presurgical candidacy will ever be developed. The structured psychological interview is probably the best tool we have for patient assessment. Interviews also allow therapeutic discussion, intervention, and direction for postoperative support. Further, only by direct contact with a psychologist can the patient be educated as to realistic expectations for surgical outcome. Psychological testing and interview are much more than "screening"; they facilitate therapy, whether that is medical or surgical.

In the ideal pain practice, a psychologist is involved with patient care preoperatively and postoperatively, in an ongoing fashion. In our current fee-for-service environment, procedures are favored over counseling. Although the psychologist may be compensated for testing, ongoing therapy, whether group or individual, is not financially sustainable for most practitioners. This is an irony of our current system, and one that may be mitigated if, or when, outcomes are valued over invasive procedures.

facilitate treatment of psychological and social issues related to chronic pain. Many psychological risk factors are treatable conditions that should be considered in overall treatment planning.

Conclusion

Since the last publication of this volume, importance has continued to be placed on psychological prescreening for surgical treatment of chronic pain; however, the field continues to strive toward greater consensus on the strongest predictors of outcome, as well as the development of a "gold standard" assessment procedure. Others have argued that the latter objective is of less critical value given what are appreciated as differences in individual referral questions as well as differences in patient populations and underlying pain etiology as a whole. In general, a skillfully conducted and broad clinical interview will serve as the primary foundation for most psychological screenings, with selected assessment tools utilized for adjunctive data collection.

In the years since the publication of the prior edition of this volume, there has been a lack of consensus on individual psychological assessment tools and predictive outcomes. Because of this, some have suggested that, with the exception of those with dementias, ongoing addiction, suicidal depression, and substance dependency, few physically appropriate patients should be excluded from surgical interventions for chronic pain based upon any single psychological screening tool. In fact, given the lack of consistent empirical evidence for predicting surgical outcomes with psychological tools, data garnered should be treated cautiously and employed to construct an individualized and phenomenological view of the patient. Psychological test data may also be specifically helpful for making adjunctive or preparatory treatment recommendations, including counseling, psychopharmacology, or biofeedback. Patients should therefore be assessed on an individual basis for their understanding of the surgical procedure, expectations for outcome, and psychological and social barriers to good outcomes, with emphasis on overall quality of life.[27,39]

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6 Oral and Transdermal Opioid Analgesics

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Chronic pain is highly prevalent and exacts an immense toll on individuals, families, and society at large. Clinical management is complicated by the heterogeneity of pain syndromes and the patients who experience them, the varied physical and psychosocial consequences of pain, and the very large number of potential therapies available. Given this complexity, therapeutic decisions must be guided by a detailed assessment, which should characterize the nature and impact of the pain and clarify treatment goals appropriate for the medical and psychiatric condition of the patient. These goals always include a realistic and sustained reduction in pain, but also may link this outcome to other outcomes, such as improved physical functioning, relief of other symptoms, enhanced coping and adaptation, and better quality of life.

The treatment strategy that emerges from this assessment may involve disease-modifying therapy, primary analgesic interventions, and treatments that target functional or other outcomes. In some cases, a single analgesic treatment—a drug, physical therapy, or an injection, for example—may be the most appropriate intervention. In other cases, often those characterized by pain, disability, and distress, consideration must be given to a multimodality strategy that addresses multiple goals concurrently.

Most chronic pain is managed by primary care providers, and analgesic drug therapy is the most common approach employed. Analgesic pharmacotherapy is accomplished with agents from three broad categories of drugs—the nonopioid analgesics (acetaminophen and nonsteroidal anti-inflammatory drugs [NSAIDS]), the so-called adjuvant analgesics (nontraditional analgesics, such as a subset of antidepressants and antiepileptic drugs), and the opioid analgesics. Opioid drugs have been used for millennia and are highly effective in appropriately selected patients who are treated according to widely accepted practices. Treatment safety depends on actions that minimize the occurrence and impact of side effects and management of the potential risks associated with so-called drug abuse outcomes, including serious nonadherence, frank abuse, addiction, overdose, and diversion.

Role of Opioid Therapy

Opioids have protean uses, and conventional practice varies with the context of care. For example, there is a long-standing international consensus that oral or parenteral opioid therapy is the mainstay treatment for patients with acute severe pain, such as that accompanying surgery or trauma. Most patients with these conditions are opioid-naïve and treatment is expected to continue for days or a few weeks, after which it is withdrawn.

Acute severe pain also may punctuate persistent pain. When persistent "background" pain is relatively well controlled using opioid therapy, these acute episodes are labeled "breakthrough pain." Breakthrough pain is prevalent and far more complex than monophasic acute pain. As discussed below, opioid treatment of breakthrough pain is considered a standard of care for populations with pain due to active cancer or another serious illness, but should not be considered in this way for populations with other types of chronic pain.

The early and aggressive use of long-term opioid therapy was originally codified for cancer pain in the so-called analgesic ladder popularized by the World Health Organization.[1] This approach, which views opioid therapy as the mainstay treatment for chronic, moderate-to-severe pain, is now understood to apply specifically to those with active cancer and other populations with serious or life-threatening illnesses, usually in the advanced stages. Clinicians who specialize in the evolving discipline of palliative care consider long-term opioid therapy a best practice for these populations.[2]

Chronic "Noncancer" Pain

There is no consensus about the proper role of long-term opioid therapy in other chronic pain populations. These patients are very heterogeneous, representing many types of disorders and very

diverse comorbidities. Although they are commonly described together as having chronic "noncancer" pain, the commonalities across patients reflected by the use of a single label are not as prominent as the diversity encountered clinically. An increasing number of these patients have chronic pain caused by stable or indolent medical illnesses, such as painful osteoarthritis, neuropathic pain such as diabetic neuropathy, and pain related to cancer therapy among survivors. Others have primary pain-related diagnoses such as chronic headache or fibromyalgia. Many others have some type of common musculoskeletal syndrome, such as low back pain. Within each of these diagnostic categories is additional heterogeneity associated with varied medical and psychiatric comorbidities.

This extraordinary heterogeneity, combined with limitations in the empirical data pertaining to long-term effectiveness and safety,[3,4] have complicated the development of evidence-based guidelines for the selection of patients for long-term opioid therapy. An expert panel convened by the American Pain Society (APS) and the American Academy of Pain Medicine (AAPM) posited a series of guidelines but noted that virtually all were based on low-quality evidence.[5] Nonetheless, they conclude that opioid therapy can be beneficial for some subpopulations of patients with so-called chronic noncancer pain and advocate a cautious approach to patient selection based on a careful and ongoing assessment of benefits and burdens. This cautious approach is embodied in the recommendation that long-term opioid therapy always should be initiated as a trial, even if it is taking place after the patient has been receiving an opioid for some time.[5] Patients should be educated that this trial will attempt to optimize pain relief and manage side effects, while monitoring both effectiveness and drug-related behaviors. The decision to proceed with long-term treatment is taken only if supported by positive outcomes and responsible drug use.

Irrespective of a patient's medical condition, the decision to offer a trial of long-term opioid therapy may be informed by consideration of several key questions:

1. Does the patient have a serious illness that would be viewed conventionally as shifting the risk-to-benefit calculus and justifying early use of opioid therapy? If so, can opioid therapy be combined with disease-modifying therapy or other analgesic strategies to enhance outcomes?
2. If the patient does not have a serious illness, have other analgesic therapies been adequately considered? More specifically, are there other interventions for pain that have a presumed therapeutic index that is likely to be as good as or better than that for opioid therapy?
3. Is the persistent pain severe enough and sufficiently consequential for the patient's well-being that the potential benefits of opioid therapy might outweigh the potential risks? Considering these potential risks,
   a. Have medical conditions that may increase the risk of side effects or serious adverse effects such as respiratory depression, delirium, and falls been adequately considered?
   b. Has the risk of drug abuse outcomes—including poor adherence, frank abuse, addiction, diversion, or unintentional overdose—been adequately considered?

Based on the information acquired to answer these questions, a clinician may decide that a trial of long-term opioid therapy is or is not justified. Alternatively, the assessment may reveal a degree of complexity that warrants referral to a specialist in pain medicine or palliative medicine.

Principles of Opioid Pharmacotherapy

Safe and effective opioid therapy requires ongoing consideration of two sets of practices. The first relates to decisions that increase the likelihood of a favorable balance between analgesia and side effects. The second relates to the assessment and management of the risks associated with abuse, addiction, unintentional overdose, and diversion.

Optimizing the Balance between Analgesia and Side Effects

Opioid Selection

Opioids can be classified as pure mu receptor agonists, agonist-antagonists (which include partial agonists at the mu receptor and mixed agonist-antagonists, which are antagonists at the mu receptor and agonists at the kappa receptor), and pure antagonists (**Table 6.1**). Tramadol and tapentadol are mixed-mechanism drugs but also may be characterized as opioids because a substantial component of their action is due to opioid receptor agonism.

In the United States, clinicians may choose among a large number of opioid drugs for the treatment of acute or chronic pain. The drugs used most commonly are the pure agonists and the mixed-mechanism agents (**Table 6.2**). A short-acting oral opioid, which may be combined with a non-opioid drug, is the conventional approach to the treatment of acute pain in the ambulatory setting. These drugs include hydrocodone, codeine, dihydrocodeine, oxycodone, tramadol, and tapentadol. Other short-acting pure agonists, such as morphine and hydromorphone,

Table 6.1 Classification of opioid analgesics for pain management in the United States

Pure agonists	Codeine Morphine Fentanyl Hydrocodone Hydromorphone Levorphanol Meperidine Methadone Oxycodone Oxymorphone	• No clinically relevant ceiling effect to analgesia; as dose is raised, analgesic is achieved or dose-limiting side effects supervene • Most commonly used for moderate-to-severe pain
Agonist-antagonists	*Mixed agonist-antagonists* Butorphanol Pentazocine Nalbuphine *Partial agonists* Buprenorphine	• Ceiling effect for analgesia • Some produce psychotomimetic side effects more readily than do pure agonists • Potential to induce acute abstinence in patients with physical dependency to agonist opioids
Pure antagonists	Methylnaltrexone Naloxone Naltrexone Alvimopan	• Administered for prevention or reversal of opioid effects

also can be used, as can short-acting mixed agonist-antagonist drugs, such as oral pentazocine or intranasal butorphanol.

Although satisfactory analgesia can be attained with any of these drugs, several are less preferable because of the potential for variation in response or side effects. Meperidine has an active metabolite, normeperidine, which may produce dysphoria, tremulousness, hyperreflexia, and seizures. This risk is elevated when the drug is administered orally, patients have renal insufficiency, or treatment continues for more than a few days.

Codeine is a prodrug that produces its effects following conversion to morphine by the hepatic enzyme CYP2D6. Genetic variability in the efficiency of this enzyme can lead to unanticipated effects. Five to 10% of patients are poor metabolizers, who produce relatively less morphine and may not respond to codeine as a result, and as many as 20% of some populations may be rapid metabolizers, who could experience a greater than expected response to standard doses of codeine.[6] Given this unpredictable variation, an opioid other than codeine should be considered.

The agonist-antagonist drugs have a ceiling effect for analgesia and respiratory depression, less abuse liability, and the capacity to induce withdrawal if administered to a patient who is already physically dependent on a pure mu agonist. Some of these drugs, such as butorphanol and pentazocine, also have a side effect profile that includes a relatively high risk of psychotomimetic effects. Clinicians can find these drugs to be useful in some contexts, but knowledge of these characteristics is necessary to ensure that they are administered and monitored appropriately.

The decision to undertake long-term opioid therapy usually is followed by a switch to a drug with a long duration of effect. The opioids conventionally used in the United States include modified-release oral formulations of morphine, hydromorphone, oxycodone, and oxymorphone; transdermal fentanyl; and the long-half-life drugs levorphanol and methadone. Buprenorphine, a partial agonist available in transdermal and transmucosal formulations, is another option.

Although morphine is the most commonly used drug for severe pain on a global level, there is substantial individual variation in the response to different opioids. A patient may experience markedly different side effects when changed from one opioid to another. This observation is the basis for so-called opioid rotation, the practice of switching opioids when side effects interfere with effective therapy.[7]

Notwithstanding such marked individual variation, there are drug-specific characteristics that may influence the decision to try one or another of the pure mu agonist opioids. Morphine, for example, has active glucuronidated metabolites that may affect outcomes in some patients. Morphine 6-glucuronide (M-6-G) binds to the mu receptor and presumably contributes to both the analgesia and side effects observed during morphine therapy; morphine 3-glucuronide (M-3-G), which is produced at higher concentrations than M-6-G and is not an opioid, may cause toxicity, such as myoclonus and agitation. Because these metabolites accumulate in patients with renal insufficiency, patients with kidney disease should be given morphine cautiously; if renal function is unstable, an opioid without active metabolites, such as fentanyl, is probably safer.[8]

Fentanyl is available in a transdermal formulation, indicated for chronic pain, and transmucosal formulations, indicated for cancer-related breakthrough pain. Transdermal fentanyl may be preferred when pill burden is high; a dosing frequency of 2 or 3 days would be beneficial; or gastrointestinal symptoms, including constipation, suggest that a nonoral formulation may be beneficial.[9]

Buprenorphine is commercially available in a low-dose transdermal patch, indicated for pain, and relatively high-dose intraoral transmucosal tablets or films, indicated for the office-based treatment of addiction. Given the latter use, some pain specialists consider buprenorphine to be potentially useful when the patient has a past or current history of drug abuse. This potential advantage has yet to be established empirically, however.[10] The transdermal buprenorphine patch available in the United States has a 7-day duration of effect and can be used to initiate opioid therapy in any patient with very limited or no opioid exposure. The sublingual formulations may be used off-label for the treatment of chronic pain but require specific knowledge of the formulation and dosing strategy.[11] In addition to the potential for withdrawal if administered to patients who are already physically dependent, a characteristic shared with other agonist-antagonist drugs, buprenorphine has a very high affinity for the opioid receptor and is difficult to reverse with naloxone.

The use of methadone for pain increased substantially during the past two decades, driven by low cost, high efficacy in some clinical situations, and perceived value in reducing the risk of abuse in patients predisposed to addiction. Unfortunately, this change became associated with a high rate of serious adverse events, including mortality. Although the drug is still considered a valued part of the analgesic pharmacopeia, it should be administered only by clinicians who understand its pharmacology and strategies to ensure safety.

Among opioids, methadone's pharmacologic profile is unique in several respects. First, the half-life is long and variable, averaging about 24 hours but ranging from less than 15 hours to more than 150 hours. Although the time to approach steady state after initiating or increasing the dose is 5 days or less in most patients, it can extend to a few weeks in some patients. This uncertainty necessitates a long period of monitoring following each dose adjustment to avoid unanticipated delayed toxicity. Second, methadone potency can be much higher than expected when the drug is administered to a patient already receiving a pure mu agonist opioid.[12] This unanticipated potency presumably is related to the d-isomer (50% of the racemic mixture in the United States), which blocks the N-methyl-d-aspartate (NMDA) receptor and may thereby augment analgesic effects and partially reverse opioid tolerance. Because of the potential for increased potency, a switch to methadone from another opioid is most safely accomplished by reducing the calculated equianalgesic dose by 75 to 90%.[12] Third, methadone can prolong the QTc interval, presumably placing some patients at risk for a life-threatening cardiac arrhythmia, torsades de pointe. Although the risk of critical prolongation (above 500 ms) appears to be very low, it is reasonable to obtain a baseline electrocardiogram (ECG) in patients who may be predisposed to a prolonged QT interval and repeat ECG monitoring at a dose of 100 mg per day and periodically thereafter.[13,14] Finally, the metabolism of methadone is complex, involving both CYP2D6 and CYP3A4, and predisposes the patient to drug-drug interactions as a result.

Approach to Dosing

Guidelines for optimizing the therapeutic index of opioid drugs have been developed from extensive clinical experience and the known pharmacology of these agents.[15,16] The management of most opioid-naïve patients with acute pain is straightforward, and benefit is typically obtained within the narrow dose range defined for the commercially available formulations. The starting dose of these formulations usually is roughly equivalent to 5 to 15 mg of oral morphine every 3 to 4 hours. "As-needed" dosing is sufficient, and titration of the dose for unrelieved pain can be accomplished by more frequent administration or escalation of the dose by an increment of 30 to 50%.

When patients are already receiving opioid therapy, the starting dose of another opioid drug is determined based on the table of equianalgesic doses (**Table 6.2**). The information in the equianalgesic dose table originates from a large number of relative potency studies that were conducted in selected populations under conditions that may be quite removed from those encountered in practice. Accordingly, the equianalgesic ratios must be adapted for safe use by applying simple consensus-based guidelines for opioid rotation.[7,17] These guidelines in the accompanying box incorporate standard reductions in the equianalgesic doses and clinical judgment.

Patients with persistent or frequently recurring pain usually are considered for fixed scheduled ("around-the-clock") dosing on the assumption that this approach is better for preventing pain and encouraging adherence. There is no evidence that the use of long-acting drugs is better than the use of short-acting drugs, however,[5] and some patients with chronic pain prefer as-needed dosing. Fixed schedule administration is usually accomplished with one of the long-acting opioids because of convenience and the likelihood that treatment adherence will be better than that obtained with frequent daily doses.

Table 6.2 Opioid drugs available in the United States

Drug	Equianalgesic (mg) doses	Half-life (hours)	Duration (hours)	Comments
Morphine	10 IV/SC/IM 20 to 30 orally	2 to 3 2 to 3	3 to 4 3 to 6	Standard for comparison; multiple routes available
Controlled-release morphine (MS Contin, Oramorph SR)	◊		8 to 12	
Sustained-release morphine (Kadian, Avinza)	◊		12 to 24	
Hydromorphone	1.5 IV/SC/IM 7.5 orally	2 to 3 2 to 3	3 to 4 3 to 6	Solubility may be beneficial for patients requiring high opioid doses and for subcutaneous administration; multiple routes available
Extended-release hydromorphone (Exalgo)	◊		24	
Codeine	200 orally	2 to 4	4 to 6	May not be preferred because of genetic variation in conversion to active metabolite, morphine
Oxycodone	15 to 20 orally	2 to 3	3 to 6	Available as a single entity or combined with aspirin or acetaminophen
Controlled-release oxycodone (Oxycontin)	◊		8 to 12	
Hydrocodone	30 orally	3 to 4	4 to 8	Only available in combination with acetaminophen
Oxymorphone	1 IV/SC/IM 10 PR 15 orally	7 to 9	3 to 6 4 to 6	
Extended-release oxymorphone (Opana ER)	◊		12	
Levorphanol	2 IV/SC 4 orally	11 to 16 11 to 16	4 to 8 4 to 8	Accumulation possible after beginning or increasing dose
Methadone	10 IV/SC/IM 20 orally	12 to 150	3 to 4 initially; may increase with repeated dosing	Available as a racemic mixture and effects due to both isomers; d-isomer is a NMDA antagonist; may reverse tolerance and augment analgesia, and may account for unanticipated high potency; potency increases if administered after another mu agonist drug, in a dose-dependent fashion May prolong the QTc and be subject to drug-drug interactions involving CYP3A4 Due to highly variable and prolonged half-life and all the above factors, methadone has the highest risk of overdose among opioids, particularly when it is initiated and doses are increased
Fentanyl IV/SQ	100 µg IV/SC (single dose)	7 to 12	0.5 to 1, but increases with repeated dosing	Can be administered as a continuous IV or SC infusion
Fentanyl transdermal (TD) system	See package insert	17 after removal	48 to 72 per patch Up to 12 after removal	Not usually recommended for opioid-naïve patients Not recommended for acute pain Absorption from patch increased with external heat or fever Onset of effect: 12 to 24 hours

Drug	Equianalgesic (mg) doses	Half-life (hours)	Duration (hours)	Comments
Oral transmucosal fentanyl citrate lozenge (ACTIQ)	–	7.6	2 (200 µg) 3.25 (800 µg)	For breakthrough pain; usually start with lowest (200 µg) or next to lowest dose
Fentanyl citrate sublingual tablet (Abstral)	–	11.5 to 25	1	For breakthrough pain; usually start with lowest (100 µg) or next to lowest dose
Fentanyl sublingual spray (Subsys)	–	5 to 12	≥ 1	
Fentanyl buccal tablet (Fentora)	–	13.3	1 to 2	
Fentanyl nasal spray (Lazanda)	–	15 to 25	≥ 1	
Fentanyl buccal soluble film (Onsolis)	–	19	≥ 1	For breakthrough pain; usually start with lowest (200 µg) or next to lowest dose
Buprenorphine injection (Buprenex)	0.3 to 0.4 IV	2 to 3	6	Partial agonist Risk of withdrawal in physically dependent patients Potential drug-drug interactions related to CYP3A4 Difficult to reverse with naloxone due to high receptor affinity
Buprenorphine transdermal patch (Butrans)	5 or 10 µg per hour patch	26 upon removal	7 days per patch	Slow onset with initial patch application requires tapering of previous opioid Prolonged duration of effect following patch removal Absorption from patch increased with external heat or fever
Tapentadol (Nucynta, Nucynta ER)	75 orally	~ 4 to 5	~ 3 to 6 immediate-release; 12 extended-release	Mixed mu opioid agonist and norepinephrine reuptake inhibitor Extended-release formulation for chronic pain Maximum dose usually 500 mg daily Risk of interaction with other serotoninergic drugs
Tramadol (Ultram, Ultram ER, ConZip, Rybix ODT, others)	–	~ 6 to 9	~ 4 to 6 immediate-release; 24 extended-release	Mixed weak mu opioid agonist and reuptake inhibitor of norepinephrine and serotonin Extended-release formulation for chronic pain Maximum dose usually 300 mg daily Risk of drug interactions with other serotoninergic drugs and inhibitors or inducers of CYP3A4 and/or 2D6 Not recommended for patients with severe renal insufficiency or seizures

A key guideline during opioid therapy is to individualize the dose by a process of titration, which safely increments the dose to identify a level associated with a favorable balance between analgesia and intolerable and unmanageable side effects. This process typically is simple during the treatment of acute pain because the range of tolerable doses is narrow and most patients demonstrate an analgesic response. After an opioid has been taken for some time, however, the effective dose during episodes of retitration becomes unpredictable. Inadequate adjustment of the dose is probably the most common reason for unsuccessful long-term therapy. There is no ceiling dose for the pure mu agonist opioids (in contrast to the agonist-antagonist classes and the mixed-mechanism drugs), and as a general rule, the dose should be increased until acceptable analgesia is produced or intolerable and unmanageable side effects supervene. If a favorable balance between analgesia and side effects is obtained, this is usually

maintained for a prolonged time. Recurrent pain or the new occurrence of side effects may suggest the need for another period of dose titration.

In populations with advanced illness, the absolute dose of the opioid usually is viewed as immaterial as long as there is a favorable balance between analgesia and side effects. This perspective is justifiably tempered, however, when treatment involves populations with so-called chronic noncancer pain. In the context of increasing recognition of the potential for serious opioid-related adverse consequences in these populations, clinicians should undertake a critical reassessment of therapy if persistent pain results in dose titration above some arbitrary limit, say a dose equivalent to 150 to 200 mg of oral morphine. This assessment should aim to determine whether the patient is experiencing toxicity or functional decline, or nonadherence to treatment—outcomes that would justify discontinuation of opioid therapy rather than further dose escalation.

Ideally, the interval between dose escalations should be long enough to allow a steady state to be approached (i.e., 2–3 days for modified-release products, 3–6 days for the transdermal patch, and 5–6 days for methadone—but sometimes longer). The intensity for monitoring of side effects and adherence is informed by whether the drug is believed to be at steady state, as well as by both medical and psychosocial considerations.

Strategies to Address Poor Opioid Responsiveness

- Enhanced side effect management to "open the therapeutic window"
- Opioid rotation to identify a drug with a better therapeutic index
- Pharmacologic approach to reduce the opioid requirement
  - Add a systemic analgesic therapy (a nonopioid or adjuvant analgesic)
  - Try neuraxial analgesia
- Nonpharmacologic approach to reduce the opioid requirement
  - Interventional
  - Neurostimulatory
  - Psychological

Guidelines for Opioid Rotation

Step 1

- Select the new drug based on prior experience, availability, cost, and other factors.
- Calculate the equianalgesic dose from the equianalgesic dose table.
- If switching to any opioid other than methadone or fentanyl, identify an "automatic dose reduction window" of 25 to 50% less than the calculated equianalgesic dose.
- If switching to methadone, the "automatic dose reduction window" is 75 to 90%; conversion to methadone rarely at a dose higher than 40 mg per day.
- If switching to transdermal fentanyl, do not do an automatic dose reduction; use the calculated equianalgesic dose included in the package insert.
- Select a dose closer to the lower bound (25% reduction) or the upper bound (50% reduction) of the "automatic dose reduction window" on the basis of a judgment that the equianalgesic dose table is relatively more or less applicable to the characteristics of the regimen or patient.
- Select a dose closer to the upper bound if the patient is receiving a relatively high dose of the current opioid, is not Caucasian, or is older or medically frail.
- Select a dose closer to the lower bound otherwise, and particularly if the patient is being switched to a different route using the same drug.

Step 2

- Based on assessment of pain severity and other medical or psychosocial characteristics, increase or decrease the calculated dose by 15 to 30% to enhance the likelihood that the initial dose will be effective or, conversely, unlikely to cause withdrawal or side effects.
- Assess response and titrate the dose of the new opioid regimen to optimize outcomes.
- If a supplemental as-needed dose is used, calculate this at 5 to 15% of the total daily opioid dose and administer at an appropriate interval; transmucosal fentanyl formulations are exceptions and always should be initiated at one of the lower doses.

Breakthrough Pain

Breakthrough pain, which is defined as a severe transitory pain that complicates controlled baseline pain during long-term opioid therapy, is prevalent in all opioid-treated populations. The use of an as-needed supplemental dose of a short-acting opioid formulation—known as a "rescue dose"—is widely considered to be a best practice when treating patients with active cancer or another serious illness.[18] In contrast, the use of a rescue dose in populations with so-called chronic noncancer pain should not be considered a standard of care, but rather a separate treatment that must be evaluated in terms of its risks and benefits. This distinction is justified again by concerns about toxicity and adherence in the heterogeneous populations with so-called noncancer pain.

The conventional approach to the treatment of breakthrough pain involves the use of a short-acting oral formulation of an opioid drug. This can be the

same drug as that administered on an around-the-clock basis or an alternative drug. The dose typically is selected to be equivalent to 5 to 15% of the total daily opioid dose[19] and is prescribed every 2 hours "as needed." Alternatively, breakthrough pain can be treated with one of the so-called transmucosal immediate-release fentanyl (TIRF) formulations. These products now include lozenge, buccal tablet, buccal patch, sublingual tablet, and nasal spray formulations.[20–24] They have a faster onset of effect than oral formulations, which may be a highly favorable characteristic for some patients. They are more expensive than oral drugs, however, and there is concern about risk. The U.S. Food and Drug Administration (FDA) recently issued a class-wide Risk Evaluation and Mitigation Strategy (REMS) for the TIRF drugs, which includes mandatory prescriber education, registration of patients, and education of patients in safe use of the drug. Further research and experience will be needed to clarify the role of these rapid-onset formulations in the treatment of cancer-related breakthrough pain.

Opioid Responsiveness and Side-Effect Management

If treatment-limiting side effects occur during dose escalation, the patient should be considered poorly responsive to the specific drug. Improving the management of side effects is one of several strategies to address this scenario (**Table 6.3**).

Gastrointestinal side effects, usually constipation, and neurocognitive effects, including somnolence and mental clouding, are highly prevalent and are commonly targeted for treatment (**Table 6.4**). Other side effects are less common but well recognized, including dry mouth, itch, urinary retention, and myoclonus.

Neuroendocrine effects are highly prevalent but less recognized. Opioids affect the hypothalamic-pituitary-adrenal axis and cause hyperprolactinemia, hypogonadism, or both.[25] These changes may cause sexual dysfunction, infertility, fatigue, accelerated bone loss, and mood disturbance in both sexes; in women, menstrual disturbances are frequent. Although there are very few studies of these outcomes, specialists often recommend testosterone therapy in hypogonadal men. Estrogen therapy in symptomatic premenopausal women also can be considered.

Opioid therapy also is associated with a syndrome of sleep-disordered breathing, which may represent exacerbation of premorbid obstructive sleep apnea or the development of a form of central sleep apnea.[26] Patients with known sleep apnea without effective therapy, those with risk factors for obstructive sleep apnea (such as obesity), and those who develop symptoms suggestive of a sleep disorder after opioid therapy is initiated should be given an opioid with caution and considered for polysomnographic evaluation.

Opioid-induced hyperalgesia sometimes is considered a side effect of opioid therapy. This phenomenon, which is well characterized in animal models, has been invoked to explain the anecdotal occurrence of escalating pain in the absence of worsening pathology during opioid therapy.[27] Little is known about its clinical presentation or relevance, or the extent to which it can be distinguished from other causes of escalating pain.[28] Based on clinical observation, it is reasonable to consider the possibility of opioid-induced hyperalgesia when pain worsens in the absence of clearly progressive pathology during aggressive opioid titration, and particularly when tremulousness, confusion, or skin sensitivity occurs simultaneously.

Risk Assessment and Management

Nonadherence, drug abuse, addiction, unintentional overdose, and diversion of drugs into the illicit marketplace are known risks of opioids and other controlled prescription drugs. To appropriately select

Table 6.3 Commonly used pharmacologic approaches in the management of opioid side effects

Opioid side effect	Treatment
Constipation	• Contact laxative plus stool softener (e.g., senna plus docusate) • Osmotic laxative (e.g., milk of magnesia, lactulose, or polyethylene glycol) • Prokinetic agent (metoclopramide) • Methylnaltrexone or oral naloxone
Nausea	• If associated with vertiginous feelings, antihistamine (e.g., scopolamine, meclizine) • If associated with early satiety, prokinetic agent (e.g., metoclopramide) • In other cases, dopamine antagonist drugs (e.g., prochlorperazine, chlorpromazine, haloperidol, metoclopramide)
Somnolence or cognitive impairment	• If analgesia is satisfactory, reduce opioid dose by 25–50% • If analgesia is satisfactory and the medical and psychiatric assessment suggests a favorable risk-to-benefit ratio, consider a trial of a psychostimulant (e.g., methylphenidate or modafinil)

Table 6.4 Principles of risk management during opioid therapy for pain

Principle	Goals	Strategies	Comment
Stratify risk	To clarify the likelihood of future aberrant drug-related behavior	Consider higher risk if: – History of alcohol or drug abuse – Family history of alcohol or drug abuse – Major psychiatric disorder Other factors suggesting risk: – Current heavy smoking – Younger age – History of automobile accidents, chronic unemployment, limited support system Factors that may lessen risk: – Poor performance status – Limited prognosis – Active recovery program – Strong social/family support	– All patients should undergo risk assessment and stratification – Although many questionnaires have been developed to predict aberrant behavior or addiction, the clinical assessment is generally used in practice
Structure therapy commensurate with risk	Practices to match adherence monitoring with level of risk, and when needed, help patients maintain control	Strategies include: – Use of urine drug screening – Small amounts prescribed – No use of short-acting drugs – Use of single pharmacy – Pill count at time of visit – Required consultations	The decision to implement one or more of these strategies is a matter of clinical judgment
Assess drug-related behaviors over time	Track drug use in tandem with all relevant outcomes	Monitor: – Drug-related behavior (need for early refills, obtaining multiple prescriptions, etc.) – Pain relief – Adverse drug effects – Effect of drug on other outcomes	Documentation of these outcomes over time is important
Respond to aberrant drug-related behaviors	Clinician compliance with laws and regulations Identifying patient needing additional management	If the patient engages in aberrant drug-related behavior: – Reassess and diagnose (addiction, other psychiatric disorder, "pseudoaddiction," family issues, criminal intent) – If diversion into the illicit marketplace is discovered, stop prescribing – Otherwise, restructure therapy to improve control and obtain consultative help as needed	With the exception of suspected diversion, which requires cessation of therapy, decisions about other types of problems are clinical
Document and communicate	Risk assessment and management should be viewed as integral to safe and effective prescribing	Document: – Plan for monitoring and education of patient and family – Monitoring of drug-related behavior on a regular basis – Response should aberrant behavior occur	It is also valuable to openly discuss the need for universal risk management with other clinicians to reduce the risk of stigmatizing patients

patients for an opioid trial, and to manage therapy safely, clinicians must have a working knowledge of these outcomes. The rise in prescription drug abuse that has occurred in the United States during the past decade underscores the need for basic skills in risk assessment and management, and has led the FDA to implement a voluntary REMS program for extended-release opioids.

All prescribing of opioids to outpatients should be preceded by risk assessment. Risks are less when therapy is relatively brief, but this does not negate the need to evaluate the potential for abuse or diversion. During long-term therapy, there is a clear imperative to assess risk and monitor drug-related behaviors over time.

Risk assessment requires understanding of the phenomena that are associated with a risk of drug abuse, addiction, or diversion. For example, the term *drug abuse* refers to the use of a drug in a manner that deviates from medical, legal, and social standards. Some clinicians label less egregious nonadherence behaviors as *misuse*. *Addiction* is a disease with a strong genetic component that is defined by craving, loss of control, compulsive use, and continued use despite harm. The biologic propensity for addiction, which affects a small minority of the population, is suggested by a family history of alcohol or drug abuse. Addiction is distinct from the physiologic phenomena of physical dependence (defined solely by the occurrence of withdrawal symptoms after abrupt dose reduction or the administration of an antagonist) and tolerance (defined by the drug-induced loss of effect over time). Finally, *diversion* is a legal concept, referring to the distribution of a drug into the illicit marketplace.

Physicians are required to stop prescribing when there is a strong likelihood that diversion of prescribed drugs is occurring. Other forms of nonadherence can be managed from within a medical context, based on the evaluation of current risk and benefit. This medical decision making is subject to review under medical practice regulations, as well as drug laws, and clinicians must take care to prescribe within conventionally accepted standards and obtain appropriate consultation with a specialist in addiction medicine, pain medicine, or palliative care when a drug-related problem exceeds the ability of the prescriber to manage it.

The approach to risk management appropriate to long-term opioid therapy is usefully characterized as a type of "universal precaution." The principles include risk stratification, structuring therapy to reduce the risk, monitoring patients for aberrant drug-related behaviors, and addressing these behaviors appropriately if they occur (**Table 6.4**).[29,30] Although risk stratification could be done using any of several questionnaires, a simple clinical assessment can suffice: Is there a personal history of alcohol or drug abuse? Is there a family history of alcohol or drug abuse? Is there a history of major psychiatric pathology? This history may be complemented by other factors, such as younger age, smoking history, social isolation or involvement with a drug abuse subculture, a history of multiple automobile accidents, or the inability to maintain employment.

Based on the risk stratification, a clinician can decide to treat with an opioid, to treat with the help of a consultant, or to consider no treatment. If a trial of opioid treatment proceeds, the structuring of therapy should be commensurate with the assessed risk. Any or all of a variety of strategies may be implemented for patients at relatively higher risk, including biofluid (urine or saliva) drug screening, the use of a written agreement, frequent visits with small prescriptions, denial of short-acting medications, restriction to a single pharmacy, pill counts, and other measures. The goal of these strategies is to enhance adherence monitoring and help the patient maintain control over drug use.

During long-term therapy, periodic assessment for four main types of outcomes is essential. These outcomes include pain relief, opioid-related side effects, physical and psychosocial functioning, and the occurrence of any aberrant drug-related behaviors.[30] If any worrisome behaviors occur, reassessment is needed. Problematic behaviors have many potential causes. Based on the assessment, the clinician may decide to discontinue treatment or continue it with a change in instructions or monitoring. A consultation may be useful at this time, and irrespective of outcome, documentation is essential.

Conclusion

Oral or transdermal opioid therapy for pain is a common analgesic strategy and has the potential for highly favorable outcomes if proper patient selection is followed by careful drug administration and monitoring of effects over time. Opioids have high analgesic potential, but also many troubling side effects and the inherent capacity to be abused by a subset of patients. Safe and effective opioid use is possible if clinicians acquire basic skills and approach the therapy with the caution and attention it deserves.

Editor's Comments

Dr. Portenoy is one of the world's experts on opioid analgesics. This chapter can serve as the definitive reference for surgeons on the use of these drugs. He also has given us an outline of *when* to use these agents for chronic noncancer pain—perhaps the biggest challenge to the practice of pain medicine and pain surgery. His requirements are rigorous, and he has asked us to consider our patients very carefully before subjecting them to the risks of long-term opiate use.

I will take the liberty of truncating his points for consideration prior to placing a patient on chronic opioid therapy:

1. Does the patient have a serious illness?
2. Have other analgesic therapies been adequately considered?
3. Do the potential benefits of opioid therapy outweigh the potential risks?
4. Have the risks of drug abuse outcomes been adequately considered?
   - Serious nonadherence to therapy
   - Frank abuse
   - Addiction
   - Overdose
   - Diversion

In my opinion, if all patients with chronic noncancer pain were carefully considered in this fashion, far fewer would be placed on opiates, and we would see far fewer patients in whom that therapy has become a separate problem, sometimes the dominant problem.

These questions are difficult and are often fraught with the conflict between what the patient wants, and claims to need, and what is in his or her best interest in the long term. In my experience, most patients who have been placed on opiates for chronic pain continue on this therapy as long as their prescribing practitioner will continue to support it. When you combine this natural history with physiologic tolerance, both the patient and the caregiver have a problem.

So how do we decide when pain is due to a "serious illness"? Most of the patients with pain we see in practice do not have cancer. The question then is, what constitutes "serious illness"? Perhaps in this context, we should replace the subjective term *serious* with *life threatening*. If this were the litmus test for chronic opioid use, then the use, and misuse, of opiate analgesics would be dramatically reduced.

There is no ultimate answer to the question of opioid use in the patient with chronic noncancer pain. As noted by Drs. Portenoy and Ahmed, even the language of "expert panels" becomes opaque when guidelines are generated. Terms like *cautious*, *tempered*, and *subpopulations of patients* are used with "patient selection based on a careful and ongoing assessment of benefits and burdens."

Current guidelines on the use of opiate analgesics in patients with chronic pain have produced an era where chronic opioid use can be considered a separate problem in many patients, and in which the drug abuse outcomes listed above are commonplace. I believe we are now at a tipping point, similar to that seen around the mid-1970s. For the ultimate benefit of our patients, I believe that opioid analgesics will be used less freely in the future, and that their use will be restricted largely to cancer pain and other life-threatening illnesses.

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7 Management of Pain by Anesthetic Techniques

Elliot Palmer, Phillip Weidner, Grace Chen, and Brett R. Stacey

The specialty of pain medicine encompasses multidisciplinary care. This includes anesthetic techniques to diagnose and ameliorate pain, specialized rehabilitation to expand functional capacity, and psychological counseling to help patients cope with pain and improve overall quality of life, in spite of pain. This chapter focuses on procedural management techniques including axial and peripheral nerve blocks and other percutaneous techniques. Such procedures have many different purposes: diagnosis of the source of the pain, planning surgical intervention, facilitation of rehabilitation, treatment of acute conditions, and treatment of cancer-related pain. There are many retrospective cohort studies and anecdotal recounts of effective injections that support the long-standing tradition of injection procedures. However, the number of randomized-placebo controlled studies has been limited. In this chapter, we review commonly performed injection techniques and the literature supporting them.

General Standards for Periprocedural Care

As with any invasive procedure, performance of anesthetic interventions in chronic pain management includes nominal risks of bleeding, infection, and allergic reaction. Each procedure also carries its own potential complications. There are recent case reports of fungal infections associated with contaminated methylprednisolone epidural injections as well as more dated reports of spinal anesthesia following facet joint injection.[1,2] Patients should be informed of these risks and potential complications, and consent should be obtained.

Bleeding diatheses, systemic infection, and localized infection in the region of the procedure are considered absolute contraindications because of the potentially devastating consequences of bleeding or infection proximal to the spinal cord. A history of allergic reaction to radiographic contrast is only a relative contraindication because it usually can be preempted by pretreatment with corticosteroids and H1 and H2 antagonists. Although patients occasionally report an allergy to a local anesthetic, true allergic reactions to local anesthetics are rare to the point of vanishing.

Basic precautions should be taken to reduce risks. If sedation is required, or the possibility for significant physiologic change is present, intravenous access should be obtained. For most procedures, it is appropriate for patients to take nothing by mouth before the procedure and to avoid driving home afterward. Fluoroscopy and ultrasound can be used to ensure accurate positioning of needles, as is discussed later in this chapter. Finally, the International Spinal Injection Society (ISIS) has published standards for performance of some procedures involving spinal injection.[3] At our institution we follow similar guidelines, which include physiologic monitoring of the patient and observation of aseptic technique with sterile skin preparation, drapes, and gloves. Sterile gowns are worn for intrathecal line placement; implantable pumps and spinal cord stimulators are placed in the operating room.

In addition to these general safety principles, guidelines should be observed in using such interventions appropriately. Before initiating an invasive diagnostic or therapeutic regimen, the natural history of a patient's complaint must be considered. For example, acute-onset back pain without associated neurologic findings typically resolves within 8 weeks, independent of any interventions.[4] Because the discussed procedures do entail risks and can be difficult to interpret, ISIS recommends that any invasive diagnostic or potentially therapeutic interventions be avoided for at least 4 weeks from the onset of symptoms and 3 weeks after initiation of more conservative, noninvasive measures. A similar strategy is followed at our institution, although exceptions are made if the indications are strong and the severity of symptoms is likely to lead to prolonged inactivity and deactivation.

Imaging

Intraprocedural fluoroscopy, and more recently ultrasound, have become essential adjuncts for performing neural blockade techniques. Fluoroscopy and radiopaque contrast material help to improve the safety and accuracy of needle placement before regional anesthetic or neurolytic interventions are performed and to verify accurate neuroaxial catheter or spinal cord stimulator electrode placement. Ultrasound helps to visualize soft tissue densities, such as nerve plexus and tissue planes demarcated by fascia that fluoroscopy does not reveal.

The celiac plexus neurolytic block demonstrates the advantages of fluoroscopy compared with the blind needle technique, but also highlights a major deficiency of this approach. This block is commonly performed using a two-needle technique at the L1 level. The aorta lies anterior and slightly to the left of the anterior margin of the L1 vertebral body. The inferior vena cava lies to the right of midline, and the kidneys are posterolateral to the great vessels. The pancreas is anterior to the celiac plexus. The celiac plexus is anterior to the diaphragmatic crura and extends anterior to and around the aorta. With such crucial organs and vessels surrounding the celiac plexus, accurate placement of the two needles is essential. The left-sided needle is advanced until it lies just posterior to the aorta on the left, and the right-sided needle is advanced to the anterolateral aspect of the aorta on the right. Using fluoroscopy, a small volume of contrast material is injected through each needle, and its spread can be observed.

The use of fluoroscopy and contrast material should not be limited to anatomically complicated procedures only. Epidural steroid injections (ESIs) traditionally have been performed using a "blind" technique without fluoroscopic guidance. The blind technique introduces the potential for erroneous needle placement and subsequent injection of steroids into unintended areas, such as the intrathecal space, leading to possible adhesive arachnoiditis. White and coworkers[5,6] found that inaccurate needle placement occurred in only 25 to 30% of blind injections, even in the hands of skilled and experienced proceduralists. Injecting variable amounts of radiologic contrast material under fluoroscopic observation before therapeutic ESI potentially improves safety and efficacy. The risk of unintended intrathecal injection and its consequences can be virtually eliminated. Moreover, the traditional practice with the blind ESI technique to proceed with a second and third steroid injection as a routine series to assess efficacy becomes unnecessary.[7] Documenting the distribution of injected materials also may explain a patient's response if a unilateral or limited epidural block is encountered. Finally, even with negative needle aspiration, a significant number of injections following blind needle placement have been shown to be intravascular.[8] Intravascular needle placement is ascertained quickly by rapid uptake and disappearance of contrast material injected under fluoroscopy in continuous pulse mode. Needle placement can be corrected easily if this intravascular contrast pattern is visualized.

Peripheral Nerve Blocks

Local anesthetics interrupt nerve conduction by sodium channel blockade, thus decreasing transmission of sensory and motor information. Coupled with knowledge of innervation patterns and nervous system anatomy, techniques to deliver local anesthetics can be powerful tools for perioperative care for extremity and abdominal surgeries. To a lesser extent, this had been also used to treat chronic pain conditions or to facilitate rehabilitation. Transient pain relief persisting until the local anesthetic effect dissipates provides the basis for diagnostic blockades. The well-documented, frequently encountered, and not well understood phenomenon of prolonged pain relief after injection of local anesthetic is the basis for therapeutic injections. Prolonged pain relief may result from altered function in the affected area, altered central nervous system function, or some undescribed mechanism. Limited controlled studies, wide variations in technique, lack of standards, and inconsistent outcome assessment limit their acceptance in the era of "evidence-based medicine."

Peripheral nerves, such as the ilioinguinal nerve,[9] intercostals nerve, and lateral femoral cutanous nerve,[10] that can cause chronic conditions have been injected with short-term good results. Neurosurgery referral for neurectomy or neuromodulation is appropriate after the efficacy subsides.

Epidural Steroid Injection

One of the most common types of injections performed by interventional pain specialists are epidural steroid injections. The procedure has been used to diagnose radicular and referred pain from specific levels of the spine and to treat disk herniation radicular pain related to neuroforaminal stenosis, spinal stenosis, and postlaminectomy syndrome.[11] Injections typically consist of both local anesthetic and steroid, although they are occasionally done with only one or the other.

Principles

Inflammation has been proposed as playing a key role in symptomatic nerve root irritation associated with herniated intervertebral disks.[12] Extruded nucleus pulposis material contains proinflammatory substances and produces an inflammatory response in the epidural space and in the underlying nerve roots. Pain and other symptoms are likely produced by a combination of this inflammatory response, edema, and the mechanical pressure on nerve roots.[13] Additionally, degenerated, symptomatic areas of the spine demonstrate sensory nerve sprouting into the outer layer of abnormal intervertebral disks, vertebral endplates, and other structures, providing additional sources of spinal pain.[14]

Proinflammatory factors such as phospholipase A2 (PLA2) is released when the nucleus annulus is interrupted. This and other proinflammatory factors such as neuropeptide Y and VIP foster the inflammatory cascade and sensitize nerve endings that produce focal pain sensations in the disk and the surrounding nerve root.[15] The goal of epidural injection is to deliver anti-inflammatory and analgesic medication to the spinal level most affected. Most commonly, this source is the disk and nerve root at the symptomatic level. The classes of medications injected—local anesthetic and steroid—are generally agreed upon, yet there remains a fairly wide variety of solutions, volumes, and delivery techniques used in modern clinical practice.[16]

It is well known that local anesthetics interrupt nerve transmission and thus can be effective for the transient relief of pain. Additionally, perineural inflammation accompanies many painful conditions, providing a rationale for including corticosteroids in these therapeutic injections. The mechanism of glucocorticoid activity is not yet fully understood. One mechanism of action is the altering of endothelial adhesiveness toward resting polymorphonuclear leukocytes. Glucocorticoids inhibit the display of chemotactic molecules on the surface of the endothelial cells, preventing leukocyte aggregation and minimizing endothelial injury, which is usually caused by cellular transmigration.[17] Steroids have numerous anti-inflammatory and membrane-stabilizing properties that have been shown to decrease edema and sensitization as well as to provide pain relief when applied to the vicinity of painful nerves.

Epidural steroid injections are indicated primarily for the treatment of radicular extremity pain that has not responded to more conservative treatments. The goals of treatment include pain relief and ultimately improvement of functional capacity. The length of epidural steroid injection efficacy is variously reported, ranging from weeks to more than a year.[18] Even short-term relief may provide the additional benefit of allowing patients to participate in physical therapy that would otherwise be prohibited by pain.

Epidural steroid injections are also commonly performed for pain related to lumbar central stenosis. The evidence for injections alleviating pain related to foraminal stenosis is better than that for central stenosis.[19] Nevertheless, patients who are not appropriate surgical candidates may find this form of injection helpful, if not curative of the stenosis.[20] There is a paucity of randomized and controlled studies regarding the use of ESI to treat mechanical or muscular axial back pain.

The two basic approaches in widespread use are interlaminar and transforaminal injection techniques. The interlaminar blind approach to the epidural space is the one that most clinicians are familiar with and is frequently employed for both perioperative and labor analgesia. The landmarks are the spinous processes, which are often easily palpable and occasionally visible (**Fig. 7.1**). The only major differences in this technique when used for chronic pain states are the more widespread use of fluoroscopic guidance and the composition of the injectate. The interlaminar approach has the advantage of simplicity, delivering most of the injectate into the epidural space, but it has the disadvantage of delivering the medications into the center of the posterior epidural space rather than focusing the medication directly at the point of presumed pathology. The transforaminal approach, on the other hand, accesses the anterior epidural space at the level of the spinal nerve. Correct application of this technique requires the use of fluoroscopy because surface landmarks and tactile sensations are unreliable in ensuring appropriate final needle position. The primary landmarks for performing this injection in the lumbar area are the transverse process above the desired nerve root (best viewed on anteroposterior [AP] projection) (**Fig. 7.2**) and the superior aspect of the nerve root foramen (best seen on lateral projection). We are aware of two additional approaches to neural injection, catheter-driven lysis of adhesions and spinal endoscopy, although neither is in widespread use and both are beyond the scope of this discussion.

Outcomes

The question of efficacy is an extremely complicated and multifaceted one. There exist a staggering number of studies of varying design and quality examining a wide variety of techniques, time courses, and end points. The resulting pool of outcome data is not cohesive and spans a range from a lack of statistically significant short- or long-term pain relief or functional capacity, to impressive improvement in both—and including just about everything in between. For this reason, a complete and exhaustive review here

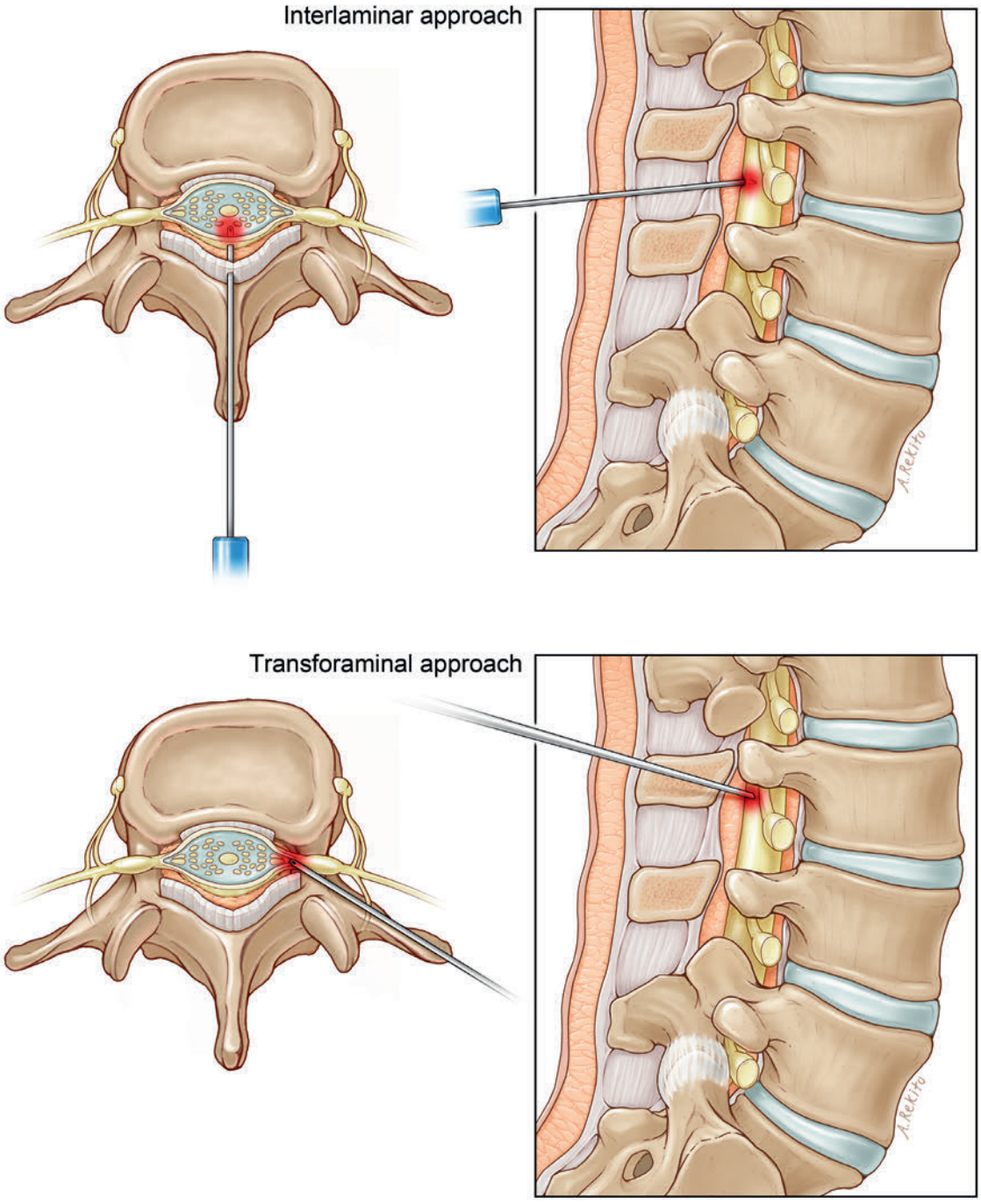

Fig. 7.1 Interlaminar epidural steroid injection. The needle is introduced percutaneously and traverses the supraspinatous ligament, the interspinatous ligament, and the ligamentum flavum.

is not practical. Instead, we have focused whenever possible on high-quality studies published in the decade prior to the release of this edition.

The best evidence behind ESI is in the treatment of radicular pain caused by a herniated intervertebral disk. Positive data from two relatively recent, prospective, randomized, placebo-controlled studies support the practice.[21,22] Much attention has also been given to the question of possible differences in the efficacy of the two aforementioned injection techniques. Whereas superiority of the transforaminal approach has long been suspected and has been suggested by retrospective studies,[23] this assertion was not confirmed by another high-quality prospective, randomized study.[24] Although that study did not demonstrate superiority outright, it did suggest

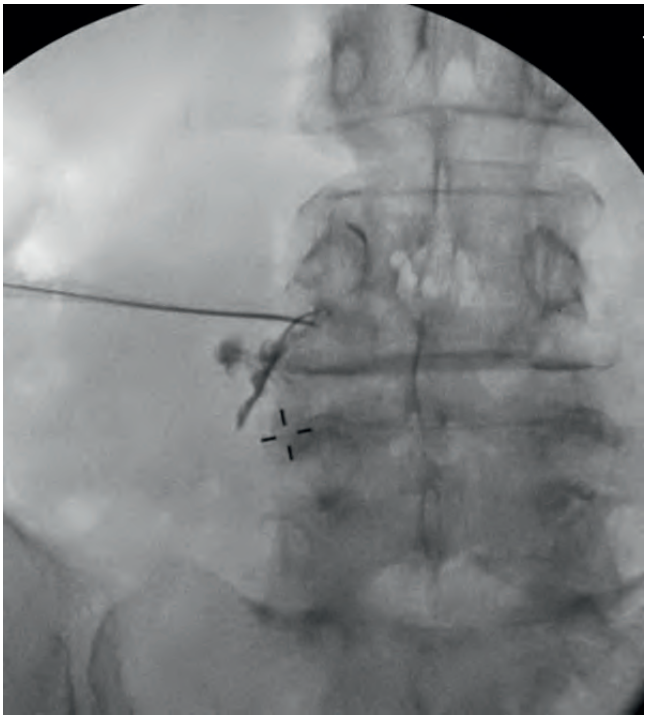

Fig. 7.2 This image shows a needle placed in the superior aspect of the right L5 neural foramen. Contrast dye is visible medial to the pedicle, indicating successful epidural spread.

that results were similar despite a significantly lower dose of medications when the transforaminal route is employed.

The literature supporting ESIs for the treatment of painful spinal stenosis is sparser and consists mainly of retrospective case control studies and reviews. The best of these do suggest at least short-term improvement for both interlaminar and transforaminal approaches.[25,26] Although no data are available at the time of this writing, a large-scale prospective randomized trial has been launched: the Lumbar Epidural Steroid Injection for Spinal Stenosis (LESS) study.

Facet Arthropathy and Radiofrequency Medial Branch Denervation

The lumbar and (later) the cervical, thoracic, and facet (or zygapophyseal) joints have been topics of considerable interest because they pertain to axial spinal pain and its minimally invasive treatment. In particular, the technique of reducing pain caused by facet joint arthropathy by selectively denervating the facet joints has gained much support because of an increasingly positive body of evidence in the medical literature.

The human spine has facet joints at each level between the C1–2 and L5–S1 joints, inclusive. These are actual synovial joints, and the capsule and synovium of each are extensively innervated with sensory fibers. These include mechanoreceptors[27] as well as fibers containing substance P[28] and numerous other neurotransmitters linked to nociception.[29] The innervation generally is accepted to be segmental and based primarily on the medial branch of the primary posterior ramus of each segmental spinal nerve; however, more recent research has indicated that there is also nonsegmental and autonomic innervation of the facet joint.[30] The lumbar facet joint has been recognized[31] as an important generator of axial spinal pain.

In addition to the facet joint capsule and its contents, the medial branch also innervates the multifidus muscle segmentally. This muscle is a significant source of pain in and of itself, and may account for some of the analgesia associated with lumbar medial branch blocks and denervations.[32] A multifidus electromyogram also may be used as an outcome determinant in studies of lumbar medial branch denervation resulting from the specific innervation.

Cervical, Thoracic, and Lumbar Medial Branch Denervation

In the late 1970s, Nikolai Bogduk and colleagues clarified the neuroanatomy of the facet joint. This, in combination with improvements in the technology available for radiofrequency neurodestructive procedures, led to increasing interest in the use of radiofrequency (RF) energy to produce lesions in the nervous supply of the facet joints. Although the definitive studies are in progress or in press at the time of this writing, initial work in the field indicates that this technique of treating axial lumbar pain is more frequently successful and less complicated than alternative means of treating pain mediated by lumbar facet arthropathy.

Radiofrequency Denervation

Various technical considerations led to the use of RF energy as the method of choice in the denervation of the medial branch (**Table 7.1**). Recent improvements in equipment include small-diameter (22 gauge) and curved probes to minimize tissue trauma and improve navigation **(Fig. 7.3)**. The lesion generator, also used for intracranial functional neurosurgery, allows for multiple settings, depending on the procedure.

Outcomes

Numerous studies have demonstrated prolonged effects of RF medial branch denervation. The procedure in the cervical region is the most thoroughly studied. In this area, 75% of the treatment group had at least 50% analgesia for a median duration of 263

Table 7.1 Lumbar medial branch denervation comparison

Characteristic	Precision of lesion size	Collateral damage due to denervation	Trauma of procedure	Ability to assess intravascular status	Ability to stimulate adjacent nerves
Type of neurotomy					
Radiofrequency	5	5	5	5	5
Cryotherapy	5	3	2	0	5
Surgical	0–5	1–3	3	5	0–5
Injection of lytic chemicals	2	1–3	5	5	0

Note: The rating scale is from 0 to 5: 0 = undesirable; 1 2 3 4 5 = desirable.

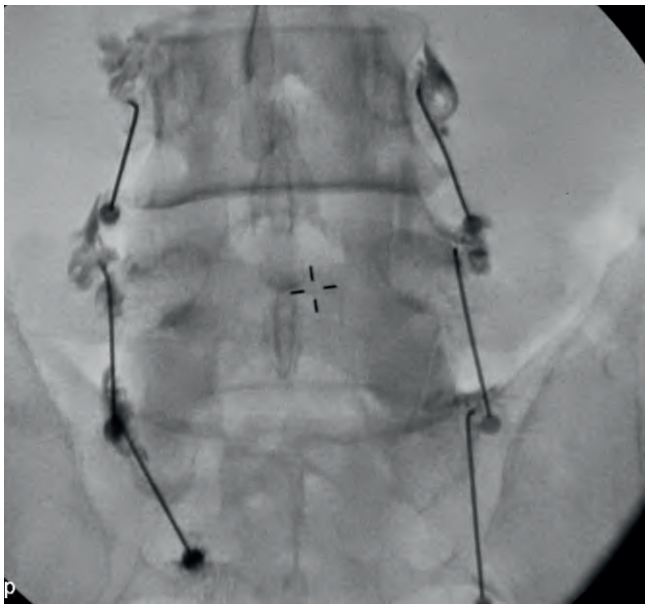

Fig. 7.3 Lumbar medial branch block under fluoroscopic guidance.

days.[33] A follow-up study of initial responders demonstrates a median analgesic duration of 422 days. In RF denervation, the neuronal contents are selectively coagulated, which interrupts neuronal function; however, the neuronal substrate remains.[34] This prevents neuroma formation but allows for regrowth of the nerve.

Thus far, the literature on this subject has studied medial branch denervation as monotherapy. There may be advantages to combining appropriate denervations with other multidisciplinary therapies, however, such as psychological and physical.

The Sympathetic Nervous System

The autonomic nervous system is composed of the sympathetic and parasympathetic nerve fibers, which work in concert to regulate the body's homeostatic functions. The sympathetic system is generally attributed with vasoconstriction, increasing heart rate, decreasing intestinal motility, and piloerection, but it also maintains a significant role in the perception of pain and visceral sensations through C fibers. These are unmyelinated nerves whose cell bodies are in the dorsal root ganglia and enter the spinal cord via the dorsal horn. Sympathetically maintained pain is typically characterized by burning or aching and is the focus of diagnostic and therapeutic techniques that can interrupt the sympathetic afferents. Conversely, interruption of the sympathetic efferents will lead to vasodilation in the area of the block and can be employed for any condition that is maintained through vasoconstriction and/or vasospasm.

Evidence/Techniques

The Sphenopalatine Ganglion Block

The sphenopalatine ganglion (also known as the sphenomaxillary ganglion, Meckel's ganglion, and the pterygopalatine ganglion) is a mixed sympathetic and parasympathetic ganglion that has been the focus of treatments for over a century. It is triangular shaped and lies in the pterygopalatine fossa, receiving input from the preganglionic parasympathetic fibers via the greater superficial petrosal nerve (branch of the facial nerve), postganglionic sympathetic fibers from the carotid plexus via the deep petrosal nerve, and sensory afferents via the maxillary division of the trigeminal nerve. Thus, through complex and overlapping systems it supplies sympathetic tone, sensory innervation, and lacrimal gland tone of the nasal cavity, palate, major cerebral arteries, face, and orbit. It is a relatively superficial structure that can either be accessed extraorally or transnasally. Commonly accepted indications for this block are acute and chronic cluster headaches, atypical headache, trigeminal neuralgia, and herpes zoster involving the ophthalmic nerve. In a recent study by Narouze, 15 chronic cluster headache patients

with positive diagnostic blocks of the sphenopalatine ganglion underwent RF ablation with significant improvement in attack frequency and intensity for up to 18 months.[35] Similarly, in a retrospective analysis by Sanders 60.7% of 56 patients treated with RF ablation experienced complete relief over a period of 12 to 70 months.[36]

Stellate Ganglion Block

The stellate ganglia (cervicothoracic ganglion or inferior cervical ganglion) is the fusion between the inferior cervical ganglion and the first thoracic ganglion. It is approximately 1 cm in length and lies anterior to the transverse process of the seventh cervical vertebra and the first rib, posterior to the vertebral artery, lateral to the carotid artery, and superior to the apex of the lung. It supplies sympathetic tone to the ipsilateral upper extremity and head. The typical indications for a stellate ganglion block are complex regional pain syndrome (CRPS) (both types I and II) of the upper limb, arterial insufficiency of the upper limb (Raynaud disease, acute frostbite, scleroderma, obliterative vascular disease), herpes zoster of the face or neck, phantom limb pain, and refractory angina.[37] Evidence for a stellate ganglion block for CRPS has been positive, although a double-blind randomized control study has not been performed to date. In a meta-analysis by Hassantash in 2003, 110 articles with 1,528 patients who underwent either a lumbar sympathetic block or stellate ganglia sympathectomy for causalgia found that 94% responded to the interventional therapy. In a recent Cochrane review on the subject, the authors state that it should be "used cautiously in clinical practice, in carefully selected patients."[38]

The classic approach to a stellate ganglion block is to pierce the skin over the C6 tubercle (Chassaignac tubercle) and then advance until the needle touches down on the tubercle. The needle is then withdrawn 2 to 3 mm and contrast is injected under fluoroscopy to rule out intravascular injection. If correctly placed, the contrast should spread along the anterolateral aspect of the vertebral bodies in both posteroanterior (PA) and lateral views. Alternatively, an ultrasound-guided technique involves directing a 25-gauge needle toward the middle of the longus colli with the end point of penetration being the prevertebral fascia in the longus colli.[39] Horner syndrome may occur on the ipsilateral side secondary to interruption of the sympathetic fibers (it is not a reliable indicator of a successful or unsuccessful block). Although a temperature increase in the ipsilateral limb is the most often used clinical indicator, a sweat test may be a more consistent and genuine indicator of a complete block.[40]

Thoracic Sympathetic Block

Thoracic sympathetic blocks are most often used for painful conditions of the chest wall including herpes zoster, postherpetic neuralgia, and phantom pain of the chest wall following mastectomy. Pain caused by tumors of the lungs, whether secondary or primary, may also yield to a thoracic sympathetic block.

The thoracic sympathetic ganglia lay lateral to the vertebral bodies and anterior to the ribs and transverse processes. The classic block technique is to enter the skin 1.5 inches lateral to the spinous process and advance perpendicular to the skin until the needle comes into contact with the transverse process. The needle is then passed inferior to the transverse process and follows the edge of the vertebral body anteriorly until the needle tip is visualized by lateral radiograph to be in the anterior third of the vertebral body. To avoid a pneumothorax, special care must be taken to hug the vertebral body medially.

Celiac/Splanchnic Nerve Block

The sympathetic chain from T5–12 gives rise to the greater, lesser, and least splanchnic nerves, which form the celiac plexus. This web of nerve fibers provide sympathetic tone to all abdominal viscera with the exception of the transverse and descending colon, rectum, and pelvic viscera.[41] For this reason, it is a powerful tool for controlling abdominal pain.

Direct comparisons of unresectable pancreatic cancer patients who have undergone celiac plexus neurolysis with those who were pharmacologically managed show greatly reduced opioid need and, as a result, such reduced medication side effect profiles.[42–45]

The story with chronic pancreatitis is not as clear, however, and both pain specialists and gastroenterologists have been plagued with a lack of clear evidence for celiac plexus blockade in this patient population.[46]

The percutaneous posterior approach varies slightly for the celiac plexus versus the splanchnic nerves, but the starting point for both is lateral to the L1 vertebra. From this point the needles are passed anteriorly to either the anterolateral aspect of the T12 vertebral body (for a splanchnic block) or to 1 to 2 cm anterior to the L1 vertebra in the case of the celiac plexus blockade. The most common side effects include hypotension and diarrhea.

Lumbar Sympathetic Block

The lumbar sympathetic chain is a retroperitoneal structure that lies at the anterolateral aspect of the vertebral bodies. Its contributions include preganglionic sympathetic fibers from T10 to L2–3 and it is noted to be more medial and anterior than the thoracic chain. It has a distinct separation from the

somatic nerves because it lies anterior to the aponeurosis of the psoas fascia and muscle. The left side is also posterior and lateral to the aorta and the right chain is posterior to the vena cava. It is a notably variable aspect of the sympathetic chain and is most commonly present at the inferior aspect of L2 and the superior aspect of L3.

The lumbar sympathetic block (LSB) is indicated for pelvic malignancies, chronic regional pain syndrome, peripheral vascular disease, postherpetic neuralgia, and acute herpes zoster. Its role in CRPS has been validated with improved functionality and long-term improvement of pain. In one study, 29 patients with documented CRPS type I underwent LSB with local anesthetic, and 25 of 29 patients had either complete relief (45%) or partial relief (41%). Another study compared patients with a positive (pain-relieving) sympathetic block with those who did not respond to a sympathetic block. They subsequently administered weekly blocks to those who responded and found that those receiving blocks had significantly superior long-term improvement of pain and functionality.[47]

The most common ("paramedian") approach is a posterior approach in which the patient is prone and the target includes the anterolateral aspect of the L3 vertebral body with the ideal position with the needle tip in the anterior third of the vertebral body on lateral radiograph and medial to the lateral margin of the vertebra on AP radiograph.

Superior Hypogastric Plexus Block

The superior hypogastric plexus is a retroperitoneal network that is typically adjacent to the anterior aspect of the fourth lumbar vertebra body to the upper aspect of the first sacral vertebra body. It is composed of both sympathetic and parasympathetic fibers (S2–S4), which innervate the bladder, rectum, uterus, vagina, and prostate. Blocking these fibers may help to distinguish the etiology of pain as a diagnostic tool (such as distinguishing between visceral pain and referred pain from lumbar pathology), but it is most frequently employed as a neurolytic technique for cancer involving the above-listed viscera.

In a study with 28 pelvic cancer patients (cervix 20, prostate 4, testicle 1, other 3) with pain refractory to other modalities, 26 patients had pain relief of 70% or more with superior hypogastric neurolysis.[48] This was followed up by another study in which 227 patients with dull, visceral pain (from gynecological, colorectal, or genitourinary [GU] cancer) had an immediate positive response (79%) and the majority (69%) had continued pain relief at 6 months.[49] Furthermore, in a randomized trial comparing superior hypogastric block with opioid use, SHP block reduced opioid consumption and pain intensity and enhanced quality of life.[50]

Ganglion Impar

The ganglion impar (ganglion of Walther) is a solitary retroperitoneal structure that supplies sympathetic input to the coccyx, rectum, anus, vulva, urethra, and vagina. It represents the cephalic tail of the sympathetic chain and is a single, fused ganglion. Indications for this block include coccygodynia and malignancies of the pelvic area.

Two techniques to block the ganglion impar are widely used, the transanococcygeal membrane technique and a transsacrococcygeal approach. In a recent prospective study involving 16 patients with chronic pelvic pain, the transsacrococcygeal approach was employed with 100% efficacy in reducing the pain by 50% with a mean time to perform a therapeutic block of 5.7 minutes.[51] A similar approach was employed in a case series using only local anesthetic for treatment of coccygodynia in which a majority of the patients reported pain relief.[52] Reig et al performed a prospective study employing RF ablation of the ganglion impar in patients with a diagnostic block with an average pain relief of 2.2 months.[53]

■ Conclusion

Injection techniques are commonly performed in the treatment of pain by a variety of practitioners in many different contexts. Despite the growth in the numbers and types of procedures performed in recent decades, evidence to define their appropriate use has accumulated at a slower pace. Since the dawn of modern pain medicine with the publishing of Bonica's 1953 text *The Management of Pain,* the need for multidisciplinary care has been recognized. Hopefully, pressures from health care systems and other financial restraints will provide increased incentives to collect meaningful data to define the appropriate role of these procedures in modern pain practice.

Editor's Comments

Anesthesiologists have been instrumental in the adoption of improved standards of acute and chronic pain care in hospitals and the outpatient environment. Our colleagues also implant neurostimulation systems in the spinal and peripheral nerves, as well as intrathecal drug administration systems. This chapter highlights the common procedures that are performed by anesthesiologists in patients with chronic pain. Dr. Stacey and associates have given us concise reviews of epidural steroid injections (ESIs) and medial branch blocks, and a more detailed treatment of various lytic autonomic blocks.

ESIs are controversial, but remain the mainstay of many interventional pain centers. The data are complex but overall indicate that ESIs:

- Are best for acute radiculitis
- Should be immediately combined with a physical rehabilitative program to optimize therapeutic benefit
- Do not consistently help back pain
- Are not useful in cases of spinal stenosis

Medial branch blocks are more likely to be of some benefit for neck pain, but the palliative effect is measured in months. Unfortunately, neck pain is usually a chronic condition, so the pain inevitably returns. Good outcomes with lumbar medial branch blocks are uncommon, and usually short-lived. I do not see the latter procedure performed with any regularity, and that may be a consequence of a lack of enthusiasm for the procedure by many insurance companies.

Autonomic blocks are used in a variety of conditions, and range from sympathetic (sphenopalatine, stellate, thoracic, celiac/splanchnic, lumbar, ganglion impar) to mixed sympathetic/parasympathetic (hypogastric). The efficacy of these blocks may be attributable to the sympatholytic effect or, more likely, the disruption of nociceptive C fibers that course through these ganglia en passant. Over the past decade, the concept of "sympathetically maintained pain" has been challenged, and it is difficult to gain perspective on how often these procedures are performed. I believe the treatment of complex regional pain syndrome (CRPS), either type I or type II (causalgia), using autonomic blocks has fallen out of favor, as evidenced by the cautious conclusion of the Cochrane review cited by the authors.

In contrast to "sympathetic blocks," celiac blocks are still used for cancer pain of the abdominal viscera and have a track record of efficacy. Similarly, superior hypogastric or ganglion impar blocks can help pelvic pain related to malignancy.

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8 Medical versus Multidimensional Management of Chronic Pain

Michael J. Cousins and Charles Brooker

Chronic pain is common and causes a significant amount of disability.[1] It is also subjective; most pain does not correlate entirely with objective criteria such as examination findings and imaging changes.[2] There are neurobiological changes that underlie some of this complexity. Every patient in pain has a range of psychosocial factors that cause part of this variability, including mood and unhelpful beliefs, but these can often be changed. Traditional disease-based classifications and treatment paradigms have failed to produce reliable improvements in most patients with chronic pain. More extensive investigation is increasingly used to try to make a diagnosis—for example, increasing use of magnetic resonance imaging in nonspecific low back pain.[3] The benefit of these investigations is questionable. In addition, the more invasive diagnostic investigations, and treatments such as drugs and surgery have limited outcomes and significant complications, including exacerbating chronic pain. Overall most medical and surgical treatments for chronic pain have poor outcomes unless applied to very carefully selected individual patients. Multidimensional assessment is important in this selection process. Nonspecific treatment effects are common in pain treatment and apply to all treatments as a component of the response observed. Attention to maximizing these nonspecific effects is likely to improve results. Awareness of placebo effects and other nonspecific treatment responses is important when assessing results of new therapies. A purely medical approach has been associated with perceptions of inadequate care unless the emotional needs of the patient are also attended to,[4] and this has implications for style of interactions as well as treatments offered. Multidisciplinary therapies are relatively safe and cost-effective and have strong evidence for their use. This chapter aims to describe how multidimensional concepts of pain can help the clinician select which patients will benefit from assessment and management of psychological and environmental factors either instead of or combined with medical and surgical interventions.

■ Principles

Epidemiology

Pain is common in our community.[1] One in 20 adults consult a primary care physician about low back pain (LBP) each year.[5] Eighteen percent of adults with no history of LBP will develop an episode of back pain in the next 3 years.[6] The period prevalence of knee pain over 1 year has been reported as 29% in the 40 to 79 age group.[7]

Psychological status is associated with pain. In a study of 1,004 patients with knee pain only 15% had radiographic evidence of arthritis, and certainly other mechanisms need to be considered.[8] For example, in knee pain an association exists with fatigue, depression, and anxiety.[9] This effect is independent of degree of osteoarthritis. Psychological factors have been reported to predict new knee pain onset.[10]

In a study of 1,480 people without generalized pain, 6% of them developed it in the next 12 months.[11] Indicators of somatization were predictive in this study. Approximately 33% of them had symptoms 7 years later.[12]

Pain in the workplace is common and predicts future pain in other remote regions of the body. A large study in Denmark showed workers with neck pain were more likely to develop LBP subsequently.[13]

In situations where the pain generator can be removed—for example, total knee arthroplasty (TKA)—the patients with the highest pain severity preoperatively are at the highest risk for postsurgical chronic pain.[14] A high percentage of patients also get no benefit from TKA.[15] There is a negative correlation between severity of arthritis and chronic pain post-TKA.[16] This strongly implies that other mechanisms are relevant apart from degree of degeneration.

In acute pain, risk factors identified for pain persistence include a variety of demographic, medical, and psychosocial factors, including younger age

group, female sex, preoperative chronic pain, and high pain levels perioperatively, but also depression, anxiety and catastrophizing, and high analgesic use perioperatively.[17]

In primary care a review of 45 studies of prognosis of patients presenting with musculoskeletal symptoms identified 11 factors that were associated with poor outcome at follow-up: higher pain severity at baseline, longer pain duration, multiple-site pain, previous pain episodes, anxiety and/or depression, higher somatic perceptions and/or distress, adverse coping strategies, low social support, older age, higher baseline disability, and greater movement restriction.[18]

Classification

With such a high prevalence of pain we need a clear classification system to guide clinical practice. Attempts have been made to classify pain syndromes, such as the International Association for the Study of Pain (IASP) classification, but it is not in common use.[19] There are many imperfections in any classification system used for pain syndromes. The suggestion has been made that if psychological issues are separately classified and assessed, there will be less variability in the underlying medical classification and a better understanding of the problems overall. Such systems are described as multiaxial. Scales such as the Multidimensional Pain Inventory attempt to do this.[20,21]

Many centers use a descriptive approach with a working diagnosis if available for the pain syndrome and then an individual description of the physical, psychological, and social factors involved.

Pathophysiology

For many years there has been an acceptance in the pain management field that pain is a complex and dynamic biopsychosocial phenomenon. This replaced more primitive understandings that conceived pain as purely a symptom of either physical or psychological illness ("dualism"). In clinical practice we are still surrounded by such views held by colleagues, insurers, and, to some extent, our patients.

The concept of both peripheral and central sensitization is dealt with elsewhere in this volume. It is interesting that different groups of animals will exhibit different pain behaviors given the same experimental injury.[22] The inherited variability in pain is likely to occur at the molecular level and has been clinically validated in HIV pain and osteoarthritis populations.[23,24]

The level of distress caused by pharmacologic tolerance and withdrawal is often overlooked in clinical situations. Withdrawal of opioids acutely will exacerbate pain and related distress. Hyperalgesia is seen experimentally in animals and clinically in patients on chronic opioid therapy.[25] Acute postoperative pain may be more severe in opioid-tolerant patients despite maintenance of usual oral opioid therapy and additional doses of parenteral opioids.[26] Gradual withdrawal of opioids may not be associated with an increase in pain, suggesting that they may cause more harm than good in some patients via opioid-induced hyperalgesic mechanisms.[27]

Can thoughts and beliefs modulate the pain itself? Current understanding of cognitive aspects of pain suggests thoughts and beliefs about pain can exacerbate it, although most believe purely psychogenic pain to be rare. Craig reviews many aspects of this and states, "Clarification is to be found in conceptualizing both pain and emotion as multidimensional and sometimes overlapping processes with reciprocal influences on each other."[28]

When combining the neurobiology of pain with psychosocial aspects it can be helpful to think of the person or animal as a series of layers with nociceptive or neuropathic stimuli that are then processed (e.g., via inhibitory circuits) to produce the pain experience. This creates a degree of suffering, which the person may display as pain behavior, which varies greatly among individuals. This then is further modulated by the environment (people and systems) that the person exists in. The cognitive-behavioral model allows for a "top-down" effect where higher processes (i.e., thoughts and behavior) influence the events at various levels of the nervous system and thus modify the overall experience of pain **(Fig. 8.1).**

As an example, consider a patient with a "well-defined" illness (e.g., breast cancer with bony metastases). There are various reasons for nociceptive stimuli: bone pain, nerve root compression, and others. Clinical experience is that patients may live long periods with this condition and their pain level often fluctuates significantly. The level of pain experienced may increase because of disease progression, and this has traditionally been viewed as the major factor and thus a reason to give more radiotherapy or opioid therapy. However, sensitization due to repeated episodes of inflammation or nerve damage can also cause pain to persist and increase. Variations in drug tolerance or metabolism (e.g., toxic metabolites) could also affect the degree of pain. The level of suffering of the patient could vary in response to family concerns, the onset of mood disturbance, bad news from the oncologist about local recurrence, or a range of other issues. The behavior demonstrated in response to this can be increased distress and more bed rest, causing muscle deconditioning and weakness, and increased nociception and pain experience. Alternatively, distress could be reduced because of the response of the treating clinicians or a supportive response from an employer. The

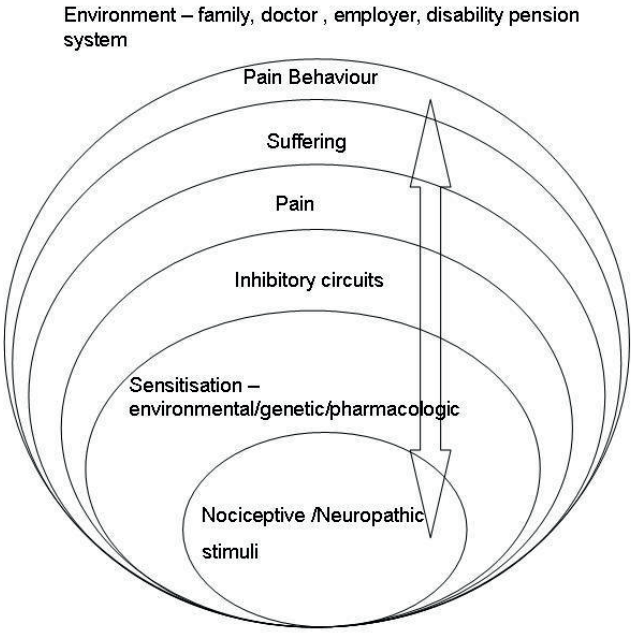

Fig. 8.1 Based on Professor Loeser's original diagram showing the layers of modulation of nociceptive impulses. There is emphasis on sensitization as an influence as well as the concept of the outer layers impacting on the inner layers. (Modified from J.D. Loeser with permission.[29])

cognitive-behavioral model also encourages patients to modify the way they think about the pain, which in turn, can affect the pain experience. The patients' behavior may change: They may pace their activities better, feel more in control, and experience less pain. Patients may change their catastrophic thoughts about the pain—for example, from "this means the end" to "this pain does not mean the cancer is getting worse"—which in turn reduces their depression and fear.

They may physically reactivate, stretching and reconditioning stiff muscles around the pain area. This potentially reduces pain experience levels and may improve aerobic condition and improve sleep. Improved sleep may improve mood, and overall pain experience may be less.

Nonspecific Mechanisms

Nonspecific mechanisms of pain relief are relevant to the discussion of pathophysiology. Placebo and nocebo responses can affect both diagnostic and treatment interventions. Some of this response is thought to be via opioid analgesia mechanisms.[30] But expectation, conditioning, and natural history of the condition need to borne in mind when determining the specific effects of a treatment that might have an impact on the mechanisms above.

Practice

As pain physicians we may regularly implant intrathecal pumps and stimulation devices as well as starting and stopping medication and working with psychologists, nurses physiotherapists, and others. We believe the fundamental issue for medical practitioners is the recognition of the multidimensional aspects of pain to allow medical and surgical therapies to be appropriately used therapeutically with maximum benefit and to direct the use of other techniques when appropriate.

In practice we assess all the factors contributing to an individual's pain experience and formulate a comprehensive treatment plan. If done early it allows identification of the numerous biopsychosocial risk factors for progression to chronic pain. These factors will also indicate the risk of iatrogenic exacerbation of pain with invasive diagnostic and treatment options. The risks of overinvestigation of LBP are well recognized and a good example of this problem.[31] Self-selection for invasive therapies needs to be guarded against. Selection criteria for discography have been shown to be partly psychological.[32] Discography itself has been shown to accelerate disk degeneration.[33]

Psychosocial factors have been shown to predict poor response to revision back surgery.[34] One reviewer noted the large predictive effect of depressed mood on results of revision surgery for adjacent segment disease compared with other surgical pathology. It was suggested that depression was a stronger factor in the decision to offer fusion for discogenic pain than for other pathologies.[35]

Identification of poor coping strategies, unhelpful beliefs, and overt psychiatric diagnoses or history of substance abuse will inform the surgeon or pain physician regarding the likely benefit of invasive treatments or habit-forming medications. In a multidisciplinary clinic typically the patients fill out questionnaires—initially with demographic data but also with diagrams to locate the pain and with verbal and numerical descriptors of pain and severity. An example is the Brief Pain Inventory (BPI).[36,37] Then the patients fill out questionnaires addressing physical and psychological function. There is a range of these "instruments," but essentially the attempt is made to assess disability, mood, self-efficacy, catastrophic beliefs, and fear-avoidance beliefs. Examples of usual assessments include the Roland and Morris Disability Questionnaire,[37] the Depression Anxiety and Stress Scale (DASS),[38] the Pain Self-Efficacy Questionnaire (PSEQ),[39] and the Pain Catastrophizing Scale.[40]

A medical assessment is performed with a detailed pain history and medication use and substance use history.[41] Often the history of a patient in the pain clinic is extensive and the questionnaire can save time.

Correlation of pain symptoms with examination is performed, with an eye out for increased degrees of sensitivity to normal stimuli (allodynia) and increased pain on pinprick testing or deep pressure (hyperalgesia), as well as exclusion of undiagnosed pathology.

A psychological evaluation is performed by a clinical psychologist trained in managing chronic pain, and should focus on coping strategies as well as looking for prior traumatic events and evidence of other psychosocial factors. Specific psychiatric diagnoses are often not present, but there are frequently unusual ways of coping with pain; or unrealistic expectations are elicited, which may raise concerns for the physician.[42]

A physiotherapy evaluation by a specialized physiotherapist gives a thorough analysis of functional restrictions and a complete musculoskeletal examination of physical restrictions and condition. Very often important contributing factors are unearthed in these assessments that would be unexpected considering the patient's initial complaints.

A face-to-face meeting should occur among the assessing specialists and professionals prior to a treatment plan being initiated. This allows a discussion of the weighting of various contributing factors, open airing of views, and corroboration of the history and examination. This is particularly helpful when some inconsistencies are alleged in the patient's presentation by the referring doctor or other agency. Most important, it allows the treating professionals to gauge the difficulty they will have applying their usual therapies in the particular individual. It allows the risks of invasive diagnostic tests and treatments to be weighed and assessed.

Multidimensional Assessment and Invasive Tests and Therapies

The decision to embark on invasive pain treatments has major implications for the patient and the multidisciplinary team. There is a degree of risk in these treatments and the outcomes are variable. Trials of therapy are, in our experience, frequently poor indicators of the longer term patient and clinician satisfaction with the outcome. The patient can become increasingly medicalized, and expectations of pain relief can rise to unattainable levels.

Outcomes of research trials of interventions in pain treatment are usually assessed in small trials, with short-term randomized controlled trials that are frequently nonblinded. The limitations on controlled studies in pain are partly cost related.[43] It is important to look at long-term outcomes, which often show a reduction in analgesia over time.[44,45]

Multidimensional initial assessment helps predict the results of interventional treatment by identifying serious psychological problems that may complicate intervention. It also identifies other factors that, if not addressed, may contraindicate the intervention (e.g., the patient has so little intention of actively managing the pain that she won't get the benefit of the intervention). It may also identify factors that can be addressed by a combined approach if required.[46] In our experience the identification of these factors after an interventional therapy is more difficult because patients often become defensive if they perceive abandonment by the doctor.

Diagnostic blocks require special mention. The multidimensional issues with pain and the subjective nature of pain reporting make diagnostic blocks an apparently attractive option with the potential ability to narrow down the source of the pain. However, this assumes several things—first, that all the pain is derived from a putative peripheral generator; second, that false-positives and false-negatives are rare; and third, that identifying the "cause of the pain" is a key goal.[47]

In the case of medial branch block this has become a cornerstone of a section of modern pain therapy. However, a multidimensional view of medial branch blocks would point out that false-positives are very common,[48] and that treatment then requires radiofrequency (RF) denervation, an invasive and expensive procedure, every 6 to 12 months (and which by no means always produces the hoped-for outcome); also, it diverts patients from attending to other urgent issues with their management, such as physical rehabilitation and cognitive-behavioral programs. This is not to say such procedures should not be done, but they probably need to be done selectively and a multidisciplinary team is more equipped to identify patients who will not benefit from diagnostic blocks and the subsequent treatment required.

Reading the various studies of medial branch blocks and RF facet denervation reveals an interesting debate between various groups of clinicians involved in the management of pain.[49–55] Many poorly conducted studies are reviewed and used to prove either point of view. One of the best-conducted studies was that of Nath et al, but this was assessed as being at high risk of bias because of some differences in baseline characteristics between the two groups.[51–53] However, one of the strengths of this study is that the diagnostic protocol was very strict. Our view is that this study was at low risk of bias and shows strong evidence for a therapeutic effect in the group selected. However, the investigators did exclude many patients with unusually long responses to diagnostic blocks, and one has to ask what the outcome of RF lesions would be in these patients and what their psychosocial characteristics were. In practice many of these patients are treated with RF lesions anyway.

If diagnostic blocks are performed, careful attention to the patient's global response to the block and complaints of other sites of pain will often be revealing. On a practical level, if the patient gets relief of the normal pain at rest but complains bitterly of pain due to the actual procedure and cannot flex the spine without precipitating pain recurrence, then this is a response that is equivocal. The multidimensional treatment plan might take the view that there is a lot of hypersensitivity that would be best treated by physical and psychological desensitization, whereas a single-handed practitioner faced with a patient desperate for anything might agree to "try a radiofrequency lesion and see how it goes."

Multidimensional Assessment and the Decision to Investigate

Risk of new pain complaints is higher in those with preexisting chronic pain elsewhere.[13] Undiagnosed pathology causing pain is considered to be less likely when the multidimensional assessment indicates that several risk factors for persistence of pain are present. The risk-benefit ratio of further investigation increases. These risks may be abstract and system based (e.g., cost). They may be indirectly affecting the patient (e.g., lost time at work, cost, reduced time for useful treatments and exercise). They may more directly affect the patient psychologically—for example, by reinforcing the medical model of care and making the patient more reliant on doctors to make decisions about him, leading to detection of minor unrelated abnormalities that create more anxiety. Procedural investigations carry more direct risks to the patient. In particular, the risk of discography has been defined.[33] This is particularly interesting because the risk is of exacerbation of the index condition itself (i.e., back pain).

Overall, then, a vicious cycle can occur of poor coping strategies and abnormal beliefs combining with pain to lead to excessive demand for investigations and reassurance and risking iatrogenic pain syndromes in already susceptible individuals. The outcome does not benefit anyone.

Multidisciplinary Treatment Plan

The multidimensional assessment and treatment of pain are difficult to incorporate into conventional primary care programs. Initiatives have included early intervention programs in the community and workplace.[56,57] These trials and reviews specifically examine whether targeting risk factors for chronicity actually works. The outcomes are tending to indicate benefit from this approach. Limited psychologically based interventions early postinjury, in patients with high psychosocial risk factors, can have potentially more of an effect on preventing the chronic pain transition than intensive programs will have years later, when such patients usually present to pain clinics.

Online educational initiatives and patient associations are attempting to make consumers and patients aware of the wider aspects of pain and the nonmedical options for dealing with them.[58]

Once a patient has been identified as needing a multidisciplinary pain management program, several decisions need to be made regarding (1) whether all appropriate investigations and medical therapies have been tried; (2) whether some of them should continue; (3) whether the patient will need to be weaned off specific drugs prior to the program; (4) whether the expectations and motivation of the patient are appropriate to enter the program; (5) timing; (6) intensity; and finally (7) whether family and workplace are supportive of the program and have the commitment required to get best results.

In terms of outcomes combined physiotherapy- and psychology-based programs incorporating self-management techniques, cognitive-behavioral therapy, and medication reduction have considerable data showing efficacy. Reviews of these and some exploration of the reasons for various outcomes have been published.[27,59]

There has been a tendency to assume psychosocial issues are intractable or personality based and therefore unchangeable. Multidisciplinary programs are expensive and demanding to set up and run. Outcomes are limited in terms of pain relief. This, however, is a superficial statement because it applies to any treatment for chronic pain. Function, drug use, mood, and durability of response are important. Multidisciplinary programs and particularly cognitive-behavioral techniques have a significant amount of data supporting their use and, importantly, their relative safety.

Analgesic Drugs

Opioids present difficult questions in pain medicine. Much has been written about the risks of opioid therapy in chronic noncancer pain.[60] It may be that correct screening of patients allows safer and more effective prescribing of opioids than has been the case until now. The view of most experts is that opioids have tended to be studied in low-risk groups but are prescribed increasingly to high-risk groups.[61] Multidimensional pain assessment and treatment minimizes inappropriate prescription to the high-risk groups and offers an alternative technique of managing pain that can avoid the high doses and dose escalation in response to the patient's distress. The evidence from published studies where doses of opioids are reduced as part of multidimensional treatment programs is that pain levels are not increased.[27]

Working with a Multidisciplinary Team

Working as the doctor in a multidisciplinary team requires demonstrating leadership while maintaining respect for other health professionals outside one's own craft group. It is important for medical practitioners to have confidence in nonmedical pain management techniques when working in a team environment. Pain can produce strong emotional responses, not only in the patient but also in the treating doctor, team members, family, and friends. Interdisciplinary care is ideal when the team of individuals assessing the patient are in regular contact while treatment occurs.

Unfortunately, in the current health funding environment, even practitioners who have a good understanding of the multidimensional issues to be tackled often feel forced to work within a purely medical model.

Conclusion

Pain has been recognized to be a multidimensional experience. Examination of the pathophysiology of pain indicates multiple factors leading to chronic pain. Persistent pain is very common, and groups at high risk of developing chronic pain and associated disability can be identified, many on the basis of psychosocial risk factors. Certain patients with acute pain are at high risk of chronic disabling pain. A similar group of patients with chronic pain are identified to be at high risk of iatrogenic pain, addiction, or other complications of therapy. Many medical treatments for pain have initial short-term efficacy with evidence then emerging of increased risk and lower benefit in the long term. Some may benefit from medical treatment but will obtain a better result if psychological and physical therapy treatments are combined. Others are better being de-medicalized and encouraged to self-manage their chronic problems. Doctors treating distressed patients with chronic pain are often asked to perform procedures that they believe have very limited benefit and high risk. It is much easier to refuse an inappropriate treatment to a distressed individual if a more appropriate option is available. Specific assessment of risk factors should be routine, and training in self-management has been shown to be effective and should be made available when required.

Editor's Comments

In this chapter, two statements struck me as exemplary of the difficulties we now face in the surgical management of pain:

> *Overall, then, a vicious cycle can occur of poor coping strategies and abnormal beliefs combining with pain to lead to excessive demand for investigations and reassurance and risking iatrogenic pain syndromes in already susceptible individuals.*

> *Unfortunately, in the current health funding environment, even practitioners who have a good understanding of the multidimensional issues to be tackled, often feel forced to work within a purely medical model.*

The authors, Drs. Brooker and Cousins, practice in Australia, a country that from 2008 to 2012 devoted 8.7% of its gross domestic product (GDP) to health care, compared with 17.9% for the United States over the same period. Despite these more limited expenditures for health care in Australia, the care of patients with chronic pain is still a problem to be reckoned with. You can glean from the quotes above that the authors recognize that the fee-for-service medical economy does not always produce the desired result for the patient or practitioner.

Along these lines, the chapter discusses the potential overuse of medications, surgery, and imaging procedures in the context of the "medical model" of chronic pain. I believe the challenge for all of us is to balance the goal of the specificity of diagnosis with the potential for therapeutic nihilism. Without specificity, we have little hope of helping our patients with chronic pain. It almost goes without saying that outcomes from specific diagnoses should include appropriate medical and surgical management. These treatments should continue to be supported, when evidence-based and appropriate. In contrast, nihilism results in generic therapy that has a poor chance of helping individual patients.

One area in which we are currently failing in the treatment of chronic pain is the area of mental health. The "current health funding environment" alluded to by the authors is shorthand for fee-for-service. For mental health practitioners, often psychologists, this translates to being paid appropriately for the performance of psychological assessments in patients with chronic pain, but not very well paid for the ongoing psychological support of the same patients. In contrast, funding for invasive pain therapies, including surgery, continues to be provided under the "medical model," even though these therapies in some cases do not have clearly proven efficacy. It is likely that a shift in some of the resources currently being provided for invasive therapies to mental health providers would represent a sizable premium to the health care system at large.

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9 The Role of the Multidisciplinary Pain Clinic

John D. Loeser

Neurosurgeons have been involved in the surgical treatment of pain since the end of the 19th century. In the last 25 years of the 20th century, increased quality of data on surgical outcomes led to the realization that most chronic pain patients do not respond adequately to surgical procedures. That is not to argue that patients with tic douloureux should not have a surgical procedure when medications fail, but, alas, they represent only a tiny fraction of the patients who complain of chronic pain. This chapter does not address the management of pain associated with cancer; instead, it concerns patients with chronic pain who have normal life expectancies and whose pain either is associated with nerve injury or is of uncertain etiology. Some such patients do respond favorably to carefully selected surgical procedures; however, the likelihood of success often has been overestimated by the uncontrolled case series that make up the bulk of the neurosurgical literature. What patients tell their surgeons in follow-up visits is not always mirrored in outcome surveys by third parties or in the continuing health care–seeking behaviors of the patients. The experiences of pain clinics in the past three decades attest to the numbers of patients who have failed to obtain adequate pain relief following a surgical procedure or, worse, multiple procedures, many of which have been undertaken to alleviate the ill effects of prior surgery. Sometimes the problem originates with an error in diagnosis, such as failing to identify a myofascial pain problem. Other patients are damaged by an inappropriate procedure. Although other types of health care interventions may have equally low likelihoods of success, they do not, in general, have significant complications and rarely, if ever, add to the patient's symptoms and signs when they fail.

The greatest number of chronic pain patients have low back pain, headaches, or other conditions whose likelihood of a sustained favorable response to surgery is low. In addition, chronic pain patients are highly likely to acquire and retain affective and environmental factors that contribute to their complaint of pain and their disability, and these are not usually amenable to surgical therapy. This is particularly true of those who are engaged in disability compensation systems, who should best be thought of as suffering from a comorbidity condition that is highly likely to impair the outcome of any type of treatment.

Special Consideration

An additional complexity surrounding the management of chronic pain patients is that many patients have acquired new neurologic deficits and sources of pain as well as pain behaviors because of the unsuccessful therapies and misinformation that they have received.

Multidisciplinary pain management has evolved to address these issues and has been shown to be cost-effective in many dimensions; more important, it is capable of addressing both the pain behaviors and the suffering that disable patients with chronic pain.[1] This chapter outlines the history of this type of health care, describes diagnostic and treatment programs, reviews outcomes, and concludes with the author's personal viewpoints on this type of pain management.

History

Recognition of the complexities of the complaint of pain and the failures of monodisciplinary therapy of any type led to the development of multidisciplinary pain clinics following World War II. Prior to that time, there were a few nerve block clinics, but these did not offer either diagnosis or pain management in a comprehensive fashion. John J. Bonica was certainly the key force behind this new type of health care, but recognition of the role of environmental

factors ("behavioral medicine") by Wilbert Fordyce and his colleagues was an equally important step in the development of this type of comprehensive pain management.[2,3] Although the principles of behavioral medicine can be applied to any type of health care problem, they are particularly useful in chronic illness in general; in the management of chronic pain, they are essential. Another issue in the early days of this type of pain management was the problem of inappropriate, excessive medications obtained from multiple doctors whose treatment plans were not known to the other treating physicians. Often, this problem was engendered by applying acute pain treatment strategies to patients with chronic pain. The development of multidisciplinary pain programs has been characterized by the shift from the dominant biomedical model of disease to a biopsychosocial model of illness. In this sense, good chronic pain diagnosis and treatment are similar to comprehensive primary care management and use similar principles.

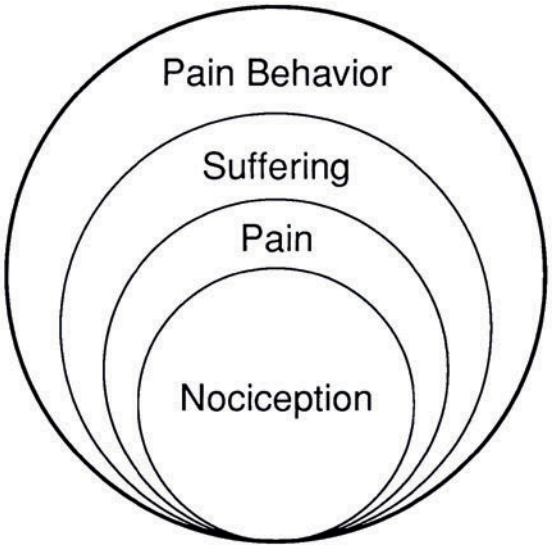

Fig. 9.1 A concept of pain emphasizing that nociception, pain, and suffering are personal, private, internal events; only pain behaviors can be measured by physicians.

Description of Multidisciplinary Pain Programs

Although there is no single format for multidisciplinary pain management, there is a generic concept and plan that can be found in almost every treatment facility of this type. This is probably because of the preeminent role of the University of Washington Multidisciplinary Pain Center and its faculty in training pain management specialists, lecturing throughout the world, and publishing scientific articles and numerous book chapters. The concept that underlies this form of treatment is best described as the biopsychosocial model, in contrast to the biomedical model that characterizes most of neurological surgery. **Fig. 9.1** depicts the components of this concept and emphasizes that only pain behaviors can be observed by physicians.[4] Nociception, pain, and suffering are personal, private, internal events whose existence can be inferred only by observing a patient's behavior. In the clinical setting, it is impossible to measure any of these internal events; only pain behaviors can be quantified by external observers. This model assumes that all human behavior, including the complaint of pain, is generated by a combination of these events occurring within the patient's body, the conscious recognition of these events, the affective responses to these and other ongoing events, and the effects of the environment on the individual's behaviors. The underlying treatment concept is to address all of these issues at one time and in a coordinated fashion so as to present the patient with a single treatment program that encompasses all of the treatable issues.

In this type of treatment program, patients are usually treated in groups of 5 to 15. The patient is asked to work on several generic issues simultaneously: physical, pharmacologic, psychological, and vocational. Programs usually emphasize physical conditioning, medication management, acquisition of coping skills and vocational skills, and gaining knowledge about pain and how the body functions. Both individual and group psychotherapy are used as appropriate for the patient's needs.

Special Consideration

The emphasis of multidisciplinary pain management is upon work done by the patient, not by the providers. Instead, the providers envision themselves as teachers, coaches, and sources of information and support.

Multidisciplinary pain management requires the collaborative efforts of a group of health care providers, including, but not limited to, physicians, nurses, psychologists, physical therapists, occupational therapists, vocational counselors, social workers, and support staff. The health care providers must act as a team, and extensive interactions between the team members must take place. Adequate space for the activities of this group also should be available, but sophisticated and expensive equipment is not required. In a managed health care environment with occult rationing (where managing costs, not care, is the transaction), it is often difficult to arrange for funding of this type of health care, despite the fact

that more outcome data are available than for any other type of treatment of chronic pain (vide infra). There are many biases against a team approach to health care, but the concept is beginning to gain traction in the 21st century.

Patient Assessment

Multidisciplinary pain management is built on thorough diagnostic assessment.[5] As for every other type of treatment, patient selection is the sine qua non of success. The first step in the process is the review of prior medical records and referral information. On this basis, an initial triage of the patient can be made in the attempt to match resources available to the needs of the patient. Patients whose problems can be dealt with by one physician are assigned to him or her as a consultation, and the full multidisciplinary evaluation can be avoided. It is important to search for problems such as an unrecognized myofascial problem that can be directly treated. Patients with problems that cannot be solved by pain treatment facilities, such as those characterized by active substance abuse, severe mental illness, or failure of similar treatment programs in the past, can be identified, and those patients should not be offered assessment. Most referrals, however, will be those who have suffered from a chronic pain problem for years and who share some or all of the following traits:

1. Pain and suffering disproportionate to the identifiable disease process
2. Inappropriate use of physician-prescribed medications
3. Depression
4. Physical deconditioning
5. Superstitious beliefs about bodily functions
6. Failure to work or carry out expected physical and cognitive activities
7. No active medical problems that can be remediated with a reasonable expectation of relief of pain

The members of the diagnostic team assess the medical, psychological, and vocational aspects of the patient's current condition. Interviewing the spouse or significant other is an essential part of this process. Standardized test instruments, such as the Minnesota Multiphasic Personality Inventory (MMPI), Beck Depression Index (BDI), Sickness Impact Profile (SIP), Center for Epidemiological Studies-Depression Scale (CES-D), McGill Pain Questionnaire (MPQ), and other well-validated specialized tests are commonly used. A 1- or 2-week activity diary that also records pain levels and medication consumption is useful as part of the initial patient evaluation. The assessment process not only identifies what is leading to the patient's symptoms; it also evaluates whether the patient will be suitable for treatment in a therapeutic group process that requires him or her to undertake intensive physical and psychological work. The evaluation always includes a team conference and a feedback session to the patient and significant other. These are essential parts of the diagnostic process and set the stage for treatment when the patient accepts the recommendations of the screening team. This assessment can be undertaken on an outpatient basis and is a process that lasts several hours for the patient and the team.

Patient Treatment

Although the original multidisciplinary pain management programs were all inpatient based, it is now apparent that outpatient programs can be equally successful, if they are of adequate intensity and duration. No controlled studies to determine the optimal duration of treatment and hours per day have been done, nor are the various components capable of being identified as to the impact of each aspect of a treatment program. In fact, it is clear that the effects of a multidisciplinary pain treatment program are greater than the sum of its parts.

Special Consideration

Common features of all programs include physical therapy, medication management, education about how the body functions, psychological treatments and learning coping skills, vocational assessment, and therapies aimed at improving the likelihood of return to work.

Programs usually have a standard daily and weekly format that may be tailored to individual patient needs. The overall length of a program may be determined also based on unique patient needs.

Typical programs operate 8 hours per day, 5 days per week, and last 3 to 4 weeks. Patients usually are domiciled in a nearby motel or facility owned by the treating institution. Some programs meet less frequently and last longer. All good programs include a prolonged follow-up period with options for brief interactions to help patients maintain their gains. Treatment teams usually include physicians, nurses, psychologists, physical and occupational therapists, vocational counselors, and other types of health care providers as appropriate to the patient mix and resources available (see the box on clinic personnel, p. 85).[5]

Each of the treatment team members makes a specific contribution to the overall program; the

Personnel in Multidisciplinary Pain Clinics

- Physicians
- Psychologists
- Nurses
- Physical therapists
- Occupational therapists
- Vocational counselors
- Social workers
- Dieticians
- Administrators
- Recreational therapists
- Support staff

Didactic Topics for Patients in Multidisciplinary Pain Treatment

- Pain mechanisms
- Gate theory
- Effects of exercise and inactivity
- Low back pain
- Medications for pain
- Sleep dysfunction
- Healing and disuse
- Hurt and harm
- Treatment goals
- Acute and chronic pain
- Cognitive and behavioral strategies
- Depression
- Headaches
- Biomechanics
- Pain behaviors
- Physiology and psychology of stress
- Surgery for pain
- Dealing with doctors
- Dealing with compensation systems

Cognitive and Behavioral Topics in Multidisciplinary Pain Management

- Anger management
- Assertiveness training
- Cognitive strategies
- Communication skills
- Coping skills
- Costs of pain
- Crisis management
- Dealing with depression
- Focused breathing
- Goal setting
- Identifying gains
- Maintenance of gains
- Quieting response
- Relaxation training
- Stress management
- Time planning

most difficult aspect of multidisciplinary pain management is identifying health care providers who will function as members of a treatment team.

The physician is responsible for the initial history and physical examination, review of outside records, and determination of the need for any further diagnostic tests. Detailed assessment of the patient's medication history is a key physician contribution. Implementation of medication management, including drug tapering by means of a pain "cocktail" technique, is also a physician role. Another important task for the physician is to review with the patient the medical issues and the findings in diagnostic tests and imaging studies. The physician also plays an essential role in the education of the patient and in legitimating all the other components of the treatment program.

The psychologist is responsible for the initial psychological evaluation, monitoring and implementing the cognitive and behavioral treatment strategies, teaching the patient coping skills, and educating the patient (see the boxes on didactic topics and on cognitive and behavioral topics).

It is important to recognize that working with chronic pain patients requires appropriate education and training of the psychologist, as well as the physician. The nurse is a key part of the treatment program, playing a major role in patient education, helping the patient practice newly learned skills, assessing medication responses, and acting as the focal point of the communications that are required to keep such a program operational.

Physical and occupational therapists provide assessment and active physical therapies for patients to improve their strength, endurance, and flexibility. They assist the patient in developing proper body mechanics and strategies for coping with the physical demands of job and everyday life. They do not provide passive modalities of treatment but instead function mainly as teachers and encouragers. The vocational counselors review the patient's work history, disabilities, and factors that may play a role in determining who goes back to work and who does not. They help in the establishment of job hardening and training activities. Some programs heavily emphasize ergonomic issues and use high technology in physical therapies; the need for this type of treatment is unclear.

Physical therapy is undertaken using behavioral medicine principles. Few, if any, passive modalities are used. Biofeedback can be a useful adjunct because it teaches the patient that he or she can gain control over various bodily functions. The emphasis

is on improving strength, endurance, and flexibility through the patient's physical activities; the therapists provide instruction, guidance, safety, and encouragement. Accomplishments, rather than pain behaviors, are rewarded. Patients maintain graphs of their daily activities that have been designed to depict progress. As patients progress, they are enrolled in more complex activities that simulate the workplace conditions.

Medications are given on a time-contingent basis to uncouple their reinforcing effects on pain behaviors. In general, a patient in a pain center program already has failed to obtain adequate relief with pain-relieving medications, and this is why they are almost always tapered via a pain cocktail technique. This is simply a method of converting all opiates to an equivalent dose of methadone and giving the active agent with a masking vehicle. The dose then is tapered over the period of treatment, always with the full knowledge of the patient. Sedative-hypnotics can be dealt with similarly, by converting them to phenobarbital. Most medications are discontinued; the common exceptions are antidepressants, which often have use in chronic pain patients. Long-term use of other medications is discouraged both because of their potential side effects and because their use undermines the philosophical concept that the patient must learn to control his or her pain and not to be dependent on health care providers or their prescriptions.

In general, psychological strategies are aimed at altering behavior rather than changing the patient's personality. Coping skills are taught because this area frequently leads to the patient's many difficulties. Couples therapy is used when appropriate. Issues brought up by the patient are addressed in either the group format or in individual therapy as needed. Depression is often a component of the chronic pain problem, and it must be addressed through psychological as well as pharmacologic strategies.

Treatment team meetings occur daily to review any patient problems; formal review of all patients is undertaken on a weekly basis. Communications with the patient's primary care providers, financial sponsors, compensation systems, and other involved parties are a major issue for such treatment programs and occupy a significant amount of professional time and effort.

Numerous articles have described different treatment programs and their individual treatment strategies, but most follow a similar game plan to that described already. Guidelines for multidisciplinary pain management facilities have been promulgated by the International Association for the Study of Pain, many national societies, and several medical specialties.[6] These are all very general and do not specify any details of the components of a treatment program. Many variations around the themes previously described have evolved, based on the availability of resources, policies of major payers, theoretic constructs, as well as the preferences and biases of those who establish such treatment facilities. My experiences at the University of Washington Multidisciplinary Pain Center and observations made during travels to pain centers throughout the world suggest the following broad principles:

1. The single most important ingredient is the existence of health care providers who are willing to work together as a team. "The magic is in the interactions" is my stock answer when I am asked to explain how to successfully carry out such a treatment program.
2. The health care providers must care about chronic illness and not be totally locked into acute disease or a specific modality of treatment, a frame of mind that is fostered by the biomedical model.
3. The commitment of the provider to the patient is essential.
4. Patients must want to change their lives and must be willing to give the program a try. They must recognize that in this type of treatment program, the patients do the therapeutic work.
5. The treatment is the start of a journey to reclaim one's life from the pain problem; long-term support is required to keep the patient on the road to recovery.
6. The attempt to treat the untreatable leads to demoralization of the treatment team; patients must be properly selected.

An important issue is the maintenance of gains that have occurred in the treatment program. Surrounded by supportive health care providers, it is a rare patient who cannot see some gains by the end of treatment. Many patients, however, are unable to maintain their gains when they return to their normal family and occupational activities. Most programs have established brief follow-up interactions to try to assist patients to keep up their physical and psychological skills and to prevent relapses.

Special Consideration

Multidisciplinary pain programs focus on psychosocial and behavioral as well as physical factors as methods of alleviating pain and suffering and restoring the patient to his or her customary activities.

Outcomes

Measuring outcome for pain treatments begins with the identification of those outcomes that will be considered important. Because pain is not a monolithic thing, there are many ways of measuring its effects on

a human being. Traditionally, physicians have looked only at the patient's verbal report, which is notoriously unreliable. Better instruments for the self-rating of pain have been developed: the Visual Analogue Scale (VAS) and Verbal Analogue Scale are easiest to use in adults, but special scales are needed for those who are prelinguistic or have communication deficits. Pain relief scales also have been established as a valid measurement technique. In summary, patient self-report is one of the outcome measures of interest. It is, after all, the traditional basis of the doctor–patient relationship. Second, we want to know the patient's functional status, in terms of specific physical exercises or activities of daily living. Several well-validated measures, such as the Oswestry Scale, Sickness Impact Profile, SF-36, and others can serve this purpose. In the clinical setting, complex measurement instruments are not required; activities of daily living are readily assessed. Third, health care consumption, such as medications consumed, emergency room visits, doctor visits, operations performed, and hospitalizations, give an index of how a specific intervention has altered the patient's utilization of resources. Finally, whether the patient has returned to his or her expected employment, either at a salaried job, in the home, or, if appropriate, carrying out the desired activities of retirement, must be ascertained. Compensation systems like to use claim closure as an outcome, but this is often an ambiguous endpoint. These four classes of outcomes capture most of the relevant variables of interest to patients, providers, payers, employers, and administrators. The remaining issue of interest is the cost of the intervention. Obviously, all these must be contrasted with other available treatments and the costs of prolonged wage replacement in the absence of health care to obtain useful data.

An array of outcomes reports are available for multidisciplinary pain treatment programs.[7–11] Not all clinics have the same patient mix, and some treatment programs are not as potent as others. My attempt at summarizing the published results and our experiences at the University of Washington Multidisciplinary Pain Center, which has been corroborated by several meta-analyses, is as follows[12–14]:

1. Pain self-ratings decrease by about 30%.
2. Consumption of opiates decreases 60%.
3. Visits to physicians for pain decrease 60%.
4. Physical activities increase 300%.
5. Gainful employment occurs in 60%.
6. These gains are maintained at 6-month, 12-month, and even longer intervals.

In addition, it must be recalled that the patients referred to multidisciplinary pain centers are far more chronic, have far more psychopathology, and are more physically disabled than patients seen in primary care physicians' offices or those referred to surgeons for such things as back pain. Indeed, most of these patients have already had one or more surgical approaches to their pain complaints fail. Typical outcomes are summarized in **Fig. 9.2**.

The meta-analysis by Flor et al evaluated 65 studies with 3,089 patients and concluded that the average reduction in pain was 20%; however, the range was wide: 0 to 60%.[12] Several studies revealed a reduction in opiate consumption that persisted long after treatment.[10,11] The Flor meta-analysis also looked at return to work and found an average of 67%, which is substantially higher than the 24% rate ascribed to standard treatments.[12] Dramatic reductions in health care consumption and additional surgery after multidisciplinary pain treatment also have been noted.[7,11] There are far too many publications about multidisciplinary

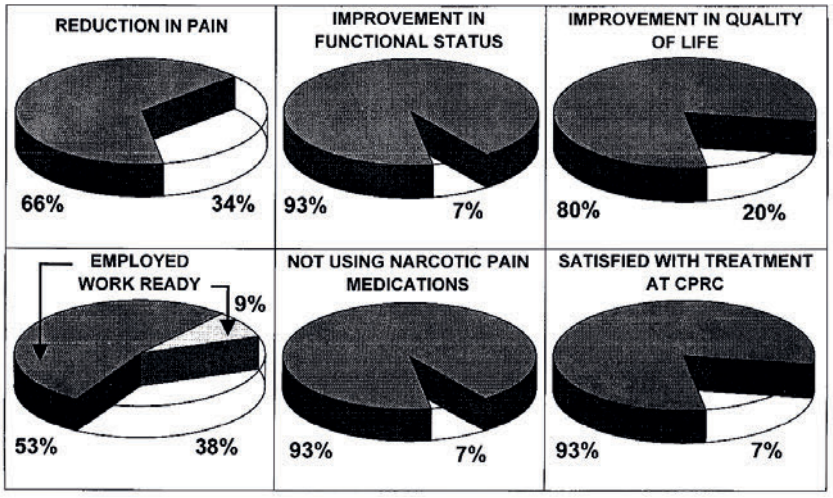

Fig. 9.2 Comprehensive Pain and Rehabilitation Center (CPRC) Program Evaluation System, November 1989 through March 1999: Outcome results at discharge (*n* = 1,831).

pain centers to review each one independently and to comment on its strengths and weaknesses. The major issue in established efficacy and cost-efficacy data is the near-total absence of any outcome results from any other type of treatment for patients with chronic pain. Stieg et al calculated that each patient treated in their pain clinic represented a savings of $280,000 in health care expenses until he or she reaches retirement age.[15] Some additional cost data are available, thanks to a study of the economics of back pain and its associated health care and compensation costs.[15] Okifuji et al extrapolated from available data and estimated a savings of $280,000,000 per year in the United States if patients currently receiving standard medical and surgical treatments were treated in multidisciplinary pain centers instead.[16,17]

Several more recent clinical trials have all showed significant benefits of multidisciplinary pain management over control groups. Becker et al reported a randomized controlled study of the results of a Danish multidisciplinary pain center (MPC) compared with a general practice- (GP-) managed group.[18] Patients (n = 189) were evaluated at referral, 3 months, and 6 months later with SF-36, Hospital Anxiety and Depression Scale (HAD), Psychological General Well-Being (PGWB), and health-related quality of life (HRQL) as well as a VAS for pain. With all of these instruments, the MPC group did better than the GP group, and their opiate consumption was less. The GP-managed patients did not change over 6 months, while the MPC group significantly improved. A definitive review of comprehensive pain programs was performed by Gatchel and Okifuji in 2005.[19] They found that MPC was most effective with respect both to patient outcomes and reduced complications and to costs of care when contrasted with all other treatment alternatives.

A trial of MPC treatment for 395 patients in Germany revealed significant treatment effects on VAS, SF-36, and CES-D; the authors concluded that MPC ameliorates pain and improves function and quality of life more effectively than any monotherapy.[20] In addition, a major component of MPC, cognitive-behavioral group treatment, was found to be more effective than usual care in a study of 110 chronic functional somatic syndromes, lending support to the concept that cognitive-behavioral strategies are useful across a wide array of diagnoses.

Conclusion

The team approach to complex chronic pain patients as found in a multidisciplinary pain treatment facility has evolved with an underlying set of principles. These include, first, the recognition that Cartesian dualism is a curse on effective health care. Second, a biopsychosocial model is required to capture all of the relevant factors. Third, the treatment must address the pain itself and not just be a search for hidden causes and specific remedies. Fourth, the treatment must address the restoration of well-being and not just aim at the alleviation of symptoms. Fifth, and finally, the illness is not just chronic pain but is also the failure to work, often ascribed erroneously to the pain instead of the patient. Pain is not a monolithic entity such as a fracture or a deficiency of some essential nutrient. Pain is, rather, a concept used to label a group of sensations, behaviors, thoughts, and emotions. Pain has many dimensions, including sensory and affective components, location, intensity, time course, and the memories and anticipated consequences that it elicits. Because pain has many facets, it should be obvious that there is no single outcome measure that captures all the relevant issues. For this reason, outcomes assessments must look at a variety of criteria to describe adequately the effects of any treatment. Furthermore, the dissociation of specific effects of a treatment from nonspecific treatment effects or the natural history of the disease process requires prospective, randomized clinical trials. This is a higher level of security than is available for almost all treatments of chronic pain. Ironically, the best outcomes data in terms of clinical trials and the widest array of predictive variables can be found for multidisciplinary pain management. It should become the gold standard against which all other treatments for chronic pain are measured. Furthermore, the well-being of those who have pain would be enhanced if the treatment principles developed in multidisciplinary pain clinics could be applied much earlier in the career of chronic pain patients, because prevention is always better than remediation.

Editor's Comments

Chronic pain is generally defined as pain that persists more than 6 months. Pain of this duration clearly exceeds that which should resolve with normal healing from an acute injury, including surgical intervention. It is also around that point that pain begins to seriously affect the long-term "psychosocial" aspects of the patient's condition, including the likelihood of returning to work.

Professor Loeser has been a consistent, eloquent, and worldwide spokesperson for the principles of the multidisciplinary pain center (MPC), based largely on the innovations of the University of Washington Multidisciplinary Pain Center, founded by Dr. John Bonica and Dr. Wilbert Fordyce. He once again delineates this strategy in the present chapter.

There is no doubt that the approach described is the most effective and most proven rehabilitative strategy for patients with chronic pain. I do not find it the least bit ironic that I make this statement in a textbook devoted to the "surgical management of pain." You will find ample commentary in this text on the paucity of evidence that supports invasive interventions for much of what we consider to be chronic pain conditions. Ideally, no patient should be subjected to surgical intervention for chronic pain without first being vetted, and potentially treated, in an MPC. Unfortunately, that is not how the "real world" today works.

Many, and perhaps most, pain centers today are as monolithic and "unidimensional" as surgery. The reasons for this are manifold. Principal among them is the fact that in our current fee-for-service environment, *interventions* provide sustenance, whereas the provision of more *cognitive* or *rehabilitative* services may not be financially sustainable. As a result, it is the rare MPC that can deliver the type of services that John Loeser describes and remain afloat.

After this chapter was submitted, I had further discussion with Dr. Loeser concerning his thoughts on the future of the MPC, particularly in light of what today runs under the banner of "health care reform." I will quote his comments:

> *It all depends upon what else is available for the care of patients who say ouch and how much health care one wants to fund. Furthermore, it is my belief that most chronic pain patients are created by physicians who do and say things that add to disability and depression, so the problem is to a large degree iatrogenic. I believe that if primary care practitioners did a better job, the number of chronic pain patients would decrease significantly. If we shift to a rational health care system, I think that pain clinics will be useful to remove the clutter of pain patients from primary care practices. Ending the opioid pandemic might also have a big impact on needs for MPC.*

Clearly, the MPC can play a major role in improving the care of chronic pain patients under any reasonable system of health care. We must make the shift toward evidence-based, cost-effective pain care, in contrast to our present system, which rewards more care rather than better care. I say this as a surgeon who would prefer to reserve surgical treatments for those who have proven to be "medically intractable," and for whom surgery offers a substantial chance of palliation.

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10 Outcome Assessment

Norman Marcus and Eric Fanaee

Fundamental to the proficient practice of medicine is the ability of the practitioner to clearly delineate which actions will likely promote the greatest benefit for the patient. Surgeons are unique among physicians because of the critical role they play in determining operative versus nonoperative management. *Outcomes assessment* is the formal study of the measurement, comparison, and evaluation of the results of specific interventions. By critically analyzing the outcomes data of actions taken in the past, practitioners can more effectively match patients to the optimal interventions available at present. A firm grasp of the latest outcomes data as well as an ability to critically evaluate the literature will enable surgeons to perform an evidence-based, risk-benefit analysis, especially when evaluating chronic pain patients for invasive surgery.

Outcomes assessment of widely utilized surgical procedures for treatment of chronic pain represents an intersection between the fields of pain medicine and surgery. The quintessential example is the surgical management of spinal pain. Pain is an internal, subjective, multidimensional, generally unpleasant experience that can vary significantly over time. It has been studied extensively throughout the history of medicine because it is the most common reason for patients to visit the physician's office.[1] The wide variety of pain effects can be observed, but the assessment of pain and pain relief relies solely on patient self-report measurements. Practitioners should know the uses and limitations of these measurements in both the clinical and research settings.

What determines a "good outcome" and who makes that final judgment? Which treatments reduce pain intensity and improve functional outcome, and at what cost? Unfortunately, despite significant advances in the fields of surgery and pain medicine, a clearly defined and universally accepted methodology for outcome research has not been achieved. Inconsistences in responses to treatment, heterogeneity of patient populations, variation in the criteria to determine success in clinical trials, and surgeon's attitudes and approaches may all confound the development of high-quality clinical recommendations. The confluence of these complexities has prompted renewed interest in standardizing and improving the criteria used to determine a meaningful benefit following surgical intervention for pain.

Today, practitioners and payers alike are increasingly going beyond merely assessing subjective pain relief, preferring to monitor improvements in physical ability and global function as benchmarks for quantifying the response to intervention. Outcome data collection is the foundation of future guidelines.

Epidemiology and the Environment of Cost Containment

Pain is a leading public health problem in the United States. Over 50 million Americans deal with low back pain alone, at a cost of over $100 billion a year.[1,2] This translates into 70 million health care visits a year, making pain the leading cause for health care utilization.[3] Back and neck problems are among the most commonly encountered pain symptoms in clinical practice,[2,4] and spine-related costs have seen a substantial and disproportionate increase relative to non–spine-related expenditures in recent years.[5] In the United States, 15% of adults have had chronic low back pain at some point in their lives, resulting in 250 million lost days of work per year and chronic disability for over 10 million Americans.[6] The drive toward improved outcomes research in pain and neurosurgery stems partially from increased pressure to justify financial reimbursement from third-party payers. An increase in health-related expenditures is unjustified without a consistent improvement in health status.

What has been the role of surgery in the management of spine pain? Many studies have shown an increase in the rates of spinal surgery versus con-

servative management over the past two decades, particularly in regard to invasive lumbar fusion procedures.[7–9] In 2007 there were 37,598 operations performed in patients ages 65 and older with a diagnosis of lumbar spinal stenosis, generating an aggregate hospital bill of $1.65 billion. Complex fusion operations showed significantly higher complication rates and higher mean hospital charges ($80,888) versus decompression alone ($23,724).[9] Generally speaking, back surgery rates have been higher in the United States than in other countries.[10] From 1997 to 2005 ICD-9 codes suggesting surgical intervention rose 40% while ICD-9 codes not supporting a surgical intervention fell 40%.[9]

Present Surgical Outcomes

Is all of this surgery "worth it"? By what measure do we determine "worth"? Do patients benefit and, if so, by how much? How long do the positive effects last? What is the difference between surgical and nonsurgical management of patients with similar back pain complaints? The answers may depend on whom you ask. Overall, the results of surgical intervention have been mixed,[11–13] although some general themes have emerged. Repeat surgeries and more complex interventions, for example, have been shown to have worse outcomes than primary ones.[9,14] A recent guideline published by the American Pain Society found spinal fusion to be superior to conservative treatment for axial spinal pain, but with only half of patients experiencing an "optimal outcome."[15]

Many of the high-quality trials comparing surgical and nonoperative treatment for spine pain have conflicting results that differ based on symptomatology, time since intervention, and outcome measure used. An example illustrating this concept is the Maine Lumbar Spine Study, which followed spinal stenosis patients for 10 years and found surgical treatment superior at 1- and 4-year follow-up. However, at the 8- to 10-year mark, low back pain relief, predominant symptom improvement, and satisfaction were similar between patients treated surgically and those treated nonsurgically. Interestingly, the study found long-term leg pain relief (a secondary endpoint) to be better in the surgical group. Outcomes in those patients who underwent more than one surgical procedure were generally poor.[6]

Another recent multicenter prospective randomized controlled trial (SPORT trial) supported the Maine Lumbar Spine Study and showed that patients with symptomatic spinal stenosis treated surgically fared better than their nonoperative counterparts when followed 4 years postoperatively.[8] Is the pain relief achieved at 1 and 4 years worth the expense and risk of surgery, even though we know that pain scores will be similar later on? Are the observed improvements clinically as well as statistically significant? Already there have been several follow-up studies to the SPORT trial,[16,17] and as time goes on we can expect more data to emerge that may clarify the long-term implications of surgical management of pain.

Clinical Guidelines and Payer Policies

Clinicians are increasingly utilizing practice guidelines in their decision-making process. However, general guidance for the assessment and treatment of chronic low back pain has historically been inconsistent.[8] Because of the multispecialty nature of low back pain, different physician professional societies have published varying guidelines. Formation of these guidelines is typically done through a series of meetings to create a consensus of guideline committee members who utilize the latest evidence-based medicine. Therefore, some baseline variability may exist depending on which experts are selected and the specific literature reviewed. Clinically significant differences in practice recommendations are apparent based upon the professional society source[15] as well as the country of origin.[10,15]

Concerns regarding the effectiveness and costs of surgical treatment for spinal disorders in patients presenting with low back pain have placed a high degree of scrutiny on the assessment of medical necessity. Both clinical guidelines and payer policies have a major impact on the choice of treatment. Insurance companies, for example, may use many different professional society guidelines when determining reimbursement. How do practitioners decide which guidelines to follow? A recent high-quality systematic review has raised serious questions regarding how recommendations are formulated, and has advocated increased collaboration between professional societies and payers.[7] The authors agree that future guidelines and payer policies should be comprehensive, transparent, evidenced-based, and collaborative.

Diagnosis and Surgical Indication

Proper diagnosis is always the first step toward achieving good outcomes. Failed back surgery syndrome, for example, has been linked with failure to clearly diagnose and treat spinal stenosis[18]; however, substantial improvement of function can occur when a definitive diagnosis can be made. This is often a challenge when evaluating a patient in pain. The imaging findings offer only one possible cause of pain, yet the same abnormal findings may be present in another patient with no pain complaints. In clinical trials evaluating specific surgical techniques, the same principles apply. Pain generators can arise

from a multitude of structures in the back. The overlying soft tissue, the intervertebral disk, ligaments, nerves, joints, and the vertebral body itself can each be responsible for causing pain. Diagnostic specificity beyond the symptom of low back pain or the presence of lumbar degeneration needs to be delineated. As noted above, the trend has been to emphasize neuraxial diagnoses supporting nerve blocks and surgery and to disregard soft tissue diagnoses for back pain.

Surgical indications vary based on diagnosis, and the same procedure can have different results depending on the precise diagnosis.[19,20] A recent policy statement by the International Society for the Advancement of Spine Surgery outlined situations for which spinal surgery is and is not indicated.[21] For example, lumbar fusion surgery is clearly indicated for conditions such as spondylolisthesis, recurrent disk herniation,[22] certain traumas, and spinal stenosis associated with instability. On the other hand, surgical management of other conditions such as degenerative disk disease in the elderly[23] or facet syndrome is more controversial.[21]

Unfortunately, it has been reported that up to 85% of patients with isolated low back pain cannot be given a precise pathoanatomical diagnosis.[24] In these situations, surgery would not be indicated because there is no evidence of its efficacy in the absence of a clear diagnosis. As discussed above, part of this difficulty stems from the fact that low back pain may originate from a wide variety of spinal and extraspinal structures and there is a poor association between imaging results and symptoms. A closer look at the role of the various soft tissue structures that may generate or contribute to pain is advocated because these account for the vast majority of low back pain generators.

Evaluating Outcomes: Collecting the Key Data on Pain, Function, and Satisfaction

When examining outcomes in regard to a surgical intervention, practitioners must first utilize evidenced-based methods for the clinical evaluation of a patient's pain, function, and quality of life. Validity (the extent to which a test measures what it is intended to measure) and reliability (the stability and reproducibility of measures of the same concept over time or across methods of gathering data) are important characteristics of any outcomes instrument. Simply asking the patient "how bad is the pain?" or "is it better now?" is neither a valid nor a reliable means of assessment. A variety of standardized pain assessment instruments have been validated,[25] each having its unique advantages and disadvantages.[26] In general, more than one type of assessment tool should be used in clinical and research settings to improve the sensitivity of detection of a therapeutic change.[27] Here we describe the most widely utilized clinical measurement devices in the research and clinical settings.

Pain Intensity Scales

The most frequently used pain intensity assessments in both clinical trials and patient care settings are the Numerical Rating Scale (NRS) and Visual Analogue Scale (VAS).[28] These tests are simple to use, with patients rating their pain on a scale with anchors of 0 and 10, 0 meaning "no pain" and 10 meaning "worst pain" (**Fig. 10.1**). The Verbal Rating Scale (VRS) is a 5-point simple Likert scale describing pain intensity as "none," "mild," "moderate," "severe," or "very severe." Although this scale has been validated for use in elderly and cognitively impaired patients, some studies find poor correlation of VRS with NRS and VAS.[26]

One limitation of pain intensity scales is that not all data points may represent equal differences. For example, in cancer patients, one study found large gaps in pain ratings between 0 and 1, 7 and 8, 8 and 9, and 9 and 10, suggesting that ratings between 2 and 6 are actually much closer together than ratings at the ends of the scale.[29] In other words, a change in pain intensity from 10 to 9 in this population reflects a greater actual decrease than, say, a change from 5 to 4. Despite this limitation, pain intensity scales continue to be utilized in a wide variety of clinical and research settings, and we expect this trend to continue because they are simple and efficient to use.

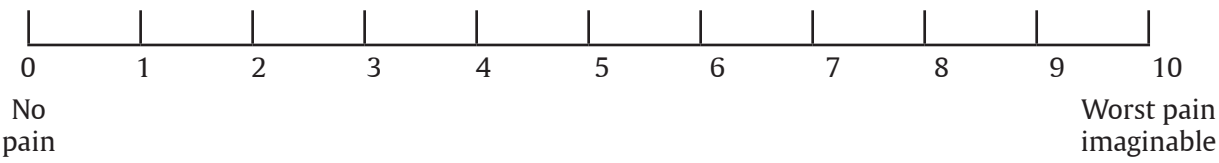

Fig. 10.1 Numerical Rating Scale (NRS) for evaluation of pain intensity.

Multidimensional Pain Measures

Simple pain intensity scales lack a comprehensive description of a given pain complaint.[30] As described above, pain is a multidimensional experience that encompasses more than simply pain intensity. Pain quality is important in determining the nature of the disease. Neuropathic pain, for example, is often described as "burning, lancinating, shooting, and cutting."[31]

The McGill Pain Questionnaire (MPQ) and its abbreviated short form (SF-MPQ) give more precise descriptions of the pain experience because, in addition to rating pain intensity, they distinguish the qualitative, sensory, and affective experiences associated with pain.[32,33] For example, patients may be asked to choose from a variety of words to describe pain, such as "cruel" or "heavy," providing a more comprehensive perspective on a patient's pain experience.

Unfortunately, despite evidence that pain quality assessments assist with diagnosis and treatment of certain conditions,[34] these responses are rarely used in outcomes assessment trials.[28] Additionally, the MPQ is not thought to be as responsive to treatment effects as global scales, and its use is further limited by its cumbersome length. We therefore advocate the appropriate use of this scale as a supplement, not a core measure in future outcomes assessment clinical trials.

Functional Assessment

Patients with chronic low back pain have lower levels of activity compared with their prepain levels and with those of normal controls.[35,36] Practitioners, payers, and researchers are increasingly relying on demonstrable functional improvement as a more reliable indicator of a positive response to intervention. To this end, many functional instruments have been developed; here we will discuss the ones most widely utilized in outcomes literature related to spinal intervention.

The Oswestry Disability Index (ODI) is a standardized patient self-report instrument that scores and rates the effect of a patient's pain on activities of daily living such as lifting, concentration, sleeping, recreation, and driving. This index is responsive to change,[37] has been used extensively by practitioners and researchers alike, and has been validated as a gold standard outcome measure for functional improvement.[38] In contrast to the global assessment provided by the ODI, there are a variety of anatomic location–specific instruments that are often used in clinical trials (such as the Neck Disability Index, or NDI).[39]

Quality of Life

The Short Form 36 (SF-36)[40] and abbreviated Short Form 12 (SF-12) instruments are both widely utilized to evaluate generic quality of life in chronic illness populations. These measures contain eight domains, including physical functioning, social functioning, role limitation due to pain, bodily pain, vitality, general health perception, emotional problems, and mental health. In regard to their application to neurosurgery, both the SF-36 and SF-12 have been validated for use in the evaluation of patients with cervical myelopathy, but they cannot detect small changes in pain and their role in determining meaningful changes in outcome in response to decompression remains unclear.[41–43]

An obvious reason for this is that both the SF-36 and SF-12 contain only one specific domain regarding the effect of pain on functional ability, namely "role limitation due to pain." The other seven domains can be effectively confounded by a wide variety of life situations that may or may not be pain related. A positive change in "emotional functioning," for example, can be due to a work promotion, recent marriage, or new addition to the family. Additionally, psychological distress is correlated with poor functional ability.[36] If a patient is going through a divorce, death in the family, or change in responsibility at work, this can cause psychological distress that is in no way related to pain but can cause a decrease in function scores on the SF-36. Therefore, researchers and clinicians should be cautious when evaluating outcomes using this measure, due to its high potential for confounders.

Recently, an expanded quality-of-life (QOL) measure was developed, the SF-61, more commonly called the Treatment Outcomes in Pain Survey (TOPS),[44] with an additional 25 items related to pain and function, and still more recently a short form, the S-TOPS.[45]

Other pain-related QOL measures commonly used in the literature include the Multidimensional Pain Inventory (MPI) and Brief Pain Inventory (BPI). Both quantify the effect of pain on activities of daily life and have been validated as outcome indicators for various pharmacologic, psychological, and surgical treatments.[46]

Pain Diaries

An overall limitation of self-report measurements is that they capture the patient's pain experience only at single time points. There can be significant memory biases in pain reporting as well as variation in pain over the interval period that may not be reflected in a single clinic visit.[28,47] Pain diaries attempt to overcome this limitation by asking patients to describe both the multidimensional and functional consequences of their pain at various times throughout the day, allowing practitioners to spot overall trends. Additionally, they are available in electronic format[48] and are being advocated as the standard of care for pain assessment.[49] We expect the continued

standardization and validation of pain diaries to result in high-fidelity data sets for both clinical and research settings.

The Intersection of Research and Clinical Practice

Measurements Used in Clinical Trials

Complicating the surgical management of chronic pain is the myriad of outcome scores used to assess treatment response in clinical trials. Practitioners may be overwhelmed and confused when determining which measurements can be extrapolated to their own patients. A systematic review showed up to 75 different outcome assessments had been used from 2001 to 2010 in clinical trials.[50] This same review recommended use of VAS, ODI, and SF-36 for pain, function, and quality of life, respectively, and recommended against using return to work and medication use because of the wide variation in the interpretation of the data. Haro et al prospectively evaluated lumbar decompression surgery in 42 spinal stenosis patients and recommended using VAS, ODI, and SF-36 scores together as an overall measure of improvement.[51] The inadequacy of the SF-36 was suggested in another systematic review of spine surgery outcomes that demonstrated a high degree of responsiveness to treatment of the VAS and ODI but only a small degree of responsiveness of the SF-36.[27] Those authors postulated that the SF-36, as a health-related QOL measure as noted above, was too nonspecific a measure to reflect small changes. We recommend using the SF-61 or TOPS survey as a health-related QOL measure in both clinical and research settings.

Statistical versus Clinical Significance

Scholars and philosophers across multiple disciplines have said that "a difference is a difference only if it makes a difference." The meaningfulness of the change in scores following treatment is a critical consideration when evaluating surgical outcome trials. Clinicians may find themselves asking, "How much of a change is required for my intervention to be considered successful?" In the literature, often a statistically demonstrable difference in trials does not translate into a clinically important difference.[52,53] Trials with negligible mean benefits may be sufficiently powered for results to be statistically significant. Because clinicians are primarily interested in performing actions that maximize therapeutic change to individual patients, identifying the thresholds considered clinically meaningful remains an important goal of outcome assessment.

Meaningful therapeutic change can be assessed by patients, family members, society, third-party payers, and providers. Thaci et al reported good correlation between patient and surgeon perception of outcomes for spine operations for degenerative disease.[54] But in the chronic pain setting, it is the patient who provides the best evidence of a positive impact.[55,56] One explanation could be that clinicians tend to place greater emphasis on anchors that reflect disease process (laboratory values, MRI findings, etc.) whereas patients place greater emphasis on symptoms, QOL, and overall treatment satisfaction. The challenge, therefore, remains in formulating and applying objective criteria to evaluate patient self-report measurements. In other words, how can we better help our patients help us?

Minimum Clinically Important Difference

There have been several attempts to bridge the great divide between statistical and clinical significance.[53] The concept of minimum clinically important difference (MCID) has been defined as "the smallest difference in score in the domain of interest that patients perceive as important, either beneficial or harmful, and that would lead the clinician to consider a change in the patient's management."[57] The determination of clinically important differences in pain intensity can be confounded by baseline pain, patient characteristics, and the magnitude and direction of change reported.[57,58] For example, in some patients small improvements in pain control may be more important than small deteriorations, although in other patients the opposite might be true. Additionally, as discussed previously, numerically equal gains on a pain scale may differ in their meaning depending on baseline health status.[29] A 54-year-old man who is able to walk independently after achieving a pain improvement of 2 would find his result far more impactful than would a 28-year-old woman experiencing the same level of improvement who walks at baseline but still cannot run. Therefore, whether or not a particular change in pain represents an important change can depend on the clinical and situational context.

In 2008 a consensus meeting of clinical and research experts by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) was convened to standardize outcome measures, pool data, and provide a basis for systematic reviews and meaningful comparisons among treatments. By critically analyzing data sets from the most compelling literature, this group made important recommendations for determining MCID in clinical trials in regard to pain, physical and emotional function, and overall QOL. Although caution is advised in making generalizations, the state-

ment does outline the exact changes in magnitude that reflect minimal importance. Interestingly, the statement points out that as little as a single point (or 15%) improvement on a NRS pain scale would be considered as minimally important by patients.[46] Improvements of 2 and 4 represent "much improved" and "very much improved," respectively. For MCID of physical functioning, the statement defines an improvement of 0.6 and 1 point on the MPI and BPI, respectively,[46] which is an important consideration in major procedures such as spinal fusion and instrumentation (**Table 10.1**).

Thresholds for Surgery

Defining success for lumbar spinal surgery remains problematic. The MCID in pain or functional outcomes is a common metric calculated independently of perceived risk and morbidity. This is an important limitation because spinal surgery can entail significant risk. Of course, surgeons make the decision to perform surgery based on evaluation of both risks and benefits. Not surprisingly, the concept of MCID is increasingly being applied to lumbar spinal surgery trials. Copay et al reported MCID values of 12.8 points for ODI, 1.2 points on NRS for back pain, and 1.6 points on NRS for leg pain.[53] Interpreting this, a patient with leg pain undergoing lumbar spinal surgery would have to be expected to achieve a decrease of at least 1.6 points on the NRS scale for that procedure to be "worth the risk." Patients deemed unlikely to achieve the "magic" 1.6-point reduction would therefore be considered poor candidates because the risk of surgery would outweigh the benefit. Another trial showed that a pain score decrease to 3 out of 10 or less, an improvement on ODI of 20 or more, or a return to some occupational activity was highly correlated with patient satisfaction at 2 years, and surgeons then used MCID to support the decision to proceed with lumbar spinal fusion.[59]

The complex methodology of how these specific values are determined is beyond the scope of this chapter, and it is important to recognize that these benchmarks apply to groups of patients; individuals may desire specific changes within outcome domains. For example, an improvement of 5 on NRS might be considered "much improved," but not if that particular patient finds sleep impairment to be the primary reason for treatment selection. As discussed previously, it is the individual patient who is looking for an improvement, not the group as a whole. Clearly, more clinical studies that attempt to use an individualized approach to determine specific important outcome domains are needed.

Despite the significant insight provided by the IMMPACT trials, a limitation of MCID is that the value can be calculated by a variety of different methodologies. As a result there can be conflicting conclusions as to which MCID is optimal, especially in regard to chronic pain outcome measures such as VAS, ODI, and SF-36.[53] For example, in a general review of low back pain treatments, Deyo reported MCID as a 30% improvement from baseline,[60] this conflicting with the IMMPACT recommendations of 15% as mentioned above. We agree with the continued use of MCID as a common starting point for both research and clinical decision making.

Table 10.1 Simplified provisional benchmarks for interpreting changes in chronic pain clinical trial outcome measures

Outcome domain and measure	Type of improvement	Change noted
Pain intensity		
0–10 numerical scale	Minimally important	10–20% decrease
	Moderately important	≥ 30% decrease
	Substantial	≥ 50% decrease
Physical functioning		
Brief Pain Inventory	Minimally important	1 point decrease
Emotional functioning		
Beck Depression Inventory	Clinically important	≥ 5 point decrease
Global rating of improvement		
Patient Global Impression of Change	Minimally important	"Minimally improved"
	Moderately important	"Much improved"
	Substantial	"Very much improved"

Source: Table adapted and modified with permission from Elsevier Publishing.

Overall Patient Satisfaction

Patient satisfaction is a growing concern in today's health care environment, and the concept of MCID can be applied to patient perception of overall outcome. The Patient Global Impression of Change (PGIC) scale is a single-item rating scale by participants concerning their response during a clinical trial using a 7-point rating scale ranging from "very much worse" to "very much improved."[61] This scale has been used in multiple chronic pain trials[62,63] and offers a quick, responsive, and simple method of charting self-assessed clinical progress in research and clinical settings. It integrates pain relief, functional improvement, and side effects while providing an easily interpretable evaluation of treatment response. The IMMPACT group has advocated the increased use and reporting of PGIC for use in clinical trials.[46] Additionally, as a practical concern, we believe neurosurgeons should consider using this simple scale when evaluating patients in the clinic due to its simplicity, validity, and ease of use (**Fig. 10.2**).

Patient Selection: Risk Factors That Influence Outcome

Failure of proper initial patient selection has been linked to the high rates of failed back surgery syndrome.[64] There are a wide variety of reasons, including socioeconomic status[2] and the presence of comorbid disease,[65] as to why this may be the case. As highly trained specialists, surgeons may place a high weight on the presence of a "fixable" pathology (such as spinal stenosis on MRI) when making the critical decision to intervene. However, the decision to offer surgery should weigh the prognostic impact of comorbidities, social histories, and expectations of treatment. Failure to account for the multifactorial baseline patient characteristics can undermine an otherwise favorable outcome for a technically proficient procedure. The literature has thus far revealed few unequivocal patient predictors, and they have explained only a low proportion of outcome variance.[63] The high rate of failed back surgery has prompted a renewed search for patient risk factors that may provide prognostic clues in clinical decision making. Recent studies by Mannion and Elfering examine the various medical and psychosocial predictor variables that influence outcome.[66] Sick leave and psychological disorders deserve special attention and are discussed in detail below.

Sick Leave and Disability

The effect of sick leave, disability, and compensation status on surgical outcomes is controversial, but most studies correlate them all with poor outcome after surgery.[67] This has been validated as both important and clinically significant through a meta-analysis that examined the effect of compensation status on outcomes of a variety of surgeries.[67] In a recent, randomized, controlled, multicenter trial, Atlas et al observed that patients with worker's compensation undergoing lumbar discectomy for sciatica reported greater improvement with surgical versus nonoperative treatment at 6 weeks and 3 months. However, at 2 years, in contrast to the nondisabled cohort, differences in pain, function, and life satisfaction in the worker's compensation group undergoing surgery approached those of the conservative treatment group, suggesting only a short-term benefit to surgery in this group.[68]

Not all studies show a negative difference in outcome based upon a patient's disability or compensation status. A systematic review by Mroz et al demonstrated that litigation patients actually responded more favorably to fusion versus nonoperative care. Patients with less physically demanding jobs and those not on sick leave again responded better with fusion than with nonoperative care.[69] Anderson et al found that higher disability scores were correlated with better outcomes in patients undergoing anterior cervical discectomy and fusion.[70] These reviews validate the viewpoint that unfavorable sociodemographic factors alone should not preclude surgery, but should be considered as part of the global assessment of individual patients when making treatment decisions.

Since your surgery how would you describe the change (if any) in ACTIVITY, LIMITATIONS, SYMPTOMS, EMOTIONS, and OVERALL QUALITY OF LIFE, related to your painful condition? Please circle the number below that matches your degree of change since beginning care.

No Change	Almost the Same	A Little Better	Somewhat Better	Moderately Better	Better	A Lot Better
1	2	3	4	5	6	7

Fig. 10.2 A modified sample Patient Global Impression of Change scale.

Psychological Disorders

Although prospectively studied,[71] the question of whether patients with various psychological disorders would benefit more from conservative versus operative treatment remains unclear. Many practitioners advocate psychological prescreening,[72] believing that certain conditions put patients at "high risk" for surgical failure. A recent systematic review showed that the effect of fusion surgery was more favorable than conservative management in patients without a personality disorder, neuroticism, or depression.[73] That same review advocated validated psychological screening tests in evaluating patients for surgery.

The lifetime prevalence rate of depression is about 5%[74] and depression has been associated with chronic pain. Therefore, a high number of chronic pain patients presenting for neurosurgical evaluation will carry a diagnosis of depression. Does the presence of depression mean that surgery will be less effective? The answers have been mixed to negative, with some scholars implicating depression as a "consistent [negative] predictor"[66] and others proclaiming that "the only consensus appears to be that there is no consensus."[63] Preoperative emotional health is linked to depression, and studies show higher presurgical scores linked with more favorable outcomes.[75,76] Sinikallio et al reported correlation of baseline life dissatisfaction (as measured by BDI) with increased pain and poorer functional ability at 2-year follow-up following lumbar spinal stenosis surgery as compared with the nondissatisfied cohort.[77]

Unfortunately, identification and pretreatment of "high-risk" psychological disorders has not yet been shown to influence outcome.[78] As we look forward to clearer delineation of the role of psychological disorders on surgical outcomes, we recommend screening patients who may be considered "at risk": those with a history of abuse, posttraumatic stress, major depression, and personality disorders. It is important to recognize that the presence of a high-risk psychological disorder alone should not necessarily preclude surgery, especially in patients who demonstrate clear pathology in the setting of failure of conservative treatment. For uncertain or intractable cases, seek the help of a mental health professional.

Conclusion

There are a wide variety of clinical and research challenges related to outcomes assessment for neurosurgical procedures for chronic pain conditions. Most of the current outcome data on spine procedures show mixed results and are confounded by a variety of patient and observer biases. The changing health care environment has resulted in increasing attention paid to the financial impact of such procedures. The availability of high-quality, clinically relevant outcomes data is a key component in the formation of practice guidelines and payer policies.

For research purposes, we advocate the use of multiple outcome domains, including pain, function, QOL, and patient satisfaction. Assessment tools that pinpoint the specific effect of pain on function such as the BPI and TOPS should be preferred over more general questionnaires such as the ODI and SF-36, which may not be as responsive to pain relief as the others. MCID values should continue to be identified and reported to bridge the gap between the research and clinical settings. Patient selection should be based on a multidimensional approach, with negative predictors such as depression weighed against the potential benefit of surgery.

Key to Abbreviations

VAS	Visual Analogue Scale
NRS	Numerical Rating Scale
VRS	Verbal Rating Scale
MPQ	McGill Pain Questionnaire
SF-MPQ	Short Form McGill Pain Questionnaire
ODI	Oswestry Disability Index
SF-36	Short Form (36 items)
SF-12	Short Form (12 items)
SF-61	Short Form (61 items)
TOPS	Treatment Outcomes in Pain Survey
MPI	Multidimensional Pain Inventory
BPI	Brief Pain Inventory
BDI	Beck Depression Inventory
MCID	Minimum clinically important difference
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
PGIC	Patient Global Impression of Change

Editor's Comments

Drs. Marcus and Fanaee have provided us with one of the most important chapters in this book. Efficacy must go hand in hand with high quality and safety for any surgical procedure. Almost all techniques described in this book remain unproven at the highest levels of evidence, and as a result the field of pain surgery is still evolving. We have to strive for *accountability* in our surgical endeavors because this is how our work will advance. Richard Dawkins has said, "Science replaces private prejudice with public, verifiable evidence." This should be a surgeon's mantra, and certainly it should be one of the guiding principles of pain surgery.

This chapter provides us with a roadmap for how to proceed with studies of pain-relieving surgery, particularly spine surgery. There is no doubt that the assessment tools are not perfect, which is one reason for using a variety of instruments. There is no single measure that will answer every question for every procedure, which is why the data must be multidimensional. It is the matrix of outcomes that can lead to a compelling argument for a particular pain treatment. With appropriate experimental design, and valid outcome measurements, we can test the procedures we now undertake with the goal of pain relief, and develop effective strategies for the future.

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11 Disability Assessment

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Individuals who complain of pain frequently demonstrate some associated disability. When searching through the literature concerning pain and disability, one is immediately struck by the complexity as well as by the varying definitions surrounding both phenomena. Physician assessment of disability requires the examiner to understand the multidimensional nature of the pain phenomenon. In addition, the evaluator of a disability should be familiar with the different definitions surrounding these terms and cognizant of their medical and legal contexts. Despite the lack of correlation between a pathological process and symptoms of pain and the lack of correlation between symptoms of pain and associated disability, a fundamental knowledge of these two phenomena is extremely important in disability evaluation.

The assessment of disability has medical, legal, and social ramifications. It is beyond the scope of this chapter to review the different disability systems, and the process of determining impairments and the ability of an individual to return to work. There are excellent resources that readers should familiarize themselves with to get the essential framework for understanding the concepts and process.[1–3] In addition, physicians are requested to fill out forms regarding the ability of their patients to work and with what restrictions. The terminology in the forms employs distinctions among the different parties that are quite significant and can be very confusing.[4]

Despite adequate treatment, musculoskeletal and neurological injuries frequently lead to residual persistent pain and disability. Although the incidence and prevalence of specific back pain seem to be essentially stable, the award of disability attributed to low back pain has increased markedly and at an accelerating rate over the past decades.[5] Fordyce emphasizes the paradox between (1) continued advances in our knowledge about neurophysiology, anatomy, pharmacology, and the psychosocial factors implicated in back pain, and (2) the fact that the number of persons who become legally categorized as disabled from low back pain has increased enormously. Patients, employers, legal professionals, and physicians all are involved in the disability system, and each is interested in determining the residual functional capacities of persons with pain so that appropriate return-to-work planning can be initiated.[6]

This chapter provides an overview on the complex relationship between pain and disability, the problems of the paradox described earlier, and a conceptual approach to the medical determination of disability.

What Is Pain?

Pain is a ubiquitous and pervasive phenomenon and one of the leading causes of people contacting their health care providers. It is a subjective symptom and, in most situations, a warning of an underlying pathology that can be identified and treated; resolution of symptoms is expected. Thus, pain serves a biologically useful function, helping the patient seek medical attention and assisting the physician in making appropriate diagnosis and treatment decisions.[7]

Despite significant advances in understanding the anatomic and neurophysiologic basis of pain over the last four decades, the problem of *persistent pain* remains frustrating to physicians and other health care professionals as well as to society in general. Contributing factors include (1) lack of a uniform definition of pain; (2) lack of clear explanation of the pain phenomenon; (3) problems with uniformly accepted and objective measurement techniques of pain; (4) the psychological and social variables relating to pain; and (5) the effects of ethnic, cultural, political, individual, and cognitive variables on the perception and reaction to pain.[7,8]

Despite the greater understanding surrounding the biochemical, neurophysiologic, and neuroanatomic processes and pathways of the pain phenomenon, it is imperative to reiterate that *pain is not merely a physiologic process.* Pain cannot be divorced from the biological, emotional, cognitive, and social context in which it arises.[8]

Special Consideration

Pain is not merely a physiologic process. It cannot be divorced from the biological, emotional, cognitive, and social context in which it arises.

Pain has been defined as a unique complex made up of afferent stimuli interacting with the emotional or affective state of the individual, modified by past experience and the person's present state of mind. Pain is generally related to nociception or tissue injury; however, it is well recognized that there could be injury to bodily tissues without pain, and there are clinical situations in which pain occurs without an identifiable injury or pathology. Thus, there is not a one-to-one relationship between injury and pain.[9]

Acute pain can therefore be viewed as a biologically meaningful, useful, and time-limited experience.[7–9] In a small but significant portion of people, pain may persist despite optimal treatment, it may recur, and it may become chronic. In any given person, it is impossible to predict the course of the condition at the first episode of pain. It is estimated that acute and chronic pain requiring treatment affects 45% of Americans annually, costing the U.S. economy $85 to $90 billion annually, with about one third of the American population estimated to have "chronic" pain.[7,8] The International Association for the Study of Pain defines pain as "an unpleasant, sensory, and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[8,10]

Loeser provided a conceptual view of the pain experience as comprising four distinct components[11]:

1. *Nociception:* Potentially tissue-damaging thermal or mechanical energy impinging on specialized nerve endings that in turn activate specific nerve fibers
2. *Pain:* Nociceptive input to the nervous system
3. *Suffering:* Negative affective response generated in the higher nervous centers by pain and other situations, including loss of love or objects, stress, anxiety, and so on
4. *Pain behavior:* Anything a patient says, does, or does not do that would lead one to infer that the patient has pain, including all forms of behavior generated by the individual commonly understood to reflect the presence of nociception, such as speech, facial expression, posture, seeking health care attention, taking medication, and refusing to work[5,11]

Special Consideration

Pain behaviors do not mean that there is a pathology, impairment, or disability. The physician should carefully take a detailed history, review past treatment records, and examine the pain claimant to determine the presence of an underlying pathology, disease, condition, or impairment and, "with the system involved," provide the answers required.

Thus, the term *pain* is commonly used in two different and somewhat divergent ways, often without the differences being appreciated. As Fordyce emphasized, the first refers to a signal system. Specialized nerve endings in the periphery of the body, when activated by adequate stimuli, send nerve impulses to the spinal cord or brainstem, and thence on to the brain. The second use of the term lumps the signal system with cognitive, emotional, and behavioral actions occurring subsequent to nociceptive stimulation and is generally conceptualized as emotions, responses, or reactions.[5,8]

People who have chronic pain, in addition to the predominant symptom, which may be similar to the pain that occurred at the time of the injury or episode, demonstrate several other features. Gildenberg and DeVaul described the features of the patient with chronic pain.[12] Such patients have attempted but were unsuccessful in finding relief after using various medical, surgical, physical, and psychological treatment approaches. They have undergone significant lifestyle changes, including dysfunction, deconditioning, drug misuse, depression, and disability, that far exceed the underlying identifiable pathology. They manifest dramatic pain behaviors far beyond what a clinician can attribute to an underlying disease process.[8–10,12] Patients with chronic pain (sometimes referred to as *chronic pain syndrome*) tend to have the following characteristic features: (1) pain persisting beyond the expected healing period of an injury or illness (this does not include pain associated with cancer); (2) pain with minimal objective clinical and laboratory findings or residual structural defects that could explain the reported degree of pain behavior; (3) pain without specific clear medical or surgical treatment to cure the underlying problem; and (4) pain associated with significant lifestyle changes as mentioned previously.[12,13]

It is important to recognize that no objective measures or techniques are available for absolute measurement of the pain experience. Thus, it is impossible to prove or disprove the existence of pain in any given person. The Commission on Evaluation of Pain, after an extensive study of this topic, states that "no one can know the pain of another person."[9] It should be emphasized, therefore, that pain behaviors, not pain itself, are observable to the outsider.

Special Consideration

The existence of pain cannot be proven or disproven. Pain behaviors, not pain, are observable to the outsider.

Pain behaviors are influenced by a variety of factors in addition to the underlying, identifiable pathological process. Some pain behaviors may be under the conscious control of an individual; however, the influence of the effects of a naturally occurring learning process, where an act that is considered a positive reinforcement by the patient for his or her expression of pain may reinforce a continuing occurrence of pain behaviors, is not under conscious control.[8,9]

What Is Disability?

Like pain, disability is a highly complex problem with a variety of interpretations and "systems." Terms such as *impairment* and *disability* are used in different settings to mean the same thing or, at times, two different things. Fordyce emphasized that the concept of disability can be traced back to medieval times, when the *whole person* concept was the guiding principle. Historically, *whole person* referred to intactness of the body. Injury that resulted in some loss of body parts or body function led to efforts to restore that person as closely as possible to the whole person inferred to have existed prior to injury.[5]

Disability and compensation systems provide rules defining disability and entitlement, as well as procedures for determining who qualifies as disabled. Rondinelli and coauthors[14] point out that in addition to historical origins and statutory requirements, there remains considerable variability with respect to definitions of disability, entitlements, benefits, claims application procedures, adjudication, and the role and relative weight given to medical versus administrative deliberations. Physicians determine the medical, physical, and psychological impairments that are essential, which may contribute to disability.

Historically, social justice systems have been traced back to over 4,000 years ago. The current systems of disability determination, although established more than a century ago in Germany, were first established in the United States as a "worker's compensation law" in 1911. The concept was to provide assistance in restoring an injured worker to competitive employment.[1,14,15]

There are different conceptual frameworks surrounding the concept of disability. The senior author has found the framework offered by Melvin and Nagi provides an excellent conceptual basis for disability by describing four components[16]:

1. *Pathology* refers to an interruption of or interference with a normal bodily process or structure. It includes the initial injury to the body from trauma, infection, metabolic disorder, or other etiology and the body's response to such injury. It also includes aggravation of a previously existing problem by an injury. Pathology is a disease or trauma that causes changes in the structure or function of the body or a specific tissue or organ.[14] Thus, *pathology is at the tissue level.* Examples of pathology include lumbosacral strain, herniated lumbar disk disease, and diabetic polyneuropathy.
2. *Impairment* is defined as an anatomic, physiologic, or psychological abnormality or loss.[14,16] Impairment is defined as "any loss or abnormality of psychological, anatomical, or physiological structure or function" and may be temporary during active pathology or may become permanent, continuing even after the pathological process is adequately treated and resolved.[14] Thus, *impairments are at the organ level.* Examples of impairments include decreased range of motion from lumbosacral strain or herniated lumbar disk, altered reflexes, decreased strength, or loss of sensation from radiculopathy or abnormal electromyography studies seen in a person with a herniated disk or diabetic polyneuropathy. Anatomic impairments include contractures, loss of limb/amputation, deformities, and decreased range of motion. Physiologic impairments include decreased cardiac output, decreased pulmonary function, abnormal electrophysiologic studies, abnormal blood chemistry, muscle weakness, and other abnormalities. Changes in cognition and memory, as seen in persons with closed head injury, and abnormalities of personality detected on the Minnesota Multi-Phasic Personality Inventory 2 (MMPI 2) are objective psychological impairments.[3] It is important to recognize that impairments are *objective* and *medically determinable* through clinical or laboratory assessments.
3. *Functional limitation* is a restriction in or lack of ability to perform an activity or function in a manner that is within the range considered normal for that person and that results from impairment. Examples of functional limitation include the inability to lift more than 20 pounds by an individual with lumbosacral disk disease and nerve compression; the inability to follow a two-step direction in a person with head trauma; the inability to do exertional activities, such as climbing stairs, in a person with severe ischemic heart disease; and the inability to function safely in the community in a person with cognitive and affective changes resulting from a closed head injury. Thus, *functional limitations are manifestations of impairment, translated in terms of the function of a body part or organ.*
4. *Disability* is defined as the inability of a person to perform his or her usual activities and the inability to assume one's usual obligations. Disability is defined as "any restriction or lack (re-

sulting from impairment) of ability to perform an activity in the manner or within the range considered normal for a human being."[14] *Disability is task specific. Permanent disability* is assumed to be present if a patient's actual or presumed ability to engage in gainful activity is reduced or absent as a result of an impairment, which in turn may or may not be combined with other factors. *Disability is at the person level.*[1,8,14]

This model has been criticized for assuming a linear and one-way relationship between pathology, impairment, and disability. However, the concept is helpful in the rehabilitation process. Thus, aggressive treatment of pathology may eliminate or minimize permanent impairments; aggressive treatment of impairments can decrease functional limitations. The limited function can be enhanced by assistive and adaptive devices, and counseling regarding acceptance of the person's limitations can decrease the perception of disability. This leads to a focus more on "abilities" and less on "disability," an important characteristic of the field of physical medicine and rehabilitation.

The international classification of impairment, disability, and handicap also proposes four different components: (1) disease, (2) impairment, (3) disability, and (4) handicap.[14] *Disease* is a pathological condition of the body, whereas *impairment* is the loss of normal anatomic, physiologic, or psychological status. *Disability,* in this context, is loss of normal function that is task specific, and *handicap* is defined as a loss of normal function that is role specific. Examples of handicap include limited access to public facilities, and environmental modifications at work and in the community can decrease handicap.[14] Thus, to summarize, *pathology is at the tissue level, impairment at the organ level, disability at the person level, and handicap at the societal level.*

In 1956 the American Medical Association (AMA) created its own set of criteria to assess impairment, resulting in the publication of *The Guides to the Evaluation of Impairment.* The *Guides* were a series of 13 publications, dating from 1958 through 1970, that addressed impairment rating practices. Although initially anatomically based, the *Guides* introduced the "diagnostic-related model" to surmount the inherent pitfalls associated with the traditional models. The most recent, sixth edition of the *Guides* embraces the International Classification of Functioning, Disability, and Health (ICF).[1] In addition to addressing impairments (physiologic functions and body parts that vary from the normal state) in terms of deviations, it takes into consideration *task execution* and *activity limitations* as well as *participation restrictions* with respect to involvement in life situations.[1]

The U.S. disability programs and systems include (1) worker's compensation insurance, usually regulated by each state; (2) Social Security disability insurance and supplemental Social Security, parts of a federal program; (3) Veterans Administration compensation and pension benefits; and (4) private disability insurance. For a more detailed description of these programs, the reader is referred to several excellent reviews.[1,14,15]

Disability is also a legal term, which is "judged administratively."[13] Legally, *disability* refers to the inability of an individual to meet social or occupational demands because of a physical or psychological disadvantage, or it refers to the fulfillment of statutory or regulatory requirements for compensation.[1,14,15]

Impairments reflect "objective signs," in contrast to symptoms. Theoretically, these signs can be measured objectively. Impairment is determined through the use of a detailed physical examination. *Palpation* is useful in the determination of muscle spasms and identifying trigger points and in assessing range of motion. Muscle strength testing, assessment of deep tendon reflexes, and neurologic examination can provide data on objective impairments. Imaging and laboratory tests, such as roentgenograms, computed tomography (CT), magnetic resonance imaging scans, blood tests, and electromyography studies can identify impairments. Personality inventory testing and cognitive function tests provide evidence of psychological impairments.

Special Consideration

Objective measurements of impairments are limited, especially for individuals with symptoms of pain, with little objective correlatable pathology. Patients with symptoms of nonspecific low back pain constitute a significant number of claims filing for disability, especially in relation to resuming social and work activities.

Assessment of causation, that is, if a particular injury or illness can be attributed to a particular event or exposure, is a complex process at times. Similarly, the assessment of the individual's ability to perform certain functions and any limitations thereof is fraught with lack of scientific evidence-based studies. However, several studies will be of assistance to the reader interested in these complex topics.[1,15,17,18]

Systems of Disability

Physicians frequently deal with situations where they are asked to complete forms for their patients or at the request of attorneys or insurance carriers. It is beyond the scope of this chapter to provide details regarding these systems and the specific requirements and processes involved in assessing causation, return-to-work determination, and understanding the different systems. The reader is referred to excellent resources.[1–3,14,15,17,18]

These disability systems include worker's compensation, tort/personal injury, Social Security, Federal Employers Liability Act, Jones Act, Federal Workers' Compensation Programs, Longshore and Harbor Workers' Compensation Act, Federal Black Lung Program, Department of Veterans Affairs, Americans With Disabilities Act, Family Medical Leave Act, and private disability systems. This chapter will present highlights of a few of these programs that physicians frequently interact with and should get to know well.

Tort Claims/Personal Injury System

Rondinelli and Katz[14] note that "the United States inherited most of its common Law from England. Civil cases were decided based on precedent (prior decisions) and common customs of society (common law) and depended on the legal doctrine of *stari decisis,* which means 'let the decision stand.'" The common law aspect is most applicable to the civil tort system. A tort is defined as a "breach of duty that gives rise to an action for damages" and civil wrongdoing. The four elements of claim must be proved before an adjudicating authority and include: (1) a legal duty existed, (2) a breach of legal duty occurred, (3) this breach of duty was the proximate or direct cause of harm or injury, and (4) harm or damage occurred as a result.

Tort cases arise out of:

1. Personal injury caused by a motor vehicle accident
2. Product liability due to a defective product
3. Medical negligence/malpractice
4. Toxic exposure
5. Slip and fall cases

Certain amendments to the United States Constitution apply here, especially the Seventh Amendment: "In suits at common law, where the value in controversy shall exceed twenty Dollars, the right of trial by jury shall be preserved."

The physician plays an important role in this system by providing information regarding the injury (diagnosis), its causal relationship with the injury, the necessity of treatment, need for future care, and permanent impairments (if any) and how these may affect the individual's vocational and other activities. The attorneys on the two sides mediate and settle, or the case may go to trial with a judge or jury. Many physicians not used to this system may be intimidated because there are discovery and trial depositions or the obligation to appear at trial. There are physicians who perform only plaintiff or defense examination, whereas others may be involved on both sides.

Frequently, independent medical examinations (IMEs), also referred to as adversarial medical examinations, are performed by physicians. By having a consistent approach, a physician may be able to develop a middle-of-the-road reputation. However, any physician, no matter how careful, may be "branded" inappropriately as a plaintiff or defense expert.

Role of the Physician in the Personal Injury System

1. *Liability:* Who was at fault for the cause of the injury/disease? This is determined by the legal system. Physicians have no role at this stage.
2. Did the accident/event cause a medical diagnostic condition, or was an underlying, preexisting condition substantially aggravated, thus explaining the presenting symptoms? In the question of causation and consequent issues, the physician has a very important role.
3. Which of the evaluations and treatments that followed the accident were directly related to the injury?
4. Has the patient reached maximum medical improvement (MMI)? This is a healing plateau where additional treatment or time is not expected to result in significant improvement.
5. What are the residual impairments (objectively determined medical findings) resulting from the injury/event, and are they "permanent"?
6. How do the impairments contribute to alterations in the person's functional activities, both work-related and social/recreational? In other words, what are the patient's task-specific abilities/disabilities? It is best to identify the functions that will be restricted because they may cause problems for the individual or others.
7. Is there a need for ongoing treatment that is directly related to the injury or event? If so, what specific treatment?

Worker's Compensation System

The worker's compensation system is the most common litigation system for a physician treating patients with pain arising from work-related injuries. This system has been in existence in the United States since 1911.

Prior to 1911, the tort system was the only recourse for an injured worker to obtain compensation after an injury at work. However, it was very burdensome to the injured worker (plaintiff) in terms of the time and expense necessary to overcome the powerful strategies used by the employers and their insurers (defense). The defense strategies used in the past have included:

1. *Contributory negligence.* A claimant can be shown to have contributed to personal injuries through his or her own actions.

2. *Assumption of risk*. It can be shown that an injury was related to an inherent risk of the job, and the worker knew or should have known about the hazards of the job.
3. *Fellow servant doctrine*. The injury occurred due to a fellow worker's negligent actions.

With these three strategies alone, it was difficult, if not impossible, to secure adequate compensation for work-related injuries.

Although worker's compensation laws were developed in other countries as well, Wisconsin became the first U.S. state to pass the Workman's Compensation Act (now the Worker's Compensation Act, Chapter 102). Shortly thereafter, New York and New Jersey passed similar acts, and by 1949 all states had enacted a worker's compensation law, which is now mandatory in almost all states.

Under the worker's compensation system, a "no fault" approach was adopted to resolve the dilemmas of the tort system. The system provides automatic coverage to employees who make a claim for "injuries that arise out of and in the course of employment." In exchange, the covered employees forgo the right to sue the employer. Exceptions are allowed for an employer's "wanton neglect" or in the case of a "third-party lawsuit." It is important that all employees and employers know their state's worker's compensation process and become familiar with the requirements because they vary from state to state in the details.

There are several types of benefits: survivor benefits in cases of death; medical and rehabilitation expense recovery; and wage loss benefits with monetary compensation. Most states provide for medical and rehabilitation treatment of the injured worker, usually to "cure and relieve" the effects of the injury. *Wage loss compensation benefits* are based on the category of disability: temporary total disability (TTD) or temporary partial disability (TPD) paid while the employee is under active treatment. Once the worker reaches MMI (the healing plateau considered to be the end of healing) payments stop.

The employee is also eligible for compensation for any residual permanent partial disability (PPD) or permanent total disability (PTD). The PPD is differentiated as scheduled (injuries to limbs, eyes, ears) or unscheduled (injuries to spine, head, torso).

The Role of the Physician in the Worker's Compensation System

1. Determine causality of the injury and any permanent impairment. Causality is defined as the association between a given cause and effect. This should be determined on the basis of "medical probability" (more likely than not, chances of 51% or greater) as opposed to "medical possibility" (less than a 50% chance). Remember, the worker's compensation system is a "no fault" system, so liability is not an issue.
2. Determine each stage of the injured worker's disability status
3. Determine the appropriate treatment that is related to the work injury
4. Once MMI is reached, assess permanent impairments, if any, and the percentage[1–3,15,17,18]

Most work injuries are appropriately diagnosed and treated, with full resolution or minimal impairment rating and compensation. However, 10 to 20% of injuries are responsible for over 80% of the costs and the contentious adversarial process. Physicians, with their own personal backgrounds and philosophies, frequently arrive at strongly conflicting opinions. Independent medical evaluations are frequently used in these situations, with many legal remedies available to the injured worker.

By understanding the "system" and providing timely and fair reports and properly filled-out forms, many injured workers can be adequately helped by a treating physician. Talmage[4] has highlighted the difficulty in communication between physicians and third parties. It is important for the treating physician to understand this process.[2–4,17]

The worker's compensation system for each state uses complex but understandable concepts, and the physician should become aware of the system applicable to the state where the patient was injured and how the "disability rating" is determined. In the United States, 44 states, 2 commonwealths, and the Federal Employees' Compensation System either mandate or recommend using the *Guides* developed by the AMA to measure impairment in worker's compensation claims.[1] Some states, like Wisconsin, do not use the AMA *Guides*, but rather have an acceptable and agreed-upon system of assessing disability ratings, which are frequently updated, contested, and legislated.

Private Disability Program

Most employers provide short-term and long-term disability for their employees. This is related to the "disability form" that most physicians fill out in any type of practice.

Short-Term Disability (STD)

An employee may be unable to work after an illness (e.g., flu, pneumonia), after an elective or emergent surgery (e.g., hysterectomy, open reduction and internal fixation of fracture from a fall at home), an injury at home or while engaging in sports (strains/sprains, contusions), or a flare-up of asthma. In

these situations, the physician may provide a note, using an office prescription form or letterhead, indicating the patient's medical condition and the days the patient was "sick" and therefore "disabled from work." This will allow the patient to receive short-term disability payments for time off work due to a medical reason. Although the contractual language varies, most employers provide up to 90 days (3 months) of STD benefits. Minor medical problems and injuries or illnesses will generally resolve within this 90-day period.

Special Considerations

It is very important that physicians promptly fill out any forms sent by the employer or third party (auto insurance, school loans, personal disability insurance carrier, etc.) so that the patient can receive the appropriate payment during the period of disability from work and can recover without additional financial concern and resume work. Failure to complete these forms properly and in a timely manner delays the disability payments. Many physicians find it time-consuming and frustrating to fill out these forms, but they are part of the medical care and of the physician's patient advocacy role, justifying the level of responsibility and respect that society has bestowed on physicians.

Long-Term Disability (LTD)

When the period of disability from an injury or illness not covered under the worker's compensation program is excessive, then long-term disability goes into effect. The time period, although depending on the policy language, is typically a year (12 months) from the initial date of disability. The forms may be sent to the physician, or the patient may bring the forms to be filled out and mailed to the appropriate party. All of these forms use simple questions and are easy to complete. Items include name and date of birth of the patient, the medical diagnosis causing the disability and keeping the patient from work, the date disability started, any surgery or hospitalization dates, and the names of all involved physicians other than the one completing the form. More frustrating questions for the physician may include: When will the patient recover? When will the patient return to full-duty work without restrictions? What types of work can the person perform with restrictions? What is the prognosis? These questions may be difficult, if not impossible, to answer. However, instead of responding with sarcastic statements due to the ambiguity, which is tempting, it is best to consider neutral answers like: "I do not know," "Difficult to determine at this time," or "Anticipate recovery and return to previous work in 2 months."

In many private disability plans, once an individual has been on LTD beyond 1 year, the criterion of a return to work, instead of a return to the person's previous work, applies; the threshold is "ability for *any* occupation." In many situations the criterion after expiration of LTD benefits is similar to the Social Security criterion for disability determination (see "Social Security System").

A very limited number of *individual disability policies* are available at higher premiums. These policies provide a greater duration of protection and allow disability payments if the holder cannot resume performance of "his or her particular job" due to a medically determined diagnostic condition over an extended period of time, perhaps indefinitely.[14]

Role of the Physician in Private Disability Systems

1. Complete all forms provided by the patient or requested by third-party payers
2. Fill out the forms addressing questions regarding:
   - Diagnosis(es) (when did the disability begin?)
   - The treatment received
   - When the patient will be able to return to some type of restricted work
   - When the patient will be able to resume full-duty work without restrictions (best medical estimate)
   - The dates during which the patient was totally disabled from work (due to the medical diagnoses)
   - What the restrictions are and expectation of how long the disability will last, in cases of permanent disability
   - Any treatment or accommodations that can facilitate a return to gainful employment

Family Medical Leave Act

The federal Family Medical Leave Act (FMLA) was enacted to provide up to 12 weeks of unpaid leave due to "medical necessity." The medical leave applies to either gender and is intended for the purposes of the birth or adoption of a child, care of immediate family members, or an employee's own illness. It provides for unpaid leave and continued hospitalization and life insurance protection for an employee during the period of absence.

Physicians are asked to fill out FMLA forms for patients who need periodic treatment (e.g., physical therapy, injections, counseling that extends over several months) for a definite medical condition or flare-up of symptoms that may need treatment. The FMLA form, although long and confusing, if appropri-

ately filled out and signed by a physician, can allow the individual to take time off work, without pay but without having to use sick days.[14]

The Role of the Physician with Regard to the FMLA

Fill this form out on a timely basis so that the patient may take the necessary unpaid time off work.

The Social Security System

The Social Security Administration (SSA) manages the largest disability program in the United States, assisting 33 to 50% of all persons who qualify as disabled. It includes Social Security Disability Insurance (SSDI), a program established in 1956 to create a fund for workers who were permanently disabled. SSDI is federally administered through SSA and funded through payroll taxes. The application for SSDI is initiated at the state level with the Bureau of Disability Determination. To be eligible, the applicant must have worked in a job covered by SSDI for a minimum period preceding the onset of disability. Pension benefits are paid to those who are totally disabled.

This system also includes Supplemental Security Income (SSI), which is also operated within the SSA as a federal-state partnership. SSI provides benefits to disabled individuals whose income and assets meet minimum criteria according to a "means test." It is funded through general revenue and does not require a work history for eligibility.

Both SSDI and SSI are based on "medically determinable impairments," defined as "an impairment that results from anatomical, physiological or psychological abnormalities which can be shown by medically acceptable clinical and laboratory diagnostic techniques." A physical or mental impairment must be established by medical evidence consisting of signs, symptoms, and laboratory findings.

Eligibility for SSDI, which pays monthly income support benefits to individuals under age 65, is limited to those who meet a working criterion of 20 out of the last 40 quarters and:

- Whose medical condition is severely incapacitating so that they are unable to "engage in any substantial gainful activity (SGA)" by reason of any medically determinable physical or mental impairment that can be expected to result in death or that has lasted or can be expected to last for a continuous period of not less than 12 months
- Who are widows or widowers of a covered individual and who meet the definition of disability
- Who are disabled offspring (children or adult) of a covered individual[14,15]

Role of the Physician in the Social Security System

1. As Rondinelli[14,] emphasizes, it is important to note that statements of symptoms, or a physician's pronouncement that the individual is disabled, without corroborating information, is insufficient to qualify for disability under the Social Security programs.
2. SSDI is an "all or none" disability system. It is a complex system, and the disability determination is made by a disability examiner through the local Disability Determination Services office, or through a hearing examiner or administrative law judge.
3. The patient should fill out the necessary application forms and forward *all* pertinent medical information from treating physicians.
4. If adequate information is not available, the SSA will have one of their "medical consultants" examine the claimant and provide medical information that will be used in the disability determination process.
5. The application uses a sequential five-step process with the option of appeal of any denial decision. The medical opinions of the treating physician, especially on medically based objective impairments, play a significant role in the determination process. Residual Functional Capacities forms are provided for physicians to fill out (there are many body-specific forms, such as for lumbar conditions, fibromyalgia, etc.).
6. Many applicants may need legal assistance to navigate through this complex process.
7. It is important to emphasize again that the physician's role is limited in this system, as opposed to the worker's compensation or personal injury systems. Primary care physicians are frequently perplexed when their patients ask them for assistance to "get them Social Security benefits" and their notes that the person is disabled, without other documentation, proves to be of no value.

Problems and Pitfalls in Assessing Disability

The physician involved in the determination of disability faces the dilemma of objectively quantifying as disability what appears to be a purely subjective phenomenon, especially in patients presenting with only pain as the major basis for disability. It is crucial that physicians play a major role in the determination of impairment by participating in the disability evaluation process.[7,8]

Several authors and groups have attempted to provide guidelines for physicians to perform disability evaluations. Assessment of permanent disability should not occur until completion of adequate and appropriate rehabilitation.[1,2,15] The rehabilitation process, especially for those with chronic pain, should be focused on improving function and clear goal setting. Ample evidence has been shown of the effectiveness of rehabilitation model programs in decreasing, if not reversing, the disability associated with chronic pain.[19]

Other factors complicate the pain–disability relationship. Grossman identified the problem of determining disability by emphasizing that disability is a concept viewed differently by the various professionals who participate in its formulation.[20] He compared the disability evaluation process to the fable of the three blind men asked to describe an elephant, each having touched only one part of the elephant's anatomy and thus viewing things extremely differently from the others. He also pointed out the paradox that the subjectivity of the symptom of pain, justified by the treating physician, is at times not admissible in court, whereas testimony from physicians not treating the patient is frequently admitted.

Weinstein, in an excellent discussion of the disability process, emphasized that work disabilities are commonly the end result of a complex process rather than a direct consequence of a discrete accident or illness.[21] He also pointed out that the "accident process" transforms an *unacceptable* disability, which is equated with weakness and failure, to an *acceptable* disability, which is neither dishonorable nor shameful. He observed that the first phase of the disability process includes a period of tension and stress, with an unwelcome dysphoric state of the worker that includes frustration, insecurity, and a sense of incompetence. This is followed by a second phase that consists of dependency and denial, in which the dependent and passive qualities, along with the inability to accept and acknowledge dependent wishes, are seen. The third phase is that of *injury,* which transforms the employee into someone who is impaired and needs help. There is sympathy because the effects have occurred as the result of an externally generated event, something that "could happen to anyone." Thus, the brief accident process transfers an unacceptable disability into an acceptable one. In the final phase of this process, disability becomes a way of life.[21]

In an interesting article, Goodman discussed the incompatibility of medicine and law.[22] Whereas law students are taught to solve problems through the "inductive or Socratic method," which teaches them to generalize from one single case, physicians are taught "deductive or Aristotelian logic." This process involves generalization of a plan of care through deductive reasoning. The conclusions reached through the deductive process need to be confirmed by studies that are reproducible and statistically significant. Thus, Goodman emphasized that physicians and attorneys involved in the disability process have difficulty communicating because of their differing backgrounds and thought processes.[22]

The basis of disability evaluation frequently depends on the physician's ability to assess "medically determinable and objective impairments." Assessment of disability is hindered by a number of difficulties and false assumptions that are the source of much controversy. First, the physical examination, performed by different physicians, cannot always provide an "objective and consistent method of identifying medically determinable impairments." Second, studies have demonstrated that physicians exhibit great diversity in their evaluation of patients with low back pain, especially in regard to nonneurologic findings such as muscle spasm and guarding.[23]

Radiologic abnormalities are frequently seen without any clinical correlation with symptoms. The Institute of Medicine, after extensive reviews of the literature, also concluded that there is a poor relationship and lack of correlation between objectively demonstrable pathology and an individual patient's functional level and disability.[8]

Special Consideration

Whenever possible, a physical and functional assessment should be incorporated in the assessment of impairment and function.

Can Functional Capacity Assessments Help?

The *functional capacity assessment* (FCA), also referred to as the functional capacity evaluation, is defined as "a quantitative measurement by indirect or direct means of a dynamic aspect of bodily activity necessary in daily living."[1,2,18] The FCA basically involves the examination and assessment of an individual's ability to perform a series of structured activities. To date, however, no "gold standard" of activities exists that can be used to assess FCA. The evaluation of residual functional capacity is a process of measuring an individual's capability to dependably sustain performance in response to a broadly defined work demand, whereas a *physical capacity evaluation* is defined as the intensive and systematic evaluation of an individual's ability to sustain work performance based on his or her present medical, physical, and psychological state and without consideration of the evaluatee's physical potential.

There is significant confusion surrounding the terms *work capacity evaluation, physical capacity evaluation, functional musculoskeletal evaluation,*

ergonomic job analysis, maximum lifting limits, and *FCA*, all of which are used interchangeably. As a result of this lack of objective methods to assess an individual's abilities and disabilities, the FCA has become a growth industry over the decade preceding this text's publication, despite the lack of valid, reproducible, reliable, and acceptable definitions and procedures.[2,18]

Variables such as motivation and cognitive and behavioral factors that affect pain and disability can significantly affect the outcome of functional capacity assessment.

Disability assessment also requires knowledge of the individual's previous education, work experience, specific job demands, and other factors such as age, gender, and socioeconomic and environmental characteristics of the patient.[1,2,13]

Special Consideration

The functional capacity assessment does not reflect what a patient should be able to do, but rather what a patient can do on a particular day, in a particular time period.

The Concept of "Activity Intolerance"

The Task Force on Pain in the Workplace, organized through the International Association for the Study of Pain, focused its analysis on the escalating costs of disability for nonspecific low back pain.[5] Observing the significant increase in disability awards for back pain in the absence of specific back injury, the task force found evidence to suggest that health care providers themselves play a major role in creating disability. The task force observed that "the best evidence suggests that [less] than 15% of persons with back pain can be assigned to one of these categories of specific low back pain." Thus, backache or nonspecific low back pain presents a particularly difficult example in the relationship between pain and suffering and disability wherein the relationship is ambiguous. Fordyce emphasized the many defects in the determination of disability, medically and legally, and in understanding the complaints of back pain for which disability is being awarded.[5]

The Boeing Company performed three studies indicating that biomechanical and ergonomic factors do not appear to be predictors of back injury. Measures of job happiness at the time of entry into the study and personality measures derived from commonly used personality tests were better predictors of future back pain. Those who measured lower on job happiness scales were 2.5 times more likely to file back injury reports, and those with higher scores on scale 3 (i.e., the hysteria scale) of the MMPI were twice as likely to file back injury reports compared with those who had lower scores. All these studies suggest that mood or psychological state has a greater predictive power, albeit modest, than do biomechanical or ergonomic measures in many work settings. The task force also identified the absence of clear age or gender incidence and prevalence patterns, suggesting that back pain–related disability relates to factors other than age or gender. Fordyce introduced the concept of *activity intolerance* as opposed to disability, and pain is one of the major reasons for activity intolerance.[5,11]

The Disability Evaluation Process

The complexity of both the pain phenomenon and the disability evaluating process has been discussed. Some of the dilemmas and controversies regarding the disability evaluation process also have been discussed; however, physicians caring for people with pain are frequently asked to assist in determining the disability status of their patients. Although controversy exists regarding the role of the attending or treating physician in evaluating the disability status, it is essential to recognize that the physician does play a key role in the current, imperfect, systems of disability.[13,19]

The use of opioids in patients with chronic pain presenting for "disability evaluation" poses additional concerns. In 2009 the U.S. Centers for Disease Control and Prevention noted that opioids were involved in 14,800 overdose deaths. Chronic pain research has documented that a high percentage of these patients reveal evidence of depressive symptoms or other psychopathology, mostly preceding the chronic pain complaints. Harmful effects of substance (opioid) abuse include hyperalgesia, endocrine problems, sleep abnormalities, immune deficiency, and cognitive impairments—all leading to a significant increase in the rate of disability. Thus, evaluating individuals with chronic pain and associated dependency or misuse of opioids requires caution in the determination of disability.

The physician plays an important role in providing opinions regarding the following issues[24]:

1. Causation of the injury and the relationship of the injury to pathology/disease
2. Identification of appropriate anatomic, physiologic, and psychological impairments after maximum medical treatment and improvements have occurred
3. Identification of the functional limitations imposed by the *permanent* impairments
4. Relationship of functional limitations to the individual's work activities and future work responsibilities, as well as recreational and social activities

5. Suggestions for future treatment and rehabilitation
6. Statements regarding whether or not the impairments are expected to last up to 12 months or will be permanent
7. Depending on the system, determination of the percentage of disability compared with the "whole person" or to the "scheduled part of the body"

In our opinion, the treating physician, after maximum medical treatment and observation of healing plateau, is best suited to apply the criteria objectively, imperfect as they may be, and to evaluate the individual's disability.

Disability evaluations are frequently requested by attorneys, Social Security agencies, insurance carriers, and other physicians. Over the last 35 years, the senior author of this chapter has performed disability evaluations on patients under his care as well as "independent medical evaluations." Such disability evaluations require a clear understanding of the concepts of pain and disability, as well as of the need to be fair and objective. Many physicians prefer not to be involved in the process, choosing instead to treat the patient's medical problems and refer the patient to other physicians who may be more comfortable with disability evaluation. *By providing adequate and comprehensive medical reports, the assessment of disability is indeed established as part of appropriate treatment for a given patient.*[24]

It is important to prepare a separate, detailed, comprehensive disability evaluation report so that society can compensate the patient for injuries and illnesses adequately. It is also important to make suggestions regarding residual functional capacity.

At a minimum, the disability report should include the following[1,2,13,15,24]:

1. History of injuries and illnesses
2. History of treatment for presenting problem
3. Medical, family, educational, work, and social history
4. Description of present pain status and its effect on physical, psychological, social, economic, and vocational status
5. Detailed neuromusculoskeletal examination (depending on the system involved)
6. Medical diagnosis
7. Summary of objective findings supporting diagnosis
8. Description of impairments
9. Description of functional limitations imposed by the impairments
10. Relationship between functional limitations and work activities
11. Relationship between functional limitations and activities of daily living as well as social and recreational activities
12. Causal relationship between injury and impairments
13. Determination of duration of impairments (permanent?). Such a determination should be done only when all appropriate medical, surgical, physical, and psychological approaches have been exhausted, and a "healing plateau" (MMI) has been reached.
14. Recommendations for future treatment, including medications, equipment, environmental modifications, medical and surgical needs, and rehabilitation needs
15. Expected future course of the condition and its prognosis, especially regarding stability
16. Percentage of impairment and disability, depending on the system involved

Conclusion

Physicians involved in the care of people with pain, especially chronic pain, are frequently asked to determine and certify disability. Timely and appropriate documentation and certification of disability provide the patient with appropriate medical care and financial support during the rehabilitation process. Appropriate insurance forms must be completed to indicate the ongoing inability of the individual to participate in work activities. Some patients may need assistance in obtaining Social Security disability benefits. In such situations, the physician should provide details of the symptoms, signs, and objective medical findings, and a listing of impairments. The Social Security Administration district office will determine whether a disability should be awarded based on the consultation of a disability examiner. In all these situations, the physician should remain objective and thorough and clearly understand the conceptual basis of disability and the complexity of the pain phenomenon.

Physicians involved in the care of those with pain must address the underlying basis for the continued pain and the associated impairments, documenting the persistence of pain and the effects of pain on the psychosocial, physical, and vocational functions so that these issues can be considered during the disability determination process. Assisting with disability determination is an important part of the physician's role in the comprehensive management of individuals with chronic pain.

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Editor's Comments

Disability evaluation is probably one of the most onerous tasks of the surgeon who cares for patients with chronic pain. Speaking from personal experience, avoidance is the initial reflex. In this chapter, Drs. Vasudevan and Ajuwon have clearly come down on the side of physician as patient advocate. As uncomfortable as this relationship might be, I agree that this is part of the contract we make when we accept a patient into our practices, particularly when the patient is postoperative.

If I were to boil down their analysis into a more simplified formulation, it would be:

- *Pain* is a biopsychosocial phenomenon, and as such is not a sufficient indication of disability.
- *Impairments* are usually associated with "objective signs" obtained from physical examination, such as weakness, sensory loss, and deep tendon reflex changes.
- *Disability* ultimately relates to task execution and activity limitations, both of which are often products of pain and either neurologic or mechanical impairment.

Recommendations from this analysis would be:

- Become familiar with the systems of disability relevant to your patient population, including state and federal programs
- Develop a basic working knowledge of the law applicable in your state to the issues of tort claims/personal injury, worker's compensation, and private disability systems
- Develop a basic working knowledge of the federal processes related to the Family Medical Leave Act and the Social Security system
- Comply with the administrative aspects of these systems, to the limit of your expertise

I have taken some liberty with the last bullet point. My own professional expertise is that of a neurosurgeon. I do not consider myself an expert in disability assessment or in many aspects thereof (e.g., physical capacity evaluations). As the patient's advocate, I also do not consider myself an unbiased evaluator. I do consider it part of my professionalism to arrange for and facilitate independent medical examinations, and disability evaluations when requested. I believe I meet this obligation by consulting with respected peer experts, who can apply their expertise in elements of this assessment that I am not competent to complete. I also believe that those who choose to provide these assessments must be specially trained and qualified, and should devote a significant part of their professional activities to this end.

Difficult as it may be, disability assessment is an important aspect of medical and surgical practice. It requires knowledge, expertise, and, in some cases, partnership with other experts to bring the process to an acceptable conclusion.

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12 Pain Treatment in the Dying Patient

Paul Bascom

This chapter will serve as a review of current palliative medicine practices with respect to pain control. Many surgical pain control options for cancer pain have been eclipsed by the hospice movement and, to some degree, better medicine. As care of the dying patient has improved, and as knowledge and skills regarding the relief of suffering have improved and been disseminated, the cases in which pain and suffering are truly intractable and requiring of surgery may be diminishing. This chapter will explore the nature of suffering in dying patients, and describe the options for relieving pain and suffering now widely available to these patients. This should provide some clarity as to what role pain surgery might play in the management of pain in the patient near death.

What Do Dying Patients Want?

The common misperception is that dying patients value freedom from pain above all else. Dying patients actually value many things as highly as pain relief or more so, including cleanliness, dignity, connectedness, humor, and trust.[1] Although receiving life-prolonging treatment is important, avoiding inappropriate prolongation of dying and achieving a sense of control are also important to patients.[2] Another common misperception is that patients want to die at home, yet in one survey dying at home was ranked last among nine preselected attributes regarding end of life. Physician beliefs can be discordant with patient preferences. Patients are more outwardly focused than physicians, valuing maintenance of mental clarity, not being a burden, and being able to help others as they approach the end of life. Generalized statements about preferences obscure the truth that a careful assessment of preferences should be undertaken with each patient. Patients are highly individual in their preferences. Ascertaining these preferences can help guide treatment recommendations.

Pain versus Suffering

Pain and suffering are not the same. This is a most important principle that has emerged from the palliative care movement. Dr. Eric Cassell, in his seminal *New England Journal of Medicine* article and subsequent book,[3,4] shared his insight that pain (and other symptoms) are experiences of the body. Suffering, on the other hand, is an experience of the person.

Persons

Persons are complex entities, consisting of the intrinsic personality and character of each individual. A person also has a past, a present, and an anticipated future. A person has a culture, a profession, and a set of hobbies and interests. Persons have families, parents, siblings, children, and social networks. Finally, Cassell postulates that every person has a secret life of hopes, dreams, and fantasies.

Suffering

Suffering occurs when there is a threat to the integrity of the person, in any or all facets. An injury that prevents an athlete from competing, or a laborer from working, causes suffering to the extent that the injury threatens the ability to continue with that fundamental life activity. Pain can cause suffering when its presence represents a threat to the integrity of the person. Without this threat to integrity, pain may not cause suffering at all. In the classic example of this, the pain of childbirth can be severe, yet it is not associated with suffering. Pain that is quite mild yet heralds the return of an incurable malignancy may be associated with intense suffering.

Relief of Suffering

Pain can be treated successfully, but the suffering will persist as long as the threat to the integrity of the person persists. Generally, as in the case of an injury or medical illness, the body recovers and in that context the suffering also is relieved. In terminal illness, the threat to integrity cannot be relieved, or even ameliorated; thus, the suffering must be alleviated by some other means. Cassell postulates that through meaning and transcendence, persons are able to achieve relief of suffering. That is perhaps the central task of palliative care, to assist in the relief of suffering for patients near the end of life, through attention to meaning and transcendence.

What Is Palliative Medicine?

Palliative medicine originated in Montreal, Canada, in 1975,[5] under the leadership of Dr. Balfour Mount, a urological surgeon. He spearheaded the creation of a palliative care unit, based on the hospice model of care, dedicated to the care of dying patients. Over the ensuing decades, palliative medicine emerged as a distinct medical subspecialty. It now has its own licensing board and mandated fellowship training.

The word *palliate* means, literally, "to cloak." This can generate the connotation[6] that palliative care is nothing more than the "covering up" of problems. Alternatively, the word *palliate* can mean "to shield or protect." This is a much more positive connotation, implying active intervention rather than passivity. The broad domains of palliative medicine include assessment and management of physical symptoms; assisting patients to identify personal goals for end-of-life care; assessment and management of psychological and spiritual needs; assessment of the patient's support system; assessment and communication of estimated prognosis; and assessment of discharge planning issues.[7]

Palliative medicine as an emerging specialty is still in the process of self-definition. The scope and structure of palliative medicine clinical services vary throughout the country, and are dependent on the nurturing of the local culture in determining the extent of involvement in clinical care. Optimally, palliative medicine is fully integrated into the fabric of medical care, as legitimate and accepted as any other medical specialty. In summary, palliative medicine refers to a body of knowledge and a set of skills available to any practitioner that can be applied to any patient with advancing disease.

What Is Hospice?

Hospice refers to a very specific program of services, constrained by very specific eligibility criteria and reimbursement models. Hospice originated in England in the 1960s as a physical place for dying patients to receive care. In the United States, the passage of the Medicare Hospice Benefit has led to the provision of hospice services primarily in a patient's home.

When to Refer

To be eligible for hospice, the patient must be in the last 6 months of life, assuming the disease runs its normal course. This is an important condition that allows some patients to receive hospice care for a year or longer. In actuality, most patients are referred to hospice in the last few weeks of life. This reflects the reality that the 6-months' prognosis is not the most important criterion for hospice care. The more important criterion for hospice eligibility is the willingness of the patient to embrace the goal of comfort and abandon the goal of extending the quantity of life. This means letting go of not only potentially life-prolonging treatments, but also the expectation of returning to the hospital for further diagnostic testing to assess the progress for the disease. For many patients and their physicians, it is not until death is quite near that they are willing to make that change in the direction of care.

Scope of Service

Hospice provides guidance and support for family caregivers and for patients with the primary goal of remaining at home for their last days, weeks, or months of life. Hospice provides multidisciplinary care, including home visits by nurses, social workers, chaplains, bath aides, and volunteers. Hospice programs also offer short-term inpatient stays for acute symptom management, or 5-day respite stays in care facilities to provide caregivers with needed relief. All medications and equipment needs related to the terminal diagnosis are provided by hospice. Importantly, hospice is paid by insurance companies on a per-diem, fixed daily rate. All medication cost must be covered under that per-diem rate. For the pain practitioner and the patient receiving complex pain care, this can be a barrier to hospice care. Many programs, particularly small ones, do not have the volume of low-cost patients to offset the expense of a patient receiving an elaborate treatment regimen for pain.

Palliative Pharmacologic Treatment for Pain beyond Opioids and Interventions

Other chapters in this book (7, 8, 30, and 40) describe various approaches to treating pain in the dying patient. These approaches are at times not completely effective or are associated with intolerable side effects or insurmountable logistic barriers. Oral and intravenous opioids are associated with tolerance and decreasing effectiveness over time. Most important, the notion that there is no dose ceiling for opioids has been refuted clearly in the laboratory and by clinical experience. The most important side effect of chronic high-dose opioid therapy is not respiratory depression, but hyperalgesia.[8] At times hyperalgesia can be ameliorated by rotation to an alternate opioid, but in other cases it presents an intractable barrier to effective analgesia. Delirium and sedation are also often ascribed to opioid therapy and are seen as dose-limiting side effects. In the dying patient, delirium and sedation more commonly are the products of advancing disease and the proximity of death. Misguided attempts to reverse sedation or delirium by decreasing opioid doses only expose the dying patient to unnecessary pain.

Interventional therapies (IT) such as intrathecal opiates or neurolytic blocks are often effective for intractable pain states. However, common contraindications to IT include coagulopathies and smoldering infection, precluding the use of IT in many dying patients.

There are several nonopioid systemic pharmacologic agents used for the treatment of pain in the dying patient, when traditional therapies are ineffective or contraindicated.

Ketamine

Ketamine is a novel dissociative anesthetic. At subanesthetic doses it can produce an analgesic effect independent of the opioid receptor action. There is a growing literature regarding the use of ketamine in intractable pain near the end of life.[9–13] Use of ketamine often may allow a dramatic reduction in opioid dosing and concomitant amelioration of opioid hyperalgesia. However, a recent randomized, placebo-controlled trial of the use of ketamine in intractable cancer pain failed to show efficacy.[14]

Barbiturates

Barbiturates were first discussed as treatment for refractory symptoms in the 1990s.[15,16] Because of their association with lethal injection for capital punishment the use of barbiturates has remained controversial. This is unfortunate because the barbiturate class of medications can be very effective in producing a degree of calm and escape from distressing pain and suffering.[17] Treatment protocols are now beginning to include barbiturates for the treatment of refractory symptoms. Phenobarbital is dispensed in 65 and 130 mg/mL vials. These can be administered SC or by slow IV push. PRN doses of 65 to 130 mg can be given every 1 hour until symptoms are controlled. Phenobarbital has a very long half-life, so once an effective loading dose is administered, subsequent doses may be required only every 4 to 24 hours. A continuous infusion is useful if preferred by patients and families for ease of administration. Barbiturates are easily administered in a home or hospice setting.

Propofol

Propofol use for refractory symptoms probably should occur only in a controlled hospital setting. There is increasing literature on its utility in intractable symptoms near the end of life.[18,19]

Patient Selection for Surgical Treatment of Pain in the Dying Patient

Most patients with even severe pain and symptoms near the end of life will achieve acceptable degrees of pain relief and escape from suffering through the treatment modalities discussed above. The question, then, is how to select the rare patient who might benefit from pain surgery as a treatment modality.

Case Examples

Case 1

Patient C.R. is a 50-year-old man with a primary sarcoma of the sacrum. It was unresectable at presentation. He received chemotherapy and radiation

therapy and achieved a complete remission. Several years later, after many months of progressive radicular symptoms, a local recurrence was confirmed, involving the entirety of the sacrum and encasing the nerve roots. No distant disease was noted. Chemotherapy and subsequent radiation therapy were administered, and disease progression was slowed somewhat. He was referred for palliative care evaluation. The patient understands that cure is no longer possible and admits, "I have to be realistic." He has debilitating pain down his leg. Urinary retention and foot drop have developed. He has only marginal pain control. He was offered referral for surgical intervention for pain. However, he preferred to tolerate this level of discomfort, employing only oral analgesics and coanalgesics. Three months later he remains uncomfortable but continues to defer surgical intervention.

Case 2

Mr. R.C. is a 50-year-old man with a primary sarcoma of the arm. This was resected successfully. However, he had severe ongoing pain in the extremity due to scar tissue, despite no evidence of recurrence disease. The following year, he developed pleural-based metastases in the chest that were associated with severe pleuritic pain. These responded radiographically to chemotherapy although disabling pain persisted. He was referred for palliative care evaluation. His wife remarked that "he isn't who he used to be." She noted that he was depressed, not the vibrant, hard-charging executive she once knew. "He hasn't allowed any of our friends over to visit or help." The palliative care consultant noted that the wife felt "helpless and frustrated and very, very worried." Referral for pain surgery led to a recommendation for chordotomy, which the patient agreed to. However, pain persisted and a follow-up computed tomography (CT) scan 2 weeks after surgery showed marked progression of disease. The patient died 2 weeks later.

Prognostication

The key question that must be answered as accurately as possible before embarking on surgical treatment of pain is: How long will the patient live? Even the most effective surgical intervention is likely not worth its attendant risks and burdens if the patient's survival is measured in just days or a few weeks. Studies have shown that doctors are not particularly accurate in their prognostication.[20] Inaccuracy in prognostication does not mean that the question should be avoided and considered unanswerable. Our palliative care team has made incorporation of estimated prognosis a central part of our patient assessment.[21] Full disclosure to the patient regarding variability or inaccuracy of prognosis should be part of every informed consent discussion.

Patient Selection

Dying patients for whom surgery should be considered will typically have slowly progressive disease, and an extended prognosis of months rather than weeks. Pain should be their primary source of distress. Those patients with extensive suffering related to psychiatric or existential issues such as anxiety or ongoing denial of mortality will likely be poor candidates for surgical intervention. In those patients, surgery may be pursued as an option because it feels better emotionally than "doing nothing." This will tend to minimize the risks and overstate the potential benefits for surgery. Furthermore, relief of pain will not lead to relief of suffering.

Death with Dignity

In 1994, Oregon became the first state to permit physicians to prescribe a lethal dose of medication for the patient near the end of life to self-administer with the goal of hastening death. Since then Washington and Montana have followed suit. Oregon's experience in "death with dignity" underscores the general message of this chapter.[22,23] Patients who seek lethal medication are motivated by a desire to control the time and manner of their death, and to avoid the inevitable dependency that accompanies progressive illness. Pain in only rare cases is a valid motivation to seek hastening of death. Most patients with pain are satisfied with the degree of pain relief provided by expert palliative care. In rare instances, medicating to the point of decreased awareness until inevitable death is a suitable alternative for patients with pain that is truly refractory to all interventions.

Editor's Comments

Dr. Bascom makes many important points in this chapter. The fact is that in most venues, referrals to surgeons for pain-relieving procedures have fallen off radically in the past decade. The risk is that, given the low utilization of these procedures, a generation of neurosurgeons and other interventionalists effectively have never seen or been taught these surgical modalities. This will have future consequences for patients with terminal illnesses who might well have benefited from pain surgery, save for the absence of available expertise. For this reason, I believe it is important that procedures that may relieve pain continue to be incorporated in the curriculum of neurosurgical training.

Dr. Bascom comments:

Dying patients for whom surgery should be considered will typically have slowly progressive disease, and an extended prognosis of months rather than weeks.

This is perhaps the most important message for the pain surgeon, in that palliative surgical procedures are likely ill conceived if the patient's predicted survival is short. In these cases, nonsurgical measures are almost always superior. Alternatively, intractable pain associated with slowly progressive disease could include such problems as disseminated prostate or breast carcinoma, and even certain nonmalignant conditions. It is for these patients that surgical pain control can offer substantial benefits, and for whom the preservation of expertise in reasonable, preferably minimally invasive surgical measures remains relevant.

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Section III

Pain Diagnoses and Their Nonsurgical Management

Section III.A

Back Pain

13 Back Pain: The Evidence for Nonsurgical Management

Richard A. Deyo and Roger Chou

Understanding the role of nonsurgical treatments for back pain or sciatica requires evaluating two types of evidence. First, we consider evidence that these treatments are more effective than placebo. Next, we consider whether these treatments can be as effective as surgical interventions.

Although the management of acute back pain or sciatica is usually nonsurgical, we focus here on chronic back pain or radiculopathy. This is the most common situation in specialty care, and especially in neurosurgical practice.

■ Principles

In comparing nonsurgical treatments with either placebo or surgery, we focus on randomized controlled trials (RCTs). These offer the greatest likelihood of arriving at valid inferences regarding treatment efficacy.

There are few RCTs focusing on surgical versus nonsurgical care for back pain or sciatica. In part, this is due to important differences between surgical trials and drug trials. Unlike pills, which are identical, every operation is unique, due to variations among patients, surgical preferences, and surgical skills. Blinding patients to therapy, if possible at all, is more difficult than in drug trials. Blinding surgeons to treatment assignment is impossible. In a drug trial, the intervention can usually be reversed (the drug stopped), but surgical alterations to anatomy are generally permanent. For all these reasons, achieving equipoise among patients and clinicians in the choice of therapy is often harder in surgical than in nonsurgical studies, making patient recruitment more difficult.

Chronic back pain fits best into a biopsychosocial model. That is, patient symptoms, presentation, and therapeutic response often depend on a complex interaction among physical pathology, psychological characteristics, and social influences. So, for example, physical examination and imaging (biology), depression (psychological characteristics), and worker's compensation proceedings (social influences) may all be important factors in choosing treatments and predicting responses.

An important philosophical shift regarding nonsurgical therapy has occurred in recent decades. Whereas bed rest was once a near-universal prescription for back pain or sciatica, multiple RCTs now indicate that it is ineffective.[1] Evidence suggests that early return to activity is preferable. In fact, evidence-based guidelines now emphasize the role of active exercise and cognitive behavioral therapy over passive treatments such as pills, office manipulations, or procedures to manage chronic back pain.

Actual practices—and insurance coverage—have sometimes lagged behind this philosophical shift. Thus, some treatments may be overused (e.g., opioid therapy, certain injections, and certain types of surgery) whereas other, more active treatments may be underused, including exercise therapy and cognitive behavioral therapy.[2,3]

■ Practice

Pharmacologic Therapies

Medications are the most frequently recommended intervention for back pain.[4–9] Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDS) are weak to moderate analgesics, but are often firstline medications because of their relative safety. However, higher doses of acetaminophen can cause liver toxicity, and most NSAIDS increase risk for myocardial infarction and gastrointestinal bleeding.

Opioids are potent analgesics for acute pain, but they have a potential for abuse and addiction, and may not be as effective for chronic pain.[10] Recent increases in prescription opioid overdoses have paralleled marked increases in prescribing, suggesting a need for greater caution in the use of opioids for chronic low back pain.[11]

Tramadol and tapentadol have a dual mode of action, effectively acting as norepinephrine reuptake inhibitors as well as having an affinity for opioid m-receptors. Their opioid receptor affinity is many times lower than that of morphine,[12,13] but their analgesic effects are only two or three times lower.

Skeletal muscle relaxants are pharmacologically unrelated drugs grouped because of their use for spasticity or musculoskeletal conditions. Drugs approved by the U.S. Food and Drug Administration (FDA) for treatment of spasticity are baclofen, tizanidine, and dantrolene; those approved for treatment of musculoskeletal conditions are carisoprodol, chlorzoxazone, cyclobenzaprine, metaxolone, methocarbamol, and orphenadrine. Other than dantrolene (rarely used for back pain because of hepatoxicity risk), effects of these drugs may be mediated through general sedation rather than direct skeletal muscle relaxation. Benzodiazepines have sedative, anxiolytic, and antiepileptic effects. Although often used as an alternative to skeletal muscle relaxants, they are not FDA-approved for this indication.

Depression is common with chronic pain.[14] However, antidepressants may have analgesic effects that are largely independent of underlying depression.[15] Analgesic effects of antidepressants vary, and seem strongest with tricyclic antidepressants and serotonin norepinephrine reuptake inhibitors (SNRIs).

Exercise Therapy

Many types of exercise are used in patients with chronic back pain, including core strengthening (e.g., abdominal and trunk extensor), flexion/extension movements, directional preference, general physical fitness, aerobic exercise, mind–body exercises (e.g., yoga and pilates), and combinations of these.[16]

Physical Modalities

Physical modalities include interferential therapy (alternating current at frequencies up to 150 Hz), low-level laser therapy (single-wavelength light between 632 and 904 nm), ultrasound, shortwave diathermy (shortwave electromagnetic radiation at 10–100 MHz), and transcutaneous electrical nerve stimulation, or TENS (electrical stimulation through surface electrodes).[17] Traction involves pulling to distract the lumbar spine.

Psychological Approaches and Interdisciplinary Rehabilitation

Psychological approaches to chronic back pain include cognitive-behavioral therapy, relaxation techniques, and biofeedback.[18] Many of these approaches focus on maladaptive behaviors such as fear avoidance (avoiding normal activities for fear they will harm the back) and catastrophizing (dwelling on the worst possible outcome). They also often address depression and anxiety. Psychological approaches are central to interdisciplinary rehabilitation, combining exercise, vocational, and behavioral components.[19]

Complementary and Alternative Medicine Treatments

The most common alternative medical applications for back pain are spinal manipulation, acupuncture, and massage. Manipulation involves extending a joint beyond its usual end range of motion using high-velocity movements. It may be used in conjunction with mobilization (low-velocity movements).

Injections

Trigger point injections use local anesthetic, with or without a steroid, theoretically relieving painful muscle spasms. Prolotherapy (or sclerotherapy) involves repeated injection of irritants into ligaments and tendinous attachments. The resulting inflammation theoretically strengthens ligaments and reduces pain.

Corticosteroid injections are performed most commonly in the epidural space, facet joint, or sacroiliac joint. Although typically used to reduce inflammation causing radiculopathy, epidural injections have also been used for axial low back pain.

Ablative Procedures

Radiofrequency denervation involves destruction of nerves using heat generated by radiofrequency current. It is most often used for presumed facet joint pain, targeting the medial branch of the primary dorsal ramus. Intradiscal electrothermal therapy (IDET) is designed to destroy nerves in the intervertebral disk for discogenic back pain. Percutaneous intradiscal radiofrequency thermocoagulation (PIRFT) is similar, but heat is generated by an alternating radiofrequency current.

■ Outcomes

Pharmacologic Therapies

Short courses of acetaminophen or NSAIDS are effective for acute exacerbations of chronic back pain.[20] NSAIDS are associated with an average improvement

of 8 points (on a 100-point scale) compared with placebo.[21] Recently, the first placebo-controlled trial of acetaminophen found no benefits in pain, function, or time to recovery in patients with acute low back pain, suggesting it is not useful for this condition.[21]

Evidence on opioids for back pain is sparse, with few high-quality or long-term trials and limited evidence of pain reduction compared with placebo or nonopioid analgesics.[22,23] Some trials found moderate effects compared with placebo (17–23 points on a 100-point pain scale).[24,25] For chronic pain in general, opioids are moderately effective (mean improvement about 30%), but effects on function are minor and trials were brief.[26,27] Opioids are generally recommended for short-term therapy in appropriately selected patients who have not responded to simple analgesics or other interventions.

Skeletal muscle relaxants are more effective than placebo for acute low back pain, but are also associated with more sedation.[28] They are an option in patients with acute exacerbations of chronic back pain. Data on effectiveness of benzodiazepines are limited. Because of their potential for addiction and abuse, they should not be used for long-term treatment of back pain, and should be used only cautiously as a short-term measure.

Data on analgesic effects of tricyclic antidepressants in patients with back pain are inconsistent.[29–31] Recent trials found the SNRI duloxetine to have a small advantage over placebo for back pain (< 1 point on 10-point scales of pain and function).[32–34] Given the small benefits and the side effects, antidepressants are not firstline medications for back pain. But depression is common with chronic pain and should be treated appropriately.

Few trials evaluated antiepileptic medications for back pain. For radiculopathy, trials of gabapentin, pregabalin, and topiramate showed small or unclear effects.[35–38] For nonradicular low back pain, one trial found topiramate more effective than placebo for pain; another trial found no difference between gabapentin and placebo in pain or function.[39,40] Better trials are needed before antiepileptics can be recommended.

Exercise Therapy

Exercise is a cornerstone of therapy for chronic low back pain. It is safe, is readily available, alleviates pain symptoms (average 10 points on a 100-point scale), improves function (average 3 points on a 100-point scale), and has additional health benefits.[41] There are no clear differences in pain relief or functional improvement among different types of exercise, although supervised programs that involve individualized regimens, stretching, and strengthening may be most effective.[43]

Physical Modalities

There is no convincing evidence that interferential therapy, shortwave diathermy, ultrasound, traction, or TENS is effective for back pain.[16,43,44] A systematic review suggested short-term relief of back pain with low-level laser therapy versus sham, but variability in treatment protocols precluded firm conclusions.[46]

Psychological Approaches and Interdisciplinary Rehabilitation

Cognitive-behavioral therapy is superior to wait-list control for short-term relief of chronic back pain.[18,46,47] Evidence is less conclusive for other psychological interventions, although some evidence suggests benefits from biofeedback and progressive relaxation. Psychological approaches may be particularly useful in patients with maladaptive coping strategies. Intensive interdisciplinary therapy, involving several hours of supervised treatment on most days, including psychological, exercise, and other components is more effective than noninterdisciplinary rehabilitation for chronic low back pain, especially in patients who are severely disabled or have a strong psychological component to their pain.[16,48]

Complementary and Alternative Medicine Treatments

Spinal manipulation is moderately superior to sham manipulation, but not compared with general practitioner care, analgesics, physical therapy, exercises, or back school.[49] Serious adverse effects (e.g., neurologic deterioration) are rare among patients without progressive or severe neurologic deficits.[50,51] Evidence on acupuncture is mixed. Although RCTs found acupuncture more effective than no acupuncture for low back pain, it is unclear whether it is more effective than sham acupuncture, perhaps due to attributes of superficial stimulation or placebo effects, which may be affected by expectations of benefit.[52,53] Massage may be effective for chronic back pain, especially in combination with exercise and education, but effects are minor.[54] All three of these interventions are reasonable options for patients with chronic low back pain.[55]

Injections

For radiculopathy, some RCTs found that epidural steroid injection decreased short-term pain compared with placebo.[17] However, results were inconsistent, functional benefits were small, and there were no effects on chronic pain or need for surgery. There is insufficient

evidence to determine whether the transforaminal approach, using fluoroscopy, is superior to translaminar or caudal approaches for epidural injections.

Trials of epidural steroid injections for spinal stenosis associated with neurogenic claudication, including the largest, well-conducted study, found no benefit versus a placebo injection.[56]

Evidence on injections for axial back pain is sparse, with few trials, small samples, and inconsistent results.[17] Their role in chronic back pain should be limited (if used at all), and only after alternatives fail. It is unclear whether their minimal efficacy is due to ineffectiveness of injections or inability to reliably identify specific pain sources.

There is no high-quality evidence that trigger point injections are effective for back pain, and trials of prolotherapy showed no benefit versus placebo injection.[17]

A single small trial evaluated epidural corticosteroid injections for axial back pain, showing no benefit.[57] Epidural steroid injections are associated with infrequent serious adverse events, including dural puncture, infection, and bleeding.[17] Two trials found no clear effects of facet joint steroid injections compared with placebo.[58,59] A small trial found periarticular sacroiliac steroid injection more effective than local anesthetic, but results have not been replicated.[60] There are no RCTs of intra-articular sacroiliac steroid injection in patients without spondyloarthropathy.

Ablative Procedures

Two small RCTs of IDET in patients with presumed discogenic back pain (based on discography) reported inconsistent results, with one finding no benefit.[61,62] Two small RCTs found no differences between PIRFT and a sham procedure.[63,64] For radiofrequency denervation, a trial using controlled facet blocks to identify subjects and an extensive denervation technique found moderately greater reduction (–1.4 to –1.9 points on a 10-point scale) in pain after 6 months compared with sham.[65] However, the study was small (n = 40), there were significant differences in baseline pain, final pain scores were similar between groups, and results did not reach statistical significance for back pain. Two sham-controlled trials for presumed facet joint pain (based on uncontrolled diagnostic blocks) reported conflicting results for radiofrequency denervation, with one finding no effect.[66,67] An additional trial (N = 82) found no difference between radiofrequency denervation and sham, but may have used an inadequate technique.[68]

A small trial (N = 20) of patients with chronic presumed sacroiliac joint pain found greater pain relief with radiofrequency denervation compared with sham denervation at 1 month (79% vs. 14%, $p < 0.05$), with benefits that persisted through 6 months.[69] Given that this was a single, very small trial, more studies are needed for confirmation.

Nonsurgical Treatments versus Surgical Care

Discectomy for Herniated Disk with Radiculopathy

Several RCTs have compared discectomy with nonsurgical care. These trials all excluded patients with major or progressive neurologic deficits, but included some patients with stable, minor deficits. All required several weeks of unsuccessful nonsurgical care prior to patient enrollment. These trials compared discectomy to a variety of nonsurgical interventions, typically including medication, physical therapy, injections, and education.[70]

Results of these trials are generally consistent, suggesting faster relief of pain with surgical than nonsurgical therapy. However, in long-term follow-up, nonsurgical treatments resulted in improvement as well; the conclusion was that surgical and nonsurgical results were similar after 1 to 4 years, depending on the study. In each trial, some patients in the nonsurgery arm—although a minority—underwent subsequent surgery. Their results seemed equivalent to those of patients who had immediate surgery, suggesting no harm in the delay.[71,72] Not only have pain relief and functional recovery been equivalent in the long run, but recovery of foot dorsiflexion or plantar flexion weakness has also been equivalent, where this was assessed.[73] Thus, people might reasonably choose either surgical or nonsurgical care, depending on their preferences for immediate relief, aversion to surgical risk, or other personal considerations.

Fusion or Disk Replacement for Axial Back Pain with Degenerated Disks

This may be the most controversial surgical indication in today's spine treatment world. Nonetheless, this is the fastest-growing indication for fusion surgery and the most common reason for performing lumbar fusion.[74]

Two randomized trials suggest a small advantage of lumbar fusion surgery over nonsurgical care for patients with one- or two-level disk degeneration, compared with nonstandardized conservative care or minimal rehabilitation.[75,76] However, two other RCTs suggest little or no advantage of fusion surgery over highly structured rehabilitation incorporating graded exercises and cognitive-behavioral therapy.[77,78] Complications of fusion surgery are more common than complications with decompression alone, making this an important consideration in clinical decisions.[79]

Disk replacement trials have suggested that this procedure is noninferior to fusion surgery. In the RCTs conducted for FDA approval, both disk replacement and fusion procedures had success rates near 50%. Neither was highly successful in helping patients to stop opioid therapy for pain.[80,81]

Overall, the evidence suggests no major advantage of surgical therapy over rigorous structured rehabilitation for patients with axial pain and disk degeneration.

Decompression for Lumbar Stenosis with Leg Pain

A few RCTs compared decompression with nonsurgical care for lumbar stenosis with leg pain.[82] Despite flaws, including many crossovers in one trial, results suggested an advantage of surgical over nonsurgical therapy in pain relief and functional recovery at 2 years of follow-up. In these trials, surgery was generally decompression alone, with few fusion procedures included. Thus, indications for fusion in lumbar stenosis remain unclear.

Evidence for the efficacy of most conservative treatments for lumbar stenosis is weak.[83,84] However, given the age and comorbidity of older patients with stenosis, and the usually indolent course of symptoms, patients should be well informed about natural history, surgical risks, and surgical benefits and be involved in treatment decisions.

Fusion for Spondylolisthesis with Leg Pain

There are randomized trials for both degenerative spondylolisthesis and isthmic spondylolisthesis suggesting a benefit of fusion surgery over nonsurgical treatments for patients with back and leg pain that have lasted for many months despite rigorous nonsurgical care.[85,86]

Repeat Surgery

One RCT compared surgical versus nonsurgical treatment following previous back surgery. This study compared instrumented posterolateral lumbar fusion with exercise plus cognitive-behavioral therapy for patients with chronic back pain following lumbar discectomy. In this trial, fusion and rehabilitation produced similar results in pain and function, with a nonsignificant trend in favor of nonsurgical therapy.[87]

Shared Decision Making

Shared decision making is a term that refers to the active involvement of patients, along with their physicians, in making decisions about elective care. Because most back surgery is elective, and aimed at pain relief, this model seems appropriate. To be meaningfully involved, patients must be well informed about their options, with best estimates of the benefits and risks of each.

Because the best evidence, tailored to diagnosis, procedure, and patient age, may not be at a surgeon's fingertips, and may be time-consuming to convey, some advocate decision aids to assist in the process. These decision aids might be written, audio, or video materials that patients could view at their convenience. The goal is not to replace discussion between doctor and patient, but to facilitate and enhance it.

A computer-based videodisc program designed for this purpose addressed surgery for lumbar herniated disks, spinal stenosis, or back pain. In an RCT, compared with written materials alone, the video program resulted in better patient knowledge about the decisions, and appeared to influence treatment decisions.[88,89]

Patients with a herniated disk who watched the video program had a relative reduction in surgery of 30%, yet their outcomes were equivalent after 1 year to those for patients who had just written materials and a higher surgery rate. In contrast, patients with lumbar stenosis who viewed the video program had more surgery, perhaps based on outcome probabilities presented in the program. Patients with back pain alone who saw the video program chose less surgery, but differences were not statistically significant. Given both the uncertainties and nuanced differences in outcome between surgical and nonsurgical care for most degenerative spinal conditions, such decision aids may become a useful adjunct in routine care.

Conclusion

Several nonsurgical treatments for chronic low back pain offer some benefit. However, the evidence supporting many popular treatments remains sparse. Some treatments are used in situations with little evidence of efficacy, whereas others may be underused. Exercise and cognitive-behavioral therapy appear to be underemployed.

Any advantage of surgery over nonsurgical care varies by indication. For patients with a lumbar herniated disk and radiculopathy, and no major neurologic deficits, discectomy offers faster relief, but long-term results are similar with or without surgery. For lumbar stenosis with leg pain, symptoms are often stable for long periods, but decompression offers advantages when nonsurgical treatments are insufficient. For this older population, surgical complications are more common, and benefits and risks must be carefully weighed. Patients with spondylo-

listhesis who fail prolonged nonsurgical care appear to benefit from fusion surgery. The value of fusion for axial back pain with degenerative disks, or for chronic back pain following disk surgery, appears to be meager and remains controversial, although the procedure is performed with increasing frequency. For elective lumbar surgery, shared decision making may be a valuable strategy for making clinical decisions.

Editor's Comments

It is always a pleasure to read work authored by Drs. Deyo and Chou. It is invigorating to have our surgical concepts of spinal care so thoroughly challenged by ugly facts.

This chapter may seem out of place in a textbook on surgical pain management. However, I would argue that two conditions make this contribution mandatory. First, the incidence of back pain dwarfs all other pain complaints. Second, the so-called failed back surgery syndrome (FBSS) is one of the most pernicious, and costly, chronic pain states. Deyo and Chou have armed us with the necessary information upon which to anchor a critical decision process on this topic.

As we will see in Chapter 14, the provision of what in retrospect appears to be inappropriate, or unnecessary, spinal surgery is probably the leading cause of FBSS. The evidence seems to support several classes of surgery, but each has its caveats.

Surgery for a herniated disk, after a relatively brief course of nonoperative management, does seem to speed up recovery, although long-term results with conservative management produce comparable outcomes. Although this may be true, most surgeons recognize that, at least in the United States, a wait of 1 to 4 years for the average patient to recover is simply not a viable option. During that long interval, occupational pressures might be substantial, employment might be jeopardized, and insurance status could deteriorate, to say nothing of familial and avocational activities. In this case, speeding up recovery is a defensible option.

Although surgery for nonspecific symptoms of "lumbar spinal stenosis," such as back pain, is dubious, decompression for the syndrome of "neurogenic claudication" (i.e., pain, weakness, and numbness in the legs that occurs when ambulating) is highly effective in relieving these symptoms. The mechanism of these symptoms appears to be hypoxia of the nerve roots of the cauda equina due to narrowing of the lumbar spinal canal, and decompression typically relieves this. This is usually very effective surgery, despite the higher incidence of medical complications in what is typically an older patient population.

I would also argue that lumbar fusion for back or leg pain thought to be due to demonstrable spondylolisthesis, either degenerative or isthmic, is also reasonable. The data seem to point in that direction, and that is the experience of most spine surgeons.

I would argue that although obtaining more data is essential, the three procedures noted above are reasonable indications for lumbar spine surgery. Unfortunately, and as the authors point out, the most common and fastest-growing indication for lumbar fusion is degenerative disk disease with attendant back pain. I would agree with their comment that "[t]he value of fusion for axial back pain with degenerative disks, or for chronic back pain following disk surgery, appears to be meager and remains controversial." Whereas many would take exception to this statement, I believe the evidence, or lack thereof, speaks for itself. If fusion does work for back pain, independent of neurogenic claudication, and for spondylolisthesis, then it should be possible to prove that it does, through a prospective randomized trial. Until that happens, we will be left with uncertainty.

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14 Failed Back Syndrome: Etiology, Assessment, and Treatment

Donlin M. Long

The term *failed back syndrome* is commonly used to denote a heterogeneous group of patients who share one characteristic: They have persisting symptoms after one or more operations on the lumbar spine. Once this general descriptor is used to identify a group of patients, it has the unfortunate effect of obscuring specific diagnoses. Physicians and others may use this pejorative categorization to excuse failure to examine these patients in detail and individualize both prognosis and therapy.

The first goal when evaluating a patient who has failed previous interventions for pain of the lumbar spine should be an accurate anatomic characterization of the abnormalities and the most specific diagnosis possible. Only then will it be feasible to individualize therapy. To take these steps, it is necessary to have a framework for thinking about these problems and a categorization schema with which to identify them. There is no universal classification system for spinal problems of any kind. I use the simple technique of beginning with categories relating to cause of problem and then try to make specific diagnoses that seem to be related to the pain complaints. Another major problem is that no one knows why most patients with low back problems have pain. Because we cannot identify the pain generators for most patients with first-time low back complaints, it is not surprising that we do not know why patients with more complex problems hurt.[1] At present, clinical correlations between pathological diagnoses and pain are the best we have to work with in most situations.[2–4]

My own personal experience is with 7,046 patients with failed back syndrome who were seen over a 30-year period. Of these patients, 2,067 eventually came to surgery. All patients were entered into the cohort sequentially and followed after initial evaluation. At 1 year, 96% of patients underwent reevaluation. Median follow-up for those operated upon was 5.6 years. Median follow-up for those who were not operated upon was 3.5 years. The median number of operations these patients had undergone was 2.1. Thus, half the patients had one or two operations and half of the patients had three or more. Of the patients who came to surgery 71.5% had undergone one or two operations and only 28.5% had undergone three or more operations. In contrast, of the 4,979 patients who did not undergo further surgery, 61.4% had undergone three or more operations and 38.6% had undergone one or two operations. Much of what I suggest here is drawn from these patients.

Theoretical Causes of Low Back Pain

Because back and leg pain often are unaccompanied by obvious diagnosable instability or clearly defined nerve root compression, extensive investigations into possible causes of the pain have been done. In some patients, it appears that the pain arises mostly from ligaments and muscle; at least no other causes have been defined. Three other lines of investigation are being followed. The first of these suggests that the pain may be neuropathic in type and may originate from minor degrees of demyelinization and sensitization probably accompanied by central receptor changes. Numerous factors and possible mechanisms are being examined, none of which are clearly applicable to typical patients with chronic back and leg pain as yet.

A second important line of inquiry suggests that the nerve activation and sensitization are secondary to the release of inflammatory products secondary to disk degeneration, spondylotic changes, or surgical trauma.[5,6]

A third general category is termed by its originators *micro-movement.* In this theory, the noxious stimuli come from small but abnormal degrees of movement in zygapophyseal joints and in and around the disk. These movements presumably would activate nociceptors in ligaments, periosteum, and muscles.

None of these has proved important in patients as yet, and investigations are ongoing. All have clinical implications. The concept that the pain is neuropathic has led to trials of drugs known to affect neuropathic pain. The theory of release of noxious products of the inflammatory cascade led some to advocate total disk removal to eliminate the inflammatory process and stabilize the spine,[7–10] and the concept of micromovement has led to fusion, mainly of the interbody type. Steroid injections are thought to affect the inflammatory process.

Causes of Failed Back Syndrome

It is convenient to think about the origins of persisting pain in broad categories that have been identified by substantial clinical experience of many experts. The first category comprises patients in whom there has been a failure to correct the underlying pathology. The original problem persists despite whatever intervention was carried out. A typical example is the patient who has ongoing foraminal compression of a nerve root following decompressive laminectomy. The second major category comprises patients who have suffered a significant complication of their operative procedure. Arachnoiditis is an example of such a problem. Failure of fusion is also very common. The third major category includes patients who had an intervention performed when they did not meet currently accepted criteria for surgery. A fourth, much smaller group is patients in whom a disease exists that simply cannot be effectively recognized or treated by any intervention currently.[11–15]

Technical Issues with Previous Surgery

The most common unrelieved abnormality was foraminal stenosis. Next came missed, inadequately removed, or an immediately recurrent disk after first surgery. Unrelieved spinal stenosis was the third factor. Uncorrected instability was fourth. Missed lateral disk, late recurrent disk, and incorrect localization of original herniation were less common.

Postsurgical Complications

The most common abnormality was demonstrated instability following surgical disruptions of the pars articularis or zygapophyseal joint. However, the simple presence of a disrupted joint did not predict pain from that abnormality. The patients with measured movement on dynamic imaging studies usually had related pain, but it was not universal. The patients without demonstrated movement did not have predictable association of the anatomic defect with pain. Apparent neural injury was the next most common diagnosis. The diagnosis was based upon the character of the pain, the physical abnormalities, and confirmatory electromyography. Postoperative infection was also an important problem. Pseudomeningocele was another common problem.

Postfusion Complications

Pseudarthrosis was the most common abnormality. Misplaced screws or other hardware components and late disruption of the construct were both important. Late loosening of screws was the most common hardware event occurring well after surgery.

A few patients were found to have been operated upon with an erroneous diagnosis. Five patients were found to have intradural tumors or cysts or nerve root tumors. Two patients had thoracic dural venous fistulaes.

A small group of patients had continued spinal pain in spite of technically successful surgery secondary to underlying spinal disease. The causes included ankylosing spondylitis, rheumatoid arthritis, Scheuermann disease, and connective tissue disorders such as Marfan and Ehlers-Danlos syndromes.

Remember that hip disease can masquerade as back pain with sciatica and so can sacroiliac joint disease. The provocative tests for both may be important to include, if the pain is sacral, gluteal, and with a nondescript sciatic component.

If there are complaints of bowel, bladder, and sexual dysfunction, a pelvic, genital, and rectal examination can be included. Most spine surgeons are not particularly expert in these examinations, and if the suspicions are strong enough, referral to urology or gynecology may be indicated.

Special Consideration

The failed back syndrome occurs in patients (1) whose original problem persists despite intervention, (2) who suffered a surgical complication, and (3) who suffer from a disease that cannot be effectively treated.

Evaluation of the Failed Back Syndrome

The history is the most important part of the initial evaluation. Physical examination rarely assists in a definitive diagnosis and is principally useful to determine a patient's deficits and levels of function, but the patient often will state the diagnosis during the history. Once the standard history is obtained

and the sequence of events is recorded, it is important to determine the patient's exact problem at this time and how it relates to the complaints that led to the initial surgery or surgeries. Where is the pain now? Where is the worst pain, and where is it referred? What improves the pain? What exacerbates it? By answering these simple questions, we learn the severity of the pain and its spatial and temporal characteristics, which are helpful in the initial diagnosis.

Initial data from the National Low Back Pain Study suggested four broad categories of complaints that have statistically significant importance to the clinician. The data were derived from analysis of 2,735 patients referred to orthopedists and neurosurgeons with complaints of back pain. The first broad category included patients complaining of *back pain only,* in whom radicular compression signs and symptoms were almost nonexistent. These patients rarely required surgery and of all groups responded best to conservative measures. The second category was patients complaining predominantly of *back pain with proximal nonradicular thigh radiation.* Evidence of nerve root compression was as rare as in the first group. These patients rarely required surgery and were more likely to respond to conservative measures. The third definitive group included patients with back pain associated with clear *radicular radiation of pain but without associated physical findings or nerve root tension signs.* These patients were likely to have evidence of nerve root compression, were much more likely to require surgery, and did well with operation, with resolution of symptoms in more than 90%. The fourth well-defined group comprised patients with *back pain, radicular pain, and associated physical findings commensurate with the nerve root compression.* Their pain tended to be the most severe, they required surgery most often, and they had the best outcome from surgery. These groupings fit exactly with clinical impressions and current practice but have not been previously documented or proven to be valid classifications. Another large category of patients complained mostly of back pain, with less specific pain related to hips, perineum, and groin. Their inclusion as a separate group has not yet been validated statistically, but at least we can note from observable data that they rarely have evidence of root compression, and surgery was chosen for them as rarely as for patients in the first two groups. They probably belong with the second group.

Current clinical practice is in keeping with these general groupings. Patients with low back pain tend to have less severe pain, and for them demonstrated instability is the current indication for surgery, except for the small group in whom correction of a major structural abnormality is feasible. Nondescript radiation of pain to the thighs has no real significance and does not indicate either root compression or instability. Leg pain in a radicular fashion, with or without associated signs, is suggestive of root compression and is a major indication for surgery if pain is severe enough.

In addition to the patterns of pain, which are extremely useful, severity is most important. Clearly, interventions are indicated only if the pain is severe and incapacitating. Therefore, establishing the severity of pain and the impact of the pain upon the patient's life is important. Aggravation and alleviation of pain are also useful. Most mechanical pain problems are worsened by activity and improved by rest. Most neuropathic pain is unaffected by activity. Neurogenic claudication suggests spinal stenosis.

Remember, the history is the place to look for the danger signals suggesting that this problem may be more than a straightforward back problem. Disk space infection usually is associated with intractable pain and chronic illness, and it may be associated with recurrent fevers. A history of previous cancer or serious systemic disease always evokes suspicion; obviously, a history of trauma is important. Associated symptoms are the typical signals that an associated disease is important in the genesis of the back and leg complaints.[16–22]

Physical Examination

The physical examination is rarely diagnostic and serves principally to establish physical impairment. Radicular findings correlate well with subsequent imaging proof of nerve root compression but are not required to warrant intervention. Specifically, the lack of physical abnormalities is not a reason to deny a patient evaluation and surgical therapy if indicated. Most of this surgery is for pain, not physical impairment.

The initial examination should include inspection of the back and range of motion. Significant abnormalities of muscle tone, local tenderness, and decreased range of motion all may be amenable to local physical measures. The standard neurologic examination of strength of individual muscle groups, knee and ankle reflexes, and sensory examination are all important and has the usual implications. Remember that reliable patients can relate more about sensory loss than is likely to be discovered by examination. Both femoral and sciatic stretch tests should be done because a positive test correlates strongly with ongoing root compression. Plain films are important and should include motion studies to demonstrate overt instability. Plain films also are the best source of information for rotational, translational, and scoliotic deformities.

Imaging the Spine

Imaging of the spine is extremely important because it may be possible to define the problem on the basis of observed imaging findings. More commonly,

however, the pain generator cannot be identified with any degree of certainty on the imaging studies, and clinical correlations may be helpful when that is the case. To make the correlations the most effective, rational spinal imaging is required.

Lumbar spine dynamic X-ray plain films, anteroposterior (AP) and lateral, of the lumbar spine with oblique films to view the pars and foramina with flexion and extension to look for motion are still important. These films also could be very helpful in determining the location of hardware.

Computed tomography (CT) is the best way to examine bony structure. With two-dimensional reconstructions, the location of hardware can be accurately determined. Most patients with failed back syndrome will require CT.

The magnetic resonance image (MRI) is also an important study. The presence of fusion with or without hardware often will obscure MRI in the operative site, so this modality is less valuable there. However, it is still an excellent way to examine the structures above and below the fusion and will also allow evaluation of paraspinous anatomy. It is the best way to find an infection and the best way to examine degenerative disease above and below fusion. Other, unexpected diagnoses may also be determined.

3-Tesla MRI is becoming widely available. This may also be done with software protocols that allow neurography. Whether the 3-Tesla examinations will improve our ability to examine ligamentous and joint injuries is as yet uncertain. The neurography definitely allows assessment of extraspinal nerve roots and complete evaluation of the lumbosacral plexus in the pelvis as well as suspected peripheral nerve entrapment or injury. When concomitant pelvic disease is suspected, pelvic neurography is currently unsurpassed as a diagnostic imaging method. With these techniques, nerve enhancement may indicate entrapment, compression, or injury.

Three-dimensional CT imaging is also useful. The three-dimensional reconstructions will demonstrate hardware without artifact and allow judgments concerning the placement of screws and other fixation devices. Bony surgical defects are well seen, and fusions can be assessed. Remember that three-dimensional reconstructions exaggerate fusion bone and may obscure a pseudarthrosis. MRI is virtually always required, in addition to CT scanning. Soft tissue and neural structures will be demonstrated effectively, and MRI is the best way to assess early diskitis.[23–27]

Neurophysiologic Studies

Electromyography studies are occasionally useful. They have greater use in the failed back syndrome than in primary low back pain and sciatica. Their greatest use is in establishing the presence or absence of concomitant peripheral neuropathy. In older patients, this is a common diagnosis and may complicate the failed back picture. The studies also may be useful in helping define a feigned neurologic deficit, but they are rarely useful in decision making and are more corroborative than anything else. I personally use electromyography in less than 10% of all failed back patients, but this is in contrast to the less than 1% of patients who have not undergone a surgical procedure.

Electromyography certainly can verify the presence of nerve injury and support that clinical impression. It is also possible for electromyography to determine whether a problem is acute or chronic. That is sometimes helpful in determining when intervention may be useful. Nerve conduction studies may separate peripheral nerve compression syndromes. Spinal-evoked potentials have not been particularly valuable.

Other Imaging Studies

A variety of tests have been described for the assessment of patients with lumbar spine problems, including epidural venography, epiduroscopy, and discography. None of these studies, including discography for the purpose of imaging the disk, has been shown to correlate with primary diagnoses or proven to demonstrate a pain generator. Abnormalities are common, but their relationship to pain syndromes has not been demonstrated. Provocative discography is discussed next, in connection with diagnostic blocks.

Diagnostic Blockade as an Adjunctive Diagnostic Technique

The Diagnostic Dilemma

The principal problem in diagnosing and deciding upon treatments that will be of value in the failed back syndrome is the same as that which plagues diagnosis and treatment of spinal pain in general. When complaints can be strongly correlated with specific abnormalities, especially when appropriate neurologic signs or symptoms are present, it is reasonable to conclude that the abnormality seen is the pain generator. This situation occurs in a minority of patients. History is useful in that it determines the severity of the pain and it may localize the pain. However, even a detailed history rarely can determine a cause. The physical examination is of value only when specific abnormalities correlate well with visualized pathology. Imaging studies alone are rarely of value. It is well known that imaging abnormalities do not correlate with complaints of pain in either the patients who have been operated upon

or those who have not. Nevertheless, the majority of spinal surgeons stop with these correlations and make important therapeutic decisions based upon them. When no obvious abnormalities are found, the conclusion is often that the patient cannot be having the pain of which he or she complains. It is also concluded that no therapies are possible, and such patients usually are relegated to physical therapy measures and pain management. Other diagnoses are used to explain the pain when there is very little actual literature or support for the correlations. Postoperative epidural scar and postoperative arachnoiditis are two prime examples. Surgeons routinely tell patients that these two features explain their pain without much supporting evidence from the literature. That does not mean that both cannot cause symptoms, but it does mean that both are consistently found in patients who have an excellent recovery and are asymptomatic. Bogduk has championed the idea of using diagnostic blocks of different spinal structures to try to determine the actual generators of pain. He, with many colleagues, has conducted a series of pioneering studies of the validity of these blocks. In spite of a 20-year history demonstrating their value, diagnostic blocks are employed by very few spinal surgeons. Most are acquainted with the potential value of therapeutic blocks, and they are widely employed. Provocative discography is utilized by many spinal surgeons, but even with this technique the desired correlations with outcome of surgery are largely lacking. Diagnostic blocks can play an important role in determining the actual generators of the pain complaints and thus be very helpful in planning reoperation. They deserve wider study and application.[28–31]

Because of the frustrations that accompany the problem of ascribing pain production to any demonstrated abnormality in the spine, provocative diagnostic blocks have been explored.[28–30] The rationale of all such blocks is straightforward. Local anesthetic blockade of a pain generator should eliminate or greatly reduce the patient's specific pain complaint. Thus, relief of pain can imply that the structures blocked are important in the genesis of pain. In actual practice, these provocative blocks have become more complicated. Provocation of typical pain has become an important part of the diagnostic test. Because virtually all blocks are painful, it is important that the pain be concordant, that is, a duplication of all or part of the patient's usual pain syndrome. It is important that the person performing the blocks be skilled so that the pain from the block itself is minimal. The entire patient experience must be carefully structured so that inadvertent prompts do not occur, where the patient is encouraged to say what the physician wants to hear rather than what actually occurs. The interrogator of the patient also must be skilled in eliciting the exact nature of the pain response so that concordance can be established.

Special Consideration

A successful block requires a skilled, careful, and discreet surgeon and an interrogator able to elicit clear information from the patient.

Some caveats are important. Bogduk and colleagues studied the use of provocative blocks in great detail. Their data indicated that placebo controls provide the most accurate block information. An alternative to placebo are multiple blocks done with different agents. Single blocks, whether negative or positive, have a higher error rate than either of these alternative procedures. Positive blocks are reliable, but negative blocks have little meaning. All these blocks are adjuncts and do not substitute for clinical judgment. Blocks in current use include blockade of zygapophyseal joints, single or multiple lumbar root blocks, and intradiscal blockade.[30]

Facet Block

Injection of local anesthetic into the innervation of zygapophyseal joints will relieve pain in the small number of patients with pain only from facet arthropathy.[31] This is only rarely useful with failed back syndrome. An occasional patient suffering from transitional facet disease above a fusion may benefit, but most patients who have undergone multiple lumbar surgeries and fusion have such obliterated anatomy that accurate blockade is not possible. Sometimes, rather than blocking the joint itself, blockade of a pseudarthrosis suspected to be painful will relieve pain and verify the clinical impression. In my experience, the facet blockade is a useful diagnostic tool in patients who have back pain only, demonstrated facet arthropathy, and failure of pain relief with adequate conservative measures. The application of diagnostic facet blocks in failed back syndrome is minimal except for the transition syndromes.

Individual Root Blockade

Occasionally, patients with sciatica have symptoms that are indistinct enough that it is hard to judge the individual root involved. Sequential blockade of possible involved nerve roots may lead to specific pain relief and settle the question of which nerve is most responsible for mediating the pain, but this circumstance is unusual.[30]

Provocative Disk Blockade

For a number of reasons, the most controversial of the diagnostic blocks are those involving intradiscal injections. One reason is the confusion of provocative

disk blockade with diagnostic radiologic study for the demonstration of disk degeneration and annular incompetence. The relationship of these radiologic findings to pain syndromes has never been certain, and there has never been evidence presented from controlled studies that surgery based on the demonstration of internal disruption of the disk and annular incompetence is beneficial. Provocative disk blockade is quite different and, with judicious use, can aid the clinical decision-making process.[32,33]

The disk is distended after percutaneous extradural needle placement in the nucleus, which is verified by fluoroscopic control. The distension is usually carried out using saline. In a normal disk, the distension should not be painful if the injection is truly intranuclear. A positive test consists of the reproduction of all, or a substantial part, of the patient's usual pain syndrome. Theoretically, it should be possible to anesthetize the disk by the injection of a local anesthetic and thereby relieve pain; practically speaking, this is difficult because the degenerated disk so often has annular tears, which would allow the local anesthetic to escape, and because there is no certainty that the intradiscal injection of local anesthetic will affect the innervation of the outer layers of the annulus. Provocation becomes the most important part of the test.

Degeneration of the disk is often verified by intradiscal injection of contrast, but the relationships between the demonstrated abnormalities and pain syndromes do not exist. By convention, failure to produce pain is a negative response, production of concordant pain is positive, and it is generally held that there must be at least one normal, non–pain-producing disk demonstrated at a control level for the test to be considered useful. The evidence that provocation of concordant pain occurs in many patients undergoing discography is strong.

The next step, which is correlation of the outcome of surgical intervention with the prediction of the disk injection, has not yet been made. The few studies currently available are anecdotal. The logical inference to be made from positive discography is excision of the offending disk with stabilization, probably by an interbody route. The definitive study, which will demonstrate the predictive power of discography for such surgery, has yet to be done. At present, the provocative disk blockade is best considered as another adjunct in clinical decision making and not a definitive test. That is, a patient who would not be a surgical candidate based on any other criteria cannot be judged to be a surgical candidate solely on the basis of positive disk blockade. There are some new data suggesting that needle puncture of an anomalous disk produces degeneration. That must be considered in the use of discography. Alternatively, intradiscal steroids can provide lasting relief in some patients.

Other Adjunctive Blocks

Sacroiliac (SI) joint disease can be mistaken for residual lumbosacral spine problems. Progressive arthritis in SI joints is not uncommon in patients with displaced lumbosacral and pelvic alignment. Of course, it can occur as an independent problem. Blockade of these joints is an effective way to determine the contribution of the SI joint to the problem.

Loose hardware is another, similar problem. In my experience, injection of local anesthetic around the questioned area of hardware will usually temporarily relieve pain when hardware movement is the issue. The same is true for pseudarthrosis. There are no definitive studies supporting this belief, but it has been my long experience with hundreds of patients that the response to blocks is a reliable indicator, as valid as the use of blocks in other, less complex problems. These blocks are never a substitute for clinical judgment but can help to support a clinical impression and strengthen the case for or against surgery.

Conservative Care of the Failed Back Syndrome Patient

Only a few problems preclude a conservative approach for all these patients. Severe instability, infection, stenosis that threatens neurologic function, and serious intercurrent disease all may need urgent treatment; however, most patients who present with failed lumbar surgery should be given an opportunity to improve without additional operations. Furthermore, only a minority of these patients ever will be candidates for any further operation, meaning that for most, pain control and conservative measures are the only options.[34–37]

Special Consideration

All patients should be given the opportunity to heal without additional surgical intervention; however, patients with severe instability, infection, stenosis that threatens neurologic function, or serious intercurrent disease may require urgent, more aggressive treatment.

The evidence that the usually prescribed physical measures alter the natural history of the acute low back problem is marginal at best; however, the improvements seen in patients with failed lumbar surgery following intensive therapy programs aimed at improving function are well documented. These patients suffer a number of physical abnormalities, such as chronic myositis, inflammation of ligamentous insertions, weakness, poor mechanical body habits, inanition brought on by prolonged

physical inactivity, tendon shortening, poor posture, and a host of other, similar physical problems. All these problems can be improved by a well-directed conservative care program, which, for most such patients, should be the first step in therapy. Unfortunately, these programs are unavailable except in a few specialized centers. Typical physical therapy measures are of no value. These patients are particularly susceptible to victimization by so-called alternative practitioners of all sorts who repeat fruitless treatments over long periods.

Comprehensive conservative programs that have been demonstrated to be effective include aggressive local measures to relieve myositis, ligament inflammation, and muscle spasm. Restoration of range of motion is important. Strengthening exercises, proper body mechanics, general conditioning, and restoration of function are all important goals. Many techniques to accomplish these aims have been described. It is important that the neurosurgeon realize that the usual regimen of heat, massage, ultrasound, and unsupervised exercise is unlikely to bring about any improvement. These patients require structured programs in which their progress is monitored. Several such programs have demonstrated their effectiveness. They require 6 months or more to be effective.

Many patients become demoralized, and many others become depressed; it may be difficult to tell the difference. The physical therapy program and supports are good treatments for demoralization, whereas depression may require active therapy. For most patients, the arousing tricyclic antidepressants are particularly effective. If sleeplessness is a major problem, the sedating antidepressants, given at bedtime, may solve both insomnia and depression. Many patients also develop chronic anxiety, which has led to the application of stress-relieving techniques such as biofeedback or other modes of stress management. Some patients develop job- and disability-related problems. Rational assistance that reinforces a clear understanding of real impairments and job-related disabilities is an important part of a comprehensive conservative program. Unfortunately, most localities do not have these comprehensive programs available. The services are fragmented and rarely directed at the patient as a whole; therefore, they are largely ineffective. When a fully organized, comprehensive program is not available, what is effective and available to the patient can be orchestrated by any informed physician.[37–41]

Psychosocial Factors and Failed Back Syndrome

It has been known for many years that chronic pain results in depression and chronic anxiety. The so-called chronic pain syndrome is characterized by these two features along with a strong tendency to misuse prescribed medications and what appears to be an inordinate effect upon all activities of daily living. The arguments about whether these are primary or secondary features are now some 40 years old. The best current evidence suggests they are both. There certainly do appear to be people without any previously existing psychosocial features who become chronically disabled by pain and exhibit all the features of the chronic pain syndrome. There is reasonable evidence derived from the widespread use of narcotics in chronic pain of benign origin, which is now the standard of care, that apparent drug-seeking behavior can be dramatically reduced by an understanding pain manager who prescribes narcotics in a consistent, rational way.[36]

The evidence is even stronger that this chronic pain syndrome occurs most commonly in patients with long histories of psychosocial issues. From the National Low Back Study, which examined acute, first-time spinal pain associated with lumbar disk herniation, spondylosis, or stenosis, we determined that the psychiatric profile of these patients in the acute stage was no different from that of the normal population. This is definitely not true among chronic pain sufferers, particularly those with failed back syndrome and long-term continuous pain. Depression and anxiety appear to be the most likely of the premorbid complaints, but in our previous examination of a large number of these patients, we found a broad spectrum of psychiatric disease represented. Social factors, particularly those related to industrial disability and workplace injury, also appear to be very important. Patients with these issues are overrepresented among the chronic failed back syndrome group. It also appears that African Americans do substantially less well with treatment for spinal problems than do all other groups. The causes for this discrepancy have not really been elucidated. It has been demonstrated that given apparently comparable disease and similar treatments, the success rates are much lower among members of this group with concurrent psychosocial issues.[41,42]

An important part of the failed back syndrome evaluation is the premorbid psychosocial history. The degree of current anxiety and depression along with associated dysfunction should be assessed. It is extremely important that depression be addressed in the course of therapy because failure to do so greatly reduces the success rate of any treatment, including medications. Unaddressed depression is the single greatest failure in the management of the chronic failed back patient in my experience. Evaluation and management of these patients is a particular problem. Most spine surgeons do not have the skills for this. In my experience, there are a very small number of psychiatrists who have an interest or understanding of the problem. The comprehensive pain

treatment centers, which were developed largely to address these issues, have now mostly disappeared in favor of individual managers. Very few of these pain managers have any background with psychosocial issues. The evaluation and treatment of the many psychosocial factors that influence the complaint of chronic pain remains a serious problem. Unless they are addressed in any specific patient, the therapy for that patient is likely to be compromised. Identifying resources available in any particular community is an important issue for the spinal surgeon. The most important lesson here is to always remember to consider these factors in making diagnoses and planning therapies.[36]

Specific Pain Management in the Failed Back Syndrome

While a conservative program is implemented, control of pain is useful for the patient and will improve the outcome of functional rehabilitation. Some of the conservative measures may exacerbate pain over the short term but provide good long-term pain relief. For these patients, pain management can be relatively short term. For others, for whom no reparative therapy is possible, pain relief becomes a major goal that includes rehabilitation of function.

As with any spinal problem, the general dictum is to do the least necessary to provide the best and most efficient result. Failure to individualize therapies by patient produces an enormous waste in the general field of spinal pain management. Physical therapy is often required by third-party payers. Although it is extremely valuable for many patients, it will be useless in many others. Some patients are candidates for therapeutic blocks to address a limited number of specific diagnoses. These blocks will be useless if used indiscriminately. A small number of patients will benefit from reoperation. Indications must be specific and the pathology to be corrected must be identified. Simone once said, "He who operates for pain will find it." The goals of management of the chronic pain syndrome are to first identify the causes of the pain and determine which may be correctible and what the probabilities of correction are. Then alternative therapies must be considered and any that seem reasonable should be interposed before surgery. The chosen program should be individualized; not every patient needs every modality known. All of these therapies treat specific diagnoses, and if they are used when these diagnoses are not present they will be inefficient and costly.[43]

Patients who are not candidates for surgery still have many options available. There is a great tendency for spinal surgeons to simply dismiss those who are not candidates for reoperation. The least that should be done is referral to a competent pain manager. As a general rule, even for patients with demonstrated abnormalities that are correctible by surgery, a conservative program is a reasonable approach rather than reoperation. The important elements are an accurate diagnosis, specification of the treatments that can be reasonably expected to bring improvement to some patients with this diagnosis, and surgery reserved for those with specific abnormalities known to be reliably correctible by reoperation.

For patients with clearly defined neuropathic pain, several categories of drugs have been proven to be useful. There is also the suggestion that these drugs may help somatic pain as well. Neurontin (gabapentin) with a beginning dose of 300 mg three or four times daily with a typical maximum dose of 2,400 mg per day, and Lyrica (pregabalin) 50 to 150 mg per day have been demonstrated to be very effective. Tegretol (carbamazepine) 200 mg three or four times daily has been used for many years but is proving less effective than many of the newer drugs. The tricyclic antidepressant Elavil (amitriptyline) 10 to 60 mg at bedtime, and nortriptyline 10 to 60 mg at bedtime have also been established as excellent therapies for a variety of neuropathic pains. Klonopin (clonazepam) 0.5 mg three times daily is another drug in common use. Cymbalta (duloxetine) 30 to 60 mg at bedtime is very effective, especially in patients with secondary depression.

There are a number of others, particularly a group originally developed for seizure control, such as Topamax (topiramate) and the antidepressant Cymbalta (duloxetine), which are also very useful. Duloxetine is extremely effective but has more side effects in my experience. Use of these drugs usually requires a long-term pain manager because of minor side effects, and drug adjustments are common in my experience, but they certainly can be started by any physician and monitored by anyone willing to spend the time to do so. Most of these medications require a 2- to 3-week trial for certainty of efficacy, but once they are established they often are effective on a long-term basis and late side effects are few.

Pain Management

Recently a new field of pain medicine has burgeoned. Practitioners of this new specialty come from many traditional fields, with anesthesiology predominant. Most employ narcotics for pain relief, often in large doses. Several drugs for neuropathic pain are available. Repeated percutaneous injections of steroids are fundamental to virtually all of these treatments. Multidisciplinary approaches are rare. The increased use of narcotics has led to a dramatic increase in misuse, misdirection, and abuse. Deaths from overdose

are epidemic. Responsible pain management can be of great benefit to some patients but patient misuse of narcotics is widespread. When symptomatic control of pain is required it is best done by specialists with proven records of rational, responsible drug prescribing and control of drug use.

When pain is of somatic origin, common practice is to begin pain relief with nonsteroidal anti-inflammatory analgesics and maintain the patient with these medications for as long as possible. When the chronic pain syndrome was identified in the 1960s and early 1970s, misuse of narcotics was a common feature in a substantial number of patients. For this reason, withdrawal from narcotics became a standard part of pain therapy.

It is among this group of patients that the largest number of those for whom no original indication for surgery could be definitely identified occurred. It is in this group that the majority of patients with concomitant psychosocial issues occur. The nonoperative care provider also needs to continuously assess depression, anxiety, and other psychological concerns. The majority of patients with major psychosocial concerns and disability fall in this category.

The biggest problem, however, is the fact that, to date, virtually no studies have appeared to indicate that adequate pain relief has been attained and maintained over a substantial period in patients with failed back syndrome or other chronic pain states. Analogies are made with the successful use of these drugs in cancer pain. It is incumbent on those who advocate long-term narcotic use in patients with otherwise intractable pain to examine improvements in function attendant on pain relief, cognitive and systemic effects of drug use, and other concerns. The detrimental effects of misuse of short-acting narcotics are well described, and we must be certain that the gains from narcotic therapy outweigh the negatives. If they do, then long-term use of narcotics in controlled circumstances is reasonable, but the data to support the efficacy of their use are lacking at present.

Evaluating Patients

Failure to Relieve Underlying Pathology

The most common surgical failure is the presence of residual spinal stenosis, usually in the lateral recess or foramen. Other problems include failure to remove a disk fragment and immediate recurrence of disk herniation because of inadequate removal of residual degeneration within the interspaces. There are also a small number of overt errors, such as operating at the wrong space and failure to recognize some underlying diagnosis.

Diagnosis of the Problem

The history related by such patients is characteristically that the original surgical procedure simply failed to relieve their symptoms. They are usually clear about the fact that symptoms before and after surgery were the same, and physical findings remain unchanged. Imaging studies demonstrate the residual abnormalities. Interpretation of the MRI is complicated by the surgical artifacts, particularly in the first 3 months after surgery, when inflammatory changes still overemphasize disk herniation and obscure the details. CT myelography is more likely to be useful in this circumstance than in almost any other.[9,23,25,27] Provided the patient's symptoms warranted surgery in the first place, the appropriate treatment now is to repeat the surgery, being certain that the pathology is corrected. In my experience, the results of second-time surgery in this circumstance are virtually as good as those for the original procedure.

Surgical Complications as a Cause of Failed Back Syndrome

Common surgical complications causing failed back syndrome include infection, iatrogenic or uncorrected instability, nerve root injury, pseudarthrosis in all its various permutations, and functional distortion of spinal biomechanics. Arachnoiditis is a rare, distinct complication that is seen most commonly in patients who have undergone multiple operations or multiple myelograms.[44]

Diskitis

The important infections are typically those that involve the intervertebral disk or that create an epidural mass that compresses nerve roots or the spinal cord. Typically, wound infections heal with appropriate treatment and do not add to the patient's impairment. By contrast, disk infections can be extremely disabling and serious. Disk space infection usually is associated with fever and a general feeling of ill-being. White blood cell count, C-reactive protein (CRP), and sedimentation rate are elevated substantially and for a long time. Pain is a cardinal symptom. It is typically in the back, extremely severe, and often exacerbated by minimal movement or activity. Sometimes the clinical presentation is much more subtle than this, and the pain, although important, is much less severe. The pain is usually local in the back, leg radiation is common but much less serious, and neurologic findings are rare. In the early stages of infection, diagnosis may be difficult, plain film changes having not yet occurred. MRI will show

inflammation but cannot definitively establish that it is not simply a postoperative residual.[45] Plain films and CT make the diagnosis only when bony abnormalities appear. With MRI, the inflammatory changes seen progress rather than regress. Persistently elevated white blood cell count, CRP, and erythrocyte sedimentation rate are common and important diagnostic points. Radioactive scans are usually positive, and those that have a higher specificity for infection, such as gallium or tagged white cell scans, are useful. Bone scan is valuable only if negative.

Special Consideration

Straightforward wound infection, although unpleasant for the patient, rarely has a long-term consequence unless it is severe enough that the infection interferes with fusion, necessitates hardware removal, or creates an unusually dense scar. Some infections healing by secondary intention so distort the biomechanics of the spine that pain may be created.

The treatment of diskitis is to identify the offending organism and treat the patient with appropriate antibiotics. In the typical patient, surgery is not required. The first step is to identify the organism by needle biopsy. Simple aspiration is associated with a low likelihood of identifying the offending organism; however, true biopsy with a biopsy needle has an excellent chance of identifying the infection. Sometimes, open exploration is the only way to obtain a culture adequately to identify the infection. Following identification of the organism, prolonged treatment with antibiotics is required. These are usually given intravenously, and the typical treatment period is about a month. During this time, the white blood cell count and sedimentation rate should improve, as should the patient's symptoms. Most patients can be treated with antibiotics alone.

If a single course of antibiotics fails to eradicate the infection, or if the patient has one of the recognized indications, surgery may be necessary. The usual indications for surgery are failure of therapy to eliminate the infection, failure of therapy to reduce pain, demonstrated progression of abnormalities in imaging studies, a significant epidural or extraspinal mass, instability from bony destruction, and the development of significant neurologic deficits. Surgical treatment is most commonly anterior exploration, removal of the disk, and fusion, followed by an additional 4 to 6 weeks of intravenous antibiotics, depending on the organism and sensitivities.

Iatrogenic Instability

Another important surgical complication is instability following surgery. This is usually of three separate origins. The first is removal of lumbar facets in the course of decompressive surgery. The integrity of the zygapophyseal joints must be compromised in some cases if adequate decompression is to be obtained. With most patients, there will be no consequences, even if joints are completely removed; however, if the anterior structures are not competent to maintain stability, spondylolisthesis or painful movement in the residual joint can occur. More commonly, the pars interarticularis is compromised during foraminotomy. The structure that maintains the stability of the superior articular process, and thus of the zygapophyseal joint, is disrupted and a free-floating joint occurs. Another common scenario is that the pars is not transected during surgery but is thinned to the point that subsequent activity causes a fracture. In our series, this occurred in 10% of the patients presenting with back pain as a major part of failed back syndrome.

All three conditions usually can be diagnosed by plain films and two- and three-dimensional CT reconstructions. The three-dimensional CT is particularly good at demonstrating these relationships. The origin of the pain can be identified by local blockade, but this is not a necessary substantiating study. Treatment is fusion; the most obvious technique is pedicle screw fixation, and this is the most commonly used method today. If an anterior fusion technique is used, a fixator is frequently required because of the posterior instability. Posterior interbody techniques may be used but run the risk of further destabilizing the spine during the healing period. Standard posterior lateral techniques also are used when major instability is not an issue.[41–44,46] There are several postural issues among this group of patients. These abnormalities, which are largely biomechanical, are not widely appreciated except for scoliosis. Sagittal pelvic alignment is extremely important in managing postural equilibrium. Assessing distortions of this alignment maybe useful in understanding some otherwise unexplainable continued pain complaints. The flat back syndrome is another typical problem. Surgical obliteration of lumbar lordosis can produce back pain, particularly with standing, walking, and exertion. Varying degrees of scoliosis are well known to be associated with back pain, and their correction may be important.[46]

Instability can be very difficult to assess. There is not even agreement about how much motion is required to constitute diagnosable instability. Measurements vary significantly in what is considered normal. The first measure of instability is obtained with dynamic films. Flexion/extension or rotational films may show actual movement. The blockade of

zygapophyseal joints and/or nerve roots at those levels may verify that the motion is the pain generator. Since there is little agreement on how much motion constitutes instability, this blockade can be very helpful in determining that motion is a pain generator with certainty.

Nerve Root Injury

Another common problem resulting in residual radicular pain is injury to one or more roots. This is usually a combination of a deficit present because of root compression and surgical manipulation. Diabetes is a major risk factor for development of the syndrome. The diagnostic difficulty is that it is impossible to tell the difference between pain generated from a compressed root and pain from root injury that is irreversible. The aim of the diagnostic studies is to make this differentiation. When two- and three-dimensional CT scan with MRI demonstrates the probability that nerve root compression persists, re-exploration is indicated, but patients must be warned that the differentiation between compression and injury is not absolute. In the absence of obvious compression, it is unlikely that further surgical decompression will be of value. Individual nerve root blocks can verify the level or levels of root involvement, although the clinical history usually will identify the roots.

Recurrent and Retained Disk Herniation

Occasionally, a patient is seen in whom the original offending disk herniation was not satisfactorily removed. The obvious goal is to identify the herniation and remove it. More commonly, we see patients who initially had a good result and then a few weeks later suffered a recurrence of pain. Repeat imaging studies demonstrate recurrent disk herniation. In the third scenario, patients develop symptoms much later, and the compression appears to be a combination of spurring, ligamentous thickening, and focal scar with or without recurrent disk herniation. Much has been made of differentiating scar from recurrent disk. The goal of imaging is to determine whether the nerve root is compressed. It does not make much difference whether the focal compression is scar or recurrent disk. The issue is the compression, not the origins of nerve root pressure.[13]

Imaging studies usually demonstrate the mass and the compression. MRI may be difficult to interpret in the first 3 months after surgery and will exaggerate the presence of root compression. Unless the MRI is obviously abnormal, CT myelography is more useful when patients must be investigated in the first 3 months after surgery.

Complication of Fusions and Fixator

The most likely complication of fusion is failure to heal. The role of the pseudarthrosis in pain production is uncertain. Many patients with apparent pseudarthroses do not have pain, but many patients with intact fusions do have pain. In patients with residual back pain and apparent failure of fusion, one cannot automatically assume that the failure of fusion is the cause of the pain. The indications for the fusion in the first place may have been incorrect, and residual or new pain may have nothing to do with the fact that the fusion has not healed solidly. One way to deal with this conundrum is to inject the apparent pseudarthrosis with local anesthetic. If the pain disappears, this strengthens the contention that the failed fusion is the source of the pain. Loose fixators are painful and virtually always indicate that the fusion has failed. The problem is recognized most readily by migration of part of the fixator system or a loosened area around the screws seen on plain radiographs or CT. Misplaced fixators are a problem. Screws that are in the disk, traverse the spinal canal, or impinge on a neural foramen all may need removal.

There is little certainty about what constitutes instability in most patients unless obvious movement of the spine is occurring. It is not surprising that instability should be even more difficult to diagnose in patients who have had previous surgery. When evaluating these patients, it is important to recognize that fusion is indicated for instability only and should not be automatically targeted for reoperation because an initial procedure failed.[47–53]

Arachnoiditis

A rare condition, originally described as a complication of infection and now well recognized to follow complicated myelography, surgery, or multiple myelograms and surgeries, is symptomatic arachnoiditis. In this condition, there is substantial intrathecal scarring that binds nerve roots to the dura and to each other. Chronic adhesive arachnoiditis as a complication of myelography and surgery is of relatively recent origin. Most patients reported in the literature have undergone multiple myelograms or a complicated myelogram and subsequent surgeries. Surgical complications in these patients are a common finding as well. Arachnoiditis as a complication of myelography alone is relatively rare. Some patients have a typical clinical syndrome, but most do not. The clinical syndrome associated with arachnoiditis is one of burning, dysesthetic pain involving one or both extremities, and often claudication symptoms. MRI can suggest the diagnosis, but CT myelography is usually required to be certain. Findings include intrathecal adhesions, loculation of spinal fluid, and

Special Consideration

It is rare that arachnoiditis results from myelography or surgery alone. It is more often a result of multiple myelographies (or a complicated myelography) and subsequent surgeries.

adherence of nerve roots; a significant block of spinal fluid flow can result. MRI has demonstrated this nerve root adherence in many post-surgery patients without symptoms, further confusing its importance in pain production.

Once the diagnosis is made, it is important to ensure that the arachnoiditis does not obscure some other, more obvious problem, such as instability or a compressed nerve root. The simple fact that arachnoiditis is present does not mean it is the sole cause of symptoms, or is even symptom producing at all.

Management of the patient with arachnoiditis generally amounts to management of symptoms. Relief of pain by using analgesic medications or spinal stimulation is the most common form of therapy. Surgery is reserved for the rare patient who has progressive neurologic loss.[11]

The Failed Back Syndrome Patient without Definitive Findings

In a previous examination of patients presenting after failure of surgery, the largest group comprised patients for whom the accepted criteria for surgery were not clearly evident before their first operation. It should not be surprising, therefore, that most patients presenting to the spinal expert after one or more ineffective operations will not harbor one of the kinds of abnormalities described here. In our series, about a third of these patients had a demonstrable abnormality that either explained the complaint or could be corrected or both. In nearly two thirds, no correctible or clearly defined causative abnormality was found. The cause of pain in these patients remains unknown. Epidural scar is the most commonly invoked explanation. Until we can successfully prevent epidural scarring, we will not know whether the presence of the scar is related to pain. Because all patients have a scar, it is important but difficult to determine when this scar is a pain generator and when it is not. Because the cause of pain before surgery was undefined for most of these patients, the consequences of surgery make it even more difficult to determine a specific generator. Reparative surgery is indicated only when a specific abnormality can be identified. Otherwise, a second operation has no more chance of success than the first. The fact that these patients do not meet current criteria for surgery and have no pain generator that can be demonstrated with current techniques does not mean they do not have pain. It does mean, however, that currently used surgical procedures have little chance of helping to alleviate the pain. This point is well illustrated by the findings of one of our recent studies. In an examination of the outcome of first surgery for more than 600 patients operated on by acknowledged experts in spinal surgery, more than 90% achieved satisfactory relief of symptoms and improvement in function. The diagnoses were varied, but all patients met current criteria for demonstrated root compression, spinal canal stenosis, or instability. By contrast, we examined 113 patients who did not meet the criteria of these experts but were operated on by other surgeons. The failure rate was greater than 90%, and many of the patients demonstrated deterioration in function and psychological status, and excessive use of medical resources. Perhaps the use of provocative diagnostic blocks, particularly disk blockade, will define the cause or causes of pain in these patients and lead to operations capable of correcting those causes. At present, the predictive power of these blocks to indicate a good outcome for many surgical procedures is unproven. All must be used as adjuncts to a thorough evaluation. Determination of the causes of spinal pain is a great challenge for those interested in this field.[7–10]

Instability can be very difficult to assess. There is not even agreement about how much motion is required to constitute diagnosable instability. Measurements vary significantly in what is considered normal. The first measure of instability is obtained in dynamic films. Flexion/extension or rotational films may show actual movement. The blockade of zygapophyseal joints and/or nerve roots at those levels may verify that the motion is the pain generator. Since there is little agreement on how much motion constitutes instability, this blockade can be very helpful in determining that motion is a pain generator with certainty. It is this group of patients that contains the largest number of those for whom no original indication for surgery could be definitely identified. This group also includes the majority of patients with concomitant psychosocial issues. The nonoperative care program must continuously assess depression, anxiety, or other psychological concerns. The majority of patients with major psychosocial concerns and disability fall in this category. There is a great tendency among the spine surgeons to simply offer a disability statement upon a patient's request. In my experience, a large number of the patients claiming long-term disability for spinal pain have few, if any, signs of a physical disability. These areas are often a matter for experts, involving issues that can be far more complex than the busy spinal surgeon can manage.[54–60]

Outcome of the Failed Back Syndrome Therapies

In a recent review of 6,500 personal cases lumped under the general term *failed back syndrome,* several important tendencies appeared. Of the patients, 2,000 came to undergo eventual reparative surgery, and 900 were candidates for spinal stimulation. The remainder were judged to require only physical measures and pain management as potential treatment options.

Nonoperative Care

There is good evidence that a vigorous therapy program aimed at elimination of the local mechanical problems from which many of these patients suffer and improvement in function with general conditioning will greatly improve their functional capacity. There is less evidence that pain complaints are improved, but the improvements in function are well documented. Many patients require less pain management and are satisfied to live with their condition. There is little evidence that traditional physical therapy modalities offer any benefit. Unfortunately, the comprehensive physical approach is available in a relatively limited number of centers in the United States. Most of those who claim to provide such an approach do not. Provided an adequate program can be defined and implemented, nonoperative therapy is an alternative for nearly all patients and should precede reparative surgery except in a few cases.[35]

Spinal Cord Stimulation

Stimulation of the spinal cord for pain control has a history of 30 years. Its efficacy, both as a last resort in pain management and as an alternative to reparative therapy, is well demonstrated. Typical patients chosen for spinal stimulation are those with intractable sciatic pain; back pain is less predictably relieved. The best results are obtained in patients who undergo thorough testing of the modality before final implantation. The major drawbacks are mechanical problems related to the device and the need for intensive maintenance. Most patients chosen by experts for this procedure achieve lasting success. The widespread growth of pain management has also dramatically increased the number of physicians who use spinal stimulation. Indications have been greatly broadened, and I see many patients in whom spinal cord stimulation has been utilized even for the treatment of a relatively acute pain process within the first year after onset and before corrective surgical repair has been considered. Spinal cord stimulation is an effective treatment but expensive. It can be used as an alternative to reoperation as demonstrated by North. Its risks are real and can be severe. The failure rate among poorly selected patients is high. The indications for use are specific, and unexplained pain for which no obvious physical abnormality is demonstrated should not be one of them.

Outcome of Surgery

It serves little purpose to discuss surgery for the failed back syndrome. This imprecise term is used to define such a multiplicity of problems that any discussion of therapy must focus on homogeneous groups within the general rubric. There are several general principles. Well-defined root compression syndromes and instability will respond to a second operation with almost the same outcome as attended the first surgery. Beyond the second operation, efficacy declines almost linearly with the number of procedures. The more specific the syndrome of instability or root compression, the better the results will be after multiple operations. Operations designed to correct underlying anatomic abnormalities are more likely to be successful than those to correct the effects of previous surgery. The presence of uncorrected comorbidities, such as depression, anxiety, underlying psychiatric disease, drug misuse, and unresolved issues of disability and litigation, all reduce the potential outcome for patients.[61–69]

The principles governing reoperation are, first, to review the initial indications for surgery; a stereotypical second operation response to failure of the first operation, such as automatically adding a fusion, is unlikely to benefit many patients.[6] The pathology must be clearly defined and whether there is a reasonable chance of correcting it must be determined.[56–61] If it cannot be corrected, spinal cord stimulation should be considered. The stimulation may be an alternative to reparative therapy as well. The best conservative care available to the patient should be implemented prior to consideration of surgery, except in unusual circumstances, and is likely to be the only alternative for most patients.

Detailed evaluation of the 7,046 patients I treated between 1967 and 1999 is instructive. The patients were equally divided by gender and the median age was 43. Of these 2,067, or 29.4%, underwent reoperation, leaving 4,978 patients, or 70.6%, who were not offered reoperation. Of the group 51.7% had undergone three or more operations (the largest number recorded was 19), 48.3% of the patients had undergone one or two operations, 37.9% were involved in some form of active disability litigation, and 4,979 were treated by methods other than operation. Of these 373 were recommended to have surgery but reoperation was refused by an insurance carrier. A total of 2,067 patients did have reoperation, 1,495 patients (21.2%) were referred to an inpatient

Table 14.1 Common diagnoses in failed back syndrome: 7,046 patients, 1967–1999

Reoperation	**29.4%**	**No reoperation**	**70.6%**
Uncorrected pathology	8.5%	Generalized spondylitic disease	26.3%
Foraminal or canal compression	5.6%	Abundant scar	12.8%
Retained disk	1.8%	Pseudarthrosis (not obvious cause of pain)	11.9%
Surgical complication	6.5%	Arachnoiditis	5.6%
Pars fracture or disruption	3.0%	Expected postoperative changes	12.8%
Neural injury	1.8%		
New diagnosis	10%		
Transition syndrome	3.2%		
Spondylolisthesis	2.7%		
Foraminal/canal stenosis	2.2%		
Complication of fusion	4.4%		
Pseudarthrosis	3.1%		

comprehensive pain treatment program, 737 (10.5%) were referred for spinal stimulation, and 2,626 were referred to a comprehensive spinal rehabilitation program and concomitant pain management.

The most common diagnoses are detailed in **Table 14.1**. This is not all-inclusive and does not include the list of patients with diagnoses representing smaller numbers who account for the difference. The diagnoses of patients for whom reoperation was recommended are found in **Table 14.2**. The types of operations performed are also included in **Table 14.2**. Since this particular experience ended before the introduction of a number of spinal fixation techniques, such as XLIF and X-Stop, these newer procedures are not included in the etiologies or in the corrective surgical procedures.

The specific results of reparative surgery are found in **Table 14.3**. Several results are obvious. The outcome for the treatment of foraminal stenosis,

Table 14.2 Common reoperative procedures performed

Foraminotomy only	27.0%
Posterior fusion—no instrumentation	19.7%
Laminectomy alone	16.6%
Discectomy/foraminotomy	11.1%
Instrumented fusion	8.3%
Discectomy alone	5.9%
CSF leak repair	1.0%
Anterior discectomy and fusion	1.8%
Other	

Table 14.3 Outcome of reoperation: Common diagnosis satisfactory results (judged by relief of pain, no narcotic analgesics, return to full function, no further therapy)

	Satisfactory result	
Diagnosis	**One or two previous surgeries**	**Three or more previous surgeries**
Technical issue		
Foraminal compression	82%	74%
Retained disk	84%	64%
Wrong level explored	87%	–
Facet removal	100%	50%
Complication		
Pars disruption	83%	37%
Neural injury	32%	–
Pseudomeningocoele	75%	–
CSF leak	85%	–
New diagnosis		
Transition syndrome	79%	30%
Spondylolisthesis	56%	37%
New disk herniation	91%	60%
Progressive scoliosis	58%	30%
Complications of fusion		
Repair pseudarthrosis	55.6%	40%
Relieve nerve compression	87%	35%
Fixator failure	84%	80%

recurrent disk herniation, and compressed root from any cause are all relatively good but declined after the second surgery. The same tendencies occur with other operations. The least satisfactory procedures related to the repair of pseudarthrosis and repair of unstable fixator systems. The same tendencies for better results after the first or second surgery are present as contrasted with more than three surgical procedures are present.

Failed back syndrome is an imprecise term that only obscures diagnosis for many patients. The key to understanding these patients is individualization of both evaluation and therapy. Remember, surgery benefits a limited number of conditions, mainly root compression and instability. Pain management is an important component of the treatment of these patients, and vigorous physical rehabilitation measures will help most of them function better. Stereotypical surgical responses based on pain complaint rather than on anatomic considerations are unlikely to be successful. For patients who do not meet current criteria for reoperation, spinal stimulation and pain management offer treatment alternatives.

Editor's Comments

Professor Long has reprised his discussion of the failed back surgery syndrome (FBSS), with modifications to the version in the first edition of this textbook. This discussion is important, since after back and neck pain, FBSS is the most common chronic pain problem that we deal with.

Dr. Long is eminently qualified to share his insights, given his long experience in this area and a personal database that exceeds 7,000 cases. I believe that it is only through long and sustained experience, combined with honesty and humility, that we can begin to tackle such a complex issue.

As he points out, diagnosis in FBSS is paramount. It is the responsibility of the physician treating a patient with FBSS not to relegate the patient to the heap of presumed intractability, but rather to get a comprehensive history, do a careful physical exam, and review or obtain relevant imaging and other testing. This is one of the most difficult tasks in medicine. No one strategy will work in all patients, so specificity is critical.

Some patients with FBSS need further surgery, but the odds of this go down dramatically after the second surgery. Other modalities, such as spinal cord stimulation, can be tried, although the long-term results in these patients are still debatable. Directed physical measures may, over a short course, be indicated, but prolonged physical therapy has almost no role in these patients. If alternative medicine has any potential value, it would be in protecting the patient from further ineffective surgery. Conservative therapy in almost all FBSS patients can be optimized, and for many, this is ultimately the best course.

As mentioned in the chapter, the use of chronic opiates in these patients over the past 30 to 40 years has evolved. In the 1970s and 1980s, withdrawal of opiate analgesics in patients with chronic pain was the general dictum. In the 1990s and 2000s, chronic opiate administration was considered both safe and effective. We now seem to be coming full circle, in that opioid abuse and diversion seem to be at epidemic levels. I suspect we will see a new era of restriction of oral opiates in practice over the next 20 years.

Finally, disability assessment (see Chapter 10) is not an expertise possessed by most practitioners. Physical capacity evaluations and disability rating are best separated from the medical and surgical care of the patient. In this instance, our advocacy for patients under our care probably interferes with an objective assessment. My view coincides with Dr. Long's:

> *There is a great tendency among the spine surgeons to simply offer a disability statement upon a patient's request. In my experience, a large number of the patients claiming long-term disability for spinal pain have few, if any, signs of a physical disability. These areas are often a matter for experts, involving issues that can be far more complex than the busy spinal surgeon can manage.*

Our role as physicians is to attempt to accurately diagnose patients with FBSS, offering optimized medical therapy and surgery when appropriate. We should not further complicate the patients' problems by adding opiate dependence to their problem lists, nor should we necessarily relegate them to lifetime disability without seeking the proper resources for assessment and characterization of their physical limitations.

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Section III.B

Craniofacial Pain

15 Craniofacial Pain Mechanisms

Barry J. Sessle

The fifth cranial nerve, the trigeminal nerve, provides the main sensory innervation of the face, mouth, and jaws. These sites represent some of the most common areas of pain in the body, and epidemiologic studies have documented the high prevalence of several acute or chronic craniofacial pain conditions.[1,2] These pain conditions range from acute pulpitis (toothache) and mucositis to arthritis of the temporomandibular joint (TMJ) and several types of headaches and temporomandibular disorders (TMD), to a number of less common neuropathic pain disorders such as trigeminal neuralgia, postherpetic neuralgia, burning mouth syndrome, and so-called atypical facial pain and atypical odontalgia.[3–5] Several of these pain conditions, especially those that are chronic, can present diagnostic and management challenges to the clinician. There are several reasons for this, including (1) the bizarre and complex nature of some of these pains, (2) the special biological, emotional, and psychological significance of the face and mouth for humans, (3) pain's character as a complex, multidimensional experience encompassing a variety of perceptual and behavioral functions, and (4) our poor understanding of the etiology, pathogenesis, and mechanisms underlying the initiation and progression of these pain conditions.[6,7] This chapter reviews recent advances in our knowledge of the mechanisms underlying pain in the craniofacial region in the hope that it will assist clinicians in their understanding of the various craniofacial pain conditions.

Peripheral Processes and Clinical Implications

Activation and Sensitization Mechanisms

The craniofacial tissues are densely innervated by primary afferent nerve fibers and have an extensive somatosensory representation in the central nervous system (CNS).[8,9] The endings of some of these afferents are large diameter and rapidly conducting (e.g., Aβ afferents) and respond to low-threshold mechanical (e.g., tactile) stimuli whereas others are smaller and slower conducting and respond to non-noxious thermal or taste stimuli. A noxious stimulus associated with, for example, injury or inflammation can excite the endings (nociceptors) of some of the other afferents that sense its occurrence. These are nociceptive afferents that are small diameter and slowly conducting (Aδ and C fibers). Several chemical mediators and cellular changes occur following the noxious stimulus, and as a consequence the nociceptive endings and their associated nociceptive afferents become activated. In some cases, a prolonged increase in their excitability (so-called *nociceptor or peripheral sensitization*) may occur, to the extent that they become more responsive to subsequent noxious stimuli or even start responding to stimuli that normally are innocuous. Some may also exhibit spontaneous (background) activity and some mechanically or thermally insensitive endings ("silent nociceptors") may be activated or sensitized by noxious chemical stimuli.

Several chemical mediators play a role in peripheral sensitization of the craniofacial nociceptive endings as well as in their activation by noxious stimuli.[9–11] The mechanisms and chemical mediators involved in producing peripheral sensitization include the chemical products of tissue injury as well as neurochemicals that are synthesized in the trigeminal ganglion cell bodies of the primary nociceptive afferents themselves. These mediators can be released from the afferent endings and include substance P, calcitonin gene-related peptide (CGRP), somatostatin, glutamate and nerve growth factors. The neuropeptide substance P released from the afferent nerve endings is especially effective in causing platelets, macrophages, mast cells, and other cells of the immune system to release inflammatory mediators such as histamine, serotonin (5-HT), bradykinins, and cytokines. The resulting redness, edema, and local temperature

increases reflect what has been termed neurogenic inflammation because it may originate from chemical mediators released from the nerve fibers themselves. Many of the chemical mediators also act on the nociceptive afferent endings and contribute to their peripheral sensitization. The afferent endings express a variety of ion channels and receptors by which they respond to these mediators or to noxious stimuli per se (**Fig. 15.1**). These include serotonergic, cholinergic, purinergic, opioid, bradykinin, histamine, prostaglandin, anandamide, excitatory amino acid and acid-sensitive receptors, adrenoreceptors, and vanilloid receptors, some of which (TRPVI) respond to protons (H^+), heat, and algesic chemicals such as capsaicin.[12–14]

It is also noteworthy that peripheral tissue injury can produce changes in the expression and activity

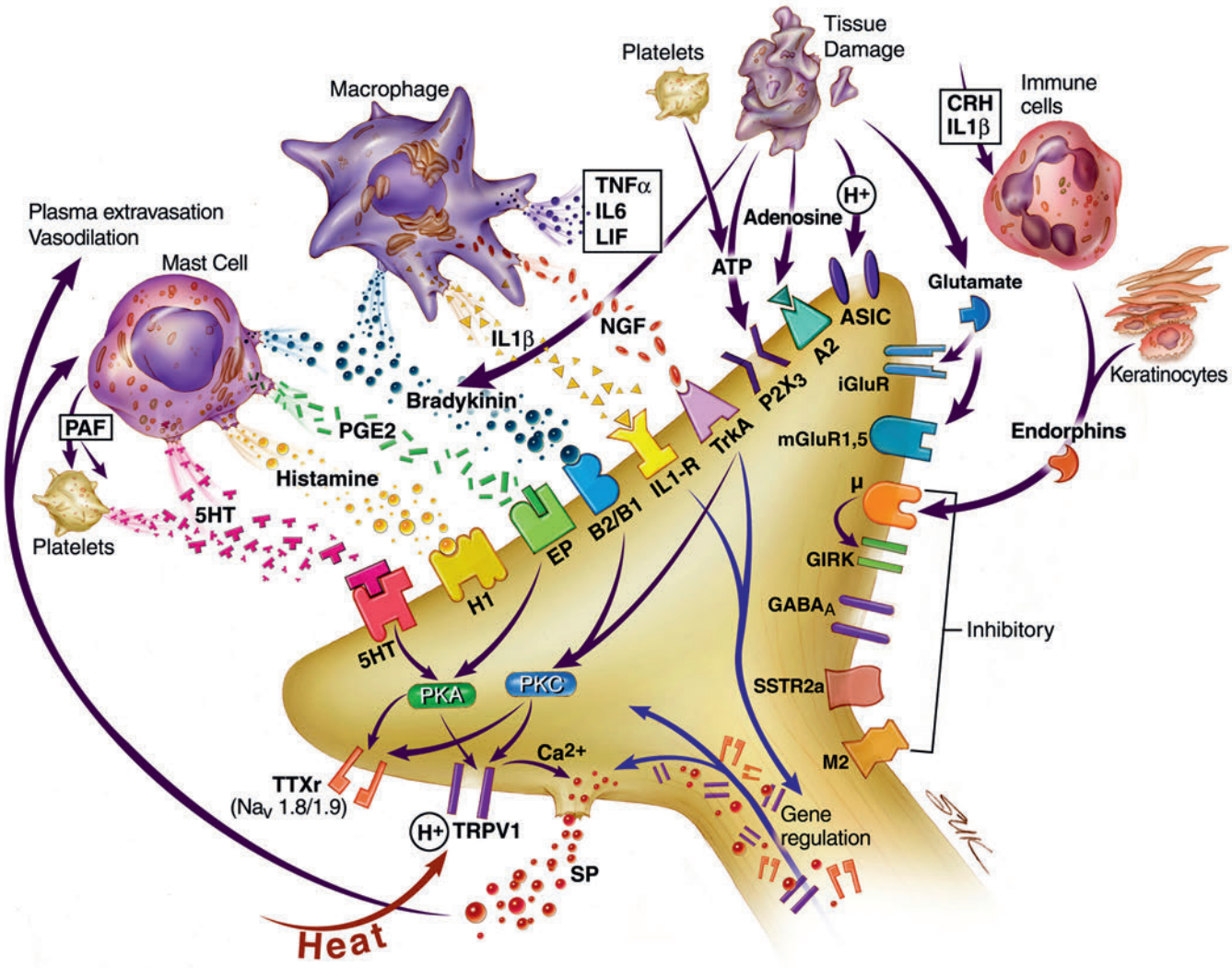

Fig. 15.1 Mediators in craniofacial tissues that are involved in peripheral sensitization following inflammation. As part of the inflammatory process, numerous chemicals are released from mast cells, immune cells, macrophages, and injured cells that act on ion channels or membrane receptors on peripheral nociceptive afferent nerve endings and thereby may alter the sensitivity of the endings. Several of the mediators are shown. Some of these mediators produce an increase in the excitability of the nociceptive afferent endings (i.e., peripheral sensitization), and others may exert inhibitory effects. ASIC, acid-sensing ion channel; CRH, corticotrophin-releasing hormone; GIRK, G-protein-coupled inward rectifying potassium channel; 5-HT, serotonin; iGluR, ionotropic glutamate receptor; IL-1b, interleukin-1-beta; IL-6, interleukin-6; LIF, leukemia inhibitory factor; μ, μ-opioid receptor; M_2, muscarinic receptor; mGluR, metabotropic glutamate receptor; NGF, nerve growth factor; PAF, platelet-activating factor; PGE_2, prostaglandin E_2; PKA, protein kinase A; PKC, protein kinase C; SSTR2A, somatostatin receptor 2A; TNF-α, tumor necrosis factor alpha; TrkA, tyrosine kinase receptor A; TRPV1, transient receptor potential vanilloid 1; TTXr, tetrodotoxin-resistant sodium channel. (From Meyer et al.[10])

of voltage-gated calcium, sodium, and potassium ion channels on nociceptive afferent endings and contribute, for example, to the spontaneous or ectopic afferent discharges that occur following nerve injury. Such changes have been implicated in the development of many types of neuropathic pain.[10,15] Nociceptive afferents also may become sensitive to sympathetic modulation following injury, and this is thought to be a factor contributing to some pain conditions such as certain types of complex regional pain syndrome.[10,16] It has also been found that chemical mediators that have long been thought to be involved in nociceptive transmission or modulation *within* the CNS, such as the excitatory amino acid glutamate, the inhibitory neurotransmitter gamma-amino butyric acid (GABA), and opioid-related chemicals such as enkephalins, also occur in peripheral tissues or nerve fibers and when released can act peripherally on the nociceptive afferents. Glutamate, for example, is synthesized in the primary afferent cell bodies and is released from not only the CNS endings of the primary afferents but also from their endings in peripheral tissues. Some afferent endings in peripheral tissues have receptors (*N*-methyl-D-aspartate [NMDA] and non-NMDA receptors) by which glutamate may excite or sensitize the nociceptive afferents. GABA and the opioid-related drug morphine in contrast may decrease afferent excitability. It is also of interest that there is a gender difference in the peripheral action of glutamate and morphine; for example, TMJ or jaw muscle nociceptive afferents show a greater sensitivity in woman than in men to the application of glutamate, but women are less sensitive than men to the peripheral application of morphine.[11,17]

In addition to these various changes and factors operating at the peripheral tissue endings of the craniofacial nociceptive afferents, it is noteworthy that injury or inflammation of the tissues as well as of afferent nerve fibers can also be associated with physiologic and neurochemical changes in the cell bodies of the primary afferents in the trigeminal ganglion.[18,19] These changes may involve modulatory influences from nonneural (satellite glial) cells that are closely associated with the trigeminal ganglion neurons, and the communication between these cells and ganglion neurons are likely involved in findings that injury to sensory nerves supplying one trigeminal division (e.g., V3) can lead to excitability changes in trigeminal ganglion neurons serving another division (e.g., V2). Also noteworthy are recent findings that animal models mimicking the clinical compression of the trigeminal ganglion or trigeminal sensory root sometimes observed in trigeminal neuralgia patients appear to reflect abnormal sensory input to the brainstem manifested in nociceptive behavior and brainstem cellular changes.[20]

Clinical Implications

Peripheral sensitization is a process marked by enhanced spontaneous firing of nociceptive afferents, an increase in their responsiveness to noxious stimuli, and a decrease in their activation threshold. These three features of peripheral sensitization thus may contribute to the spontaneous pain, hyperalgesia, and allodynia that characterize many pain states, such as the tactile sensitivity of sunburnt skin, the thermal sensitivity and spontaneous pain of an inflamed tooth, and the increased postoperative sensitivity of a tissue that has undergone surgery. In addition, the chemical mediators that are released as part of the peripheral sensitization process may spread through the tissues to act upon adjacent nociceptive afferent endings, and thereby contribute to the spread of pain that occurs following tissue injury.

Gender differences in pain involve environmental and psychosocial influences and also differences in CNS nociceptive mechanisms.[2] In addition, the physiologically based gender differences noted above in TMJ and jaw muscle nociceptive afferents to glutamate and opioid-related substances (i.e., morphine) may also contribute to the gender differences in many craniofacial pain conditions involving these tissues. Most of these pain conditions, especially those that are chronic (e.g., TMD, burning mouth syndrome), have a female predominance,[2] and research findings indicate that peripheral or central physiologically based gender differences in nociceptive processes can explain in large part the female predominance.

Our increased understanding of the processes involved in the activation or peripheral sensitization of nociceptive afferents has led to the development of pharmacologic agents targeting specific chemical processes involving these afferents.[12,14,21] For example, many common nonsteroidal anti-inflammatory drugs (NSAIDS) as well as several recently developed analgesics (e.g., cyclooxygenase-2 [COX-2] inhibitors) exert their main analgesic actions by influencing the excitability of nociceptive afferent endings in peripheral tissues. And in the case of nerve blocks, local anesthetics are effective in eliminating pain resulting from peripheral tissue injury because they interfere with the ionic channels and currents involved in the initiation and conduction of action potentials from the tissues along nociceptive afferents into the CNS. The various chemical mediators contributing to peripheral nociceptive activation, sensitization, and related events (e.g., inflammation), plus the recent evidence for the involvement of satellite glial cells in the trigeminal ganglion, represent additional potential peripheral targets for the development of new or more effective therapeutic approaches to control pain.[12–14,21]

CNS Processes and Clinical Implications

Brainstem

The primary afferents innervating the various cutaneous, intraoral, deep (e.g., TMJ, muscle), and cerebrovascular tissues of the craniofacial region project to the trigeminal brainstem sensory nuclear complex (VBSNC), where they synapse on second-order neurons. The nociceptive signals carried into the brainstem by the Aδ and C fiber nociceptive afferents are transmitted to second-order nociceptive neurons by the release of excitatory amino acids (e.g., glutamate) and other neurochemicals such as neuropeptides (e.g., substance P) from the brainstem endings of the primary afferents; these mediators activate the VBSNC neurons by interacting with the glutamatergic (e.g., NMDA, AMPA) and neurokinin receptors or ion channels of the neurons.

The VBSNC is made up of several morphologically distinct subdivisions, and it has properties consistent with its strategic role as the major brainstem relay of somatosensory information (touch, temperature, pain) from the face and mouth (**Fig. 15.2**). There is extensive clinical, behavioral, morphologic, and electrophysiologic evidence of the particular involvement of its most caudal component (subnucleus caudalis) in craniofacial nociceptive transmission.[8,9,22–25] For example, the neurosurgical operation of trigeminal tractotomy (formerly used to relieve trigeminal neuralgia) or experimentally induced lesioning in behavioral experiments in animals disrupts the flow of sensory signals from the nociceptive primary afferents into subnucleus caudalis and produces facial analgesia. Also, from a morphologic viewpoint, subnucleus caudalis resembles the spinal dorsal horn, which is so critical in spinal nociceptive mechanisms. Electrophysiologically, many of the caudalis neurons function as nociceptive transmission neurons because they receive and are activated by the nociceptive primary afferent inputs to the subnucleus and they project to the brainstem and/or higher brain areas involved in pain perception and behavior. Their properties contrast with those of low-threshold mechanosensitive and thermosensitive VBSNC neurons implicated, respectively, in orofacial touch and temperature sensibility. These caudalis nociceptive transmission neurons have been categorized as either nociceptive-specific (NS) neurons or wide-dynamic-range (WDR) neurons, and analogous neurons exist in the spinal dorsal horn. The WDR neurons are activated by nonnoxious (e.g., tactile) stimuli as well as by noxious stimuli, and receive large-diameter (Aβ) and small-diameter (Aδ and C fiber) afferent inputs; NS neurons, in contrast, normally respond only to noxious stimuli (e.g., pinch, heat) applied to a localized craniofacial receptive field and receive small-diameter afferent inputs from Aδ and C fibers.

Because of its close structural and functional homology with the spinal dorsal horn, subnucleus caudalis has also become known as the medullary dorsal horn, although some differences between the two structures do exist.[22,23] Nonetheless, the traditional view that subnucleus caudalis is the only or the essential brainstem element in craniofacial nociceptive transmission no longer applies in light of evidence that some of the more rostral subdivisions of the VBSNC, especially subnuclei interpolaris and oralis, may also play an important role. For example, the transitional region between subnuclei caudalis and interpolaris has recently been shown to be important in muscle, autonomic, and endocrine responses and modulatory influences related to orofacial pain, and subnucleus oralis may contribute to ascending nociceptive pathways and nociceptive reflexes.[8,9,26]

Thalamus and Cortex

Neurons at all levels of the VBSNC, including subnucleus caudalis, project to other brainstem regions that include those (e.g., the parabrachial nucleus) involved in affective or hormonal functions; to the reticular formation and cranial nerve motor nuclei that provide the central substrate underlying autonomic and muscle reflex responses to noxious stimuli; and to the raphe system, which gives rise to descending CNS pathways that can modulate nociceptive transmission (see below).[8,9,27] In addition, many VBSNC neurons project to the contralateral thalamus via direct or multisynaptic paths.[8,9,27] The thalamic regions receiving and relaying somatosensory information are the ventroposterior nucleus (or ventrobasal complex in the subprimate) as well as the medial thalamus and posterior group of nuclei. These regions contain NS and WDR neurons, as well as low-threshold mechanoreceptive and thermoreceptive neurons; in general, these different types of neurons have properties that are similar to those described for analogous neurons in the subthalamic relays such as subnucleus caudalis. Some may project to other thalamic regions (e.g., the thalamic reticular nucleus), where they may have a role in the modulation of sleep and wakefulness.[28] Many, however, project to the overlying somatosensory cerebral cortex, where their relayed signals are processed to provide for the detection and localization of tactile, thermal, or noxious stimuli.

The properties of nociceptive neurons in the thalamic ventroposterior nucleus and their connections with the overlying somatosensory cortex indicate that most are involved in defining the spatiotemporal features of peripheral stimuli, and thus function in the sensory-discriminative dimension of pain.

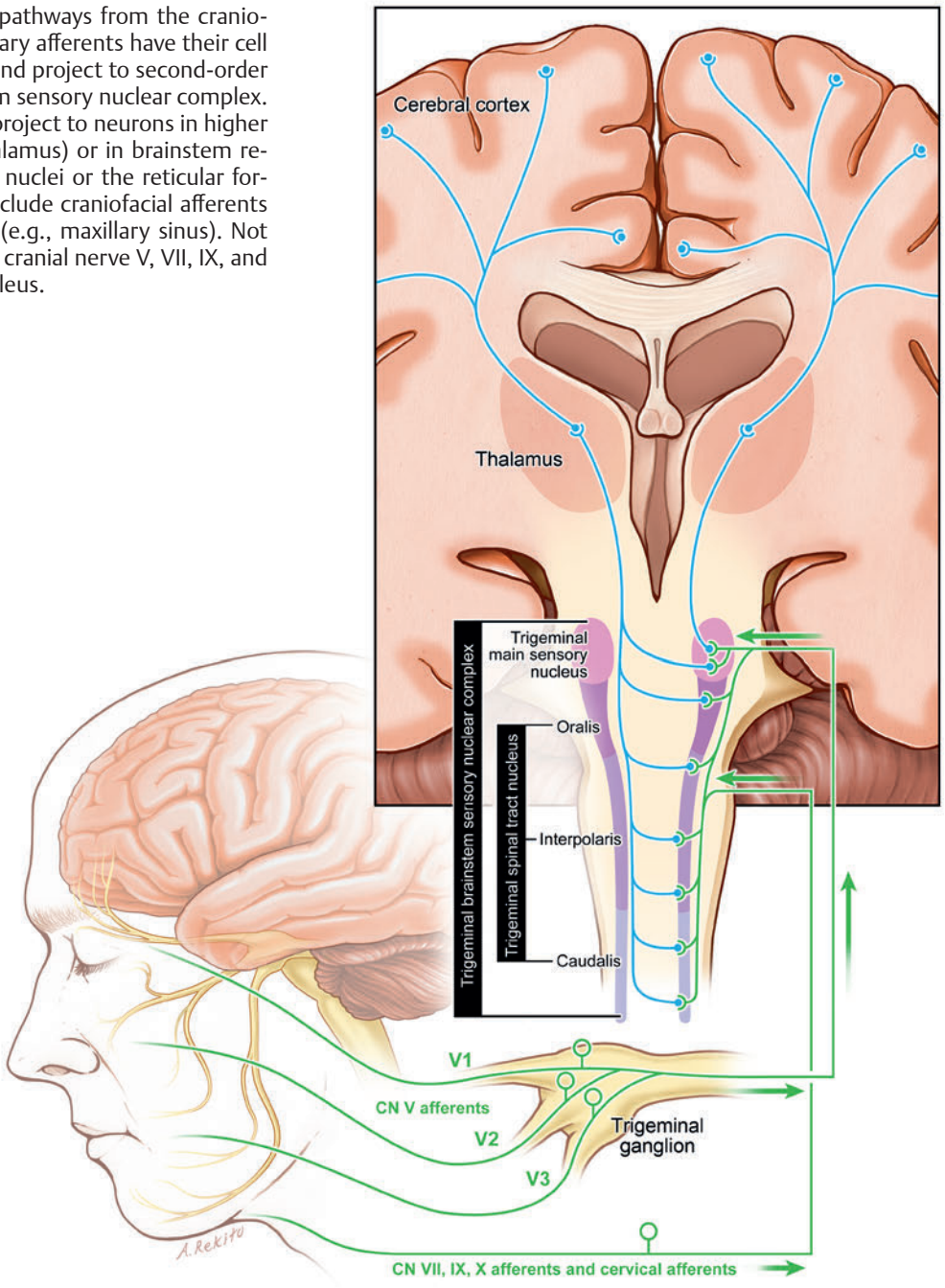

Fig. 15.2 Major somatosensory pathways from the craniofacial region. Most trigeminal primary afferents have their cell bodies in the trigeminal ganglion and project to second-order neurons in the trigeminal brainstem sensory nuclear complex. These second-order neurons may project to neurons in higher levels of the brain (e.g., in the thalamus) or in brainstem regions such as cranial nerve motor nuclei or the reticular formation. The sensory inputs also include craniofacial afferents supplying the cornea and sinuses (e.g., maxillary sinus). Not shown are the projections of many cranial nerve V, VII, IX, and X afferents to the solitary tract nucleus.

On the other hand, nociceptive neurons in the more medial nuclei (e.g., the intralaminar nuclei and parafascicular nucleus) and the posterior group generally have properties and connections (e.g., with the anterior cingulate cortex) suggestive of a role more in the affective or motivational dimension of pain. This is consistent with the properties of somatosensory cortical nociceptive neurons that indicate their likely role in the localization and intensity coding of noxious stimuli; nociceptive neurons in other cortical regions, such as the anterior cingulate cortex, have properties consistent with a role in the affective and motivational dimensions of pain.[27,29,30] These findings are consistent with recent brain imaging findings that experimentally induced noxious stimuli or pain conditions in humans are associated with the activation of several cortical regions, including the somatosensory cortex and anterior cingulate cortices.[27,30]

Modulatory Processes and Influences

At each level of the trigeminal nociceptive pathway, the transmission process may vary depending on such diverse factors as maturational stage, gender, and age of the individual; genetic, nutritional, and immunologic influences; and the individual's behavioral state. Modification of the ascending nociceptive signals can occur at thalamic and cortical neuronal levels, and also at the VBSNC.[8,9,31] The intricate organization of the VBSNC, especially subnucleus caudalis, as well as the numerous afferent inputs to the VBSNC from peripheral tissues and from several brain regions, provide the neural circuitry for several interactions between these many inputs. The activity of caudalis nociceptive neurons can, for example, be suppressed by influences from within caudalis itself (such as its substantia gelatinosa) as well as from other parts of the spinal cord, brainstem, and higher centers including the reticular formation, periaqueductal gray, rostroventral medial medulla, and sensorimotor cortex. These modulatory influences result from endogenous neurochemicals such as opioids, 5-HT, norepinephrine, and GABA being released from the descending projections. Some of these neurochemicals also are involved in the so-called segmental inhibition of the neurons, which can be induced by peripheral stimuli that activate inhibitory interneurons within subnucleus caudalis.

Modulation of trigeminal nociceptive transmission also occurs in the form of neuroplastic changes that can be manifested in VBSN, thalamic, and cortical nociceptive neurons as a result of nociceptive afferent inputs evoked by injury or inflammation. In the trigeminal nociceptive system, it has been most studied in subnucleus caudalis, and has been found to involve in particular the release from brainstem endings of trigeminal nociceptive afferents of excitatory amino acids that act via NMDA receptor mechanisms to induce a cascade of intracellular events in caudalis nociceptive neurons.[8,9,19,24] The neuroplasticity is manifested as an increase in neuronal excitability (e.g., increased receptive field size and responses to noxious stimuli and decreased activation threshold) and reflects what has been termed *central sensitization* of the nociceptive neurons (**Fig. 15.3**). Central sensitization of caudalis nociceptive neurons has now been well documented in several acute as well as chronic inflammation or neuropathic pain models. Moreover, central sensitization of thalamic and cortical nociceptive neurons can occur, although it may depend on the functional integrity of subnucleus caudalis for its expression. Whereas central sensitization is normally reversal, its persistence is thought to lead to the development and maintenance of a chronic pain state.[8,9,19,24] Its expression in subnucleus caudalis, however, appears to be dependent on the functional integrity of medullary glial cells.[18] Furthermore, caudalis central sensitization and the accompanying nociceptive behavior that occur in animal models of craniofacial inflammatory or neuropathic pain can be overcome by drugs (e.g., morphine, pregabalin) that are often clinically effective in chronic pain patients.[8,14,32,33]

Related to this are the convergent afferent inputs to many nociceptive neurons. For example, nociceptive afferent inputs relayed to many caudalis nociceptive neurons appear to derive exclusively from cutaneous (and oral mucosal) tissues and endow these neurons with coding properties used for the detection and discrimination of superficial craniofacial pain. However, nociceptive information from other craniofacial tissues (e.g., tooth pulp, muscle, TMJ, meninges) is predominantly processed by subsets of caudalis nociceptive neurons that receive extensive convergent afferent inputs from these tissues as well as cutaneous afferent inputs.[8,24] These convergence patterns may not only occur in caudalis nociceptive neurons but may also be manifested in the analogous neurons in the thalamus and cortex, and reflect mechanisms contributing to deep pain. In addition, however, such convergence may also contribute to the poor localization, spread, and referral of pain that are typical of craniofacial pain conditions involving the TMJ and associated musculature, such as TMD, and those involving intracranial tissues (e.g., meninges) and more superficial tissues, such as some types of headaches.[8,24,34] Nonetheless, the pain referral mechanisms likely depend not only on the convergent patterns of afferent inputs to the nociceptive neurons but also on the neuroplastic changes expressed as an increased excitability (i.e., central sensitization) that may be generated in them by these inputs as a result of injury or inflammation. There is evidence to suggest that some of the afferent inputs are normally "weak" but may be "unmasked" in such pathophysiologic situations and become more effective in exciting the nociceptive neurons that have become hyperexcitable through the central sensitization process. As a consequence, pain is perceived as coming from the tissues supplied by these particular afferents.

Clinical Implications

As noted above, many nociceptive neurons can be excited only by natural stimulation of cutaneous tissues and have properties and projections consistent with a role in superficial craniofacial pain. Such a neural substrate assists the clinician in the diagnosis of pain associated with injury or inflammation, especially of the facial skin or oral mucosa. However, the convergence patterns of afferent inputs to many of the nociceptive neurons underlie the mechanisms contributing to deep pain, but may also underlie the

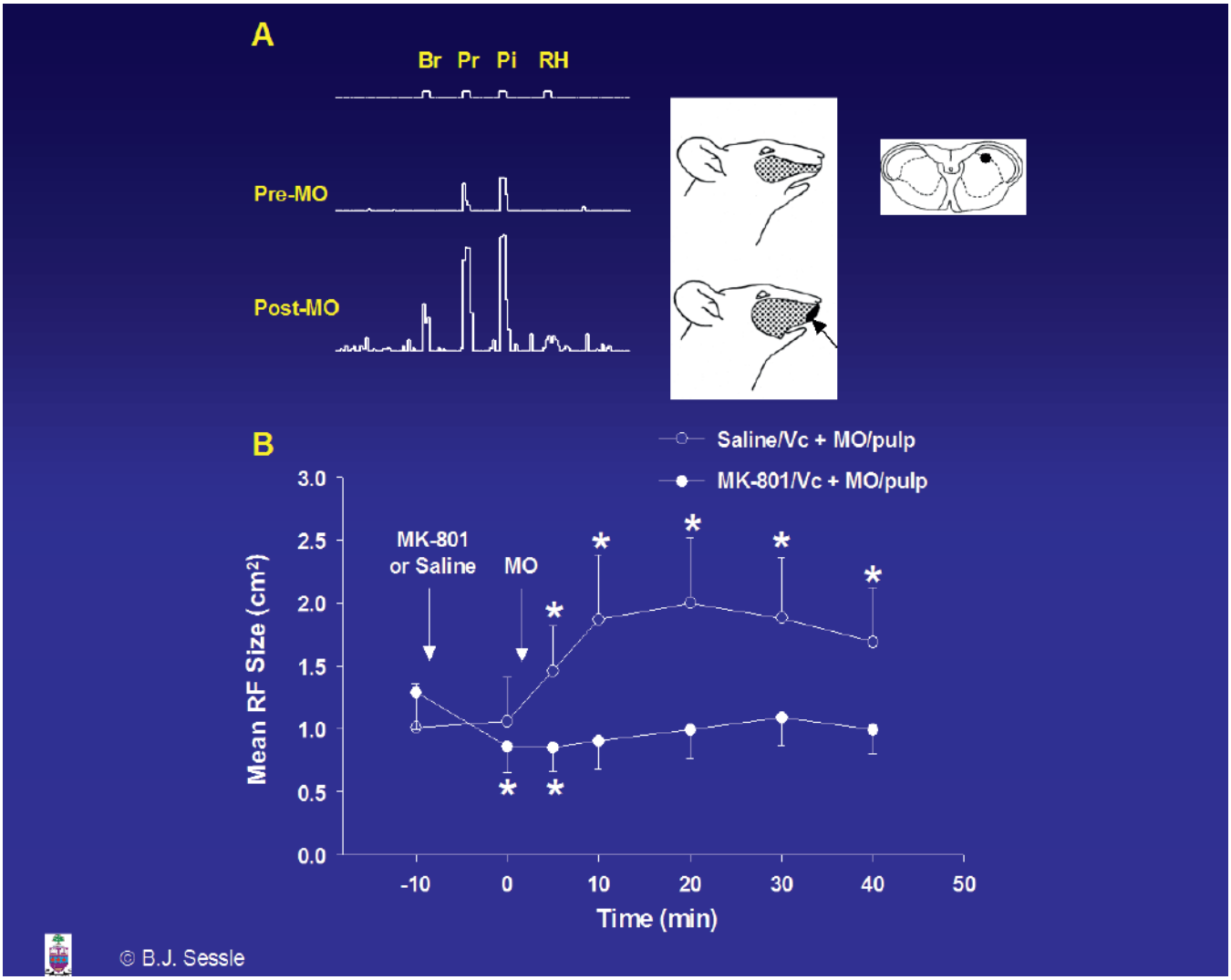

Fig. 15.3 Central sensitization of a nociceptive-specific neuron in the rat trigeminal subnucleus caudalis (Vc). (**a**) Neuron that underwent neuroplastic changes in its response and mechanoreceptive field (MF) properties after application of the inflammatory irritant mustard oil (MO) to the right maxillary molar pulp of the rat. The top series of traces show the neuronal responses to brush (Br), pressure (Pr), pinch (Pi), and radiant heat (RH) applied to the MF in control conditions prior to MO application (i.e., Pre-MO). The bottom traces show the neuronal responses to the same stimuli 20 minutes after MO application (i.e., Post-MO). Note that following MO application to the molar pulp, the neuron developed a lowered activation threshold to such an extent that it became responsive to Br and RH of the MF; it also became more strongly responsive to Pi stimuli. On the right is shown the expansion of the neuron's MF, 10 minutes after MO application. These neuroplastic changes in the MF and response properties of the neuron reflect a central sensitization. The neuronal recording site of the neuron in subnucleus caudalis is shown on the far right. (**b**) Graph showing both the time course of the MF expansion after MO application and the ability of the NMDA receptor antagonist MK-801 (but not its vehicle, isotonic saline) applied to caudalis in preventing this MF expansion, pointing to the involvement of NMDA receptor mechanisms in the production of the central sensitization in the caudalis neuron. (Adapted from Chiang CY, Park SJ, Kwan CL, Hu JW, Sessle BJ. NMDA receptor mechanisms contribute to neuroplasticity induced in caudalis nociceptive neurons by tooth pulp stimulation. J Neurophysiol 1998;80:2621–2631.)

poor localization, spread, and referral of pain that are typical of many craniofacial pain conditions that can present diagnostic and management problems for the clinician.

The central sensitization that accompanies neuroplastic alterations of the nociceptive neurons induced by injury or inflammation of craniofacial tissue and nerves includes neuronal receptive field expansion, which also may play a role in the spread and referral of pain, as noted above. Other features of central sensitization of nociceptive neurons—namely spontaneous activity, hyperexcitable responses to noxious stimuli, and decreased activation threshold—may also represent mechanisms that, along with peripheral sensitization (see above), explain the spontaneous pain, hyperalgesia, and allodynia that characterize several craniofacial pain conditions. An example is TMD because these peripheral and central processes can explain the ongoing pain, increased pain sensitivity (i.e., hyperalgesia), lowered threshold for evoking pain (i.e., allodynia), and the diffuse, often referred character of TMD pain. Another example is the pain of a long-term arthritis; this may involve central sensitization of nociceptive neurons in central nociceptive pathways as well as peripheral sensitization of the afferents in the inflamed region. Nonetheless, it is noteworthy that central sensitization, as well as peripheral sensitization, appear to be normal physiologic reactions to noxious stimulation, and in most situations they are reversible and the pain state resolves. If, however, they become maintained, chronic or persistent pain may result. Unfortunately, the factors predisposing to the prolongation of these reactions to tissue injury or inflammation are not yet well understood, but probably include genetic as well as environmental, immunologic, and psychophysiologic factors.

Central sensitization depends on nociceptive afferent inputs for its initiation and perhaps also for its maintenance. This supports the incorporation into clinical practice of approaches (e.g., local anesthesia, preoperative and postoperative analgesic drugs) that reduce nociceptive afferent inputs into the CNS and thus reduce the risk for the development of central sensitization and a persistent pain state. Of related interest are several studies in experimental animals and humans to determine if preemptive analgesia would be effective in reducing postoperative pain.[35–37] However, the findings have been mixed, and a number of factors have been identified that may account for the variability in efficacy. These include the time-limiting action of a local anesthetic used for preemptive analgesia, since nociceptive afferent inputs can soon become operational again after the local anesthetic block has worn off, at which time they can induce central sensitization in the CNS.

The modulatory influences on the nociceptive neurons of behavioral factors, including state of alertness, sleep, distraction, and attention, are examples where descending influences operating at the VBSNC and higher brain levels may affect craniofacial pain. Descending influences that suppress the nociceptive neurons have been implicated as intrinsic mechanisms contributing to the analgesic effects of several procedures used to control pain, such as deep brain stimulation, and opioid-related (e.g., morphine) and 5-HT agonist (e.g., amitriptylene) drugs. The development and application of physical procedures (such as acupuncture or transcutaneous electrical nerve stimulation) appear also to utilize some of these endogenous neurochemicals and intrinsic pain modulatory circuits. Psychological and behavioral approaches have become recognized as effective methods to manage pain, and these act in part by descending modulatory circuits, reflecting the relevance of the biopsychosocial model to pain management. Further knowledge of these modulatory processes should lead to the development of new or improved therapeutic approaches, including the potential to target also nonneural elements (e.g., glial cells) in view of the recent discovery of their critical role in craniofacial pain mechanisms.

■ Conclusion

Recent research studies have identified several peripheral and CNS processes underlying neural mechanisms accounting for acute or chronic craniofacial pain. These include peripheral sensitization and central sensitization, which have features that can account for the spontaneous nature, allodynia, hyperalgesia, and spread and referral of pain resulting from injury or inflammation of craniofacial tissues and nerves. Several modulatory factors and mechanisms influencing these processes have been identified, and their further elucidation holds out the promise for the development of new or improved management approaches for craniofacial pain states.

Acknowledgments

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Editor's Comments

This chapter focuses on the issues discussed in Chapters 1 and 3 concerning nociception, and on the central processing of that information. The difference is that Professor Sessle examines the unique role and function of the trigeminal system in this regard.

Facial pain is a common target for surgical intervention. Trigeminal neuralgia (TN) is unusual in its surgical tractability (see Chapters 42–47). Because we are somewhat entranced by our success in that disorder, we tend to forget how many other facial pain syndromes resist our best surgical efforts. Furthermore, misapplication of procedures that are known to be successful for TN, in other craniofacial pain disorders can lead to disappointment or worse. Ultimately, my belief is that a fundamental understanding of the mechanism of facial pain is pivotal to the development and employment of surgical procedures for facial pain.

Why is it that so many craniofacial pain disorders fail to yield to surgical intervention? Classical postinjury neuropathic pains of the face (trigeminal neuropathic pain, or TNP), anesthesia dolorosa and its variants (trigeminal deafferentation pain, or TDP), trigeminal postherpetic neuralgia (PHN), and temporomandibular disorders (TMD) represent special challenges for which no satisfactory surgical solution has yet been found. Their pathophysiologies may be best appreciated, if not completely understood, in the context of Dr. Sessle's comments. In these instances, our current theoretical model for the genesis of the pain has not led to improved care, medical or surgical. Successful therapies remain a tantalizing future prospect.

For other craniofacial pain conditions, the pathology may be of such complexity that it is difficult to separate the condition from the patient's psychological construct. Conditions such as "atypical facial pain" or "burning mouth syndrome" defy precise definition, and might be considered "disputed" diagnoses. The suffering these patients feel is real enough, but our understanding is lacking. My point is that in the case of deafferentation pains of the face, and other, more disputed diagnoses, the absence of a firm theoretical grasp of the relevant pathophysiology has severely hampered attempts at medical and surgical therapy.

In his 1905 monograph *The Surgical Treatment of Facial Neuralgia*, Hutchinson framed the issue as eloquently as I have seen:

> *The surgeon . . . is chiefly concerned with the question: "What cases of neuralgia are suited for operative treatment, and what are the best methods to employ?" The answer, obviously, should depend upon a scientific classification, based solely upon the causes of neuralgia; at present such a classification is impossible.*

This chapter outlines the foundations for our understanding of the workings of the trigeminal sensory system. As our base of knowledge improves, so too, we may hope, will our therapies.

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16 Evidence-Based Approach to the Treatment of Facial Pain

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Physicians are increasingly expected to show that their practice is supported by good-quality evidence. What determines the validity of the evidence remains a matter of debate, with opinions ranging from acceptance of case series to insistence on nothing less than randomized controlled trials (RCTs). Although there is wide recognition of the fact that in terms of efficacy (i.e., whether a treatment works or not), randomization and control offer the highest level of evidence, there is much less unanimity about the clinical applicability of such trials in individual cases. This debate has been active since the introduction of evidence-based medicine (EBM) in the 1970s with little abatement.

EBM builds on the goal of ensuring that a given diagnostic procedure or treatment is as accurate, effective, and unbiased as possible. According to a frequently quoted definition, EBM is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.[1] Several hierarchic scales have been developed to measure the strength of evidence.[2–6] In all, the strongest evidence comes from adequately powered RCTs employing a design that limits bias and ensures the objectivity of measurement of outcome. The weakest evidence comes from uncontrolled case series, case reports, and expert opinion.[4,5] Uncontrolled trials overestimate the treatment effect substantially, and relying on such a series could even allow a conclusion that is opposite a conclusion derived from a systematic review of RCTs.[7,8] Virtually all contemporary treatment guidelines rely on the hierarchic classification of strength of evidence for their recommendations.

The Importance of Randomization and Control

RCTs by their very nature are restricted by the study conditions and are justifiably criticized for providing only a population-based estimate of efficacy without taking into consideration individual variation in response. Although the rules of RCTs help to reduce the bias inherent in clinical practice to tolerable levels, this achievement comes at the price of stringent patient selection, short duration trials, trial-specific clinical settings, and outcome measures better suited for statistical analyses than for measuring the real clinical impact. These drawbacks withstanding the benefit of addressing the research question of efficacy and, specifically, benefit over risk, are best handled through RCTs. They are not intended for direct implementation in individual cases; they are not cookbook instructions that override clinical judgment.[9] They provide the physician with the least biased information on the measured efficacy of a treatment against an alternative comparator treatment or no treatment (or placebo). How to apply this information to clinical practice is left to the clinician's judgment. Studies that lack randomization and control will yield results applicable to that particular study population, but nothing can be inferred about their generalizability. They do not address the very essence of the matter: whether a particular treatment is superior to an alternative treatment or a sham or placebo.

Observational studies do have an important role as a source of evidence provided that their limitations are acknowledged and taken into account in interpreting the results. The biggest limitation is related to selection bias, but other factors such as variability in the provision of the intervention and unblinded assessment of outcome also weaken these studies. Although RCTs are not immune to bias, it is the nature of RCTs, when done appropriately, to rely on a strict protocol, which many observational studies do not tend to do. Observational studies are well suited for discovery and innovation and as pilot studies of the feasibility of (usually larger) controlled trials.[10]

Random allocation of patients to receive one of two or more treatments remains the best approach for controlling the wide array of confounding factors that are either unknown or unavoidable and will

inevitably influence the outcome of any intervention. In facial pain a major confounder arises from comorbidity. Facial pain patients frequently have widespread pain,[11,12] depression, and other psychological problems,[13,14] and they frequently require and have received treatment from a wide range of specialists.[15] Additional variability comes from difficult-to-measure factors that influence the investigator's decision to enter or not enter the patient into a study. These are factors such as patient preference, patient behavior, clinical intuition, and logistics.[16]

Blinding, another important method of controlling for confounders, is thought to be virtually impossible in surgery, but there are several options available that ensure blinding of patients and outcome assessors.[17,18] Strict randomization and blinding protocols have been successfully implemented in various clinical trials of interventions for facial pain (e.g., comparison of conventional radiofrequency versus pulsed radiofrequency treatment of the gasserian ganglion in trigeminal neuralgia [TN],[19,20] sham-controlled stimulation of the sphenopalatine ganglion,[21] and placebo-controlled local anesthetic blockade[22] of the greater occipital nerves for cluster headache [CH]). When due to the nature of the intervention blinding is not possible, randomizing patients to early or late intervention, allowing a patient to cross over to the comparator treatment after a predetermined period, use of an independent assessor oblivious to the details of the intervention, and using patients as their own controls (e.g., being subjected to different intensities of neural stimulation)[23] may help to compensate for this limitation. Studies on laminectomy in sciatica or spinal cord stimulation in failed back surgery syndrome show that even when sham-controlled trials are not possible, well-designed comparative trials are, and they yield results that generally are helpful to the practicing clinician.[24,25]

Sham procedures in RCTs raise important ethical issues and provoke strong opinions for and against their use in surgery.[26] The fact remains that such studies have been performed following ethical review and subsequently published; examples include controlled trials of arthroscopic debridement of the osteoarthritic knee and adhesiolysis in abdominal pain—both unequivocally showing the limitations of these widely used treatments.[27,28]

Some investigators object to RCTs on pragmatic grounds, arguing that they incur considerable cost, are time-consuming, and may be obsolete by the time the results come out.[18] An alternative approach that has been proposed is to rely on carefully collected clinical data from wide-ranging clinical practice to multicenter-maintained databases and subject all the acquired information to sophisticated statistical analyses.[29] It is unlikely, however, that such an approach could be applied to chronic facial pain, for which a wide variety of treatments are available without general consensus as to preference.

The problem is illustrated in **Table 16.1**. My patient with chronic CH had stopped responding to pharmacotherapy. I therefore conducted a thorough literature search to find an answer to the question: What is the efficacy of current surgical options for the management of chronic CH? I expected to find sufficient evidence for some procedures to allow me to justify a particular treatment. I restricted my search to studies that reportedly included chronic CH patients whose pain was refractory to drug therapy and who had been followed up formally post-procedure. The outcome of interest had to indicate a measurement of CH attack activity, and the study had to be completed with acceptable attrition rates. Any technique or anatomic target was acceptable. I identified 13 different types of treatments, even after rejecting several that I believe have become obsolete (alcohol injection into supraorbital and infraorbital nerves or trigeminal ganglion, avulsion of supraorbital or infraorbital nerves, sphenopalatine ganglionectomy, sectioning of the intermedius or greater petrosal nerves, and trigeminal tractotomy) or for which the data were too limited (balloon compression of the trigeminal ganglion, cauterization of the maxillary nerve, and vagus nerve stimulation).

The final list consisted of 39 studies.[21,30–66] With two exceptions all were small case series, with no control group and mostly without independent outcome assessment. As such they carried a high risk of bias.[5,6] The two RCTs were small but sufficient for a Phase II trial and were considered to be of low risk. However, one of them was designed to measure the treatment effect of the intervention on acute attacks, not prevention, and therefore was not optimized for the research question.[21] The second small pilot study suffered from a methodological uncertainty because the RCT phase may have been carried out over too short a period.[63] If one were to use the American Academy of Neurology (AAN) tool for the strength of the evidence,[5] 34 of the 37 studies would have been classified as Class IV (denoting high risk of bias), 1 as Class III (moderately high risk of bias), and 2 as Class I (low risk of bias).

There were no major differences between the groups in duration of CH pain, age range of participants, gender distribution, or nature of failed pharmacotherapy. Older case series included more patients with previous surgical failures. Because of the rather concise way older papers present adverse events, their comparison with the more contemporary ones in this respect is not feasible; however, major complications were rare in general. Reference was made to sensory abnormalities after gasserian gangliolysis that appear higher after stereotactic radiosurgery in CH than in TN, and the same observation has been

Table 16.1 Outcome of interventions for cluster headache: Extracted from publications dated 1982–2013

Intervention	Lead author	N	Short-term response	F/U long-term	Resolution of CH attacks (or percentage reduction)	Adverse effects	Comment	EBM level
SPGB LA	Felisati 2006[30]	21	5/21 no attacks > 3 mo	12–24 mo	2/21 no attacks	1 epistaxis	Rpt blocks less effective	Class IV
	Pipolo 2010[31]	15	8/15 no attacks > 1 mo	8–28 mo	3/15 no attacks	2 epistaxis	Up to 4 blocks	Class IV
SPG RF	Salar 1987[32]	7	ND	6–34 mo	7/7 no attacks	7/7 ache, orbital	Up to 3 RF blocks	Class IV
	Sanders 1997[33]	10	ND	24 ± 10 mo	3/10 no attacks	epistaxis; ache in orbital region	Up to 3 RF blocks	Class IV
	Narouze 2009[34]	15	MAF and MAI reduced	12 mo	3/15 no attacks	hypoesthesia V2 in 1/15	New contralateral CH in 2 pts	Class IV
	Oomen 2012[35]	3	ND	12 mo	2/3 complete/near-complete resolution	None reported	4 RF blocks in 1 pt	Class IV
SPG PRF	Bayer 2005[36]	8	Data on all facial pain only; 21% reported to be pain free	4–52 mo	Unclear re: CH	None reported	Data available for 31/46 patients	Class IV
	Chua 2011[37]	2	1 pt no attacks 4 mo	N/A	N/A	None reported		Class IV
SPG STIM	Schoenen 2013[21]	28	12/28 responders; mean MAF decrease 88% during trial with real, sham, suboptimal stimulation	3–8 wk	N/A	5 device related; 26 (83%) sensory change; 12 (35%) local pain	Attack frequency 2° end point only	Class I (in part)
ONS	Burns 2007[38]	8	No immediate improvement	8–27 mo	2/8 > 90%	4 lead related, 1 scar pain	5 new battery	Class IV
	Magis 2011[39]	8	No immediate improvement	16–22 mo	5/8 > 90%; 2 entirely pain-free	1 lead migration	4 new battery	Class IV
	Magis 2007[40]	15	10 excellent early response	11–64 mo	8/15 complete; 3/15 > 90% reduced MAF	1 lead migration, 3 sig. infections	1/8 off medication	Class IV
	Fontaine 2011[41]	14	2 delayed (1 mo, 5 mo)	12 mo	6/13 > 90% improvement	1 expant, 1 wound debridement	Includes pts from Magis 2007	Class IV
	Mueller 2011[42]	10	Improvement on average after 20 days	3–18 mo	4/10 > 75%, none pain-free	1 lead infection, 1 IPG discomfort	3/13 stopped medication	Class IV
	Mammis 2011[43]	1	< 50% improvement	36 mo	1/1 very few attacks	None reported	2 reops because of complications combined with SO and IO stimulation	Class IV

Table 16.1 Outcome of interventions for cluster headache: Extracted from publications dated 1982–2013 *(Continued)*

Intervention	Lead author	N	Short-term response	F/U long-term	Resolution of CH attacks (or percentage reduction)	Adverse effects	Comment	EBM level
SONS	Narouze 2007[44]	1	Attacks stopped 2 mo after implant	16 mo	1/1 no attacks	None reported	Recurrence after stimulator off	Class IV
	Vaisman 2012[45]	4	ND	18–36 mo	3/4 > 75%	1 skin erosion	2 explants; 1 pin-free after explant	Class IV
SCS high	Wolter 2011[46]	7	ND	3–78 mo	1/7 no attacks, 3/7 > 80%	3 lead migrations 2 lead breakages	5 lead revisions required	Class IV
TG glycerol	Waltz 1985[47]	5	Short-lived remissions only	1–32 mo	No complete/near-complete resolution	None reported	Several blocks at 3 month intervals	Class IV
	Ekbom 1987[48]	6	4/6 no attacks in first 3 weeks	9–66 mo	3/6 complete/near-complete resolution	1 meningitis	1/3 responders on regular pizotifen	Class IV
	Pieper 2000[49]	18	15/18 immediate pain relief (2 pts had two injections)	40–78 mo	8/18 “pain-free”	Hypesthesia		Class III
TG RF	Maxwell 1982[50]	8	8/8 no attacks initially	7–59 mo	5/8 no attacks	None apart from hypesthesia	Selected for RF after +ve block	Class IV
	Watson 1983[51]	13	8/13 initial response	10–105 mo	“Significant relief” lasting 5–36 mo “Excellent/v. good”	None apart from hypesthesia		Class IV
	Mathew 1988[52]	27	17/27 initial relief of CH	6–63 mo	2/7 no recurrence	2 anesthesia dolorosa		Class IV
	Taha 1995[53]	7	7/7 excellent initial reponse	2–20 y	3/7 mild recurrence	1 keratitis		Class IV
TG SRS	Ford 1998[54]	5	4/5 relief within 2 weeks	8–14 mo	3/5 no recurrence	1 nausea (2 wk) 2 deaffer pain		Class IV
	Donnet 2005[55]	10	6/10 initially good relief (2 wk–2 yr) before regressing	24–48 mo	2/10 no recurrence	5/10 face numb		Class IV
	McClelland 2006[56]	10		5–88 mo	0/10 with good response	1/4 deaffer pain		Class IV
	Kano 2011[57]	4	2/4	mean 34	2/4 complete resolution of attacks	3/4 hypesthesia		Class IV
TG rhizotomy	Watson 1983[51]	8	6/8 initial response > 3 mo	Up to 8 y	2 pts pain-free > 4 y and > 8 y	No details	3 patients “pain relief” 30-44 mo	Class IV
	Jarrar 2003[58]	17	ND	1 mo–19 y	12/17 complete, 3 > 75%	1 meningitis 1 CSF leak 1 mild anesthesia dolorosa 1 death	pt died after 2nd surgery	Class IV

Intervention	Lead author	N	Short-term response	F/U long-term	Resolution of CH attacks (or percentage reduction)	Adverse effects	Comment	EBM level
MVD	Lovely 1998[59]	28	15/28 > 90% initially	12–144 mo	9/28 > 90%	1 wound infection 1 CSF leak		Class IV
DBS	Schoenen 2005[60]	6	1 not implanted, 1 died post-op	12–17 mo		1 fatal i.c. hemorrhage Periop. TIA Transient/mild Op site infection Transient hemiparesis Syncope	Pilot study	Class IV
	Starr 2007[61]	4	1/4 early improvement 0 complete/near-complete	12 mo	3/4 complete/ near-complete	1 electrode breakage	2 pts: Frequent re-programming Repetitive re-programming	Class IV
	Bartsch 2008[62]	6	4/6 90–100% control in weeks 1 mo RCT DBS off vs. on; NS	9–15 mo	3/6 near-complete	4 op site infection	5/6 responders stimulator off	Class IV
	Fontaine 2010[63]	11	Open label extension study	10 mo	3/11 pain-free	2 electrode displacements		Class I (Class III)
	Seijo 2011[64]	5	5/5 dramatic early improvement in first 2 wk	12–48 mo	4/5 complete/ near-complete	1 asymptomatic i.c. hemorrhage		Class IV
	Leone 2013[65]	19	3/17 pain relief in first mo	72–144	6/17 near-complete	1 post-op seizure	3/17 off drugs	Class IV
	Piacentino 2014[66]	4	3/4 immediate improvement	60 m	3/4 near-complete	None reported	All remain on medication	Class IV

Abbreviations: SPGB LA, local anesthetic block of sphenopalatine ganglion; SPG RF, sphenopalatine ganglion radiofrequency lesioning; SPG PRF, sphenopalatine ganglion pulsed radiofrequency treatment; SPG STIM, sphenopalatine ganglion stimulation; ONS, occipital nerve stimulation; SONS, supraorbital nerve stimulation; SCS high, high cervical spinal cord stimulation; TG glycerol, glycerolysis of trigeminal ganglion; TG RF, trigeminal ganglion radiofrequency lesioning; TG SRS, stereotactic radiosurgery of trigeminal nerve root; TG rhizotomy, trigeminal rhizotomy; MVD, microvascular decompression; DBS, deep brain stimulation; ND, no data presented; CH, cluster headache; RCT, randomized controlled trial; mo, month; y, year; CSF, cerebrospinal fluid.

made for radiofrequency lesioning.[51,55,57] Mortality was very low; in fact, a single reported death was related to deep brain stimulation.[60]

It must be as obvious to the reader as it was to me that the literature does not offer justification for the physician to recommend one procedure over another, or for the patient to make an informed choice. There appears to be no single intervention that would perform so poorly that one would reject it outright, and no procedure that would stand out as particularly effective with little risk of severe side effects. To allow for some comparability between procedures, I elected to list for each procedure the duration of "complete" or "near-complete" resolution of attacks (the latter defined as >75% reduction in the number of attacks) and serious complications even if some of them were secondary outcomes. This was done with full acknowledgment that some uncertainty remains as to the nature of cessation of attacks because discontinuation of prophylactic medication was not systematically reported by authors. **Table 16.1** lacks many details (e.g., need for repeat procedures to maintain the effect or details of minor complications), but adding them would not change the main outcome of the review. The bottom line is that case series reporting does not accumulate knowledge.

The main hurdle of the listed studies is lack of methodological rigor, which is unfortunate. A study implementing a scientifically robust protocol is not beyond the skills of most clinicians, and the current EBM-minded climate is supportive of such. There is little merit in single units reporting on their first few patients who have undergone a new surgical treatment, and leaving it at that. With some extra effort the procedures, outcomes, and data collection methods must be standardized in a way that is compatible with acknowledged clinical need and allows hypothesis testing at the same time. Because primary facial pain conditions are rare and surgical interventions infrequent, it is almost inevitable that meaningful data can be accumulated only when indications, recruitment, procedural details, outcome measures, and follow-up have been standardized within a large collaborative network. Such a network would enable adequately powered clinical trials. A large database that is compiled according to standards established by consensus would serve as an instrument for audit and as a base for data-mining exercises for hypothesis testing or development of gold standards. The first step in that direction is to run trials to see which of the many procedures available survive scientific scrutiny.

Despite their rarity, primary facial pain conditions, CH included, deserve to remain in the EBM domain. There are no ethical or logistic issues that would prevent RCTs or prospective non-randomized trials that are designed to minimize bias. In fact, sham-controlled studies have been done[21,63] and further studies are under way.[67,68] Many other procedures could be chosen for similar sham-controlled trials. Because the sensory innervation within the pterygopalatine fossa is limited, stimulation,[21] blockade,[30] and lesioning of the ganglion[33,37] can be performed in a way that maintains blinding of both participants and outcome assessors. A matched control-comparator study between occipital nerve stimulation and sphenopalatine ganglion stimulation is not out of order, and neither is comparing lesioning of the trigeminal ganglion versus the sphenopalatine ganglion. A sham-controlled RCT on the effect of SRS on cluster headache is doable, although the results from nonrandomized pilot studies cast some doubt over the desirability of such a study.[56,57] A similar approach is possible for most primary facial pains, including trigeminal neuropathy and TN.[69]

It is likely that all new innovations in the management of facial pain, many of them based on neuromodulation, will be subjected to RCTs or other controlled trials, leaving the role of neuroablative treatments in doubt, even if past-published case series, with all their faults, suggest substantial potential.

The Role of Observational Studies

In certain circumstances an RCT is impractical or unnecessary. It has been suggested that if the signal-to-noise ratio (SNR) is sufficiently high, case studies may well suffice.[70] In chronic pain, including facial pain, such a situation is relatively rare. In TN neurosurgical interventions with very high early responder rates do represent a high SNR. However, the fact that there are treatments that are comparable and are in wide use itself invites an RCT of comparator treatments, something that has not happened between different neuroablative treatments, or between microvascular decompression and neuroablative treatments.

When randomization and blinding are not possible, a carefully conducted prospective matched controlled study will be able to provide a clinically useful result, as long as meticulous attention is paid to the methodology. The investigators should apply well-defined eligibility criteria prior to the commencement of the study, agree on a strict timetable of onset and cessation of the study, and apply intention-to-treat (ITT) methodology for statistical analysis. Critically, by using standardized and blinded assessment of the outcome, ensuring consistent application of the intervention throughout

the study, maintaining low levels of attrition, and employing a properly matched control group, a nonrandomized study will achieve a Class II or Class III status (see below) and allow it to be included in future systematic reviews that increasingly look outside the domain of RCTs.

Rating the Strength of Evidence for Recommendations: Focused Systematic Review of Management of Trigeminal Neuralgia

Whereas for most primary facial pain conditions the paucity of published trials renders systematic reviews futile, the situation is slightly different in the case of TN. Published data are not sufficient for meta-analyses of the efficacy of its surgical management,[69] but an alternative way of evaluating the strength of evidence is to classify individual diagnostic and treatment studies on the basis of how reliably they are able to answer a clinically relevant question.[5,71] This approach was used to develop guidelines for the management of TN in 2008.[72] According to the AAN Practice Parameter methodology,[71] the task force reviewed publications up to the end of 2006 to answer several clinical questions they considered relevant. The strength of evidence and subsequent recommendations regarding both diagnostic investigations and therapeutic interventions were determined using the AAN criteria as published in 2004.[71] The new criteria for classification, published in 2011 and presented in **Tables 16.2** and **16.3**, are similar to the previous ones, but the important change is that the AAN Practice Committee now prefers the GRADE methodology in forming recommendations.[2,5] In GRADE, the initial level of quality based on the study design (randomized high, nonrandomized low) can be rated up or down, depending on effect size, dose response, imprecision, indirectness, and inconsistency. Following is a brief review of the recommendation presented in the 2008 Practice Parameter, with the author's proposal on the update based on the AAN 2011 Clinical Practice Guideline. Because few high-quality studies have been published since the previous review on the five pertinent clinical questions, the update changes are rather limited. (It should be noted that the proposed changes are informal, made exclusively at the author's discretion and for illustration only, and they do not constitute a formal recommendation because they have not been commissioned or reviewed by the AAN Practice Committee.)

Diagnosis of Trigeminal Neuralgia

For diagnostic investigations, the questions relate to the differential diagnosis of classic (idiopathic) TN as opposed to symptomatic TN, and the role of imaging in showing the presence or lack of any structural lesion.

In 2008 four Class II and one Class I studies demonstrated a higher risk for symptomatic TN in the young and those with bilateral trigeminal involvement or sensory deficits, but not sufficiently to allow a predictive rule to be created.[72] Five Class I–III studies demonstrated a relative high sensitivity (94%) and specificity (87%) for the ability of neurophysiologic reflex testing to distinguish classic TN from symptomatic TN, whereas evoked potentials were less reliable. The previous level B recommendation is valid today also because no relevant new material has been published. According to the 2011 criteria, the evidence for the usefulness of these tests remains moderately high, and therefore clinicians may choose to use them to distinguish symptomatic TN from classic or typical TN.

The question of whether a dedicated magnetic resonance image (MRI) could be designed to show the presence or lack of vascular compression in a patient with the clinical diagnosis of TN remained unanswered in 2008 because five Class I and two Class III studies showed considerable inconsistency in the results (sensitivity ranging from 52 to 100% and specificity from 29 to 93% when findings at operation were compared with blinded assessment of the preoperative scan).[72] However, with further Class I studies published since the review in which sophisticated techniques were used (3D FIESTA or 3D CISS and 3D TOF MRA)—achieving high sensitivity (96.7 to 97.2%) and 100% specificity in MRI showing a vascular contact between the nerve and a blood vessel witnessed at operation—the accuracy of preoperative imaging can be rated as very high.[73,74] In other words, the quality of evidence is so high that a neurosurgeon can expect to find a vascular contact at operation if preoperative MRI shows one. However, that does not directly translate to an obligatory recommendation on arranging an MRI in all patients before the operation. (This would require high-quality evidence that poorer results are obtained if no MRI is done.) In my judgment the recommendation should read, "MRI should be performed prior to microvascular decompression"—an important difference from "must be performed" (recommendation level B).[5]

Surgical Treatment of Trigeminal Neuralgia

Surgical treatments have always dominated the management of TN. The question of what is the optimal time to offer surgery to a patient with TN has

Table 16.2 AAN 2011 Guidelines for Classification of Strength of Evidence for Therapeutic Interventions

	AAN classification
Class I	– Randomized, controlled clinical trial (RCT) in a representative population – Masked or objective outcome assessment – Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences – Also required: a. Concealed allocation b. Primary outcome(s) clearly defined c. Exclusion/inclusion criteria clearly defined d. Adequate accounting for dropouts (with at least 80% of enrolled subjects successfully completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias e. For noninferiority or equivalence trials to prove efficacy for one or both drugs the following are also required[a]: 1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority 2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective) 3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment 4. The interpretation of the study results is based on per-protocol analysis that accounts for dropouts or crossovers
Class II	– Cohort study meeting criteria a–e (see Class I) or an RCT that lacks one or two of criteria b–e (see Class I) – All relevant baseline characteristics are presented and substantially equivalent among study groups or there is appropriate statistical adjustment for differences – Masked or objective outcome assessment
Class III	– Controlled studies (including well-defined natural history controls or patients serving as own controls) – A description of major confounding differences between treatment groups that could affect outcome[b] – Outcome assessment masked, objective, or performed by someone who is not a member of the treatment team
Class IV	– Did not include patients with the disease – Did not include patients receiving different interventions – Undefined or unaccepted interventions or outcome measures – No measure of effectiveness or statistical precision presented or calculable

[a] Numbers 1–3 in Class Ie are required for Class II in equivalent trials. If any of the three is missing, the class is automatically downgraded to Class III.

[b] Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Table 16.3 AAN 2011 Guidelines for Classification of Strength of Evidence for Diagnostic Accuracy

	AAN classification
Class I	– Cohort survey with prospective data collection – Includes a broad spectrum of persons suspected of having the disease – Disease status determination is objective or made without the knowledge of diagnostic test result – Also required: a. Inclusion criteria defined b. At least 80% of enrolled subjects have both the diagnostic test and disease status measured
Class II	– Cohort study with retrospective data collection or case-control study – Includes a broad spectrum of persons with and without the disease – The diagnostic test result and disease status are determined objectively or without knowledge of one another
Class III	– Cohort or case-control study – Narrow spectrum of persons with and without the disease – The diagnostic test result and disease status are determined objectively, without knowledge of the other or by different investigators
Class IV	– Did not include persons suspected of the disease – Did not include patients with and without the disease – Undefined or unaccepted independent reference standard – No measures of diagnostic accuracy or statistical precision presented or calculable

obvious clinical importance. However, no studies were identified in 2008 or by the author in 2013 that could answer this question. No published studies exist that prospectively compare long-term results of early versus late surgical intervention (recommendation level U).

In 2008 the task force raised the question of which surgical technique would, as they put it, "give the longest pain-free period interventions with the fewest complications and good quality of life." At that time no preference was considered possible, and the situation in 2013 had not changed much. There are a large number of case series published on percutaneous ganglion-level neuroablative procedures involving thousands of patients, but these are mostly at the Class IV level. From four Class III-level studies the duration of relief from trigeminal pain can be estimated to be 87% at 1 year postoperatively and 50 to 70% at 3 years; however, at 5 years at least one half of the patients will have relapsed.[70] Three controlled trials (two Class I, one Class III), not available for the previous review and comparing different radiofrequency methods, do not appreciably change these figures.[19,20,75] Despite the comparator study design used in these three trials, the results are inconsistent and rule out a recommendation as to the best radiofrequency method in TN. No prospective head-to-head comparison studies have been published with respect to the many ganglion-level neuroablative treatments, or between them and microvascular decompression (MVD).[69] Two European Class III observational studies evaluating outcomes retrospectively over the same period in their units concur that MVD provides a longer pain-free period in typical TN (TN1) than radiofrequency lesioning or glycerolysis of the trigeminal ganglion.[76,77] Although these were nonrandomized studies, the effect sizes they show in favor of MVD are substantial; in addition, the low levels of recurrence in the two studies are consistent with several Class III studies (reviewed for the 2008 Practice Parameter) showing the mean percentages for remission at 1, 3, and 5 years to be 85, 77, and 75%, respectively.[72] Therefore, based on the AAN 2011 criteria, upgrading the quality of evidence to the moderate level is possible, with the recommendation that MVD be chosen as the firstline treatment for typical (classic) TN (TN1) (recommendation level C).

The best way of managing patients with TN2, or those with preoperative MRI suggesting venous rather than arterial compression of the nerve, has not been rigorously studied, and the "no recommendation" advice must still be presumed to be correct.[72]

Conclusion

In primary facial pain refractory to pharmacotherapy, surgical options are many, but except for a few small trials, they have not been subjected to rigorous scientific scrutiny. With the advancement of imaging and neurophysiologic methods for assessment of associated pathology and the rapid development of new neuromodulation methods, such trials have become necessary. It has taken over four decades, since its publication date, for Jannetta's seminal paper on MVD in TN to earn a level C recommendation.[78] Early comparator trials of, say, MVD versus gasserian ganglion radiofrequency lesioning—for which there was a scientific need considering the debate that went on at the time—would likely have resolved a lot of the issues regarding efficacy and adverse effects more satisfactorily compared with the situation today. It is to be expected that the emerging neuromodulation methods designed for many primary facial pain syndromes will undergo sham-controlled trials in the near future and, depending on their success, feature strongly in systematic reviews and guidelines. Because of the current paucity of RCTs in the field, they will likely quickly develop preferential status as an intervention. Methods that have been used before with some success (e.g., neuroablative techniques in chronic CH) will easily be sidelined unless they are tested against the newer methods. Such a skewed development would not necessarily be in the patients' best interest. There are opportunities for both randomized and nonrandomized trials in the field that could change the situation, which at present is clearly unsatisfactory.

Editor's Comments

My recommendation is to read this chapter, and then Chapter 58 by Dr. Robert Coffey. The messages in these chapters are very similar. Philosopher George Santayana (1863–1952) wrote, "Those that cannot remember the past are condemned to repeat it." Without better studies, we will be forever victimized by "eminence"-based medicine, in contrast to evidence-based medicine. The "experts" of the day will dominate the discussion, and the literature, until they are replaced by the next generation of "experts." As Dr. Nurmikko points out, this is a tough cycle to break. Doing so will require courage and discipline.

I was intrigued by Dr. Nurmikko's comment that newer procedures that are subject to ostensibly more rigorous scientific study will predictably displace older procedures that in many cases are the time-tested products of experience. If the quality of evidence is going to become the sole determinant of the future of a procedure, particularly an ablative procedure, then it is time we begin the hard work of testing some of our long-cherished beliefs.

For example, there is no high-quality study of the long-term results of trigeminal rhizotomy for trigeminal neuralgia (TN). How would this compare with the outcome from microvascular decompression (MVD)? Dr. Nurmikko points out that no comparative trial of percutaneous trigeminal rhizolysis and MVD has ever been done for TN, and the same can be said of other ablative procedures such as radiosurgery. He suggests that for the diagnosis of cluster headache other comparisons, such as occipital nerve stimulation (ONS) and sphenopalatine ganglion stimulation, or lesioning of the trigeminal ganglion versus ablation of the sphenopalatine ganglion, could be tested in well-designed studies.

Given the lack of evidence, clinical equipoise must be our default mind-set. The originators of the major surgical procedures for TN are either no longer with us or close to retirement. It is the current generation of neurosurgeons, who are free of the bias that comes with a career of championing a particular procedure, who are now able to ask the important questions and make the necessary structured comparisons.

I appreciate that Dr. Nurmikko has outlined how we might proceed with the next important step in the evolution of surgery for craniofacial pain.

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Section III.C

Trigeminal Neuralgia

17 Trigeminal Neuralgia

Kim J. Burchiel and Shirley McCartney

Trigeminal neuralgia (TN) is one of the most characteristic and discrete diagnostic entities in pain medicine. It is unique in our field in that it is usually readily diagnosed and can be treated, usually effectively, with either medication or surgery. Despite this relative clarity, the condition is rare, and it is often misdiagnosed and mistreated.

The purpose of this chapter is to provide information that can lead to the accurate diagnosis and proper management of this condition. There are many resources in the literature on this condition. This chapter demonstrates the authors' approach to TN.

■ Principles

Classification

As with any pain condition, diagnosis is paramount. The diagnosis of TN is purely historical. Previously, TN was broken into three basic parts: TN (tic douloureux), atypical TN, and atypical facial pain.

"Classic" cases of TN typically share several features, and diagnosis is straightforward:

- Onset in middle-aged to older patients
- Sudden unilateral lancinating electric shock–like pains in the jaw (mandibular, or third division [V3]), cheek (maxillary, or second division [V2]), or eye and forehead (ophthalmic, or first division [V1]) with little to no pain between episodes
- Perioral or other area pain triggers such as talking, touching, eating, brushing teeth, washing the face, or shaving
- Pain-free intervals often lasting months to years after initial onset, gradually shortening and eventually disappearing over the course of the condition
- Progressive intractability to medical therapy

So-called atypical TN cases are characterized by varying degrees of constant pain in the face, which can be described as burning, aching, or throbbing. Patients with constant facial pain, but with little to no lancinating pain, have been labeled as having "atypical facial pain."

The difficulty with this tripartite approach to the diagnosis of TN is that there are no clear boundaries around each subset. This makes diagnosis somewhat subjective, particularly at the intersections of the three entities. Probably as a result of this confusion in terminology, no natural history study of TN has ever been conducted, despite the fact that the condition has been known for at least 300 years.[1,2] Our lack of understanding of the course of TN has certainly inhibited progress in the understanding of this condition.

In the interest of clarifying the diagnosis of facial pain, the senior author developed a schema for characterizing TN.[3] This paradigm divides TN into two types, each having a spontaneous onset. TN Type 1 (TN1) is characterized by pains that are ≥ 50% brief, lancinating, or electrical, and TN Type 2 (TN2) are pains that are ≥ 50% constant, burning, or aching. Pain-free intervals are more common in TN1. Both types may have triggers, although this is more common in TN1, and both may be progressive. Other facial pain diagnoses are included in this classification scheme:

- Symptomatic trigeminal neuralgia (STN), related to multiple sclerosis
- Trigeminal neuropathic pain (TNP), which is a more constant pain following *accidental* or *inadvertent* injury to the trigeminal system
- Trigeminal deafferentation pain (TDP), sometimes referred to as "anesthesia dolorosa," which follows *intentional* destruction of some part of the trigeminal system
- Postherpetic neuralgia (PHN) that follows a clear outbreak of herpes zoster in the ophthalmic division, usually in older (≥ 80 years) patients

Table 17.1 Six diagnostic facial pain categories to characterize almost all patients

Pain type	Abbreviation
Trigeminal neuralgia	
Type 1 (mostly episodic pain)	TN1
Type 2 (mostly constant pain)	TN2
Symptomatic TN (from multiple sclerosis)	STN
Postherpetic neuralgia (after facial shingles)	PHN
Trigeminal neuropathic pain (unintentional nerve injury)	TNP
Trigeminal deafferentation pain (intentional nerve injury)	TDP
Atypical facial pain (psychogenic)	AFP

In the authors' experience, these six diagnostic categories (summarized in **Table 17.1**) can be used to characterize almost all patients who present themselves to a busy facial pain practice.

In this classification, atypical facial pain (AFP) persists as a rare diagnostic possibility, and specifically refers to patients with pain that appears to be related to their psychological state ("somatoform pain disorder"), and can only be diagnosed based on a complete history, psychological testing, and interview.

One of the goals of this new diagnostic scheme was to implement this strategy in an online format that would allow patients to self-diagnose their facial pain, to seek appropriate medical attention by providing resources based on the diagnosis, and to avoid unnecessary procedures (such as dental work or extractions). Using this schema, a diagnostic questionnaire was created.[4,5] This questionnaire was administered to a number of patients personally interviewed and examined by the authors. The answers to the questions (inputs) for a given patient were used to "train" a form of "expert system" software (neural network), with the desired output (diagnosis) being the clinical diagnosis of the senior author for the same patient. This questionnaire has now been available online for more than a decade, it is anonymous, and it does not retain patient answers or even count the number of views. Over time, and with continued development and "training," the software has become proficient at the accurate diagnosis of facial pain:

https://neurosurgery.ohsu.edu/tgn.php

The current iteration of this questionnaire (**Table 17.2**) has over a 92% sensitivity and an 88% specificity for TN1 (**Table 17.3**). The Facial Pain Association website is also a valuable resource for patients:

http://www.fpa-support.org

Pathophysiology

The best evidence at present indicates that TN1 is a unique disorder that originates from hyperactivity in the trigeminal retrogasserian nerve related to demyelination in the root from vascular compression or other intrinsic pathology that produces high-frequency after-discharges. These after-discharges invade (retrograde) one or more neuronal cell bodies in the ganglion, producing depolarization and release of excitatory neurotransmitters into the extracellular milieu of the ganglion, with a chain-reaction wave of depolarization of cells in one or more divisions—the "ignition hypothesis" of Devor.[6] This wave of cellular depolarization is felt by the patient as a sudden spread of shocklike pains across one or more trigeminal divisions.

TN2 is likely more akin to neuropathic pains elsewhere in the nervous system, driven primarily by deafferentation of second- (and higher) order somatosensory neurons.

Thus, the diagnosis of TN can be achieved by taking the patient's history, and an advanced web diagnostic system has been implemented that can act as a diagnostic screening tool. The unique features of TN1 are likely the product of a unique set of physiologic conditions that magnify focal pathophysiology in the retrogasserian root within the trigeminal ganglion.

Clinical Assessment

Most patients seen in the Facial Pain Clinic at Oregon Health & Science University (OHSU) will take the online questionnaire prior to their visit. These results are more advisory to the patient, and they help determine what the diagnosis is prior to being seen in the clinic. Once the patient is registered in the clinic for a consultation visit, the questionnaire is again administered, and this time the results become part of the patient's medical record. The patient's answers are then reviewed by an experienced clinician, to verify that the patient responded to the questionnaire in accord with his or her actual history. The history is then recorded, with a detailed neurologic exam. The neurosurgeon will then assign a diagnosis and discuss further therapy, medical or surgical, with the patient.

Practice

Routine Imaging

Trigeminal neuralgia, or at least its more "classical" form (TN1), should be readily diagnosed. The absence of a neurologic deficit, in particular facial

Table 17.2 Facial Pain Questionnaire*

Trigeminal Neuralgia: Diagnostic Questionnaire			
Diagnostic questions			
Here at OHSU's Department of Neurological Surgery we have developed a helpful questionnaire for the diagnosis and treatment of patients suffering from various types of trigeminal neuralgia.			
1	Do you have facial pain?	yes	no
2	Do you remember exactly where you were the moment your facial pain started?	yes	no
3	When you have pain, is it predominantly in your face (i.e., forehead, eye, cheek, nose, upper/lower jaw, teeth, lips, etc.)?	yes	no
4	Do you have pain just on one side of your face?	yes	no
5	When you have pain, is it predominantly deep in your ear?	yes	no
6	When you have pain, is it predominantly in the back of your throat or tongue, near the area of your tonsil?	yes	no
7	Is your pain either entirely or mostly brief (seconds to minutes) and unpredictable sensations (electrical, shocking, stabbing, shooting)?	yes	no
8	Do you have any constant background facial pain (e.g., aching, burning, throbbing, stinging)?	yes	no
9	Do you have constant background facial pain (aching, burning, throbbing, stinging) for more than half of your waking hours?	yes	no
10	Do you have any constant facial numbness?	yes	no
11	Can your pain start by something touching your face (e.g., by eating, washing your face, shaving, brushing teeth, wind)?	yes	no
12	Since your pain began have you ever experienced periods of weeks, months, or years, when you were pain-free? (This would not include periods after any pain-relieving surgery or while you were on medications for your pain.)	yes	no
13	Have you ever taken Tegretol (carbamazepine), Neurontin (gabapentin), Lioresal (baclofen), Trileptal (oxcarbazepine), Topamax (topiramate), Zonegran (zonisamide), or any other anticonvulsant medication for your pain?	yes	no
14	Did you ever experience any major reduction in facial pain (partial or complete) from taking any of the medications listed in Question 13, or any other anticonvulsant medication?	yes	no
15	Have you ever had trigeminal nerve surgery for your pain (e.g., neurectomy, radiofrequency [RF] rhizotomy/gangliolysis, glycerol injection, balloon compression, rhizotomy, microvascular decompression [MVD], gamma knife)?	yes	no
16	Have you ever experienced any major reduction in facial pain (partial or complete) from trigeminal nerve surgery for your pain (e.g., neurectomy, RF rhizotomy/gangliolysis, glycerol injection, balloon compression, rhizotomy, MVD, gamma knife)?	yes	no
17	Did your current pain start only after trigeminal nerve surgery (neurectomy, radiofrequency [RF] rhizotomy/gangliolysis, glycerol injection, balloon compression, rhizotomy, microvascular decompression [MVD], gamma knife)? (If this is a recurrence of your original pain after a successful trigeminal nerve surgery, answer "no.")	yes	no
18	Did your pain start after facial zoster or "shingles" rash (herpes zoster, not to be confused with "fever blisters" around the mouth)?	yes	no
19	Do you have multiple sclerosis?	yes	no
20	Did your pain start after a facial injury?	yes	no
21	Did your pain start only after facial surgery (oral surgery; ear, nose or throat [ENT] surgery; plastic surgery)?	yes	no
22	When you place your index finger right in front of your ear on both sides at once and feel your jaw open and close, does the area under your finger on either side hurt?	yes	no

Source: Adapted from Limonadi et al.[5]

*World Wide Web uniform resource locator: https://neurosurgery.ohsu.edu/tgn.php

Note: Highlighted questions (1, 2, 5, and 6) were added to the original 18-item binomial (yes/no) questionnaire.

Table 17.3 Artificial neural network (ANN current network and example networks) sensitivity and specificity data for diagnoses: TN1, TN2, TNP, TDP, STN, PHN, AFP, NIN, GPN, and TMJ from randomly generated train and test data sets

	TN1	TN2	TNP	TDP	STN	PHN	AFP	NIN	GPN	TMJ
Current ANN (installed 07/24/12)										
Sensitivity	0.924	0.625	0.867	0	1	1	0	0.5	0	0
Specificity	0.878	0.964	0.952	1	1	1	0.99	0.99	1	0.99
ANN example 1										
Specificity	0.833	0.444	0.8	0	1	1	1	0.5	0.5	0
Sensitivity	0.857	0.964	0.9143	0.9916	1	1	1	0.9831	0.966	1
ANN example 2										
Sensitivity	0.961	0.667	0.733	0	1	1	1	NA	NA	NA
Specificity	0.861	0.9524	1	1	1	1	0.991	NA	NA	NA
ANN example 3										
Sensitivity	NA	0.889	0.8	1	1	1	1	NA	NA	NA
Specificity	NA	0.963	0.952	0.971	1	1	0.971	NA	NA	NA
ANN example 4										
Sensitivity	0.894	0.5	0.889	0	1	1	1	NA	NA	NA
Specificity	0.914	0.940	0.9337	1	0.994	0.989	0.995	NA	NA	NA
ANN example 5										
Sensitivity	NA	0.792	0.74	0.333	1	0.667	1	NA	NA	NA
Specificity	NA	0.869	0.884	0.970	1	1	0.971	NA	NA	NA

Source: Reprinted from *Stereotactic and Functional Neurosurgery.*

Note: Input size determines which question responses are used for train/test data set selection (historically, an 18- or 22-question input is available; see **Table 17.2**). Output selection determines which diagnoses are evolved as outputs. Current ANN (installed July 24, 2012): input size = 22 questions, output selection = 10 diagnoses; ANN example 1: input size = 22 questions, output selection = 10 diagnoses; ANN example 2: input size = 22 questions, output selection = 7 diagnoses; ANN example 3: input size = 18 questions, output selection = 7 diagnoses (TN1 not selected as diagnosis); ANN example 4: input size = 18 questions, output selection = 7 diagnoses; ANN example 5: input size = 18 questions, output selection = 6 diagnoses (TN1 not selected as diagnosis).

sensory loss at routine bedside examination, is an important negative. The value of routine imaging, in the absence of a neurologic deficit, is debatable. Many clinicians will obtain a brain magnetic resonance imaging (MRI) with and without contrast. The yield on these studies is extremely low, with etiologies for TN such as tumor, cerebral aneurysm, or arteriovenous malformation making up much less than 1% of cases. Imaging with the intent of demonstrating the presence, or lack, of vascular compression of the nerve is discussed in detail in Chapter 41, on microvascular decompression (MVD).

Drug Therapy

An evidence-based approach to the medical management of TN is well covered in Chapter 16. For TN1 the initial treatment is almost always anticonvulsant therapy. Relief from TN1 can be achieved in almost every case. The mainstay of this therapy is carbamazepine (Tegretol), although oxcarbazepine (Trileptal) may cause fewer sedative side effects. Hyponatremia can occur with either drug but is more common with oxcarbazepine, and serum sodium must be monitored carefully during the initial phases of therapy. The leukocyte count can also be affected by these drugs, typically by carbamazepine, and should be monitored. White cell count suppression is relatively common but rarely serious. Other anticonvulsants can also be considered, including gabapentin (Neurontin) and topiramate (Topamax), both of which have also been used with success.

Of note, a clinically significant response of the patient's facial pain to an anticonvulsant further strengthens the case for the diagnosis of TN1.

TN2 more resembles a typical neuropathic pain, in the sense that this pain tends to be constant and may be described as burning, there may be some degree of sensory loss, and allodynia may be pres-

ent. These types of pains are difficult to treat in any part of the body, and the trigeminal distribution is no exception. Drug therapy may not alleviate all, or any, of these pains. For these more persistent facial pains, treatment often poses a challenge. Agents such as gabapentin (Neurontin) or pregabalin (Lyrica) may be effective. As with other neuropathic pains, antidepressants (tricyclics, or selective serotonin reuptake inhibitors [SSRIs]) can be useful adjuncts. Failure to completely respond is common, and some degree of persistent pain is the norm.

Opiates do not have a significant impact on TN; they at best "take the edge off" and should not be part of the routine long-term medical management of TN. Nonsteroidal anti-inflammatory drugs (NSAIDS) and antidepressant medications are notably ineffective in controlling the primary pain, but may be used for secondary consequences of the neuralgia.

Medical Intractability

As alluded to, TN is a progressive condition marked by shortening and eventual disappearance of pain-free intervals, and resistance to drug therapy. Once the patient has reached the point where the medications either are ineffective or produce unacceptable side effects, a consideration of medical intractability should occur. This decision is one for the patient, family, and clinician and should be made jointly. If the conclusion is affirmative, some type of procedure should be considered.

Procedures

Surgical procedures fall into two broad categories: destructive and MVD. Destructive procedures take advantage of decades-long experience demonstrating that almost any disruption to the trigeminal nerve will alleviate the pain for a long interval. This disruption can take the form of radiation injury (radiosurgery), thermal injury (radiofrequency rhizolysis), chemical injury (glycerol rhizolysis), or physical injury (neurectomy, balloon rhizolysis, or surgical rhizotomy). Each procedure has its own level of efficacy, natural history, and complication rate. In general, the more destructive the procedure, the longer the pain relief and the higher the sensory complication rate related to the degree of deafferentation. Conduct of these procedures is dictated by a balance between pain relief and potential attendant complications.

Outcomes

TN1 is usually responsive to medical and surgical therapy. Aspects of TN2 in patients with TN1/TN2 overlap pain complaints, or symptoms of "pure" TN2, may not respond adequately to either medical or surgical therapy, further evidence that the pathophysiology of TN2 is different from that of TN1.

The nature of, and outcomes from, destructive procedures for TN are covered in Chapters 42, 44–49, and 51. MVD seems to be the one exception to the rule that damage to the trigeminal system is required to alleviate TN. Chapter 41 discusses this procedure, and the additional imaging that a surgeon can employ for surgical decision making.

Conclusion

Trigeminal neuralgia is diagnosed based on history. In the routine evaluation of patients with TN, imaging has a limited role. There are excellent medical and surgical therapies available.

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18 Trigeminal Neuropathic Pain and Anesthesia Dolorosa

David A. Levine, Charles E. Argoff, and Julie Pilitsis

Trigeminal neuropathic pain (TNP) and anesthesia dolorosa (AD) are chronic neuropathic pain conditions that occur as a result of trigeminal nerve injury. Both are often related to surgical procedures and severely affect patient quality of life. The pain, which is described as excruciating, is highly resistant to treatment because of its combination of central and peripheral nervous system mechanisms. This chapter discusses the diagnosis, etiology, and nonsurgical management of the disorders, with a focus on pharmacologic intervention.

■ Trigeminal Neuropathic Pain

Principles

TNP is an unremitting orofacial pain disorder characterized by inadvertent injury to the trigeminal nerve. Sources of such injury include facial trauma, stroke, or surgery anywhere in the vicinity of the nerve, including oral, ear, nose, throat, posterior fossa, and skull base surgeries. Most commonly, neurosurgeons see TNP in patients who have undergone procedures that inadvertently injured the trigeminal system, or dental procedures where the nerve has been damaged. The pain is commonly described as constant throbbing or burning in the affected area, and both positive and negative sensory symptoms are common. TNP was previously classified under atypical facial pain, a nonspecific term used to describe any unusual presentations of trigeminal neuralgia.[1] The classification has since been refined to include TNP as its own entity **(Table 18.1)**.

TNP has a significant adverse effect on quality of life, impacting work, recreation, and socialization. In addition to debilitating pain, patients experience consequential depression, fatigue, and difficulty sleeping. Treatment is difficult due to the pain's resistance to medications, mutability in response to psychological state, and a lack of understanding of the mechanisms behind the disease. Patients with TNP have often seen a number of physicians and dentists before being correctly diagnosed. As a result of their chronic illness and its challenging management, many patients suffering from TNP have low expectations when visiting their physicians.[2] Such patients are also at a greater risk of suffering from mental defeat, catastrophism, anxiety, and depression, which can all exacerbate their pain.[3]

The distribution of pain should be determined: bilateral, unilateral, V1, V2, V3, minor trigeminal branches, and specific locations as marked on a facial diagram. Often the distribution is atypical and reflective of injury to a smaller branch of the trigeminal nerve. Quality of pain should also be assessed: pain descriptors, continuous or intermittent, positive sensory symptoms (hyperalgesia, hyperesthesia, allodynia), and negative sensory symptoms (hypoalgesia, hypoesthesia). Sensitive sensory tests to determine these characteristics can be accomplished using blink reflex habituation in addition to tactile and thermal quantitative sensory testing devices.[4] In addition, masseter strength should be assessed.

The cause of damage to the trigeminal nerve resulting in TNP is most often dental treatment, including tooth extraction and endodontic procedures. Some patients with TNP may have dental treatment for their pain, which often results in no ameliorative effect and can worsen the pain.[5] Neurosurgical procedures are also a common source of TNP **(Table 18.2)**.

Approximately 10% of trigeminal nerve injuries will develop into long-term neuropathic pain.[6] The lingual and inferior alveolar nerves are the most commonly affected trigeminal branches following dental surgery. Third molar (wisdom tooth) extraction is the most frequent cause of trigeminal nerve injury. Although this complication occurs in less than 0.5% of patients, the procedure is routinely performed, with millions of extractions per year.[6,7]

Table 18.1 Classifications of facial pain

Diagnosis	Defining characteristic
Trigeminal neuralgia 1	Idiopathic—paroxysms
Trigeminal neuralgia 2	Idiopathic—paroxysms with continuous pain
Trigeminal neuropathic pain	Unintentional injury
Trigeminal deafferentation pain (including anesthesia dolorosa)	Following intentional, denervating procedure
Symptomatic trigeminal neuralgia	Associated with multiple sclerosis
Postherpetic trigeminal neuralgia	Associated with herpes zoster
Atypical facial pain	Somatoform pain disorder

Source: Modified from Eller JL, Raslan AM, Burchiel KJ. Trigeminal neuralgia: definition and classification. Neurosurg Focus 2005;18(5):E3.

Table 18.2 Procedures associated with trigeminal nerve injury

Procedure	Percentage of cases
Third molar extraction	60.5
Local anesthetic injection	16.7
Orthognathic surgery	7.1
Mandibular implant surgery	6.2
Trauma	2.7
Endodontic therapy	1.7
Other/unknown	5.1

Sources: Data from Tay AB, Zuniga JR. Clinical characteristics of trigeminal nerve injury referrals to a university centre. Int J Oral Maxillofac Surg Oct 2007;36(10):922–927; Hillerup S. Iatrogenic injury to oral branches of the trigeminal nerve: records of 449 cases. Clin Oral Investig 2007;11(2):133–142; Pogrel MA, Thamby S. The etiology of altered sensation in the inferior alveolar, lingual, and mental nerves as a result of dental treatment. J Calif Dent Assoc 1999;27(7):531, 534–538.

Etiology

A combination of peripheral and central nervous system changes following trigeminal injury are involved in the etiology of TNP, causing a disconnect between nociception and cortical perception of pain. Reduced tactile and temperature sensation suggest damage of peripheral, small unmyelinated and large myelinated fibers. Abnormal temporal summation of pain suggests central hyperexcitability.[5]

Peripherally, dysregulation of the synthesis and functioning of sodium channels and other receptor proteins leads to abnormal neuronal activity, ectopic discharge, allodynia, and hyperalgesia. Cutaneous axons of small-caliber fibers have higher rates of discharge in regions of chronically painful skin than in normal skin. This is in part because of increased sodium channel expression in keratinocytes, increasing small-fiber afferent depolarization. Skin biopsies in regions of neuropathic pain demonstrate a loss of small-caliber axon innervation. Although the loss of innervation itself is not the cause of pain, cutaneous small-caliber axon density is a valuable tool for differentiating neuropathy from other pain conditions.[8]

Neuroplastic modifications of nociceptive signal processing, neuroglia-caused inflammation, and activation of *N*-methyl-D-aspartate (NMDA) receptors are all implicated in central hyperexcitability.[9] Compared with healthy controls, patients with TNP displayed reduced μ-opioid receptors in the nucleus accumbens and their pain levels were inversely proportional to the availability of receptors.[10] Neuroimmune interactions are thought to contribute to the development of chronic pain via proinflammatory agents (including tumor necrosis factor alpha (TNF-α)) produced by microglial cells following injury. Inhibiting proinflammatory factors and stimulating the production of their anti-inflammatory counterparts may improve the currently limited efficacy of analgesics used in neuropathic pain treatment.[11,12] Neurotrophins have also been implicated in causing pain after nerve injury, with various antagonists currently being developed.[13]

Practice and Outcomes

The treatment strategy for patients with TNP should holistically take into account their severity of pain, sensitivity to particular medications, and psychological outlook. Medical management of neuropathic pain is complex and typically requires a combination of coanalgesics, maintaining a fine balance between pain relief and adverse side effects.[14] The majority of medications prescribed for the treatment of TNP affect the entire central nervous system and are likely to be dose limited because of side effects. Localized pain management via topical analgesics offers the opportunity for more targeted drug administration with fewer side effects. Unfortunately, because there is a scarcity of high-quality clinical trials and thus a lack of quality evidence-based data, TNP treatment does not strictly follow evidence-based recommendations.[15] Most of the available research on neuropathic pain is heterogeneous, and it is unclear whether the conclusions can be extrapolated to TNP.

Anticonvulsant Drugs

Gabapentin and Pregabalin

Gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica) are successful in treating other neuropathic pain disorders and TNP in rodent models, although there have been no clinical trials published for their TNP use specifically. Repeated, intraperitoneal injection of gabapentin in TNP-modeled rats alleviated mechanical allodynia and hyper-responsiveness to von Frey filament stimulation.[16] Single doses of pregabalin administered intraperitoneally attenuated mechanical and medullary dorsal horn hypersensitivity in rat models of TNP.[17,18] Side effects of the two drugs include dizziness, somnolence, peripheral edema, weight gain, headache, and dry mouth. Gabapentin and pregabalin decrease central sensitization by their action as calcium channel alpha-2-delta ligands.[9]

It may be desirable to switch the patient from a three-times-per-day immediate-release gabapentin (Neurontin) regimen to a once-per-day extended-release pill (Gralise) in order to minimize side effects and compliance difficulty **(Table 18.3)**. Twice-daily prodrug medication with gabapentin enacarbil (Horizant) is an additional option, although dosing is not interchangeable with other forms of gabapentin.

Carbamazepine and Oxcarbazepine

Carbamazepine is the only FDA-approved oral medication for trigeminal neuralgia. Its proposed mechanisms of action include sodium channel blockade and gamma aminobutyric acid (GABA) receptor potentiation. Trials regarding its efficacy in controlling neuropathic pain have been mixed.[19] Oxcarbazepine is a derivative of carbamazepine with a similar mechanism of action, often used if carbamazepine is poorly tolerated or ineffective. One oxcarbazepine study for patients with diabetic neuropathy reported a significant decrease in pain and more restful sleep, with a number needed to treat of 6, compared with placebo.[20] Two other oxcarbazepine studies for participants with diabetic neuropathy reported no significant difference in pain compared with placebo.[21,22] In a rodent model of TNP, carbamazepine alone and in conjunction with B vitamins reduced thermal hyperalgesia.[23]

Table 18.3 Switching from immediate-release to extended-release gabapentin, using a total daily dosage of 2,400 mg

Days before switch	800 mg immediate-release PO q8h
Morning of switch	800 mg immediate-release PO
Afternoon	800 mg immediate-release PO
Evening	2,400 mg extended-release PO with meal
Following days	2,400 mg extended-release PO every day with evening meal

Source: Data from Chen C, Cowles VE, Hou E. Pharmacokinetics of gabapentin in a novel gastric-retentive extended-release formulation: comparison with an immediate-release formulation and effect of dose escalation and food. J Clin Pharmacol 2011;51(3):346–358.

Lamotrigine

A small randomized controlled test (RCT) of six subjects with TNP and trigeminal allodynia who were orally administered the anticonvulsant lamotrigine for 9 weeks had decreased heat hyperalgesia, though the participants were also given gabapentin for 6 of the 9 weeks.[24] A 2011 Cochrane review recommends against the use of lamotrigine for treatment of diabetic neuropathy and other neuropathic pain disorders given more effective anticonvulsants such as gabapentin.[25] Lamotrigine in combination with gabapentin, a tricyclic antidepressant, or a nonopioid analgesic was not an effective adjuvant for treatment of neuropathic pain.[26]

NMDA Receptor Antagonists

NMDA receptor antagonists may be beneficial in reducing pain due to TNP. There is ongoing research regarding the efficacy and route of administration of ketamine and its more active enantiomer, (S)-ketamine. Topical, intranasal, and intravenous drug delivery of ketamine have produced mixed results.[27–29] A RCT showed high doses of dextromethorphan had no effect on chronic facial pain relief, possibly due to a poor therapeutic ratio of the drug when administered orally.[30] Synthetic NMDA and AMPA kinate receptor antagonists are currently undergoing clinical trials.[13]

Topical Drugs

Lidocaine Patch

A mixed, small-case report study suggests that long-term application of 5% lidocaine plaster/patch (Versatis) can be effective in reducing pain due to TNP.[31] Lidocaine plaster has been shown to be effective in topically treating other neuropathic pain disorders.[32] Lidocaine functions by locally blocking sodium channels and primary sensory neurons.[33] In a study of painful diabetic neuropathy, long-term usage of topical lidocaine changed the subtype of sodium channels in the skin, which may be predictive of its analgesic effect.[34] Side effects are generally limited to mild skin reactions.[9]

Capsaicin Patch

High concentrations of topical capsaicin (8%) applied over the area where painful symptoms are felt is an effective treatment for various neuropathic pain disorders, although initially painful side effects necessitate application under local anesthetic. There is concern over whether capsaicin patches should be applied to the face, although some studies reported no difficulties.[35,36] Capsaicin functions by desensitizing transient receptor potential vanilloid receptor 1 (TRPV-1) sensory actions in nociceptive fibers after several days of its application.[9] Synthetic TRPV1 antagonists are currently undergoing clinical trials.[13]

Antidepressants

Antidepressant medications alleviate pain independent of their mood-altering effects, although the latter effect can be beneficial because many TNP patients suffer from mood disorders, which can exacerbate their pain.

Serotonin–Norepinephrine Reuptake Inhibitors

The most commonly prescribed serotonin–norepinephrine reuptake inhibitors (SNRIs) are duloxetine and venlafaxine. Side effects include gastrointestinal disturbances, nausea, reduced appetite, sedation, and dizziness.[9] SNRIs hypothetically function by strengthening the descending inhibitory control of pain.[13]

Selective Serotonin Reuptake Inhibitors

There are RCTs on the efficacy of selective serotonin reuptake inhibitors (SSRIs) to relieve pain caused by polyneuropathy and diabetic neuropathy.[37] In a rodent model of TNP, fluvoxamine reduced allodynia and increased pain thresholds compared with animals that did not receive the drug.[38]

Tricyclic Antidepressants

The tricyclic antidepressants (TCAs) function via sodium channel blockage and monoamine reuptake inhibition. Amitriptyline is the predominant choice for treating neuropathic pain. Although TCAs may be slightly more efficacious than newer antidepressants (number needed to treat is 3 vs. 4–7), their high incidence of side effects, including anticholinergic effects and the development of tolerance, lead some to recommend SNRIs a better first choice.[39]

Opioids

Tramadol inhibits the reuptake of serotonin and norepinephrine, and its metabolite is a μ-opioid receptor agonist. It is commonly administered with acetaminophen, the combination being efficacious in treating painful diabetic neuropathy. The use of stronger opioids is discouraged due to the risk of misuse as well as significant side effects, particularly with long-term usage. Opioid dosages to treat neuropathic pain may be higher than those required to treat nociceptive pain.[9,40] One study found that neuropathic pain relief required anywhere from a zero to threefold increase in opioid dosage compared with nociceptive pain relief. Patient sensitivity as well as pain etiology influence opiate responsiveness.[41]

Cannabinoids

Oromucosal cannabinoids reduced symptoms in refractory peripheral neuropathic pain, although they are not currently approved for the treatment of neuropathic pain in the United States.[42] Peripheral cannabinoid receptor targeting is being explored with topical and limited central nervous system (CNS) availability drugs.[13]

Other Treatments

Botulinum Toxin

Botulinum toxin (onabotulinum toxin A) injections reduced diabetic neuropathic pain in an 18-patient RCT, with side effects limited to temporary pain at the site of injection. Pain reduction took 4 weeks to achieve maximum effect and the relief lasted for 12 weeks.[43] In a single patient study, subcutaneous injection of onabotulinum toxin A reduced the area and severity of neuropathic pain after trigeminal nerve injury.[44] Onabotulinum toxin A injection in rats with induced trigeminal neuropathy resulted in decreased neurotransmitter release from the trigeminal ganglion and reduced mechanical allodynia.[45] The antinociceptive quality of onabotulinum toxin A is theorized to be caused by inhibition of the release of acetylcholine, glutamate, and neuropeptides (including substance P and calcitonin gene-related peptide), limiting neurogenic inflammation and peripheral sensitization.[46] In our practice, we typically administer botulinum toxin as described in **Fig. 18.1**.

Cell Transplantation

A future avenue of treatment under investigation is the transplantation of cells into the central nervous system to provide local and continuous production of therapeutic molecules.[47] Reconstruction of lost or altered neuronal circuitry is an additional, more complex possibility. Sources of implanted cells currently undergoing animal research range from primary tissue fragments to engineered stem cell lines. Inhibitory GABA-ergic neurons could be administered to

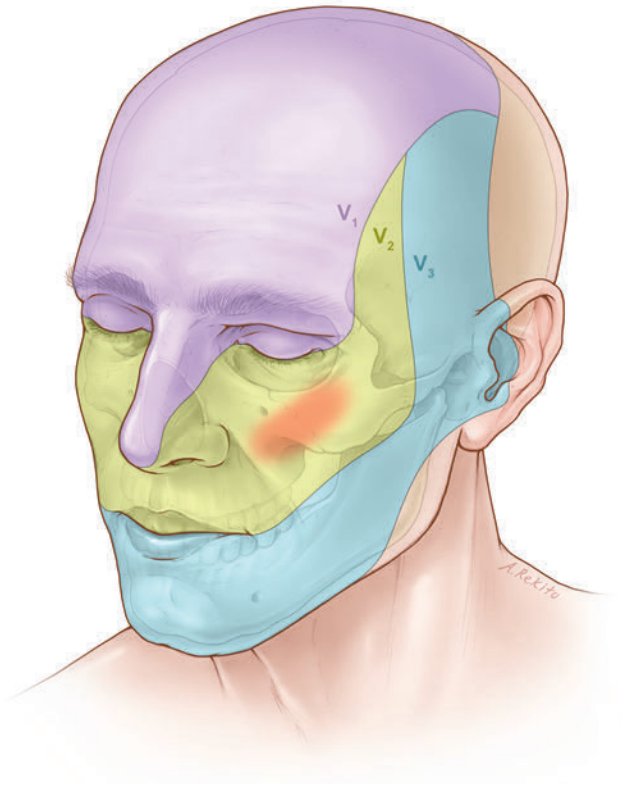

Fig. 18.1 Representative patient demonstrating major trigeminal nerve dermatomes with left side V_2 pain (in red). We inject 10 to 20 U of onabotulinum toxin A subcutaneously, at above and below the area of pain. With this dosage, we are able to inject unilaterally because no facial paresis occurs. The purple area represents the ophthalmic dermatome, yellow is maxillary, and blue is mandibular.

mitigate hyperexcitability states following injury, and neuroprotective or neurotrophic secreting cells could prevent inflammation and neuronal death. Catecholamines and opiates released by immortalized cell lines may be used to provide local pain relief.

Complementary and Alternative Medicine

Complementary and alternative medicine therapies such as acupuncture, massage, yoga, and craniosacral therapy are effective in helping patients manage chronic pain and improve their quality of life.[48–51] Psychological treatments are also effectual adjuvants to pharmacologic management of TNP. Limited studies have shown that biofeedback, hypnosis, relaxation techniques, behavioral therapy, and cognitive-behavioral therapy reduce neuropathic and chronic pains in some patients.[3] At the very least, any safe activities that enhance the mood and social support of the patient should be encouraged.

Combination Therapy

Evidence-based combination therapy is an area of interest. A 2012 Cochrane review of RCTs for neuropathic pain suggests that although at least 45% of patients receive more than one drug to treat their pain, there are few quality studies that evaluate combination pharmacotherapy. Gabapentin plus opioid (morphine or oxycodone) was an effective combination over gabapentin alone, although there was an increased frequency of side effect–related dropouts.[52] Combination therapy of gabapentin with opioids or TCA is proposed by the European Federation of Neurological Societies guidelines for patients who do not respond to singular drug administration.[53] The International Association for the Study of Pain guidelines also call for further research on polypharmacy because there is mixed efficacy depending on the neuropathic pain condition being treated.[54] Combinations of nortriptyline and gabapentin as well as pregabalin and topical 5% lidocaine were more effective than any of the medications administered alone.

Treatment Guidelines

Little research has been conducted on the medical treatment of TNP specifically, but the evidence-based pharmacologic recommendations of other neuropathic pain disorders may serve as a guide (**Tables 18.4, 18.5, 18.6**). These guidelines take into account clinical efficacy, side-effect profiles, effect on health-related quality of life, convenience, and cost. A recent meta-analysis of pharmacologic RCTs for the treatment of neuropathic pain includes the number needed to treat and number needed to harm of antidepressants, anticonvulsants, opioids, topical lidocaine, cannabinoids, NMDA antagonists, and topical capsaicin.[37] Our treatment algorithm integrates the recommended guidelines and our clinical experiences, with emphasis on the value of combination therapy (**Table 18.7**).

■ Anesthesia Dolorosa

Principles

AD is a type of deafferentation trigeminal pain where an insensate or hypoesthetic region of the face is in severe pain.[1] AD is an iatrogenic compli-

Our Expanded List of Therapies, in Order of Effectiveness

Anticonvulsants
- Gabapentin
- Pregabalin
- Carbamazepine
- Lamotrigine
- Topiramate
- Divalproex sodium

Antidepressants
- TCA
- SNRI
- SSRI
- Lidocaine

Opioids
- Tramadol
- Oxycodone

Complementary and Alternative Therapy
- Psychotherapy
- Biofeedback
- Acupuncture

Miscellaneous
- Clonidine
- NMDA antagonists
- Topical capsaicin

Table 18.5 Canadian Pain Society evidence-based guidelines for the pharmacologic management of neuropathic pain

First-line	
AEDs	Gabapentin, pregabalin
TCAs	
Second-line	
SNRIs	Duloxetine, venlafaxine
Topicals	Lidocaine
Third-line	
Opioids	Tramadol, oxycodone, morphine
Fourth-line	
Cannabinoids	
Other opioids	Methadone
SSRIs	Citalopram, paroxetine
Other AEDs	Lamotrigine, topiramate, valproic acid
Miscellaneous	Mexiletine, clonidine

Abbreviations: AED, antiepileptic drug; PO q8h, by mouth every 8 hours.

Source: Data from Moulin DE, Clark AJ, Gilron I, et al. Pharmacological management of chronic neuropathic pain—consensus statement and guidelines from the Canadian Pain Society. Pain Res Manag 2007;12(1):13–21.

Table 18.4 International Association for the Study of Pain evidence-based guidelines for the pharmacologic management of neuropathic pain

First-line	
AEDs	Gabapentin, pregabalin
TCAs	Nortriptyline, desipramine
SNRIs	Duloxetine, venlafaxine
Topicals	Lidocaine
Second-line	
Opioids	Tramadol, other analgesics
Third-line	
Other topicals	Capsaicin
Other antidepressants	Bupropion, citalopram, paroxetine
Other AEDs	Carbamazepine, lamotrigine, topiramate, valproic acid
Miscellaneous	Dextromethorphan, memantine, mexiletine

Source: Data from Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clin Proc Mar 2010;85(3 Suppl):S3–S14.

Table 18.6 European Federation of Neurological Societies evidence-based guidelines for the pharmacologic management of neuropathic pain

First-line	
AEDs	Gabapentin, pregabalin
TCAs	
SNRIs	Duloxetine, venlafaxine
Topicals	Lidocaine
Second-line	
Opioids	Tramadol, oxycodone
Cannabinoids	
Other topicals	Capsaicin
Miscellaneous	Botulinum toxin, NMDA antagonists

Source: Data from Attal et al.[53]

Table 18.7 Our treatment algorithm for trigeminal neuropathic pain

If the first-line of therapy does not provide pain relief, move on to the second, and so on. Each subsequent line of therapy includes concurrent use of the prior treatments.			
First	**Second**	**Third**	**Fourth**
Anticonvulsants			
Antidepressants			
Topical lidocaine			
	Opioids		
	Complementary and alternative medicine		
		Miscellaneous	
			Botulinum toxin

cation following surgical deafferentation of the trigeminal ganglion or its branches for the treatment of trigeminal neuralgia, although the disease can rarely be the result of trauma.[55] The pain develops weeks to months after trigeminal nerve manipulation and may be described as burning, crawling, itching, or tearing.[56,57] Unlike partial nerve injury, as seen in TNP, AD-associated pain is central in nature and does not depend on peripheral stimuli.[56,57] In cases where there is partial numbness, allodynia and hyperalgesia may also be present. The pain is usually continuous and can exhibit lancinating paroxysms. Depending on the affected area, drooling may be present. As with TNP, the distribution and quality of symptoms should be assessed.

Rhizotomy of the trigeminal ganglion as treatment for trigeminal neuralgia resulted in AD in 0.0 to 1.7% of patients depending on the surgical technique (**Table 18.8**).

Practice and Outcomes

As with other deafferentation pain, including phantom limb pain and postmastectomy pain syndrome, cortical reorganization is theorized to play a role in causing AD-associated pain.[58,59] Modulation of such a reorganization following trigeminal damage may be achievable through biofeedback mechanisms and central stimulation.[60,61]

Because AD is speculated to be caused by deafferentation hypersensitivity of central trigeminal neurons, inhibitory medications are suggested.[57] A combination of gabapentin (Neurontin, Gralise) and carbamazepine or gabapentin alone may occasionally be satisfactory in treating pain due to AD.[55,57] Gabapentin is a structural analogue of GABA, although its precise mechanism of action is unknown.[62] Related drugs, gabapentin enacarbil (Horizant, a gabapentin prodrug) and pregabalin (Lyrica, a gabapentin deriv-

Table 18.8 Frequency of anesthesia dolorosa depending on surgical procedure

	Frequency (%)
Radiofrequency rhizotomy	1.65
Cyberknife surgery	1.45
Glycerol rhizotomy	0.47
Balloon compression	0.11
Microvascular decompression	0.06
Gamma knife surgery	0.00

Sources: Data from Jackson TP, Gaeta R. Neurolytic blocks revisited. Curr Pain Headache Rep 2008;12(1):7–13; Taha JM, Tew JM Jr. Comparison of surgical treatments for trigeminal neuralgia: reevaluation of radiofrequency rhizotomy. Neurosurgery 1996;38(5):865–871; Cruccu G, Gronseth G, Alksne J, et al. AAN-EFNS guidelines on trigeminal neuralgia management. Eur J Neurol 2008;15(10):1013–1028; Patil CG, Veeravagu A, Bower RS, et al. CyberKnife radiosurgical rhizotomy for the treatment of atypical trigeminal nerve pain. Neurosurg Focus 2007;23(6):E9; Lim M, Villavicencio AT, Burneikiene S, et al. CyberKnife radiosurgery for idiopathic trigeminal neuralgia. Neurosurg Focus 2005;18(5):E9; Villavicencio AT, Lim M, Burneikiene S, et al. Cyberknife radiosurgery for trigeminal neuralgia treatment: a preliminary multicenter experience. Neurosurgery 2008;62(3):647–655; Lazzara BM, Ortiz O, Bordia R, et al. Cyberknife radiosurgery in treating trigeminal neuralgia. J Neurointerv Surg 2013;5(1):81–85; Fariselli L, Marras C, De Santis M, Marchetti M, Milanesi I, Broggi G. CyberKnife radiosurgery as a first treatment for idiopathic trigeminal neuralgia. Neurosurgery 2009;64(2 Suppl):A96–A101; Tang CT, Chang SD, Tseng KY, Liu MY, Ju DT. CyberKnife stereotactic radiosurgical rhizotomy for refractory trigeminal neuralgia. J Clin Neurosci 2011;18(11):1449–1453; Xu-Hui W, Chun Z, Guang-Jian S, et al. Long-term outcomes of percutaneous retrogasserian glycerol rhizotomy in 3370 patients with trigeminal neuralgia. Turk Neurosurg 2011;21(1):48–52; Brown JA, Pilitsis JG. Percutaneous balloon compression for the treatment of trigeminal neuralgia: results in 56 patients based on balloon compression pressure monitoring. Neurosurg Focus 2005;18(5):E10.

Note: A search for *anesthesia dolorosa* was conducted on the PubMed database. A total of 11 articles and reviews from 1996 to 2013 were selected that referenced the disorder as a complication of neurosurgical treatment for trigeminal neuralgia.

ative), produce similar effects but are absorbed more rapidly and demonstrate increased bioavailability, although there are no published reports of their prescription for AD.[63,64]

Medical management of AD is among the most difficult of all facial neuralgias because of the pain's resistance to treatment. The recommended pharmacologic treatment strategy is similar to that for TNP, although the efficacy rate is much lower. Medications to treat neuropathic pain provide little to no relief for AD, including antidepressants, anticonvulsant drugs, NMDA receptor antagonists, topicals, and opioids.[30,56,65]

Systemic, intravenous lidocaine has been reported to provide temporary pain relief in peripheral neuropathic pain as well as centrally caused pain disorders, including chronic pain following thalamic hemorrhage and encephalitis.[66–68] In the case of pain following encephalitis, the patient experienced symptoms similar to AD, with sensory loss, constant burning pain, and paroxysms. Repeated lidocaine infusions over the course of 5 days were successful in reducing this patient's pain and paroxysms for the following 3 months. Sustained intravenous lidocaine drips of 5.0 and 7.5 mg/kg/h over 4 hours every 4 weeks relieved diabetic neuropathic pain between infusions. Higher doses increased the risk of adverse effects, such as sedation, ataxia, bradycardia, and hypotension.[69]

Many rodent models of deafferentation pain use the endpoint of autotomy (self-mutilation) to measure the efficacy of medical treatments.[70] For example, guanethidine decreased autotomy in rodents with induced AD of the legs.[71] Although autotomy is a response to pain, there is no direct evidence that its reduction is caused by medication-induced pain relief rather than confounding variables. Several carryover drug trials in humans have failed to provide pain relief.[72]

Treatments for phantom limb pain may provide future direction for alleviating AD. High doses of morphine and ketamine provided pain relief in several patients with phantom limb pain and brachial plexus avulsion.[67]

Conclusion

Trigeminal neuropathic pain and anesthesia dolorosa are chronic pain conditions that are often the result of surgical complications. The mixed central and peripheral mechanisms of the diseases necessitate systemic drugs with significant side effects. Medical management is difficult, particularly of anesthesia dolorosa, which is resistant to local analgesics. Fortunately, there is a diverse selection of treatment options, including alternative medicines, psychotherapy, anticonvulsants, topical drugs, antidepressants, opioids, botulinum toxin, and other emerging therapies. Although significant trial and error is required without robust evidence-based clinical research on the two disorders, combination therapy can provide pain relief with minimal adverse effects.

Editor's Comments

The treatment of deafferentation pains of the trigeminal system is very difficult. The diagnosis should not be, but frequently is. My experience very much parallels that of Dr. Pilitsis and colleagues, in that inadvertent injury to the peripheral trigeminal nerve occurs most frequently in complicated dental extractions, oral surgery, and even, on occasion, the intraneural injection of local anesthetic during routine dentistry. Dentists and oral surgeons seem to see this so rarely that it is a real source of confusion and misdiagnosis.

One can understand the confusion that dentists and oral surgeons sometimes exhibit, since trigeminal pain related to routine extraction is an exceptional rarity, given the frequency of these procedures. The loss of deciduous teeth is essentially *never* accompanied by chronic neuropathic pain, which is a further testament to the resiliency of dental nerves to very peripheral "neurectomy." However, I would hope that a fundamental element of dental and oral surgical curricula acknowledges the pain that can occur after procedures disrupt major divisions of the trigeminal system such as the mandibular, inferior alveolar, lingual, maxillary, and anterior superior alveolar nerves. When one of these nerves has been injured, some degree of sensory loss in the distribution of the nerves usually ensues, and the pain generally radiates into the territory of that nerve, although pain radiation can also be over a broader area.

As noted in the chapter, it is common for these patients to undergo further dental procedures, including root canals and extractions, in the honest interest of improving the pain. Although there is no good natural history data on this practice, I suspect that the majority of these efforts are unhelpful, and potentially may worsen the pain. *(Continued on p. 188.)*

Other cases of TNP come from traumatic injuries to the face, including facial bone fractures. This leaves incidental or unavoidable injury to the trigeminal divisions, ganglion, or root from the skull base or posterior fossa surgery. As the authors point out, most of these injuries produce numbness, not overt pain. To some degree this may be due to how the patient describes the sensation, since numbness and mild paresthesias may be unpleasant or overtly painful to some individuals, and seemingly annoying but not life-consuming to others.

There is no doubt that nerve injuries can produce neuropathic pain, which in the trigeminal system, at maximum, is associated with complete anesthesia and the dreaded condition of anesthesia dolorosa. In our classification system, *unintentional* trigeminal injury associated with pain is "trigeminal neuropathic pain" (TNP), whereas *intentional* injury (e.g., rhizolysis or rhizotomy) it is termed "trigeminal deafferentation pain" (TDP). The difference between these two entities may be more historic than physiologic. However, the possible difference may be quantitative, in that the *degree* of injury and deafferentation tends to be less in most patients with TNP in comparison to those with TDP.

Chapters 35–37, 40, and 49 discuss surgical options for TNP and TDP, but as with medical management, these pains can remain intractable even with the most advanced surgical approaches. As with many difficult problems that we approach, prevention will play a major role in this condition. This may come from improvements in education of dentists and physicians, and possibly from preemptive anesthetic or analgesic measures, which if employed early, may reduce the incidence of these painful consequences of trigeminal nerve injury.

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Section III.D

Nontrigeminal Cranial Neuralgias

19 Glossopharyngeal, Geniculate, and Other Cranial Neuralgias

Adam Griffith and Louis Anthony Whitworth

Although there is extensive research and literature published regarding trigeminal neuralgia (TN), the other cranial neuralgias are uncommon, less well studied, and rarely seen in clinical practice. Neuralgia refers to pain in the region or territory supplied by a nerve or nerve root, and the cranial neuralgias that are discussed here involve branches of cranial nerves V, VII, IX, and X (**Table 19.1**).

Cranial Neuralgias

- Trigeminal neuralgia
  - Classical trigeminal neuralgia
  - Symptomatic trigeminal neuralgia
- Glossopharyngeal neuralgia
  - Classical glossopharyngeal neuralgia
  - Symptomatic glossopharyngeal neuralgia
- Nervus intermedius (geniculate) neuralgia
- Superior laryngeal neuralgia
- Supraorbital neuralgia
- Occipital neuralgia

Generally, these neuralgias are characterized by pain in their respective somatic sensory distributions, although other, more serious symptoms such as syncope in the case of vagal nerve involvement can occur. The pain for most of these can vary but is usually described as lancinating or electric in quality and is at maximal intensity at onset.

Many of these disorders are difficult to diagnose because of their overlap in sensory innervations, the dearth of clinical signs, and the lack of confirmatory testing. Research has helped improve our understanding of the pathophysiology of trigeminal neuralgia, and it is believed the other cranial neuralgias share similar mechanisms, whether it's a compressive or inflammatory lesion or more complicated central etiology.[1] As research continues to improve our understanding of these rare disorders, it is imperative for clinicians to be able to provide diagnosis and treatment during their evaluation of facial pain.

Glossopharyngeal Neuralgia

Often misdiagnosed as trigeminal neuralgia, glossopharyngeal neuralgia (GN) is an uncommon condition important to neurosurgeons and all those who evaluate pain. Its original description by Weisenberg in 1910 involved a 35-year-old man with a right cerebellopontine angle tumor mistreated as TN.[2,3] GNs overlap with TN and their relative rarity can lead to a delay in the appropriate diagnosis. With symptoms ranging from debilitating facial pain to death in the case of vagal involvement, it's important for the clinician to be cognizant of its many secondary causes and provide the appropriate workup to rule out an organic source.

Principles

The glossopharyngeal nerve is a mixed nerve comprised of motor, sensory, and parasympathetic fibers. It exits the medulla laterally, rostral to the vagus nerve. It supplies parasympathetic fibers from the inferior salivatory nucleus to the parotid gland via the otic ganglion and lesser superficial petrosal nerve.[4] Motor fibers originate from the nucleus ambiguus and pass to the stylopharyngeus muscle.[4] The sensory distribution is complex and involves visceral, somatic, and special sensory afferents. Somatic sensory afferents are located in the auricle, mastoid, and external auditory meatus. The special sensory afferents from the posterior third of the tongue travel to the inferior glossopharyngeal ganglion, where they eventually synapse in the nucleus solitarius.[4] The visceral sensory afferents arise from the inferior ganglia and supply sensation to the tonsils, posterior third of the tongue, pharynx, soft palate, and carotid body and sinus.[4] Through the carotid sinus nerve, they supply special receptors in the carotid body and sinus responsible for reflex control of respiration, blood pressure, and heart rate.[4]

Table 19.1 Classification of cranial neuralgias

Neuralgia	Cranial nerve	Pathophysiology	Presentation	Management (when medically refractory)
Glossopharyngeal	IX, X (rarely)	Idiopathic, compressive lesion, or underlying disorder (e.g., tumor, aneurysm)	Severe, transient stabbing pain in ear, posterior tongue, and pharynx with painful triggers	Microvascular decompression or rhizotomy of IX and upper rootlets of X, stereotactic radiosurgery
Geniculate (nervus intermedius)	VII	Vascular compression, mutation of specific voltage-gated sodium channel	Intermittent pain located deep within the auditory canal	Sectioning nervus intermedius, microvascular decompression, geniculate ganglion resection
Superior laryngeal	X	Underlying compressive lesions, posttraumatic, postoperative	Unilateral pain in lateral throat, beneath mandible with painful triggers	Local anesthetic block, sectioning of the nerve
Nasociliary	V (branch of ophthalmic)	Idiopathic, posttraumatic	Pain that radiates to orbit, eyebrow, nose, or jaw precipitated by touching lateral aspect of nose	Local anesthetic block or sectioning of the nerve
Supraorbital	V (branch of frontal)	Idiopathic, tumors, post-traumatic, postinfectious	Pain in the territory of the supraorbital notch and medial part of forehead	Local anesthetic block, nerve ablation, peripheral nerve stimulation

Centrally, these afferents terminate in the nucleus solitarius tract in the medulla before eventually reaching the cortex through the ventral posterior medial nucleus of the thalamus. In the cases associated with cardio-depression and syncope, the most accepted theory involves ephapses, or artificial synapses, which occur between the fibers of both the glossopharyngeal and vagus nerves in the region of their ganglia or an anomalous communication between the nucleus solitarius and the nucleus ambiguus centrally.[5–7]

Similar to TN, GN may be idiopathic or secondary to other causes. One of the most reliable and widely used classification schemes is by the International Headache Society. Their most recent revision describes the idiopathic form as classical GN that, by definition, is not attributed to another disorder or causative lesion. The secondary, or symptomatic, form is always due to a compressive lesion or underlying disorder. Reported causes include vascular compression from a tortuous vertebral artery or the posterior inferior cerebellar artery, cerebellopontine angle tumors, multiple sclerosis, trauma, parapharyngeal lesions, Eagle syndrome secondary to an elongated styloid process, cranial base tumors, Chiari type 1 malformation, and Sjögren syndrome.[6–15]

The pathogenesis involves the dorsal root entry zones of the glossopharyngeal and vagus nerves.[7] Although the process is not entirely understood, it is believed that vascular compression of the nerve root entry zone causes demyelination and ephaptic transmission.[7] Another hypothesis implicates hyperactive and hyperexcitable neurons, which may be due to activation of the *N*-methyl-D-aspartic receptor.[16]

Practice

Glossopharyngeal neuralgia refers to a severe, transient stabbing pain usually located in the ear, posterior tongue, tonsillar fossa, pharynx, or beneath the angle of the jaw.[17] Pain is usually described as sharp, stabbing, shooting, or lancinating and is stereotyped within patients.[14,17] The pain episodes usually last from a fraction of a second to several minutes.[17] Triggers for the pain include chewing, swallowing, coughing, talking, and yawning. Classic GN is usually seen in older patients (sixth and seventh decades of life), is unilateral, and occurs more often on the left[8,15,18,19] (although a recent review reported a preponderance of right-sided involvement).[20] It is a rare disorder with an occurrence of about 1 case per 100,000, or about one hundredth the incidence of TN.[21,22] As defined by the International Headache Society, the two forms of GN are classic versus symptomatic. As stated earlier, the classic form is not attributed to an underlying disorder, unlike the symptomatic form, in which a causative lesion has been identified.[17] In addition, aching pain may persist between paroxysms in the symptomatic form in contrast to the classic form, in which there will be periods of remission without pain.[17]

With vagal involvement, asystole, convulsions, and syncope have been reported, with some calling the condition vagoglossopharyngeal neuralgia.[3,6,8,23,24] As previously noted, it is believed that ephaptic coupling occurs between the fibers of cranial nerves IX and X during severe neuralgic pain. These abnormal connections are responsible for the cardiodepression with slowing of electroencephalographic (EEG)

activity, cerebral hypoxia, convulsions, and syncope, which occur in proportion to the duration of the syncopal episode.[24]

The diagnosis of GN is based upon its pain pattern, although a formal workup must be undertaken to rule out an underlying etiology. After a thorough history has been taken, a comprehensive evaluation of cranial nerve IX must be performed. Although paresis of the stylopharyngeus muscle may be negligible, dysphagia and lowering of the palatal arch may be present at rest.[25] Taste and sensation are tested over the posterior third of the tongue, with these being affected ipsilateral to the nerve. In addition, sensation is tested over the soft palate and tonsils. Reflex functions should also be tested. The glossopharyngeal nerve is responsible for the afferent arc of the reflex, whereas both the vagus and glossopharyngeal nerves are involved in the efferent arc. The gag reflex results in tongue retraction and pharyngeal constriction, and the palatal reflex elicits ipsilateral deviation of the uvula and controls the rise of the soft palate.[25]

In addition, a high-resolution contrasted magnetic resonance image (MRI) should be obtained to rule out a primary cause.

Outcomes

The treatment of GN can be medical or surgical, and recently radiosurgery has been performed. Pharmacotherapy is based on anticonvulsant drugs successfully used for TN. Carbamazepine is usually the first-line treatment, and alternative medications such as gabapentin, pregabalin, oxcarbazepine, lamotrigine, phenytoin, and baclofen have been used, although there are no major trials describing their efficacy.[1,26]

When medication fails, open, percutaneous, and radiosurgical options should be considered. Open surgical options include craniotomy for microvascular decompression or rhizotomy of the glossopharyngeal and upper rootlets of the vagus nerve. Historically, other surgical treatment modalities have been performed, including tractotomy, and motor cortex stimulation has been described but, as of yet, not adequately explored.[27–29] Percutaneous rhizotomy can also be performed, although this has not gained wide acceptance.[20,30] Recently, stereotactic radiosurgery has been used as a minimally invasive approach to treat GN, although larger studies have yet to be performed.[20,31–33]

Geniculate Neuralgia

Also known as nervus intermedius neuralgia, geniculate neuralgia is another rare disorder among the cranial neuralgias. In 1907 Hunt originally described a condition characterized by herpes zoster involvement of the geniculate ganglion.[34] Ramsay Hunt syndrome refers to the reactivation of the herpes zoster virus, causing severe otalgia along with facial paralysis. By definition, his description and the syndrome for which it's named involve herpes zoster. This and other postherpetic neuralgias are discussed in more detail in a later chapter. When these pain symptoms occur in the absence of herpes infection, the diagnosis of geniculate, or nervus intermedius, neuralgia is given.

Principles

The facial nerve is a mixed motor and sensory nerve and is made up of the facial nerve proper and nervus intermedius.[4] The nervus intermedius, which is located between the facial nerve proper and the vestibulocochlear nerve, carries general visceral efferent, special visceral afferent, and general somatic afferent fibers.[4] From the superior salivatory nucleus, carrying visceral efferent fibers, the nervus intermedius sends preganglionic parasympathetic fibers that travel through the geniculate ganglion to the pterygopalatine ganglion, where they synapse, eventually sending parasympathetic innervation to the lacrimal gland.[4] In addition, it sends parasympathetic fibers via the chorda tympani nerve from the facial nerve proper, just before its extracranial path, to innervate the sublingual and submandibular glands.[4] The visceral afferent component of the nervus intermedius, with cell bodies in the geniculate ganglion, carries taste sensation from the anterior two thirds of the tongue via the chorda tympani nerve to the nucleus solitarius tract in the medulla.[4] The cell bodies of the general somatic afferents lie in the geniculate ganglion, and they carry cutaneous sensation from the external auditory canal and skin behind the ear to the trigeminal tract, where these fibers lie with those of cranial nerves IX and X.[4,35] The diagnostic dilemma for many clinicians results from the overlap in the innervation of the ear, which includes cranial nerves V, VII, IX, and X and cervical roots II and III from the cervical plexus, so otalgia may be produced from involvement of any of these nerves.[36]

The pathophysiologic mechanism is still unclear. As with the other cranial neuralgias, there are many proposed theories, but the underlying cause is believed to be damage to the central-peripheral myelin junction, or Obersteiner–Redlich zone. Recently, it was shown that the central myelin segment of the nervus intermedius is closer to the brainstem than that of other cranial nerves, leading many to believe that this may play a role in the pathogenesis of nervus intermedius neuralgia.[37] This finding is consistent with the theory of vascular compression, usually by the anterior inferior cerebellar artery, which has been described by many.[38–47] Another pro-

posed theory involves the mutation of one of the voltage-gated sodium channels (Nav 1.7), a family of which is believed to play a major role in the pathogenesis of neuropathic pain. It has been shown that a mutation in Nav 1.7 results in neural hyper-excitability and neuropathic pain.[45,48–50]

Practice

Geniculate neuralgia is characterized by brief paroxysms of pain located deep within the auditory canal.[17] The diagnostic criteria according to the International Classification of Headache Disorders (ICHD) includes intermittent pain episodes lasting for seconds or minutes, and the presence of a trigger area in the posterior region of the auditory canal.[17] Although there is a frequent association with herpes zoster, accurate diagnosis is based on the absence of any causative or structural lesion. Geniculate neuralgia may be accompanied by disorders of taste, salivation, and lacrimation.[17] Although rare, it does appear to have a higher prevalence in women.[22]

Before the correct diagnosis can be made, other causes of otalgia must be ruled out. A complete neuro-otologic examination must be performed, including an audiogram, vestibular tests, and auditory-evoked potentials, all of which must be normal.[51] Contrast-enhanced MRI of the brain and facial nerve must be negative. Although the nervus intermedius is a small structure, it has been shown that it can be reliably identified with 3-T MRI.[52] With the sparse innervation of the nervus intermedius, clinicians should be mindful that some patients may have an otalgic variant of GN.[17]

Outcomes

Treatment, as with other cranial neuralgias, begins with medical therapy. Due to the rarity of geniculate neuralgia, there is a lack of research on pharmacotherapy for the disorder, so the medications used for other cranial neuralgias are typically administered, with carbamazepine the first-line medication.[53] When medication fails, there are surgical options that have been described, including sectioning of the nervus intermedius, microvascular decompression, and resection of the geniculate ganglion.[39–42,45,51]

Other Cranial Neuralgias

Although they are seldom seen, it's important to review the other identified cranial neuralgias to help prevent misdiagnosis. Head and neck pain is mediated by afferent fibers of the trigeminal nerve, nervus intermedius, glossopharyngeal, vagus, and the upper cervical roots via the occipital nerves.[17] As previously mentioned, any compression, irritation, or other lesion involving these nerves or their branches can produce pain in the area innervated. These other lesser known neuralgias involve branches of the vagus and trigeminal nerves.

Superior Laryngeal Neuralgia

Superior laryngeal neuralgia, as the name implies, involves the superior laryngeal nerve, a branch of the vagus nerve. It descends lateral to the pharynx and enters the larynx, crossing the hyoid membrane. It is involved in the sensorimotor innervation of the larynx and in the glottic reflex.[22] Patients affected are usually middle-aged, healthy men.[54] It's an extremely rare disorder characterized by severe, unilateral pain in the lateral aspect of the throat, submandibular region, and, rarely, underneath the ear.[17,22,54,55] The attacks usually last from seconds to minutes with longer periods of remission.[55] Triggers include swallowing, turning the head, coughing, or straining the voice.[17,54,55] The attacks can be stimulated by compression on the point of entry through the thyrohyoid membrane or on the pyriform sinus wall where the nerve runs surperficially.[13,17,22] Several causes have been reported, including mass lesions, trauma, deviated hyoid bone, upper airway infections, in addition to posttraumatic and postoperative effects.[13,55–58] The pharmacologic treatment is identical to that of TN.[54] In refractory cases, local anesthetic block can provide both diagnostic and therapeutic value.[17,22,54,57–59] Sectioning of the superior laryngeal nerve is often curative.

Nasociliary Neuralgia

Previously termed Charlin neuralgia, nasociliary neuralgia is a rare condition that manifests symptoms localized to the medial frontal region, with radiation to the orbit, eyebrow, nose, or jaw.[17,60,61] The nasociliary nerve is a terminal branch of the ophthalmic nerve dividing into the infratrochlear and ethmoidal nerves as well as contributing branches to the ciliary nerve. The stabbing pain, lasting seconds to hours, is often triggered by touching the lateral aspect of the nose.[17,62] Accompanying symptoms include lacrimation, conjunctival injection, nasal congestion, sneezing, and ocular pain.[60,62] Pain is abated by block or section of the nerve or by the application of cocaine to the affected nostril.[17,60–62] With its symptoms overlapping those of cluster headache, accurate diagnosis can be difficult, which may explain the various reported features and few published reports.

Supraorbital Neuralgia

Another rare disorder, supraorbital neuralgia is characterized by pain in the region of the supraorbital notch and medial aspect of the forehead. With each episode, there is usually tenderness over the nerve in the supraorbital notch, and the pain is abolished by local anesthetic blockade of the nerve.[17,62,63] The supraorbital nerve is a terminal branch of the frontal nerve, which is one of the branches of the first division of the trigeminal nerve. It passes through the edge of the orbit in the supraorbital foramen to supply the lateral aspect of the forehead. Supraorbital neuralgia is usually idiopathic, although it has been attributed to other causes such as trauma, tumors, or infections.[63–66] The age of onset is around 30 to 40 years with both men and women affected.[63,65–68] Treatment includes medications used for the other neuralgias, in particular, gabapentin, pregabalin, and amitriptyline, along with topical capsaicin, which is effective for some patients.[63,68] In refractory cases, surgical decompression of the foramen or sectioning of the nerve may be required, although peripheral nerve stimulation has been reported as an alternative.[67,69–71]

Conclusion

Successful management of the evaluation of facial pain requires an understanding and awareness of all the subtypes of cranial neuralgias. For the clinician, it's important to rule out a secondary cause for anyone presenting with facial pain. For many patients a multidisciplinary team can provide the best and most successful approach to care. As clinicians become more familiar with the cranial neuralgias other than TN, the diagnosis of atypical facial pain will likely be replaced by more specific and accurate diagnoses.

Editor's Comments

One of the cranial neuralgias that is mentioned in this chapter, glossopharyngeal neuralgia, is common enough that it is seen with some regularity in a neurosurgical pain practice. Once a course of one or more anticonvulsants has been tried and has failed to control the pain, surgery for the condition may be indicated. In my experience, rhizotomy of the glossopharyngeal nerve, sectioning of the most rostral filament of the vagus nerve, and microvascular decompression of the remainder of cranial nerve X, if neurovascular compression is demonstrated, is the most effective and durable procedure. Remarkably, the neurologic deficit from this procedure is minimal, and usually amounts to some slight numbness in the retropharynx. The procedure is highly reliable in relieving this severe pain.

Intermedius neuralgia is another story. I certainly feel that I have correctly diagnosed this disorder in rare patients, and have performed rhizotomy of the nervus intermedius branches (usually two) that lie between cranial nerves VII and VIII. I have not seen any predisposition to neurovascular compression of the VII/VIII complex in most of these cases. The diagnosis of this condition is purely historical, and should be limited to those patients that describe sudden stabbing ("ice pick in my ear") pains that are felt deep in the external auditory canal. Medical therapy using anticonvulsants can be tried, but is usually not successful. Surprisingly, the potential complications of this rhizotomy are somewhat *more* daunting than those associated with glossopharyngeal rhizotomy, in that theoretically both hearing and facial motor function can be inadvertently compromised by the procedure. In my view, monitoring of brainstem auditory evoked responses (BAERs) and facial electromyography (EMG) is mandatory during the operation. Further, most neurosurgeons have *never* seen the nervus intermedius, despite previous trips to the cerebellopontine angle. The nervus intermedius is not in a convenient location, and the inexperienced surgeon should request the presence of a more seasoned veteran before undertaking this procedure. Overall, this is a diagnosis that still puzzles—and worries—me.

I have seen supraorbital neuralgia only in the postsurgical or posttraumatic setting. The best treatment for this may well be neurostimulation, as discussed in Chapter 35.

Any chapter that purports to illuminate "other cranial neuralgias" should address the extremely rare variants of the superior laryngeal and nasociliary neuralgias. I am grateful to the authors for their comprehensive treatment of these topics. I have never made either of these diagnoses, and may well have unknowingly missed the opportunity in the past. It is also possible that these diagnoses were mistakenly described long ago, and live on only through perpetuating discussions such as the present one. We must at least be suspicious of that possibility.

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20 Occipital Neuralgia: Clinical and Pathophysiologic Considerations

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Occipital neuralgia (ON) is described as unilateral lancinating pain that extends from the suboccipital region up to the cranial vertex. Generally, pain in the suboccipital and high cervical region—be it spontaneous or posttraumatic—is far more common than true ON. More common maladies, such as migraine headache, craniocervical arthrosis or arthritis, Chiari malformations, diabetes, gout, and neoplastic or infectious disease of the head or neck, may mimic ON. True ON is typically idiopathic in nature, yet important secondary causes must be ruled out. Classically, decompressive and destructive techniques have been used to treat ON. The last decade has seen the emergence of peripheral occipital neurostimulation (ONS) not only for occipital neuralgia, but also for other headache disorders such as migraine and cluster headache. This therapeutic convergence emphasizes the possibility of a pathophysiologic link among these seemingly varied disorders, via confluent anatomical and functional nociceptive pathways[1,2] (**Table 20.1**).

The second edition of the International Classification of Headache Disorders (ICHD-2) categorizes headaches as (1) primary headaches, (2) secondary headaches, and (3) cranial neuralgias (www.ihs-classification.org).[3] Cranial neuralgias (trigeminal, occipital, and glossopharyngeal neuralgias being the most common) are paroxysmal painful disorders of the head characterized by some shared features such as unilateral symptoms, transience and recurrence of attacks, superficial and "shocklike" quality of pain, and the presence of triggering factors. In general, these disorders harbor a relatively high risk for underlying compressive or inflammatory disease, which must be ruled out.

The ICHD-2 strictly defines ON as paroxysmal shooting or jabbing pain in the dermatomes of the greater (major) or lesser (minor) occipital nerves (**Fig. 20.1**).[3] The greater occipital neuralgia (GON) pain originates suboccipitally and radiates over the vertex, whereas lesser occipital neuralgia (LON) produces pain radiating to the retroauricular and mastoid region. Neuralgia of the nearby greater auricular nerve involves the angle of the mandible. Interparoxysmal aching, dysesthesia, or hypoesthesia may accompany neuralgia pain. The pain may be accompanied by visual disturbance, nausea, dizziness, or tinnitus; however, such associated symptoms are more suggestive of migraine. Pressure or percussion over the greater or lesser occipital nerves usually reproduces the pain. Involvement of the greater occipital nerve (GON) is far more common (90%) than that of the lesser occipital nerve (LON, 10%).[4] Elsewhere it has been reported that both branches appear involved in approximately 9% of cases.[5] Any contribution of the smaller medial third (least) occipital nerve (TON) to occipital neuralgia is poorly defined. Pathophysiology remains poorly understood, but is generally thought to include myofascial or vascular compression and irritation of involved nerves.

Occipital nerve blockade (ONB) with local anesthetic infiltration in the region of the GON and/or LON is often undertaken to consolidate the suspected diagnosis of occipital neuralgia and to provide temporary relief. However, blockade in the suboccipital region is often imprecise, anesthetizing a variety of nearby structures and alleviating more common myofascial or arthritis pain. Further, blockade of the GON or C2 dorsal root has been shown to relieve primary migraine headache and secondary cervicogenic headaches, in which pain is referred frontally from a trigger point in the neck or suboccipital region.[6–8] Thus, misleading conclusions can be derived from pain relief after suboccipital injection, confounding the specificity of ONB as a diagnostic maneuver and potentially exposing patients to inappropriate surgical interventions (**Table 20.1**).

Noiceptive Anatomy of the Suboccipital-Occipital Region

The skeletal elements of the occiput, C1, and C2 are unique relative to the remaining spine, lacking the typical facet joints and intervertebral foramina that

Table 20.1 Diagnostic dilemma and therapeutic convergence: multiple headache syndromes may respond to occipital nerve blockade (ONB) or occipital neurostimulation (ONS)

Diagnosis	Definition/characteristics[a]	Presumed mechanism	Response to ONB and/or ONS
Occipital neuralgia	Paroxysmal jabbing pain in the distribution of the GON or LON, sometimes accompanied by diminished sensation or dysesthesia and commonly associated with tenderness over the nerve concerned	Musculofascial or vascular irritation of GON or LON	Unilateral occipital/suboccipital tenderness responsive to ONB and ONS[58–60]
Migraine headache	Recurrent moderate to severe pain lasting 4–72 h with unilateral location, pulsating quality, moderate to severe intensity, aggravated by routine physical activity, and associated with nausea and/or photophobia and phonophobia; +/– aura	Neuronal hyperexcitability (especially in the occipital cortex), secondary vascular dilation	May include occipital/suboccipital tenderness often responsive to ONB and ONS[2,8,64–66]
Cluster headache	Episodic clusters of attacks of severe unilateral orbital, supraorbital, or temporal pain accompanied by ipsilateral autonomic symptoms (conjunctival injection, rhinorrhea, etc.)	Neuronal hyperexcitability (possibly related to the hypothalamus), secondary vascular dilation	Pain in the trigeminal dermatomes (not occipital), despite responsiveness to ONS[68–71]
Cervicogenic (secondary) headache	Pain, referred from a source in the neck and perceived in the head and/or face, abolished following diagnostic blockade of a cervical structure, and resolves after successful treatment of the causative lesion	Musculofascial or vascular irritation of cervical nerves, dural traction at the occipital-cervical junction	Responds to blockade of a suboccipital or cervical structure[7]

Note: Although occipital nerve blockade (ONB) is thought to be useful for the diagnosis of occipital neuralgia (ON), relief of pain may be nonspecific. Likewise, occipital neurostimulation (ONS) provides relief for several headache disorders involving pain in the suboccipital-occipital regions.

Abbreviations: GON, greater occipital nerve; h, hours; LON, lesser occipital nerve.

[a]www.ihs-classification.org

are present in the subaxial spine. The majority of nodding and lateral rotation is possible because of this unique anatomy, but the neural elements at the C1 and C2 levels seem relatively less protected than those associated with the subaxial spine.

The C1 dorsal root exits above the C1 posterior arch and below the medially directed vertebral artery, extends through the suboccipital venous plexus to the suboccipital triangle of the neck, and gives off terminal muscular branches and a communicating branch to the GON.[9] There is no clear dermatomal representation of the C1 root, leading to the common misperception that it does not exist.

The C2 dorsal root ganglion is just inferior to the C1 posterior arch and covered by dense investing fascia continuous with the atlantoaxial membrane.[9,10] The short spinal nerve distal to the root ganglion is covered by the epidural venous plexus, within which the spinal nerve divides into two dorsal and ventral rami. The C2 dorsal root ganglion, short spinal nerve, and dorsal and ventral rami are 1 to 2 cm medial to the superiorly directed vertebral artery. The ventral ramus supplies the atlantoaxial joint and the cervical plexus. The C2 dorsal ramus runs deep to the obliquus capitus inferior muscle and divides into medial and lateral branches. The medial branch receives communicating branches from C1 and C3, becoming the GON.

According to Vital et al, the GON can be divided anatomically into three parts by two bends,[11] the first two of which continue in the suboccipital triangle. The GON is formed by the dorsal ramus of the C2 nerve root. The first nerve segment travels between the origin of the nerve and the obliquus capitus inferior muscle, beneath which the nerve makes its first bend in a medial direction. The second nerve segment runs cephalad deep to the semispinalis capitus muscle and superficial to the obliquus capitus inferior, rectus capitus major (posterior), and rectus capitus minor (anterior) muscles. It surfaces by perforating the semispinalis capitus muscle approximately 1.5 cm lateral to midline and 3 cm inferior to the external occipital protuberance,[12] making its second turn in a lateral direction. The third segment travels farther laterally, perforating the aponeurosis of the trapezius muscle near the superior nuchal line to begin its subcutaneous course. The GON usually branches to the middle and superior occipital

regions after perforating this aponeurosis.[11] The occipital artery and GON typically cross each other in the nuchal subcutaneous layer, and it has been noted in one anatomic cadaveric study that the GON was found consistently superficial to the artery at the cross point.[13] Notably, an indentation of the GON due to the occipital artery was observed in all of 24 cadaveric specimens, possibly undermining the view that such contact alone is a sufficient pathologic feature to cause pain.

The cutaneous branches of the GON supply the occipital skin and the posterior aspect of the external ear with extension forward to the coronal suture, where there is communication with the supraorbital nerve. Muscles innervated by the C2 nerve root and GON include the occipital belly of the occipitofrontalis, obliquus capitus inferior, longissimus capitus, splenius capitus, and semispinalis capitus.

The C3 dorsal root gives off its dorsal ramus, which exits by a conventional C2–C3 intervertebral foramen (typical of the subaxial spine), dividing into medial, lateral, and communicating branches with C2 and C4.[9,10] The lateral branch forms the LON, which perforates the splenius capitus muscle and travels cephalad to the posterior border of the sternocleidomastoid muscle 7 to 9 cm lateral to the external occipital protuberance along the intermastoid line. The LON branches subcutaneously to innervate the skin of the rostral neck and lateral suboccipital and mastoid regions[12,14] (**Fig. 20.1**). Muscles innervated along its course include the multifidus, longissimus capitus, splenius, and semispinalis.

The TON arises from the medial branch of the C3 dorsal ramus and travels medially under the splenius capitus and trapezius muscles, perforating the midline aponeurosis of the trapezius muscle (nuchal ligament) approximately 5 cm inferior to the external occipital protuberance. It travels cephalad in the subcutaneous space to innervate the midline suboccipital and inferior occipital regions.[15]

The three pairs of occipital nerves (GON, LON, and TON) provide sensory innervation of the back of the head, bilaterally. Nociceptive fibers project to the upper cervical spinal dorsal horns that are continuous with the trigeminal nucleus caudalis, where nociceptive fibers of the trigeminal nerve synapse (**Fig. 20.2**). Taken together, the upper cervical dorsal horns of C1–C3 and the trigeminal nucleus caudalis form a functional entity termed the *trigeminocervical complex* (TCC)[16–20] (**Fig. 20.2**). From the TCC, ascending nociceptive information is transmitted to higher centers (thalamus and cortex). Descending antinociceptive or pronociceptive feedback mechanisms—produced by pain-modulatory structures such as the periaqueductal gray (PAG), the dorsolateral pontomesencephalic tegmentum (DLPT), and rostral ventromedial medulla (RVM)—exert control over neurons of the TCC.

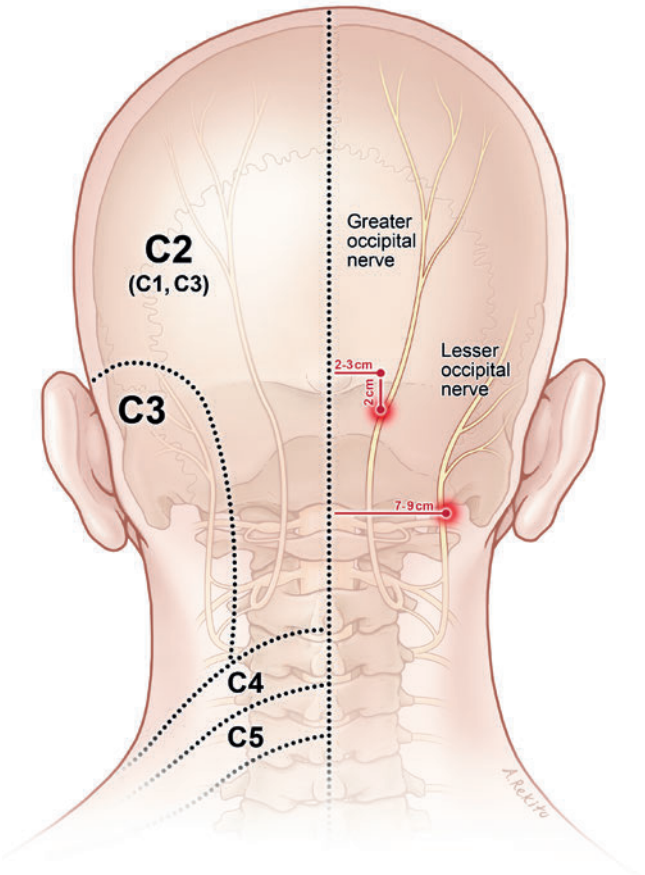

Fig. 20.1 Occipital neuralgia (ON) is described as paroxysmal shooting or jabbing pain in the dermatomes of the greater or lesser occipital nerves (GON, LON). The GON derives from the C2 dorsal ramus with lesser contributions from the C1 and C3 dorsal rami and provides sensation to the occipital region. The LON derives mostly from the C3 dorsal ramus with some C2 contribution and provides sensation to the mastoid and lateral suboccipital region. Occipital nerve blockade (ONB) is generally achieved by anesthetic infiltration at the suboccipital sites shown.

Experimental studies in animals and humans have demonstrated convergence of trigeminal and upper cervical nociceptive signals, and thus loss of spatial specificity at the level of the second-order neurons of the TCC.[16–20] The functional continuum between occipital and trigeminal nociceptive inputs provides a biological substrate by which (1) primary headache disorders (e.g., migraine and cluster headache) that are characterized by activation of the trigeminovascular system often exhibit pain in the occipital as well as trigeminal territories, (2) pain from an occipital-cervical source can be referred to the trigeminal territory (e.g., cervicogenic headache), and (3) treatments targeting the occipital nerves or upper cervical dorsal rami (e.g., ONB and ONS) provide benefits for not only occipital neuralgia, but also primary and secondary headache disorders.

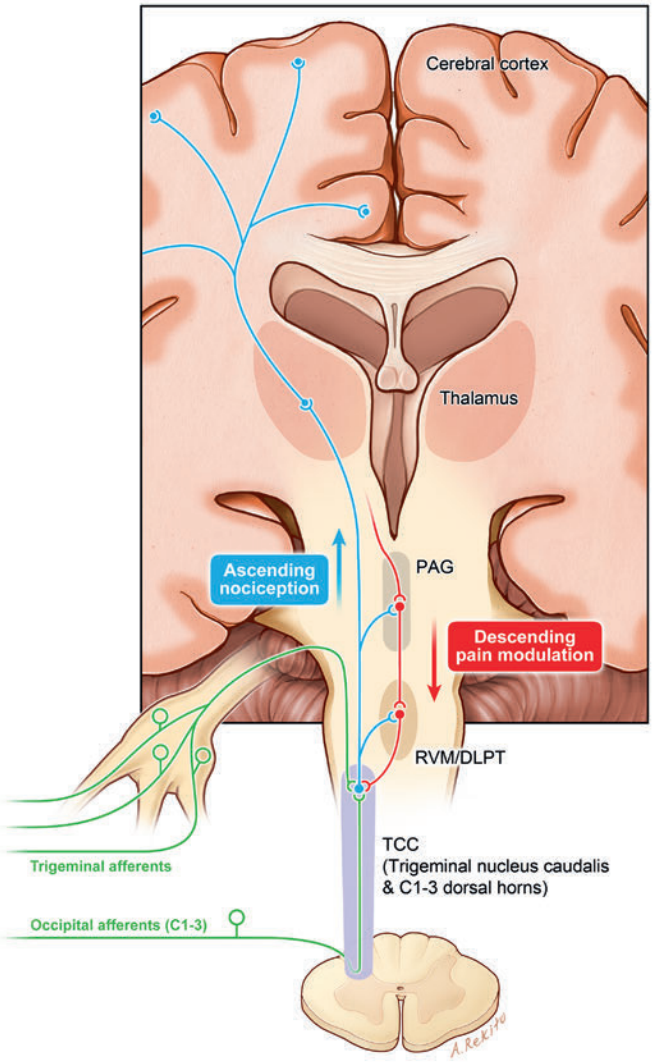

Fig. 20.2 Schematic illustration of the functional anatomy of cranial-cervical pain modulatory pathways. Nociceptive trigeminal fibers and C1–3 afferents synapse and converge in the trigeminal nucleus caudalis and dorsal horns, forming a functional continuum, the trigeminocervical complex (TCC), from which information is relayed to higher centers (e.g., thalamus and cortex). It also projects to supraspinal relay centers from which the TCC is subject to feedback inhibitory antinociceptive projections by pain-modulatory circuits in the brainstem. Such pain-modulatory structures include the periaqueductal gray (PAG), rostral ventromedial medulla (RVM), and dorsolateral pontomesencephalic tegmentum (DLPT). Convergence of nociceptive input at the second-order neurons of the TCC may explain in part the loss of spatial specificity in cranial-cervical pain (referred pain) in headache syndromes as well as the shared therapeutic benefit of occipital neurostimulation for multiple pain syndromes.

Etiology

Any consistent underlying genetic contribution to most cases of ON remains unknown. Familial occipital neuralgia has rarely been reported in Swiss and Chinese families with an X-linked dominant or autosomal dominant mode of transmission in either series.[21,22] However, the cause of primary ON remains sporadic and idiopathic in most cases. Although not generally verifiable, it is believed that primary ON is incited by damage or irritation (i.e., trauma, myofascial or vascular compression, or inflammation) to the occipital nerve(s).[4,13,23,24]

Given the phenomenologic similarity and the similar anatomy to cranial neuralgias (trigeminal, occipital, glossopharyngeal, etc.), ON is likely to share some common pathophysiologic mechanisms with cranial ones. Compressive etiologies would seemingly be supported by varying degrees of clinical improvement in these syndromes following surgical decompression/neurolysis—division of musculofascial tissue and/or separation of the artery and nerve(s). Notably, hyperexcitability of a chronically irritated nerve (from compression or inflammation) seems to represent a *necessary* condition, but is not *sufficient* to cause a particular neuralgia.[25] Compression or inflammation (such as that exerted at the root entry zone in a trigeminal nerve[26–28]) is associated with microvascular ischemic damage and demyelinization of fast tactile (A-β) fibers in cranial nerves. The result is A-β fiber hypersensitivity, and inappropriate cross talk between slow nociceptive (A-δ) fibers in the nerve and with nociceptive C-type sensory neurons at the level of the dorsal root ganglion.[25] A-δ and C-type fiber activity may contribute to pain generation in response to tactile stimuli (allodynia). Injury to A-β fibers also leads to sensitivity of wide-dynamic-range (WDR) neurons, a group of second-order nociceptive neurons in the lamina V of dorsal horn and trigeminal nerve nuclei (TCC) that are characterized by progressively facilitated excitability following repeat stimulation. WDR neurons receive convergent tactile information from A-β fibers and nociceptive information from A-δ and C fibers. WDR sensitization facilitates nociceptive input to the thalamus, also promoting inter-paroxysmal dysasthesia and allodynia.[25] Although this mechanism is generally accepted in the neurosurgical community, there is reason for skepticism. It fails to explain the immediate relief of tic pain following microvascular decompression (MVD), since the recovery of myelin and damaged fibers would not be expected to occur immediately.

Most isolated idiopathic ON is presumed to result from some combination of musculofascial or vascular (i.e., occipital or vertebral artery) compression or irritation. It has been noted that the GON may change course with respect to its two bends, with a more vertical course in flexion and a more horizontal course in extension,[10] but the clinical-anatomical ramifications of this are unclear. Although spasm of

the trapezius has been postulated as a cause of nerve irritation, in fact contraction of this muscle would be expected to decompress the nerve as it emerges from its aponeurosis.[10] In contrast, the nerve does perforate the semispinalis capitus muscle, making this a possible site of entrapment. If this is the case, the resulting compression could also explain the interparoxysmal aching dysesthesia reported in many patients.

History is often positive for "whiplash" injury if not overt skull base trauma.[4] However, the GON and C2 dorsal ramus do not generally appear susceptible to bony compression in extremes of extension, as demonstrated in cadaveric studies.[9,10] Rather, suboccipital-occipital lancinating pain clearly following such injury could indicate referred pain from a trigger point in the occipitocervical and atlantoaxial joints, which are susceptible to flexion-extension injury and which are innervated by the C1 and C2 rami. Hence, C2 root block or other procedures might improve pain that is not caused by definite ON.

Although ON is idiopathic, a variety of uncommonly reported secondary causes of lancinating pain thought to be ON have been described (see the corresponding box).

Epidemiology

Although chronic headaches (present > 15 days/month) are common in the general population, with a reported annual incidence rate of 3%,[29] the epidemiology of headaches specifically involving the occipital region remains poorly characterized. Likewise, very little data are available regarding the prevalence or incidence of ON in the general population. One observational study relying on retrospective analysis of a large electronic integrated primary care database from the Netherlands over a 10-year period identified an incidence of 2 per 100,000 person-years (0.002%).[30] By comparison, the overall incidence rate of craniofacial pain syndromes (including trigeminal neuralgia, postherpetic neuralgia, ON, local neuralgia, glossopharyngeal neuralgia, cluster headache, atypical facial pain, and paroxysmal hemicranias) was 39 per 100,000 person-years (0.039%). Trigeminal neuralgia, the most common syndrome studied, accounted for 22 per 100,000 person-years (0.022%). The incidence of ON increased with age, peaking in the seventh decade of life, and appeared more common in women (57%). Incidence lacked seasonal and annual variation over 10 years.[30]

Diagnosis

By *history*, patients describe paroxysms or constant shooting or jabbing pain in the suboccipital region or neck and radiating over the cranium.[3,4] Pain may radiate to the face/orbit due to overlapping C2 and trigeminal nucleus caudalis distributions. Interparoxysmal paresthesias or dysesthesias commonly occur. It has been reported that complaints of visual impairment/ocular pain (67%), tinnitus (33%), dizziness (50%), nausea (50%), and nasal congestion (17%) may be present because of connections with cranial nerves VIII, IX, and X and the cervical sympathetic chain[4]; however, such features invite caution to rule out migraine, cluster headache, or other syndromes.

Physical exam may reveal hypodysesthesia or dysesthesia in the distributions of the GON or LON and/or tenderness to pressure or percussion (Tinel sign). The diagnosis is supported by temporary improvement following local anesthetic blockade,[3] although the use of ONB diagnostically is not entirely specific due to clinical benefits with other headache syndromes.[7,8]

Although the diagnosis is predominantly clinical, *imaging* is recommended to rule out secondary pathological causes of neuralgia.[4] Craniocervical X-rays or computer tomography evaluates osseous pathology including neoplastic or degenerative changes. Magnetic resonance (MR) imaging helps to rule out abnormalities of the cervical and occipital soft tissues. Vascular imaging such as an MR angiogram may be useful to evaluate potential vascular causes.

Differential diagnosis may include any disorder associated with occipital or suboccipital pain. In general, cervical rheumatoid arthritis, degenerative C1–C2 arthrosis, trauma in whiplash injury, prior skull base injury or surgery, cervical myelitis, bleeding from cervicomedullary vascular lesions, schwannomas of the craniocervical junction or the GON, compression of the cervical roots by an anomalous ectatic vertebral or posterior inferior cerebellar artery, intra- and extra-axial neoplasm, infection with occipital adenopathy, congenital anomaly such as Arnold-Chiari type I malformation, and metabolic disorders such as diabetes or gout should be ruled out. Primary headache syndromes—especially migraine, cluster headache, tension headache, hemicrania continua, and cervicogenic headache—may be confused with ON. Similar pain may be caused by osteoarthritic spondylopathy of upper cervical and craniocervical structures (C2–C3 facet, atlantoaxial, and atlantooccipital joints). Other purported secondary causes of ON are listed in the corresponding box.

Reported Secondary Causes of Occipital Neuralgia

Vascular causes
- Irritation of the GON by branches of the occipital artery[23,31]
- Irritation of C1/C2 nerve roots by an aberrant branch or course of the posterior inferior cerebellar artery or vertebral artery[31,32]
- Cervical-medullary dural arteriovenous fistula (AVF)[33] or cavernous malformation[34,35]
- Giant cell arteritis involving the occipital arteries, even in the setting of a normal erythrocyte sedimentation rate.[36,37] Although this has been speculated to be an under-appreciated cause, a prospective series of surgical neurolysis that included routine occipital artery biopsy at the intersection of artery and nerve did not support arteritis as a routine underlying cause of ON–related headaches.[38]

Neurogenic causes
- Schwannoma of the occipital nerve or the area of the craniocervical junction[39,40]
- Transverse myelitis or multiple sclerosis involving the C2 region[41–43]
- Neurotrophic viral infections including syphilis[44] and herpes.[45] The combination of facial herpes lesions with pain in the C2 and C3 regions[45] reinforces the notion of anatomical-functional connectivity of the trigeminocervical complex (TCC).

Osteogenic causes
- C1/C2 arthrosis, atlantodental sclerosis, callus formation after C1/C2 fracture[46–49]
- Cervical osteochondroma[50]
- Osteolytic lesion of the cranium[51]
- Congenital foramen transversarium abnormality[52]

Iatrogenic cause
- C1 lateral mass screw irritating the C2 nerve root[53–55]

Treatment Options for Occipital Neuralgia

Conservative
- Physical/occupational therapy

Pharmacologic
- Analgesics (nonsteroidal anti-inflammatory agents)
- Tricyclic antidepressants
- Antiepileptics

Percutaneous
- GON and LON anesthetic infiltration (block)
- Botulinum toxin infiltration
- Percutaneous pulsed radiofrequency treatment

Open surgical
- Implanted occipital nerve stimulation (ONS)
- Occipital nerve release (decompression/neurolysis)
- Occipital neurectomy
- C2 dorsal ganglionectomy
- C2–C3 dorsal rhizotomy

Treatment Overview

Treatment options are outlined in the box so titled.

Initial conservative management for primary idiopathic ON should focus on reducing secondary muscle tension and on improving posture. Pharmacologic treatments are similar to other neuralgias/neuropathies and may include nonsteroidal anti-inflammatory agents (opiates would not be expected to benefit true neuralgic pain), tricyclic antidepressants, and antiepileptics (carbamazepine, gabapentin, pregabalin, etc.).

Percutaneous interventional management usually begins with local anesthesia (lidocaine, bupivacaine) blocks with or without corticosteroids. This approach is often used successfully in the interim management of ON and other headaches (especially migraine and cluster headache).[8] Tenderness over the GON is strongly predictive of outcome.[6] Notably, in all conditions in which the effect is observed, the response time (weeks) so far exceeds the local anesthetic effect (hours) that a mechanism of action may well be through prolonged changes in brain nociceptive pathways. Botulinum toxin A infiltration for ON has also been described in a small number of patients, but these results are preliminary and inconclusive.[56]

The typical target of infiltration of the GON is along its course where the nerve penetrates the aponeurosis of the trapezius muscle (**Fig. 20.1**). Inclusion of corticosteroid has not been definitely shown to improve outcome, but could be associated with increased alopecia of the infiltrated region and can probably be avoided. A typical landmark for GON infiltration would be 2 to 3 cm lateral and 2 cm inferior to external occipital protuberance (inion).[11] The

LON may be more variable, but can be infiltrated 7 to 9 cm lateral to the external occipital protuberance and just above an intersection with the intermastoid line (**Fig. 20.1**).

Percutaneous pulsed radiofrequency lesioning for occipital neuralgia does not seem as widely practiced, but a prospective trial testing this intervention in 19 patients showed significant improvements in pain scores and quality-of-life parameters with reduction of medications for up to 6 months.[57] A thermocouple is introduced percutaneously in awake patients using the landmarks described above to locate the GON and LON with a 50-Hz, 0.5-V current until the patient reports paresthesia in the appropriate dermatomes. Subsequently, pulsed radiofrequency treatment (45 V, 20 ms, 2 Hz) lasting 120 seconds with a maximum temperature of 42°C is performed twice.[4]

Subcutaneous peripheral neurostimulation for ONS, including technical aspects, is covered in greater detail elsewhere in this text (Chapter 36). In brief, good results with ONS, a minimally invasive reversible therapy, have been reported in several studies.[58–63] In general, the best results with peripheral neuromodulation are achieved with paresthesia concordancy; that is, neurostimulator-induced paresthesia should, to the best degree possible, cover the anatomic region of perceived pain.[2] Paresthesia concordancy is an accepted clinical indicator that the portion of the nervous system relevant to the pain perception is being stimulated. In patients with ON (or headaches primarily involving the occipital region), ONS produces clear concordant paresthesia (that is in a C2–C3 distribution), which is the same area of perceived or referred pain. By contrast, mixed positive results have been achieved treating migraine headaches with isolated ONS.[64–66] When combined with stimulation of the supraorbital nerve, ONS may be more effective for migraine pain.[67] However, select patients with a suboccipital-cervical source of pain, such as cervicogenic headaches, in which referred frontal pain improves with occipital nerve anesthesia block,[7] might benefit from ONS. Notably, cluster headache can respond favorably to ONS despite clear paresthesia discordancy.[68–71]

The mechanism(s) by which ONS delivers an analgesic effect is unclear.[1] ONS depolarizes the occipital nerves and anterograde impulses traverse the sensory fibers to penetrate the central nervous system (CNS). Although conditions in which concordant anesthesia is achieved show greatest benefit (i.e., ON), the beneficial effects of ONS in other headache disorders suggest at least some nonspecific mechanism of pain relief. The relevant mechanism of action may in fact differ depending upon the condition. One potential mechanism includes the alteration of conduction velocity and amplitude of the A-α, A-β, and A-δ fibers. Further, in accordance with the "gate-control theory,"[72] interplay of segmental spinal inhibiting effects and descending pain inhibitory pathways may contribute to analgesic effects of ONS. Given the loss of nociceptive specificity of the TCC, electrical ONS may have an antinociceptive effect in the territories of the trigeminal as well as occipital nerves. In this regard, a notable functional imaging study in chronic migraine patients supports the idea that ONS may influence supraspinal structures involved in central nociceptive processing, such as the pons, pulvinar thalamus, and cingulate cortex.[16]

Open microsurgical peripheral nerve release (decompression/neurolysis) involves a direct skin incision, dissection of subcutaneous tissue to identify the course of the nerve emerging from the aponeurosis of the trapezius muscle near the occiput, and microscopic dissection of the tendinous aponeurosis and any artery branches or adenopathy in contact with the nerve.[73] Sectioning of the obliquus capitus inferior muscle that the nerve traverses inferiorly has been advocated by some.[74] Modern experiences with neurolysis indicate favorable outcomes with respect to improved headache with temporary scalp hypoesthesia reported as a typical result.[23,24,74] More proximal decompression of the fascia investing the C2 root and resection of the venous plexus overlying the ganglion has been described, but may be associated with unintended thermal injury to the ganglion.[73]

Open peripheral occipital neurectomy is the classic treatment for ON,[73] commonly utilized prior to the introduction of ONS. A linear incision is made along the superior nuchal line and the occipital artery pulsation is used to locate the nearby nerve. The nerve is dissected to its exit from the aponeurosis of the trapezius, grasped with a hemostat, twisted, and avulsed. This results in scalp anesthesia, and the nerve may regenerate or develop a neuroma[75,76] in several months to a year with return of pain. Other treatments of historical interest include C2 dorsal ganglionectomy[73] and intradural C2–C3 dorsal rhizotomy.[77,78] Notably, ganglionectomy risks anesthesia dolorosa, and cervical rhizotomy is associated with considerable nausea, vomiting, and vertigo.

Conclusion

Occipital regional pain is a feature of several headache syndromes. ON is a distinct headache disorder that shares some clinical and pathophysiologic features with other cranial neuralgias, primary and secondary headache disorders, and other causes of pain with trigger points in the upper cervical region. Convergence of trigeminal and upper cervical noci-

ceptive pathways and loss of spatial specificity at the level of the second-order neurons of the TCC may explain referred pain between trigeminal and occipital dermatomes in related headache syndromes. Tenderness along the course of the occipital nerves and relief by selective nerve block is consistent with ON, but the maneuver is generally not specific. Whereas secondary treatable causes such as systemic inflammatory disease, tumors, and arthrosis must be ruled out, ON is typically idiopathic and presumed to result from compression or irritation along the course of the GON or LON. When medical management fails and repeated occipital nerve anesthetic blockade becomes impractical, ONS or open neurolysis may be indicated. As a testament to the convergence of nociceptive pathways, ONS has found clinical utility not only in ON, but also in the treatment of migraine and cluster headache.

Editor's Comments

Occipital neuralgia (ON) presents a diagnostic challenge because of the wide variety of symptoms, surgical findings, and postsurgical outcomes. Drs. Willie and Boulis have provided an excellent overview of the topic. The diagnosis is problematic since so many entities may overlap to produce an aggregate syndrome, anchored in occipital pain. The problem is that there is no hallmark of ON, and thus, in everyday practice, it is difficult to know where the boundaries of this diagnosis lie.

Their definition and that of the ICHD-2 emphasize "paroxysmal shooting" or lancinating neuralgic pain in the diagnosis of ON. However, as the authors state, "interparoxysmal aching dysesthesia . . . may accompany neuralgic pain." Thus, both lancination and aching are part of the ON syndrome.

The authors of this chapter rightfully acknowledge that "cervical arthritis . . . may mimic" ON, and further that "cervicogenic headache may be confused with occipital neuralgia." In addition, spondylopathy of the C2–C3 facet, as well as the atlantoaxial and atlanto-occipital joints, may cause similar pains. Given the commonality of cervical osteoarthritis, it is highly likely that much, if not most, of what we consider to be ON may be referred pain from upper cervical arthritis.

I agree that some patients with the presumptive diagnosis of ON also seem to have radiation of pain into the face or orbit. I would further agree with the authors, and I have long felt, that this might be related to the neuroanatomic contiguity of the upper cervical dorsal horn and the spinal trigeminal nucleus. The interplay of these neuronal pools is not difficult to hypothesize. The association of facial or orbital pain only serves to make this diagnosis difficult.

Thus, the diagnosis of ON effectively becomes a litany of symptoms that include occipital pain, which may be lancinating or aching, in the C2 and C3 dermatomes but that also may incorporate pain in the trigeminal distribution.

We have previously reported on the surgical removal of the second (C2) or third (C3) cervical sensory dorsal root ganglion for the treatment of ON.[79] We reported on 20 patients who had undergone C2 and/or C3 ganglionectomies for intractable occipital pain. All patients reported preoperative pain relief following cervical nerve blocks. Average visual analogue scale scores were 9.4 preoperatively and 2.6 immediately after the surgical procedure. The percentage of patients reporting short-term pain relief (< 3 months) was 95%. In 13 patients (65%), pain returned after an average of 12 months (C2 ganglionectomy) and 8.4 months (C3 ganglionectomy). Long-term results were excellent, moderate, and poor in 20, 40, and 40% of patients, respectively.

In our series, cervical ganglionectomy offered relief to a majority of patients immediately after the procedure, but the effect was short-lived. Nerve block did not necessarily predict long-term benefit and therefore cannot justify surgery by itself.

Because of the uncertainty of the diagnosis, and the lack of a durable response to destructive procedures, a neuromodulation approach to this condition is almost certainly preferable. Occipital nerve stimulation (ONS) is described in a later discussion, and I comment on this treatment modality after that chapter.

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Section III.E

Postsurgical Neuropathic Pain

21 Postmastectomy Pain Syndrome

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Breast cancer is the most common malignancy affecting women worldwide (29% of all cancers). After lung cancer, it is the leading cause of cancer-related deaths in women.[1–3] In the United States, the incidence of invasive breast cancer between 2010 and 2012 increased from 207,090 to 225,870 in women and 1,970 to 2,190 in men.[1,4] Despite the increase in incidence, the number of deaths related to breast cancer has been steadily decreasing over the years. This has been attributed to advancements in early detection and treatment of the disease.[1]

Given its predilection for younger women in their reproductive years,[3] morbidity associated with the disease and the therapies to treat the disease deserve careful consideration from physicians. A number of postsurgical complications may occur, including infection, lymphedema, seroma, and pain.[5] Most of these are self-limiting. One of the more debilitating complications of mastectomy is a chronic pain condition known as postmastectomy pain syndrome (PMPS). This syndrome was first described by Wood[6] and is defined by the International Association for the Study of Pain (IASP) as "chronic pain in the anterior aspect of the thorax, axilla, and/or upper half of the arm beginning after mastectomy or quadrantectomy, and persisting for longer than 3 months following surgery."[5,7] The incidence of chronic pain following mastectomy may be over 50% according to some authors and may be potentiated by adjuvant chemotherapy or radiotherapy.[8] Therefore, a thorough understanding of its pathophysiology, etiology, and early diagnosis is critical for the treating physician.

Principles

Types of Breast Cancer and Surgical Intervention

There are a variety of breast cancers, with ductal and lobular adenocarcinomas being the most common.[2] Staging according to the American Joint Committee on Cancer (AJCC) ranges from the noninvasive stage 0 to the metastatic stage IV.[9] Treatment primarily involves surgery, which alone may be curative for many patients, but may also require adjuvant chemotherapy, radiation, hormonal, or immunologic therapy to further reduce the risk of recurrence and improve survival.

Types of Surgery for Breast Cancer[8]

Lumpectomy with sentinel node biopsy: Breast-conserving complete resection of the primary tumor while leaving remaining healthy tissue. It usually involves biopsy of the nearest node to identify possible spread of the cancer. If node involvement is confirmed, then axillary node resection is also performed.

Simple total mastectomy: Removal of the entire breast tissue without lymph node or muscular resection

Modified radical mastectomy: Removal of the entire breast tissue with lymph node resection

Radical mastectomy: Removal of the entire breast tissue and pectoralis muscles, with lymph node resection

The extent of surgical intervention (see the corresponding box) ranges from a localized lumpectomy to total radical mastectomy as determined by tumor size, location, and staging. Skin- or nipple-sparing mastectomies are more recent techniques involving preservation of the nipple–areola complex primarily for cosmetic purposes.[10] There is a difference of opinion in the literature as to which surgical procedure is associated with a higher incidence of chronic postoperative pain; some suggest that chronic pain is more common with less invasive surgeries[5,11] whereas others have associated higher rates and intensity of pain with invasive radical mastectomy.[5,12] Chronic pain is more likely related to surgical approach rather than invasiveness. Approaches more susceptible to intercostobrachial nerve (ICBN) damage will result in

higher incidence and intensity of reported postoperative pain.[5,8] Radiation therapy has also been reported to play a role according to one prospective study.[13]

Pathophysiology of Postmastectomy Pain

Pathophysiology

The principal cause of chronic postmastectomy pain is neuropathic in nature. Neuropathic pain (NP), as defined by the updated 2011 IASP taxonomy,[14] is a clinical description that requires a lesion or disease of the somatosensory nervous system. NP has characteristic symptoms, including burning, tingling, or shocklike sensations. A diagnostic questionnaire entitled the DN4—from its original French title, *Douleur Neuropathique*—was developed and validated by Bouhassira et al as a neuropathic pain scale.[15] With four or more positive symptoms the diagnosis of NP is likely. NP following mastectomy may be due to three proposed mechanisms: phantom breast pain, neuroma, and neuralgia.[8]

Phantom Breast Pain

The first etiology is known as phantom breast pain, a phenomenon that is similar to phantom limb pain associated with amputations. Patients will describe pain in areas of previously present tissue such as the nipple or areola. Although the exact mechanism is uncertain, some have hypothesized the involvement of peripheral, spinal, and cortical components[16] (see the corresponding box). A prominent mechanism is the cortical reorganization of sensory input based on an understanding of the somatosensory homunculus.[17]

Mechanisms of Phantom Pain

Peripheral: The regeneration of surviving portions of neurons form neuromas that emit ectopic discharges maintaining persistent pain from what is perceived to be previously present tissue

Spinal: Reorganization in the dorsal horn of the spinal cord may lead to branching of α-β fibers—normally responsible for touch and pressure sensation—into the lamina previously containing terminal C fibers. Consequently, innocuous touch and pressure stimuli is translated and transmitted as slow, secondary pain.

Cortical: Reorganization may also occur in the primary sensory cortex where neurons of somatotopically adjacent neurons (represented by the homunculus) may occupy the deafferented region. Signals from healthy tissue may then be interpreted as amputated tissue sensation.

Neuroma Pain

Neuromas may also contribute to neuropathic pain. These are developed from scar tissue due to impaired regeneration of severed nerve axons, and they emit ectopic discharges of action potentials, leading to overall hyperexcitability of the sensory system.[8,16] Those who had lumpectomy, axillary dissection, and radiotherapy were more likely to have neuroma-related pain compared with those who had radical mastectomy.[18] Neuromas may be surgically resected[19] with concurrent nerve grafts to improve regeneration or reimplantation into muscle.[8,20] Successful pain relief, however, is not always achieved.

Neuralgia

NP can also be due to neuralgia, which is defined as "pain in the distribution of a nerve or nerves."[14] Postmastectomy neuralgia may be caused by damage to any nerve such as the medial or lateral pectoral, long thoracic, intercostal, or thoracodorsal nerves.[12] It is, however, more commonly due to severing of the ICBN.[8,21,22] The response is persistent spontaneous ectopic impulses (similar to neuromas) causing pain and paresthesias, frequently in the upper axilla and medial upper arm. Surgical approaches in which the ICBN is most vulnerable result in higher rates of neuralgia. Axillary lymph node dissection, in particular, is reported to double the rate (51 vs. 23%) of chronic pain compared with procedures not involving lymph node dissection.[23] Still, surgical technique attempting to preserve the ICBN may be difficult. It has been shown that up to 35% of patients may still have damage to the ICBN despite its perceived preservation during the surgery.[24]

Practice

Preventive Measures

Management of PMPS begins perioperatively with measures to optimize acute postoperative pain management. Although difficult, careful surgical technique avoiding the ICBN may prevent chronic neuropathic pain, which has been identified as one of the most common causes of chronic postmastectomy pain.[12,22] Additionally, increased performance of sentinel lymph node biopsy prevents unnecessary axillary lymph node dissection, thereby reducing the risk of ICBN or other nerve damage.[24]

Along with superior surgical technique, a number of perioperative pharmacologic treatments have been studied. Perioperative administration of a topical eutectic mixture of local anesthetics (EMLA),[25] alone or combined with oral gabapentin and topical ropivacaine,[26] both have shown significant

improvement of pain at 3 months and 6 months, respectively, compared with placebo. Conversely, gabapentin,[27] mexiletine,[27] amantadine,[28] and ketamine[29] all failed to show significant improvement when compared with placebo. The stimulus for such research appears to be related to evidence that aggressive treatment of acute postoperative pain may prevent the development of chronic pain.[30,31]

Pharmacologic Management of Chronic PMPS

Much of the discussion to this point has pointed out the neuropathic nature of postmastectomy pain. Because of this relationship, the predominant strategy for pharmacologic intervention follows basic neuropathic guidelines. There are several types of neuropathic pain syndromes described in the literature. However, much of the major research available is focused on painful diabetic peripheral neuropathy or postherpetic neuralgia.[32,33] There is a concern as to how the data regarding these two conditions may be generalized to other neuropathic conditions. Many authors have concluded that such guidelines may be generalized until further studies indicate the contrary. Only a few randomized control trials (RCTs) exist specifically for PMPS management, all of which involve medications used for neuropathic pain such as topical capsaicin and oral amitriptyline. Readers are advised to review the detailed, stepwise approach to neuropathic pain along with recommended dosing regimens provided by Dworkin et al.[32,34] The general categories of pharmacologic therapy for PMPS and neuropathic pain are detailed next.

Antidepressants

Antidepressants with both serotonin and norepinephrine reuptake inhibition have shown to be effective in treating a number of neuropathic pain conditions.[32,33] These include both tricyclic antidepressants (TCAs) and selective serotonin and norepinephrine reuptake inhibitors (SSNRIs). The exact mechanism for pain relief is not clear at this time, although it is thought that serotonin and norepinephrine neuromodulation in the descending pathways plays a significant role in inhibiting ascending pain sensation. Moreover, TCAs have been shown to activate δ-opioid receptors, thereby mediating further analgesic effects.[35] These have the added benefit of low cost and the potential benefit of addressing depression, which may be an associated comorbidity in many chronic pain patients.[32] Practitioners should monitor adverse effects (see **Table 21.1**) of these medications, particularly tertiary amine TCAs (i.e., amitriptyline and imipramine).[33]

Calcium Channel $\alpha_2\delta$ Ligands

Although initially developed as anticonvulsants, gabapentin and pregabalin have been shown to be efficacious for a number of neuropathic conditions as well. By binding to the $\alpha_2\delta$ subunit of voltage-gated calcium channels that regulate the release and inhibit activity of these channels, neuronal excitation of postsynaptic cells at spinal and higher centers is impeded.[36] Generally speaking, these medications should be started at low doses and titrated to effective doses to minimize adverse effects such as sedation, dizziness, and cognitive dysfunction.[32]

Topical Lidocaine

The 5% topical concentration of lidocaine comes in both a patch and gel formulation. By inhibiting voltage-gated sodium channels, influx of sodium is prevented as well as the resultant action potential generation.[37] Although a number of systemic side effects are common with local anesthetics, given the superficial application and minimal systemic absorption of this lidocaine preparation, only mild local reactions are experienced. Such reactions include skin irritation,[38] allergic hypersensitivity,[39] and tachyphylaxis (a sudden decrease in drug response).[40] The patch should not be used around open wounds or near the incision until proper healing has been ensured. Since topical lidocaine is most appropriate for well-localized pain,[32,33] it is a reasonable and relatively inexpensive treatment for PMPS that may also be used in combination with oral medications.

Opioid Analgesics and Tramadol

Despite high-quality evidence of efficacy regarding neuropathic conditions, opioid analgesics are considered second- or third-line therapies predominantly due to their significant long-term safety issues and dependence potential. Tramadol, which is a weak agonist of the μ-opioid receptors, also demonstrates serotonin and norepinephrine reuptake inhibition, providing a dual effect on modulating neuropathic pain. It may be preferred to traditional opioid medication due to its decreased abuse potential.[34] Tramadol should be avoided in patients with seizure history, however, because it may decrease the seizure threshold.[41] Both types of medication, nonetheless, may provide rapid pain relief. Hence, they may be considered first-line treatments for acute neuropathic pain or exacerbations of severe pain. They may also be used concomitantly with other first-line drugs during the titration period. Chronic usage, however, is not initially encouraged except when first-line drugs are not tolerated or effective in adequately improving pain.[32]

Table 21.1 Neuropathic pain guidelines[33,35]

Medication	Recommendation	Mechanism of action	Major side effects
TCA[a] Amitriptyline Nortriptyline Imipramine Desipramine	First-line	Increased serotonin and norepinephrine and (+)δ-opioid receptors	Anticholinergic symptoms (dry mouth, orthostatic hypotension, constipation, urinary retention); cardiac toxicity; suicidal ideation
SSNRI Duloxetine Venlafaxine	First-line	Serotonin + norepinephrine → (+) modulating pain inhibitory pathways	Duloxetine: nausea Venlafaxine: cardiac conduction abnormalities, withdrawal syndrome
CC $\alpha_2\delta$ L Gabapentin Pregabalin	First-line	Binds $\alpha_2\delta$ subunit of calcium channels → (–) action potential of sensory nerves	Dizziness; sedation
Topical lidocaine 5%	First-line	(–) voltage-gated sodium channels	Rash; skin irritation
Opioids	Second-line[b]	(+) opioid receptors	Sedation; constipation; nausea; abuse; respiratory depression
Tramadol	Second-line[b]	(+)μ-opioid receptors amine reuptake inhibition	Similar to opioids but also lowers seizure threshold and may interact with SSRI/SNRI to cause serotonin syndrome

Abbreviations: TCA, tricyclic antidepressant; SSNRI, selective serotonin and norepinephrine reuptake inhibitor; CC $\alpha_2\delta$ L, calcium channel $\alpha_2\delta$ ligand.
[a]Secondary amines (i.e., nortriptyline and desipramine) carry a decreased risk of adverse reactions compared with tertiary amines (i.e., amitriptyline and imipramine).
[b]These may be considered first-line in cases of intractable acute pain, during titration of first-line medications, or during exacerbations of pain.

Topical Capsaicin

An extract from chili peppers, capsaicin activates the transient receptor potential vanilloid subtype 1 (TRPV1) receptor, which is also activated by heat.[42] Chronic activation of this receptor causes paradoxical desensitization, likely due to depletion of the neurotransmitter substance P, involved in pain sensation.[43] Traditionally, this has been used in low-concentration formulations (0.025–0.075%) showing inconsistent results in NP research. More recently, however, a higher concentration (8%) preparation has shown promising results for the treatment of postherpetic neuralgia in a multi-center double-blinded RCT.[44] Another RCT specific to PMPS was conducted by Watson et al in 1992.[45] In this study, 62% of patients with high-concentration capsaicin experienced 50% or greater overall pain relief. These studies suggest that high-concentration capsaicin may be a viable treatment option, albeit secondary to the more established recommendations.

Combinations

A combination of the medications may provide additive relief of pain according to a number of studies.[46–49] Studied combinations include morphine, oxycodone, or nortriptyline with gabapentin, and topical lidocaine with pregabalin. These combinations had the added benefit of lowering required medication dosage, reducing escape medication usage, and improving sleep. However, results have failed to demonstrate a clear reduction in the adverse effects of the medications despite the lower doses involved. Accordingly, combination therapy has been recommended only if inadequate partial relief is experienced after an appropriate trial of single-drug therapy.[32,34]

Interventional Treatments

If the ICBN is suspected to be responsible for the chronic pain and is refractory to medical therapy, interventional treatment may be attempted. Innervation to the breast region is predominantly supplied by medial and lateral cutaneous branches of the third through sixth intercostal nerves. The ICBN—the lateral cutaneous branch of the T2 intercostal nerve—may be targeted using local anesthetic such as bupivacaine. Arnér et al[50] demonstrated that peripheral nerve block may provide both diagnostic and therapeutic benefits for NP, albeit short term. Local anesthetic may also be combined with steroid for potential long-term relief, although evidence for this is predominantly empirical.[51]

More long-term relief may be achieved with pulsed radiofrequency ablation (PRFA), involving radiofrequency oscillations resulting in heat denervation. A retrospective study involving 49 patients by Cohen et al[52] compared PRFA of the dorsal root ganglion (DRG) versus the intercostal nerve or pharmacotherapy (secondary amine TCA or gabapentin or oxcarbazepine). At 6 weeks they found that 61.5% of the DRG PRFA group experienced > 50% pain relief compared with 21.4 and 27.3% of the intercostal nerve PRFA and pharmacotherapy groups, respectively. The study was limited, however, because it was retrospective without randomization or control.

Outcomes

In the absence of authoritative PMPS treatment guidelines, the RCTs mentioned above provide practitioners with insights regarding effective management strategies. Since neuropathic treatment principles predominate PMPS, however, it is appropriate to reference evidence-based guidelines for the care of NP syndromes. Although there are a few well-established guidelines available,[33] these authors have chosen to detail those established by the Neuropathic Pain Special Interest Group of the IASP (NeuPSIG) given its endorsement by a number of international pain societies, including but not limited to the American Pain Society (APS), Finnish Pain Society (FPS), Mexican Pain Society (MPS), and Canadian Pain Society (CPS). Differences between the above-mentioned guidelines are discussed in an article by O'Connor et al.[33]

The NeuPSIG[32,34] recommendations (see **Table 21.1**) are organized into three fundamental levels of strength. First-line recommendation is provided for treatments with efficacy demonstrated in multiple RCT studies, consistent with the Oxford Centre for Evidence-Based Medicine grade A recommendation. Second-line recommendation is for treatments also supported by multiple RCTs (grade A) but for which certain reservations were maintained by the authors of the NeuPSIG relative to other medications. Finally, third-line recommendation is provided if a treatment is supported by only one RCT or if two or more RCTs were inconsistent (grade B). These may include certain antidepressants, anticonvulsants, and other medications whose details may be found elsewhere.[32,34] Generally, these are reserved for cases where first- or second-line drugs are not tolerated or appropriately efficacious. More recent treatments such as high-concentration topical capsaicin or botulinum toxin are not yet included in these guidelines because more research is warranted.

Editor's Comments

Dr. Raja and his colleagues from Johns Hopkins have done a very nice job of bringing us up to date on this important pain syndrome. Clearly, pharmacologic treatment, in some cases preemptive, is the preferred approach to this condition.

Given the incidence of breast cancer, the postmastectomy pain syndrome (PMPS) should be better recognized. If almost 226,000 persons, mostly women, in the United States have breast cancer, and up to 50% experience chronic pain after breast surgery, then well over 100,000 individuals have some form of this syndrome. This would be an incidence of 0.03% in the general population, compared with a more familiar pain syndrome, trigeminal neuralgia, which is reported to have a 0.01% incidence. By this reckoning, PMPS is three times more common than trigeminal neuralgia, yet is almost unknown outside of the field of oncology!

On review of this chapter, I performed a search for any series published since 1996 referable to the surgical treatment of this condition, and could find none. Although several years ago there seemed to be a brief flurry of interest in T2 neurectomy, or multilevel upper thoracic dorsal root ganglionectomy (centered on T2) for PMPS, no follow-up series has made it to publication. This may be due to the fact that these procedures do not work very well, in alignment with my own experience with destructive approaches for this condition. It is also surprising that essentially nothing has been written about the use of spinal cord stimulation (SCS) for PMPS, since neuropathic pain (NP) is one of the principal indications for SCS.

Under-recognition of PMPS may underlie what appears to be a gap in the pain surgery literature. Surgeons who have experience, positive or negative, with attempted invasive approaches to this syndrome should memorialize their efforts. I would be particularly interested in the outcome of a series of patients with medically intractable PMPS who underwent a trial of SCS. Fortunately, survival rates in patients with breast cancer continue to improve. With that changing natural history, the numbers of individuals who have the burden of chronic pain after breast surgery will also increase. We need to focus more attention on this disorder and its effective treatment.

Conclusion

The treatment of breast cancer via mastectomy may be curative of this potentially fatal disease. However, PMPS remains one of its most common and debilitating complications. PMPS may be caused by three main mechanisms: phantom breast syndrome, neuroma formation, and neuralgia. All of these conditions are fundamentally neuropathic in nature. In terms of management, early detection combined with aggressive management of acute pain may avert chronic symptoms. In cases of pain lasting longer than 3 months, however, principles of treatment focus on resolving discomfort and debility associated with chronicity of pain. Given the preponderant neuropathic nature of postmastectomy pain, commonly due to ICBN neuralgia, NP guidelines may be used to guide treatment. Nonetheless, a comprehensive multidisciplinary methodology of treatment combining clinical expertise with supportive patient interaction may provide relief to those who suffer this experience.

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22 Postherniorrhaphy Pain Syndrome

Andrew Zacest

Chronic postsurgical pain has been increasingly recognized and studied since the publication by Crombie et al in 1998[1] identifying trauma and surgery as significant risk factors for chronic pain. Since then, numerous publications have studied the incidence of chronic pain following various surgical procedures, with figures ranging from 10 to 60% and severe chronic pain occurring in 2 to 10% of patients.[2–4] According to the International Association for the Study of Pain (IASP), pain that persists longer than 3 months, beyond the usual time for healing, is defined as chronic.[5] Chronic postsurgical pain is a serious health problem associated with depression, loss of work, or medicolegal complications and is a significant economic cost to society. Also, it is, at least theoretically, preventable.

Inguinal hernia repair is one of the most commonly performed general surgical procedures worldwide. Most patients preoperatively have mild to moderate discomfort and one third of patients have no pain.[6] Following herniorrhaphy, however, chronic pain has been reported in 11 to 39% and severe pain in 0.5 to 6%. Variation in these figures is based upon the definition of pain, methodology used, duration of time since surgery, and surgical technique used.[7–11] Chronic pain, which is often difficult to treat, has become the most common serious long-term complication following hernia repair.[6]

Postherniorrhaphy pain syndrome (PHPS), which refers to a differential diagnosis of groin pain following hernia repair, remains incompletely understood. The main reasons for this confusion include a lack of understanding of the pathophysiology of development of chronic pain and the lack of uniform classification of pain syndromes. In spite of this, there have been recent attempts to clarify the definition and find a consensus approach to its diagnosis and treatment.[12] Clearly, a better understanding of the pathophysiology would permit a more uniform approach to clinical diagnosis, nomenclature, and hence treatment.

The pathophysiology of PHPS has generally been considered from two separate but overlapping perspectives. The biological or structural perspective considers that pain arises following surgery from damage to somatic, visceral, or neural structures resulting in nociceptive, visceral, or neuropathic pain. The neural structures most at risk during hernia surgery include the ilioinguinal, iliohypogastric, and genitofemoral nerves. In support of this hypothesis is increasing evidence that, in common with other postsurgical pain syndromes, meticulous identification and preservation of these nerves intra-operatively substantially reduce the likelihood of chronic postoperative pain.[8,12] Furthermore, observation at surgery has shown that perineural fibrosis; nerve entrapment by suture, staple, or prosthetic device; or actual nerve damage, including partial or complete section, are observable in patients with neuropathic pain.[13,14] In one case report histopathologic examination of a section of ilioinguinal nerve entrapped in mesh revealed axonal loss with regeneration of chronic inflammatory and granulomatous infiltrate in the nerve and severely low numbers of myelinated axons with features of a chronic inflammatory, demyelinating peripheral neuropathy.[14] These findings suggest the potential not only for acute nerve injury but chronic inflammatory nerve damage with the use of mesh. Such observation may assist in understanding mechanisms for the development of both neuropathic and nociceptive pain. Using this biomedical approach, Loos et al proposed a classification of postherniorrhaphy pain syndromes into group 1 (neuropathic pain), group 2 (nonneuropathic pain, including periostitis pubis and recurrent hernia), and group 3 (a tender spermatic cord),[15] analogous to neuropathic, nociceptive, and visceral etiologies, respectively.

The second perspective considers that the transition from acute to chronic postsurgical pain is multifactorial and involves a comprehensive interplay of preoperative, intraoperative, and postoperative

patient and environmental factors.[4,5] In support of this hypothesis are studies that have examined risk factors for the development of chronic postsurgical pain. These have shown that preoperative pain level, psychological factors, a history of pain disorder, younger age, operative approach, operation duration, revision surgery, anesthetic technique, severe early postoperative pain, and postoperative complications[6,8,9,11,16] are associated with the development of chronic postsurgical pain.

In summary, the pathophysiology of chronic postherniorrhaphy pain needs to consider both what type or types of pain may be manifesting as well as a multitude of biopsychosocial variables that may collectively contribute to the pain experience for a given patient. Improvements in the understanding of pathophysiology should lead to better classification and evidence-based treatment of this pain syndrome.

The clinical assessment of the patient with PHPS depends upon a history, examination, and investigations focused on identifying the likely pathophysiology and psychosocial and environmental factors that influence the patient's pain experience. These are discussed individually.

The history of the pain complaint, described in numerous questionnaires,[7,9,15,17] should include the preoperative symptoms, preoperative expectations, past history of pain complaints, depression, work status, and earlier levels of functional incapacity. Prior treatment of earlier pain management approaches and its efficacy are noted. Details of the surgical treatment, including surgical approach (open or laparascopic), use of mesh, operative time, operative findings, especially identification of injury to nerves, and postoperative complications should be sought. The evolution of the postoperative pain and descriptors will allow differentiation between neuropathic and nociceptive components. Pain characteristics, including the timing of the onset of pain following operation, intensity, location, exacerbating and relieving triggers, frequency, neurologic symptoms of sensory loss, allodynia, and functional restrictions, are recorded. For example, historical features of neuropathic pain suggestive of nerve injury would include a history of sensory loss or disturbance, triggerability of parasthesia with localized pressure, and improvement of symptoms with a membrane stabilizer or anticonvulsant medication. It is also evident that many patients may have combinations of nociceptive and neuropathic features.

Physical examination of the patient with chronic postsurgical pain allows an opportunity to assess the patient as a whole as well as clarifying potential mechanisms involved in the pathophysiology. General examination should observe pain behavior, dress and appearance, affect and mood, functional capacity, and the presence of other pain disorders. Abdominal examination should exclude the presence of recurrent hernia, localized bone tenderness (e.g., periostitis), and impaired or painful hip or spine movements. The tender or trigger areas should be defined, particularly in relation to the surgical incision. Neurologic examination should concentrate on abnormalities of the sensory examination, including hyperesthesia (increased sensistivity), hypoesthesia (reduced sensation), or allodynia (pain due to a stimulus not usually painful). Tinel sign may indicate the location of nerve injury or neuroma. Quantitative sensory testing (QST), a clinical test to assess sensory and pain thresholds by comparing them against normative data,[18,19] has been used in experimental settings to examine patients with postherniorrhaphy pain.[20] In one study investigators noted large- and small-fiber dysfunction and abnormal temporal summation, suggesting a neuropathic origin to the patient's symptoms. Interestingly, the authors speculated whether these findings might relate to direct nerve injury or delayed injury from mesh-induced inflammation.

Local anesthetic block has been used and recommended by a number of authors to confirm or refute the diagnosis of a nociceptive or neuropathic origin of the patient's pain.[15,17,21–23] For example, Loos et al suggested infiltration of 10-mL local anesthesia into the trigger area if a neuropathic origin was considered. Alternatively, if pubic periostitis was considered, a combination of local anesthetic and steroid would be injected and the response—for example, visual analogue pain score—assessed. Zacest et al,[17] who used nerve block as a diagnostic test prior to nerve exploration, required that, to be considered positive, the nerve block produce both proximal and distal relief of symptoms. Herein lies a potential danger of over-interpreting focal pain relief from local anesthetic infiltration.

Treatment options for persistent postoperative pain include treatments directed toward prevention and those for established pain. Given that established chronic pain is notoriously difficult to treat, any measures that may prevent or minimize the development of chronic postsurgical pain should be identified. Once the diagnosis is established, however, management will depend upon the classification of the patient's pain, putative pain generators, and the presence of pain comorbidities. These interventions and the evidence, where available, are discussed in turn.

Prevention is better than a cure, and this is arguably nowhere more true than in postsurgical pain. Although the current lack of evidence from prospective trials specific for herniorrhaphy limits treatment recommendations, the following options could be considered. The option to operate should be carefully weighed in asymptomatic patients, and the possibility of chronic postoperative pain should be included in the discussion with the patient in the consent process. For example, Page et al[24] noted that 1 year following

hernia surgery 75% of all patients had pain and that previously asymptomatic patients had significant pain, calling into question whether asymptomatic patients should have surgery. In the future, risk indices to predict postoperative pain,[25] in early clinical development at present, may be useful in aiding surgical selection, and in particular allow better informed consent about the risk of this complication.

Psychosocial predictors of chronic pain have been studied in general and for postherniorrhaphy pain. In a recent systematic review[16] depression, psychological vulnerability, stress, and late return to work were shown to have likely associations with postoperative pain. Cognitive factors, including preoperative optimism and perceived control over postoperative pain, were associated with increased postoperative pain following herniorrhaphy in a study by Powell et al[11] suggesting a potential role for intervention in patients with high levels of distress preoperatively. Whether these factors are associations or causal remains to be determined in prospectively designed trials; however, they can be measured and are potentially treatable preoperatively.

The potential benefit of preemptive analgesia has not been specifically studied for postherniorrhaphy pain, although benefit has been reported with the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine and the α2δ ligands gabapentin and pregabalin in other surgeries.[26] The potential benefit of an antineuropathic drug given preemptively may be important in postherniorrhaphy pain, which may have a significant neuropathic component.

Intraoperative factors include anesthetic and surgical techniques and probably contribute most toward the development of pain because this is the critical time to limit the degree of nerve and tissue damage and the central nervous system's response to surgery. Preincision infiltration of local anesthesia in patients undergoing herniorrhaphy is associated with reduced postoperative pain,[27] a known risk factor for chronic pain. In contrast, no maintenance anesthetic technique has been shown to reduce the incidence of chronic pain.

Surgical factors that reduce the likelihood of postoperative pain involve the minimization of tissue and nerve damage. The main surgical factors that have been examined for hernia repair include the surgical approach, the use of mesh, and the identification and treatment of nerves in the surgical field. Laparoscopic repair is associated with less postoperative pain and less sensory loss compared with open repair in most studies, although the hernia recurrence rate is higher and there is a learning curve.[28–30] The role of mesh in postoperative pain has been extensively studied. Mesh per se does not appear to increase the rate of severe pain, although there may be subtle differences depending on whether light or heavy mesh is used.[12,31–33] The presence of mesh does, however, increase the difficulty of further surgery, particularly if nerve identification is necessary.[17] The use of glue rather than suture to affix the mesh has also been explored, with reports of reduced postoperative pain with glue.[34]

The surgical factor that appears to be most significant in the development of postoperative pain is nerve injury. The most convincing data that identification and preservation of all three inguinal region nerves reduce the likelihood of pain come from the studies of Alfieri[8] and Izard.[35] The first multicenter Italian study showed that lack of nerve identification was significantly correlated with chronic pain, that the risk of pain was correlated with the number of nerves not identified, and that division of nerves was clearly correlated with the presence of pain. The rate of postoperative pain was 0% in patients in whom all three nerves were identified and preserved, and overall severe postoperative pain at 1 year was 0.5%. In the second study, a single-center and single-surgeon series, postoperative pain occurred in 1% with a nerve preservation approach that was introduced in the middle of the time period studied. Clearly, nerve identification and preservation, if they can be achieved, are the gold standard of surgical care. What to do if nerves are inadvertently injured during surgery is somewhat more difficult to determine; however, one consensus paper recommended extended neurectomy rather than standard neurectomy pending further evidence.[12]

Postoperative pain, particularly if poorly controlled, has consistently been identified as a risk factor for chronic postoperative pain.[2,4,5] Multimodal analgesia including local wound infiltration has been reported in two comparison studies[36,37] with minimal analgesic requirements required in the bupivicaine group compared with the normal saline infiltration group postherniorrhaphy. Although trials have centered on preemptive treatment with antineuropathic agents after other surgeries,[4,5] acute neuropathic pain can be difficult to identify postoperatively and has not been addressed in trials postherniorrhaphy.

The management of established chronic postherniorrhaphy pain is more difficult than the use of preventive therapies but follows the same principles as discussed before. As a general rule, treatment for nociceptive pain should be directed at the nociceptive focus. In the review by Loos et al[15] the differential diagnosis of nonneuropathic pain postsurgery included recurrent hernia; pubic periostitis; and referred pain from urological, spinal, muscular, or orthopedic pathology. If a nonspecific, nonsurgical cause was identified, pharmacologic treatment was recommended. The involvement of a comprehensive pain clinic may be helpful.

The treatment of neuropathic pain following herniorrhaphy remains a controversial but much

discussed topic in the literature. Options include medication, nonsurgical anesthetic interventions, surgical neurectomy with or without mesh removal, and neuromodulation. Nonsurgical treatment with suitable pharmacologic therapy, depending upon the type of pain, would seem reasonable at first. The pharmacologic principles should not differ from those for other types of neuropathic pain, and evidence-based algorithms for neuropathic pain incorporating numbers needed to treat (NNT) and numbers need to harm (NNH) have been published, although they are limited in postoperative pain groups.[38] In addition, input from a comprehensive pain management unit and treatment of comorbities of pain, including depression, are recommended.

Anesthetic interventions that have been used for postherniorrhaphy pain include local anesthetic blocks,[23] continuous ilioinguinal blockade using a catheter technique,[21] local cryotherapy, and pulsed radiofrequency of lumbar roots.[39] The main limitation of these techniques is a limited duration of response, although the morbidity is low. Peripheral nerve stimulation has also been subject to trial in this pain syndrome in small numbers of selected patients and may be a minimally invasive, albeit expensive, option.[40] Spinal cord stimulation options are discussed in other chapters.

Surgical neurectomy is the major surgical option for the treatment of postherniorrhaphy pain in those patients with neuropathic pain due to nerve injury. Controversy exists, however, over a number of issues, including the correct diagnosis of a painful neuroma, whom to operate on, when to operate, what operation to perform, particularly limited versus triple neurectomy, how to identify the nerves in the postoperative field, and what to do with the nerve stump when cut. A consensus approach has been sought and expert guidelines, based on surgical series, published on this topic.[12] However, the approaches and outcomes of individual authors are worth examining in detail.

A selective surgical approach has been practiced by some authors. Zacest et al[17] selected patients for surgical neurectomy on the basis of concordant history, examination, and nerve block. Surgery was performed in some patients under local anesthesia to assist in localization of the potential neuroma. A neuroma was identified in most cases on the ilioinguinal nerve; the proximal nerve ending was cut, doubly ligated, and buried into muscle. Based on long-term telephone follow-up (mean 34 months), 28% of patients were completely pain free, 39% improved, and 33% were worse or no better. The authors concluded that although short-term results were encouraging, a majority of patients in the long term, about two thirds, had some degree of recurrent pain, which tends historically to be more common with nerve-destructive procedures.

In contrast, triple neurectomy has been advocated by others.[13,41] Amid reported a series of 49 patients who underwent triple neurectomy for neuropathic pain after hernia repair. Selection criteria for surgery were not reported. At surgery 12% had a neuroma, 20% had nerve entrapment, and 68% had perineural fibrosis. At 1 month postoperatively 80% of patients were relieved of pain and no long-term follow-up was performed. In the series of Madura,[41] preoperative evaluation consisted of history, examination utilizing an extension and twist maneuver to reproduce the pain, and nerve block. Surgery was done under local or general anesthesia, involved identification of all nerves followed by proximal section and crushing and ligating of proximal ends, followed by application of alcohol or phenol to prevent neuroma growth. At 1 month 72% had pain relief and a further 10% of patients had improvement of symptoms. The limiting factor in both these often-quoted series is the short follow-up of pain outcome, something that needs to be addressed in future work.

What is the future? Progress in the area of persistent postsurgical pain will require a significant research initative as recommended by one author.[5] Although a number of risk factors have been discussed in this chapter, genetic and pharmacogenetic factors have not been, but will become important. Risk profiling, based on numerous prospectively determined variables, will be developed further. Improvements in neurophysiologic assessment of pain that are valid, standardized, and repeatable and that can followed up long term will evolve. Interventions utilizing these tools will then need to be subjected to trial in carefully designed prospective studies to weigh their merit. The findings of such studies will need to be individualized to high-risk patients.

In summary, PHPS describes a combination of nociceptive and neuropathic pain conditions, archetypical of a number of postsurgical pain syndromes, and remains a serious long-term complication. Improvements in patient outcome will ultimately come only from a better understanding of the pathophysiology and the application of this knowledge to produce a shared terminology toward the development of specific therapies—medical, surgical, and multidisciplinary—that can be tested by trial prospectively to improve patient outcomes. If postsurgical pain can be used successfully as a model for the development of chronic pain, researchers will have a unique opportunity to study and formulate evidence-based interventions to prevent the evolution of acute to chronic pain in humans, which will benefit the patient and society at large. Surgeons will need to make this their new objective in treating patients.

Editor's Comments

Postherniorrhaphy pain syndrome (PHPS) is a pernicious and disabling problem. It has been estimated that some 20 million surgical procedures for inguinal herniorrhaphy are performed worldwide every year. If the incidence of severe postoperative pain ranges from 0.5 to 6%, then approximately 100,000 to 1.2 million new individuals suffer from this pain every year. That this syndrome is so poorly understood underscores the fact that high-quality studies on the issue are largely lacking.

As Dr. Zacest points out, and as with most pain "syndromes," there are probably multiple origins and mechanisms for these pains. He mentions neuropathic pain related to injury to the ilioinguinal or genitofemoral nerve, and he discusses the presumably nociceptive syndrome of "periostitis pubis." Neurosurgeons, and other interventional pain practitioners, are often far down the chain of consultation for these patients, and it is unlikely that we would be able to mount the proper studies to elucidate best practice in this area. However, we can, and should, advocate for better randomized, prospective studies.

As it now stands, neurectomy of the ilioinguinal nerve has limited success, but is a relatively straightforward procedure. Spinal cord stimulation can be tried, but midline or groin stimulation can be difficult. Both of these therapies can be considered in medically intractable cases. I am in full agreement that prevention and a new paradigm for general surgical practice in these herniorrhaphy procedures are vital.

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Section III.F

Posttraumatic Neuropathic Pain

23 Stump, Phantom, and Avulsion Pain

Jessica N. Bentley, Osama N. Kashlan, and Oren Sagher

Stump, phantom, and avulsion pain represent a unique category of posttraumatic pain syndromes, with likely contributions by both central and peripheral mechanisms that are not well understood. Together they are characterized by pain that is often refractory to multiple modes of therapy, and present a difficult challenge to primary and specialty physicians. As is often the case in chronic pain, the missed days of work, limitation of daily activities, and frequent ER visits make the associated costs of these diseases significant.[1] Whereas surgical options do exist, well-established guidelines are unavailable to support one treatment over another. Here, we highlight the key findings in these varied syndromes and present the available medical, alternative, and surgical therapies for each.

Principles

Stump Pain

Stump pain, also called residual limb pain, is defined as pain that occurs in the remaining appendage following amputation, and has a wide range of etiologies. It is variably described as an intermittent or constant aching, burning, throbbing, or stabbing pain, and at times is accompanied by spasms.[2,3] Stump pain does not uniformly affect one area of the limb; some individuals experience it in a specific dermatomal distribution, whereas others perceive a more generalized, ill-defined sensation.[4]

Potential risk factors for developing stump pain are controversial. Age is one risk factor, with younger patients being more likely affected.[4] Patients with traumatic amputations are more likely to report residual limb pain as opposed to vascular amputees. Removal of lower limbs is associated with nearly two times higher incidence of residual limb pain in comparison to upper-limb amputations.[4] Other risk factors include the presence of preamputation pain, prosthesis misfit, and the generalized health status of the patient.[4,5]

Phantom Pain

The terms *phantom pain* and *stump pain* are often used interchangeably in the literature; however, they represent clinically distinct phenomena. Phantom pain is discomfort felt in the area of a missing body part. Ambroise Paré is credited with the first description of phantom limb pain in Western literature in 1552.[6,7] However, the term was not coined until 1871, when Silas Weir Mitchell gave it its common designation.[7] It is important to differentiate phantom limb pain from nonpainful phantom sensations, which are very common after amputation, affecting between 76 to 98% of all amputees.[8,9] These sensations involve the perception of the missing limb's presence and movements, sometimes with the amputated extremity being held in an abnormal position with anatomically impossible postures, or having an abnormal shape.[9–12] These perceptions usually abate over time, with variability among amputees regarding their intensity.[9] Even though phantom sensations are most prevalent after amputation of an extremity, they have been reported after the loss of other body parts, including breast, rectum, penis, testicles, eye, tongue, teeth, and internal organs.[8,11,13] Phantom sensations can even occur in patients with a congenital limb defect.[8,9,14]

Telescoping is another nonpainful sensation that occurs in 30 to 50% of amputees, and in 20% of patients with phantom pain.[8,10,11,15] More commonly experienced in amputated upper limbs, telescoping is the sensation that the extremity is becoming progressively shorter over time, until the patient is left with just the most distal part of the phantom arm or foot seemingly dangling from the stump.[8,15] The etiology of telescoping is unclear, but one theory suggests it is explained by over-representation of the distal extremities in the somatosensory cortex.[8]

Significant association exists between the prevalence of phantom pain and phantom sensations, and some experts consider phantom pain to be a high-intensity form of phantom sensations.[9] Phantom pain has a wide range of descriptions, ranging from episodic painful shocks to constant, excruciating tingling, piercing, stabbing, burning, throbbing, or cramping pain.[6] Patients with phantom limb pain often note that their missing limb ordinarily occupies a certain normal posture, and during painful episodes will be fixed in a painful, contorted position.[8] This pain may be elicited or exacerbated by a range of physical factors, such as changes in weather, pressure on the residual limb, attentional focus, or emotional distress.[11–13]

The prevalence of phantom limb pain is estimated at 50 to 80% of patients with missing limbs.[9,11,13,16] **Table 23.1** summarizes the risk factors associated with this pain, some associated with contrasting views in the literature, and many of which are shared with stump pain.

Avulsion Pain

Avulsion of a nerve refers to complete disconnection of the nerve root, or rootlets, from the spinal cord, proximal to the ganglion. Nerve "rupture" is reserved for disconnections distal to the ganglion. Avulsion is usually the result of high-velocity trauma, typically sustained in motor vehicle accidents. The most frequently affected nerve roots are those of the brachial and lumbosacral plexi.[17] Avulsion leads to pain in up to 90% of patients, occurring within the first 48 hours in 80% of cases. Most patients who will be affected will present by 3 months.[18,19] The severity of the pain has been correlated to the number of avulsed roots.[20]

The pain produced by this lesion is characterized by having both chronic and paroxysmal components.[19] The chronic pain is described as a steady, burning, pins-and-needles, or crushing, twisting sensation. Some patients liken it to boiling water being poured on the hand, or feel as though the extremity were on fire. C5 lesions commonly cause shoulder pain, and C6 injury often results in thumb and index finger involvement. C7–T1 avulsion frequently causes pain from the elbow to hand, but no lesion has been shown to follow a consistent dermatomal pattern.[1,21] Superimposed on this background of constant pain, shooting paroxysms of intense, sharp pain are also common. Although there may be associated precipitating factors, such as changes in weather or emotional states, this pain is often unpredictable, occurring as often as once per week to once every few minutes. As in the other pain states presented here, concurrent illness or infection increases the limb pain. In any case, these syndromes are debilitating in a large majority of patients.[21]

The pathophysiologic bases for stump, phantom, and avulsion pain continue to elude researchers. There are many theories that attempt to explain these phenomena, and it is likely that both peripheral and central changes contribute to the experience of pain from these sources. Possible mechanisms include upregulation or novel expression of voltage-sensitive sodium channels,[6,11] development of nonfunctional connections between axons that cause spontaneous discharges,[11] altered transduction of mechanical and thermal sensations,[6,11] and substance P expression in myelinated A-β fibers, which normally convey nonnociceptive touch and proprioceptive information.[13] Interleukins, tumor necrosis factor–alpha, neurokinins, and tachykinins are up-regulated, also likely playing a role in pain generation.[22–25]

Specifically, cortical reorganization of the primary somatosensory cortex is thought to play a major role in the genesis and maintenance of phantom limb pain.[26,27] Several studies have shown invasion by adja-

Table 23.1 Risk factors for the development of phantom pain

Risk factor	Comment	Level of evidence	References
Age	No correlation	III	4, 9, 76
Phantom sensations	11 times more likely	III	9
Stump pain	1.9 increased RR	III	9
Reason for amputation	No correlation	II, III	76 (II), 4, 9 (III)
Gender	No correlation Incr. prevalence in women	III II	9, 17 76
Preamputation pain	Increases pain No correlation	II III	19 9, 21
Upper versus lower extremity	Increase in UE No correlation	II III	76 4
Time after amputation	Decrease in prevalence No correlation	II III	76 4, 9

cent cortical zones into locations formerly representing the amputated limb in the primary somatosensory and motor cortices.[12,26,28,29] This reorganization, even though enabling the central nervous system (CNS) to conform to the current needs of an organism, bears the risk for maladaptive reorganization, which is thought to be the case in phantom pain.[28]

Practice

As in many chronic pain states, effective treatment of these notoriously difficult pain conditions requires a multidisciplinary approach. In stump pain, the patient's primary provider should frequently assess the stump to monitor for wound breakdown, bony exostoses, or changes in morphology that may require revision of orthoses.[30] The etiology of stump pain is important to discern because various generators of pain are treated differently. One study categorizes stump pain either as arising from neuromas or from other, nonneuromal causes, including infection, biomechanical abnormalities, systemic neuropathies, local scarring or contracture, or underlying disease.[31] In 1993 Davis[32] proposed a classification system dividing stump pain into six types: neurogenic, prosthetic, arthrogenic, referred, sympathetically mediated, and emanating from abnormal stump tissue.[32,33] **Table 23.2** presents the characteristic features of each of these types.

Table 23.2 Davis classification of stump pain

Type	Comment
Neurogenic	– Associated with neuroma – May be caused by haphazardly arranged nerve fibers
Prosthetic	– More common than neurogenic pain – Due to mechanical problems of stump – Frequent evaluation of stump necessary
Arthrogenic	– Emanates from nearby structure (joint, ligament, tendon) – Likely arises from new stresses to these areas postamputation
Sympathetically mediated	– Described as burning pain or allodynia – Likely due to adrenergic sensitivity of neuroma afferents
Abnormal stump tissue	– Due to abnormalities of skin or bone (infection, tumors, bony exostoses)

Special Consideration

Frequent assessment of the stump should be made to rule out reversible causes of pain such as chronic infection, wound breakdown, bony exostoses, or changes in morphology causing orthotic misfit.

In the workup for phantom pain, the differential diagnosis should include radicular pain, angina if in upper extremities, malignant growths, and infections, such as postherpetic neuralgia.[34] Once these diagnoses have been ruled out, pharmacologic treatment is a reasonable next step. Unfortunately, due to the lack of robust, reproducible data, the efficacy of drugs used to treat phantom pain is largely extrapolated from results obtained in a variety of other neuropathic pain syndromes.[22] Even studies specific to phantom pain patients are limited to uncontrolled short-term assessments, and further limited by small sample sizes.[12] Moreover, there is considerable debate regarding these studies' conclusions, inhibiting the ability to propose coherent guidelines.

The diagnosis of avulsion pain is typically made based on the clinical history of pain in the affected arm, although the pattern may not follow the expected distribution. Imaging is considered useful in the workup of nerve avulsion, with CT myelography considered the standard. Typical findings suggesting a preganglionic avulsion include obliteration of the tip of the root sleeve and meningoceles, although not all avulsions will result in meningocele formation, and a meningocele can occasionally be found in association with normal roots.[35]

Special Consideration

CT myelography is considered the imaging of choice to assess pseudomeningocele formation, a finding suggesting nerve root avulsion.

Outcomes

Medical Management

Although no Level I or II evidence is available for a definitive treatment algorithm, most would agree that initial management of posttraumatic pain must be conservative. As is the overarching principle in any medical condition, one must exhaust all conservative therapies before moving on to the more invasive surgical management. By the time patients reach the neurosurgeon, they are likely to have been on multiple different medications and frustrated by a lack of clinical improvement. Unfortunately, not all patients are appropriate candidates for surgical therapy, and a thorough history must be obtained to ensure that operations are offered only to those who are suitable candidates. The history should include a review of all previous therapies, including

all failed and effective medications, injections, physical therapies, alternative therapies, and devices used, along with the degree of pain alleviation. A medication should be deemed a "failure" only if given at the appropriate dose for an adequate duration. It is of paramount importance that reversible causes of pain be ruled out. Specifically, in stump pain, Level IV evidence recommends early surgical treatment for certain conditions such as chronic infection refractory to medical therapy, bony spurs, and defective skin grafts inhibiting adequate prosthetic fitting.[30]

Pharmacologic management often begins with nonnarcotic analgesics and nonsteroidal anti-inflammatory drugs. Failure of these leads most commonly to opioid analgesics, and fortunately, a subset of patients will have adequate relief with these. For those who do not, many other classes have been tried with variable success. In stump pain and phantom limb pain, anti-inflammatory drugs rarely are efficacious alone, and it seems that opioids provide the most reliable control.[7,54] Antidepressants are also routinely used, with studies showing mixed results. As an example, amitriptyline has been shown to provide excellent and durable stump pain control in treatment-naive patients, without adverse events (Level II evidence).[36] However, another trial demonstrated that amitriptyline administered for 6 weeks had no effect on stump pain (Level I evidence).[37] Other possibilities include Doxepin (Level IV),[38] chlorimipramine, and nortriptyline (Level I evidence).[39]

Many medications in the anticonvulsant class have been used for treatment of stump, phantom, and avulsion pain. Carbamazepine, clonazepam, phenytoin, and valproic acid variably relieve postamputation pain in a substantial percentage of patients with lancinating pain, with carbamazepine and clonazepam affording the best results (Level IV evidence).[33,40]

Other classes of medication have been used with varying success. Sodium channel blockers and *N*-methyl-D-aspartate (NMDA) receptor antagonists such as ketamine and memantine have been used. Dextromethorphan is another NMDA antagonist with possible efficacy in phantom limb pain (Level IV evidence).[41] Baclofen and other muscle relaxers, benzodiazepines, and corticosteroids have also been tried, as well as calcitonin, propranolol, and nifedipine.[12,14,22] Capsaicin, clonidine, and antipsychotic medications such as phenothiazines have also been used.[10]

In avulsion pain specifically, a Level A recommendation is made for the first-line use of either gabapentin or pregabalin or the tricyclic antidepressant (TCA) amitriptyline or imipramine. A Level B recommendation supports the use of opiates or lamotrigine as second-line therapy.[42] Gilron et al[43,44] has shown in two double-blinded randomized controlled trials (RCTs) that gabapentin in combination with either morphine or amitriptyline is more efficacious than any one agent alone. **Fig. 23.1** and **Fig. 23.2** summarize proposed treatment algorithms.

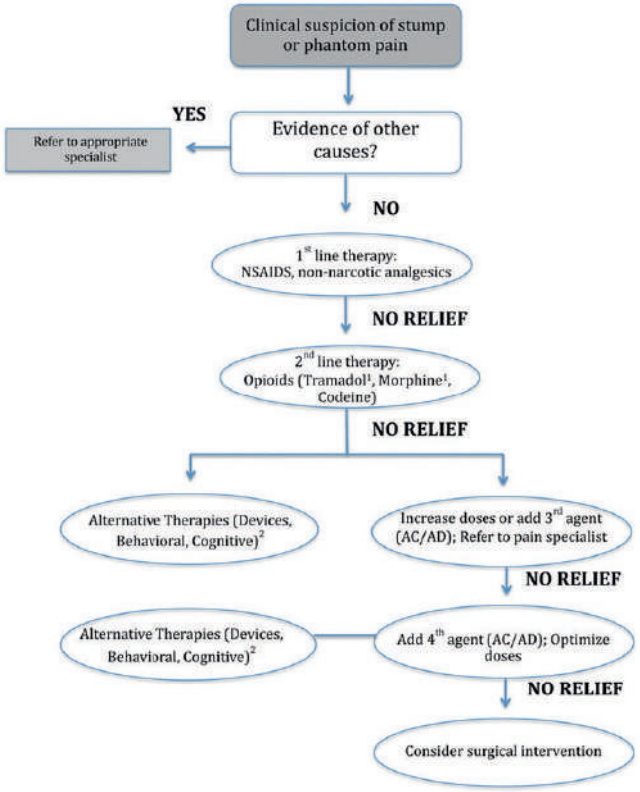

Fig. 23.1 Proposed treatment algorithm for stump and phantom pain. AC, anticonvulsant; AD, antidepressant; TCA, tricyclic antidepressant; SNRI, selective norepinephrine reuptake inhibitor.
[1]Tramadol and morphine shown to be especially efficacious.[36]
[2]Refer to text for options.

Alternative Treatments

Transcutaneous electrical nerve stimulation (TENS) has been used in many varied pain states, and, due to its relatively low rate of adverse effects, is recommended before surgical options are entertained. According to a Cochrane review,[45] the available literature on TENS for stump pain is not adequate to assess its effectiveness, and the same is true in phantom limb pain and avulsion injuries. In avulsion, the success of this modality rests on the ability of the dorsal columns to transmit vibratory sensations, and in patients with complete avulsions in which degeneration of these fibers occurs, TENS is likely to be disappointing.[1]

Other possible alternatives tried in stump pain include shortwave diathermy, vibration therapy, ultrasonics, acupuncture, and ice pack placement (Level IV evidence).[3] Historically, percussing the neuromas for 15 minutes with a piece of wood or a mallet was used to deaden the neuroma.[3] Behavioral therapies that potentially help with stump pain include mirror box therapy, and physical therapy with exercise or massage (Level IV evidence).[31] Steroid injections, nerve blocks,[3,31,46] and botulinum toxin A and B[47] injections

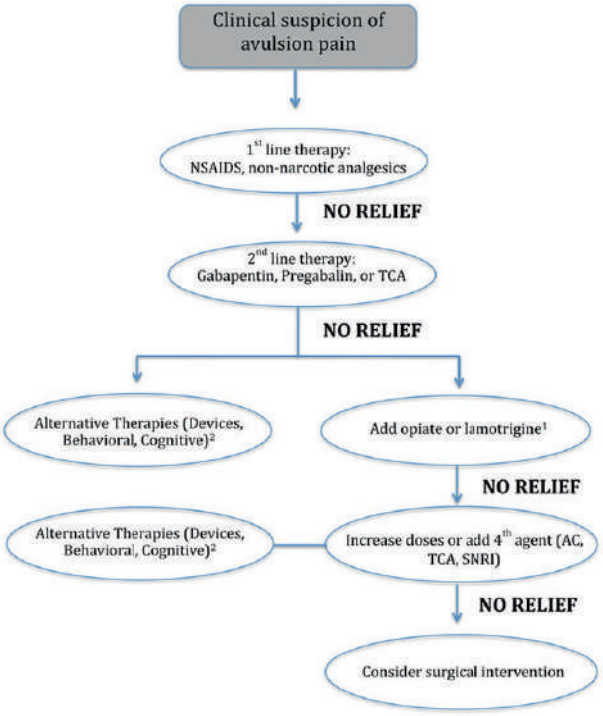

Fig. 23.2 Proposed treatment algorithm for avulsion pain. [1]Gabapentin in combination with either morphine or amitriptyline is more efficacious than any one agent alone.[43,44] [2]Refer to text for options.

have also been tried (Level IV evidence). In phantom pain, brachial plexus blocks, injections of local anesthetics into nerve endings, and phenol injections may be helpful (Level IV evidence).[10,27,48,49] Pulsed radiofrequency ablation may be effective, and, according to one study, the most effective nonmedical treatment of phantom pain was pulsed radiofrequency treatment of the stump neuroma and the area adjacent to the dorsal root ganglion (Level V evidence).[34]

Wearable devices may be beneficial for phantom limb pain, and include myoelectric prostheses and limb covers. Myoelectric prostheses allow the user to control movements such as grasping or flexion by giving muscle commands, which may work by providing afferent feedback that substitutes for the missing limb.[10] The limb cover, also called an electromagnetic stump liner, is proposed to work by shielding high-frequency electromagnetic fields that may cause cellular damage and trigger phantom limb pain.[50] However, a recent RCT provided Level I evidence that noninvasive limb covers do not significantly decrease the intensity or frequency of phantom pain.[50]

Surgical Treatment

The surgical workup for stump pain includes a physical examination aimed at localizing an area of pain or numbness, locating possible pressure points, and determining the path of Tinel sign.[31] Some procedures are aimed at neuroma excision or revision. Other surgical treatments that have been described for treatment of stump pain, albeit with limited success, include interruption of the regional sympathetics, a stellate ganglionectomy in patients with sympathetically mediated pain, or cordotomy (Level V evidence).[3] Procedures with a high failure rate for treatment of stump pain include posterior rhizotomy and dorsal root entry zone (DREZ) lesioning (Level IV evidence).[3,51,52] Dorsal column stimulation seems to hold some promise for medically intractable stump pain (Level IV evidence).[3,33,53] Peripheral nerve stimulation, with percutaneously placed leads, has been shown in one case report to be helpful in alleviation of stump pain when confined to the distribution of one or two nerves (Level IV evidence).[54]

Of interest is the importance of the perioperative period in stump and phantom pain. Epidural blocks or perineural medication infusion during the time of initial amputation could potentially affect the long-term incidence of stump pain, although in two randomized prospective trials, neither showed a benefit in preventing stump pain (Level I evidence).[55,56] The mechanism by which preoperative analgesics and anesthetics work is believed to be prevention of the noxious stimulus from the amputated site from triggering hyperplastic changes and central sensitization.[14,57] Although supported only by limited data, continuous perioperative sciatic nerve block provides effective analgesia before and after lower limb amputation, and may lower the incidence of phantom pain (Level IV evidence).[58]

Because stump pain is considered to be a risk factor for developing phantom pain, it is not surprising that resecting a painful neuroma alleviates phantom limb pain in some patients.[13,59] If phantom limb pain is believed to be sympathetically mediated, a sympathectomy could be an initial surgical treatment option. Other options that have been tried include ganglionectomy, rhizotomy, and DREZ lesioning.[22]

Primary surgical repair of avulsed roots at the time of injury may be enough to decrease pain from this pathology, with Level II evidence supporting primary repair even when far removed from the initial injury (Level III evidence).[60] Berman et al[61,62] provided Level II evidence that nerve transfer, usually with intercostal or spinal accessory nerves, resulted in pain relief in 84% of 19 patients, with an average time to surgery of 28.6 months. Pain levels were noted to improve several months prior to return of motor function, perhaps suggesting pain reduction was secondary to reinnervation by nerve fibers in the muscle.[20,61,62]

If primary repair is not effective or feasible, many techniques have been tried in avulsion pain with varying success. Included in these are the anterolateral cordotomy, mesencephalotomy, spinotha-

lamic tractotomy, medullary tractotomy, and medial thalamotomy, although these have been largely supplanted by DREZ lesioning.[1,63–65] In 1979 Nashold and Ostdahl[66] described the radiofrequency DREZotomy, with the publication of a modification in 1989; the microsurgical DREZotomy, described by Sindou also in the 1970s, utilizes a similar technique.[67,68] In both, the dorsolateral sulcus is identified and incised, bipolarcoagulated or thermocoagulated, destroying the medial aspect of Lissauer's tract with extension through lamina V, as shown in **Fig. 23.3**.[1,65,67–69] At 12 years postprocedure, 59.8% of 55 patients continued to experience good or excellent pain relief (Level IV evidence).[65] In 2011 a prospective study showed that 84.6% experienced excellent or good relief of their paroxysmal pain, and 73.1% continued to have good relief of continuous pain, in an average follow-up of 60 months (Level IV evidence).[1] Cetas et al[70] provided a comprehensive literature review showing that 54 to 86% of patients experienced a 50% or greater decrease in pain, and included case series ranging from 3 to 124 patients, with associated follow-up of 1 month to 18 years.

Special Consideration

For patients experiencing avulsion pain refractory to conservative management, DREZ lesioning is an appropriate initial surgical treatment.

For patients having undergone DREZ and experiencing good relief of paroxysmal pain, but still debilitated by the continuous component, motor cortex stimulation may be beneficial as an adjunct therapy. Ali et al[71] reported a prospective study in which subdural grid electrodes were placed over motor cortex with stimulation applied over a 1- to 2-week period, after which the electrodes were implanted in successful trials. In this small study of 11 patients, 50% had good pain control during the trial, and 42% continued to experience good control at an average follow-up of 47 months. Interestingly, the pain control was limited strictly to the continuous component, with none of the patients reporting paroxysmal pain relief at the last visit (Level III evidence).[72] Mechanistically, this is perhaps a reflection of thalamic and cingulate mediation of the continuous component, which are better modulated by cortical stimulation, whereas the paroxysmal pain may be mediated by spinal structures.[71]

Deep brain stimulation (DBS) has also been tried in both phantom and avulsion pain.[22] A meta-analysis published in 2005[73] showed that DBS was especially effective for nociceptive pain in which the periventricular or periaqueductal gray was targeted. For neuropathic pain, ventroposterolateral or ventroposteromedial thalamic stimulation, or internal capsule stimulation provided some relief.

Spinal cord stimulation has also been used with varying results for treatment of stump pain,

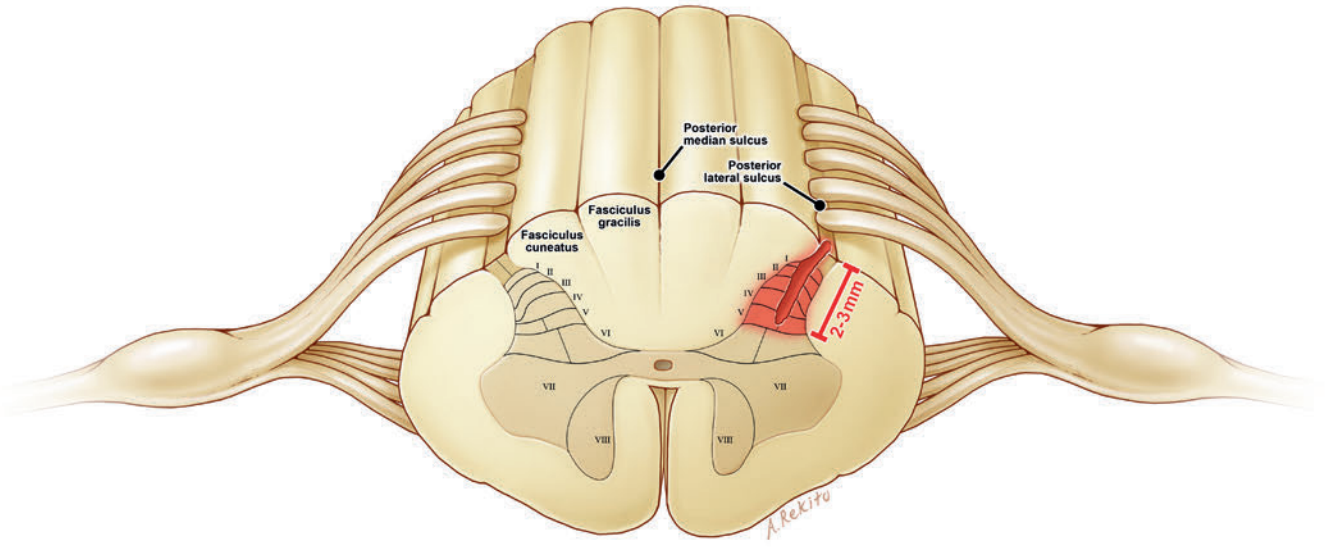

Fig. 23.3 Schematic presentation of the junctional DREZ lesion for pain syndromes. The DREZ lesion extends 2 to 3 mm deep in the dorsal horn (gray and black area along the dorsolateral fissure). Fg, fasciculus gracilis; Fc, fasciculus cuneatus; Lm and Ll, medial and lateral part of Lissauer's tract; I–X, Rexed's laminae; DSCT, dorsal spinocerebellar tract; LCST, lateral corticospinal tract; ACST, anterior corticospinal tract; ASCT, anterior spinocerebellar tract; LST, lateral spinothalamic tract; AST, anterior spinothalamic tract. (Reprinted with permission from Prestor B. Microsurgical junctional DREZ coagulation for treatment of deafferentation pain syndromes. Surg Neurol 2001;56(4):259–265.)

phantom limb pain, and avulsion pain. Its use for phantom limb pain began in 1969 and is believed to act by stimulating large A-fibers, thereby inhibiting ascending pain transmission.[74] In postamputation pain, although some patients have found significant and durable relief, it has not been regarded as a consistently effective treatment, largely due to the degeneration of these fibers following injury. Dorsal column stimulation was found to have only a 39% success rate for postamputation pain at 5 years, decreased from 52.4% at 2 years (Level IV evidence).[53] In avulsion injury, it may be a viable alternative in those who have failed DREZ lesioning. Patient selection likely plays an important role in the efficacy of this modality, and it has been suggested that preoperative SSEP central conduction time may predict success.[75]

Conclusion

Posttraumatic pain syndromes represent a broad spectrum of disorders, and here we present an overview of the key principles of the major types of traumatic pain, pathophysiology, and both medical and surgical treatment options. It is important to assess for reversible causes of pain and to obtain a thorough history including all previously tried therapies. Due to the lack of robust clinical trials supporting surgical interventions, only refractory cases should be addressed surgically. Determining the most efficacious treatment is challenging because the evidence to support one over another is limited; however, for appropriately chosen candidates, multiple surgical

Editor's Comments

Stump, phantom, and root avulsion pain syndromes are all classic examples of neuropathic pain. The fact that these three entities respond so differently to medical and surgical therapies highlights the conclusion that all neuropathic pain is not created equal. In fact, and as Sagher and colleagues point out, even within a specific syndrome, such as one related to nerve root avulsion, a specific surgical modality (e.g., DREZ) might work well for the paroxysmal aspect of the pain, and not at all for the more constant component. This is fairly strong evidence that the mechanisms and generators of the various forms of neuropathic pain are likely different, even within a given etiology. We should speak in terms of neuropathic *pains*. It is therefore not hard to understand why therapy that works well for one complaint may not work at all for a closely related pain.

For example, DREZ is said to work best for conditions in which either a formed painful phantom is present or nerve root avulsion can be implicated in the etiology of the pain. In contrast, DREZ lesions do *not* seem to work well for pain of peripheral nerve origin, such as for painful neuromas, peripheral neuropathy, and nonavulsive direct plexus injury.

If a stump is painful, it is likely due to the presence of neuromas at or near the site of amputation. The pain is often mechanosensitive, and a Tinel sign, radiating paresthesias into the phantom limb, can sometimes be elicited by tapping on the neuroma. This pain can often be relieved by peripheral nerve block aimed at the implicated nerve(s). Despite this, DREZ is not a good option to treat this pain. Although phantom sensations can occur, or be elicted, a formed painful phantom is not typical, and nerve root avulsion is not the mechanism of injury.

If a specific area of mechanosensitivity in a stump can be detected with an associated Tinel sign, resection of an isolated neuroma may be helpful, particularly if the proximal cut end of the nerve can be transposed outside of the area of contact with the patient's prosthetic limb. Unfortunately, most stump pains are much more complicated than this. Pain is often distributed in the stump, and a single nerve block rarely relieves all the pain. If stump pain is diffuse, the practitioner may be tempted to directly denervate the entire stump by multiple neurectomies or dorsal root ganglionectomies. This is not only extremely difficult, but, as is so often the case with neuropathic pains, there is a real chance that further deafferentation will only exacerbate the pain. At minimum, complete denervation of a stump could result in eventual tissue injury and breakdown, since protective sensation would be compromised as well.

We hear considerably more about DREZ lesions in Chapter 56. As the authors point out, the use of the DREZ procedure for phantom pains, and those related to plexus avulsion, has largely supplanted most other central destructive procedures for these pains. Anterolateral cordotomy, mesencephalic tractotomy, and medial thalamotomy are rarely performed for stump, phantom, and nerve root avulsion pain, and as a result high-quality data to support their use are effectively absent.

My own experience with neuromodulation for stump pain, such as spinal cord stimulation (SCS), has not been consistently positive. Although SCS can be relatively easily tested as a palliative therapy for stump pain, only a minority of patients seem to benefit. This book includes discussions of motor cortex stimulation (Chapter 36), and deep brain stimulation (Chapter 37). Readers may judge for themselves whether or not the evidence to support either of these modalities for stump, phantom, or nerve root avulsion pain does, in fact, exist.

therapies exist, including DREZ, spinal cord stimulation, and DBS. Nerve blocks, sympathectomies, and ganglionectomies have also been tried. As is true in many chronic pain states, patients seem to respond differently to different modalities, so that one treatment algorithm may not apply to all. This underscores the need for persistence in arranging trials of multiple therapies to achieve the desired result.

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24 Pain Following Spinal Cord Injury

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Damage to the spinal cord remains among the most devastating traumatic injuries a person can experience. Nearly 15,000 Americans sustain a serious traumatic spinal cord injury (SCI) each year, primarily as a result of motor vehicle accidents. Such injuries pose enormous physical, emotional, and economic burdens on the patient, his or her family, and society in general. Superimposed on the neurologic deficits sustained by SCI victims is pain. Acute pain from SCI is experienced by the vast majority of these patients, and approximately 70% of SCI patients suffer from chronic pain, which can be extremely difficult to effectively treat.[1] This pain can cause an already severely disabling injury to become more intolerable. The purpose of this chapter is to discuss the issue of pain after SCI with special emphasis on chronic pain, a central or neuropathic type of pain. Traumatic SCI is the etiology most commonly referenced because of the greater general experience with chronic, central pain in these patients.

Principles

SCI-related pain is recognized as one of the most challenging pain conditions to treat. Patients who have pain in the subacute period following SCI have a high probability of experiencing chronic pain 3 to 5 years postinjury.[2] There are multiple anatomic sites for pain generation after SCI, including abnormal activity in the spinal cord and brain.

SCI has been shown to be associated with a decrease in overall γ-aminobutyric acid (GABA) tone in the dorsal horn of the spinal cord.[3] GABA-ergic pathways provide critical inhibitory input, which serves to prevent the development of neuropathic pain. In both mice and rat models, pharmacologic blockade of $GABA_A$ or $GABA_B$ receptors has resulted in models of neuropathic pain states.[4–6] A number of mechanisms contribute to the depressed GABA-ergic tone, including a down-regulation of glutamic acid decarboxylase, which is responsible for the conversion of L-glutamate into GABA in both neurons and glia.[3] In addition, a concomitant overexpression of GABA transporters further results in decreased extracellular GABA levels.[7]

Persistent neuronal hyperexcitability of neurons in the dorsal horn of the spinal cord is a consistent finding in SCI.[8] A number of pathophysiologic mechanisms have been identified in the development and maintenance of a hyperexcitable state. In a rat model of SCI, down-regulation of the potassium chloride exporter KCC2 and elevated NKCC1 function at the level of the lesion led to decreased GABA function and altered Cl^- homeostasis. These interactions were found to correlate with neuronal hyperexcitability and a neuropathic pain state.[9] In addition, the loss of inhibitory interneurons containing GABA and glycine is seen in SCI, further altering the normal homeostasis, creating a predisposition for neuropathic pain.[10] Changes in *N*-methyl-D-aspartate (NMDA), non-NMDA, and metabotropic glutamate receptors, among others, have also been demonstrated to lead to an increase in excitatory activity, and hence a decrease in inhibition of pain transmission.[11]

Along with disruptions in spinal cord physiology, SCI is also associated at the cerebral level with alterations in thalamocortical circuitry.[12] In an interesting study by Wrigley et al,[13] 20 patients with SCI were studied, of which half had neuropathic pain and half did not. The somatosensory cortex was mapped using functional magnetic resonance imaging (MRI) during sensory stimulation of the little finger, thumb, and lip. Reorganization of S1 was seen with the portion of S1 representing the little finger moving medially toward the leg representation. There was a significant difference in the amount of reorganization seen between patients with neuropathic pain and those patients without pain. MR spectroscopy is another imaging modality that has been used to understand the metabolic alterations that occur in SCI patients with chronic neuropathic pain.[14] When analyzing the anterior cingular cortex in patients with SCI and high-impact neuropathic pain, MR spectroscopy

demonstrated significantly higher levels of myoinositol, creatine, and choline compared with patients with SCI and low-impact neuropathic pain. The ratio of glutamate-glutamine/myoinositol was found to be useful in discriminating between patients with high-impact, low-impact, and no neuropathic pain. These findings provide a useful quantitative mechanism for assessing neuropathic pain in SCI, and longitudinally following treatment.

Practice

Identification of the type of pain is the most critical aspect in treating SCI-related pain. Historically there have been a number of different classifications for pain experienced by patients with SCI. This has led to limitations in outcomes studies and a non-uniform means for treating patients. The International Spinal Cord Injury Pain (ISCIP) classification is a method for classifying the pain associated with spinal cord injury[15] (**Table 24.1**). The ISCIP classification is divided into three tiers. Tier 1 divides pain according to the type of pain experienced: nociceptive, neuropathic, other, or unknown. Tier 2 divides the pain further into the subtype of pain, and Tier 3 seeks to identify the source of the pain.

Nociceptive pain is broadly divided into musculoskeletal pain and visceral pain. Musculoskeletal pain is common in the acute setting after SCI, and in the chronic setting overuse syndromes can affect the arms and shoulders. Treatment of musculoskeletal pain in the chronic setting is often directed at mobility and lifestyle modifications to remove the aggravating cause. For example, if the pain is precipitated by excessive transfers, additional adaptive equipment or attendant care may be necessary. If medications are needed, nonsteroidal anti-inflammatory drugs are the first-line therapy, and mild analgesics can also be beneficial.

Visceral nociceptive pain may often need diagnostic investigations, including ultrasound or CT scans, and laboratory assessments such as urine analysis, liver function tests, and blood work to assess the cause of the discomfort. If bladder distension or bowel obstruction is a causative agent, modifications to bowel and bladder programs may be necessary to prevent autonomic dysreflexia.

Although these nociceptive conditions can lead to significant morbidity and limitations in function, neuropathic pain in SCI, especially below the level of the injury, remains a daunting challenge in treating patients. For patients with above-level neuropathic pain, investigations should be undertaken to identify correctable pathologies. Carpal tunnel syndrome and cubital tunnel syndrome are both syndromes that can be surgically treated with excellent results. MRI of the spine may also be useful in excluding spinal syringomyelia, which is another cause for above-level or at-level pain SCI patients. In patients with above-level neuropathic pain without clear structural etiology, and that is resistant to medical management, spinal cord stimulation may provide a viable treatment option.

At-level neuropathic pain, variably referred to as transitional or segmental pain, is likely secondary to local damage of nerve roots or the spinal cord. This category of pain presents within two levels of the site of injury. The pain is dermatomal and may be associated with allodynia or hyperesthesia.[16] More easily treated causes of at-level neuropathic pain include spinal instability and nerve root compression. If no direct surgical intervention can be provided to fix a structural problem, and if medical management does not prove effective, this pain may be amenable to DREZotomy or spinal cord stimulation.

Below-level neuropathic pain is the most challenging pain phenomenon to treat in SCI patients. Patients

Table 24.1 ISCIP classification

Broad type (Tier I)	Broad system (Tier 2)	Specific structure/pathology (Tier 3)
Nociceptive	Musculoskeletal	Bone, joint, muscle
		Mechanical instability
		Muscle spasm
		Secondary overuse syndromes
	Visceral	Renal stone, bowel, dysreflexia
Neuropathic	Above-level	Compressive mononeuropathies
		Complex regional pain syndrome
	At-level	Nerve root compression
		Syringomyelia
		Spinal cord trauma
	Below-level	Spinal cord trauma/ischemia

commonly develop diffuse and widespread pain below the level of the SCI. A variety of symptoms are described, including stabbing, aching, and burning pains. Patients may also develop hyperalgesia. Patients with complete or incomplete injuries may develop below-level neuropathic pain. In patients with incomplete SCI, an allodynic component of the pain is more common because there is some preservation of the sensory tracts.

As with all chronic pain, psychological influences on the pain syndrome must be identified and addressed. Many psychosocial issues confound the results from pain assessment in this patient population. Anson et al[17] reported the perception by the patient that the community at large contributed to the patient's overall well-being and reduced the severity of pain. Without such support, chronic pain may lead to dysfunctional coping mechanisms.

Neurocognitive deficits are often present in patients with SCI as a result of their injuries and can primarily lead to suffering, but may also play a significant role in how a patient responds to a chronic pain state.[16] For patients with significant mood dysfunction, the judicious use of anxiolytics and antidepressants may prove beneficial, as can engagement in a program of cognitive-behavioral therapy.

Outcomes

Medical Management

Gabapentinoids, which include both gabapentin and pregabalin, are first-line treatments for neuropathic pain associated with SCI. Their effectiveness in neuropathic pain is linked to their interaction with voltage-gated N-type calcium ion channels, the $\alpha_2\delta$ subunit, and indirectly with the NMDA receptor. By increasing the activity of inhibitory neurons, gabapentinoids can decrease the transmission of nociceptive signals.[18]

A recent randomized trial of patients with SCI and neuropathic pain demonstrated that pregabalin at doses between 150 and 600 mg/day was effective in reducing pain by more than 30%.[19] The main side effects reported were somnolence and dizziness. Studies have also demonstrated gabapentin to be superior to placebo in reducing pain associated with SCI.[20]

There is no strong evidence to support the use of lamotrigine, valproic acid, or levitiracetam in SCI-related pain.

In the acute setting, parenteral administration of the sodium channel blocker lidocaine has been shown to be helpful in the management of SCI neuropathic pain.[21] However, this is not a viable treatment option for chronic neuropathic pain. The oral congener of lidocaine, Mexilitene, did not reduce pain more than placebo in a controlled trial.[22]

The use of intrathecal drug de1ivery is another potential treatment option for patients with neuropathic SCI pain. The use of intrathecal baclofen is a well-established therapy for spasticity and may help with spasm-related pain due to SCI. In a rat model of SCI, intrathecal administration of baclofen was found to have an antinociceptive effect, and the coadministration of the NMDA receptor antagonist ketamine led to a synergistic antinociceptive effect.[23] In addition, in human patients with SCI, the heat pain perception threshold was found to increase significantly after the intrathecal administration of 50 μg of baclofen.[24] This study also found a significant decrease in evoked pain perception, and the amplitude of contact heat-evoked potentials decreased significantly after intrathecal injection.

In a study of 15 patients with SCI and neuropathic pain, neither the administration of intrathecal morphine alone nor clonidine alone demonstrated significant pain relief compared with placebo. However, when the combination of intrathecal morphine and clonidine was administered, 7 of the 15 patients experienced greater than 50% pain relief. This is in comparison to 5 of the 15 who experienced greater than 50% pain relief with saline alone.[25] There are very limited data to support the use of intrathecal morphine, clonidine, or baclofen specifically for the treatment of SCI-related neuropathic pain. Further studies are needed to document efficacy for this indication.[26]

Surgical Management

Dorsal root entry zone (DREZ) lesions have been used to treat SCI-induced central pain with variable results. In 1986 Friedman and Nashold[27] reported their large series of 56 patients with SCI who had developed neuropathic pain caudal to the level of injury. Laminectomies were performed to expose two levels cephalad to the level of injury and at least one level caudal to the level of injury. Multiple lesions were made bilaterally using a radiofrequency technique. Follow-up ranged from 6 months to 6 years. A good result was found in 28 patients (50%), which was defined as being completely free of pain or having pain that did not interfere with daily activities or require analgesics. A fair outcome was found in 5 patients (8.9%), defined as still requiring nonnarcotic analgesics, and 23 patients (41%) had a poor outcome. The authors found that patients with pain at the site of injury and extending caudally for a variable number of dermatomes had a better pain outcome than those patients who had more diffuse pain or pain predominantly in the sacral dermatomes.

Besides DREZ, a number of other ablative techniques have been applied to the pain of spinal cord injury. Although cordotomy, cordectomy, myelotomy, thalamotomy, cingulotomy and other ablative techniques have been used with varying degrees of success, their use today for the treatment of chronic neuropathic pain secondary to SCI is very limited.

More recently, in 2002, Falci et al[28] reported their experiences with DREZ lesioning for post-SCI neuropathic pain performed using electrophysiologic guidance. The surgical procedure consisted of a multilevel decompression cranial to the injury site and at least one level caudal to the injury. Monopolar electrodes were then used to search for spontaneous electrical hyperactivity from the DREZ. Segments in which electrical hyperactivity were recorded were then ablated using a radiofrequency technique. In some patients, transcutaneous C-fiber stimulation was used to induce DREZ electrical hyperactivity. Lesioning was performed to abolish this hyperactivity. The follow-up period ranged from 1 to 7 years, and during this time 84% of patients experienced 100% pain relief, and 88% of patients experienced between 50 and 100% pain relief.

Motor cortex stimulation (MCS) has been applied to a variety of neuropathic pain states, including SCI. A recent review evaluated the outcome of seven patients with SCI who had been reported in the literature as having been treated with MCS.[29] Of the seven patients reported, four were found to have a long-term successful pain outcome. Surgical technique varied, with some patients receiving bilateral epidural stimulation and some unilateral. Although the data are very limited, a trial of MCS may be a reasonable consideration in patients who have failed all other modalities and continue to have debilitating pain.

Deep brain stimulation (DBS) for pain associated with SCI, however, has not been shown to have long-term efficacy for a significant number of patients. A review of published DBS for pain series revealed 19 patients with SCI who have been treated with DBS.[29] Targets varied and included the VPL nucleus of the thalamus, periventricular gray, and periaqueductal gray matter. Of the 19 patients implanted, only 3 had long-term effective pain relief. Additional, more structured studies will be needed before DBS can be accepted as an effective intervention for SCI pain.

Because current methods of spinal cord stimulation (SCS) are dependent on paresthesia generation, this therapy is likely not an effective intervention for patients with complete SCI. However, for patients with neuropathic pain associated with incomplete SCI, and for patients with pain at the level of the injury, SCS may be a reasonable intervention for a trial. There are very limited data to provide quantitative data on outcomes and patient selection.

Conclusion

The existence of chronic central pain after SCI has been recognized for roughly 100 years. In that time, great strides have been made in the management of acute spinal cord trauma, largely born out of wartime experiences. Over the past 50 years, considerable interest has been directed toward chronic problems associated with this condition, particularly chronic pain. The most common cause of SCI is direct trauma, and the most disabling long-term feature, beyond functional limitations, is neuropathic pain. Such pain can occur with injury to any level, whether complete or incomplete. Nearly two thirds of SCI patients suffer from this malady, which can persist for decades beyond the original accident.

Assessment of this type of pain is difficult because of the many superimposed factors, including the overall functional disability and psychosocial elements. Treatment involves the careful, tailored application of a variety of medicines that attack different mechanisms of the pain experience, from inflammation to depression.

Although historically both cordotomy and myelotomy have been used with varying success in the treat-

Editor's Comments

Drs. Simpson and Viswanathan describe spinal cord injury pain (SCIP) as a complex entity, and it is. As **Table 24.1** illustrates, it is also not one thing. It is a complex array of conditions, so it should not be thought of as pain, but rather as *pains*. For this reason, accurate diagnosis is crucial. Pain that is projected into the insensate regions caudal to a spinal cord injury is, for the most part, surgically intractable, but nociceptive pains are not. Neuropathic pains at the segmental level of injury can be addressed with DREZ lesions, as described in Chapter 56.

Single-center case series that claim high rates of success for subsegmental neuropathic SCIP must be viewed with considerable skepticism until their results can be replicated by other investigators. My own view is that a surgical approach to these patients using DREZ, myelotomy, or even cordectomy has little chance of success. Deep brain stimulation (DBS) and motor cortex stimulation (MCS) for SCIP remain unproven modalities. As the authors point out, intrathecal pharmacotherapy has also not proven effective.

It is conceivable that as our ability to reconstruct the injured spinal cord advances, we may see a parallel improvement in our ability to manage central pain related to SCIP. Until then, we must be vigilant in our efforts to identify pain diagnoses that are medically and surgically treatable.

ment of SCI-related neuropathic pain, DREZotomy is the destruction lesion with the best data to support its use for at-level neuropathic pain. Our understanding of neuromodulation, with both MCS and advanced SCS, may provide additional treatment options in refractory cases. The use of intrathecal drug delivery devices to administer medications directly to the central nervous system will remain a valuable adjunct, especially as our ability to target the biochemical aberrations present in SCI improves. A tremendous number of investigations over the past 10 years have helped illuminate the mechanisms that contribute to SCI neuropathic pain; over the next decade we hope to see this understanding translated into improved therapeutic interventions.

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Section III.G

Other Neuropathic Pains

25 Complex Regional Pain Syndrome: Type I and Type II

Michael Stanton-Hicks

Complex regional pain syndrome (CRPS) embodies a number of painful states occurring as a consequence of some injury that are characterized by symptoms and signs that exceed the expected severity and duration of the particular inciting event. These pain syndromes include the clinical characteristics of spontaneous pain, allodynia, hyperalgesia or hypoalgesia, edema, autonomic abnormalities, motor disturbances, and trophic signs. The original terminology for CRPS Type I was reflex sympathetic dystrophy,[1] and CRPS Type II was formerly causalgia.[2] CRPS I most commonly occurs after minor injuries such as sprains or limb fractures. It may also develop spontaneously without any known preceding event. CRPS II is always associated with a known peripheral nerve injury.

One of the first descriptions of CRPS was that by Ambrois Paré,[3] who described a condition that resembles the clinical features of this syndrome. Charcot[4] and Sudeck[5] each clearly defined the clinical features attributed to the condition now known as CRPS. The term *reflex sympathetic dystrophy* (RSD) was favored among many other synonyms in the English-speaking world, whereas *Morbus Sudeck* has found common use in the Germanic countries.

Introduction of the CRPS terminology has enabled diagnostic criteria to be developed, with the premise accepted that these criteria needed to be validated in terms of their sensitivity and specificity to enhance recognition and improve the subsequent treatment of patients with these syndromes. Furthermore, having standardized diagnostic criteria will improve communication, foster research, and ultimately help to identify a mechanistic basis for clinical management.

Epidemiology

A population study in Olmstead County, Minnesota, undertaken by Sandroni et al[6] calculated an incidence of CRPS I of 5.5 per 100,000 person-years. In contrast, de Mos et al[7] determined an incidence of 26.2 per 100,000 years. They, however, used a Dutch scale, in addition to the International Association for the Study of Pain (IASP) criteria, which no doubt increased the sensitivity, thereby including more patients. It is interesting to compare these results with the earlier study by Veldman et al,[8] which clearly demonstrated that CRPS I occurs with greater frequency than CRPS II; the incidence of CRPS II varied between 2 and 14% with a mean of 4%. Although current estimates suggest an incidence of CRPS I of 1 to 2% following fractures, some isolated reports and the well-controlled data,[9] who found an incidence of 8% after Colles fracture. Whereas CRPS tends to occur in one extremity, in about 8% of cases it may be expressed in another extremity or, less often, another body region. The extension of CRPS to another extremity is more frequently ipsilateral. Furthermore, careful sensory testing will demonstrate altered sensory perception thresholds for touch, pinprick, heat, and cold on the ipsilateral side.[10]

Clinical Characteristics

Although the most common precipitating trigger for CRPS is injury to a distal extremity (65%), including sprain, contusions, and fractures, the traumatic incident may be distant from the clinical manifestation, such as myocardial infarction or cerebral vascular accident (CVA).[11] Patients will frequently describe burning symptoms or spontaneous, severe pain that may be of a sharp or tingling nature in the distal part of the extremity. They may also describe a deep, gnawing, aching type of pain. The pain, as stated above, is quite disproportionate in intensity to that expected from the inciting event. Sensory disturbances occur early and are most pronounced distal in the affected extremity but typically do not conform to dermatomes or nerve territories. Pain can be elicited by temperature change, particularly cold, and weather

changes such as an advancing low-pressure system: air movement over the skin and pressure at joints exacerbates the symptoms. Patients will frequently volunteer that they cannot hold objects and tend to "drop things" when the upper extremity is involved.

Autonomic Abnormalities

Autonomic abnormalities are manifested by fluctuating edema, alterations in sweating, and skin blood flow changes. Early CRPS is usually associated with warm skin[11,12]; in advanced cases, the skin temperature changes to cold and sweating abnormalities may reflect hyperhydrosis or hypohydrosis, particularly in those patients with CRPS I.

Trophic Changes

Early clinical features are altered hair and nail growth, which may slow or become faster. If the condition is refractory to treatment, integumentary changes involve the skin, which may lose its texture, become glossy, or form vesicles or ulcers. Deep tissue changes include fibrosis, osteoporosis, ankylosis, and tendon shortening. Microcirculatory changes similar to those seen in diabetes mellitus, when allowed to continue, are responsible for the above deep and superficial tissue responses.

Motor Abnormalities

Muscles in the affected limb are typically weak in patients with CRPS and although only recently acknowledged for inclusion in the IASP diagnostic criteria, motor disturbances were described by Deuschl et al,[13] Bhatia et al,[14] Blumbert and Jänig,[15] and Schwartzman and Kerrigan.[16] More than 50% of patients with CRPS will show some motor abnormalities that include weakness, trauma, impaired fine movements, and dystonia, in about 10% of cases. Most cases show no abnormality on the electromyogram (EMG). The recent functional magnetic resonance imaging (fMRI) studies by Maihöfner et al[17] and Schilder et al,[18] in which they observed cortical activations induced by finger tapping with the CRPS extremity, demonstrated significant reorganization of central motor circuits in the ipsilateral motor cortex. These results serve to underscore the adaptive changes within the central nervous system (CNS), manifested as motor incoordination/dysfunction, that contribute to the signs and symptoms of CRPS.[19] The "neglect-like" syndrome described by Galer et al[20] compounds the disuse features in the affected extremity. Of note are similar cortical responses found on the contralateral side.[19,21]

Sympathetic Nervous System

Many human studies have demonstrated that cutaneous nociceptors develop catecholamine sensitivity after nerve resection. An increase in the a-adrenoceptor population on primary afferent nociceptors has been demonstrated.[22] Torebjörk et al[23] showed that subcutaneous injection of norepinephrine into the symptomatic area of a CRPS patient will evoke spontaneous pain and dynamic mechanical hyperalgesia/allodynia that has previously been relieved by sympathetic block. Ali et al[24] repeated this observation after nerve injury. A similar study by Baron and Jänig[25] was undertaken in CRPS I patients (without a nerve lesion) in which maximum sympathetic activity was induced by whole-body cooling (**Fig. 25.1**). Spontaneous pain and mechanical hyperalgesia, both dynamic and punctate, were elicited in those patients who had previously been classified as having SMP, demonstrated by a positive sympathetic block. The foregoing observations reflect an interaction between sympathetic and primary efferent neurons located most likely in the skin. Teasell and Arnold,[26] and Drummond et al[27] have demonstrated this relationship in animal models of neuropathic pain.

Fig. 25.2 shows the hypothetical relationship between the coupling of sympathetic adrenergic neurons and primary afferent neurons in peripheral tissues that is responsible for SMP. These authors point out that a mechanism for such coupling has not yet been discovered in humans. A similar argument cannot be made for patients with CRPS II, who may have a different mechanism.[28,29] That SMP is not present in all patients, even early in the course of the disease, suggests that multiple factors are involved. The interaction between nitric oxide (NO) (vasodilator) and endothelin (vasoconstrictor) may confound any attempt to normalize sympathetic reflexes and may lead to even more intense vasoconstriction, setting in motion tissue hypoxia, acidosis, and production of free radicals.[30]

In a blinded, controlled prospective study using quantitative measurements, Price et al[31] demonstrated that pain relief can be realized after sympathetic block. The pain relief outlasted the conduction block of sympathetic neurons in some cases, sometimes permanently. The authors suggested that activity in sympathetic neurons maintains a positive feedback via the primary afferent neuron. Although this has not been demonstrated in animals, it is likely that activity in sympathetic neurons can maintain a central state of hyperexcitability of neurons in the spinal dorsal horn as a result of excitation of afferent neurons initiated by an external noxious event. During a temporary sympathetic block, the central hyperexcitability is turned off and may in some cases not be switched on again until the block wears off.

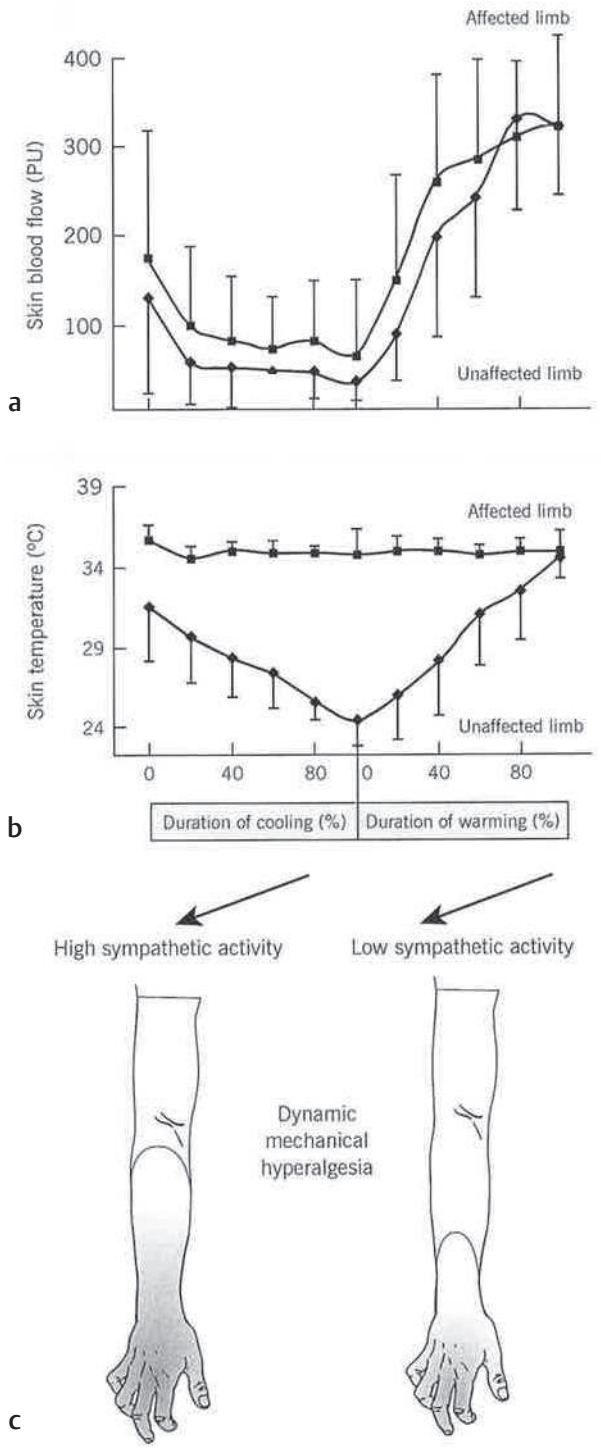

Fig. 25.1 A recording of the skin blood flow and skin temperature during whole-body cooling and warming. (**a, b, c**) High sympathetic vasoconstrictor activity during cooling induces a drop in skin blood flow on the affected and unaffected extremity (laser Doppler flowmetry). The forearm temperature on the affected side was clamped at 35°C—a marked increase in the area of dynamic mechanical allodynia. (Reprinted with permission from Cousins and Bridenbaugh's Neural Blockade in Clinical Anesthesia and Pain Medicine, 4th ed., Lippincott Williams & Wilkins; modified from Baron,[25] with permission.)

Baron et al[32] proposed that sympathetic innervation of deep somatic structures may be more important to this hypothetical positive feedback circuit. As stated above, some patients respond dramatically to sympatholytic procedures with both a reduction in the inflammatory process and edema, as well as amelioration of pain. Animal studies support these clinical observations. In the normal state, cytokines act through β_2-adrenoreceptors on immune cells, which in turn inhibit the production and the release of proinflammatory cytokines. However, under the pathology of chronic inflammation, these immune cells down-regulate the expression of β_2-adrenoreceptors and in turn up-regulate the expression of α_1-adrenoreceptors.[33] The reader should be reminded by the observations and prophetic statement of Livingstone:

> Evidently the part played by the sympathetic nerves is an important one, otherwise an interruption of their activities would not succeed in curing the causalgic state as often as it does. I do not know how the sympathetics contribute to the causalgic states, nor how it happens that a periarterial sympathectomy, a ganglionectomy or even a temporary interruption of their functions by novacaine injection, may act to terminate the syndrome. . . . The sympathetic nerves may contribute to the development of peripheral tissue changes, which may lead to additional afferent impulses adding themselves to those of the trigger point to assail the spinal cord centers. This is not equivalent to saying that the sympathetic dysfunction causes the causalgic syndrome. It would be more correct to say that the trigger point caused it, but I believe that neither statement is wholly true. Instead, the trigger point starts the central disturbance, the central process in its turn involves the sympathetic nerves and the somatic motor nerves, and the peripheral effects brought about by the motor activity of each, initiate afferent impulses which add themselves to those from the trigger point to sustain and augment the central activity. The sympathetic nerve activity is but one part of this vicious cycle. The peripheral reason why I hesitate to accept either the trigger point or the sympathetic nerves as the sole cause of the causalgic state, is that either one of them may be eliminated without establishing a cure. I believe that the syndrome is cured only when the underlying pathologic activity as a whole, loses its momentum. Sometimes the syndrome may be cured by the removal of the trigger point without doing anything to the sympathetic

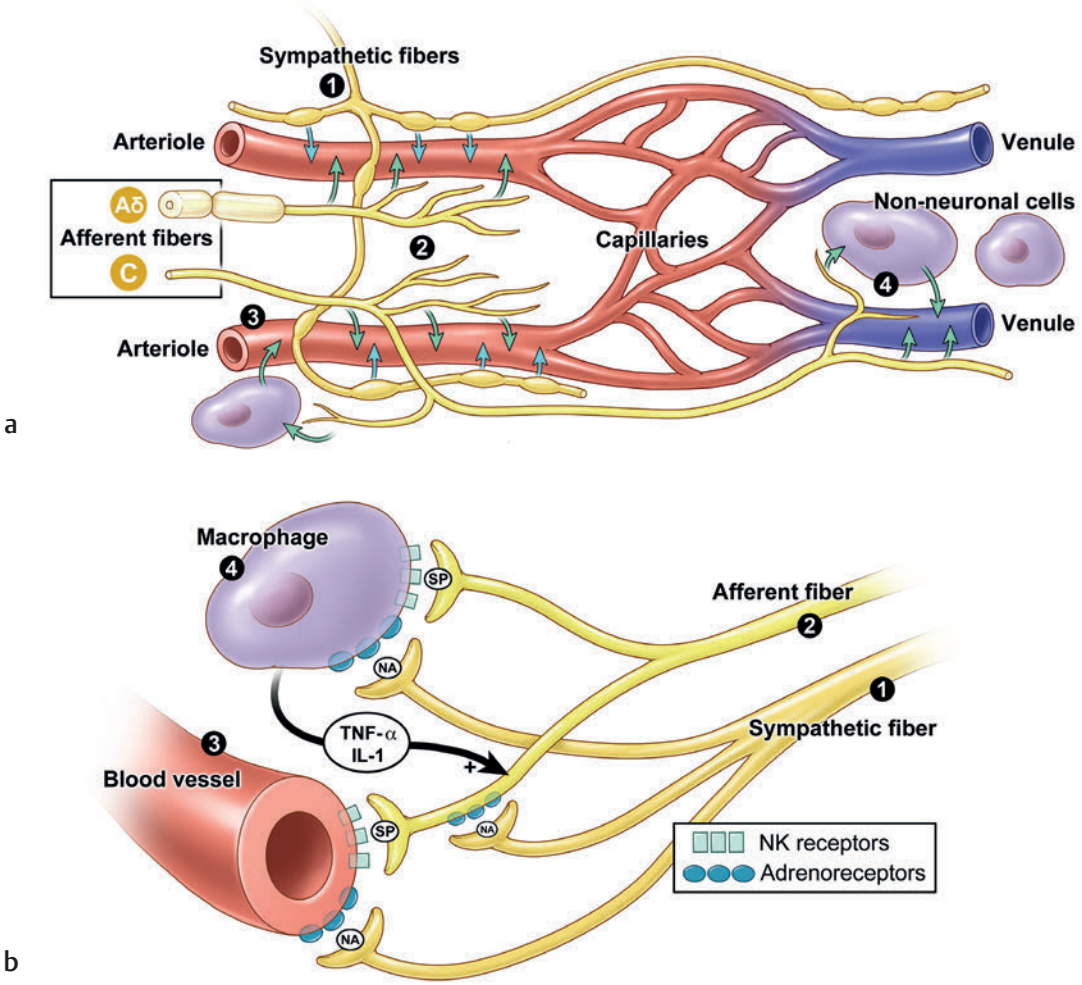

Fig. 25.2 (**a**) The micro environment of primary afferents that affect myelinated A and unmyelinated C fibers 2. The vascular bed consists of arterioles innervated by sympathetic and afferent fibers, capillaries (not innervated and not influenced by nerve fibers), and venules, which have an indirect relationship with nerve fibers. Postganglionic noradrenergic fibers 1 supply blood vessels (BVs). 3 BVs release noradrenaline (NA) and many other vasoactive substances, causing v1asoconstriction. Activation of primary afferents (A and C fibers 2) causes vasodilation in precapillary arterioles with extravasation of plasma in postcapillary venules (C fibers only) by expression of substance P (SP) and other vasoactive compounds, including calcitonin gene-related peptide (CGRP). Nonneuronal cells (mast cells) and macrophages 4 also have vasoactive affects. External influences such as environmental temperature change or metabolic state of the tissue will also affect the foregoing changes. (**b**) Sympathetic noradrenergic fibers 1, peptidergic afferents 2, blood vessels 3, and macrophages 4 react with each other. Afferent nerve fibers that are sensitized activate macrophages (MPs), very likely by SP release. Immune cells release cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1), both of which activate afferent fibers. Both SP and CGRP released from afferent nerve fibers react with neurokinen-1 (NK-1) receptors in blood vessels, causing arterial vasodilation, plasma extravasation, and neurogenic inflammation. Sympathetic fibers interact with this system at three level: (1) via adrenoreceptors, mainly α-, on blood vessels—vasoconstriction; (2) via adrenoreceptors, mainly β-, on macrophages—release of cytokines; and (3) via adrenoreceptors, mainly α-, on afferents—fiber sensitization. (Modified from Jänig W, Baron R. Complex regional pain syndrome: mystery explained? Lancet Neurol 2003;2(11):687–697.)

nerves; sometimes the elimination of the sympathetic influence results in a cure even though the trigger point is left untreated; but in both of these events the cure, that is, the complete disappearance of the signs and symptoms, does not occur until the central process has subsided. . . . This interpretation has afforded me a new approach to other clinical problems than the ones under discussion, and a new attitude towards treatment. I am beginning to feel that the central disturbance is the essential factor in many diseases, and that there should be a better means of eliminating pain than by chordotomy or posterior root section or other anatomic interruptions of nerve continuity.

Autoimmune Aspects

Cytokines and Cell-Mediated Information

During the last decade a number of investigators have shown the increase of inflammatory cytokines, interleukin (IL)-6 and tumor necrosis factor alpha (TNF)-α, as well as tryptase, in the affected extremity in comparison with the uninvolved extremity.[34,35] Also shown in CRPS patients with hyperalgesia were high levels of TNF-α.[36,37] Skin biopsies of CRPS patients demonstrate a significant increase in Langerhans cells, which can release proinflammatory cytokines and other immune factors. IL-6, TNF-α, and tryptase are observed in artificial blisters in the affected extremity. The reduction in hair growth may also relate to the increase in proinflammatory cytokines, TNF-α, and IL-1. Increases of IL-1β and IL-6 are found in the cerebrospinal fluid (CSF). Osteoporosis, a feature of long-standing CRPS, is consistent with an inflammatory process. IL-1 and IL-6 cause osteoclast proliferation and suppress osteoblast formation. Although this pathology is first seen at periarticular regions, it will eventually involve the bone shaft. Several studies have reported on the frequency of polymorphisms in a number of tissues at the cellular level including cytokines, adrenergic receptors, and muscarinic receptors. Autoimmune antibodies from CRPS patients have been identified in rat sympathetic neurons by Blaes et al[38] and Kohr et al.[39] Campylobactor immunoreactivity has been seen in patients with early CRPS.[40]

Diagnosis

In 1995 the diagnostic criteria for CRPS were standardized.[41,42] Although these criteria were sufficiently sensitive to include most cases of actual CRPS, their specificity was very low. As a result, both internal and external validation studies were undertaken to improve specificity and therefore the usefulness of the diagnostic criteria.[43,44] To adequately discriminate between CRPS and non-CRPS patients, a decision rule required two of four sign categories and four of four symptom categories to be positive. This rule yielded a sensitivity of 0.70 while retaining a specificity of 0.94. This had the effect of increasing the probability of ensuring an accurate diagnosis of CRPS to 80% and a non-CRPS diagnosis to 90%. This decision rule is deemed to support what have been termed research criteria. A similar but less stringent decision rule for clinical diagnosis requires two of four sign categories and three of four symptom categories, which yields a sensitivity of 0.85 and a specificity of 0.69. This rule still identifies a high probability of capturing most patients with CRPS while selecting out those patients who do not have the syndrome—a workable compromise. These conditions now form the basis of what is recognized as the Budapest criteria, named after the pivotal meeting site where they were developed (**Fig. 25.3**; also see the accompanying box).

Revised Diagnostic Criteria for Complex Regional Pain Syndrome

Categories

1. Positive sensory abnormalities
   - Spontaneous pain
   - Mechanical hyperalgesia
   - Thermal hyperalgesia
   - Deep somatic hyperalgesia
2. Vascular abnormalities
   - Vasodilation
   - Vasoconstriction
   - Skin temperature asymmetries
   - Skin color changes
3. Edema, sweating abnormalities
   - Swelling
   - Hyperhidrosis
   - Hypohidrosis
4. Motor, trophic changes
   - Motor weakness
   - Tremor
   - Dystonia
   - Coordination deficits
   - Nail, hair changes
   - Skin atrophy
   - Joint stiffness
   - Soft tissue

Interpretation

Clinical use: ≥ 1 symptom(s) of ≥ 3 categories each *and* ≥ 1 sign(s) of ≥ categories each: Sensitivity 0.85, Specificity 0.60.

Research use: ≥ 1 symptom(s) of = 4 categories each *and* ≥ 1 sign(s) of ≥ 2 categories each: Sensitivity 0.70, Specificity 0.96.

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Diagnostic Tests

There are no specific tests for CRPS. Several tests can monitor the pathologic changes that occur throughout the course of CRPS. Some of these have a specificity that is adequate to help with a differential diagnosis, although most of the diagnostic procedures

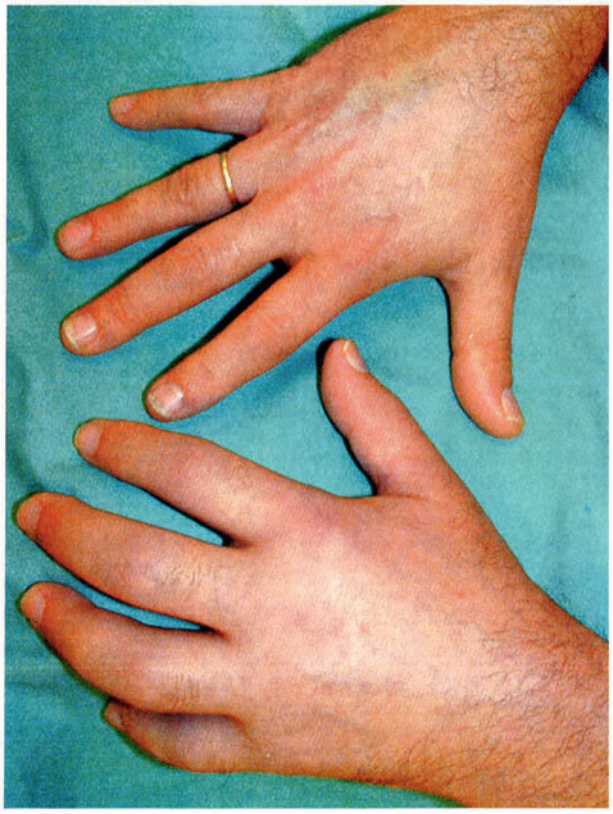

Fig. 25.3 Patient with CRPS Type I–upper extremity following wrist sprain. (Reprinted with permission from Cousins and Bridenbaugh's Neural Blockade in Clinical Anesthesia and Pain Medicine, 4th ed., Lippincott Williams & Wilkins.)

have a fairly wide false-positive/false-negative spread. Also, the time of onset (not of diagnosis of CRPS) until the time when the test is executed will have a significant bearing on the reliability and interpretation of the results.

Table 25.1 lists tests that have been used during the past 20 years.

Management of CRPS

An interdisciplinary approach using both traditional and empirical measures that emphasize functional restoration is recommended to obtain the best possible patient outcome. The results of two international conferences[45,46] support functional restoration by physiotherapeutic rehabilitation measures. Unfortunately, statistical evidence in support of functional restoration is surprisingly low.

The use of mirror box treatment for CRPS Type I can reduce pain and improve function.[47] Studies using recognition training of hand laterality and imaging movements can materially improve function in CRPS patients. Added to this is graded motor imagery (GMI), which, used with or without mirror box therapy, has been found useful in improving function in conjunction with regular physical therapy.[48] GMI extended over a 6-week period with 2 weeks spent in each phase of treatment has shown significant promise. The final and third stage involves viewing the reflected image of the unaffected extremity moving through different planes of movement. These treatments are based on what has been learned from cortical imaging of patients with these syndromes. There is evidence that although the theoretical basis for these programs is still evolving, its utility in improving patient function is already becoming established.[49]

Psychological Approaches

Behavioral management should be available in a multidisciplinary setting for all patients with CRPS.[50] In some of these patients, because of the psychological impact of their condition, it may be appropriate to use cognitive-behavorial therapy (CBT) early in

Table 25.1 Supplementary tests for CRPS

Test	Sensitivity	Specificity	Helpful?
1. Plain X-rays (late in disease)	73	57	No
2. Phase bone scan (early disease)	97	86	Possibly
3. Temperature side differences	76	93	Yes, during sympathetic stimulation
4. Quantitative sensory testing	High	Low	Impractical except research
5. Laser Doppler scintigraphy	High	High	Practical if equipment available
6. Quantitative sudomotor axon reflex test (QSART)	High	Fair	Requires special laboratory
7. Magnetic resonance imaging (MRI) (Koch et al 1991)	91	17	Impractical
Future tests under investigation			
fMRI cortical reorganization	–	–	–
Magnetoencephalography	–	–	–

their treatment strategy. One such study in children by Lee et al demonstrated the long-lasting reduction of all symptoms when such therapy was included with physical therapy and graded exposure therapy. The authors also suggest that three principles should be followed: (1) education about the nature of the disease is important for all patients and their families; (2) patients whose condition has lasted more than 2 months should be evaluated psychologically and treated with CBT; and (3) any psychiatric comorbidities or major ongoing life stress issues should be addressed concurrently.[51]

Pharmacologic Approaches

Medications that are used for the management of CRPS should be administered primarily on a symptomatic basis or for the treatment of known pathologic manifestations. Pain medications are mainly a means to facilitate the restoration of function in concert with other physical and or behavioral measures included in rehabilitation.[52]

Very few clinical trials of any drugs specifically employed for treating CRPS have been undertaken, and most of these have been small, uncontrolled studies with inconclusive endpoints.[53] No medications have been specifically approved by the FDA for CRPS. Because of the many similarities between CRPS and painful diabetic neuropathy, a lot of the medications other than specific analgesics such as anticonvulsants are also used for CRPS. Levels of evidence will be used as an indicator in favor of or against the use of a particular drug, as follows: Level 1 evidence describes the results of a systematic review or meta-analysis; Level 2 evidence reflects one or more well-designed randomized clinical trials (RCTs); Level 3 evidence combines nonrandomized trials or open-label trials; and Level 4 evidence consists of case reports or expert opinion.

In early CRPS, a trial of all corticosteroids should be tried first. This is generally administered in a tapering dose over 1 to 10 days (Level 3 evidence).[53] These drugs have several effects. By decreasing inflammation, reducing ectopic electrical activity and stabilizing excitable membranes, the drugs frequently bring an immediate improvement of symptoms and well-being.[54] The use of opioids has not been studied. There are several RCTs supporting the use of opioids in postherpetic neuralgia (PHN) and painful diabetic neuropathy (PDN) (Level 2 evidence). In blinded crossover studies, agents such as Tramadol, morphine, oxycodone, and levorphenol clearly provide more analgesia than placebo, but no long-term studies of any opioids in the treatment of neuropathic pain have been undertaken. Most experts suggest that opioids, if used, should only be incorporated in an interdisciplinary comprehensive pain treatment program.

Calcitonin is used primarily to inhibit bone resorption by osteoclast activity, thereby lowering serum calcium levels (Level 1 evidence, including a systematic meta-analysis[55] and a number of placebo-controlled RCTs in which calcitonin was given intranasally[56,57]). Biphosphonates have been demonstrated to have some analgesic effect in early CRPS (Level 2 evidence based on two small RTCs[58]). A more recent meta-analysis, however, does not support the use of these agents in managing CRPS.[59,60] A number of investigators have studied free radical scavengers (antioxidants). The premise is based on a belief that CRPS may be caused or is potentiated by oxygen-derived free radical damage to deep and superficial tissues. Free radicals may initiate the inflammatory activity and may be a cause of the microangiopathy that is such a hallmark of CRPS. Dimethylsulfoxide (DMSO) in a fatty cream was used in a small study of 32 patients[61] (Level 1 evidence).

Prophylactic vitamin C has been shown to reduce or prevent the incidence of CRPS in Colles fracture of the wrist,[62] another example of antioxidant properties.

A number of α-adrenergic antagonists have been used in several studies.[63] Phenoxybenzamine (Dibenzylene) was found efficacious in 40 patients.[64] If tolerated, a-adrenoceptor blockers can significantly reduce a-receptor coupling–induced pain and the accompanying vasoconstriction in “cold” CRPS.

Antiepileptics

By decreasing CNS hyperexcitability, antiepileptics may have a specific inhibitory effect on hyperalgesia. Gabapentin was initially studied by Mellick and Mellick,[65] who determined its efficacy in CRPS patients. An analogue of gabapentin, pregabalin, can be equally if not more effective than gabapentin in some patients (Level 1 support for treatment of PDN).

Although there are no supportive studies for the use of Topiramate, this antiepileptic has been found useful in the high percentage of patients who retain water and gain weight while taking gabapentin or pregabalin. Topiramate seems to have a similar beneficial effect on hyperalgesia, allodynia, and the burning dysesthesia associated with this syndrome.

Antidepressants

Tricyclic antidepressants (TCAs) have been studied extensively for the treatment of neuropathic pain. There is abundant evidence that the serotonin reuptake blocking agents and norepinephrine reuptake inhibitors are also efficacious[66,67] and selective norepinephrine blockers such as desipramine do

reduce pain in PDN and PHN (Levels 1 and 2 support for treatment of PHN). No studies of either TCAs or selective serotonin reuptake inhibitors (SSRIs) have been undertaken for the treatment of CRPS. Nevertheless, these medications can be very useful in the treatment of the reactive depression so prevalent in CRPS patients. Some of the tricyclics, such as amitriptyline, nortriptyline, and doxepin, have sedative properties, which are useful to initiate sleep, the lack of which impacts a high percentage of patients. Antidepressants also can potentiate the effects of anticonvulsants.

GABA

The presynaptic inhibitory transmitter γ-aminobutyric acid (GABA) is probably impaired in CRPS patients who manifest a movement disorder. Benzodiazepines or baclofen ($GABA_A$ and $GABA_B$) agonists can be used in the treatment of patients with CRPS.[16,67] Whereas the benzodiazepines can be taken orally, baclofen is efficacious only if delivered by the intrathecal route.

A number of CRPS patients with dystonia who were entered into a small placebo-controlled study involving intrathecal baclofen infusion had a good response.[68]

NMDA Receptor Blockers

N-methyl-D-aspartate (NMDA) is involved in the up-regulation and changes in gene transcription that occur in CRPS II, and probably also CRPS I. The agents most frequently studied have been ketamine, dextromethorphan, and memantine. Dextromethorphan has been found efficacious in diabetic neuropathy, but no such studies have been published concerning CRPS. In a small number of patients, memantine was found to reduce the excitatory symptoms of CRPS. Also noted in one patient who underwent pre- and post-fMRI evaluation was the return of the translocated somatomotor image to its normal cortical site.[69,70]

Ketamine

Ketamine has now been studied in several prospective studies. These have employed either subanesthetic or anesthetic intravenous administration. The study by Correll et al[71] observed that 50% of patients who were treated responded with 50% pain relief. In another study, by Kiefer et al,[72] a continuous solution of ketamine under anesthesia for a week resulted in 50% of the patients having almost complete pain relief for 12 months (Level 3 evidence).

Clonidine

Clonidine has been used via oral, transdermal, epidural, and intrathecal routes for the treatment of CRPS. A small case series of transdermal clonidine did demonstrate some benefit in a small area of painful skin[73] (Level 3 evidence). The hyperalgesic area presumably responded to presynaptic catecholamine inhibition in superficial tissues.

Topical Local Anesthetics

There is good Level 2 evidence that topical local anesthetics are effective in the treatment of CRPS. These are available in gels, creams, viscous solutions, and patches. Most frequently prescribed is the lidocaine patch, which consists of 4% lidocaine in a transdermal preparation that can be used to treat allodynic/hyperalgesic skin. With continued use, there is generally an overall reduction in the degree of skin sensitivity. Another advantage of the patch is that it can be sized to fit the affected surface area.[74] One study by Meier et al[75] demonstrated good efficacy in CRPS patients with superficial neuropathic pain. Another, smaller study by Devers and Galer[76] obtained similar results.

Interventional Therapy

Sympathetic Blockade

Most local anesthetic blocks of the sympathetic nervous system are usually accomplished at the level of the stellate ganglion and the thoracic or lumbar sympathetic ganglia. Under pathologic circumstances, sympathetic blocks generally exceed their expected pharmacologic duration. The continuing use of sympathetic blocks after an initial effective response with relief of symptoms is not recommended due to a lack of scientific support. The terms *sympathetically maintained pain* (SMP) and *sympathetically independent pain* (SIP)[77,78] describe a spectrum of pain relief to no pain relief after a technically successful sympathetic block (**Fig 25.4**).

A technically successful sympathetic block can be determined by temperature measurement: a greater than 95% sympatholysis can be expected if the temperature at a toe or finger pulp exceeds 34°C.[79–81] In addition to the anatomic block of the sympathetic nervous system, intravenous sympatholysis is also described. Intravenous regional anesthesia (IVRA) has been widely used. Many agents, including guanethidine, phentolamine, bretylium, reserpine, and clonidine, have been used either alone or in combination with other agents.[82] There is little evidence to support the continuing use of IVRA as an alternative to neural block of the sympathetic chain.

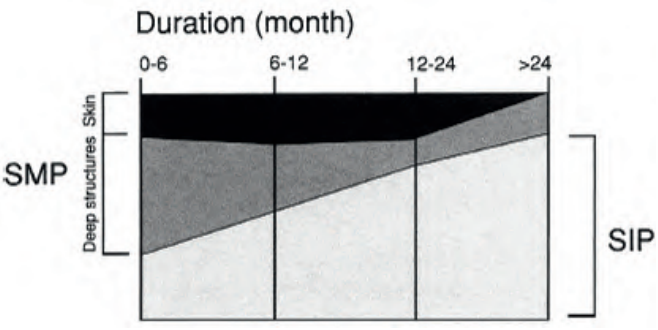

Fig. 25.4 Components of sympathetic maintained pain (SMP). Two components of pain depend on cutaneous sympathetic innervation (skin SMP) and on deep somatic sympathetic innervation (deep SMP) in contrast with that pain component not maintained by sympathetic activity (sympathetically independent pain [SIP]). The interaction between SMP and SIP occurs during the course of the syndrome. (Reprinted with permission from Cousins and Bridenbaugh's Neural Blockade in Clinical Anesthesia and Pain Medicine, 4th ed., Lippincott Williams & Wilkins; modified from Schattschneider J, Binder A, Siebrecht D, et al. Complex regional pain syndromes: The influence of cutaneous and deep somatic sympathetic innervation on pain. Clin J Pain 2006;22:240–244, with permission.)

In early or acute CRPS, more than 80% of patients report a positive effect (i.e., relief of pain). Although the continued (chronic) use of sympathetic blocks, as already stated, is controversial,[30,83–85] they are a means of determining the difference between SMP and SIP, and may be useful to address allodynia that is preventing physical therapy and in some cases can completely reverse the patient's symptoms.

In summary, while there is Level 2 evidence to support the use of a sympathetic block—whether in the cervical, thoracic, or lumbar region—as a determinent of SMP/SIP, its use as a treatment for chronic CRPS is questionable. However, many treatment algorithms do incorporate the use of a sympathetic block in early management, and it may be repeated in those cases where significant resolution of symptoms is achieved. In all of the studies in which IVRS was used, no significant benefit was realized.

Neurostimulation

North et al provided the parameters to use when selecting spinal cord stimulation (SCS) for treatment of neuropathic pain.[86] The Neuromodulation Therapy Access Coalition (NTAC) has identified three RCTs six long-term follow-up studies, and six short-term follow-up studies, together with numerous other studies supporting the use of SCS for CRPS. In one study, 36 patients were randomized to receive SCS plus physical therapy and the remaining 18 physical therapy alone.[87] The stimulator was implanted only in those cases where the trial was successful. Although there was no clinical improvement in functional status, all patients had an improvement in quality of life (QOL). When the same patients were followed 2 years later, the SCS-plus-physical-therapy group had significantly improved pain relief and QOL in comparison with the group using physical therapy alone.[88] Patients were then seen 5 years after their initial implant, and 20 were significantly better than those who underwent physical therapy alone. All patients volunteered that they would undergo the same treatment again.[89]

A third RCT compared the analgesic effects of sustained-release morphine (90 mg per day) and carbamazepine (600 mg per day).[90] All patients with CRPS had been pretreated with SCS. In 43 of these patients, the SCS was turned off before they received their pain medication or placebo. Patients were asked to turn their SCS on should their pain become intolerable. Interestingly, in comparison with placebo, carbamazepine significantly delayed the return of pain but morphine did not. The same authors then undertook a prospective clinical study that also demonstrated a favorable response to SCS in patients with severe disability.[91] Of these patients, 35 then returned to SCS. Almost all the published studies of SCS treatment of CRPS are retrospective. A Health Technology Assessment publication in 2009 determined that the cost-effectiveness and clinical efficacy of SCS for treating neuropathic pain, including CRPS I and ischemic conditions, was superior to conservative medical management (CMM), and also offers a considerable cost savings over CMM.[92] The basis for the survey were 6,000 citations from 13 electronic databases and 11 RCTs, 3 that addressed only neuropathic pain. A methodological study in Europe found that SCS improved pain and dysfunction in patients who previously failed CMM (Level 2 evidence).[93]

Prager and Chang[94] reported on the temporary use of SCS to provide analgesia in patients who were undergoing motor disability treatments and exercise therapy. Of note is that five of the eight patients after 4 weeks were sufficiently improved for their leads to be removed. Stanton-Hicks[95] reported on the use of SCS as an adjunct to facilitate a multidisciplinary exercise therapy program in children who were completely refractory to any occupational or physical therapy because of severe allodynia. In an important case report of seven children who had failed all conservative measures, two of whom were extremely disabled with severe contractures, SCS was implemented to facilitate their physiotherapeutic/behavioral rehabilitation. All children went into remission; four SCS systems were explanted and all had good outcomes at 2 years,[96] Peripheral nerve stimulation (PNS) for more local applications is a useful alternative—or adjunct—to SCS in some cases. The study by

Hassenbusch et al is a good example. They used PNS to good effect in 32 patients with severe disability from CRPS Type I and Type II.[97] There is overwhelming evidence in the current literature that builds on anecdotal reports during the past 30 years that SCS in appropriately selected patients is effective as an adjunct to other therapeutic interventions—in particular, rehabilitation—to achieve a remission of this condition. This treatment may be used effectively in combination with CBT and may be particularly advantageous either before or after such intervention. There is good evidence that improvement in mental, social, and physical function facilitated by SCS enhances the success of CBT.[98]

Intrathecal Therapy

The intrathecal route for analgesic or adjunctive medication in CRPS can be considered in those cases that have not only proven to be refractory to CMM, but also failed to respond to neurostimulation techniques.[99] This route of administration is limited to the use of adjuncts such as local anesthetics (bupivacaine, ropivacaine) and clonidine, and to the analgesics, morphine, hydromorphone, fentanyl, sufentanyl, and baclofen.[100] Intrathecal opioid administration is associated with tolerance, for which reason it is limited to the relatively few patients who have not demonstrated any tolerance or tendency for dose escalation during their management with oral opioid analgesics. Intrathecal baclofen is a very successful medication for the treatment of dystonia, severe tremors, and other motor manifestations of CRPS and should be used in any patient who has developed these symptoms. Van Hilten et al[101] found baclofen to be very useful in the treatment of dystonia and other severe movement disorders in CRPS patients.

Intrathecal ziconotide, the *n*–calcium channel blocking agent, can be highly effective in a small subset of CRPS patients who have been refractory to all other measures.[102] About 33 to 35% of all patients in trials will respond with greater than 50% reduction in their symptoms without concurrent side effects that would otherwise preclude the use of this drug. Trials are best achieved through the use of an indwelling, small-gauge (24 G) intrathecal catheter over a period of 3 to 5 days. As an alternative, intrathecal bolus injections of ziconotide given sequentially in increasing doses may be used as a screening test for efficacy.[103] If this test is successful, the continued titration of the drug in an implanted system may require 2 or 3 months to reach its maximum effect. This author prefers the use of an indwelling, intrathecal catheter and titration over several days to determine an analgesic dose. Because ziconotide is cleared at almost the same rate as the CSF turnover, any side effects are short-lived and the drug is not associated with withdrawal problems.

Hyperbaric Oxygen

In cases where skin lesions due to ischemia such as ulceration, blisters, or skin maceration remain refractory to topical measures and wound care, hyperbaric oxygen therapy (HBO) can be very useful. HBO may also arrest the progression of the movement disorder when there is little response to rehabilitation. The RCT study by Kiralp et al demonstrated improvement in flexion, and decreases in edema and pain level (Level 2 evidence).[104]

Rehabilitation: Physical Measures

A combination of psychological, physical, and neuromuscular modalities are required if the impact of CRPS on these biological characteristics is to be reversed. The aim of treatment/management is the restoration of function. This is usually achieved by a multidisciplinary team in which one physician—frequently an anesthesiologist, physiatrist, neurosurgeon, or orthopedist—takes the responsibility of coordinating all members of the team. Indispensable to such a team are vocational counselors, psychologists, social workers, orthopedic technicians, physical/occupational therapists, recreational therapists, and other nursing or prosthetic technicians as required. Obviously, the emphasis on rehabilitation will depend on the pathology. In the case of CRPS I the impairment may be minimal, with mere loss of motor strength. In other cases, particularly with cold exposure, there may be severe and rapid functional loss that can lead to chronic disability or, in extreme cases, loss of tissue integrity, ulceration, and infection such that even amputation may become a consideration. In the treatment algorithm (**Fig. 25.5**), based on a consensus group,[45,46] the basic principle of functional restoration guidelines is a timed approach that allows various interventions to be added in support of the physical methods used to reestablish function. In cases where allodynia/hyperalgesia prevents progress in the algorithm, it may be necessary to perform a sympathetic block to help the patient endure more aggressive therapy. Should kinesiophobia prevail, CBT can be used to reassure the patient that movement is appropriate and will do no harm. Few publications support particular physical therapeutic maneuvers that can favorably influence progression in the physiotherapeutic algorithm[105] level II evidence,[106] and[107] level III evidence.

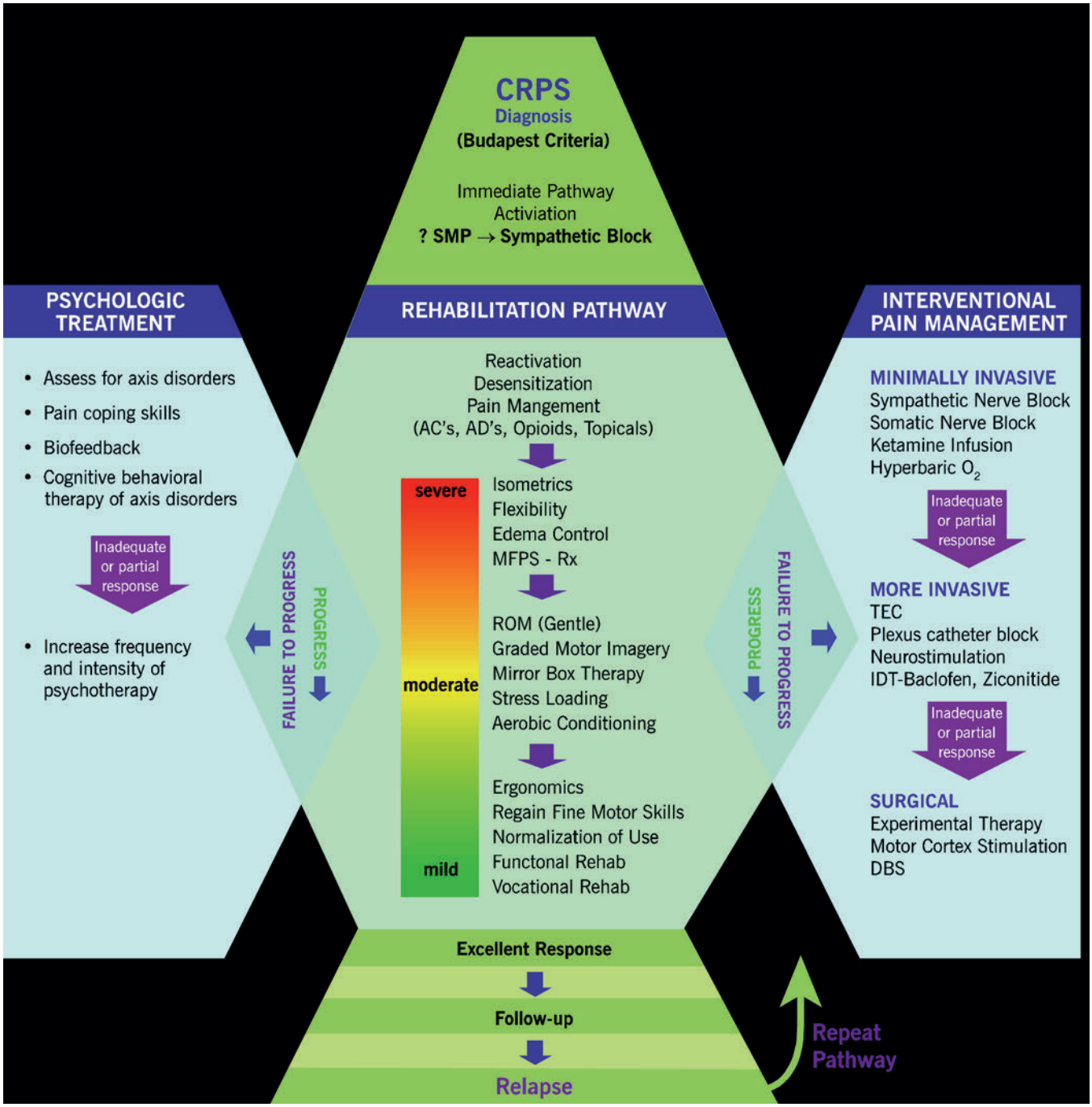

Fig. 25.5 The multidisciplinary care continuum for chronic regional pain syndrome. All components, including rehabilitation and interventional measures, are simultaneously applied in a time-contingent fashion. A severity gauge is added to temper the degree with which functional modalities are applied throughout the course of functional restoration. (The algorithm has been modified and redrawn from M. Stanton-Hicks et al.[46])

Although the foregoing studies have all contributed to traditional physiotherapeutic approaches, there is almost no statistical evidence to support interdisciplinary measures for the management of CRPS. Nevertheless Flor et al[108] and Guzmán et al[109] have shown the benefit of interdisciplinary approaches for chronic neuropathic pain and chronic low back pain (Level 1 evidence).

That physical function must be a "core domain" is the conclusion of the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT), when recording the efficacy of

treatment.[110] Functional restoration is the basis of treatment strategy. The frequency of motor dysfunction,[111] disuse, muscle spasm, and intense pain require urgent attention from an interdisciplinary team. These aspects of the syndrome underscore the use of modalities such as those already referred to, mirror box therapy and graded motor imagery, to address the altered central processing and so-called neglect syndrome.[50,112] Undoubtedly, the nociceptive traffic arising in the periphery after trauma rapidly sets the stage for central sensitization in CRPS in susceptible individuals. Based on this pathophysiology, with an increase in large-fiber modulation,[113] many, if not all, of the core modalities used in the physiotherapeutic algorithm are designed to reduce symptoms and improve function. These actions, which have been demonstrated in animal work,[114] can be directly translated to human responses.

It is within the foregoing framework that one can achieve a successful remission or at least a significant reduction of symptoms in most patients.

Conclusion

Although there is little evidence to support the use of surgical sympathectomy, surgical intervention may be necessary to correct the consequences of trophic change that does not respond to functional restoration (e.g., correction of an equinus foot/ankle deformity by tendon lengthening). These measures can be safely performed under continuous local anesthetic techniques. Also, amputation may be necessary when the life of the patient is threatened by infection or gangrene.

Editor's Comments

Complex regional pain syndrome (CRPS) remains a controversial diagnosis. Dr. Stanton-Hicks is a world expert in this diagnosis, and he presents a scholarly discussion of the evidence for the diagnosis, how it might be established, and how to treat it, both medically and surgically.

CRPS Type I is probably the most contentious form of the condition because, as he points out, it can be the consequence of trivial injury "characterized by symptoms and signs that exceed the expected severity and duration of the particular inciting events." In other words, the protean consequences of the syndrome seem disproportionate to the cause. Having seen my share of patients with CRPS I, I can attest that they are truly suffering.

There are no definitive tests for CRPS, and the diagnostic criteria that have been applied have been vague and inclusive. The "Budapest criteria" are hailed as an improvement over the IASP criteria, but still have a sensitivity of only 0.85 (false-negative rate 15%) and a specificity of 0.69 (false-positive rate 39%). My intention is not to criticize the author, but to highlight the challenge of CRPS diagnosis.

There seems to be little argument that a rehabilitative approach to CRPS is the most widely acknowledged "best practice" in this disorder. It is almost certainly the final common pathway for effective therapeutic strategies for CRPS. The impetus for this stems from the recognition that many, if not most, of the signs and symptoms of CRPS are those of profound disuse.

This book is a compendium of surgical strategies for pain. Is there a role for surgery in CRPS? I would submit that the answer to this question remains elusive. Sympathectomy has been used in the past for CRPS, particularly for CRPS II, the "causalgia" (literally "burning pain") of Silas Weir Mitchell. Possibly for reasons of fashion, or possibly due to the availability of neuromodulation, sympathectomy for causalgia has effectively disappeared.[115] It is of some interest that the data to refute sympathectomy for CRPS are as poor as the data to support it.[116]

The more common surgical approach to CRPS is spinal cord stimulation (SCS). As Dr. Stanton-Hicks points out, "There is overwhelming evidence in the current literature that builds on the anecdotal reports during the past 30 years that SCS in appropriately selected patients is effective as an adjunct to other therapeutic interventions—in particular, rehabilitation—to achieve a remission of this condition."

As described in this chapter, there is only one randomized prospective trial of SCS for CRPS, and that was a comparison of SCS combined with physical therapy (PT) versus PT alone. This trial was originally described by Kemler et al[87] and revisited in a later publication.[89] In this study SCS plus PT was superior to PT alone for pain outcomes at 6-month and 2-year follow-up. At 5 years posttreatment, SCS plus PT produced results *similar to those following PT for pain relief and all other measured variables*. In a subgroup analysis, the results with regard to global perceived effect ($p = 0.02$) and pain relief ($p = 0.06$) in 20 patients with an implant exceeded those in 13 patients who received PT. The authors concluded that despite the diminishing effectiveness of SCS over time, 95% of patients with an implant would repeat the treatment for the same result.

Despite these disappointing results, neurosurgeons continue to advocate for the use of SCS for CRPS, and for further studies on the SCS procedure to treat CRPS.[117]

I am indebted to Dr. Stanton-Hicks for providing the basis for continued discussion on the surgical treatment of CRPS.

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26 Postherpetic Neuralgia: Are There Neurosurgical Options?

C. Peter N. Watson

> "There are no prospective randomized controlled studies of surgical procedures for the management of the pain of postherpetic neuralgia. It is exceedingly unlikely that any will be undertaken. Indeed only a very small fraction of patients who have undergone surgery have been reported in the literature, hence the true utility of any operation remains largely unknown." (John D. Loeser, 2001[1])

> "The efficient physician is he who amuses his patients while nature effects a cure." (*The Philosophical Dictionary*, Voltaire [1694–1778])

When the previous version of this chapter appeared in the last edition of this book (2002), the situation mirrored the first quotation and we stated that "surgical procedures do not appear to be useful for most patients with postherpetic neuralgia (PHN)" and that "the results of the few surgical procedures reported have been discouraging, and for most patients are not an option because of age, risk, and limited benefits." This chapter updates this neurosurgical literature. A search was conducted for articles in English using "postherpetic neuralgia and surgery" in PubMed, Medline, Ovid, and Embase. Regional anesthesia approaches are not discussed. The literature continues to consist of case reports and case series (Class III level of evidence). References chosen are the most recent reports or reviews or original seminal articles. As of the time of this review, the first quotation stands. However, although the case report occupies a lower tier, a carefully chosen medically intractable case or cases, without a control, with well-documented outcome measures, and with good long-term follow-up can be compelling. A nonsurgical extreme case in point is that it only takes one case of uniformly fatal meningococcal meningitis that is cured by penicillin to indicate efficacy.

The discussion regarding surgery focuses on pitfalls in the assessment of a published case report, selecting intractable patients for surgery, and the specific difficulty in surgically treating PHN based on the neuropathologic changes that are associated with this condition. With this in mind, these operations and the results are organized anatomically in a logical progression from the periphery to the cerebral cortex.

The second quotation highlights one important aspect of the interpretation of uncontrolled studies in PHN: many patients with persistent pain after herpes zoster (HZ)— some early and quickly (especially in younger age groups), some more slowly—improve by virtue of the natural history of the disease.[2] For example, that any uncontrolled study of nerve blocks for acute zoster in patients of all ages will have excellent results based on the natural history of resolution, which occurs as " nature effects a cure." Targeting patients over 60 years of age with PHN of 6 months duration or more selects out a mostly intractable group, unlikely to improve with time. The natural history and other factors plague and confound the interpretation of many uncontrolled studies in many of these case reports of neurosurgical procedures.

The surgeon reader may find all of this somewhat discouraging, but this chapter, in addition, updates the discussion with important advances in medical management made since the last edition. Because of the increased incidence of HZ and PHN with age, for one approaching even the fourth decade there may be a personal interest in this common and disabling disease with its intractable pain and threat to vision. These medical advances involve (1) the treatment of PHN (the best medical treatment still leaves some virtually medically untreatable patients for whom surgical treatment needs to be considered almost as a "hail Mary" option, but keeping in mind the principle of "primum non nocere"), (2) the aggressive, timely treatment of acute HZ, and (3) excitement about successful prevention with the zoster vaccine.

Principles

Definition

PHN is neuropathic (nerve injury) pain (NP) and is the most common and feared complication of herpes zoster (HZ). PHN may be defined arbitrarily in different ways and for different purposes. It is pain that persists after rash healing. This may be tallied at 1 month or, for clinical trials, at 3 or 6 months; many patients improve in the weeks following the initial eruption, and therefore a definition including a longer duration means greater pain stability, especially for randomized controlled trials (RCTs) of crossover design.

Epidemiology and Natural History

HZ, the precursor of PHN, results from reactivation of the varicella-zoster virus (VZV) in the spinal and cranial sensory ganglia, often as long as a half century following a primary infection with varicella (chickenpox), usually during childhood. HZ is characterized by a unilateral, cutaneous, painful, vesicular rash typically in a single dermatome (usually midthoracic or trigeminal ophthalmic division), often resulting in PHN, which is the most common neurological disease.[3]

In Canada (population nearly 35,000,000) there are 130,000 cases of HZ and 17,000 of PHN per year.[4] The incidence is directly related to age (**Fig. 26.1**)[2] and due to decreased cell-mediated immunity. Overall about 10% of HZ cases will have pain at 1 month after the rash, and this may rise to as much as 50% at age 60.[4] The increase in HZ and PHN that begins at ages 50 to 60 provides the rationale for vaccination commencing at this time. Because PHN may fail to resolve within a year in a proportion of patients, the prevalence of PHN is cumulative and higher. Because the population is aging, and with the increase in immune-suppressed groups afflicted with cancer and HIV, HZ and PHN will likely increase. Also, older age groups no longer have the boost in immunity that may occur due to exposure to children with chickenpox from prevention due to varicella vaccination in childhood.

Pathology and Putative Pain Mechanisms

There is considerable information about the pathology and possible pathogenesis of PHN. It has been known for more than 100 years that pathologically there is an acute hemorrhagic inflammation in one dorsal root ganglion at the stage of the eruption of HZ.[5] Inflammation then extends proximally and distally. Proximally it extends into the spinal cord.[5,6] After months, there is significant scarring and loss of neurons in the dorsal root ganglion, and atrophy and scarring of the dorsal horn of the spinal cord (**Figs. 26.2** and **26.3**).[5,6] Some of these long-standing cases have persistent inflammatory cells.[6] An assessment of the nerve fiber population in the peripheral nerve after the eruption of HZ shows a predominance of small (some probably pain-conducting) fibers and a deficiency in large myelinated (pain-inhibitory) fibers.

Despite various and fairly consistent guidelines (**Fig. 26.4**)[7–9] for NP for several drugs, PHN may be difficult or impossible to treat even with opioids. Pathologic evidence suggests that VZV causes permanent damage to the central and peripheral nervous systems, probably destroying sites of intrinsic pain-inhibitory mechanisms where analgesics act, especially the dorsal horn of the spinal cord[5,6] (**Figs. 26.2** and **26.3**).

Practice

Clinical Features

When the acute rash has healed, the affected skin often exhibits a reddish, purple, or brownish hue (**Fig. 26.5**). Once this subsides, pale scarring often remains (**Fig. 26.6**). Occasionally severe pain with no residual scar may occur, or the scars in very-long-duration cases are barely perceptible. A steady burning or aching may occur and also a paroxysmal, lancinating pain. Both may occur spontaneously and are often aggravated by any contact with the involved skin, such as friction from even the lightest clothing (allodynia). Firm pressure on the skin may curiously be soothing. Some patients describe unbearable itch, formication (sensation of ants crawling on the skin), or other forms of dysesthesia. As well as clothing contact, these symptoms may be exacerbated by physical activity, temperature change, and emotional upset.

The scarred areas are usually at least hypoesthetic and often anesthetic to punctate touch, cold, and pain, and yet paradoxically the skin often exhibits marked pain on *moving* tactile stimulation (dynamic mechanical allodynia) or cold, increased pain to the noxious stimulation of a pinprick (hyperalgesia), or an increased sensitivity to moving touch stimuli (hyperesthesia) (**Figs. 26.5** and **26.6**). The affected, scarred skin often reveals a loss of sensation to pinprick, temperature, and touch over a wider area than the scars and an even wider area of sensitive or painful skin (**Figs. 26.5** and **26.6**). This sensitive skin may paradoxically include the area anesthetic to punctate touch when it is elicited by light stroking or skin traction between thumb and forefinger, an effect that may be caused by summation on hypersensitive, deafferented spinal dorsal horn neurons with expanded receptive fields.

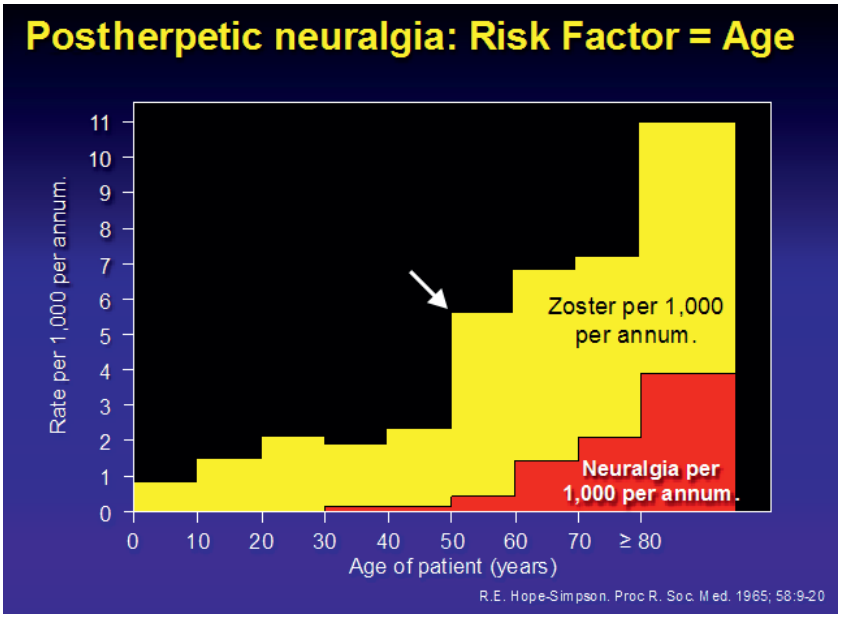

Fig. 26.1 Hope-Simpson's[2] graph of the increasing incidence of herpes zoster and postherpetic neuralgia with age 2. The increase in herpes zoster and PHN after age 50 (*arrow*) is the rationale for the use of the zoster vaccine beginning at this age.

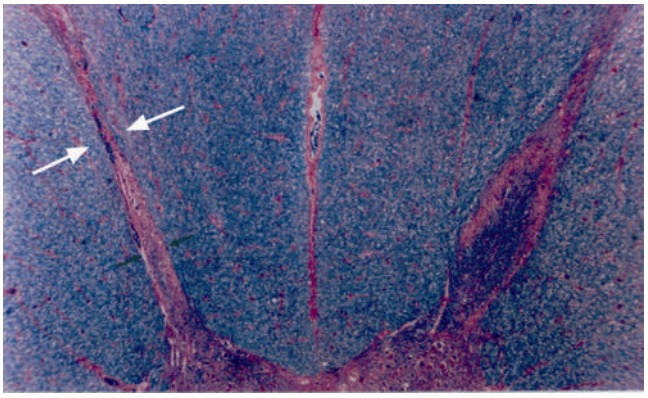

Fig. 26.2 Atrophy of the dorsal horn of the spinal cord in postherpetic neuralgia (*arrows*).[5]

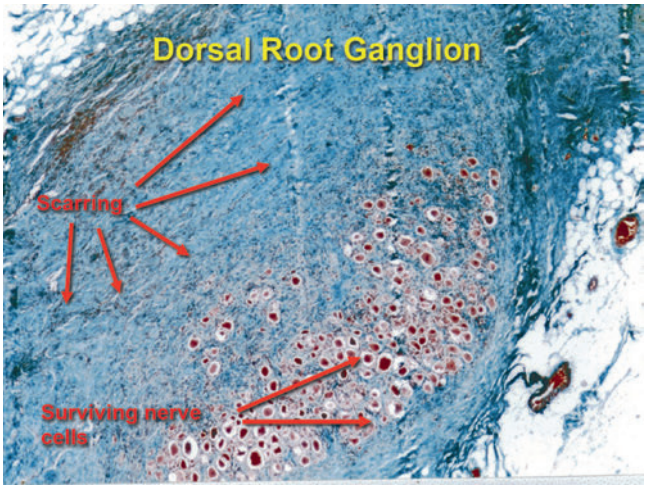

Fig. 26.3 Scarring in the dorsal root ganglion with postherpetic neuralgia (*arrows*).[5]

(1) **First choice:** tricyclic antidepressant (amitriptyline/nortriptyline) or gabapentin or pregabalin (add additional agents sequentially if partial but inadequate relief)
(2) **Second choice:** serotonin/norepinephrine reuptake inhibitor (SNRI) = (duloxetine)[++] and topical lidocaine*
(3) **Third choice:** tramadol or opioid (morphine, oxycodone, hydromorphone, transdermal fentanyl)
(4) **Fourth line agents**[+]

Fig. 26.4 Stepwise pharmacologic management of neuropathic pain.[7]
*5% gel or cream or lidocaine patch—useful for focal neuropathy such as postherpetic neuralgia (the lidocaine patch is not available in Canada).
[+]Cannabinoids, methadone, lamotrigine, topiramate, valproic acid.
[++]Do not add serotonin noradrenaline reuptake inhibitors (SNRIs) to tricyclic antidepressants (TCAs).

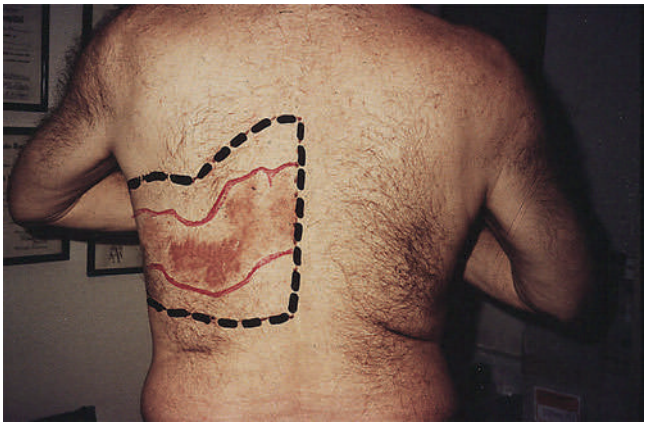

Fig. 26.5 Postherpetic neuralgia 3 months after the rash. Skin lesions soon after rash healing surrounded by an area of anesthesia to punctate touch (*solid line*) and pinprick, with wider area of pain on moving touch of cotton or tissue (*interrupted line*). Moving the hair on this hirsute individual is exquisitely painful. Firm pressure is soothing.

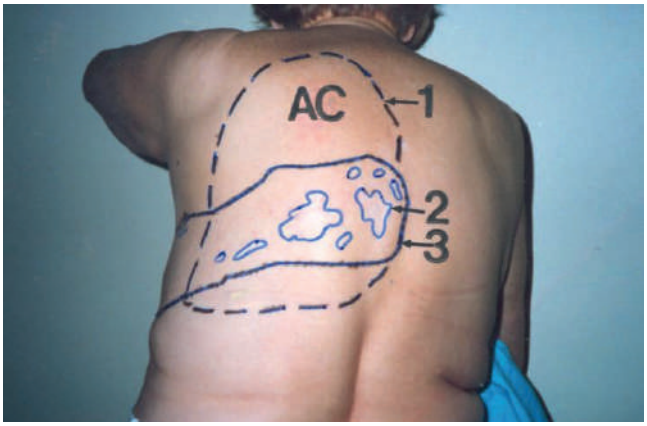

Fig. 26.6 Long-duration postherpetic neuralgia 12 months after the rash. (1) Margin of allodynia (pain from stroking with cotton), (2) scarring, (3) area of sensory loss.

Outcomes

Management Options

There are three possible approaches to managing PHN: (1) the treatment of established PHN, (2) the prevention of PHN by early and aggressive treatment of HZ, and (3) the prevention of HZ and PHN by vaccination. The treatment of PHN remains difficult and follows reasonably consistent guidelines in Canada, Europe, and the United States (**Fig. 26.4**).[7–9] These guidelines view gabapentinoids, tricyclic antidepressants (TCAs), and serotonin norepinephrine reuptake inhibitors (SNRIs) as initial choices and reserve opioids for refractory cases. Differing pharmacodynamics of the various drugs used to treat PHN and the limitations of monotherapy provide a rationale for the use of combinations of these drugs, which may also limit adverse effects because of lower doses. TCAs and SNRIs potentiate the inhibitory neurotransmitters noradrenaline and serotonin in pain-inhibitory pathways descending from the brainstem to the spinal cord. Gabapentinoids are $\alpha_2\delta$ calcium channel modulators, and opioids act on spinal and brainstem opioid receptors. Despite this specific knowledge regarding pharmacodynamics, a good mechanism-based treatment continues to elude us. Although the shocklike pain component resembles trigeminal neuralgia (TN), the sodium channel blocker carbamazepine (the closest we have to a mechanism-based treatment and so successful in TN) is usually a failure in PHN. Drugs such as TCAs, gabapentinoids, and opioids ameliorate indiscriminantly all features of the pain—that is, the steady burning, shocklike pain, and sensitivity of the skin (allodynia). We can achieve moderate or better improvement in only half to two thirds of patients with established PHN, and few have complete relief. There are very few comparative drug trials, and comparative clinically meaningful data (numbers needed to treat [NNT] for 50% or more improvement) are presented in **Table 26.1**. Perhaps one reason for the intractability is the severe damage to the dorsal horn of the spinal cord (**Fig. 26.2**) so that receptors where pain-inhibitory drugs such as opioids, TCAs, and gabapentinoids might act have been destroyed or damaged. This scenario argues very strongly for prevention by vaccination and early, aggressive treatment of HZ in an attempt to prevent this situation.

Prevention is achieved by the early and aggressive treatment of HZ and by vaccination. The former is problematic because this approach presumably works better if done in a timely fashion. Often the pain occurs days before the rash onset, making the diagnosis difficult, or one might have pain without a rash (zoster sine herpete). If unilateral, dermatomal, burning/jabbing pain occurs suddenly without a rash and involves the forehead or midthoracic area (common sites for zoster), it is reasonable to commence treatment with an antiviral agent; these are safe drugs and early prevention of viral replication is probably important. Even with timely administration, the effect of this treatment appears limited in preventing severe PHN. The choices are the oral antivirals famciclovir and valaciclovir. Valaciclovir is a prodrug for acyclovir but is better absorbed orally. For severely affected patients or immune-compromised patients, acyclovir can be given intravenously. The problem is that the data indicate that these are not very effective or not useful at all at preventing severe PHN. One can also concurrently treat acute zoster aggressively by giving a TCA, such as nortriptyline or amitriptyline,[10] or a gabapentinoid or both as soon as HZ occurs. It is

Table 26.1 Number needed to treat (NNT) data for at least 50% relief in postherpetic neuralgia and some other neuropathic pain conditions

Drug*	PHN	PDN	PN, NP	Central pain	FM	Comments
TCAs	2.1	3.5	2.6 PN	2.7		
Collins 2000	2.7	1.3	3.6 NP			Review
Sindrup, Jensen 2000	2.8		2.1 PN			Review
Saarto, Wiffen 2010			2.7 PN			Review
Finnerup 2010			2.2 NP			Review
Imipramine						
Sindrup 2003						RCT
Saarto, Wiffen 2010						Review
SSRIs			6.7 PN			
Sindrup, Jensen 2000			6.8 PN			Review
Finnerup 2010						Review
SNRIs (venlafaxine, duloxetine)						
Finnerup 2010			5.0			Review
Venlafaxine		4.5	5.2 PN			
Sindrup 2003			3.1 NP			RCT
Rowbotham 2004						RCT
Saarto, Wiffen 2010						Review
Duloxetine		5.3			5.8	
Kajdasz 2007		5.7			5.7	Review
60 mg/day		5.8			8	
120 mg/day		5.7				
Sultan 2008		6				Review
60 mg/day						
120 mg/day						
Lunn 2009						Review
60 mg/day						
Gabapentin	5.0		4.1 PN			
Sindrup, Jensen 2000	4.3		6.4 NP			Review
Rice 2001						RCT
Finnerup 2010						Review
Pregabalin	3.4		4.5 PN	5.6		
Dworkin 2003	4.2					RCT
Finnerup 2010						Review
Oxycodone	2.5	2.6				
Watson 1998						RCT
Watson 2003						RCT
Tramadol	4.3		3.4 PN			
Harati 1998	4.8		4.9 NP			RCT
Sindrup, Jensen 2000						Review
Finnerup 2010						Review

Note: Caution should be used in interpreting these figures because they involve studies of differing experimental designs, numbers of patients, and data analyses.

Abbreviations: PHN, postherpetic neuralgia; FM, fibromyalgia; PDN, painful diabetic neuropathy; NP, neuropathic pain; PN, painful neuropathy; RCT, randomized controlled trial; TCAs, tricyclic antidepressants.

*The individual references may be found in the reference list from Watson et al.[40]

good medicine to relieve severe, acute HZ pain with strong medications, including opioids; this may also have a preventive effect, but this is largely unproven.

The shingles prevention vaccine[11] is the first truly preventive measure for a NP problem, specifically PHN. It reduces the incidence of HZ by about 50% and the occurrence of PHN by two thirds; thus, many vaccinated individuals, if they get HZ, experience attenuated or shortened symptoms. This live, attenuated vaccine, which is 14 times the potency of varicella vaccine, has few adverse effects (primarily injection site reactions) and is approved for immune-competent adults ages 50 years and older. The reader is referred to a recent update on HZ vaccination.[12] There are some logistical

problems with the vaccine in Canada (it is frozen), but in other countries it is refrigerator stable. The vaccine may not be covered by government health plans or by private insurance in some countries, and in Canada it costs about $200. The frozen vaccine has to be reconstituted in the physician's office and must be given within 30 minutes or it loses efficacy. The answers to frequently asked questions about the vaccine, such as duration of protection, efficacy, effective age, previous HZ, concomitant administration with other vaccines, use in immune-compromised patients, and others, can be obtained from the guide by Shapiro et al.[12]

Neurosurgical Approaches

This chapter in the previous edition (2002) documented poor results in some older reports with cordotomy, rhizotomy, and sympathectomy.[13] A review of surgical procedures for this disease in 1951[14] concluded that almost every operation was said to work occasionally for this disease but none consistently. White and Sweet came to similar conclusions.[15] These procedures included retrogasserian rhizotomy, avulsion of the supraorbital nerve or gasserian ganglion, greater superficial petrosal neurectomy, trigeminal tractotomy, stereotactic thalamotomy and mesencephalotomy, sympathectomy, and sensory corticectomy. Resection of the underlying skin in the involved areas also rarely seemed to provide long-term pain relief, despite initial reports of good results.[13,16] Stereotactic trigeminal tractotomy was reported successful in three patients but with less than a year follow-up.[17] Dorsal root entry zone (DREZ) lesions were reported useful in 10 of 17 cases.[18,19] Stimulation of the nucleus ventroposteromedialis was suggested,[20] with one in three a good result.

With respect to these and the updated reports to follow, one issue, as can be seen from the diffuse peripheral and central nervous system pathologic changes (**Figs. 26.2** and **26.3**), is that there is no clearly localized lesion (as there is in trigeminal neuralgia). The pathologic anatomy is messy with widespread inflammation and scarring involving nerve, ganglion, root, and the dorsal horn in spinal cases. We know little about dysfunction, but the pathophysiology can involve various mechanisms (ectopic discharges and increased excitation both peripherally and centrally, and loss of central inhibitory mechanisms).

The literature reviewed since the previous edition has revealed case reports and case series of various surgical options, which include (1) peripheral procedures, including skin excision, peripheral nerve stimulation, gamma knife radiosurgery (also central), ganglionectomy (radiofrequency, surgical); and (2) central nervous system interventions, such as DREZ lesions, spinal cord stimulation, trigeminal tractotomy, deep brain stimulation, and motor cortex stimulation.

There are a number of important issues for the surgeon to consider in both evaluating this literature and in selecting suitable surgical candidates and publishing the results. For a credible interpretation of these case reports one needs to bear in mind some important factors (see the accompanying box). Many case reports lack at least some of this information.

The review begins by discussing these reports, moving from the peripheral procedures centrally. A summary of these and possible deficiencies in the following articles are found in **Table 26.2**.

Special Considerations

Suggested optimal criteria for assessing a published case report or selecting patients for surgery for postherpetic neuralgia:

1. Severe daily pain (7–10 on a 10-point scale for at least half the day)
2. A correct diagnosis:
   a. Usually segmental neuropathic pain in the same dermatome as the herpetic rash (vesicles on an erythematous base), with V1 or midthoracic dermatomes the most common sites (other sites are possible)
   b. Residual pale or pigmented dermatomal scarring in rash dermatome (not always present)
   c. Steady burning pain ± electric shocks ± skin sensitivity with pain on moving touch (dynamic mechanical allodynia) in the affected and adjacent dermatomes (due to expanded receptive fields)
3. Age of 60 or older (these patients are less likely to improve with time)
4. Pain of more than 6 months' duration (pain unlikely to improve with time)
5. Failure of appropriate medical therapy (gabapentinoids [gabapentin, pregabalin]), TCAs (amitriptyline, nortriptyline), opioids, or combinations of these
6. Rating scales (see points 7–9 below) before and after surgery
7. Pain rating scales, such as 0 to 10, category (mild, moderate, severe), and visual analogue scale (VAS)
8. Depression and anxiety scales: the Hospital Anxiety and Depression Scale (HADS)[21]
9. Function rating scales: Brief Pain Inventory (BPI),[22] Pain Disability Index (PDI)[23,24]
10. Quality of life rating: Short Form McGill Questionnaire version 2 (SF12v2)[25]
11. Follow-up status at least at 1 year
12. For a heterogeneous group of neuropathic pain cases, follow-up data on specific disorders such as PHN should be reported.

Table 26.2 A summary of the articles and comments regarding deficiencies in quality

Author(s), date(s), surgery	PHN: age, duration, location, number	Medical treatment	Outcome measures	Results	Follow-up	Conclusion
Petersen et al 2002, 2007[26,27] Skin resection	Age 70 8 years Right T6 *N* = 1	Gabapentin, nortriptyline, methadone, lidocaine patch	VAS daily pain 0–10 allodynia	Free of allodynia Reduced meds, 50% better at 1 year, pain worse at 5.5 years	5.5 years	Skin resection not advised by authors *Comment:* A well-written case report
Johnson and Burchiel 2004[28] Peripheral nerve stimulation (PNS)	Ages 44, 61, 83, 86 Mean duration for all 10 was 47.5 months V1, V2 *N* = 4/10	Medical failure Anticonvulsant, tricyclic antidepressant, gabapentin, topical anesthetic, neurectomy, gangliolysis, MVD	50% relief or better	2/4 had 50% decrease in pain meds and were satisfied 30% adverse effects 80% had 50% relief at 2 years	27 months	PNS of V1 or V2 effective, prospective trial needed 50% (2/4) benefited
Kim et al 2008[29] Radiofrequency ganglionectomy	Age 47–86 years Mean duration 30 months Spinal PHN *N* = 49	Not stated	VAS pain	Excellent in 3, in the rest pain improved Reduced meds VAS from severe to mild or moderate	12 weeks	Further research needed *Comment:* Unclear details of PHN, medical treatment not clear, short follow-up
Urgosik et al 2000[30] Leksell gamma knife (Elekta Instrument, Stockholm, Sweden)	Age 64–86 years No duration stated Postherpetic V nerve neuralgia *N* = 16	Not stated	% pain (0% = pain free, 100% = no change) (Excellent = 0–20%, very good = 21–40%, good = 41–60%)	Median 44% at least good (60% pain relief or more)	Median 33 months (range 8–34 months)	Relatively successful and safe for V PHN *Comment:* Problems here with diagnosis, duration of PHN, outcome measures
Keep et al 2005[31] Gamma knife	Ages 56, 61, 83 Duration 18 and 21 months, and unknown in one V nerve PHN *N* = 3	Intensive medical treatment	0–10 scale before and after surgery	2/3 had good result	4.5 years, 6 months	Effect promising, a larger study required
Rath et al 1996, 1997[32,33] DREZ lesions	Mean age = 73 (65–82) years Duration= 6 months to 13 years Spinal PHN *N* = 10	Extensive medical treatment	Pain as percentage of pre-operative levels	2/10 good, major side effects in 6/10	47 and 54 months	DREZ surgery abandoned for PHN

Author(s), date(s), surgery	PHN: age, duration, location, number	Medical treatment	Outcome measures	Results	Follow-up	Conclusion
Samreen and Friedman 2009[34] Nucleus caudalis DREZ V1 PHN	Age 79 years 7 weeks duration V1 PHN 7 weeks *N* = 1	Large doses of narcotics On Tegretol, Lyrica, hydromorphone, hydrocodone	0–10 scale	No pain at 1 year	1 year	*Comment:* Short duration of PHN means it could have improved by natural history but 60% chance it would not
Kanpolat et al 2008[35] V nerve tract and nucleus lesions	Age and duration unknown V nerve PHN *N* = 3/65	Unknown	VAS	No or mild pain at follow-up	Specific follow-up duration not known for these three PHN cases	*Comment:* Details missing as noted
Green et al 2003[36] Deep brain stimulation (DBS)	Age of onset 20 Duration 10 years V1 PHN Steady and jabbing pain	Maximal medical therapy (amitriptyline, carbamazepine, lamotrigine, phenytoin)	VAS	No pain	6 months	*Comment:* An unusual case clinically for PHN (young at onset, no detail re rash, scarring to be convincing, intractability unusual at her age); longer follow-up would be optimal
Brown et al 2005[37] Motor cortex stimulation (MCS)	Ages 51, 59 Duration of all 10 mean 6 years (1–12) *N* = 2/10 with V nerve PHN	Prior medical therapy	VAS McGill Pain Questionnaire 50% pain reduction at 10 months	No or mild pain at most recent follow-up	Mean follow-up entire group 10 months (range 3 months to 2 years)	*Comment:* Clinical details incomplete, follow-up details for two cases lumped with entire group
Esfahani et al 2011[38] Motor cortex stimulation (MCS)	Age 41 10 years duration "Two HZ rashes and Ramsay Hunt" *N* = 1	Refractory to muscle relaxants, antiepileptics, baclofen, carbamazepine, clonazepam, duloxetine, gabapentin, tramadol, responded to occipital nerve blocks	VAS	VAS 10/10 to 0/10 and off all meds at most recent follow-up	Unknown precisely	*Comment:* An unusual case because of young age, recurrent zoster, response to blocks of C2; follow-up duration unknown
Ebel 1996[39] Motor cortex stimulation (MCS)	Age 81 12 months duration Allodynia *N* = 1	Carbamazepine 600 mg	Excellent pain control No rating scales before	No rating scales after	At 6 months pain noted to become resistant	*Comment:* Wrong drug for PHN, inadequate medical therapy, no rating scales used

Abbreviations: DREZ, dorsal root entry zone; VAS, visual analogue scale.

Petersen et al[26] have reported a case of the relief of PHN by surgical removal of the painful skin and reviewed the literature back to 1900. This is an exemplary case report, dealing with a 65-year-old man with severe and medically intractable PHN of 8 years' duration, using established pain rating scales, and providing follow-up of 1 year postoperatively, at which time the patient said he was at least 50% better, had no allodynia, and had reduced medication. Unfortunately, in a subsequent publication[27] the researchers reported that at 5½ years postop the pain exceeded presurgery ratings, and they concluded that this form of surgery is not recommended.

A retrospective pilot study of peripheral nerve stimulation for 10 patients with medically refractory trigeminal neuropathic pain included 4 patients with PHN in V1 or V2.[28] Of the four, two reported 50% or better relief, a decrease in pain medication, and satisfaction at a median 27 months' follow-up.

Pulsed radiofrequency ganglionectomy was carried out in 49 subjects with PHN and assessed at 12 weeks postop.[29] They reported "55% pain reduction" and "3 had excellent pain reduction and 8 had partial relief but needed more medication," and that the remainder "experienced pain improvement and maintained or reduced their medication" and had an "improved quality of life."

A study involving gamma knife radiosurgery for trigeminal PHN[30] directed at the root of the trigeminal nerve alone in 16 patients reported good relief in 8 patients at 6 months (onset of relief: median of 1 month) and failure in the other 8. At 1 year 6 of 7, at 2 years 4 of 6, and at 3 years 3 of 5 persisted with significant relief. Another article[31] combined gamma knife surgery targets of the trigeminal nerve and centromedian nucleus in 3 patients, with 2 of the 3 having good results for 4½ years and 6 months.

DREZ lesions were reported for 10 cases of spinal PHN in two articles describing the same patients,[32,33] with only 2 having good results at 47 and 54 months but with major complications in 6 of the 10. DREZ treatment was "abandoned" by this group because of these results. A case report describes nucleus caudalis DREZ in a 79-year-old woman with V1 PHN for 7 weeks on large doses of narcotics with total relief at 1 year.[34]

A review of the literature and experience with 65 patients undergoing computed tomography (CT)-guided percutaneous trigeminal tractotomy-nucleotomy for a variety of facial pain syndromes over 20 years has been reported.[35] Included were 3 patients with PHN who were described as having good relief at follow-up. Mean follow-up in the entire group was 5.3 years (6 months–6 years), but specific follow-up duration of the PHN cases was not available. There was considerable discussion appended to this article by eminent neurosurgeons K.J. Burchiel, N.M. Boulis, O. Sagher, J.M. Henderson, and D.M. Long. Caution was registered about the need for experience, risk, and the need for continued and detailed follow-up, and the comments were generally complimentary.

A case report of deep brain stimulation[36] in a 30-year-old woman with presumed V1 PHN reported no pain at 6 months' follow-up.

In a study of motor cortex stimulation 2 of 10 neuropathic pain patients had trigeminal PHN.[37] Ten months after surgery all 10 patients had at least 50% pain reduction. Moderate and severe ratings in PHN became 0 and mild in the 2 PHN sufferers "at most recent follow-up" (entire group mean was 10 months, range 3 months–2 years). A case report of motor cortex stimulation[38] of intractable V1 and V2 PHN of 10 years' duration reported no pain at "most recent follow-up." One 81-year-old woman with V1 and V2 PHN for 12 months was treated with motor cortex stimulation for severe allodynia with excellent pain control lasting 6 months but with recurrence at that time.[39]

Conclusion

The response to the question in the chapter title is that neurosurgical procedures may help some patients with long-standing, medically intractable PHN. It is not possible to recommend any one procedure for all neurosurgical centers, but it is reasonable to begin with the ones that are the safest and simplest and that have some evidence of success.

A review of recent articles has revealed some potential deficiencies in these accounts (**Table 26.2**) The neurosurgical literature and the selection of refractory cases of PHN for surgical procedures must be evaluated very carefully, and suggestions are outlined (see the earlier box). Patients should be referred to a center with the technical facilities necessary, where the surgery is carried out by experienced neurosurgeons, and, optimally, where significant numbers of cases of the specific neurosurgical procedure have been performed and the results published in good-quality journals and with full disclosure of the limited benefits and risks. Continued publication of well-worked-up and good-quality case reports and case series is important.

Established PHN remains a challenging problem. Although we have made moderate advances in drug treatment, a proportion of patients are inadequately or not relieved of this neuropathic pain. The principles of drug treatment of chronic PHN follow guidelines for neuropathic pain in general.[7–9] The prevention of PHN appears to be key at this point in time. Attempted prevention at the stage of the rash or acute pain onset of HZ is important and is good practice for the relief of severe acute pain but of uncertain value in the prevention of severe PHN. The zoster prevention vaccine appears important at present in the immune-competent patient 50 years of age or older and is safe and moderately effective at preventing PHN.

Editor's Comments

Postherpetic neuralgia represents a major pain disorder that will only increase in an aging population. Comparing the United States with Canada, we can expect approximately 150,000 new cases every year. This ranks well above many of the pain syndromes that are discussed in this book.

As Dr. Watson indicates, the evidence for a surgical approach to this disorder is sparse. A number of procedures have been tried, but the structural deficiencies in reported cases, or case series, are highlighted in this chapter. Given the predictable tendency to report positive outcomes, one can only guess at the number of procedures performed annually for this condition without benefit.

As pointed out, we do have a legacy of destructive procedures for PHN. Unfortunately, these procedures have proven disappointing. For example, the initial reports of DREZ lesions for PHN were very compelling, yet almost 30 years have now passed since the initial reports without a single further supportive case series. The evidence we do have to support ablative procedures clearly does not meet contemporary standards.

Why is it that destructive approaches seem to fail? The answer lies, as Watson alludes, in the extensive damage to the peripheral and central nervous system (particularly the dorsal horn) seen in patients with PHN. There are probably multiple mechanisms for neuropathic pain at play in this condition, and these can probably be sorted out by careful postoperative reporting. We may find that no one surgical procedure will ultimately be effective, and that multiple surgical techniques may produce more positive results. For example, my own experience with DREZ for thoracic PHN is that the superficial allodynia can be relieved, but the "deeper" visceral pain cannot. This implies that the latter pain is organized well rostral to the segmental level(s) of the DREZ lesions, and potentially must be dealt with by other means such as motor cortex stimulation (MCS) or deep brain stimulation (DBS).

From my own perspective, surgeons are loath to perform highly invasive procedures on older patients without some reasonable assurance of success with minimal morbidity. As an alternative, neuromodulation procedures, such as peripheral nerve or spinal cord stimulation (SCS), are often tried. In my experience unequivocal success with neurostimulation for PHN is almost unheard of. MCS and DBS are performed at only a few centers, and even in these settings sporadic referrals and insurance funding represent further barriers. In the defense of surgeons, it is difficult to accumulate experience with this condition, much less organize a research protocol.

Preemptive therapy appears to be the most promising line of treatment, and failing that, informed medical management of established PHN is clearly the best alternative. However, there will still be individuals who develop medically intractable PHN, and it is incumbent on neurosurgeons who wish to treat this condition to report their outcomes honestly and completely. As organized neurosurgery turns more toward outcomes registries, perhaps this, and other pain disorders, can be incorporated into the archive, helping us to begin to understand surgical practice in the area of pain surgery and to gain insights into which procedures work for which conditions.

Patients with PHN are typically older and more infirm. Highly invasive major surgery is probably never going to be an easy option for their care. Areas for consideration of more organized prospective protocols for the surgical treatment of PHN include stimulation of the peripheral nerve, motor cortex, and sensory thalamus, as well as image-guided tractotomy-nucleotomy. The former have the two advantages of being testable and reversible; the latter is selective and minimally invasive.

I continue to believe that there is a role for surgery in PHN. We just have to prove it.

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27 Central Pain Secondary to Intracranial Lesions

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Riddoch defined central pain as "spontaneous pain and painful overreaction to objective stimulation, resulting from lesions confined to the central nervous system, including dysesthesias of a disagreeable kind."[1] Subsequent studies demonstrated clearly that an injury anywhere along the pathway from spinothalamic tract cells to cortex may result in severe, intractable, central pain.[2–4] A more recent definition is that central pain is "pain arising as a direct consequence of a lesion or disease affecting the central somatosensory system."[5] This definition recognizes that a disturbance of the central somatosensory system is the essential feature of central pain.

Poststroke central pain (PSCP) was first recognized by Dejerine and Roussy as referring to patients who develop pain following stroke.[6] Their patients had "a lesion occupying the external and posterior regions of the thalamus and extending through the internal and median nuclei, as well as part of the posterior limb of the internal capsule." They characterized the pain syndrome following a thalamic lesion as (1) slight hemiparesis without spasticity; (2) abnormal sensation, including decreased sensitivity to touch, pain, and temperature sometimes with a presence of cutaneous hyperalgesia; (3) hemiataxia with hemiastereognosia; (4) intolerable pain on the hemiparetic side that is paroxysmal; and (5) choreoathetoid movements. PSCP is a category within brain central pain that includes patients having central pain secondary lesions other than stroke.

The International Association for the Study of Pain (IASP) taxonomy report described brain central pain as a "diffuse unilateral pain, contralateral to a cerebral lesion, often burning, with allodynia, hypoesthesia, hypoalgesia, hyperpathia, dysesthesias and neurological signs of damage to structures that supply the affected region."[7] The etiology of this disorder remains elusive as does the treatment. This chapter reviews the incidence, mechanisms, clinical features, and treatment of brain central pain. The content of this chapter reflects previous reviews of this subject.[4,8]

Incidence

A prospective study found that 8% (16 of 207) of patients developed PSCP following stroke,[9] and a lower proportion was found in the study of patients with clinically identified somatic sensory abnormalities following stroke.[10] Cases of brain central pain have been reported following thalamic damage caused by vascular lesions (infarct, hemorrhage, vascular malformation), tumor, cranial trauma, and *Toxoplasma* abscess.[11–16]

De Salles and Bittar reported a unique case of a patient who developed brain central pain following stereotaxic biopsy.[17] Two weeks after the biopsy, the patient started to complain of dysesthesias that worsened over the next 4 weeks. The postoperative magnetic resonance image (MRI) showed that the needle had passed precisely through the medial aspect of the ventral posterior (VP, corresponding to Hassler's nucleus ventral caudal, Vc[18]) nucleus, with some possible involvement of the medial lemniscus immediately caudal to the VP nucleus. This report is consistent with previous claims that stereotactic lesions that spare the VP lateral but cause injury to the ventrolateral, dorsomedial, centrum medianum, anterior, intralaminar and reticular thalamic nuclei rarely cause central pain.[11,18,19]

Although thalamic lesions are considered to be the most common intracranial lesion to cause brain central pain, disturbances of the parietal lobe, basal ganglia, and spinothalamic tract distant from the cerebral hemispheres can cause central pain.[20–23] It is estimated that 78% of PSCP results from supratentorial lesions.[3] Bowsher et al correlated MRI findings with sensory changes in patients with PSCP.[24] In general, lesions anywhere along the pathway from spinothalamic tract to the thalamocortical system can result in central pain. Of the 70 central poststroke patients examined, 3 had no evident lesion on the MRI; 9 had infratentorial lesions; 27 had lesions

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confined to the thalamus plus or minus the internal capsule; 18 had lesions of parietal cortex, including or excluding the insula; 6 had combined infratentorial, supratentorial, and cortical lesions; and 7 had infratentorial and supratentorial lesions only.[24] No significant relationship was found between the size of the lesion and the presence of pain secondary to intracranial lesions.[9]

Mechanisms

Our poor understanding of brain central pain is indicated by the numerous proposed mechanisms.[2] Historically, it has been proposed that pain secondary to intracranial lesions is the result of activity produced by the irritable focus created at the site of injury.[6] At present, the location of neurons with abnormal neuronal activity that might contribute to the mechanism of central pain is unclear. Anatomic and clinical evidence strongly suggests that the damage must produce injury to the spinothalamic pathways or the cortical structures to which they project.

It has been proposed that thalamic bursting (low-threshold spike [LTS] pattern) occurs at a higher rate among neurons in the region of the VP nucleus in patients with central pain secondary to spinal lesions as opposed to those with movement disorders.[25–27] Another report found no difference in the thalamic burst rate between patients with chronic pain and those with movement disorder.[28] In the latter report, most of the neuronal recordings were made outside Vc in patients with peripheral neuropathic pain rather than central pain. The presence of bursting was reported by numbers of bursting cells rather than burst parameters, so that spike trains consisting of single spikes and bursts may have been missed.[29] Therefore, this study does not exclude the possibility that bursting activity in Vc is involved in the mechanism of central pain.

At the level of the thalamus, physiologic evidence strongly suggests that VP is involved in mechanisms of central pain syndromes. Lesions isolated to this nucleus can be associated with brain central pain,[30] although not all such lesions are associated with central pain.[31]

Certainly VP is involved in both innocuous mechanoreception and pain-signaling pathways. VP and the area below and behind receive spinothalamic inputs.[32] Cells within as well as posterior to VP respond to painful thermal stimuli.[33,34] Electrical stimulation of the area where these cells are recorded can produce the sensation of pain,[35,36] and pain sensations can be diminished by lesions of this nucleus.[30,31] Functional imaging studies of patients with PSCP demonstrate that cold stimuli leading to hyperalgesia produce activation in the cortical terminal zone of VP.[23,30] Therefore, the evidence of pain-related activity in VP is consistent with its involvement in central pain.

Sympathetic dysfunction has also been proposed as a mechanism of central pain. In some patients there are signs of sympathetic dysfunction, such as edema, altered sweating, and lowered skin temperature.[37] A few patients report pain relief following sympathetic blockade,[38] which suggests that this mechanism does contribute to the pain experienced by some patients with brain central pain, but not most patients. Hypothalamic dysfunction has been proposed as being involved in the mechanism of central pain.

Emotional stress can potentiate the central pain state, which might indicate a role of the hypothalamus and the limbic system as part of the pain inhibitory control system.[37,39] Destruction of VP in the cat results in an increase in hypothalamic potentials evoked by peripheral stimulation.[40] The resulting increase in the input of pain afferents on the hypothalamus is a possible mechanism for central pain and the associated emotional and vegetative components.

In pain following spinal cord transaction, the mechanism may involve bursting activity produced by hyperpolarization of the thalamic cells secondary to interruption of the spinothalamic tract.[27,41]

An exclusive role for the VP thalamic nucleus in central pain secondary to intracranial lesions seems unlikely because a lesion of this nucleus is not necessarily associated with central pain.[30,31] Consequently, theories involving this nucleus would be expected to invoke disinhibition of normal sensory processing.[30,39]

Another hypothesis focuses on the role of the reticular thalamic nucleus and the medial and intralaminar thalamic regions that receive input from the spinothalamic tract.[32] This hypothesis proposes that a lesion removes the normal inhibitory activity exerted by the reticular thalamic nucleus on the medial and intralaminar thalamic nuclei. The consequence is an increase in abnormal neural activity in the latter region, leading to central pain and hypersensitivity.[42,43]

Based on the results of precentral (motor) cortical stimulation on thalamic pain, Tsubokawa et al proposed that central pain is caused by the loss of normal inhibitory mechanisms.[44] Unlike previous hypotheses focusing on the thalamus, this hypothesis proposes that cortical nociceptive neurons are deafferented.[44–46] Another proposal is that the lateral spinothalamic tract pathway to the insula via the thalamus is damaged, which causes a disinhibition of activity in the medial spinothalamic tract to the anterior cingulate cortex via the thalamus.[47] This is inconsistent with functional imaging studies of patients with brain central pain which demonstrate increased activation of paracentral but not anterior cingulate cortex during cold hyperalgesia[23,30] and painful heat stimulation.[48]

Clinical Features

The diagnosis of brain central pain depends largely on clinical and radiologic evidence of injury to pathways that mediate pain and temperature sensation. It has been suggested that thalamic pain cases preferentially involve diencephalic lesions on the right side,[11,49] although this is not found in most series of such patients.[32]

A latent period between the occurrence of intracranial lesions and the onset of pain is a common but not an invariant feature of central pain syndromes (**Table 27.1**).[49,50] The onset of pain following intracranial damage may occur from days to 3 years after the lesion.[42,51–54]

Somatosensory testing is useful in identifying patients who develop pain secondary to intracranial lesions. Common somatosensory abnormalities include paresthesias, dysesthesias, hyperpathia, spatial and temporal summation, numbness, and allodynia.[54,55] Painful paresthesias, often described as burning, aching, and pricking, are a classic feature of central pain, although this need not be the case. A wide spectrum of words are used to describe the pain: aching, lancinating, pricking, lacerating, pressing, shooting, squeezing, throbbing, cutting, crushing, splitting, stinging, icy, sore and stabbing, cramping, smarting, and pulling. Most patients experience more than one type of pain. The pain may be superficial, deep, or mixed with no relationship between the quality of the pain and the location of the lesion.[39]

The intensity of long-standing central pain is high as demonstrated in **Table 27.2**. Even if the pain is less intense, most patients report a significant degree of suffering that is the result of the constant presence of the pain that occurs in 23 of 27 patients.[39] Overall, pain intensity is highest with lesions that involve the thalamus, ranging from 68 to 98 on a visual analogue scale (VAS), which scores from 0 to 100 (**Table 27.2**).[39] Pain intensity can be increased by external stimuli, such as joint movements, cold, and light touch. Emotional stimuli can also aggravate the pain.[39]

Table 27.1 Time of onset of pain following lesions of the thalamus

Period	Patients (%)
Immediate	18
Delay, within 1 week	18
1 week–1 month	20
1–3 months	15
3–6 months	12
6 months–1 year	6
> 12 months	11

Table 27.2 Pain intensity (VAS 0–100) in patients with pain following intracranial lesions

Lesion site	Number of patients	VAS score	
		Mean	Range
Brainstem	8	61	39–94
Thalamus	9	79	68–98
Extrathalamic	6	50	30–91

Numerous abnormalities on quantitative sensory testing (QST) are associated with brain central pain. In virtually all cases, there is a decrease in temperature detection or pain sensibility or both, as measured by warm and cold detection thresholds and by heat and cold pain thresholds.[9,39,54–56] Pain may be produced or exacerbated by voluntary or passive movement of a joint, which is known as kinesthetic allodynia. The pain and unpleasant tingling that may occur during movement of the extremity may be severe enough to render the patient functionally paralyzed. Stimuli originating from visceral processes, such as a full bladder or bowel, can also affect the quality of the pain, although this is usually a feature of central pain following spinal cord injury.

In the case of cortical lesions, the results of a recent study demonstrate warm and cold hypoesthesia based on QST thresholds in all subjects with lesions of parietal or insular cortex or both.[57] The largest degree of thermal hypoesthesia by threshold measures was found in the subject with the largest lesion, which involved extensive parietal and insular lobar lesions.[58] Suprathreshold measures demonstrated that sensory loss for painful and nonpainful hot and cold modalities was maximal for the largest parietal lesions.

Subjects with relatively small lesions restricted to the posterior insula and retroinsula showed central pain and cold allodynia, based on thresholds and clinical assessment.[57] A study of two patients with lesions of the insula and adjacent cortical lobes confirmed normal heat pain thresholds but increased ratings of heat pain compared with controls.[48]

In a large series of patients (n = 270) investigated for somatosensory abnormalities following stroke, 5 subjects were identified who presented central pain and pure thermalgesic sensory loss contralateral to the cortical stroke. All of these patients had involvement of the posterior insula and medial parietal operculum. Lemniscal sensory modalities and somatosensory-evoked potentials to nonnoxious inputs were preserved, while thermal and pain sensations were profoundly altered, and laser-evoked potentials were abnormal in all 5 patients studied.[10] Therefore, several lines of evidence suggest that lesions of the posterior insula and parietal operculum are particularly associated with PSCP.

Another important observation is that some patients with injuries or diseases of the central nervous system (CNS) may experience thermal hypoesthesia or hypoalgesia as a result of a CNS lesion without developing central pain.[57] This has also been demonstrated for patients with lesions of the spinal cord[59,60] and brain.[9,10]

Nevertheless, the most common abnormality in brain central pain is loss of pain and temperature sensibility. The function of the somatosensory pathways can be assessed objectively by neurophysiologic techniques, such as measuring the somatosensory-evoked potentials (SEPs) following electrical stimulation of the median and tibial/sural nerves.[42,61] Because this stimulation activates large primary afferent fibers, abnormal SEPs reflect an alteration in vibration and touch modalities. The technique of recording SEPs has been used to identify different subtypes of the thalamic syndrome.[42,61] Peripheral stimulation of afferents that innervate the spinothalamic tract may be accomplished by the use of a laser to activate cutaneous nociceptors.[62–64] Decreases in laser-evoked potentials (LEPs) are common in central pain but are not invariable.[65–68]

Treatment

The large number of treatment options reflects the general intractability of central pain. Although many treatments are claimed to be effective for the relief of central pain, most studies have used small groups of patients, and the therapeutic treatments have rarely been evaluated with well-designed clinical trials.

Treatment methods for central pain include:

- Pharmacologic
  - Antidepressant drugs
  - Antiepileptic drugs
  - Analgesics (including local)
  - Naloxone
- Nonpharmacologic
- Spinal cord stimulation
- Deep brain stimulation (DBS)
- Motor cortex stimulation
- Transcutaneous electrical nerve stimulation
- Sympathetic nerve blockade
- Mesencephalic tractotomy
- Thalamotomy
- Hypophysectomy

Pharmacologic Treatments

Tricyclic Antidepressants

Tricyclic antidepressants were the first class of drugs proven effective for brain central pain syndromes. Leijon and Boivie performed a double-blind, three-phase, crossover, placebo-controlled trial of the pain-relieving effect of amitriptyline and carbamazepine in 15 patients with PSCP.[69] Amitriptyline, but not carbamazepine, caused a significant reduction of pain (10/15 patients) compared with placebo. Depression scores or clinical ratings did not account for the effect. Responders were evident after 2 weeks of treatment and had higher blood levels of amitriptyline.

Gonzales et al reported on two patients with acquired immunodeficiency syndrome (AIDS) who developed thalamic pain from *Toxoplasma* abscesses in the thalamic region.[16] Treatment with amitriptyline (125–150 mg/day) provided substantial pain relief in both cases. In one patient, the pain returned when amitriptyline was discontinued and nortriptyline was substituted. Reinstatement of amitriptyline again produced analgesia.

The hypothesis that amytriptyline is effective for the prevention of PSCP was examined in a randomized, double-blind, placebo-controlled or trial of amytriptyline.[70,71] At the 1-year follow-up, no statistically significant benefit was found for the treatment with amytriptyline.[71]

To a varying degree, antidepressants influence serotonergic, noradrenergic, cholinergic, and dopaminergic systems; however, amitriptyline exerts a stronger therapeutic effect than the specific serotonin reuptake blockers.[72] The mechanisms of the analgesic effect of tricyclic antidepressants are not known, although genetic variants of an enzyme influencing these neurotransmitters show a substantial effect upon pain sensitivity.[73]

Antiepileptics

Lamotrigine has been proven to be effective in the treatment of PSCP. A randomized, inactive placebo-controlled crossover trial of the antiepileptic agent lamotrigine has been carried out in a consecutive series of patients with PSCP seen at two hospitals.[74] Specifically, this study showed a relatively small but significant decrease versus placebo in pain ratings for the last week of the trial (30%), at doses of 200 mg/day. No significant effect was found at lower doses (25 or 50 mg/day); 44% (12/27) of patients were identified as responders. Lamotrigine was associated with a decrease in spontaneous pain among those patients with incomplete spinal cord injury or brush-evoked allodynia.[75]

Pregabalin was studied in a randomized, blinded, placebo-controlled trial in a population with central pain secondary to intracranial or spinal lesions, which were not analyzed separately.[76] Significant improvements were noted in VAS pain and health status while side effects included dizziness, somnolence, and nausea.

Other antiepileptic drugs, including carbamazepine, are often considered most suited to relieving

paroxysmal-type central pain. Carbamazepine was reported effective in the treatment of tabetic, lightening pains in multiple sclerosis (MS).[77] Leijon and Boivie, however, did not find a significant effect of carbamazepine on the global assessment of PSCP in their double-blind, crossover, placebo-controlled trial.[69] No relationship was found between plasma concentrations of carbamazepine and pain relief at doses that produced moderate to severe unpleasant side effects in 36% of the patients tested. The lack of pain relief and the incidence of unpleasant side effects limit the use of carbamazepine except for the treatment of lightening pain.

Opioids and Cannabinoids

The use of opioids in the treatment of chronic pain has been advocated but is controversial.[78,79] An acute, single-blinded trial of opioids provided strong evidence for a low sensitivity of central pain to opioid.[78] Doses up to 30 to 50 mg morphine over 2 hours failed to have an effect on central poststroke pain.[80] In addition, acute intravenous naloxone was found to be no more effective than placebo in diminishing PSCP.[81]

A large study examined the efficacy of high- versus low-dose levorphanol therapy treatment of brain central pain and neuropathic pain of peripheral origin.[79] Among all diagnoses, those with the brain central pain syndrome had only a 16% decrease in pain and 7 of the 10 patients withdrew from the trial, leading to the conclusion that this pain syndrome does not respond to opioids. Overall, the results of these studies suggest the lack of efficacy of opioids for pain secondary to intracranial lesions.[78,79,82]

The evidence for the efficacy of cannabinoids for the treatment of pain has been mixed. One randomized controlled trial of cannabinoids in MS patients produced significant decreases in pain.[83] The central pain in this population may result from both spinal and brain lesions. A similar study in patients with chronic pain that was mostly of neuropathic origin did not find an analgesic effect.[84] However, this study did find significant improvements in symptom control, particularly in the case of insomnia.

Local and General Anesthetics

Only a few reports have described a benefit of local anesthetics in the relief of brain central pain. Awerbuch studied the effect of mexiletine, a structural analogue of lidocaine, in patients with "thalamic pain."[85] A 4-week uncontrolled trial was carried out in nine patients with "thalamic pain" and found improvement in eight patients and side effects in two patients (nausea and dizziness).[85] In five patients, oral mexiletine (10 mg/kg daily), an oral analogue of lidocaine, produced a significant reduction in pain during a 10-week trial. Edwards et al found that infusion of intravenous lidocaine (1–5 mg/kg) decreased pain caused by thalamic infarct.[86]

There have also been a number of trials of local anesthetic agents for the treatment of PSCP. Edmondson and colleagues also found an analgesic effect in response to intravenous lidocaine in four out of four patients. Mexiletine produced durable analgesia after 1 year in two of four patients, and intolerable side effects developed in the other two patients.[87] Lidocaine-induced spinal block successfully relieved PSCP with allodynia in two of three patients. Among these three patients, two had thalamic lesions; one had a successful outcome; and the other was a treatment failure.[88]

In a mixed population of patients with chronic "nonmalignant" pain, the infusion of putative gamma-aminobutyric acid (GABA) agonist propofol produced substantial relief of both spontaneous and evoked pain.[89] The same group subsequently carried out a double-blind, placebo crossover trial a subhypnotic bolus dose of propofol for the treatment of central pain secondary to either brain or spinal lesions.[90] Decreases in spontaneous pain and allodynia (both cold and tactile) were significantly greater following injections of propofol than placebo. Differences between central pain secondary to spinal and cranial lesions were not significant. Four patients, with central pain secondary to a spinal lesion or thalamic hemorrhage, had worse pain after propofol but not after placebo. Overall, the injections were well tolerated without hemodynamic side effects. Burning at the site of injection was observed for a few patients, and some patients complained of short-lasting lightheadedness in both the propofol and placebo groups.

Surgical Treatments

Because pharmacologic treatment has been relatively ineffective for the relief of pain secondary to intracranial lesions, various surgical treatments have been proposed, including electric stimulation procedures, sympathectomy, and ablative procedures.[91]

Electric Stimulation

Spinal Cord Stimulation

Reviews of the literature indicate that spinal cord stimulation is not effective for central pain secondary to intracranial lesions.[3,4,92,93] This is consistent with the conclusions of the European Database Study of Neurostimulation for the Treatment of Pain based upon a formal review of the literature.[94] This review concluded that there is no evidence of the effectiveness of spinal cord stimulation for the treatment brain central pain.[95]

Deep Brain Stimulation

The lemniscal pathways, the VP thalamic nucleus, and the posterior limb of the internal capsule are primary targets for stimulation in the treatment of brain central pain. One report concluded that 5 of 12 patients with this diagnosis had pain relief following thalamic stimulation.[3] Hosobuchi reported the results of subcortical electrical stimulation for control of intractable pain.[96] Of the 13 patients with "thalamic pain," 8 had initial success, and 6 reported long-term success (2 years) with permanent electrode implantation. Levy reported that among 25 patients with stimulation of the thalamus or internal capsule for "thalamic pain," there was a 56% improvement from the stimulation trial and 24% had a good long-term outcome.[97] Kumar reported on five patients with "thalamic pain" of whom only one had enough thalamic tissue for placement of an electrode[98]; in the others, stimulating electrodes were placed in the internal capsule. Only one of the five had a good long-term outcome.

A more recent study reported some beneficial effects on allodynia related to stimulation of periventricular gray (PVG). However, no benefit was observed on the ongoing chronic (burning) pain or the attacks of lancinating pain. Stimulation in Vc increased the pain in many cases.[99] In a series of 15 patients with PSCP, DBS was considered to be successful (pain relief >30%) in 67% of patients at long-term follow-up.[100] In a study of 21 patients with various neuropathic pain conditions, it concluded that DBS had low efficacy, with only 24% of patients maintaining long-term benefit, as measured by their willingness to continue DBS stimulation after 5 years.[101] Among eight patients with PSCP, four had successful trials of stimulation, but the duration of this effect was less than 1 year after implantation of the permanent lead.[101]

The European database study summarized the world literature and reported on the response to DBS in 45 patients with brain central pain, of whom 24 (53%) were reported as successes during the trial whereas 14 (31%) had success with chronic stimulation.[95] It was concluded that for the treatment of PSCP, "DBS results are equivocal and require further comparative trials."

Motor Cortex Stimulation

Tsubokawa et al were the first to report that chronic motor cortex stimulation (MCS) attenuated not only spontaneous pain but also allodynia and hyperpathia associated with intracranial lesions.[102] In a more recent review, 53% of patients with "thalamic pain" and 33% of patients with "suprathalamic pain" responded to MCS.[103] Patients with pain following intracranial lesions that were ketamine and thiamylal sensitive but morphine resistant experienced long-lasting pain reduction with chronic MCS therapy. This finding suggests that pharmacologic classification of PSCP by the morphine, thiamylal, and ketamine tests may predict the effects of MCS.[103]

Imaging studies in patients with neuropathic pain may give clues to the mechanism of the analgesic effect of MCS. Poststimulation activations were observed in the middle and anterior cingulate gyrus, orbitofrontal cortex, putamen, thalamus, and brainstem (periaqueductal gray and pons) and were correlated with pain relief.[104] Studies of the endogenous opioid system have demonstrated decreased binding of the labeled opioid (diprenorphine) following MCS in the anterior cingulate cortex, periaqueductal gray, and prefrontal cortex.[105] This decrease in binding suggests that MCS produces release of endogenous opioids so that there are fewer receptors vacant to bind with diprenorphine.

Peyron et al investigated the effects of MCS as a treatment of refractory PSCP in two patients.[22] In a patient with pain secondary to a parietal infarct sparing the thalamus, a pronounced analgesic effect (70%) was noted when stimulation was applied continuously for 5 to 6 hours per day. The pain relief remained stable for the duration of the 22-month follow-up. At one point, 14 months after surgery, the stimulator was stopped for a period of 8 days, without reappearance of pain. There was no comment on sensory side effects associated with the stimulation.

Nguyen et al have reported the effect of MCS for relief of neuropathic pain.[20] Of the 10 patients with PSCP, 6 subjects had a 40 to 60% reduction of VAS pain ratings. In general, patients were stimulated for 3-hour intervals, which were separated by 3-hour intervals without stimulation. The stimulation was relatively free from side effects. When present, side effects were related to the intensity of the stimulation. No motor activation phenomena or episodes of epilepsy occurred in any of the patients. The mechanisms by which chronic MCS yields useful pain relief are unclear.

As noted by Nguyen et al, the effect of chronic MCS might be due to tonic depolarization and inactivation of the cortex.[20] Alternatively, chronic MCS might excite pyramidal neurons, leading to analgesia based upon descending inhibitory pathways to the spinal cord.[22] Regardless of the mechanism, MCS is a useful therapy.

A retrospective study with long-term follow-up (average 3.6 years, range 1–10 years) has confirmed the results reported by Nugyen.[107] Seventeen patients with chronic neuropathic pain, in which 7 cases of PSCP were included, were treated with epidural stimulation electrodes. The placement of the electrodes was followed by a stimulation trial including double-blind assessment of pain intensity, which identified a positive response in 3 of the 7 patients with PSCP. These results were apparently maintained at last follow-up.[106] Similar results were

found in another report with a long-term follow-up (27 months).[107] Of the 13 patients with PSCP, 9 (77%) had substantial pain relief, as did 1 of 3 patients with central pain following spinal cord injury.[107]

The overall level of evidence supporting the use of MCS for the treatment of pain has been assessed in detail.[95,108] The European Database Study of Neurostimulation for the Treatment of Pain concluded that MCS is useful in 50 to 60% of patients with either PSCP or trigeminal neuropathic pain. In particular, a total of 143 patients with PSCP who were identified in case series were reported to have a success rate of approximately 50%.[95] Most of these case series were class IV, defined as retrospective noncontrolled series. Two studies can be classified as class III evidence based on the presence of a control for the effect of MCS. In the first of these studies, Katayama et al reported success rates of 48% for MCS, 7% for spinal cord stimulation and 25% for DBS in the treatment of patients with PSCP.[109]

In the second study of class III evidence, Nuti et al reported on a prospective comparison of pre- versus post-MCS status in consecutive patients with neuropathic pain.[110] These patients mostly had PSCP (77%, 24/31) whereas most of the rest had central pain of spinal origin. Overall, pain relief was graded at excellent or good in 52% of cases, and the same proportion of patients had a decrease in intake of analgesic medication. Patients with ischemic PSCP tended to have the largest decreases in pain VAS and in analgesic medication during the pre- versus post-MCS interval.

Complications are frequent and include seizures, which may occur in as many as 41% of patients, usually during implantation of the stimulator.[106] Kindling of epileptic foci by repeated stimulation and epilepsy have not occurred. Bezard et al have studied the effect of MCS in monkeys.[111] Although stimulation could cause seizures, neither epilepsy nor a reduced threshold for kindling of seizures occurred. Epidural hematomas have been associated with the MCS surgery, but not with neurologic injury. Stimulator pocket infections and electrode wire fractures have occurred, which are well-known complications of the implantation of neuromodulation equipment overall.[95,106]

Transcutaneous Electric Nerve Stimulation

Transcutaneous electric nerve stimulation (TENS) has been reported to be effective in some patients who develop pain secondary to intracranial lesions. In a recent long-term study, Leijon and Boivie found that 4 out of 15 patients with PSCP pain resulting from infratentorial lesions responded to conventional or acupuncture-like TENS.[112] The patients reported pain between pre- versus post-TENS treatment of 57 versus 20%. Although 1 patient reported pain relief that lasted for only a few weeks, 3 of the patients continued to report relief of TENS when assessed after 2 years.

Eriksson et al found that five of seven patients with brain central pain experienced long-term pain relief.[113] The location of the damage likely accounts for the report by Long, who found a poor outcome for TENS in "thalamic pain."[114] The results of these studies suggest that TENS is worth a trial in cases of PSCP due to infratentorial lesions, especially if the patient has not suffered a significant loss of touch and vibration sensibility in the painful region.[39,112]

Sympathectomy

Chronic pain and hyperpathia arising from a lesion in the CNS may be abolished by blocking the sympathetic supply to the periphery. Sympathetic blockade in the form of stellate ganglion and lumbar sympathetic blocks or local venous guanethedine blocks has abolished or diminished the ongoing pain and allodynia in eight patients with PSCP as well as benefiting the accompanying dystonia.[38]

Ablative Neurosurgical Procedures

A variety of operative treatments have been tried for central pain states, and have been reported to be effective based on class IV evidence.[94] Neurosurgical brain lesions have been reported to produce varying degrees of pain relief.[115–120] Stereotactic coagulation of the dorsolateral tegmentum of the mesencephalon at or below the posterior commissure was reported to decrease brain central pain in six of eight subjects. This therapeutic effect remained at the longest follow-up period of 30 months.[117] After medial thalamotomy, a 50 to 100% improvement was reported in 60% of patients with central pain.[25,121]

Interestingly, stereotactic chemical hypophysectomy was reported to give 80 to 100% pain relief in three patients with PSCP.[122] The patients were still pain free at 19, 39, and 58 months following the procedure. The mechanism of action remains unclear but may be related to stimulation of a hypothalamic analgesic mechanism. Another patient with PSCP was reported to have an excellent result.[123] The complications of these procedures are those that can occur with any stereotactic neurosurgical procedure, including intracranial hemorrhage, infection, and seizure.

Other Treatments

Electroconvulsive therapy has been tried without success.[124] Patients with pain following intracranial damage may benefit from admission to a pain treatment center. These centers provide an inpatient, structured environment to facilitate care.[125] Daily

activities include physical and occupational therapies, vocational counseling, relaxation, recreation, and individual psychotherapy as well as ongoing medical care. All these modalities may have merit in the management of pain.

The combination of aerobic exercise, relaxation techniques, physiotherapy (passive and active assisted exercises, superficial heat, ultrasound, cold, and hydrotherapy), and the capacity to monitor medical treatments in a supervised environment have demonstrated real benefit to patients with neuropathic pain, including those with brain central pain.[78,125]

It should be noted that in some cases, PSCP can occur in or be confused with posthemiplegic dystonia. Motoi et al reported a case in which a patient who had pain following a thalamic infarct experienced pain relief following botulinum toxin injection into the biceps brachii, triceps brachii, and wrist flexor muscles.[126] The patient's pain disappeared with improvement of the patient's dystonia, perhaps indicating that the pain was caused by the dystonic muscle contraction.

Taken together, the results from uncontrolled studies indicate that there is no single pharmacologic or surgical procedure or neurostimulation technique that relieves pain in most cases. With this in mind, a stepwise treatment approach has been proposed.[127] The approach is to begin with pharmacologic treatment using noninvasive stimulation procedures and psychosocial support. If the patient is unresponsive, additional pharmacologic treatments should be tried. In the last step, psychiatric treatment for underlying problems that are the consequence of the pain (e.g., severe depression and risk of suicide) should be considered. Invasive electric and neurosurgical ablative techniques may be considered at this time. For all treatment modalities, there is an urgent need for controlled studies.

Conclusion

There are few data regarding the functional outcome of brain central pain. Although central pain can remit spontaneously in some patients, there has never been a prospective study to document these anecdotal observations (Casey, personal communication 1989; Tasker, personal communication 1989).[128] In most cases, pain is a chronic condition that lasts throughout the life of the patient. Some investigators estimate that the chronicity of this condition can be predicted from the duration of the condition at the time of entry of a patient into a trial of medical therapy. In a study of patients with PSCP, patients suffered with pain an average of more than 4 years before entering the trial.[39] Current therapy may have some influence on the duration of central pain because treatment with noradrenergic tricyclics can decrease pain for up to 2 years in 50% of patients.[69]

There are several sources of disability in patients who suffer from brain central pain. As in other chronic pain conditions, the intensity of pain is less disabling than the fact that it is continuous and chronic.[80] These patients often have neurologic deficits in addition to pain.[39] Deficits, such as motor or cognitive impairment, are themselves a significant source of disability. For example, patients with kinesthetic allodynia have pain that is produced by changes in body position, ambulation, or movement of the extremities.[39] This can be a hindrance to therapy and a significant source of disability.

Coexisting depression is often a source of disability in patients with chronic pain. Although there are no studies of depression in patients who develop brain central pain, there is clear evidence of depression in trials of pharmacologic therapies for central pain.[129] Emotional and mental states, such as focused attention, can increase the pain level and can be a significant source of disability.

Editor's Comments

Taken together, the results from uncontrolled studies indicate that there is no single pharmacologic or surgical procedure or neurostimulation technique that relieves pain in most cases.

Dr. Lenz and his colleagues have produced a detailed assessment of poststroke central pain (PSCP), including a nice summary of the current theories of the genesis of this pain. It is a fascinating topic, and one that will occupy neuroscientists for many years to come. Our lack of a fundamental model for this pain is paralleled by a lack of a reliable method for treatment.

None of the pharmacologic methods reviewed here shows efficacy long term, although a course of an antidepressant agent should certainly be one of the first options. No other medications, including anticonvulsants, opioid analgesics, cannabinoids, local anesthetics, or even propofol, have proven to be helpful in the long term.

Ablative neurosurgical procedures are probably not a viable alternative, so as in other instances of neuropathic pain, neuromodulation is the preferred approach. However, the results of deep brain stimulation (DBS) for PSCP have been disappointing. Motor cortex stimulation (MCS) may have a role, but this is by no means proven. This will be explored in Chapter 36.

As with other difficult pain problems, an iterative approach to the treatment of these patients is the most logical course of action. This should start with medical therapy, and if this is ineffective, therapy can incorporate surgery, depending on the patient's condition, and motivation to pursue invasive strategies.

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Section III.H

Cancer Pain

28 Cancer Pain

Ashwin Viswanathan and Eduardo Bruera

The majority of patients with cancer will experience pain during the course of the illness. A recent meta-analysis assessed pain in cancer patients and found the overall presence of pain to be greater than 50%, with 64% of patients with advanced disease experiencing pain.[1] The impact of cancer pain is likely much larger in developing nations, where access to opioids remains a continuing issue.[2]

Pain in cancer patients is rarely an isolated problem: social, psychological, and spiritual factors can contribute to the experience and impact of pain. In a high-volume inpatient palliative care center, delirium was seen in one third of patients,[3] and the presence of delirium has been noted to correlate with differing patterns of pain perception and analgesic treatment.[4] Emotional suffering is another condition that can lead to pharmaco-resistant pain.[5]

Pain in patients with active cancer can arise from direct tumor invasion, side effects of cancer treatment, or exacerbation of preexisting medical conditions.[6] Pain experienced by cancer survivors is a recently recognized entity and can require a different approach from the treatment of patients with active cancer.[7] This chapter focuses on the management of pain in patients with active cancer.

■ Principles

Assessment of Cancer Pain

Both subjective and objective assessments of the patient's pain are essential for developing a comprehensive treatment plan. The most common unidimensional assessment is the numerical rating scale (NRS), which is an 11-point scale in which the patient rates his or her pain on a scale from 0 (no pain) to 10 (worst pain imaginable). In using the NRS, it is essential to ascertain from the patient what an acceptable level of pain management would entail. Patients with higher pain intensity as determined by the NRS have been shown to require longer times to achieve stable pain control, higher final opioid doses, and the use of more adjuvant modalities.[8]

The two most commonly used multidimensional assessments for pain are the Brief Pain Inventory (BPI) and the Edmonton Symptom Assessment Scale (ESAS).[9,10] The BPI uses a 0 to 10 NRS used to assess the impact of pain on general activity, mood, walking ability, work, relation with others, sleep, and enjoyment of life.[10] The ESAS uses the NRS to assess physical and psychological symptoms in eight dimensions, along with an assessment of a global sense of well-being.[9] In patients with intact cognition, the assessments are rated by the patient during serial visits. In patients who have a mild degree of cognitive impairment, the assessments are provided by the patient in association with family or a member of the treatment team. In patients who have developed significant cognitive impairment, the patient's family or staff provide the assessment. Although ratings given by family or caregivers will differ from those given by the patient,[11] the ESAS has a high degree of inter-rater reliability and correlates highly with the Support Team Assessment Schedule.[12]

Obtaining a careful history regarding the patient's pain will help to optimize the therapy. Quality of the pain will help determine whether the pain is somatic versus visceral, and nociceptive versus neuropathic. Often patients with cancer present with mixed pain types. Somatic nociceptive pain is often described as sharp, squeezing, or stabbing, whereas neuropathic pain may be described as burning, tingling, or shooting. Understanding the temporal relationship to the pain will help in ensuring optimal dosing and breakthrough pain regimens.

Cancer Pain Syndromes

Pain in cancer patients may be either acute or chronic. Acute pain is often the result of iatrogenic intervention and includes postoperative pain, pain associated

with the administration of chemotherapeutic agents, and pain from the toxicity of the chemotherapeutic agents themselves.[13] Chronic pain in cancer patients is usually defined as pain associated with a lesion that is unlikely to remit, pain that is recurrent over months, or pain that has persisted for more than 3 months.[14] **Table 28.1** details some of the more common cancer pain syndromes.

Bone metastases are among the most common causes of cancer-related pain,[15] and approximately half of cancer patients have tumor involvement of bones and joints.[16] Management of pain related to spinal metastases not only can lead to debilitating pain, but is also a common cause of neurologic debilitation in cancer patients.

Craniofacial pain is another common pain syndrome and can arise from a number of factors. Over half of patients with primary or metastatic brain tumors will have headaches, and metastases to the base of the skull can lead to a number of pain syndromes, including parasellar syndrome, middle cranial fossa syndrome, jugular foramen syndrome, and occipital condyle syndrome.[13]

Neuropathic pain, either from tumor involvement or from cytotoxic chemotherapy, is another significant source of pain in cancer patients. Malignant brachial plexopathy can be seen in patients with lymphoma, lung cancer, or breast cancer, and painful lumbosacral plexopathy can be seen in patients with colorectal, cervical, or breast cancer or sarcoma.[13]

Tumor involvement of the peritoneum, retroperitoneum, or intra-abdominal structures can lead to a number of visceral pain syndromes. Tumors of the liver can lead to hepatic distension syndrome, which can also refer pain to the right scapular region. Tumors of the pancreas, through infiltration of the posterior abdominal wall, can lead to epigastric or low thoracic back pain.[17] Other visceral pain syndromes include peritoneal carcinomatosis, perineal pain due to tumors of the lower gastrointestinal or reproductive tract, and adrenal pain syndrome.[13]

In a prospective, multicenter study, physicians assessed the pains of patients with cancer.[16] More than 1,000 patients were assessed, and a wide variety of pathologies including lung, breast, and head and neck cancer were represented. Of these patients, 92% had pain attributable to their tumors, and 21% of patients had pain resulting from cancer treatment. The majority (75%) of patients had one pain causing their symptoms, and another 17% reported two main pains. Patients with purely somatic nociceptive pains accounted for 32% of patients, and 15% of patients had purely visceral nociceptive pains. Mixed pain etiologies are most commonly seen, however.

Table 28.1 Cancer pain syndromes

Bone invasion	Multifocal bone pain Vertebral body invasion Base of skull metastases
Nerve invasion	Mononeuropathy Cervical plexopathy Brachial plexopathy Lumbosacral plexopathy
Visceral invasion	Retroperitoneal syndrome Hepatic distension syndrome Bowel/ureteric obstruction
Neuraxial involvement	Spinal cord compression Leptomeningeal metastases Meningeal carcinomatosis
Chemotherapy-induced polyneuropathy	Vincristine Vinblastine Cisplatinum
Postsurgical syndromes	Mastectomy Thoracotomy Radical neck dissection Nephrectomy Amputation
Radiation induced	Brachial plexopathy Chronic enteritis Chronic prostatitis Burning perineum syndrome

Practice

The World Health Organization (WHO) recommendations for the treatment of cancer pain continue to serve as a foundation for treatment.[18] The guidelines are centered on five phrases: “by the mouth,” “by the clock,” “by the ladder,” “for the individual,” and “attention to detail.” The phrase “by the ladder” refers to the sequential use of medications to control pain. The first rung of the ladder involves the use of nonopioid analgesics, such as ibuprofen, acetylsalicylic acid (ASA), or paracetamol. In addition, an adjuvant medication such as amitriptyline, carbamazepine, or dexamethasone may be used. If pain is not adequately controlled, opioids for mild to moderate pain should be started, such as codeine, either in combination with or instead of the nonopioid analgesics. If the patient’s pain is still not adequately controlled, opioids for moderate to severe pain should be begun. These include morphine, methadone, and hydromorphone, among others. Again, these can be used alone or in combination with nonopioid analgesics and adjuvant medications.

Pharmacological Treatment

Opioid Analgesia

Opioids used in the treatment of cancer pain are typically pure μ-agonist opioids. It is important to individualize the opioid therapy for a patient given differences in how a given patient may respond to the various opioids.[19,20] In addition, given the number of opioids available at differing dosages, strict adherence to the WHO ladder may not be necessary. The important concept is to start at a safe dosage, and titrate the dosage appropriately to the desired therapeutic effect. In addition, the physician must be prepared to change opioids if one does not produce analgesia.

Methadone possesses unique properties that must be understood by the practitioner. As a synthetic opioid, it is very easily manufactured and hence is relatively inexpensive compared with morphine.[21] In addition, methadone may be a good opioid choice in the setting of renal insufficiency, given that it does not have known active metabolites and does not undergo significant renal elimination. Methadone has also been shown to have *N*-methyl-D-aspartate (NMDA) receptor antagonist properties, which may be beneficial in modulating NMDA-induced hyperalgesia.[22] However, methadone does have a longer and more unpredictable half-life, and the equianalgesic ratio with other opioids is variable from patient to patient. Hence, care must be taken with the initiation of and rotation to methadone. A recent retrospective study of methadone initiation and rotation in the outpatient setting demonstrated that this technique can be used safely and effectively.[23]

Adjuvant Analgesic Drugs

Corticosteroids are commonly used for patients with advanced cancer and pain, due to observations that these medications can improve pain and increase the comfort of terminally ill patients.[24,25] For patients with a predominantly neuropathic pain syndrome, gabapentin and pregabalin are first-line treatments,[26] and tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs) may also provide benefit. The benzodiazepines clonazepam and alprazolam have also been used as adjuvant medications in the management of neuropathic pain. Although there is some evidence to support a primary analgesic effect, their efficacy may also be related to anxiolytic effects.[27]

Nonpharmacologic Approaches

Psychological approaches to palliative care form an integral part of holistic care. Therapies can include cognitive-behavioral therapy, psychoeducation, and supportive psychotherapy.[28] Cognitive-behavioral therapy can use techniques such as biofeedback, imagery, and distraction and attention diversion to reduce the disability of chronic cancer pain.

A number of targeted procedural interventions can be applied in the management of certain cancer pain syndromes. Abdominal pains due to malignancy may be responsive to a celiac plexus block (CPB) in the case of upper abdominal pain.[29] Patients with pain in the lower abdomen due to tumors in the pelvis may be candidates for a plexus hypogastricus block.

There has been a renewed interest in neurosurgical ablative techniques for the management of cancer pain. These techniques as well as outcomes are covered in detail in other chapters. The most commonly used ablative techniques for the management of cancer pain include percutaneous cordotomy, myelotomy, dorsal root entry zone (DREZ), and cingulotomy.

The implantation of an intrathecal drug delivery (IDD) system is another option to consider in cancer patients for whom oral administration of opioids results in intolerable side effects, or in whom pain relief cannot be attained despite appropriate opioid dosing. Commonly used intrathecal medications include morphine, hydromorphone, bupivacaine, and ziconotide.

■ Outcomes

Pharmacologic Treatment

Based on early literature, the WHO estimated that 70 to 90% of patients will achieve effective pain relief using the WHO recommendations for cancer pain treatment. However, controlled studies of pain relief achieved using the WHO recommendations have been difficult.[30,31]

Data suggest that under-treatment of pain may continue to be a factor in inadequate cancer pain management. In 2008 Deandrea et al[32] reviewed 26 studies that had used the Pain Management Index (PMI) to assess the treatment of cancer pain. Under the PMI, a patient's index is calculated as the difference between the patient's worst pain and the most potent level of analgesic being prescribed.[33] The patient's worst pain is given a score of 0 (no pain), 1 (NRS 1–3, mild pain), 2 (NRS 4–7, moderate pain), or 3 (NRS 8–10, severe pain). The prescribed level of analgesic is scored as 0 (no analgesic), 1 (nonopioid), 2 (weak opioid), or 3 (strong opioid). The PMI is calculated as the difference between the level of analgesic and the patient's pain score, and can hence range between +3 and –3. The study found that 43% of patients had a negative PMI, reflecting inadequate treatment of the patient's pain.

The impact of under-treatment is significant because ineffective outpatient management of pain is a significant predictor of impending hospital admission within 30 days.[34] In a retrospective review of over 100,000 outpatient encounters at a single center, 4.5% of encounters were associated with a pain intensity score (PIS) between 7 and 10. These patients were 96% more likely to be admitted within 30 days than patients with a PIS less than 4. Patients with a PIS between 4 and 6 were 43% more likely to be admitted than those patients with PIS less than 4.

A recent large study of patients presenting to an outpatient supportive care center emphasizes that adequate pain management for cancer patients requires time and dedication from the treatment team.[35] Out of 1,612 consecutive patients, 45% achieved pain treatment response by their first follow-up visit. However, 31% of patients continued to have pain scores ≥ 4, and 32% of patients who initially reported mild pain reported worsened pain in the first follow-up visit. Careful, frequent follow-up and interdisciplinary approaches are suggested to expeditiously achieve symptom control.

Interventional Management

Careful outcomes research for interventional procedures for cancer pain is needed. There are few high-quality studies assessing the impact of neurosurgical or interventional approaches for cancer pain. A recent double-blind, randomized, controlled trial of CPB used in the treatment of pain due to unresectable pancreatic cancer demonstrated that patients who underwent CPB experienced greater pain relief than those patients who were medically managed.[36] The mean NRS at 6 months postprocedure was 0.8 in the CPB group (baseline 4.4) and 2.0 in the group treated medically (baseline 4.1). Interestingly, however, CPB was not associated with improved quality of life, decreased opioid usage, or improved survival.

Neurolytic superior hypogastric plexus block for the treatment of pelvic pain from gastrointestinal or genitourinary malignancies has been shown to significantly reduce pain and decrease opioid usage.[37] Of the patients who responded to an anesthetic block, 72% who underwent neurolytic block had satisfactory pain relief as defined by a visual analogue score (VAS) less than 4, and 28% had moderate pain control, with a VAS between 4 and 7. Patients with extensive retroperitoneal disease may not respond to this treatment due to limited spread of the neurolytic agent.

One industry-sponsored randomized trial of IDD compared comprehensive medical management (CMM) with the intrathecal administration of opioids either alone or in combination with a local anesthetic.[38] Patients included in the trial had a VAS ≥ 5, despite a morphine equivalent dose of 200 mg/day. The mean VAS of 72 patients randomized to CMM was 7.81 ± 1.63 at baseline, and was reduced by 3.05 ± 3.16 at 4 weeks. Of the 71 patients randomized to IDD, the mean VAS at baseline was 7.57 ± 1.79 and was reduced by 3.9 ± 3.42 at 4 weeks. This difference did not reach statistical significance; however, a significant difference was reported in the number of patients who either had a 20% reduction in VAS or had a 20% reduction in drug toxicity. Reduction in fatigue and depressed level of consciousness was also reported in the IDD group.

Conclusion

Our understanding of cancer-related pain and the necessity of a multidimensional, interdisciplinary approach to the management of symptoms has grown tremendously since the introduction of the WHO guidelines in 1986. Although the WHO treatment guidelines continue to serve as an important foundation for treatment, ongoing efforts to minimize the morbidity of cancer-related pain are essential. The role and timing of interventional approaches are not well understood, and carefully designed prospective trials are needed to document an improvement in pain and quality of life. As more patients continue to survive their cancer, the field of chronic pain management in patients without active cancer will need to be emphasized as well.

Editor's Comments

This chapter highlights the complexity of cancer pain and the inherent need for its care to be multidisciplinary. In any organization that cares for individuals with cancer, there is a need to understand the problem of cancer pain and to promote a high degree of cooperation between medical oncologists; radiation oncologists; specialists in the medical, interventional, and surgical management of pain; and other disciplines.

Drs. Viswanathan and Bruera practice in an institution that is renowned for cancer care, and their collaborative focus is apparent. Unfortunately, my impression is that this level of integrated care in cancer pain is uncommon.

Cancer patients fear pain more than death. Two thirds of cancer patients have pain associated with their disease, and in more than half of those patients the pain is poorly controlled. The authors cite results placing that figure between 31 and 43%, which is entirely consistent with my estimate. They also cite evidence that uncontrolled cancer pain is highly correlated with readmission to the hospital. We are in an era of increasing emphasis on keeping patients out of the hospital, and readmission has negative impacts on patients and their families, but also financial consequences for the health care facility.

We clearly can do better with the management of cancer pain, and in my opinion, surgical pain management can play a major role in this effort. Of all the modalities available to a patient with pain secondary to cancer, it is probably the most misunderstood, underutilized, and underdeveloped. There is certainly plenty of "headroom" to improve and implement surgical therapies to relieve cancer pain.

We will see in subsequent chapters that exemplary procedures such as cordotomy and myelotomy not only can be pain relieving, but can also liberate the patient from high-dose opioids and other agents that, at a certain point in the disease, diminish the patient's quality of life. Although the hospice movement has changed end-of-life care, there is still probably room in this field to attempt to relieve pain, and preserve useful life, prior to terminal care. It is in this aspect of cancer pain care that I see an opportunity for pain surgery to make a positive contribution.

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Section III.I

Postoperative Pain

29 Postoperative Pain

Julio A. Gonzalez-Sotomayor, Jeffrey L. Moller, and Ansgar M. Brambrink

Neurosurgical patients often have pain associated with their diseases or treatments, and often experience altered consciousness.

Pain after craniotomy is more common than generally assumed, and it can be moderate to severe in a significant number of patients.[1] Nevertheless, in approximately 50% of the patients, pain remains undertreated by the perioperative team.[2] Spine surgery patients frequently live with chronic pain preoperatively and after surgery require high, and sometimes very high, doses of opioids to achieve satisfactory analgesia.[3]

The treatment of perioperative pain in neurosurgical patients poses a dilemma. In most cases disease process, pain perception, and site of pain treatment are located in the same structure: the central nervous system. When treating pain in these patients the provider runs the risk of masking new subtle or even major pathologic changes in the area of concern because the most important "vital sign" of the central nervous system—the neurologic examination—is instantaneously affected by the most powerful systemic analgesics.

Further complicating the issue is the fact that untreated pain may lead to increased anxiety and to a hyperadrenergic state with secondary hemodynamic, immunologic, and neuropsychiatric adverse effects. Postoperative hypertensive episodes can jeopardize hemostasis with devastating consequences (e.g., intracranial hemorrhage after craniotomy).[4] Agitation and delirium may contribute to events such as falls, traumatic removal of catheters, or even long-term mental health consequences such as posttraumatic stress disorder.

Another challenge is that patients with altered mental status are not able to determine or verbalize pain and primarily present with nonspecific symptoms such as agitation. If the primary treatment is directed at the symptoms alone, these patients may end up receiving sedatives for agitation, which could worsen the delirious status because the primary cause is not addressed and many sedatives themselves are deliriogenic.

On the other hand, analgesics may be useful as primary therapy for agitation caused by insufficiently treated pain. However, some analgesic agents, especially opioids, have sedative properties, which may contribute to the cognitive dysfunction and can lead to respiratory depression and hypoxemia.

Withholding pain medication out of fear of an adverse outcome may be equally disadvantageous for the patient, as discussed above, but in addition poses a significant ethical dilemma because control of pain and relief of anxiety and distress are primary therapeutic goals for every health care provider.

It is therefore not surprising that the conflicting goals discussed above, in the absence of specific and evidence-based guidelines, frequently result in clinical practices that vary greatly between practitioners and, in many cases, provide suboptimal care, from a patient's perspective.

Recent years have seen increased awareness about the negative consequences of inadequately managed perioperative pain after neurosurgical operations. Improved understanding of the mechanisms of pain and subsequent development of new treatments have advanced the clinical practice of analgesia in this challenging patient population.

This chapter supports the development of an evidence-based approach to the management of perioperative pain in patients undergoing brain or spine surgery as well as other neurosurgical procedures (e.g., implantation of intrathecal pumps or spinal cord stimulators). Other sections describe the challenges presented by opioid-tolerant patients and the current level of knowledge regarding persistent surgical pain in the neurosurgical patient. The authors consider the implementation of multimodal analgesia regimen as the key to success in the management of perioperative pain in this challenging and often opioid-tolerant patient population. The following section provides the rationale for this approach.

The Concept of Multimodal Analgesia

Opioids are potent analgesics and remain the main pharmacologic intervention in managing moderate to severe postoperative pain. Unfortunately, the use of effective doses is frequently limited by associated adverse effects. Sedation and hypoventilation are of particular concern in patients following neurosurgical operations. Effective doses are also difficult to attain in the growing population of patients who consume opioids preoperatively. These patients have developed different levels of opioid tolerance and are at high risk for experiencing uncontrolled postoperative pain. Patients after spine surgery and their health care providers are often challenged with this problem. Alternative analgesic agents are required when the effectiveness of opioids becomes limited by adverse effects or tolerance. Undertreated postoperative pain results in the patient's suffering and in potentially increased rates of complications.[5,6]

From a clinical practice perspective, multimodal analgesia (MA) can be simplified as a pharmacologic strategy to supplement a reduced dose of opioids while providing effective postoperative pain control. The concept of MA describes a pain management modality that combines different analgesic agents with different mechanisms of action. By using the agents' additive and synergistic effects, optimal analgesia can be achieved with lower doses of the individual agents, which helps reduce the incidence of adverse effects. The various analgesic agents can be administered by different routes and at different times during the preoperative, intraoperative, and postoperative periods. The MA concept is not new but today, with better understanding of pain mechanisms and pathways, more analgesic agents are evaluated as potential components of this analgesia modality. Compared with single-drug therapy, MA has demonstrated better pain control, decreased adverse effects, and increased patient satisfaction.[7,8] An effective MA should play a key role in so-called fast-track programs, which are evidence-based protocols designed to enhance postoperative recovery and improve outcome at lower health care costs.[9] Practice guidelines from the American Society of Anesthesiologists Task Force on Acute Pain Management states that MA in the perioperative setting should be used whenever possible.[10] Effective perioperative MA has also shown a preventive effect against the development of chronic ("persistent") postsurgical pain.[11] Persistent surgical pain (PSP) is an unfortunate consequence of surgery where acute postsurgical pain does not go away in the expected amount of time and transitions into chronic pain instead. The mechanisms of PSP are poorly understood, but the intensity of the acute pain immediately after surgery has been consistently identified as a risk factor. Questions regarding the adequate combination of analgesic agents and the duration of treatment for prevention of PSP remain unanswered.[12] The authors have dedicated a specific section to PSP at the end of this chapter.

Evidence supporting the use of MA in different surgical subspecialties and identification of its optimal components continues to grow. Not all analgesic agents are suitable for all surgical patients or to all surgical settings. The selection of a particular MA strategy should consider the patient's preexisting medical conditions, the type of surgery, and the drug's known adverse effects and contraindications.

The next section describes the pharmacologic agents most commonly used as part of a MA treatment concept in the general surgical population. This discussion is followed by a review of specific evidence regarding their use in the perioperative management of pain in neurosurgical patients.

Multimodal Analgesia Components

Opioids

The analgesic and most of the adverse effects of opioids result from their interaction with well-defined receptors located in the central nervous system. The main areas of receptor expression include the amygdala, the mesencephalic reticular formation, the periaqueductal gray matter, the rostral ventromedial medulla, and the substantia gelatinosa in the spinal cord. Four different opioid receptors have been currently identified: μ (mu), δ (delta), κ (kappa), and the nociceptin/orphanin FQ peptide (NOP) receptor.[13] Depending on the type of interaction with the receptor, opioids are classified as full agonists, partial agonists, combined agonist-antagonists, or full antagonists. The mechanisms of analgesia are complex and include the inhibition of ascending transmission of nociceptive input by blocking substance P release from the primary sensory neuron at the level of the dorsal horn of the spinal cord. Opioids also activate inhibitory circuits that descend from the midbrain to the dorsal horn of the spinal cord. The role of peripheral opioid receptors in analgesia remains to be elucidated.

The most common adverse effects include sedation, respiratory depression, pruritus, constipation, urinary retention, nausea, and vomiting. The interaction with peripherally located receptors may also explain some of the gastrointestinal and urinary adverse effects. Other adverse effects include histamine release by morphine and meperidine, and neurotoxicity of normeperidine, the main meperidine metabolite.[14] Opioid receptor-mediated adverse effects can be reversed by opioid antagonists. Unfortunately, the use of an antagonist will reverse anal-

gesia as well. Despite their associated adverse effects, opioids remain the cornerstone therapy in controlling moderate to severe postoperative pain because no other type of drug has paralleled their potency and efficacy in this setting.

Acetaminophen and Nonsteroidal Anti-inflammatory Drugs

Prostaglandins are essential in producing inflammation and pain. At a peripheral level, they stimulate pain-transmitting fibers directly and indirectly by increasing sensitivity to other algogenic neurotransmitters (peripheral sensitization). Prostaglandins have also proven to be a key component in the regulation of membrane excitability of dorsal horn neurons, leading to central sensitization.[15] Nonsteroidal anti-inflammatory drugs (NSAIDs) exert their analgesic effects by blocking the production of prostaglandins through inhibition of cyclooxygenase enzymes types 1 and 2 (COX-1, COX-2). Depending on the extent of enzyme inhibition, NSAIDs are classified as nonselective COX-1/COX-2 inhibitors or selective COX-2 inhibitors. NSAIDs have demonstrated effectiveness in controlling pain and decreasing use of opioids in a variety of surgical procedures. Nevertheless, their use in postoperative pain management is still controversial due to their potential adverse effects. COX-1 inhibition has been associated with increased risk of bleeding in some surgical settings.[16] Selective COX-2 inhibitors are not associated with an increased risk of bleeding, and they have also shown a decreased association with gastrointestinal toxicity compared with nonselective NSAIDs.[17,18] On the other hand, the use of selective COX-2 inhibitors in patients with significant cardiac disease has been associated with an increased risk of myocardial ischemia.[19] Specifically, the use of rofecoxib was associated with an increased risk of myocardial infarction compared with the nonselective NSAID naproxen or placebo, which resulted in its withdrawal from the market.[20,21] The use of NSAIDs in spine surgeries remains a topic of debate due to the inhibitory effects on bone formation.[22,23] An editorial has pointed to the need for more clarity with regard to the safety and efficacy of NSAIDs in neurosurgery.[24]

The analgesic mechanisms of acetaminophen are still poorly understood. Evidence supports a central antinociceptive effect. Its COX inhibitory properties seem to be different from the inhibition produced by NSAIDs[25] and may explain the lack of adverse effects described for NSAIDs. At clinically recommended doses, its major advantages over NSAIDs are its lack of interference with platelet function, resulting in no increased risk of bleeding, and its safe administration in patients with a history of peptic disease. Acetaminophen has been demonstrated to be an effective analgesic in the perioperative period.[26,27] Current practice guidelines for acute pain management in the perioperative setting recommend that, unless contraindicated, all patients should receive an around-the-clock regimen of NSAIDs, COX-2 inhibitors, or acetaminophen.[10]

Gabapentinoids

Gabapentin and pregabalin bind to the a_2d subunit of voltage-dependent calcium channels in activated neurons in the spinal cord and brain, thus inhibiting calcium influx and preventing the release of excitatory neurotransmitters.[28] Both drugs are used as anticonvulsants and in the treatment of neuropathic pain. Pregabalin has a more favorable pharmacokinetic profile, with improved bioavailability and faster achievement of therapeutic levels. Several meta-analyses have confirmed the efficacy of gabapentin in reducing postoperative opioid use and pain.[29–31] Pregabalin has also been found to be effective at reducing acute postoperative pain.[32,33] However, the addition of gabapentinoids to the MA strategy has been frequently associated with increased sedation in the early postoperative period.[30,34]

Local Anesthetics

Local anesthetics inhibit sodium influx through voltage-gated sodium channels in the neuronal cell membrane. When the influx of sodium is interrupted, an action potential cannot arise and pain signal transmission to the central nervous system is inhibited. Local anesthetics can be administered by different routes, including wound infiltration and peripheral nerve blocks, or be delivered near the central nervous system epidurally or intrathecally. Regionally delivered local anesthetics have been extensively used in the perioperative setting not only for postoperative analgesia but also for surgical anesthesia. Local anesthetics have proven to be effective in decreasing postoperative pain and use of opioids.[35,36] The role of systemically delivered local anesthetic in the perioperative setting was recently summarized by Vigneault.[37] In a systematic review of randomized controlled trials, he showed that perioperative intravenous (IV) infusion of lidocaine decreased postoperative pain and use of opioids, as well as ileus duration, emesis, and length of stay. These benefits were mainly seen after abdominal surgeries. Analgesic techniques including use of local anesthetic have also been associated with better outcome.[38]

α_2-Adrenergic Agonists

α_2-adrenergic agonists produce analgesia by interaction with α_2 receptors within the locus coeruleus and the spinal cord.[39] Blaudszun[40] conducted a systematic

review and meta-analysis of randomized placebo-controlled trials evaluating the role of systemically administered clonidine or dexmedetomidine in postoperative pain and opioid consumption. He found that the perioperative systemic administration of α_2 agonists decreased postoperative opioid consumption, pain intensity, and nausea. The use of clonidine and dexmedetomidine was also associated with an increased incidence of hypotension and bradycardia. Engelman[41] showed that the addition of intrathecal clonidine to intrathecal morphine resulted in a small improvement in postoperative analgesia but the incidence of hypotension was also increased. In a recent systematic review and meta-analysis, Abdallah[42] showed that dexmedetomidine prolonged sensory and motor blockades with no incidence in hypotension when added to spinal local anesthetics. As an adjuvant to local anesthetic in brachial plexus anesthesia, dexmedetomidine prolonged motor blockade but did not prolong sensory blockade. It also increased the incidence of bradycardia.

N-Methyl-D-Aspartate Receptor Antagonists

Glutamate is the main excitatory neurotransmitter in the central nervous system. In the dorsal horn of the spinal cord, glutamate is released from primary afferent terminals and binds postsynaptic receptors to depolarize second-order neurons and thus transmits the nociceptive signal to the brain. A variety of glutamate receptors have been described, including the a-amino-3-hydroxy-5-methyl-4-isoxasole propionic acid (AMPA) receptor, the *N*-methyl-D-aspartate (NMDA) receptor, the kainate receptor, and multiple metabotropic receptors. The AMPA receptor is associated with the fast transmission of pain signals at the level of the spinal cord. The NMDA receptor has been demonstrated to play a role in the development of central sensitization and, separately, in the mechanisms underlying opioid analgesia and opioid tolerance. Ketamine has been the most commonly used NMDA receptor antagonist in the perioperative setting. Ketamine has been shown to reduce opioid requirements and to decrease nausea and vomiting during the first 24 hours following surgery, with mild or no associated adverse effects.[43,44] The effects of memantine use in the perioperative setting remain unclear. Nikolajsen[45] and Maier[46] showed that memantine had no beneficial effect in patients with established chronic phantom limb pain. On the other hand, in a randomized, double-blinded, placebo-controlled trial, Schley[47] showed that using memantine immediately after upper limb amputation for 4 weeks revealed an almost fourfold decrease in the incidence of phantom limb pain 6 months after surgery.

Antidepressants

Antidepressant effects result from enhancing noradrenergic and/or serotonergic mechanisms at the level of the central nervous system.[48] The early generations of antidepressants (e.g., tricyclics [TCAs] and monoamine oxidase inhibitors [MAOs]) have gradually been replaced by the newer selective serotonin reuptake inhibitors (SSRIs) and the serotonin-norepinephrine reuptake inhibitors (SNRIs), which have more favorable profiles regarding possible adverse effects. Serotonin and norepinephrine also modulate descending inhibitory pain pathways in the central nervous system. Duloxetine, one of the newer SNRIs, has shown to be effective in treating several chronic pain disorders, including diabetic peripheral neuropathic pain, fibromyalgia, chronic musculoskeletal pain due to chronic osteoarthritis, and chronic low back pain.[49] On the other hand, there is a lack of research regarding the role of antidepressants in perioperative pain management. Recently, in a small, randomized, blinded, controlled trial, Ho[50] showed that duloxetine decreased the use of IV morphine patient-controlled analgesia (PCA) during the first 48 hours after total knee arthroplasty.

Managing Pain after Neurosurgical Procedures

Postoperative Pain Management after Craniotomy

Pain after craniotomy may not be as severe as pain after major spine surgery or thoracotomy, but multiple studies have confirmed that postcraniotomy patients experience pain, and in many of them, pain is moderate or severe.[51] Uncontrolled pain and the associated sympathetic stimulation may result in undesirable effects, including psychological distress, hypertension, tachycardia, elevated intracranial pressure, and increased risk of bleeding, vomiting, and cardiovascular complications. On the other hand, the overuse of analgesics, opioids in particular, may result in nausea, vomiting, sedation, and respiratory depression. A fast recovery from general anesthesia to make possible an early neurological evaluation and rapid detection of complications has become current practice in modern neurosurgery. The main challenge to pain management providers is to bring the patient to a comfortable level of analgesia while keeping the patient alert enough to cooperate with the neurologic examination.

As mentioned in the previous section, MA takes advantage of the summative and synergistic effects of combining analgesic drugs with different mechanisms

of action, so that lower effective doses can be used, with lower risk of developing adverse effects. The following text presents the current evidence for the use of different MA components in postcraniotomy patients.

Acetaminophen

In a randomized, blinded, controlled study, Verchère[4] showed that when scheduled IV propacetamol, the prodrug of acetaminophen, is used as a single analgesic drug, it does not provide adequate analgesia after supratentorial craniotomy. The addition of on-demand tramadol or on-demand nalbuphine was necessary to control pain. Similarly, in a prospective, nonblinded study of 43 patients Nair[52] demonstrated that acetaminophen 1 g orally every 6 hours alone is not an effective analgesic after supratentorial craniotomy. With this regimen, inadequate analgesia presented in 63% of patients in the first 12 hours, and in 12% of them pain was severe.

Special Considerations

Scheduled acetaminophen has an opioid-sparing effect and should be part of a multimodal analgesia strategy. It should not be used as a sole analgesic after craniotomy.

Nonsteroidal Anti-inflammatory Drugs

Nonselective COX-1/COX-2 Inhibitors

Bauer[53] performed a retrospective review of 51 children following craniotomy for tumor resection or biopsy. Postoperative analgesia was attempted by alternating scheduled ibuprofen and scheduled acetaminophen. Rescue morphine was used upon nurse discretion to ensure patient comfort, and 54.9% of children received postoperative morphine for breakthrough pain. One patient presented with moderate postoperative hemorrhage in the tumor cavity but was asymptomatic and required no intervention. Authors concluded that their analgesia strategy did not result in any significant postoperative hemorrhage. In a randomized, nonblinded, controlled study, Na[54] compared an IV PCA containing fentanyl and ketorolac with on-demand fentanyl or on-demand ketorolac in 106 patients following supratentorial and infratentorial craniotomies. The fentanyl–ketorolac PCA provided better analgesia without any major adverse events or any disturbances on postoperative neurologic examination compared with the on-demand regimen. Dolmatova[51] compared a scheduled regimen of lornoxicam, a non-selective NSAID available in Asia and Europe, with an on-demand regimen of lornoxicam in 126 patients following supratentorial and infratentorial craniotomies. Patients receiving the scheduled drug presented with better pain control and fewer patients in this group required rescue tramadol. In the on-demand group, more than 50% of patients experienced moderate to severe pain. Postoperative hematomas, renal failure, or peptic ulcers were not observed in either group.

Special Considerations

The addition of nonselective NSAIDs improves analgesia. They have an opioid-sparing effect and are more effective when used around the clock than on-demand. Their use in small trials has not shown an increase in complication rate. Their safe use in craniotomy patients remains to be proven in larger populations.

Selective COX-2 Inhibitors

In a small, randomized, single-blinded study, Rahimi[55] showed that the addition of scheduled rofecoxib to on-demand oxycodone/acetaminophen after craniotomy resulted in better pain control and less use of opioid. The group receiving rofecoxib also presented with a shorter length of stay in hospital. However, rofecoxib was withdrawn from the market after its association with increased cardiac ischemia.[20,21] In a randomized, blinded, controlled trial Williams[56] demonstrated no analgesic benefit by adding IV parecoxib at dural closure time to a MA regimen including bupivacaine scalp infiltration before incision, scheduled IV acetaminophen, and IV morphine PCA during the first 24 hours after supratentorial craniotomy. At present, no studies have been conducted to evaluate perioperative use of celecoxib in postcraniotomy patients.

Special Considerations

There is no evidence supporting the use of currently available selective COX-2 inhibitors in postcraniotomy patients.

Opioids

Verchère[4] showed that acetaminophen is not an effective analgesic as a sole component and that the addition of opioids is required. He showed that nalbuphine was more effective than tramadol in accomplishing this task. Tramadol was associated with a

trend toward higher incidence of nausea and vomiting compared with nalbuphine. Some neuroanesthesiologists have mentioned that postcraniotomy patients are unlikely to benefit from PCA because of mental status impairment after surgery.[57] In contrast, in a randomized, controlled study, Jellish[58] demonstrated that after skull base craniotomy IV morphine PCA reduced pain scores and rescue analgesic dosing compared to on-demand IV morphine. Moreover, Morad[59] compared IV fentanyl PCA to on-demand IV fentanyl during the first 16 hours following surgery. He showed that IV fentanyl PCA was more effective than on-demand IV fentanyl, when added to scalp infiltration and scheduled acetaminophen. There was no major adverse event in this study. Sudheer[60] compared IV morphine PCA with IV tramadol PCA and with intramuscular (IM) codeine during the first 24 hours following surgery. The three groups presented with similar increases in arterial carbon dioxide level ($PaCO_2$) and no increased risk of excess sedation. The use of morphine resulted in better pain control and higher patient satisfaction. The tramadol group showed the highest level of pain and nausea, and the lowest level of patient satisfaction. On the other hand, Rahimi[61] in a nonplacebo control study showed that scheduled tramadol resulted in less pain and shorter length of stay when added to oral oxycodone/acetaminophen and on-demand IV morphine. Na[54] conducted a prospective, randomized, controlled study to compare the use of IV PCA containing fentanyl and ketorolac to the same drugs given on an on-demand IV basis during the first 24 hours after surgery. The PCA group showed better pain control and there were no major adverse events in any groups. Despite the higher consumption of fentanyl and ketorolac in the PCA group, there was no interference with the neurologic examination.

Special Considerations

Opioids are required by the majority of patients. They should be part of the MA strategy in postcraniotomy patients. The use of full μ-receptor agonists fentanyl and morphine results in better analgesia and no increase in side effects compared with the less potent opioids tramadol and codeine. PCA has shown to be effective in this patient population, with no increase of adverse effects in any of the reviewed studies. The IM route should be abandoned.

Gabapentinoids

Ture[62] studied the analgesic effect of gabapentin when used as a prophylactic anticonvulsant in supratentorial craniotomy. In a randomized, blinded, controlled trial he compared gabapentin 1,200 mg daily to phenytoin 300 mg daily, initiated 7 days before surgery and continued for at least 6 months postoperatively. All patients received dexamethasone for about a week after surgery. Postoperative pain was managed with IV morphine PCA. Patients receiving gabapentin reported a small but significant decrease in pain during only the first hour following surgery, but consumed 28% less morphine and required less antiemetic therapy throughout the 48-hour study period compared with patients receiving phenytoin. In addition, gabapentin use resulted in decreased doses of remifentanil and propofol during general anesthesia. Nevertheless, gabapentin use resulted in longer extubation time and increased sedation during the first 2 hours following surgery. These results are encouraging because they demonstrate the opioid-sparing effect of gabapentin as part of a MA regimen following craniotomy. However, the anticonvulsant dose used in this study was associated with undesired initial sedating effects that may limit its use in this population.

Special Considerations

The perioperative use of gabapentin in craniotomy patients has shown an opioid-sparing effect. The minimal analgesic dose to avoid prolonged sedation after surgery remains to be identified.

Local Anesthetics

Surgical Wound and Pin Site Infiltration

In a randomized, blinded, controlled trial, Biswas[63] studied the effects of preincisional infiltration of local anesthetic in postoperative pain following elective supratentorial craniotomy. He compared the infiltration of 25 mL of 0.25% bupivacaine without epinephrine along the proposed line of incision with 2 μg/kg of IV fentanyl given before surgical incision. There was no difference in postoperative pain or in requirements for rescue analgesics between the two groups during the first 48 hours after surgery. Hansen[64] conducted a systematic review of randomized clinical trials to evaluate the current evidence regarding analgesia following craniotomy. He identified five studies comparing scalp and/or skull pin site infiltration with bupivacaine or ropivacaine versus placebo.[65–69] Bloomfield[66] showed a reduction in visual analogue scale (VAS) score only upon admission to the postanesthesia care unit (PACU) when bupivacaine was used. Saringcarinkul[69] reported a significantly reduced verbal numeric scale (VNS) score only for the first hour after surgery when bupivacaine with epinephrine was injected before skin closure. Law-Koune[68] compared infiltration with bupivacaine or ropivacaine and placebo before final

closure of the scalp, to show no difference in VAS scores between groups. Both local anesthetic groups showed reduced use of morphine consumption only in the first 2 hours compared with the placebo group. On the other hand, El-Dawlatly[67] demonstrated that infiltration of the skull pin sites with bupivacaine reduced VAS scores up to 48 hours postoperatively. Batoz[65] also showed that ropivacaine reduced VAS scores up to 24 hours postoperatively, but without reduction of overall analgesic requirements. The pooled data from these five trials included a total of 112 patients receiving infiltration with local anesthetic and 137 controls. No major side effects were reported in any of the studies.

Special Considerations

Wound and skull pin site infiltrations in patients undergoing craniotomy are associated with reduced pain during the first few hours after craniotomy, but they do not seem to reduce the requirements for rescue analgesics. Available data show no difference between bupivacaine and ropivacaine.

Scalp Nerve Block

A skull block can be performed by infiltrating 2 to 5 mL of local anesthetic at the level of the nerves that innervate the scalp. The technique, as described by Pinosky,[70] consists of blockade of the supraorbital and supratrochlear nerves as they emerge from the orbit above the eyebrow; the auriculotemporal and the greater auricular nerves are each blocked anterior and posterior to the ear at the level of the tragus. The greater and lesser occipital nerves are blocked by infiltration along the superior nuchal line at the midpoint between the occipital protuberance and the mastoid process. Optionally, the zygomaticotemporal nerve can be blocked lateral to the orbit. Nerves can be blocked unilaterally or bilaterally, or only a subgroup of them can be blocked to accommodate surgery requirements. In a recent systematic review, Guilfoyle[71] identified seven randomized, controlled trials, including a total of 325 patients, where the main goal was to evaluate the analgesic effect of a scalp nerve block (SNB) in supratentorial craniotomy. Five of these trials compared SNB with blocks performed with saline, with or without epinephrine.[72–76] The other two trials compared SNB with IV fentanyl[77] or no block.[78] The subsequent meta-analysis of the pooled data from these seven trials demonstrated that SNB was effective at reducing pain after supratentorial craniotomy. SNB performed before surgical incision was effective up to 6 to 8 hours after surgery. When SNB was performed after incision closure but before extubation, analgesia was prolonged up to 12 hours following surgery. There was also an overall reduction in the opioid requirements over the first 24 hours postoperatively when SNB was performed. The decision to perform a SNB before or after surgery should consider other surgical parameters in addition to the duration of postoperative analgesia. For awake craniotomy a SNB performed before surgery is generally considered necessary to minimize patient discomfort and use of sedatives that may interfere with neurologic assessment. A preoperative SNB may also have the advantage of blunting hemodynamic responses to skull pinning, skin incision, flap dissection, and craniotomy. The resulting reduction of general anesthetic requirements may facilitate an earlier emergence and lessen cognitive dysfunction in the immediate postoperative period. The small sample sizes of available published studies preclude an accurate estimation of the incidence of adverse effects and complications from SNB. These complications may include bleeding and infection at nerve block puncture sites, intravascular injection of local anesthetic, subarachnoid injection, and transient facial palsy. In a study by Guilfoyle[71] no complication was reported in the 170 patients who underwent the block.

Special Considerations

Scalp nerve block in craniotomy patients is effective in reducing pain during the first 6 to 12 hours after surgery and opioid requirements over the first 24 hours postoperatively. The question regarding the optimal local anesthetic for this indication remains unanswered.

N-Methyl-D-Aspartate Receptor Antagonists

In an early study, Sari[79] demonstrated in eight patients that anesthetic doses of IV ketamine (3 mg/kg) resulted in increased calculated cerebral blood flow (CBF) and cerebrospinal fluid (CSF) pressure measured through a lumbar catheter. These ketamine effects could be minimized or abolished by the induction of modest levels of hyperventilation-induced hypocarbia. In an 8-year-old patient, Wyte[80] also showed that an anesthetic dose of IV ketamine (2 mg/kg) resulted in a transient increase in intracranial pressure (ICP) measured through an external ventriculostomy. More recently, Himmelseher[81] conducted an extensive literature review to evaluate the cerebral hemodynamic and neuroprotective effects of ketamine in humans. She concluded that, under conditions of controlled ventilation and sedation, ketamine did not increase ICP. Instead, a greater cerebral perfusion pressure (CPP) was maintained when ketamine was used for sedation than when opioids were administered and the need for vasopressors

was reduced. Experimental data from the laboratory indicate neuroprotective effects for ketamine but evidence for neuroprotection in humans is not available.

Special Considerations

At present, no systematic study has evaluated the role of subanesthetic doses of IV ketamine or other NMDA receptor antagonist as a component of multimodal analgesia in craniotomy patients.

α_2-Adrenergic Agonists

In a randomized controlled trial, Stapelfeldt[82] studied the effects of clonidine in preventing shivering during the first 2 hours after supratentorial craniotomy. Whereas 3 µg/kg of IV clonidine (compared with saline) administered at the beginning of dural closure drug effectively prevented shivering after mild hypothermia, it did not delay emergence from anesthesia or have any clinically significant sedative or hemodynamic effects. Interestingly, VAS scores for pain or analgesic requirements were also not different between the clonidine and the saline groups. Tanskanen[83] in a double-blinded, randomized, controlled design evaluated the hemodynamic and respiratory effects of two doses of dexmedetomidine versus control in supratentorial craniotomy patients. Although postoperative pain was only a secondary endpoint, the study showed no difference in oxycodone use between the dexmedetomidine and the control groups during the early postoperative period.

Special Considerations

No study has been designed specifically to evaluate the role of α_2-adrenergic agonists in postoperative pain management following craniotomy.

Postoperative Pain Management after Spine Surgery

Managing postoperative pain for patients undergoing major spine surgery is undoubtedly one of the most challenging scenarios for the pain management provider. The extent of surgery often parallels the intensity of pain, in part as a result of the respective tissue manipulation and disruption. Thus, the difficulty in obtaining satisfactory pain relief seems to increase proportionally to the number of spinal levels involved. Patients scheduled to undergo spine surgery typically have experienced chronic pain for longer periods of time and frequently have been exposed to a wide range of pain medications prior to surgery. Compared with patients with other neurosurgical problems, patients with spine pathology have significantly decreased functional status and higher level of chronic pain preoperatively.[84,85] Patients with chronic back pain present with changes in the way nociception is processed in the central nervous system. There is facilitation of excitatory inputs, making these patients more sensitive to pain signals.[86] Moreover, the preoperative chronic exposure to opioid medications is common in this population and results in opioid tolerance and, sometimes, in opioid-induced hyperalgesia (OIH).[87] Both conditions result in diminished analgesic effects of opioids. Despite best efforts, patients after spinal surgery often continue to have significant residual pain.[85]

Opioids

Opioids remain the cornerstone in the management of postoperative pain after spine surgery. They are mostly administered intravenously until the patient can tolerate oral intake. Other routes of administration include intramuscular[88] and subcutaneous,[89] as well as delivery into the epidural space[90–92] or intrathecal space.[90,93] Current efforts are focused on developing strategies to minimize the use of opioids in the perioperative period to decrease their potential adverse effects without compromising analgesia. The implementation of MA, as described above, has shown the most promising results in the management of postoperative pain in this challenging patient population. Rajpal[7] showed that perioperative use of MA has an opioid-sparing effect with decreased time spent with moderate or severe pain, improved side effects, and high patient satisfaction. Mathiesen[94] showed that standardized comprehensive MA in combination with proactive management of postoperative nausea and vomiting reduced opioid consumption, improved postoperative mobilization, and decreased levels of nausea, sedation, and dizziness after major spine surgery. Lee[95] pointed out that preemptive and multimodal analgesia for perioperative pain management in spinal surgery may lead to a better quality of life and higher patient satisfaction.

Special Considerations

Opioids should always be part of the strategy to manage postoperative pain after spine surgery. No opioid has proven to be superior to others when equianalgesic doses are used. Research continues to determine the role of neuraxially delivered opioids in this population. Comprehensive postoperative strategies including multimodal analgesics and antiemetics decrease opioid requirements without compromising effective pain reduction.

Acetaminophen

Hernández-Palazón[96] compared the use of propacetamol, a prodrug of acetaminophen, to placebo for 72 hours in patients after elective decompressive lumbar laminectomy with spinal fusion. The use of propacetamol resulted in mild improvement of analgesia, less sedation, and a 46% reduction in morphine use compared with placebo. In a prospective, double-blinded, randomized, placebo-controlled study, Cakan[97] showed that the use of IV acetaminophen during the first 24 hours after laminectomy and discectomy resulted in better analgesia, better patient satisfaction, and less vomiting compared with placebo. The use of IV acetaminophen did not decrease morphine PCA consumption. In pediatric patients undergoing major spine surgery, the use of IV acetaminophen every 8 hours postoperatively resulted also in a decrease in VAS scores compared with placebo, but oxycodone consumption during the first 24 hours after surgery was not decreased either.[98]

Special Considerations

Acetaminophen effectively improves analgesia when added to opioids and should be part of the MA strategy in the management of pain after spine surgery. Its opioid-sparing effects remain controversial.

Nonsteroidal Anti-inflammatory Drugs

Nonselective COX-1/COX-2 Inhibitors

Cassinelli[99] studied the analgesic effects of ketorolac after one- or two-segment lumbar laminectomy for symptomatic spinal stenosis. Patients received three consecutive doses of ketorolac or placebo, starting at the time of surgical wound closure. Patients in the ketorolac group showed decreased pain score and morphine use during the first 24 hours postoperatively. There were no adverse effects associated with the use of ketorolac, although the study sample was relatively small. In a meta-analysis of randomized controlled trials assessing the analgesic effects of NSAIDs in the perioperative period of patients after lumbar spine surgery, Jirarattanaphochai[100] showed improved analgesia and reduced opioid requirements when NSAIDs were used. There was no difference in the incidence or severity of adverse effects between the 400 patients who received NSAIDs and those who did not.

Despite the proven analgesic effects of NSAIDs, their use remains controversial among providers due to concerns about inhibition of bone healing and increased risk for nonunion in spinal fusion and their potential increased risk for bleeding. In a retrospective study, Glassman[22] showed a fivefold increase in the incidence of pseudarthrosis in patients receiving postoperative ketorolac after an instrumented lumbar spinal fusion compared with a group of patients who did not receive ketorolac. The nonunion rate seemed to increase in a linear way with increasing number of ketorolac doses. Patients in the ketorolac group received an average of 10 (range 1–39) consecutive doses of ketorolac 30 mg following a loading dose of 60 mg. The results led the authors to recommend that NSAIDs be avoided in the early postoperative period of instrumented spinal fusions. A decade later, Sucato[23] showed no difference in pseudarthrosis incidence in a retrospective review comparing patients who had postoperative ketorolac and those who did not, following a posterior spinal fusion and instrumentation for adolescent idiopathic scoliosis. In this study, the average number of doses of ketorolac given to patients was 7 (range 1–14) for an average of 27 mg (range 15–60), administered all within the first 48 hours of surgery. Pradhan[101] also conducted a retrospective study to determine the incidence of nonunion after lumbar spine fusion in adult patients receiving ketorolac as adjunctive analgesic for 48 hours postoperatively. The group of 228 nonsmoker patients who received ketorolac presented a pseudarthrosis incidence rate of 5% at 34 months after surgery, similar to the rate of 6% seen in the control group of 177 patients. In this study, all patients received the same dose and duration of the drug, 30 mg intravenously every 6 hours for a total of 48 hours (total 240 mg). Finally, Li[102] performed a meta-analysis of retrospective studies evaluating the effects of NSAIDs in lumbar spine fusion and suggested that short time exposure (≤ 14 days) to high doses of ketorolac (≥ 120 mg daily) increased the risk of nonunion. In contrast, short time exposure to lower doses of NSAIDs showed no difference in nonunion incidence compared with the control group.

Special Considerations

The use of nonselective NSAIDs after spine surgery improves analgesia and decreases opioid requirements. At recommended doses, studies have not shown an increase in adverse effects. Specifically, ketorolac at doses < 120 mg daily for 48 hours after spine fusion has not been associated with increased incidence of pseudarthrosis or postoperative bleeding. NSAIDs should be part of the perioperative multimodal analgesia in patients undergoing spine surgery.

Selective COX-2 Inhibitors

In a placebo-controlled, randomized, and double-blinded trial, Jirarattanaphochai[103] studied the effects of parecoxib, a selective COX-2 inhibitor available in

Europe and Asia, in 120 patients undergoing lumbar spine surgery. A preoperative dose of parecoxib, followed by a 48-hour treatment, resulted in a 30% decrease in pain scores and 39% reduction in morphine-PCA use compared with placebo. Parecoxib was not associated with increased risk of adverse effects. In contrast, when Grundmann[104] studied a single dose of parecoxib preoperatively in patients undergoing lumbar microdiscectomy, he found no better pain relief in a group treated with parecoxib compared with placebo. Karst[105] showed that celecoxib use did not decrease pain scores or piritramide-PCA requirements in the first 72 hours in patients after single-level lumbar microdiscectomy. However, these results may have been influenced by the fact that 20 out of 34 of the patients in this study also received a high dose of intraoperative IV dexamethasone, which has also shown analgesic effects in this type of surgery.[106]

Special Considerations

There is a lack of studies regarding use of selective COX-2 inhibitors in patients undergoing spine surgery. The analgesic effects of parecoxib, which is not available in the United States, remain controversial. There is no evidence for the use of celecoxib in this patient population.

Gabapentinoids

In patients undergoing a single-level laminectomy, a preincisional or postincisional single dose of gabapentin, 900 or 1,200 mg, resulted in improved VAS pain scores during the first 12 hours after surgery and in a decrease in morphine consumption in the first 24 hours postoperatively.[107] Radhakrishnan[108] was unable to confirm these findings when gabapentin 800 mg, divided into two doses, was given preoperatively to patients undergoing lumbar laminectomy and discectomy. There was no improvement in postoperative analgesia or decreased use of morphine in patients receiving gabapentin compared with the ones receiving placebo. In this study, follow-up was limited to the first 8 hours after surgery. Pandey[109] studied different doses of gabapentin given 2 hours before surgery in patients undergoing a single-level discectomy. The four studied doses, 300, 600, 900, and 1,200 mg, all resulted in decreased VAS pain scores and in decreased fentanyl consumption during the first 24 hours after surgery compared with placebo. Doses of gabapentin higher than 300 mg resulted in a better VAS pain score, but additional reduction in fentanyl use was not seen with doses above 600 mg. There was also a tendency toward an increased incidence of side effects at higher doses of gabapentin. The authors suggest a single dose of 600 mg of gabapentin as the optimal preoperative dose in this group of patients. Rusy[110] conducted a double-blind, randomized, controlled trial in children and adolescents undergoing spinal fusion for idiopathic scoliosis to study the analgesic effects of gabapentin when given preoperatively and continued for 5 days postoperatively. Patients receiving gabapentin presented with decreased pain scores in the recovery room and on the morning after surgery. Gabapentin-treated patients also consumed less morphine during the first 2 days after surgery compared with the placebo group. There was no difference in adverse effects between the gabapentin and placebo groups.

In a prospective, randomized, controlled, double-blinded trial, Kim[111] compared two doses of perioperative pregabalin with placebo in patients undergoing elective posterior lumbar spinal fusion. He showed that pregabalin 150 mg preoperatively followed by 150 mg 12 hours later was effective in decreasing fentanyl-PCA consumption for 48 hours after surgery without increasing the incidence of adverse effects. In patients receiving the lower dose of pregabalin (75 mg every 12 hours), VAS pain score and fentanyl consumption were not different compared with the placebo group. Gianesello[112] studied the effects of preoperative pregabalin 300 mg followed by 150 mg twice a day for 48 hours postoperatively in patients undergoing elective decompressive lumbar laminectomy. The use of pregabalin resulted in lower VAS pain scores during the first 12 hours after surgery and in a decrease in morphine consumption during the first 48 hours postoperatively, compared with placebo. Postoperative nausea, vomiting, and incidence of constipation were lower in the pregabalin group than in the placebo group.

Ozgencil[113] compared the perioperative use of gabapentin 1,200 mg daily and pregabalin 300 mg daily with placebo in patients undergoing elective decompressive lumbar laminectomy and discectomy. Both the gabapentin and the pregabalin groups presented with decreased VAS pain score during the first 6 hours after surgery and a decrease in morphine consumption during the first 24 hours postoperatively, compared with the placebo group. In addition, patients treated with gabapentin and pregabalin showed significantly less preoperative anxiety, pruritus, and postoperative shivering, and with either drug patient satisfaction was significantly higher than in the placebo group. There was no difference between the use of gabapentin and pregabalin at the studied doses.

Special Considerations

The use of gabapentinoids in patients undergoing spine surgery decreases pain scores and opioid requirements. Optimal doses and treatment intervals remain to be determined in this patient population. As of today, gabapentin 600 mg or pregabalin 300 mg preoperatively seems to be an appropriate dose to improve postoperative analgesia without increasing adverse effects.

Local Anesthetics

Intravenous Lidocaine Infusion (IVLI)

In a randomized, double-blinded, placebo controlled study, Kim evaluated the effects of intravenous lidocaine infusion (IVLI) in patients undergoing a single level lumbar laminectomy and microdiscectomy.[114] Patients assigned to the lidocaine group received an IV lidocaine bolus during induction of general anesthesia, followed by a continuous infusion of IV lidocaine that was discontinued at the end of the surgery. The use of IVLI resulted in decreased pain scores and decreased use of IV fentanyl during the first 24 hours after surgery. Moreover, patients in the lidocaine group had a hospital stay one day shorter than patients in the control group. Inclusion criteria for this study were restricted to healthy, relatively young, opioid naïve patients with no history of previous spine surgeries.

Farag evaluated the analgesic effects of IVLI in patients undergoing moderate to complex spine surgeries including at least three vertebral levels.[115] In a randomized, double-blinded, placebo controlled fashion, IVLI was started at induction of general anesthesia and continued up to 8 hours postoperatively in the postanesthesia care unit. The use of IVLI resulted in decreased adjusted pain scores during the first 48 hours after surgery but failed to show a significant decrease in opioid use during that same period of time. Patients included in this study underwent surgeries of unequal levels of complexity, with and without instrumentation, performed at different level of the spine from cervical to sacral, and presented with different degrees of preoperative opioid tolerance. The heterogeneity of this study population and its relatively small size (n = 115) may have prevented authors from controlling for these confounding factors, making study results difficult to interpret and extrapolate.

Special Considerations

The number of studies evaluating the use of perioperative IVLI in spine surgeries is still limited. Initial results show decreased pain scores during the first 24–48 hours of the postoperative period in patients receiving IVLI. Future studies in larger populations are needed to confirm this analgesic effect and other potential benefits like reduction in postoperative opioid demands and shorter hospital stays. The impact of the extension of the surgery, the section of the spine to be intervened, the use of instrumentation, and the level of preoperative opioid tolerance need to be taken into account. The optimal dose of IV lidocaine and the need for a postoperative infusion remain to be determined as well.

N-Methyl-D-Aspartate Receptor Antagonists

The use of a single bolus dose of IV ketamine (0.15 mg/kg) administered in combination with IV morphine (0.1 mg/kg) after induction of anesthesia showed a decrease in postoperative morphine consumption up to 24 hours and a decrease in VAS pain scores up to 48 hours after lumbar disk surgery in opioid-naive patients.[116] Patients receiving the combination of ketamine and morphine also had a decreased incidence of nausea during the first 48 hours after surgery compared with patients receiving morphine alone. Other studies have confirmed the opioid-sparing effect of ketamine in patients undergoing multilevel lumbar spine surgery with instrumentation and fusion[117] and in patients undergoing cervical spine surgery.[118] Urban[119] studied the effects of perioperative ketamine in opioid-tolerant patients (i.e., patients taking more than 60 mg of oral oxycodone equivalents daily) undergoing one- or two-level posterior lumbar fusions with segmental instrumentation. Patients receiving ketamine 0.2 mg/kg at induction of general anesthesia followed by 2 µg/kg/hour for the next 24 hours had decreased pain scores for the first 24 hours after surgery compared with patients who did not receive ketamine. The use of ketamine did not result in a significant reduction in opioid consumption postoperatively. In contrast, Subramaniam[120] concluded that IV bolus ketamine 0.15 mg/kg at induction of anesthesia followed immediately by an infusion of 2 µg/kg/min for the next 24 hours did not improve postoperative analgesia in opioid-tolerant patients undergoing lumbar or thoracolumbar laminectomy and fusion for back pain. In this study, patients also received an infusion of epidural bupivacaine during the study period, which may have masked potential benefits from ketamine. In contrast, in a more recent randomized, prospective, double-blinded, and placebo-controlled trial involving opioid-tolerant patients undergoing major lumbar spine surgery, a bolus of ketamine 0.5 mg/kg on induction of anesthesia followed by an intraoperative infusion of 10 µg/kg/min resulted in 37% reduction in opioid consumption the first 48 hours postoperatively, and sustained improvement in VAS pain scores and morphine consumption compared with placebo at 6 weeks.[121] The greatest benefit from ketamine was actually noticed in patients taking greater than 40 mg of oral morphine equivalents per day preoperatively. Despite the higher doses used relative to previous investigations, the incidence of adverse effects was similar between patients in the ketamine versus the placebo group.

Special Considerations

The perioperative use of ketamine in patients undergoing spine surgery results in improved analgesia and decreased opioid requirements with no significant adverse effects. These benefits seem to be more significant in opioid-tolerant patients and may potentially be dose dependent.

Neuraxially Delivered Analgesics

An alternative method of pain control in spine surgeries involves placement of medication within the epidural space or thecal sac, typically by the surgeon on the open field. This analgesia strategy has been controversial due to the small size of studies, nonuniform medications and dosages across studies, and the potential increase in neurologic and respiratory complications. Tobias[122] conducted a review of the evidence regarding the use of neuraxial techniques to provide analgesia after spine surgery in the pediatric population. He concluded that available data were insufficient to support the superiority of these techniques over systemic opioids in controlling postoperative pain, but he did note that neuraxial-based methods were associated with decreased intraoperative blood loss and quicker return of bowel function postoperatively. Since this review, other studies have continued to look at the analgesic effects of neuraxial techniques. A randomized, controlled study of 84 consecutive adult patients undergoing posterior discectomy caudal to T12 found that a preoperative caudal injection of 15 mL of 0.5% bupivacaine with 1 mL (50 mg) of tramadol hydrochloride and 4 mL of distilled water resulted in significantly better postoperative pain scores for up to 24 hours compared with the control group.[92] The only adverse event noted in this adult population was transient urinary retention requiring catheterization. In a retrospective review of 407 pediatric patients undergoing posterior spinal fusion for scoliosis, the intrathecal (IT) application of morphine at a mean dose of 14 µg/kg (range 9–19 µg/kg) resulted in an immediate VAS postoperative pain score of 0.5 out of 10, significantly lower than the VAS of 5.1/10 seen in the IV opioid control group. That dose of IT morphine was not associated with increased incidence of adverse effects compared with the control group. In contrast, IT morphine at doses of 20 µg/kg or higher resulted in increased incidence of respiratory depression and admission to the pediatric intensive care unit (PICU).[93] More recently, Milbrandt[90] conducted a retrospective study in 138 adolescents undergoing posterior spinal fusion for idiopathic scoliosis repair. He found that a single IT administration of morphine at 7 µg/kg provided the most effective immediate postoperative pain control compared with a continuous epidural infusion with bupivacaine 0.1% plus hydromorphone 20 µg/mL or to IV morphine-PCA. At 24 hours after surgery, the continuous epidural infusion provided better analgesia than single-dose IT or IV-PCA morphine The epidural analgesia group had a faster return to solid food consumption, but also a statistically significant increase in transient neurologic changes and respiratory depression compared with the IT and IV morphine groups, respectively. In a randomized, double-blinded, controlled study conducted in adults undergoing noncervical laminectomies, Mishra[91] showed that buprenorphine-soaked gelatin sponges placed in the epidural space resulted in better analgesia and less sedation in the early postoperative period compared with the control group. The incidence of nausea was also higher in the group receiving buprenorphine. In a small prospective nonblinded study, Blumenthal[123] compared the analgesic efficacy of continuous double epidural catheter infusion of ropivacaine with continuous IV morphine infusion after scoliosis repair in adolescents and young adults. The epidural analgesia group presented with improved postoperative analgesia, earlier recovery of bowel function, fewer opioid-related adverse effects, and higher patient satisfaction. In a recent nonrandomized, nonblinded study, Mathiesen[94] compared patients receiving a new standardized comprehensive MA–antiemesis treatment regimen with a historic group of patients receiving usual care after elective posterior spine fusion on more than three spine segments. The standardized comprehensive regimen included acetaminophen, NSAIDs, gabapentin, ketamine, steroids, ondansetron and epidural bupivacaine infusion or morphine IV PCA. Compared with the historic group, patients receiving the comprehensive analgesic and antiemetic protocol showed reduced opioid consumption, improved postoperative mobilization, and decreased levels of nausea, sedation, and dizziness.

Special Considerations

In patients undergoing spine surgery, the use of single injection of neuraxial opioids with or without local anesthetics improves analgesia for the first 24 hours after surgery. Prolonged analgesic benefits seem to require continuous neuraxial drug infusion. There is no evidence of neurologic complications or increased incidence of infection associated with direct neuraxial drug application. Nevertheless, the safety of this approach needs confirmation from studies in larger populations. The appropriate drug or drug combination, the optimal delivery system (i.e., epidural vs. intrathecally), and the best treatment duration remain unknown.

Postoperative Pain Management after Other Neurosurgical Procedures

A subgroup of chronic pain patients will require neurosurgical interventions to control pain that has not responded to conservative or less invasive therapies. Examples of these neurosurgical interventions include implantation of intrathecal pumps, spinal cord or peripheral nerve stimulators, neuroablative craniofacial procedures, and cordotomies. These patients have often been exposed to

chronic opioid treatment before their surgery and have developed opioid tolerance. They may have also failed treatments with other analgesic agents commonly used in the perioperative setting. Thus, even if the surgical procedure may not appear too extensive, their postoperative pain management may be quite challenging. A successful analgesia strategy should start with advance planning and by early institution of MA, even prior to the surgical incision. In the patient taking opioids preoperatively, whereas the basal long-acting opioid may not require immediate postoperative adjustment, on-demand short-acting opioids are likely necessary for the first few postoperative days to treat the new surgical site pain. Later on, as the surgical site heals and the surgical pain decreases, the patient may be able to taper the total dose of opioids as a function of the success of the surgical procedure.

Patients being implanted with an intrathecal pump have typically undergone a successful percutaneous trial, where tolerance and response to an intrathecal opioid was tested. The dose of the intrathecal opioid should provide adequate control of the chronic pain without resulting in symptoms of sedation or withdrawal. The guidelines from the International Neuromodulation Society for the management of patients receiving an intrathecal pump have recently been updated.[124] After implantation, most patients will require on-demand short-acting opioids to manage the acute surgical pain while the constantly infused intrathecal opioid from the new pump will control their chronic pain. It is important to remember that opioid-tolerant patients have developed resistance to the analgesic effect of opioids and that standard postprocedure doses of opioids will likely be ineffective in this patient population. A higher dose of the short-acting opioid may be required to provide adequate pain relief during the first few postoperative days.

Most patients scheduled to undergo a cordotomy take high doses of opioids and have developed significant opioid tolerance. When the procedure results in a dramatic pain reduction, the provider may feel tempted to stop opioid treatment immediately. It is important to realize that the potential for very unpleasant and potentially dangerous withdrawal symptoms exists if opioids are discontinued or reduced too aggressively. A gradual tapering is required to avoid withdrawal while the patient's new opioid requirements are being determined.

Opioid Tolerance and Opioid-Induced Hyperalgesia

Patients who have been exposed to opioids preoperatively may have developed tolerance to the analgesic effects of these drugs. Tolerance is defined as a state of adaptation in which exposure to a drug induces changes that result in the diminution of one or more of the drug's effects over time.[125] In other words, the opioid-tolerant patient is resistant to standard doses of opioids normally used to manage postoperative pain and is at high risk of experiencing suffering and complications from uncontrolled pain. The group of opioid-tolerant patients includes (1) patients who are on a chronic opioid treatment for a chronic pain condition, (2) patients who are currently abusing opioids, and (3) previous opioid-abusing patients on current maintenance therapy with drugs like methadone or buprenorphine. The dose and time exposure necessary to develop opioid tolerance have not been clearly defined. The consumption of 60 mg of oral morphine equivalents daily for 1 week has been suggested as the minimal exposure for one to be considered an opioid-tolerant individual.[126] There is no formal classification of degrees of opioid tolerance, but most health care providers would agree that patients on very high doses of opioids represent a particularly challenging subset of patients when managing their pain in the perioperative period. The neurosurgical practice encounters opioid tolerance most frequently in patients who present for spine surgery and those with chronic headaches. In contrast, patients who currently consume opioids for recreational reasons or are on replacement therapy can be encountered with any medical problem requiring neurosurgical intervention.

During opioid therapy, a decline in the analgesic effect has traditionally been thought to result from the development of tolerance or baseline disease progression. Today it is recognized that opioids also can activate pronociceptive mechanisms, resulting in increased pain sensitivity, a phenomenon known as opioid-induced hyperalgesia (OIH). This state is characterized by a paradoxical response where a patient receiving opioids for the treatment of pain may actually become more sensitive to pain.

The mechanisms underlying opioid tolerance and OIH are complex, multifactorial, and still not fully understood. Tolerance may involve alterations in receptor regulation, desensitization and internalization, glutaminergic activation, as well as glial activation. OIH mechanisms seem to involve glutaminergic activation, altered opioid intracellular signaling involving G protein–coupled receptor switching, substance P and neurokinin-1 receptors, spinal dynorphin, toll-like receptor (TLR) signaling, and glial cell dysfunction.[127] The incidence as well as the pathophysiologic mechanisms and consequences of tolerance and OIH in the neurosurgical population are widely unknown and require further investigation.

Opioid tolerance and OIH have similar clinical manifestations (i.e., decreased analgesic effects). The difference resides in their management. Tolerance

may be addressed by increasing the opioid dose, a strategy that may result in aggravated pain if, indeed, the patient suffers from OIH. Approaches to manage OIH aim at treating pain while trying to modulate its expression. Treatment steps include a reduction of the opioid dose by careful titration, opioid rotation, avoiding periods of relative opioid abstinence and withdrawal, and instituting MA with adjuvant therapies such as NSAIDs, NMDA receptor antagonists, and regional or neuraxial anesthetic techniques where appropriate.[128]

Effective management of acute postoperative pain is challenging in the opioid-tolerant patient. For the same type of surgical intervention, compared with the opioid-naive patient, the opioid-tolerant patient will require higher doses of opioids than the doses included in "standard" order sets and for longer periods of time.[129] Unfortunately, the delivery of large doses of opioids does not always provide adequate analgesia, and in case of OIH may actually worsen pain. Moreover, the administration of large doses of opioids in the perioperative period can result in increased risk of opioid-related adverse effects, specifically sedation and respiratory depression,[130] which are of particular concern after neurosurgical interventions.

Effective pain management should start in the preoperative period by systematic identification of patients who have developed opioid tolerance or OIH. Detailed documentation of preoperative opioid treatment, including drugs and doses, is particularly important if adequate analgesia is to be achieved and withdrawal to be avoided. The perioperative analgesia strategy should consider patient preferences and past experiences. Reassurance of patients that acute pain management is a priority of the treatment team is often required, as well as careful explanations that adequate analgesia, although more difficult than in the opioid naive, is possible despite previous negative experiences with institutional pain management. Home doses of opioids should be taken on the day of surgery, even if the patient is fasting, or be administered intraoperatively if preoperative administration was missed. Intraoperatively, the anesthesia provider should expect higher opioid requirements and the need for a more aggressive opioid titration toward the end of surgery to allow a smooth emergence from anesthesia. MA should be implemented early preoperatively and continued during the entire perioperative period. A structured plan is particularly important in patients with OIH, as explained above.

Effective perioperative care of the opioid-tolerant patient, particularly one on very high doses preoperatively, requires a collaborative and multidisciplinary approach that includes the anesthesiology team. It is important for all team members to consider OIH as a differential diagnosis if opioid treatment unexpectedly does not result in the desired analgesic effects. Early involvement of pain medicine specialists, psychiatrists, physiotherapists, social workers, and providers specialized in addiction, whenever considered appropriate, increases the chances of a successful outcome. Good communication and clear definition of roles between different managing teams may help minimize fragmentation in the treatment plan and conflicts within the multidisciplinary team, and between patient and provider.[125]

Special Considerations

Patients affected by opioid tolerance or OIH should be identified by targeted preoperative evaluation. During the preoperative visit affected patients should be reassured that specific efforts will be made to provide effective analgesia and avoid withdrawal throughout the entire perioperative period. Successful management of this challenging patient population requires a well-coordinated multidisciplinary team guided by protocols, which include comprehensive multimodal strategies for the systematic treatment of postoperative pain and potential adverse effects of the respective interventions.

■ Persistent Surgical Pain (PSP)

A subset of patients undergoing surgery will continue to have postoperative pain for periods of time longer than the expected duration for the particular surgical procedure. In other words, "normal" surgical pain will transition to persistent surgical pain (PSP). Although there is no consensus for the exact definition of PSP, the following criteria proposed by Macrae[131] seem to have gained widespread acceptance: (1) pain that develops after surgery, (2) is of at least 2 months' duration, and (3) where other etiologies have been excluded. The lack of a unique definition may account for the significant variability of the reported incidence of PSP in the general surgical population. For instance, an incidence of 5 to 65% has been reported after thoracotomy, 20 to 50% after mastectomy, and 50 to 85% after limb amputation.[129] The mechanism of PSP is considered multifactorial and clearly requires further clarification through systematic research. Nevertheless, a neuropathic component has consistently been identified.[130] The transition from acute to chronic pain is thought to arise from a maladaptive response involving neuroplasticity at several critical levels, including peripheral sensitization, central sensitization, and descending modulation of nociceptive impulses.[12] Other contributing factors may be unfavorable interactions between the patient's individual anatomy and tissue repair, psychosocial features, surgical indication and timing, as well as a strong desire of the patient for a surgical

procedure to improve the chronic pain syndrome.[133,134] Unfortunately, most available data were provided by studies with specific methodological limitations. However, factors that have consistently shown an association with the development of PSP include significant preoperative pain, severe immediate postoperative pain, and nerve damage.[135] The early implementation of effective pain management in the perioperative period based on a multimodal concept as well as the development of less destructive surgical techniques have been proposed as measures to decrease the incidence of PSP. Despite the increase in research in recent years, the efficacy of these strategies in preventing PSP remains to be proven.[132,136]

In the neurosurgical population, research regarding PSP has mainly focused on patients undergoing craniotomy. This clinical setting allows the identification of chronic headache that develops as a result of surgery in patients with no headache preoperatively.

In a retrospective review of 102 patients undergoing craniotomy, Gee[137] reported that out of 58 patients without headache prior to surgery, 11 developed persistent headache postoperatively, suggesting an incidence of PSP in this patient population of around 20%. The affected patients described the pain as mild to moderate and not interfering with daily life activities. In more than 50% of the cases persistent pain was located over the surgical site, suggesting surgical trauma as the most likely etiology. The remainder of the new-onset headaches were generalized, similar to tension-type headaches. In more than 80% of the cases, persistent postoperative headache completely resolved within 1 to3 years after surgery. Rimaaja[138] conducted a survey in patients after craniotomy for acoustic neuroma and defined new postoperative headache as (1) no preoperative headache or easy differentiation between preoperative and postoperative headaches, (2) onset of headache within 1 week after the operation, (3) duration of headache of at least 3 months, and (4) no new postoperative migraine or tension-type headache. The study found that 83 out of 192 patients (51%) had developed a new-onset headache postoperatively. Only 26% of the patients reported a gradual alleviation of headache during the first postoperative year.

Little is known about the mechanisms, prevention, and treatment of PSP after craniotomy. Proposed mechanisms include pericranial muscle retraction and trauma, reduced CSF pressure, dural irritation, aseptic meningitis, and neck muscle spasm that results from surgical positioning of the head and neck during craniotomy.[139] There is a need for more research to evaluate options for prevention of PSP after craniotomy. A recent prospective study (n = 52) showed that scalp infiltration with ropivacaine at the end of surgery decreased the incidence of persistent headache at 2 months after surgery from 56% in the control group to 8% in the ropivacaine group.[65] However, studies in larger populations and with longer follow-up periods are necessary to confirm this effect. A wide range of pharmacologic treatments have been used for PSP after craniotomy. Rimaaja[136] reported that NSAIDs and acetaminophen were effective in 79% of patients. In a retrospective review of 126 patients following anterior temporal lobectomy for intractable epilepsy, Kaur[140] reported that 4% of patients with PSP had medically uncontrolled headaches and that an additional 3% continued using prescription drugs for headache even 1 year after surgery. At present no study has rigorously investigated the best pharmacologic and nonpharmacologic treatments for PSP after craniotomy.

Accurate diagnosis of PSP poses a problem after back surgery. Patients presenting for spine surgery typically have a history of chronic pain preceding the surgical intervention, which excludes the diagnosis of PSP. Only if the new postoperative pain after spinal surgery has features that can be clearly defined as different from the preoperative pain would a new diagnosis of PSP be possible. Thus, PSP in patients with chronic back pain is difficult to study. In contrast, pain that does not resolve after spine surgery has been extensively investigated but the details are beyond the scope of this chapter. The phenomenon is frequently called “failed back surgery syndrome” (FBSS) or “postlaminectomy syndrome.” The incidence has been estimated at 10 to 40% and is considered to increase with subsequent spine procedures.[133,134] The management of FBSS represents a significant challenge to health care providers. It has recently been suggested that a multidisciplinary team evaluate patients with chronic back pain before scheduling spine surgery in an effort to identify potentially amendable psychosocial and biological factors. Based on such data, stepwise treatment plans may be developed that would start with the least invasive intervention. Some authors have emphasized a strategy of “self-management” and “empowerment” that would allow patients to actively participate in the course of their treatment that is aimed at preventing repeated surgical interventions and long-term disability.[141]

As in the general surgical population, early and effective management of acute postsurgical pain by combining different analgesic agents (multimodal strategy) may also prove to be preventive for PSP after neurosurgical procedures.[2,142,143]

Special Considerations

Triggers and mechanisms for the transition from acute to chronic pain after neurosurgical operations remain unclear. Early and effective multimodal perioperative pain management in combination with goal-directed surgery aimed at less disruption of tissues in particular nerves may decrease incidence of PSP.

Editor's Comments

This chapter deviates from the litany of pain diagnoses and pain-relieving procedures that make up the majority of this book. I asked Dr. Brambrink and colleagues to review the postoperative analgesic care of neurosurgical patients because I am not aware of a similar review in the literature.

Taking a cue from the title of this book, this chapter could be retitled "Surgeons Managing Pain." Surgery is, in fact, an act of controlled violence, a means to an end. Postoperative pain is a predictable consequence of our procedures and, as such, is a continuation of the act of surgery.

Most neurosurgeons feel a strong sense of accomplishment when a difficult operation has been concluded successfully. Yet, according to this chapter, many of our patients suffer unnecessary postprocedural pain. It suggests that we do not apply the same rigor and diligence to the control of postoperative pain as we do to the conduct of the evaluation and surgical treatment of our patients.

Pain surgery is a field where evidence of efficacy is still somewhat lacking. However, there is considerable evidence of best practice in the management of postoperative pain, as exemplified by the authors. We should take advantage of this existing evidence base. There seems to be a substantial opportunity for us to develop postoperative analgesic protocols that can be procedure specific. Reducing postoperative pain will improve the early mobilization of our patients and help diminish complications of prolonged bed rest, such as deep venous thrombosis (DVT) and pulmonary embolism (PE). Further, improved analgesia would speed discharge and enhance patient satisfaction, both important quality measures.

In summary, this is a topic that has not gotten enough attention. I would suggest that we take these strategies and apply them to our patient populations in a thoughtful and organized manner, to improve both the safety and quality of our surgical care.

Conclusion

Despite increased awareness that neurosurgical procedures, including craniotomies, are associated with significant perioperative pain, neurosurgical patients are still frequently managed restrictively based on valid concerns by practitioners regarding interference with the neurologic examination.

There is mounting evidence that multimodal pain management (i.e., the application of several effective drugs and techniques in parallel) appears to be particularly well suited for neurosurgical patients. It is important to understand that multimodal treatments not only reduce the degree of adverse effects compared with regimes that rely only on one class of drug, but they are also more effective because they capitalize on synergistic effects of combined therapies. In addition to opioids, several classes of drugs and techniques are currently available to design individualized multimodal treatment regimes for neurosurgical patients.

Patients who have developed opioid tolerance or opioid-induced hyperalgesia pose a particular challenge. This group frequently includes patients requiring spine surgery. Successful pain management for opioid-tolerant patients should be based on anticipation and adequate planning by the teams involved in their care. When available, an early consultation with pain management experts, and a thorough discussion regarding the patient's expectations and the therapeutic options of the provider team are particularly promising to achieve treatment success in this patient population.

Optimized perioperative pain control in neurosurgical patients not only reduces pain and suffering but is currently also considered the best preventive measure against persistent surgical pain. Successful short-term interventions to minimize perioperative pain may have a direct impact on the incidence of this type of chronic pain after a surgical intervention.

There is an urgent need for high-powered clinical research to determine the best possible strategies for treating perioperative pain and improving the quality of life and long-term outcome of neurosurgical patients.

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Section IV

Surgical Procedures for Pain

Section IV.A

Neuromodulation

Section IV.A.1

Spinal Cord Stimulation

30 Spinal Cord Stimulation: Mechanisms of Action

Bengt Linderoth and Björn A. Meyerson

Spinal cord stimulation (SCS) has developed into an indispensable treatment modality in the management of certain chronic pain conditions. The method is a direct clinical spin-off from the well-known gate control theory for segmental pain suppression.[1] The general idea is to apply electrical stimulation to an easily accessible neural structure—to the large-diameter afferents in the dorsal columns of the spinal cord, which via the central collaterals connect to the "gating mechanisms" in the dorsal horns.

SCS was enthusiastically adopted by many neurosurgeons and widely used for a variety of pain conditions of different causes. This initial, rather uncritical use of the method resulted in poor long-term results, and the popularity of the method declined. With the development during the 1980s of the awareness that optimal pain therapy rests firmly on a thorough analysis of the pain condition, its different components, and their causes, the types of pain most successfully responding to SCS could be defined properly. Thus, it was not until the mid-1980s that SCS was recognized as a routine treatment for certain forms of chronic pain.

Today it is estimated that more than 30,000 SCS systems are implanted worldwide each year. This large number of devices represents a considerable amount of money. The increasing costs for health care call for efficient usage on correct indications of all types of treatments. It is not until recent years that the application of SCS has been subjected to randomized, controlled studies that have provided relatively high levels of evidence for its efficacy for some of the most common indications.[2–4] The understanding of the mode of action is a prerequisite for the acceptance and further refinement of SCS technology, as well as the inclusion of new indications and the development of strategies to improve the efficacy of the method. It is not until the last two decades that more solid data on the physiologic and biochemical mechanisms behind the pain-relieving effects of SCS have accumulated.

It is well known that SCS is preferentially effective for certain forms of neuropathic pain,[5–8] and at present there is no convincing evidence that SCS has a *direct* positive effect on nociceptive forms of pain. Neuropathic pain is the most important indication, but SCS may also effectively influence certain ischemic pain conditions, namely pain associated with tissue ischemia attributable to peripheral vascular disease and intractable angina pectoris. It has been known since the pioneer report by Cook et al in 1976[9] that SCS may relieve pain due to disturbed peripheral circulation caused by arteriosclerosis or diabetic vasculopathy. In particular, the ischemic pain present in conditions with peripheral vasospasm may respond positively to SCS.[7–11] Intractable angina pectoris appears presently to be the most rewarding indication for SCS, often with more than 80% of patients experiencing significant pain relief.[12–14] It should be pointed out that, besides relief of ischemic pain, SCS appears to have favorable effects on the ischemic condition per se.[12,14] There is much evidence indicating that the mechanisms for pain relief by SCS in neuropathic and in ischemic pain conditions are fundamentally different, and they are therefore dealt with separately here.

■ Neuropathic Pain

Spinal Segmental Mechanisms

Neurophysiologic Mechanisms

The presupposed basis for the pain-relieving effect of SCS according to the gate control theory[1] was that nociceptive input from the periphery could be inhibited at the first dorsal horn (DH) relay by stimulation-induced antidromic activation of collaterals of large dorsal column fibers projecting onto the same spinal segment (see also Chapters 1–3). When

studied in experimental animals, these inhibitory effects were short lasting and exerted on the afferent discharge in response to acute noxious stimuli mediated by Aδ and C fibers. Such a mechanism is not concordant with clinical experiences of SCS. If its effects in patients were produced by such a mechanism, it would be expected to be particularly effective in suppressing acute, nociceptive pain (e.g., ulcer pain, postoperative pain, fracture pain). It is indeed a paradox that the main concept of the gate control theory, inhibition of nociceptive signals, which was the basis for development of SCS, cannot be reproduced with its clinical applications.

Details of the gate control theory have been much discussed and, in some studies, it has not been possible to confirm the predicted presynaptic inhibition of Aδ mechanoreceptor DH neurons produced by Aβ fiber activation.[15] Moreover, it is not clear whether the gating mechanisms are equally effective on nociceptive-specific neurons and on wide-dynamic-range (WDR) cells. However, the enormous impact of the basic concept of a segmental modulation of pain based on the interplay between large and thin fiber input as postulated by the theory is indisputable. The viability of the basic principle of the gate control concept is substantiated by an editorial by A. Dickenson from 2002 stating, "Gate control theory stands the test of time."[16] Moreover, the clinical spin-offs in the form of SCS and the later development of transcutaneous electrical nerve stimulation (TENS) provided important means for managing some forms of neuropathic and ischemic pain for which available pharmacotherapy, blockades, and ablative surgery have proven ineffective.

Early Studies

In the 1970s many animal experiments were performed with the aim of exploring the mechanisms of SCS based on its putative selective effects on nociception by using acute, noxious stimuli (e.g., heat, pinch, pressure, electrical stimuli, application of algogenic substances).[17–20] It is apparent that most of the early experimental studies performed to explore the mechanisms of SCS did not adequately mimic the conditions in which SCS is applied in patients. Only healthy, intact animals were employed and submitted to painful nociceptive stimuli, and SCS was applied with awkward current parameters that would be impossible to use in the clinic. In almost all studies the effects recorded were often brief, lasting only for milliseconds or seconds.

Studies in Animal Models of Neuropathic Pain

Animal models of neuropathic pain created by a complete or partial injury of the sciatic nerve, its branches, or the corresponding spinal nerves have been used extensively in basic studies of such pain as well as pain therapy. The signs of neuropathy demonstrated in such animals, generally rats, consist of hypersensitivity to tactile and thermal stimuli applied to the nerve-injured paw, resulting in decreased withdrawal thresholds. This abnormally increased sensitivity is similar to that which is demonstrable as allodynia and hyperalgesia in some patients presenting with chronic pain resulting from nerve injury.[21] The usage of models of neuropathic pain in studies on SCS mechanisms was, to the best of our knowledge, first documented in a publication from 1995.[22]

In a series of experiments using rats with sciatic nerve lesions produced according to the procedures developed by Bennett and Xie[23] and Seltzer et al,[24] we studied the effect of SCS, via a miniature cathode implanted in the dorsal epidural space, on tactile hypersensitivity ("allodynia") in awake, freely moving animals. SCS was applied with stimulus parameters similar to those used in clinical practice.[22,25] Twenty to 30 minutes of SCS could produce a marked increase in the abnormally low withdrawal thresholds to innocuous mechanical stimuli (von Frey filaments) applied to the nerve-ligated leg. This threshold elevation usually persisted for about 40 minutes after cessation of the stimulation[22] (**Fig. 30.1**).

In our laboratory, a series of electrophysiologic studies on DH neuronal activity and responses to SCS in lightly anesthetized rats subjected to partial sciatic nerve lesion according to Seltzer et al have been performed.[24,26,27] The nerve lesion resulted in a significant increase in both spontaneous and evoked discharges in the WDR neurons. SCS, applied with "clinical current parameters," induced a significant depression of the principal exaggerated response as well as of the after-discharges in rats presenting with hypersensitivity (**Fig. 30.2**); there was no effect in animals without this sign of neuropathy. These observations indicate that SCS may provide a suppressive action on the WDR neuron hyperexcitability, associated with a decrease in the tactile hypersensitivity. In the clinical setting, this may correspond to the beneficial effect of SCS not only on allodynia but also on the spontaneous neuropathic pain.

In a similar recent study from another group, the intensity of SCS was monitored and set at the lowest current that evoked an Aαβ compound action potential only. It was found that besides attenuating effects on WDR neurons, there was a blocking of their wind-up responses.[28] A supplementary study demonstrated that the reduction of mechanical hypersensitivity could be produced by SCS recruiting only a small fraction of antidromically activated dorsal column (DC) Aβ fibers.[29] It has further been demonstrated that SCS significantly decreased the duration of the long-term potentiation (LTP) response to C fiber activation from about 6 hours to about 30 minutes.[30] It

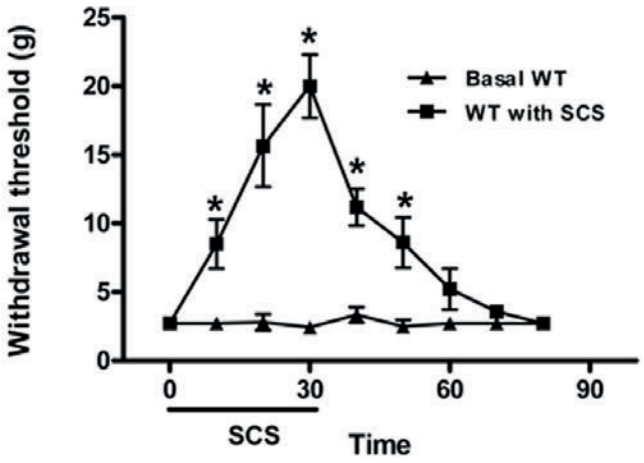

Fig. 30.1 Effect of SCS on tactile hypersensitivity evaluated with von Frey filaments in an animal model of neuropathy. During 30 minutes of SCS, the mean withdrawal threshold in responding rats increased from 2.5 to 20 g on the nerve-lesioned side, while thresholds were unaffected during sham stimulation.

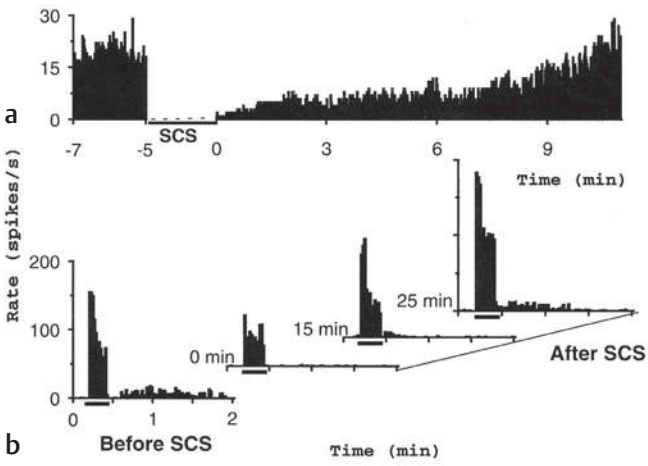

Fig. 30.2 Recordings from wide-dynamic-range (WDR) neurons in the dorsal horn of a rat displaying tactile hypersensitivity after sciatic nerve lesion. (**a**) Recording from a spontaneously discharging DH neuron. Spinal cord stimulation (SCS), applied with clinical parameters for 5 minutes, markedly suppressed the spontaneous discharge. The original firing rate did not recur until 10 minutes after the stimulus ended. (**b**) Innocuous stimulation of the receptive field (stroke with brush; horizontal bars) evokes a prominent after-discharge. After SCS, the principal response is markedly reduced and the after-discharge is suppressed. The original response does not recover until 25 minutes after SCS.

should be noted that in these experiments only the sensitized C fiber response was influenced and neither the normal C nor Aβ functions were affected.

The effect of SCS on the initial, coarse fiber–mediated component of the flexor reflex has been explored in rat models of mononeuropathy.[22] It was found that the thresholds of the electrically evoked flexor reflex, assessed under light anesthesia, were significantly lower in the nerve-lesioned leg than in the intact, contralateral one. SCS selectively increased the abnormally low-threshold first component of the flexor reflex. This component appears with a latency of about 12 milliseconds and conceivably represents the activation of Aβ fibers.[31] The late, C fiber–mediated component of the reflex was not influenced by SCS. It should be noted that SCS did not affect the flexor reflex in the intact leg. The effect on the early flexor reflex component was retained after spinal cord transection rostrally to the site of the SCS, indicating that this selective effect on low-threshold afferent fiber functions may be present *without* the involvement of supraspinal mechanisms.[32]

There is much evidence that the phenomenon of tactile allodynia is predominantly mediated by low-threshold Aβ fibers[33,34] and that it represents a central state of hyperexcitability.[35] The plasticity changes in the spinal cord after peripheral nerve injury are manifested, for example, by a persisting augmented responsiveness and a high degree of spontaneous discharge of DH neurons. It appears that these changes of excitability affect WDR cells more than nociceptive-specific neurons.[36] The selective effect of SCS on Aβ fiber functions demonstrated in our behavioral studies as well as in our studies of the flexor reflex is at variance with previous investigations performed on normal animals and focused on the SCS effects on responses to acute noxious stimuli.

Another animal model supposed to represent neuropathic/deafferentation pain is the autotomy model following peripheral nerve or spinal root section. We investigated whether SCS influences the incidence and severity of autotomy after section of the sciatic nerve.[37] In this study, SCS was applied in awake, freely moving rats for 30 minutes daily for 10 days. If the SCS "treatment" was begun at the time of the nerve section or 3 days before ("preemptive SCS"), the start of the autotomy behavior was markedly delayed compared with that in nonstimulated animals. The extent and incidence of autotomy also were significantly lower during the entire observation period of 10 weeks in these "pretreated" animals compared with the nonstimulated animals and with those that were subjected to SCS when the first signs of autotomy were observed ("therapeutic SCS"). These results suggest that SCS, even applied infrequently and for a limited time, may induce long-lasting changes of spinal functions. Such plastic changes within the spinal circuitry may be the physiologic basis for why a few exceptional patients have their pain adequately controlled by applying SCS only once or twice weekly. Furthermore, there are reports of some cases in which SCS appears to have

a curative effect in that patients' need of stimulation was successively reduced over the years, eventually permitting explantation of the SCS system.[38]

Experimental Studies in SCS Patients

There is much evidence indicating, as mentioned, that SCS is efficacious only, at least preferentially, for neuropathic pain. In the early 1970s it was reported that if a patient acquires an acute nociceptive pain in a leg treated by SCS, this new pain is not abolished by the stimulation.[39] In a study from 1975 it was described that SCS produced a threshold increase both for pinch and heat stimuli applied in hyperalgesic areas, an effect that was not present in normal skin within the paresthetic area.[40,41] It was further demonstrated that SCS may interfere with the perception of tactile and vibratory stimuli applied to normal skin. Conceivably, this effect is due to interference with dorsal column function and might correspond clinically to the experiences reported by some patients that cross-country walking is difficult during SCS treatment with paresthesiae projected to the legs and feet.

Some studies in humans used the recruitment of nociceptive reflexes. García-Larrea et al[42] reported that SCS in patients may suppress a nociceptive flexor reflex. Electric stimuli applied to the innervation area of the sural nerve induced contraction of the biceps femoris when the intensity of the stimulation was perceived as a "pricking" sensation. The flexor response, called RIII, appears with a latency of about 80 milliseconds and conceivably mirrors the activation of Aδ afferents. SCS could effectively suppress this reflex, and this effect was found to be predictive for pain relief. These findings appeared to be clinically useful because they provided an objective correlate to the pain-relieving effect of the SCS. They are difficult to explain, however, in view of the clinical experience that SCS is preferentially efficacious for neuropathic and not for nociceptive forms of pain. Moreover, the suppressive effect on a nociceptive flexor reflex is incompatible with the findings that SCS does not influence the perception of induced mechanical pain in normal skin, as referred to in the preceding discussion. It also should be noted that the reflex attenuation during SCS might be due to an effect on the motor neuron excitability because SCS, when applied for spasticity, also may influence the so-called H reflex.[43]

Neurotransmitter Mechanisms

When applied for neuropathic pain, intermittent SCS of 30 minutes' duration may produce several hours of pain relief after the stimulus is off, indicating long-lasting modulation of neural activity. These long-term effects presumably reflect changes in the local transmitter systems in the DH or in supraspinal loci. Data from humans on biochemical correlates to the beneficial effects of SCS are sparse and partly contradictory.[44] Animal experiments in recent years have provided more consistent data, which are reviewed below.

GABA

Some experimental studies focused on the role of amino acids in the effect of SCS. Starting with the important observation by Duggan and Foong in 1985[45] that SCS is accompanied by a release of gamma-aminobutyric acid (GABA) in the DH, the possible role of this transmitter in the mode of action of SCS has been the focus of interest. It has been shown that the basic release of GABA in the DH is significantly lower in rats displaying signs of neuropathy after nerve injury than in intact animals, indicating a dysfunction of the spinal GABA system.[46] In rats with hypersensitivity responding to SCS by normalization of the withdrawal threshold, the release of GABA increased significantly after SCS. In animals not responding to SCS, the GABA release was unaffected. It has recently been reported that following SCS there is decreased intracellular GABA immunoreactivity in SCS-responding rats.[47] Because GABA is considered a major inhibitory spinal transmitter that is involved in both presynaptic and postsynaptic inhibition at the DH relay of primary afferents, it is probable that the stimulation-induced increase indicates an important role for GABA in the effect of SCS.

Subsequently, it was demonstrated that the attenuating effect of SCS on hypersensitivity could be counteracted by intrathecal (IT) injection of a $GABA_B$ receptor antagonist.[48,49] Conversely, the $GABA_B$ agonist baclofen or of GABA itself, in per se subeffective doses, could transform SCS-nonresponding to SCS-responding rats.

It is known from in vitro experiments that enhancement of GABA-ergic transmission in the DH may result in a decreased release of the excitatory amino acids (EAAs), an effect possibly mediated presynaptically. Further microdialysis studies in our laboratory have demonstrated that the release of GABA and the activation of the $GABA_B$ receptors by SCS can attenuate the release of the EAAs glutamate and aspartate in the DH.[49] Thus, it appears that SCS may act by restoring normal extracellular GABA levels in the DH, exerting its effect mainly via the $GABA_B$ receptors.

Acetylcholine

It has been shown that clonidine, an α_2-adrenoreceptor agonist, in rat neuropathic models may enhance the SCS response.[50] It is known, however, that an analgesic effect of clonidine involves cholinergic mechanisms, and therefore, the extracellular release of

acetylcholine in the DH was assessed using microdialysis.[51] There was a significantly augmented release produced by SCS in responding but not in nonresponding animals. Supplementary behavioral studies demonstrated that acetylcholine acted mainly via muscarinic M_4 receptors, and the SCS effect could be enhanced by IT administration of a very low dose of a muscarinic receptor agonist.[51,52]

Adenosine

Animal studies have indicated that the central neuromodulator adenosine is also involved in the SCS effect.[53] A synergistic action seems to be present in the effect of SCS on experimental hypersensitivity simultaneously mediated by $GABA_B$ and adenosine A_1 receptor activations. If both these receptors are blocked simultaneously, the SCS effect is abolished.[54]

Serotonin

Apart from a couple of early experimental studies performed on intact animals, where spinal 5HT release with SCS was reported,[55] only recently has it been demonstrated that serotonin is involved in the spinal segmental SCS mechanisms. The stimulation results in an augmented 5HT content in the dorsal spinal cord and there is increased immunoreactivity in the 5HT terminals in the DH.[56] Serotonin IT may enhance the SCS effect, and conversely, some receptor antagonists may have attenuating effects.[57] It should be noted that there are no intraspinal serotonergic neuronal cell bodies, and all the spinal 5HT originates from terminals of cell bodies in the nucleus raphe magnus complex projecting caudally to the DH (see below).

Supraspinal Mechanisms

Animal Studies

The involvement of supraspinal mechanisms mediated by spinobulbar, spinothalamic, and spinocortical connections and their respective descending pain-controlling pathways has, since the mid-1970s, been implicated in the SCS effects.[58] For obvious reasons, the notion of the involvement of supraspinal centers is in line with the fact that orthodromic activation of the dorsal columns is relayed through the dorsal column nuclei and projected onto nuclei in the brainstem, to the sensory thalamus, and to the cortex. The key issue is whether the SCS effects necessarily depend on "gating mechanisms" activated by connections between the lemniscal system and centers in the brainstem, mesencephalon, thalamus, and hypothalamus, from which descending pain-controlling pathways originate. In a series of reports, Saadé and his associates[59–61] argued that the inhibitory effects on nociceptive transmission in the DH could not be attributed solely to antidromic activation of dorsal columns because they persisted after transection of these pathways caudally to the stimulating electrode. Instead, they concluded that the inhibition was due to activation of a supraspinal loop mediated via the dorsal column nuclei, the raphe system, and the dorsolateral funiculi (DLF).

Rees and Roberts[62] and colleagues focused on the possible role of the anterior pretectal nucleus (APtN) in the SCS effect. They demonstrated that stimulation of the dorsal columns could excite cells in the APtN, where a profound analgesia by the inhibition of nociceptive DH neurons may be produced. This effect was abolished by transection of the dorsal columns rostrally to the site of the stimulation. It was further shown that an important component of these inhibitory effects was mediated through the DLF because, after destruction of this pathway, the SCS-produced suppression of DH nociceptive neuron discharge was attenuated.

An important study giving further support to the engagement of a spinal-supraspinal-spinal loop in SCS is that of El-Khoury et al,[63] where animal models of neuropathy were used. They showed that the inhibition of hypersensitivity following nerve injury produced by dorsal column nuclear (DCn) stimulation could be retained also after chronic section of the DCs. In a subsequent study the effects of low thoracic and DCn stimulation were shown to be comparable and could both be preserved although reduced by about 50% after DC lesions.[64]

The finding that the spinal 5HT content is increased in SCS-responding animals clearly indicates that supraspinal mechanisms are involved.[56] Microrecordings from the rostroventromedial medulla (RVM) revealed that SCS in responding animals produced a massive discharge of the so-called OFF cells and of 5HT-like cells (**Fig. 30.3**).[65] One could argue that these activation patterns are of no functional significance for the mode of action of SCS and that the descending pathways mediating the augmented 5HT release are the result of a spread of current and a direct activation of the DLF. However, this possibility was ruled out using a backfiring technique. Furthermore, the content of 5HT in the ipsilateral DH was significantly increased in SCS-responding but not in nonresponding rats, which would be unlikely had there been a direct activation of DLF due to spread of current from the SCS.[65]

In a subsequent study, it was demonstrated that cells in the locus coeruleus were markedly activated by SCS in responding animals but not in nonresponding ones. However, there are no findings suggesting that the descending noradrenergic pain-controlling system, originating from locus coeruleus and adjacent nuclei, is engaged in the SCS effects.[105]

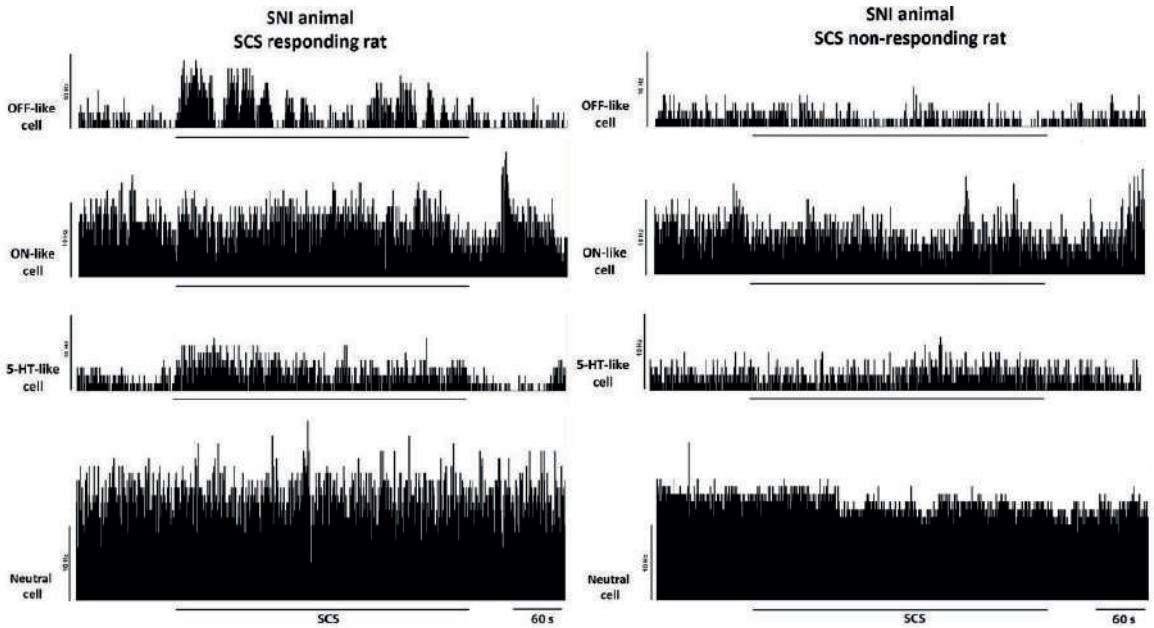

Fig. 30.3 Examples of single unit recordings of ON-like, OFF-like, 5HT-like, and neutral cells in the rostroventromedial medulla (RVM) in a SCS-responding animal and in a SCS-nonresponding animal. SCS was applied for 6 minutes. Note the activity increase in OFF-like and 5HT-like neurons during SCS. Scale bar = 60 seconds. (From Song Z et al.[65])

Human Studies

There are but a few studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) for examining changes in cerebral blood flow associated with SCS treatment of neuropathic pain. In general, extensive changes representing activation as well as deactivation in a number of cerebral structures have been described. However, the results are relatively inconsistent and in some cases contradictory. Thus, in a recent fMRI study the most prominent changes related to SCS-induced pain relief appeared as a deactivation in the medial thalamus and the rostral anterior cingulated cortex (ACC).[66] Similar results were reported in a SPECT study,[67] whereas an activation of ACC was documented in a PET study.[68] Obvious problems with these studies are changes that are induced by the SCS-evoked paresthesiae per se and the lack of study patients with no or little pain-relieving effect as well as controls without pain but subjected to SCS.

Conclusions

In neuropathic pain, the prime target of SCS is the hyperexcitable second-order DH neurons. Presently, there are only data substantiating inhibitory effects on WDR cells, but it cannot be excluded that nociceptive-specific cells are also affected. It appears that the pathologic processing of Aβ and Aδ, as well as C fiber–mediated mechanical, cold, and heat afferent barrage is attenuated. The sensitization of the DH nociceptive neurons following a peripheral nerve lesion is associated with a complex pattern of up-regulations and down-regulations of transmitters/neuromodulators in the primary afferent ganglion cells as well as in the DH.[69] A dysfunctional GABA-ergic system is considered to be of pivotal importance, and the pain relief of SCS appears to a large extent to closely relate to an increased GABA release, which attenuates an enhanced EAA activity possibly mediated mainly via the $GABA_B$ receptor. GABA may act both presynaptically and postsynaptically. SCS also induces acetylcholine release acting via muscarinic receptors, which may be sited on GABA-ergic interneurons. There is much evidence that supraspinal mechanisms are involved as a result of the orthodromic activation of the DCs. Attenuation of behavioral signs of neuropathy can be produced also by SCS applied rostral to transection of the DCs. SCS effects are partly dependent on activation of spinal 5HT receptors, and the increased release of spinal 5HT is the result of cellular activation in the RVM, which may also contribute to the augmented segmental GABA release. Data indicating an engagement of the descending noradrenergic pain-controlling system in the effect of SCS are so far lacking, although cells in the locus coeruleus are markedly activated by concurrent SCS applied at a lumbar level. Current experimental data clearly indicate that SCS when applied for neuropathic pain engages both segmental spinal and supraspinal mechanisms. These mechanisms operate in concert and it appears that they are of comparable importance. Cor-

responding data from humans are sparse, and further investigations are needed to ascertain whether similar dual mechanisms are involved in the clinical mode of SCS action. The mechanisms discussed in this section are schematically illustrated in **Fig. 30.4.**

New Stimulation Algorithms

In recent years several entirely new modes of stimulation have been presented. A common feature of these is that the stimulators can be set to supply effective stimulation of the spinal cord without producing any subjective sensations (paresthesiae or other sensory cues). Further, these new techniques focus on alleviation of a pain component that is commonly considered resistant to conventional SCS, that is, low back pain, alone or combined with leg pain.[8]

One of the new algorithms utilizes kilohertz frequencies (up to 10 kHz) of short-duration, biphasic pulses.[106,107] So far, the reported clinical outcomes are inconsistent. It has long been known that application of electric pulses with frequencies of this magnitude induces local reversible blocks of nerve transmission. However, there are no data indicating that SCS applied with high frequencies is associated with disturbance of tactile sensibility, and therefore it is difficult to conceptualize the underlying physiologic mechanisms. To date, there are only three experimental studies published.[107–109] In one of the studies[109] care was taken specifically to adapt the current parameters to mimic the clinical situation. It was demonstrated that 10 kHz stimulation neither activated nor blocked transmission in the dorsal columns, and it was concluded that the effector mechanism is probably spinal/segmental.

Another novel technique is the use of a bursting mode (internal frequency 500 Hz; bursts delivered with 40 Hz) of SCS also aiming at subparesthetic stimulation.[110] It has been reported that this form of SCS may also alleviate the low back pain component, although the effect on leg pain is comparable to that obtainable with conventional SCS. The authors argue that burst stimulation produces a more prominent activation of cortical areas involved in pain modulation. However, a recent experimental study has demonstrated that burst stimulation did not produce any activation of the DC fibers, making the prospect of supraspinal involvement less likely.[111]

Although some promising clinical outcomes have been reported, the new SCS paradigms still lack solid scientific bases and the understanding of their modes of action is still poor.

■ Ischemic Pain and Peripheral Vascular Disease

The observation that SCS can be effective also in ischemic pain dates from 1976 with the pioneer report by Cook et al.[9] It may seem strange that SCS,

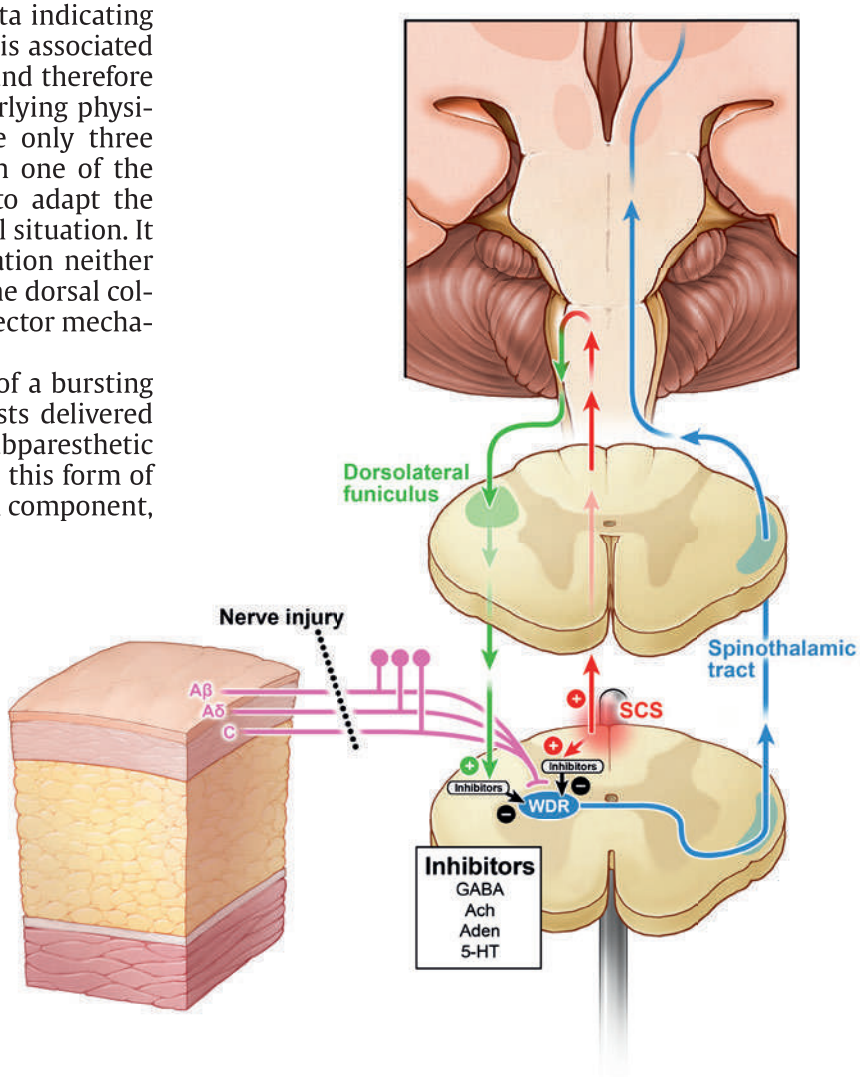

Fig. 30.4 A schematic diagram showing a lumbar slice of the spinal cord with SCS applied just rostral to this level. The antidromic impulses generated in the dorsal columns activate inhibitory interneurons—among them GABA-ergic, cholinergic, and adenosinergic—that reduce the activation (and release of excitatory transmitters) of the hyperexcitable second-order neurons, among them WDR cells. The orthodromic ascending DC impulses activate circuitries in the brainstem ultimately giving rise to descending impulses via the dorsolateral funiculi amplifying the inhibitory processes at the spinal level.[65]

which otherwise has proven to be effective only in neuropathic forms of pain, can also ameliorate a nociceptive pain condition. However, both clinical observations and animal studies indicate that pain reduction is secondary to an effect of SCS on the tissue ischemia and not directly on the pain-generating neuronal mechanisms.

Peripheral vascular disease (PVD) can affect the vascular system on both the arterial and venous sides of the capillaries. Clinical experience has demonstrated that SCS is primarily effective for flow obstructions on the arterial side caused by either vascular wall pathology, thrombus, or vasospasm (peripheral arterial occlusive diseases [PAODs]). Morbidity and mortality in PAOD are relatively high because effective pharmacologic treatments are limited once surgical revascularization procedures have failed. Since no adequate animal models of PAOD that generate ischemic pain in the limbs are available, normal anesthetized animals have been used to explore the physiologic mechanisms of SCS-induced changes in peripheral blood flow.[70–73] Cutaneous blood flow, and in some studies also the calculated vascular resistance, in the glabrous skin of the hindpaws have been determined using laser Doppler flowmetry. Clinical observations and animal studies using these techniques as well as the outcome of interventional treatments have resulted in the formulation of two different theories that can elucidate possible mechanisms of SCS-induced vasodilation (**Fig. 30.5**). The first one implies that the SCS effect depends on inhibition of the sympathetic outflow transmitted via nicotinic receptors in the ganglia and acting mainly on α_1-receptors at the nerve-end organ junction. The result of the diminished vasoconstrictor tone is peripheral dilation recorded as increased capillary flow in animal models.[70,71] The second theory implies that SCS antidromically activates sensory fibers in the dorsal roots that release vasodilatory substances distally, in particular the calcitonin gene-related peptide (CGRP)[73,74] and nitric oxide (NO). Both these mechanisms may contribute to the SCS-induced vasodilation depending on the background level of sympathetic nervous system activity. In animal experiments, cooling of the skin increases sympathetic activity and thereby favors the "antisympathetic mechanism" of SCS, whereas at normal room temperature the antidromic mechanism dominates.[75] **Fig. 30.5** schematically illustrates the possible mechanisms discussed above.

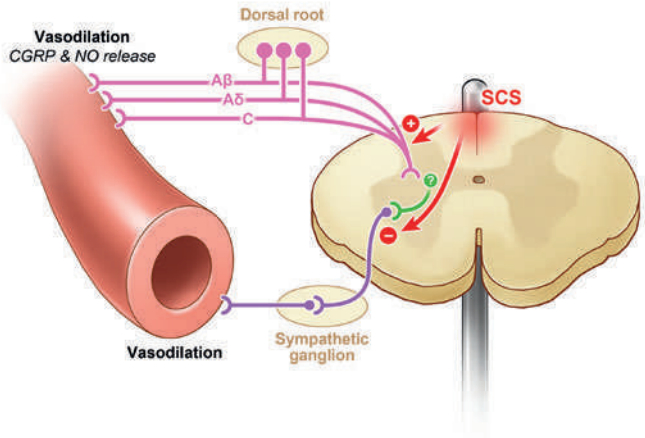

Fig. 30.5 A schematic illustration of the effects of spinal cord stimulation (SCS) of the low thoracic-lumbar dorsal columns on mechanisms that produce vasodilation of peripheral vasculature. SCS activates interneurons that may decrease the activity of sympathetic preganglionic neurons and reduce the release of catecholamines from sympathetic postganglionic neurons. Simultaneously, SCS antidromically activates dorsal root afferent fibers, resulting in peripheral release of calcitonin gene-related peptid (CGRP) and nitric oxide (NO).[7]

The role of CGRP was supported by another study in rats showing that preemptive SCS decreased vasospasm induced by manipulation of a vessel supplying a skin flap.[76] Furthermore, SCS increased the survival rate of a neurovascular skin flap in the rat that was made ischemic by occluding the blood supply to it for 12 hours.[77] This protective effect of SCS, as evaluated 1 week after the main experiment, was significantly attenuated by the concomitant administration of a CGRP receptor antagonist. It has also been reported that preoperative administration of antiadrenergic drugs such as guanethidine, reserpine, and 6-hydroxydopamine may increase flap survival, pointing to the significance of sympathetic vasoconstrictor activity for the flap ischemia.[78] Thus, it is possible that SCS may reduce vasospasm and provide cytoprotection both by releasing vasodilators from sensory fibers activated antidromically and by suppression of sympathetic vasoconstrictor activity.

SCS applied at the spinal L1–L2 segments antidromically activates large-diameter Aβ DC axons with collaterals to the superficial DH.[22,28] A recent study has shown that SCS, at 90% of the motor threshold intensity (MT), produces increased phosphorylation of extracellular signal-regulated kinase (ERK) and protein kinase B (AKT) in neurons of the superficial DHs.[79] When ERK and AKT signaling pathways in the spinal cord were blocked pharmacologically SCS-induced vasodilation was diminished. In addition, muscimol, a $GABA_A$ agonist, topically applied on the spinal cord reduced the SCS-induced vasodilation.[80] These results suggest that ERK and AKT are contained in GABA-ergic neurons. These interneurons can act postsynaptically on sympathetic preganglionic neurons. It is known that SCS may induce release of GABA, which can suppress sympathetic preganglionic neuronal activity, thereby contributing to peripheral vasodilation. The release of GABA may also produce depolarization of $TRPV_1$-containing primary afferent fibers, which are in large part composed of C fiber

axons.[81,82] These fibers can transmit action potentials antidromically to nerve endings in the limb, releasing CGRP that binds to receptors on endothelial cells. The activation of these receptors leads to production and subsequent release of NO, which results in relaxation of vascular smooth muscle cells.[73] The net result of sympathetic vasoconstrictor inhibition and the release of vasodilatory substances is relaxation of vascular wall smooth muscle that leads to increased peripheral blood flow.

Up to the present most animal studies have utilized SCS frequencies that are routinely applied in the clinic (i.e., 40–80 Hz), but in a recent study higher SCS frequencies (up to 500 Hz) were tried at intensities 30 to 90% of MT.[83] This study showed that although the MTs for SCS at all frequencies were similar, SCS at 500 Hz induced a significantly larger blood flow elevation in the hindpaw than did SCS at 50 Hz. The effects of these frequencies and intensities seem to depend on activation of $TRPV_1$-containing fibers and the release of CGRP. Thus, further trials with new stimulation parameters are warranted to increase the benefits of SCS.

Angina Pectoris and Cardiac Disease

Angina pectoris is one symptom of ischemic heart disease. The common mechanisms that decrease blood supply to the heart are vasospasm and occlusion of coronary vessels. A large population of patients with chronic angina pectoris are unresponsive to conventional treatments.[12,84,85] Neuromodulation treatment of angina pectoris started with TENS in the mid-1980s,[86] and soon continued with SCS first published by Murphy and Giles in 1987 and Mannheimer et al in 1988.[12,87]

Application of SCS at T1–T2, or at higher cervical levels, provides pain relief by reducing the frequency and to some extent also the severity of angina attacks; the intake of short-acting nitrates is also reduced.[13,88,89] As a consequence, SCS clearly improves the quality of life in these patients. SCS for angina has proven very efficacious, producing marked pain relief in more than 80% of patients. However, the mechanisms producing pain relief and improved heart function remain unclear.

Although early animal data demonstrated direct inhibitory effects of SCS on cardiac nociception,[90] subsequent clinical studies have clearly proven that SCS does not merely relieve pain but also improves the function of the heart. The presence of angina pectoris is the result of an imbalance between the supply of and the demand for oxygen in the heart. Resolution of the cardiac ischemia seems to be the primary factor, and relief of the angina is secondary to this.[91] Some investigators have proposed a stimulation-induced flow increase or redistribution of blood supply,[91] whereas others interpret the reduction of coronary ischemia (decreased ST changes, reversal of lactate production) as being mainly due to a decreased cardiomyocyte oxygen demand.[85,91]

Studies have been performed to determine the role of blood flow changes in relieving angina pectoris with SCS. In a human experimental study, PET was utilized to provide some, albeit weak, evidence for flow redistribution with SCS.[92] The same problem was addressed in an animal study by utilizing the distribution of isotope-labeled microspheres in the hearts of anesthetized, artificially ventilated dogs.[93] The results of this experimental study failed to confirm the existence of a local flow increase, or redistribution in the myocardium, or to show any changes in the pressure–volume relationships during SCS. However, a limitation of the study was that occlusion of the left anterior descending coronary (LAD) artery was performed with acute and not chronic occlusion in healthy dogs. Considering that patients suffer from long-term coronary ischemic disease, it would be more appropriate to conduct such studies in canine hearts with previous infarctions following long-term ischemia and with additional acute critical episodes.

In patients with compromised coronary arterial blood supply, SCS applied during standardized workloads comparable to hard exercise and rapid cardiac pacing, markedly reduces the magnitude of ST segment changes in the electrocardiograph (ECG).[91,94] These results support the conception that SCS improves the working capacity of the heart.

There exists no proper animal model of angina mimicking the syndrome in humans. The animal studies discussed below are instead focused on various deleterious effects of experimentally induced chronic and/or acute coronary ischemia. To mimic the development of chronic ischemic heart disease in an animal model of myocardial ischemia, a slowly expanding material lining the inside of a metal constrictor ring was implanted around the proximal left circumflex coronary artery in a group of dogs.[95] This technique progressively reduces blood flow through the artery and facilitates the development of collaterals, creating a collateral-dependent myocardial ischemia substrate. In subsequent acute experiments the exposed heart was paced at a basal rate of 150 beats/minute. An ECG plaque was used to record from 191 sites on the left ventricle supplied by the left coronary artery occluded by the constrictor. To stress the heart, either angiotensin II, administered via the local arterial supply to the right atrial ganglionated plexus, was used, or rapid ventricular pacing was applied via a standard pacemaker. Both these maneuvers produced an elevation of the ST segments that, however, was markedly attenuated

during SCS. In a similar way, ST segment responses were largely unchanged when rapid ventricular pacing (240 beats/min during 60 seconds) was induced during SCS. These experiments indicate that SCS may attenuate the deleterious effects that stressors, especially chemical activation of the intrinsic cardiac nervous system (ICN), exert on a myocardium with reduced reserve capacity. This observation led to the conclusion that SCS produces anti-ischemic effects that contribute to improved cardiac function.

Further evidence to support the anti-ischemic effects of SCS on the heart is the observation that preemptive SCS appears to have a protective effect on the myocardium, making it more resistant to critical ischemia as demonstrated by rabbit experiments with LAD occlusion during 30 minutes. In these studies the infarct size was markedly reduced by the preemptive SCS. However, the protective effects of SCS therapy were lost if SCS was started after ischemia induction.[96] Patients with SCS therapy for chronic therapy-resistant angina are recommended to use their stimulators at low amplitude most of the day or at least for 6 to 8 hours and to increase the amplitude when needed during an angina attack or when physical stress is expected to produce angina. Thus, the validity of this clinical recommendation is substantiated by experimental data.

Within experimental cardiology there is a well-known phenomenon that a short ischemic episode preceding a longer occlusion of a coronary vessel induces complicated protective processes in the myocardium that diminish the resulting infarct size. This phenomenon is called ischemic preconditioning, and the details are still not completely known.[97] Recent studies indicate that SCS-induced local release of catecholamines in the myocardium may trigger protective changes related to mechanisms behind such ischemic preconditioning but without producing any signs of ischemic changes in the heart. There are also other signs indicating that SCS may induce a state similar to that following a short ischemic period—for example, by activating protein kinase C, a substance that is pivotal in ischemic preconditioning.[96]

An important part of the "general common pathways" in the communication between the central nervous system (CNS) and the heart is the ICN. The ICN is located in the cardiac ganglionated plexuses covered by epicardial fat pads situated on the myocardium.[98] The ICN plexuses are composed of mixed somatosensory, sympathetic, and parasympathetic fibers. The ICN plays a critical role in coordinating regional cardiac function and providing rapid reflex coordination of autonomic neuronal inflow to the heart.[99] In critical ischemia, the ICN is vigorously activated.[100,101] The ICN responds to ischemic stress by a marked activity increase even if the ischemic region is situated far away from the neuron population.[101] If the increased activity persists, it may result in spreading dysrhythmias that may lead to more generalized ischemia and/or to ventricular fibrillation. Several experimental studies have clearly shown that SCS may potently inhibit and stabilize the activity of the ICN, especially during a critical ischemic challenge.

In patients with angina, SCS can relieve the symptoms and signs of ischemia for long periods after the stimulation is terminated, which may relate to prolonged effects of SCS on ICN activity observed for 45 to 60 minutes after SCS stimulation has been turned off in dogs.[100] Modulation of the ICN may be one mechanism that protects the heart from more severe ischemic threats due to generalized arrhythmias.[102] Other researchers have confirmed the observation that experimental animals display less arrhythmia during ischemic provocation when being subjected to SCS. Experiments by Lopshire et al[103] demonstrated that SCS might improve cardiac function in canine heart failure following an experimental myocardial infarction and continued stress by high-frequency pacing over 8 weeks. In addition, acute experiments with experimental occlusion of the LAD carried out with or without SCS on Landrace pigs showed that the stimulation provided positive effects as displayed in the vectorized ECG.[104]

Some of the pathways and mechanisms behind the beneficial effects of SCS on cardiac function discussed above are schematically summarized in **Fig. 30.6**.

Conclusion

Data on the mechanisms of action behind the beneficial effects of SCS in ischemic conditions are mainly derived from experiments performed in healthy animals, animals submitted to acute ischemia, or models of chronic ischemia without observable ischemic pain. Therefore, these experimental findings pertain only to the effects of the stimulation on various measures of ischemia, heart failure, and arrhythmias and not specifically to pain associated with coronary ischemia. The animal studies that are most relevant to the clinical syndromes are experiments in canine hearts rendered malfunctional by slow occlusion of a coronary artery or by initial creation of an infarct, followed by a period of pharmacologic stress, or by high-frequency pacing. Basic studies of SCS in ischemia only indicate that SCS can relieve ischemia whereas clinical studies have demonstrated that pain relief in ischemic syndromes always requires a parallel reduction of signs of tissue ischemia. The animal studies clearly also demonstrate that the stimulation-induced reduction of ischemia is created via several fundamentally different routes.

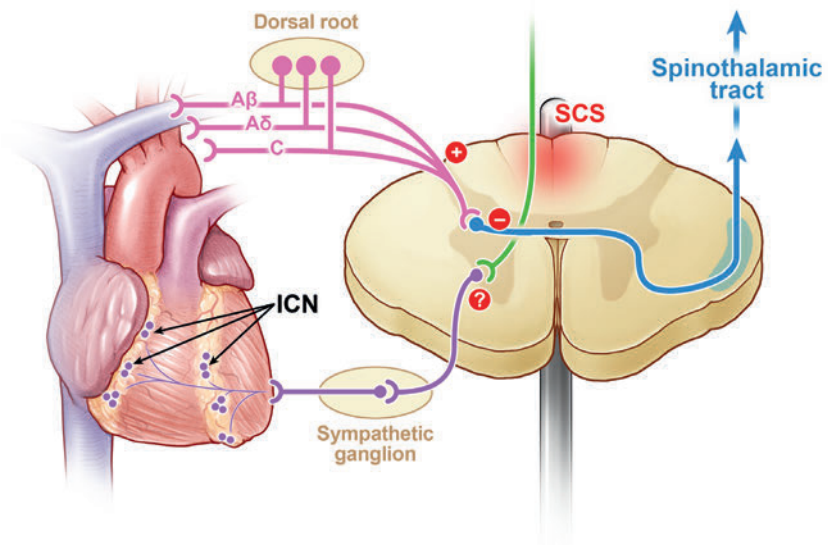

Fig. 30.6 A diagram illustrating effects of SCS of the upper thoracic spinal cord on neuronal mechanisms that improve cardiac function and pain resulting from ischemic heart disease. Spinal cord stimulation activates interneurons that may (1) reduce the activity short term of spinothalamic tract (STT) cells; (2) modulate the activity of sympathetic preganglionic neurons; and (3) stabilize the intrinsic cardiac nervous system (ICN), reduce ischemia, and decrease infarct size. In addition, a protective effect on ischemic cardiomyocytes related to local release of catecholamines and moderation of other neurochemical changes related to "ischemic preconditioning" has recently been demonstrated (see text).[7]

Editor's Comments

The physiology of pain relief produced by spinal cord stimulation (SCS) has been a long-standing interest of Professors Linderoth and Meyerson. The latter was an early adopter of this technology, and the first author completed his PhD thesis on this subject about 20 years ago. Thus, the Karolinska group has since the early 1970s dedicated much research time to examining and mapping the neurophysiologic and biochemical mechanisms behind the beneficial effects of spinal stimulation. There are no more qualified individuals in the world to update us on these mechanisms.

Their message is clear. SCS seems to be effective for both neuropathic pain, and in relieving ischemia. The explanation for the pain relief is far clearer than that for ischemia. Clinically, SCS is far more effective for neuropathic pain than it is for nociceptive pain. There are good correlates for this in the experimental evidence. In models of neuropathic pain, SCS seems to work by both segmental and suprasegmental processes. SCS does seem to suppress the abnormal activity of wide-dynamic-range (WDR) neurons in the dorsal horn (DH), including "wind-up" and long-term potentiation (LTP). The effect does seem to be related to enhanced GABA release (in particular, GABA acting on the B receptor), both presynaptic and postsynaptic. Excitatory amino acid (EAA, i.e., glutamate and aspartate) release in the DH is inhibited. Acetylcholine and adenosine release is also facilitated, and 5HT concentrations in the DH are also increased, presumably released from the synaptic terminals of suprasegmental axons projecting into the DH from the medulla.

Suprasegmental involvement by SCS probably is mediated by the dorsal column nuclei, the midline raphe system (medullary), through the dorsal lateral funiculus (DLF). In human studies the medial thalamus and rostral anterior cingulate show decreased blood flow during SCS, presumably an indication of decreased metabolic activity.

Thus, the mechanisms of action of SCS are complex, and would not at all have been predicted by the gate control theory. It is important to keep in mind the body of knowledge that supports SCS on the clinical level, and to also remember their rejoinder that proper patient selection (Chapter 31) is still the major determinant of success.

SCS for ischemia has never taken root in the United States to the degree that it has in Europe. The reasons for this are not entirely clear, but my own view is that the medical subcultures of cardiology and vascular disease essentially do not overlap with that of pain medicine. Despite numerous attempts by the pain cognoscenti, over decades, to offer what appears to be an effective therapy, patients with ischemic pain are simply not referred by practitioners who care for patients with angina or vasculopathy to an SCS expert, for a trial of stimulation. The fact that our Medicare system, and essentially all insurance companies, will not pay for this therapy may also have something to do with its lack of deployment.

Finally, *any* practitioner who is interested in SCS should read this chapter. SCS has too often been cast into the realm of voodoo. Clearly, the work of these two authors, over many years, has demonstrated the scientific basis for what I agree is "an indispensable treatment modality in the management of certain chronic pain conditions."

General Conclusions

This review of mechanisms behind the benefits of SCS both in the clinic and as observed in animal studies should clearly demonstrate that many different mechanisms are activated. In particular, the mechanisms involved when SCS is used to treat neuropathic pain act directly upon the pathologic activity in the spinal neuronal circuitry supposedly generating the painful sensation.

In ischemic pain syndromes, on the other hand, SCS seems to act primarily on tissue ischemia, and pain alleviation is obtained secondarily to reversion of the ischemia. The SCS actions on cardiac dysfunction and angina pectoris are more complicated, and here we are merely beginning to understand how benefits on refractory angina and on heart failure may be accomplished with the use of neuromodulation techniques.

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31 Spinal Cord Stimulation: Patient Selection

Richard B. North and Giancarlo Barolat

Soon after the introduction of percutaneous electrodes and a mere 5 years after Shealy had initiated the therapy,[1] Hosobuchi et al conducted the first spinal cord stimulation (SCS) screening trial.[2] Patient selection was already an issue: Clinicians needed to understand why SCS successfully reduced pain in some patients but not in others. Today patient selection for SCS remains a multistage process that begins with a referring physician and ends with a specialist deciding whether to offer a screening trial and then (in consultation with the patient) whether to proceed with SCS implantation after the trial. All referring physicians should understand which patients might be candidates for an SCS screening trial and how the specialist will interpret the trial's outcome.

SCS screening trials are usually minimally invasive, technically straightforward percutaneous procedures. For patients with complicated (e.g., postsurgical) anatomy, however, a plate/paddle electrode might be required. (Details about the techniques and equipment involved in an SCS screening trial are provided elsewhere in this book.) SCS screening trials not only help define the optimal position of the electrode and patterns of stimulation, they also emulate the chronic therapy more accurately than do other types of prognostic trials for other modalities. The results of a screening trial offer the best prognosis of SCS outcome.

Indications

SCS is offered as a treatment for chronic neuropathic pain, ischemic conditions (to improve blood flow as well as for pain control), and conditions that cause visceral pain. SCS patients will ideally obtain a specific diagnosis sufficient to explain the type of pain they are suffering. Pain, however, is often mixed: Primarily neuropathic pain might have nociceptive components (signaling actual or impending tissue damage) and/or ischemic components, and primarily ischemic pain might have neuropathic and/or nociceptive components.

SCS for Neuropathic Pain

In the United States, treatment of chronic neuropathic pain is the most common (and most accepted) indication for SCS. Neuropathic pain responds better to SCS than does nociceptive pain, and it is technically easier to overlap the lower extremities with stimulation paresthesia than the low back; thus, it is easier to treat radicular or radiating neuopathic pain than axial low back pain, which commonly has nociceptive components. With the development of programmable multicontact devices and the refinement of implantation and programming techniques, the selection criteria for an SCS screening trial now include patients with predominantly axial low back pain.[3]

SCS is used to treat neuropathic pain caused by, for example, failed back surgery syndrome,[4,5] a spinal cord lesion with well-circumscribed segmental pain,[6] peripheral nerve injury,[7] phantom limb/postamputation syndrome,[8] postherpetic neuralgia,[9] and complex regional pain syndrome.[10]

SCS for Ischemic Conditions

SCS is used to treat conditions that cause ischemic pain, such as refractory angina pectoris[11] (including syndrome X[12]), peripheral arterial occlusive disease,[13] frostbite,[14] Raynaud syndrome,[15] and diabetic neuropathy.[16] SCS can have a positive effect not only on ischemic pain but also on the underlying microcirculation. Whereas SCS might be considered a front-line therapy in patients with Raynaud syndrome or frostbite, it is generally reserved as a last option for those with refractory angina pectoris or peripheral arterial occlusive disease. Thus, the outcome criteria used to document the impact of SCS on ischemia extend beyond pain control to include patient survival, limb salvage, and microcirculation improvement.[17]

SCS for Visceral Disease

SCS is also being used to treat several diseases that cause visceral dysfunction and pain—for example, interstitial cystitis,[18] pancreatitis,[19] urinary urgency and frequency,[20] pelvic pain,[21,22] vulvodynia,[23] and abdominal pain.[24] In these cases, SCS can have a positive impact on the underlying disease as well as its symptoms.

Techniques

Techniques of Patient Selection for an SCS Screening Trial

A patient with an appropriate diagnosis as noted above should be considered for SCS after less or equally invasive alternative therapies have failed to provide relief or have provided relief only with intolerable side effects. In most cases, patients won't be referred for SCS until such therapies have failed or are contraindicated. For patients with failed back surgery syndrome, however, unless a repeat lumbosacral procedure is required to address a neurologic deficit that might become permanent, it is appropriate to offer an SCS screening trial rather than a repeat lumbosacral surgical procedure, even in the presence of a potentially surgically remediable condition, such as disk herniation.[5]

Information to determine a patient's suitability for a screening trial is gathered from several sources:

- The history, which must include information about pain location and intensity, therapies that have failed, current medications, allergies, and comorbid pain conditions. If the patient had prior lumbosacral surgical procedures, the operative records will provide important information.
- A physical examination, which could reveal abnormalities that require surgical intervention before or instead of SCS and should provide information on functional aspects of the patient's pain.
- Imaging studies, such as magnetic resonance imaging (MRI), which will reveal the presence of stenosis, disk herniation, or another anatomic abnormality that could increase the procedural risk of SCS. An MRI will also document the depth of dorsal cerebrospinal fluid and the position of the spinal cord, and this information will contribute to the selection of the SCS equipment and implantation site.
- A psychological evaluation, which should uncover any major untreated psychiatric or personality disorder, issue of secondary gain that could confound SCS outcomes, serious drug habituation problem, or abnormal illness behavior. SCS patients must also demonstrate the cognitive and physical abilities necessary to operate the programming equipment.

All of these factors must be addressed prior to a screening trial using a laminectomy procedure or implantation for chronic therapy.

Additional selection criteria for patients with angina or syndrome X include:

- New York Heart Association Class III or IV angina
- Revascularization therapy contraindicated
- Demonstrated reversible myocardial ischemia
- No recent (< 6 mo) acute myocardial infarction
- Absence of comorbid heart disease (e.g., peri- or myocarditis)

Additional selection criteria for patients with peripheral arterial occlusive disease are:

- Severe pain at rest
- Reconstructive vascular surgery contraindicated
- Any ischemic ulcer is < 3 cm in diameter
- Any gangrene is dry
- $TcPO_2$ between 10 and 30 mm Hg[25]

The following are potential contraindications to SCS, even before a screening trial:

- Age under 18 years (Per device labeling, the safety of SCS has not been established in children; however, the authors have implanted patients under age 18 and have not observed any untoward side effects or complications.)
- Unresolved major psychiatric comorbidity
- Unresolved likelihood of secondary gain
- Active and untreated substance abuse disorder
- Inconsistent or abnormal findings in the history, pain description and rating, diagnostic studies, or physical examination (such as a predominance of nonorganic signs, e.g., Waddell sign) are nonspecific.[26] Symptoms or signs that seem odd or uncommon should be interpreted with caution.
- Alternative therapies with a risk/benefit ratio comparable to that of SCS have not been ruled out.
- Occupational risk (e.g., the patient works on a ladder)
- Local or systemic infection (Chronic or ongoing septicemia is an absolute contraindication.)
- Foreseeable need for an MRI, unless MRI safe systems are utilized.
- Potentially disabling neurologic deficit attributable to a surgically correctible problem (e.g., nerve compression)
- Presence of a demand pacemaker (But see the 2003 study[27] in which thoracic SCS was safely used in angina patients with a pacemaker.)

- Presence of a cardioverter defibrillator (But see the 1998 report of Monahan et al.[28])
- Presence of another major comorbid chronic pain syndrome (This generally would be a contraindication for participation in an SCS clinical trial because it could confuse results.)
- Anticoagulant or antiplatelet therapy that cannot be reversed temporarily to allow SCS implantation
- Ulcers close to implantation sites
- Pregnancy (But SCS might be safer than other forms of pain therapy.[29])
- Brief life expectancy (But SCS with an external pulse generator might be useful.)

Possible Prognostic Factors

Several investigators have attempted to identify prognostic factors of success by statistical analysis of patient-specific characteristics (age,[30,31] gender,[32] number of prior surgical procedures, time since last surgical procedure, presence of an issue of secondary gain, etc.) or pain-specific characteristics[33] as well as by the technical aspects of treatment (type of electrodes[34–36] or pulse generators[37]). Whereas improved outcomes are well documented for certain technical improvements, such as programmable multicontact devices, the most useful clinical prognostic factor is the degree to which pain is relieved during the SCS screening trial.

Techniques of an SCS Screening Trial

A screening trial in a patient with the most common indication for SCS, failed back surgery syndrome, involves placement of a low thoracic electrode, and so there is usually no impediment to percutaneous placement at the thoracolumbar junction. In some cases, as noted above, electrodes must be placed by an open surgical technique because the postoperative changes (e.g., posterior instrumentation or laminectomy defect) involve the intended electrode level(s). Other indications for SCS, which might not involve spinal pathology, are likewise generally amenable to a percutaneous trial. The equipment involved and implantation techniques are detailed later in this book. Two technical decisions, however, merit discussion here.

First, during the screening trial, a percutaneous SCS electrode may be either anchored subcutaneously and connected with temporary percutaneous extension wires, or allowed to emerge from its insertion point and secured only to the skin. Advantages of the first approach (anchored, with tunneled extension) include the following:

1. Eliminating the expense of a second electrode should the patient pass the trial
2. Allowing the trial to be conducted with the definitive electrode in the definitive position

Advantages of the second approach (strictly percutaneous, strictly temporary, with a second stage only if the trial is successful) include the following:

1. Eliminating the need for two trips to the operating room, with its associated expense, because no incision is required and no foreign body is implanted permanently. The operating room is required only if a patient receives a permanent implant. An anchored, tunneled electrode always requires a second trip to the operating room, if only to remove the electrode after an unsuccessful trial.
2. Providing the opportunity to improve the position of the temporary electrode, which was placed in a naive patient, with a permanent electrode placed in a now experienced patient
3. Providing the opportunity to select the most appropriate permanent electrode based upon the results of the trial (e.g., a paddle electrode in a patient whose otherwise successful percutaneous trial was confounded by stimulation-evoked midback pain, attributable to recruitment of small pain fibers in ligamentum flavum)[37]
4. Avoiding the pain associated with the incision, anchoring, and tunneling. Such pain might require analgesics and confound interpretation of the trial. In some instances, a "tunnelled trial" is performed with a paddle lead. In this instance, if the trial is successful, the lead is left in place and the IPG is inserted in the second procedure. Such a trial is indicated in situations where placement of a percutaneous lead is not possible or when the percutaneous lead cannot be steered to the correct location.

■ Outcomes

In our experience 80 to 90% of patients referred specifically for SCS pass the initial records review (before we schedule an appointment). Once seen, 80 to 90% progress to a screening trial, and 65 to 85% pass the screening trial.

What Constitutes a Successful Screening Trial?

Interpreting the results of an SCS screening trial should be straightforward. The purpose of the trial is to establish that pain relief will be adequate and satisfactory to the patient (who must prefer the feeling of paresthesia to the pain and must be content to live with an implanted device). SCS is not expected to alleviate pain completely (although that outcome can occur), and patients must understand this. The patient must also understand that we do not believe

that SCS reduces nociceptive pain, including pain from ulcers or gangrene in patients with peripheral arterial occlusive disease.

Technical success (overlapping pain with comfortable paresthesia) is necessary (but not sufficient) to achieve clinical success (reduction in pain). Although some investigators report the use of subperception stimulation,[38] we must await more evidence before we can determine if this technique is successful. In the meantime, the technical goal of a screening trial is to achieve as much pain/paresthesia coverage as possible with stimulation at a level that is above perception and below that which elicits discomfort and/or involuntary movement.

Clinical success occurs when a patient reports at least 50% reduction in pain by standard rating methods and demonstrates improved or stable analgesic requirements despite provocative activities. (Some investigators, however, consider this percentage of relief to be too stringent.[39]) Patients with peripheral arterial occlusive disease should also demonstrate a clear increase in $TcPO_2$ or in some other objective indicator of microflow improvement. If the clinical results of a technically adequate trial are not convincing to the patient and the physician, prolonging the trial period can help to clarify the situation.

In our experience, 65 to 85% of patients pass the screening trial, and nearly all patients who pass the screening trial receive an implanted system for chronic use.

Repeat Trials

In some cases, patients experience uncomfortable paresthesia outside the bounds of the target area; this situation can warrant a repeat trial, sometimes with an insulated electrode that can prevent this side effect.[40] A repeat trial is also in order when the disappearance of initial clinical success occurs with technical problems (e.g., electrode migration). Sometimes a trial must be aborted because of an adverse,

Editor's Comments

As mentioned in this chapter, patient selection is of paramount importance in utilizing spinal cord stimulation (SCS) for the treatment of chronic medically intractable pain. Drs. North and Barolat are both masters of this technique, and both have contributed substantially to our understanding of the application of this procedure. They have presented their paradigm for patient selection in a clear and succinct manner, and I concur with almost all aspects of their report.

One area that remains difficult is the treatment of low back pain with SCS. As they note, back pain probably has a major nociceptive component, and therefore is not a priori as responsive to SCS as is neuropathic extremity pain. Furthermore, as alluded to in the chapter, production of paresthesias in the midline back—a *must* for successful pain relief—is more problematic than it is in the dermatomes of the lower extremities.

The authors of this chapter believe that patients with "predominant axial low back pain" should be considered candidates for SCS. Based on my experience, I am not convinced. In the condition that is clearly the most common indication for SCS, the failed back surgery syndrome (FBSS), I have experienced initial success with both back and leg pain, only to be disappointed with the discontinuation of back pain relief in longer term follow-up. As a result, I have avoided this indication for SCS.

As has been demonstrated previously by Dr. North,[5] in prospective trials, SCS almost certainly produces superior, and more cost-effective, outcomes than repeated major back surgery for FBSS. It continues to amaze me that we routinely see patients subjected to multiple major spinal surgeries, for which the outcomes are unproven by almost any measure, while the application of SCS in these same patients is often considered exceptional, even "experimental," by insurance or worker's compensation providers. The production of further evidence of the superiority of SCS over repeated spine surgery remains a challenge for the specialty of pain surgery. However, there is almost no other question in our field that can potentially have as much impact on the quality and cost of care.

I am gratified that the authors have included psychological evaluation in their screening procedures. This has been inconsistent as an area of practice, and in the reported literature on SCS. At the very least, it is important to document aspects of the patient's history that might confound the outcome of SCS, including major depression, a strong tendency to convert psychological stress to physical symptoms (somatization), prior history of drug abuse, or major secondary gain related to the pain problem. The last motivation may be relevant in cases in which a worker's compensation claim is being actively adjudicated. In fact, active litigation related to the pain condition is probably a substantial contraindication to proceeding with an SCS trial.

Overall, setting goals for SCS and the establishment of reasonable expectations are of great importance before one sets about to conduct a trial of SCS. Despite these caveats, SCS remains a unique tool for the relief of chronic pain, in that it is both testable and reversible. It is at once a venerable technique and a target for further study and refinement.

temporary biological response (epidural hematoma, infection) that must be resolved. After resolution, the trial can be repeated.

What Causes Trial Failure?

An SCS screening trial fails when it is impossible to cover the pain with comfortable paresthesia (technical failure), when pain–paresthesia overlap is technically successful but does not reduce pain (clinical failure), or if a psychological complication (e.g., the patient develops an aversion to an implanted device) occurs (patient-related failure).

Conclusion

To obtain a positive outcome with SCS treatment, we must offer the therapy to the correct patient with the correct indication. In addition, we must use the correct equipment and the correct technique; this means that the implanting physician must have the proper education and experience. Patient selection for an SCS screening trial can be liberal if interpreted conservatively, and it can be considered before every other therapy has been exhausted.

Patient selection for an SCS screening trial conducted as part of a clinical trial must be more rigid to avoid introducing unnecessary uncontrollable factors into the trial.

Several categories of independent variables are pertinent to patient selection and have demonstrable associations with SCS outcome:

1. Organic disease/diagnosis
   a. Primary
   b. Iatrogenic
2. Psychological status
   a. Premorbid
   b. Secondary
3. Treatment
   a. Choice of SCS; choice of device
   b. Trial methodology and technical success
   c. Trial interpretation

All of these variables should be considered in the selection of patients for device implantation.

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32 Spinal Cord Stimulation: Equipment and Implantation Techniques

Giancarlo Barolat and Richard B. North

Spinal cord stimulation (SCS), a reversible neuromodulation technique, is one of the safest and most effective procedures available for the long-term management of certain chronic pain conditions.[1–11] Even though a seemingly straightforward procedure, SCS implantation is technically demanding and requires care in planning and execution. The implanter has to be fastidious about the correct positioning of the electrode(s), in the longitudinal and in the transverse directions[12,13]; about the placement of the implanted pulse generator (IPG); about the location of the subcutaneous leads; and about the system connections. If any one of these factors is not optimal, the effectiveness of the whole procedure is jeopardized. This chapter discusses SCS equipment and some technical details of system implantation.

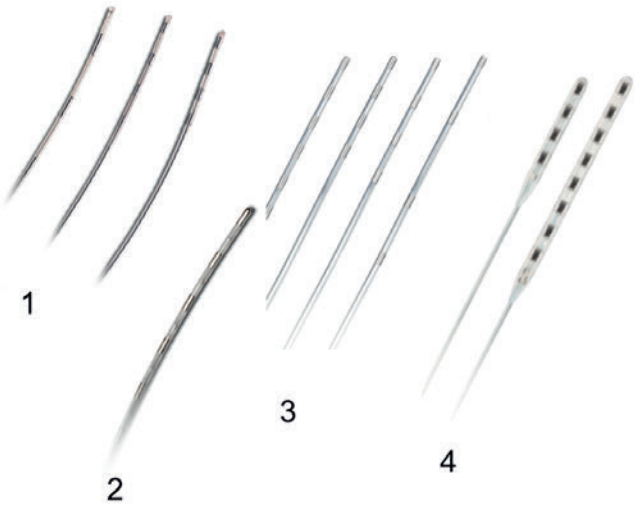

Fig. 32.1 Percutaneously inserted electrodes (not in scale). 1–3, cylindrical electrodes; 4, St. Jude S-Line percutaneously insertable paddle electrodes.

■ Equipment

SCS equipment includes electrodes (sometimes known as "leads," a term that includes the wires that are part of the electrode assembly), IPG, external controller, and charger. Radiofrequency receivers, although extensively used in the past and still used by some patients, are no longer being produced.

Electrodes

Electrodes (**Figs. 32.1** and **32.2**) can be classified according to their shape (cylindrical or plate/paddle) or implantation technique (percutaneous or laminectomy). The recently introduced St. Jude Medical S-Series electrode (St. Jude Neuromodulation, Austin, TX, USA), however, has blurred this distinction because it is a paddle electrode that can be implanted using a percutaneous ovoid catheter (Epiducer).[14]

Percutaneous electrodes can be used for a screening trial or implanted for chronic use. Most percutaneous electrodes are either quadripolar or octapolar. One 16-contact percutaneous electrode, the Infinion (Boston Scientific, Valencia, CA, USA), is available. Some electrodes connect directly to the IPG; others connect through an intermediate splitter or subcutaneous extension cable.

For the screening trial, a percutaneous electrode may be inserted in a fluoroscopy room and secured only at the needle insertion site; such an electrode is easily removed at the bedside or in the office. Alternatively, a percutaneous electrode may be inserted in an operating room and anchored subcutaneously. This method has the potential advantages of (1) saving the cost of a second electrode for chronic use and (2) ensuring that the permanent configuration reproduces a successful temporary one. Corresponding disadvantages are (1) the cost of a trip to the operating room for insertion; (2) the potential cost of a trip to the operating room for removal after an unsuccessful trial; (3) accepting the electrode posi-

Fig. 32.2 Paddle electrodes (not in scale).

tion achieved in a naive patient, rather than taking advantage of an opportunity to improve it after the patient has experienced trial stimulation; (4) the possibility that significant postoperative pain from the incision and anchoring procedure might confuse interpretation of trial results; (5) the possibility of creating a bias toward a positive trial; and (6) greater risk that an infection introduced by the temporary configuration will persist and involve the pulse generator.

Placement of percutaneous electrodes must be performed under fluoroscopic guidance, which requires personnel to wear heavy shielded garments and potentially exposes the patient and the implanting physician and staff to nonnegligible levels of radiation. The percutaneous approach is appealing, however, because it allows electrode insertion without muscle dissection or removal of bone tissue. In addition, percutaneous electrodes can be advanced through several segments in the epidural space to allow testing of several spinal cord levels. Multiple parallel percutaneous electrodes can be used to increase the number and variety of stimulation configurations that are tested. In the United States most implanters insert temporary electrodes for the screening trial, but in Europe most screening trials take place with electrodes implanted and anchored as if for chronic use.

Paddle electrodes are usually implanted for chronic use but can also be used for a screening trial (and can be removed or left in place if the trial is not a success). The simplest paddle electrode is quadripolar (e.g., the Medtronic [Minneapolis, MN, USA) Resume or Resume-TL, the St. Jude Lamitrode], with four contacts arranged linearly on a single paddle. Electrodes with 8 or 16 contacts increase the potential for stimulating multiple targets. These electrodes include the Specify 3998 and the Specify 2x8 (both Medtronic), the Lamitrode 44 and 88 (both St. Jude Neuromodulation), and the Artisan (Boston Scientific). These electrodes comprise two columns of narrowly spaced contacts. When centered symmetrically on the physiologic midline, the electrodes allow elective stimulation on either side or bilaterally.[2] Coupled with a "dual channel" control system, these electrodes allow great flexibility of stimulation. Some paddle electrodes have more than two columns of contacts, such as the St. Jude Penta (five columns) and the Medtronic Specify 3999 (three columns).

Implantation of paddle electrodes requires surgical placement under direct vision. The amount of actual bone removed can be minimal; in the cervical area, often no bone removal is necessary. Most paddle lead implants can be done through a small (1–1½ inch) skin incision. By advancing the electrode in a cephalad or caudal direction, one can explore at least four spinal levels in the thoracic spine and four or five levels in the cervical spine. Multiple arrays or different electrode configurations also can be constructed with laminectomy electrodes.

The main advantages of paddle electrodes are their insulated dorsal surface (which ensures that all the stimulating current is delivered to the intraspinal structure and thus can reduce the incidence of unwanted or uncomfortable stimulation), the inherent stability of each column of contacts with respect to the others, and their inherently greater stability once encapsulated in the dorsal epidural space, which potentially reduces their propensity to migrate, compared with inadequately secured percutaneous electrodes.

For low thoracic electrode placement for failed back surgery syndrome, which is the most common clinical application of SCS, the pattern of stimulation-induced paresthesia provided by insulated paddle electrodes seems to be superior to that produced by percutaneous electrodes.[15] In a randomized, controlled trial, the technical performance of laminectomy electrodes significantly exceeded that of percutaneous electrodes[16,17]: concordance of stimulation paresthesia with pain was statistically better for laminectomy electrodes, and power requirements were lower by half.

Some situations clearly indicate one or the other of these two methods (i.e., a percutaneous system for trial electrode placement in a fluoroscopy suite, or a

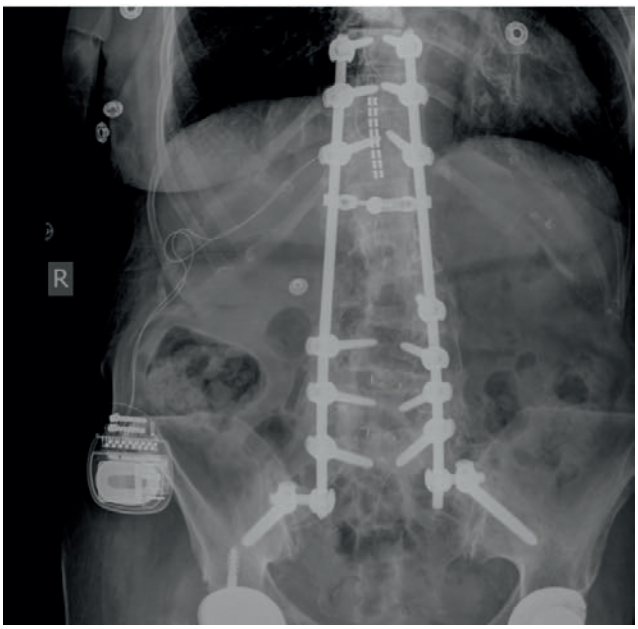

Fig. 32.3 Thoracic paddle electrode placed in previously instrumented thoracic spine.

paddle electrode for patients with a history of certain types of spine surgery) (**Figs. 32.3** and **32.4**). Otherwise, the choice of trial electrode is dictated by individual preferences and practice patterns. A skilled implanter usually can achieve a similar stimulation matrix with either a laminectomy or percutaneous electrode(s). The choice of permanent electrode can be dictated by the results of the trial (e.g., a paddle electrode to mitigate stimulation-evoked pain, attributable to recruitment of small fibers in ligamentum flavum,[16] or to improve low back coverage[17]).

Implanted Pulse Generator

Stimulation is delivered as charge-balanced pulses from an IPG (**Fig. 32.5**) powered by a battery through lead(s) to electrode contacts in the epidural space. Some SCS systems contain a nonrechargeable lithium battery; others contain a transcutaneously rechargeable battery. The introduction of the rechargeable battery has allowed manufacturers to reduce the size of the IPG while increasing its service life.

IPGs are activated and controlled by telemetry to and from an external control unit, or by a small external magnet, through the intact overlying skin. Stimulation is delivered at rates up to 10,000 Hz, pulse widths up to 1 ms, and amplitudes up to about 25 mA, adjustable in small increments. The life span of the battery varies with daily patterns of use and with stimulation parameters and number of active contacts. Most patients can expect, with conservative to average use, that a nonrechargeable battery will last 2 to 5 years. A rechargeable battery will have a much longer life, at least 9 years. The Medtronic rechargeable system is unique in that it is designed to shut off and require replacement at 9 years.

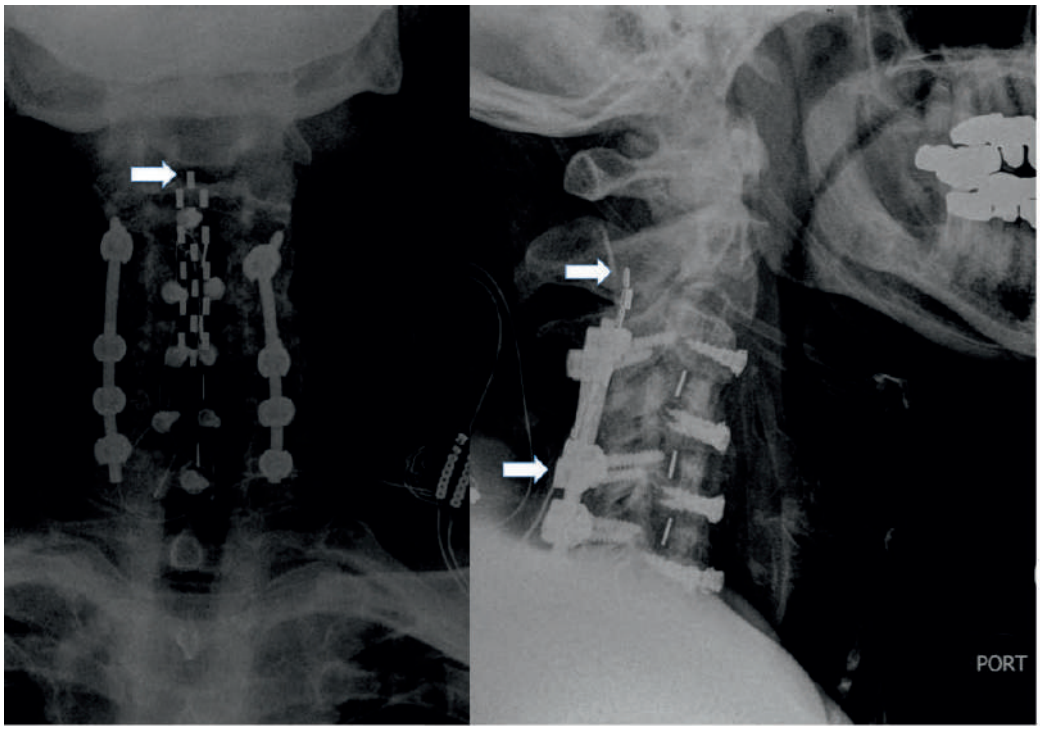

Fig. 32.4 Cervical paddle electrode placed in previously instrumented cervical spine.

Fig. 32.5 Implantable pulse generators (not in scale). Precision images courtesy of Boston Scientific. © 2014 Boston Scientific Corporation or its affiliates. All rights reserved. RestoreSensor SureScan MRI neurostimulator with leads reprinted with the permission of Medtronic, Inc. © 2013. Eon Mini rechargeable IPG (implantable pulse generator) image courtesy of St. Jude Medical. Eon Mini and St. Jude Medical are trademarks of St. Jude Medical, 2014. All rights reserved.)

Medtronics' RestoreSensor IPG is the first neurostimulator to adjust stimulation automatically as the patient changes position. This IPG uses AdaptiveStim technology, which automatically correlates changes in body position with the required level of stimulation. AdaptiveStim also records data regarding patient activity that clinicians can use to assess, evaluate, and optimize a patient's neurostimulation experience.

The Boston Scientific system employs multiple independent current control (each contact has a dedicated power source), which could result in a more discrete distribution of the current in the neural structures than is available with the other IPGs. The Boston Scientific Spectra pulse generator is the only one offering 32 independent stimulation channels.

Nevro (Menlo Park, CA, USA) produces an IPG that can deliver stimulation up to 10,000 Hz. As of this writing, it has not received FDA approval for use in the United States.

Operative Technique

Intraoperative Anesthetic Management and Testing

Electrodes can be implanted with the patient under monitored anesthesia (local anesthetic and intravenous sedation) or under general anesthesia. Unlike SCS applied for motor disorders or for ischemic conditions, conventional SCS for pain requires that stimulation-induced paresthesia cover a patient's area(s) of pain. Thus, it is logical that testing an awake and cooperative patient yields the best results.

When implantation is performed using general anesthesia, one can rely only on radiologic position and on evoked motor or sensory responses, and cannot obtain specific information about the distribution of the paresthesia or about discomfort at or near the therapeutic threshold. It is author G.B.'s preference, therefore, even when the implantation of the electrode is performed under general anesthesia, to rouse the patient during the procedure to ensure proper electrode placement; intraoperative wake-up is safely performed in over 90% of his cases. Author R.N. prefers local anesthesia, supplemented by brief sedation as necessary, and finds it applicable to over 90% of cases. Thus, both authors prefer to engage in meaningful conversation with an awake and cooperative patient during the intraoperative testing phase of a screening trial or implantation for chronic use. Of course, the safety of the procedure is paramount, and anesthetic technique has to be determined on an individual basis.

When conducting intraoperative testing, the implanting surgeon must be aware of the different responses that stimulation of the various intraspinal structures will elicit. The strategy for electrode placement in both the transverse and the longitudinal directions varies according to the pain topography and intraoperative-elicited responses.[8,9]

If the implantation is performed with the patient under general anesthesia, one must rely on three factors for electrode placement:

1. *Intraoperative X-ray*. Intraoperative localization, either by plain radiograph or fluoroscopy, can be used to locate the spine level and lateralization of the electrode. Correlation between right and left electrode locations and lateralization of paresthesia is imperfect, however, because the physiologic midline of the spinal cord does not always correspond with the radiologic midline.[10] Even when the image shows a centrally placed electrode, stimulation might not elicit bilateral, symmetric sensory (or motor) effects.
2. *Motor testing*. Stimulation is delivered through the implanted epidural electrode at a rate of 2 to 5 Hz, and elicited motor contractions are observed or recorded through previously inserted needle electrodes in the desired muscle groups. If stimulation through the epidural electrode triggers motor contractions in the painful extremity(ies), paresthesia will likely also be perceived there with a therapeutic level of stimulation. This principle is usually reliable in the cervical area, but direct patient reports

of sensory effects are more useful in the low thoracic spine. In GB's experience (since he routinely performs evoked motor potentials followed by patient wake-up) in about 50% of instances the information provided by the motor potentials is not satisfactory and the lead(s) must be repositioned.

3. *Evoked potentials*. Some researchers have advocated the use of somatosensory evoked potentials or compound action potentials to localize the position of the electrode. [18,19] We have used these techniques in a minority of cases, in which direct patient feedback is not feasible. Like motor stimulation, they represent a proxy for direct patient reports, which remain the "gold standard." As a general rule, implantation with the patient under general anesthesia with no intraoperative wake-up test cannot provide the same level of accuracy of placement as implantation with sensory feedback from the awake patient, who ultimately will be the judge.

Percutaneous Electrode Placement

Patient Positioning

Percutaneous electrode placement is routinely performed with the patient in a comfortable prone position on a padded fluoroscopy table. A pillow underneath the abdomen will create some degree of kyphosis, which might facilitate electrode insertion. It is important to ensure that the patient's trunk (for thoracolumbar placement) or neck (for cervical placement) is in a neutral position without rotation or twisting.

Occasionally, if a patient cannot tolerate the prone position, the procedure can be performed in the lateral decubitus position, but this makes intraoperative fluoroscopic assessment more difficult, and electrode position with respect to the midline might not be maintained postoperatively. In some centers, the procedure is routinely performed with the patient seated, which emulates the position in which the device will likely be most used, might add to the patient's comfort during insertion, and might increase the implanter's ability to obtain thoracolumbar kyphosis, which facilitates insertion of the needle in the epidural space.

Percutaneous Electrode Insertion

The level of electrode insertion is determined by several factors. Ideally, several centimeters of the electrode body should lie within the epidural space to minimize dislodgment, and thus insertion should start at least two spine segments below the desired target. Another consideration is choosing a relatively kyphotic level, to facilitate achieving a shallow angle of approach to the epidural space. Yet another consideration is choosing a level that will minimize the risk of injury at the cervical or lumbar cord enlargement. Commonly chosen levels, therefore, are at or just below the cervicothoracic and thoracolumbar junctions.

The fluoroscopy equipment must be ready to function in both the anteroposterior and lateral planes at the time of Tuohy needle insertion. The Tuohy needle is inserted at as shallow an angle (as nearly parallel to the spinal canal) as possible. In the thoracic area, this can be accomplished with either a midline or paramedian approach; in the upper lumbar area, a paramedian approach is required. A shallow angle greatly facilitates subsequent electrode insertion and control of the electrode in the epidural space. A paramedian insertion allows such a shallow angle of needle placement and avoids placing the electrode between two adjacent spinous processes. (Extension of the spine can pinch a lead between two spinous processes; this can lead to fatigue fracture.)

When the epidural space is satisfactorily identified, the electrode is gently inserted and steered under anteroposterior (and, as necessary, lateral) fluoroscopic guidance, with test stimulation at representative contact combinations along its length as it is advanced, level by level, to establish its position with respect to the physiologic midline and the target segments. Once the desired electrode location in the epidural space has been established, the emerging lead must be secured for stability. A temporary percutaneous electrode is commonly secured by a skin suture; special devices and techniques for permanent anchorage via an incision have evolved to mitigate the problem of postoperative migration.[20]

Paddle Electrode Placement

Two basic positions can be used: prone or semilateral. The prone position allows a straightforward appreciation of spatial relations and is the one generally used for posterior surgical approaches to the spine. The prone position is used for implantation under general orotracheal anesthesia without intraoperative patient wake-up. The potential difficulty in airway management, however, limits the use of generous intravenous sedation to supplement local anesthesia in the prone patient.

In the semilateral position, the patient lies in a "park bench" position, exposing the spine as well as the flank, abdomen, or buttock for the IPG implant. In this position, airway management is easier and thus safer than in the prone position, and the anesthesiologist feels more comfortable in administering general anesthesia (usually with a laryngeal mask) and then waking up and extubating the patient for intra-operative testing. Deep sedation is also admin-

istered more safely in this position than in the prone position. One must be aware, however, that because of variable rotation of the body, three-dimensional visualization of the operated structures may be less intuitive. This problem is compounded in the cervical area where rotation and flexion/extension of the spine occur.

Based on his experience with more than 8,000 implanted paddle electrodes, one of the authors (G.B.) prefers the semilateral position; the other (R.N.) prefers the prone position, based on limited experience with laminectomy electrodes and a large amount of experience with percutaneous electrodes under local anesthesia, which he finds applicable to the majority of permanent SCS implants. Individual patient considerations and practitioner experiences and preferences should guide these choices.

In the planning phase of the procedure, the implanting surgeon must be aware of the varying angulation of the spinous processes at different spinal levels and of the correlation between the various spinal levels and the patterns of stimulation-induced paresthesia.[12] All three manufacturers of paddle electrodes recommend imaging (typically MRI) before implantation to assess the diameter of the spinal canal; this improves patient safety.[21] Some (author R.N. included) prefer imaging even before percutaneous electrode placement. Prior to incision or needle placement, a radiographic or fluoroscopic image is taken in the operating room with metallic markers placed on the skin at the level of the planned incision. This allows precise marking of the entry level.

In a typical case, with ample spinal canal diameter to accommodate the paddle electrode safely, it is introduced beneath the intact neural arch into the dorsal epidural space through a minimal exposure. Subperiosteal dissection usually can be limited to the upper half of the spinous process inferior to the desired interlaminar space and to at least the inferior two thirds of the spinous process superior to it. Parts of the superior spinous process can be incrementally removed until the ligamentum flavum is exposed. Insertion of a paddle lead can also be performed without removing the spinous process nor the supraspinous ligament. This preserves the structure of the spine and minimizes postoperative pain and spine instability. Following removal of the ligamentum flavum, and a limited laminectomy as necessary to accommodate the electrode(s) safely, the dorsal epidural space is dissected bluntly, and then the electrode is inserted at a shallow angle. Cases with significant stenosis at the planned level of electrode implantation can be addressed by decompressive laminectomy. After placement of the electrode, the emerging lead can be anchored in the same fashion as for percutaneous leads.

Implantation of the IPG

The position of the IPG is crucial and must be comfortable for the patient. The most common placement sites include the abdomen, the fat pad in the posterior iliac area, the infraclavicular area, and the lateral chest wall area. In most cases, the IPG is placed in the subcutaneous tissue. In thin patients, it can be useful to place the IPG under the fascia. The unit can be secured to the underlying tissues with nonabsorbable sutures. In patients with abundant adipose tissue or loose subcutaneous tissue, the IPG may be placed in a Dacron pouch to reduce the chance of unwanted movement. This pouch can be secured with multiple sutures to both the deep and the superficial subcutaneous layers. This maneuver will minimize, but not completely eliminate, the risk of migration and tilting. The subcutaneous pocket is made with either blunt (fingers, Kelly clamps) or sharp (scissors, cutting coagulator) dissection. The pocket should be only slightly larger than the IPG to reduce the likelihood of migration. Ideally, the whole unit (including the connectors) will lie completely within the pocket and will not cross underneath the skin incision.

Conclusion

Refinements in surgical technique, along with device development, continue to improve the safety, efficacy, and reliability of SCS, as is appropriate for neuromodulation, which is intended as reversible therapy. SCS is increasingly the treatment of choice for complex, refractory chronic pain conditions.

Editor's Comments

This chapter is a companion piece with Chapter 31. Two of the most notable spinal cord stimulaton (SCS) implanters, Dr. Rick North and Dr. Giancarlo Barolat, have shared with us their combined wisdom on the implantation of SCS devices. Each surgeon elucidates the "ideal" method for implantation, and this is a product of experience, the nature of the unique patient population, and the clinical setting. I have my own preferences, but the differences are fairly trivial.

What we have not dealt with in this section is an objective assessment of the outcome of SCS. Although some of these results are mentioned in passing in the first of these two chapters, a structured review of the literature will be presented in Chapter 58.

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Section IV.A.2

Peripheral Nerve Stimulation

33 Peripheral Nerve Stimulation

Viraat Harsh and Ashwin Viswanathan

In 1967 Patrick Wall and William Sweet[1] described the first experience with the use of peripheral nerve stimulation (PNS). Their initial explorations into PNS were based upon one of the predictions of the "gate control" theory of pain as delineated by Ronald Melzack and Patrick Wall 2 years prior.[2] Specifically, they postulated that stimulation of large-diameter cutaneous afferent fibers can lead to decreased pain perception. With this as the basis, Wall and Sweet inserted needle electrodes into their own infraorbital nerves and were able to produce paresthesias in the sensory distribution of the nerve. Square wave pulses were used with a frequency of 100 Hz and pulse width of 0.1 ms. During the period of electrical stimulation and for a short duration following, the investigators developed hypalgesia in the distribution of the nerve. With this positive foundation, they then treated eight patients with severe cutaneous pain with peripheral nerve stimulation.

Since this initial report, PNS has attracted significant interest, both as applied to specific nerves and as applied to subcutaneous peripheral nerve fields. Craniofacial pain is likely the most common indication for PNS today, targeting the occipital, supraorbital, and infraorbital nerves. However, a broad range of targets and surgical techniques have been used in an effort to treat chronic regional neuropathic pain.

The gate control theory provides a useful framework to understand a possible mechanism for PNS. The gate control theory postulates that both large- and small-diameter axons provide sensory input to the cells of the substantia gelatinosa in the dorsal horn of the spinal cord. The substantia gelatinosa serves as a gate control system that modulates the input from the large- and small-diameter fibers before they influence the first central transmission (T) cells in the dorsal horn. The summation of the excitatory input from the large-diameter fibers and the inhibitory input from the small-diameter fibers modulates the overall inhibitory activity of the substantia gelatinosa. Hence, an increase in the excitatory input from the large-diameter fibers will, in turn, increase the inhibitory output from the substantia gelatinosa, which will decrease the nociceptive output from the T cells to higher processing centers.

Although the gate control theory can provide one basis for pain relief seen with stimulation of large-diameter afferent fibers, other experiments have shown that the gate control theory does not account for all of the interactions between the large- and small-diameter afferents.[3]

Other mechanisms for PNS have also been proposed. Campbell and Taub[4] performed transcutaneous electrical stimulation of the digital nerves and recorded compound action potentials (CAP) from the median nerve. With lower amplitude continuous stimulation (10–12 V, 100 Hz, 1 ms pulse width), the authors found an increased threshold for touch, but not for pain. With the amplitude of stimulation increased to 50 V, but with periodic stimulation, patients experienced pain, and the CAP demonstrated the presence of Ad waves. When the stimulus was changed from periodic to continuous, the sensation of pain disappeared along with the Ad waves seen on the CAP. This experiment suggests that a peripheral mechanism may also account for the mechanism of PNS.

More recently, Ristić et al[5] applied PNS to the superficial radial nerve trunk and recorded cortical laser-evoked potentials after painful stimulation. Mechanical and thermal perception thresholds were also measured. The authors found a significant reduction in the mechanical perception threshold induced by PNS due to a collision of orthodromic and antidromic Ab fiber activity. These data support the concept that a peripheral mechanism may also be involved in the analgesia attained through PNS.

■ Indications

Appropriate candidates for PNS are patients with chronic neuropathic pain in the distribution of a peripheral nerve. Electrodes are generally placed

proximally to the injury site. Historically most commonly treated nerves are the ulnar, median, radial, posterior tibial, and common peroneal nerves. The last 5 years has seen a significant rise in the use of peripheral nerve stimulation for the treatment of craniofacial pain. Leads targeting the supraorbital, infraorbital, and occipital nerves have been effectively used in the treatment of these neuralgias.

Factors in evaluating a patient for PNS are:

- A demonstrated pathology for the pain complaint
- Failure of more conservative therapies, including surgery
- No significant drug dependence issues
- Adequate patient motivation and intelligence
- Clear understanding that PNS can reduce pain but cannot cure the underlying disease or problem
- Successful trial stimulation
- Pain arising from an identifiable nerve, with temporary pain relief resulting from use of selective nerve blocking techniques.

Prior to considering PNS, the patient should have undergone a trial of medications for neuropathic pain and either have had no pain relief or had significant side effects from the medications, which precluded their use. As with all implantable neuromodulatory devices for pain, implantation of a PNS is predicated on a successful trial. Depending on the target nerve, a percutaneous or open surgical approach may be used for the trial.

Techniques

The first step in the treatment process is performing a trial of the peripheral nerve stimulation. Both percutaneous and open surgical techniques can be used for placement of the trial electrodes. A criterion of 50% reduction in pain is accepted as a successful trial.

The technique for the placement of leads for the occipital, supraorbital, and infraorbital nerves is detailed elsewhere. These leads are most commonly placed using a percutaneous technique. A percutaneous technique has also been applied for PNS trials targeting the median, radial, ulnar, peroneal, and posterior tibial nerves. For percutaneous trials targeting larger nerves of the upper and lower extremities, the use of ultrasound guidance can be beneficial to ensure proper lead location.[6] A percutaneous technique can be performed under monitored anesthesia care or under general anesthesia. Radiographic placement for most percutaneous trials is usually adequate to ensure appropriate location, obviating the need for an awake patient and hence maximizing patient comfort.

An open surgical technique is the most commonly used approach in PNS for targeting nerves of the upper and lower extremities. Microsurgical technique is used to expose a segment of the involved nerve proximal to the injury and site of pain. Generally, a span of 4 to 5 cm of the nerve must be dissected free from the surrounding tissues to allow room for the trial electrode. Some authors have advocated the use of a fascial sling to serve as a barrier between the electrode and the nerve, analogous to the role the dura serves in spinal cord stimulation. However, with the ability to more finely control the amplitude of stimulation with the newer pulse generators, this may not be necessary. If a fascial sling is desired, a piece of fascia 4 cm × 1 cm may be harvested locally. The electrode can then be placed on the nerve and secured to the surrounding fascia to minimize the risk of lead migration. **Fig. 33.1** illustrates the technique for implantation of a paddle electrode for ulnar nerve stimulation. Typically, a 4-contact electrode is used for peripheral nerve stimulation, but as technology continues to evolve, 8- or 16-contact paddles can also be considered.

If a percutaneous technique is chosen, the lead used for the trial will be anchored to the exit site. Most device manufacturers offer a locking anchor for percutaneous leads, which can prevent migration during the trial. After a trial of 5 to 7 days, the percutaneous lead can be removed in clinic. If the trial was successful, the patient will return to the operating room for placement of the permanent lead and implantable pulse generator (IPG). If an open surgical technique is chosen for placement of the trial electrode, an extension cable is connected to the surgically placed paddle lead, and the extension cable is externalized. This maintains the sterility of the paddle electrode. If this trial is not successful, the patient is returned to the operating room for removal of the extension cable and paddle electrode. If however, there is a successful trial, the patient is returned to the operating room, the externalized extension cable is removed, and the paddle electrode is then connected to an IPG.

Various locations can be used for the IPG, the most common being the infraclavicular, subcostal, and posterior superior buttock regions. If the targeted nerve is in the lower extremity, the IPG may also be placed in the lateral thigh. Depending on the length of the lead used (commonly between 40–70 cm), an extension cable may be necessary to connect the IPG.

PNS typically uses a lower voltage than spinal cord stimulation, with therapeutic levels of stimulation generally between 0.5 and 3 V. Common pulse widths are between 120 and 400 μs and rates range from 50 to 80 Hz. Intermittent cyclical stimulation is often adequate and can help to prolong battery life and, in the case of a rechargeable IPG, increase the interval between rechargings.

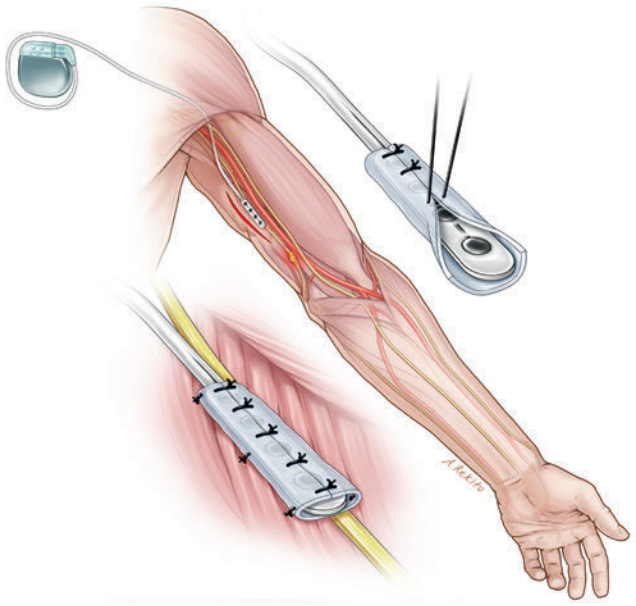

Fig. 33.1 Surgical technique for implantation of a paddle electrode for ulnar nerve stimulation. After exposure of an adequate segment of the ulnar nerve, a fascial cuff is harvested and secured around the electrode. The electrode may then be placed above or below the ulnar nerve and tacked down to the surrounding fascia to prevent migration.

Outcomes

Peripheral Nerve Stimulation

Hassenbusch et al[7] prospectively treated 32 patients with PNS for stage III reflex sympathetic dystrophy. Preoperative symptoms included allodynia, deep burning pain, vasomotor tone changes, trophic changes, motor weakness, temperature changes, temporary improvement after sympathetic blockade, and a history of trauma to the affected nerve. Targeted nerves included the median, ulnar, radial, common peroneal, and posterior tibial. Of the 32 patients who underwent a trial, 30 (94%) underwent permanent implantation. Follow-up ranged from 2 to 4 years, and long-term good or fair pain relief was seen in 19 patients (63%).

In 2000 Novak and Mackinnon[8] reported their experience with PNS in patients who had suffered an injury to a peripheral nerve. Seventeen patients were treated; 12 underwent PNS of the upper extremity and 5 of the lower extremity. Targeted nerves included the ulnar (n = 10), median (n = 1), radial (n = 1), and posterior tibial (n = 5). Over a mean follow-up time of 21 months, excellent pain relief was reported by 5 patients, good by 6 patients, fair by 4 patients, and poor by 2 patients. Of the 12 patients not working preoperatively, 6 returned to work.

In 2007 Mobbs et al[9] reported their experience with 45 patients who underwent a trial of peripheral nerve stimulation in the treatment of pain due to nerve trauma, iatrogenic injury from surgery or percutaneous interventions, or continued pain after peripheral nerve tumor resection or decompression. Only 4 patients failed the trial and did not proceed to permanent implantation. Nerves targeted included the median (n = 11), ulnar (n = 10), brachial plexus (n = 9), radial (n = 3), suprascapular (n = 1), common peroneal (n = 2), sural (n = 2), posterior tibial (n = 2), and sciatic (n = 1). Over a mean follow-up of 31 months, an overall good result was seen in 23 out of 38 patients (61%). The mean verbal pain score (VPS) preoperatively was 9 and, on 1-month follow-up, was 5.1. This level of efficacy was maintained with a mean VPS of 5.2 at last follow-up.

Anatomically guided percutaneous and ultrasound-guided percutaneous techniques have also been successfully applied for PNS. Small series of patients have been treated for ilioinguinal neuralgia[10,11] and testicular pain.[12] In 2009 Huntoon and Burgher[6] reported their series of eight patients who underwent ultrasound-guided percutaneous trial of PNS for neuropathic pain that responded to a peripheral nerve block. Targeted nerves included radial (n = 3), ulnar (n = 2), posterior tibial (n = 1), median (n = 1), and common peroneal (n = 2). Six of eight patients had a successful trial and underwent permanent percutaneous implantation. Over a minimum follow-up of 8 months, 83% of the patients had greater than 50% pain relief.

Subcutaneous Field Stimulation

Subcutaneous field stimulation (SFS) is a relatively new procedure, in practice for over a decade now. It involves implanting leads in the painful area itself rather than directly over a specified peripheral nerve (**Fig. 33.2**). Recently, the use of two parallel electrodes placed on either side of the painful region, one serving as anode and the other as cathode, has been described[13] (**Fig. 33.3**). The procedure for the implantation of the leads and IPG are similar as for percutaneous PNS, detailed above. Patients with axial low back pain, neck pain, or intercostal neuralgia may be good candidates for SFS.

In a large, multicenter, retrospective series of 119 patients from seven Austrian centers, Sator-Katzenschlager et al[14] reported outcomes for patients treated with low back pain (n = 29), failed back surgery syndrome (n = 37), cervical neck pain (n = 15), postherpetic neuralgia (n = 12), and other focal pain syndromes. Of the 119 patients in the trial, 111 patients experienced more than 50% reduction in pain on the numerical rating scale (NRS) in the

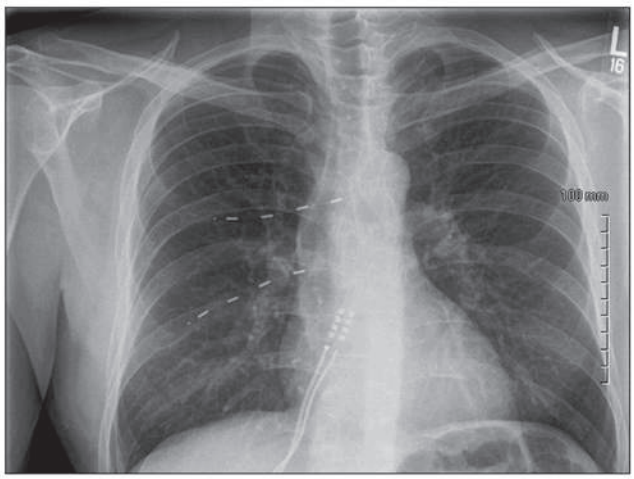

Fig. 33.2 Subcutaneous field stimulation (SFS) applied to a patient with localized pain following thoracic ganglionectomy. Leads are placed in the region of maximal pain intensity.

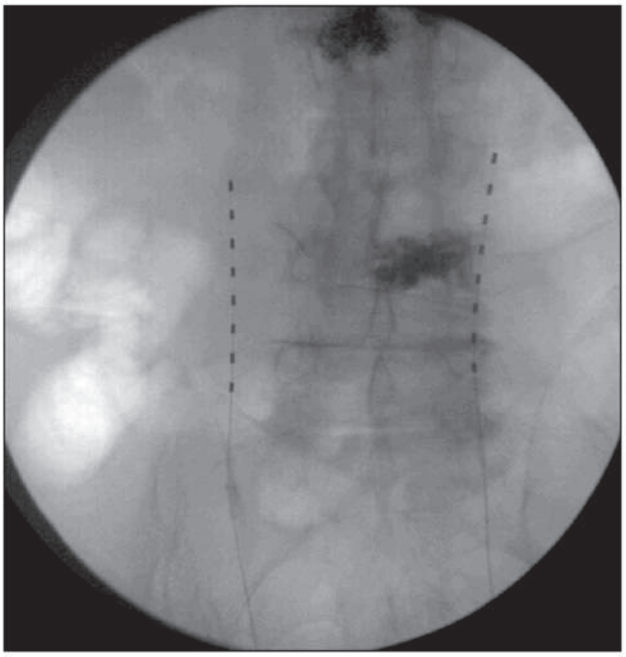

Fig. 33.3 Subcutaneous field stimulation (SFS) applied for axial lower back pain that did not respond to spinal cord stimulation (SCS). Two parallel electrodes are placed, each centered on the point of maximal pain, marked preoperatively.

1- to 2-week trial period. After permanent electrode implantation 92% of patients showed continued pain relief 3 months after the procedure, with mean NRS reduction from 8.2 to 4.0. The authors also noted a reduction in the strength and dosages of opioids used. Of the patients implanted, 24% developed complications, including infection in 7 patients (6%), lead migration in 14 patients (13%), and lead fracture in 6 patients (5%).

SFS is also being increasingly used as an adjunct to spinal cord stimulation (SCS) that fails to relieve axial symptoms adequately. Hamm-Faber et al[15] treated 11 patients with failed back surgery syndrome in whom SCS was not adequate for treating low back pain. In 9 of these patients SFS was used along with SCS to treat the pain, and in 2 patients SFS was used alone. Significant improvements were seen in pain scales and in the usage of pain medication, adding support for the use of SFS in patients with localized pain syndromes.

Conclusion

Peripheral nerve neurostimulation has evolved over the last 30 years to become an important therapy in the control of intractable pain caused by peripheral mononeuropathies and sympathetically mediated pain syndromes. The growing successful experience with PNS for craniofacial pain suggests a wide variety of applications for localized pain control of conditions including postthoracotomy pain, postherniorrhaphy pain, and incisional neuroma pain. Newer percutaneous techniques using multipolar wire electrodes placed adjacent to peripheral nerves without the need for extensive dissection should help to foster PNS as a reasonable neuroaugmentation alternative to more destructive methods of chronic pain control.

Editor's Comments

Peripheral nerve stimulation (PNS) was the first clinical application of the gate control theory proposed by Melzack and Wall in 1965. As described in this chapter, it has been used ever since to treat neuropathic pain of suspected peripheral origin.

Although the initial indications for PNS were directed at discrete nerve injuries, over time the method has been generalized to treat painful regions. The bridge to that application was occipital nerve stimulation (ONS) for occipital neuralgia because these stimulation electrodes were placed simply in the *vicinity* of the greater and lesser occipital nerves, the hope being that the nerves would be recruited by stimulation prior to the overlying musculature. The use of this approach for supraorbital and infraorbital neuralgias is similar.

As described by the authors, PNS is now being applied subcutaneously to painful regions, such as the low back, with no attempt to target a specific nerve. Subcutaneous field stimulation (SFS) is being used to treat axial back and neck pain. I doubt this is what Sweet and Wall had in mind when they stimulated their own infraorbital nerves.

The quality of evidence to support these procedures is still rather low. Follow-up is short even for retrospective trials, sometimes measured in months, and there have been no prospective randomized trials. Further, all the reports have been from the implanting surgeons. It would seem a simple matter to conduct a high-quality trial of PNS, which could incorporate no stimulation, or off-target stimulation as a control. Unbiased follow-up by a third, unconcerned party would add to the validity, as would the use of accepted outcome measures. The fact that this has not been accomplished in the almost 50 years since the inception of this technique attests to the facts that patients who are considered for PNS are uncommon in most centers, and that the potential health impact of PNS is so marginal as to be below the radar of most granting agencies. It is difficult for any center to mount a reasonable trial under these circumstances.

Unless PNS is subjected to better analysis, it is likely that insurance or governmental funding for this procedure will continue to diminish, and that it will not remain part of our surgical armamentarium. At least in the United States, the impact of health care reform will focus attention on these unproven and expensive modalities. It may be time for the manufacturers of these devices to support a prospective trial, coordinated by a contract research organization (CRO), to determine if these procedures can stand up to the scrutiny of a well-conducted study. A study like this would be viewed as a positive, and long-overdue, development in our field, regardless of the outcome.

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34 Occipital Nerve Stimulation

Richard L. Weiner

Neurostimulation for chronic headaches has evolved significantly over the years since the author's first intraoperative observation in 1993[1] that subcutaneous stimulation via percutaneously placed "off-the-shelf" spinal cord stimulator wire electrodes produces paresthesias in a dermatomal or myotomal distribution without the need for direct peripheral nerve contact. Additionally, these paresthesias were capable of reducing pain perception in a manner similar to spinal cord or direct peripheral nerve stimulation with generally lower voltage and similar frequency and pulse width settings.

The early application of this discovery was in treating a group of patients presenting with intractable occipital neuralgia and reported in a seminal paper in 1999.[2] The diagnosis of occipital neuralgia is felt by headache neurologists to be a relatively rare occurrence in a typical headache practice. It is described as a paroxysmal, sharp, lancinating head pain in the distribution of a greater, lesser, or third occipital nerve very similar to a trigeminal neuralgia attack. This classification was certainly not well understood in the neurosurgical literature at a time when most neurosurgeons would only encounter these patients as referrals for occipital nerve excision due to intractable pain. The original group of patients reported in the 1999 publication were initially diagnosed with occipital neuralgia from a variety of etiologies, including head injury and cervical trauma. The publication of a new headache classification,[3] timely input from neurology colleagues, and a repeat evaluation of the original reported occipital nerve stimulation (ONS) series[4] clarified that most patients presenting with occipital headaches in the study group were actually diagnosed as having chronic migraine headaches as a primary headache condition rather than secondary headaches, under which occipital and other cranial neuralgias are listed. Still, the initial excellent outcomes from these intractable headache patients, coupled with subsequent reports from numerous clinical investigators,[5–7] has led to a resurgence of activity in the field of chronic pain management, with the recognition that the subcutaneous tissues throughout the craniofacial, body, and extremity regions are viable areas in which to consider the use of neurostimulation for treatment of a large number of chronic pain conditions.

Whereas neuromodulation may be indicated for a variety of craniofacial syndromes, including cluster headaches, posttraumatic neuralgia, trigeminal neuralgia, and persistent idiopathic facial pain,[8–10] the scope of this discussion, although limited to pain in and around the occipital region, neurostimulation techniques, outcomes, and future trends, is applicable to a much wider array of indications.

Indications

ONS delivers a small electrical charge, producing usually agreeable paresthesias when placed subcutaneously in the region of one or more occipital nerves, without the need for direct nerve contact to control pain in patients unresponsive to medications or other conservative treatment. The typical device is a spinal cord stimulator system comprising an implantable pulse generator (IPG; chest, abdomen, or upper buttock region placement) attached to extension leads tunneled and connected to subcutaneously placed, standard multicontact electrodes directed either horizontally or diagonally from the skull base at approximately the C1 level to cover the areas of maximal pain in the occipital regions as identified by the patient. Continuous or intermittent stimulation has been used for pain control.

Subcutaneous placement of one or more multicontact leads, using either a wire or a paddle[11] configuration, is usually surgically straightforward and avoids the need for surgical cut-down to expose major peripheral nerves. This has been a major factor in the emergence of this form of neuromodulation as a safe, effective, and easily reproducible technique for pain control. Similar to evaluations for spinal cord

stimulator implants, a temporary trial period of up to several weeks is usually indicated to predict success with a permanent implanted device. Patients have time to decide if the paresthesias are agreeable and produce pain relief both in sedentary and active modes. It also gives the implanter some idea of the stimulation parameters that might be required with a permanent device.

Current indications include:

- Occipital neuralgia
- Chronic daily occipitally mediated migraine headaches (transformed migraine)
- Intermittent migraine headaches with occipital triggers
- Chronic neuropathic pain—occipital distribution
- Posttraumatic neuropathic pain (blunt trauma, postop incisional pain)
- Cervicogenic occipital pain

Relative contraindications include:

- Debilitating chronic systemic diseases
- Excessive narcotic intake/dependency
- Psychological issues predictive of poor outcomes
- Diffuse pain in about the craniofacial region
- Active infection

■ Techniques

Trial Stimulation

Successful percutaneous wire trial electrode placement (temporary or permanent) depends on several factors:

- Subcutaneous space identification
- Electrode contact depth
- Outline of greatest painful areas
- Appropriate patient

The patient is given short-acting IV sedation either in the prone or lateral position followed by Tuohy needle or 14-gauge angiocatheter insertion (local anesthetic infiltrated at the skin entrance site) on either side of the midline (or unilaterally if indicated) inferior to the area of identified pain at the upper cervical region posteriorly. The needle/catheter is directed in the subcutaneous space cephalad from left to right and right to left of midline (**Fig. 34.1**) to just beyond the area of defined maximal pain, which is usually a couple of finger breadths off the midline for greater occipital nerve pain and more lateral for lesser occipital nerve pain. It is paramount to avoid any damage to the dermis layer when the needle or catheter is being inserted for both temporary and permanent electrode placement to avoid the risk of erosion and subsequent infection.

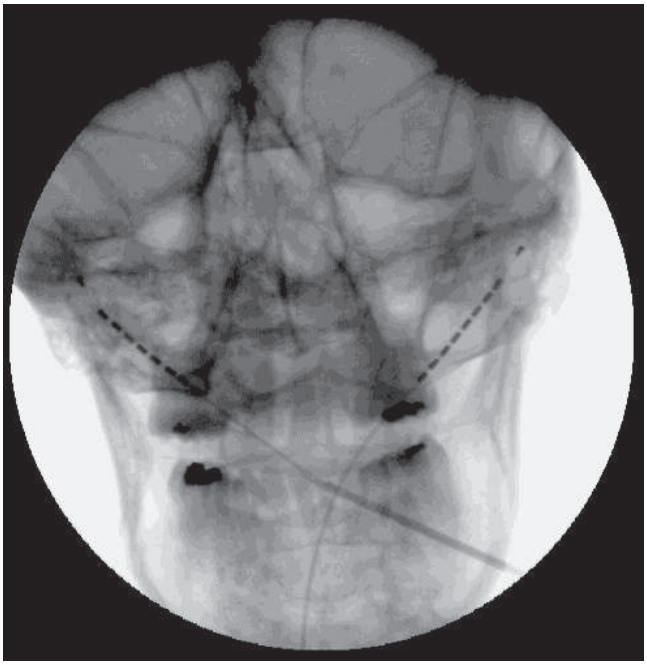

Fig. 34.1 Crossed temporary leads directed superolaterally.

The patient is awakened and temporary stimulation current is then applied to verify electrode location. The patient should feel paresthesias into the scalp area around the electrode array with polarity shifting utilized to maximize effective paresthesia coverage around the painful areas. A grabbing sensation or muscle twitching usually indicates the electrodes are deep to the fascia with the cervical musculature and will need to be repositioned. Leads placed too superficially within the dermis will lead to erosion and possible infection (temporary and permanent electrode placement). The leads exiting the insertion site are then sutured to the skin with supplied anchors and antibiotic dressings applied (**Fig. 34.2**). The externalized lead extensions must then be secured with enough tape and lead coiling to prevent lead pullout.

Permanent Implantation

The temporary electrodes should be removed in the clinic by the operator, who can then carefully interview the patient regarding stimulation response and pain control as well as medication usage and the desire to continue toward or decline a permanent implant. Permanent placement of electrodes is usually delayed at least 2 weeks to allow healing around the puncture sites and minimize the risk of infection. Care should be taken to avoid incisions in or immediately adjacent to the healing puncture sites. For patients with permanent temporary leads, the

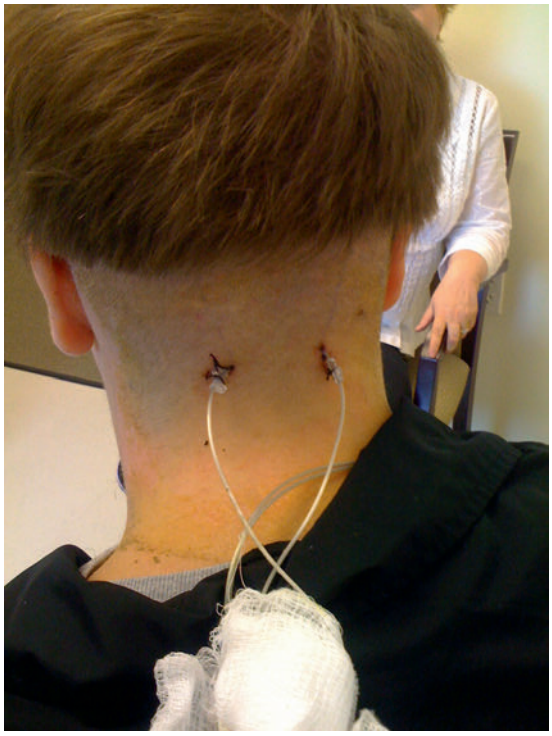

Fig. 34.2 Temporary lead placement.

externalized lead extensions can be carefully cut so the distal lead connects to permanent subcutaneous extensions tunneled to the IPG.

Suitable candidates for implantation should be made to understand some caveats to the permanent occipital nerve stimulation or other subcutaneous permanent implant device. Some patients may be referred for permanent implants after having been in a trial elsewhere, and it is imperative that they be properly counseled regarding their expectations and limitations of the device.

Limitations

As of this writing, ONS and other subcutaneous neurostimulation procedures remain off label in the United States but have received approvals in Europe and Australia.

1. No system to date is completely magnetic resonance imaging (MRI) compatible, and patients requiring periodic MRI evaluation for unrelated medical issues may be unable to comply.
2. Cautions apply with regard to operating machinery and driving, similar to those for spinal cord stimulation because there could be a rare voltage or current surge that might startle the patient.
3. The risks of infection and lead migration or extrusion with current systems remain the chief complication.
4. Stimulation tolerance with loss of pain control can occur in up to 20% of cases over time.

Expectations

1. There is a spectrum of utilization and response to ONS therapy. This includes intermittent use when a headache onset is perceived, all the way to constant use with chronic daily headaches.
2. These devices may be considered as adjunctive therapy for many intractable headache sufferers, which will still require other treatment modalities to minimize pain.
3. The implants are usually not curative.
4. Underlying behavior and narcotic intake issues still need to be treated and monitored.

Procedure Considerations

Implantable Devices

Most ONS implants are comprised of a rechargeable pulse generator, lead extension(s), and one or more multicontact wire electrodes. Paddle electrodes have also been used in some patients who may need a broader region of stimulation or who have had electrode migration issues, although some surgical dissection is necessary in the subcutaneous space for correct placement. There are currently three main power source options available for the implanter to consider: primary cell nonrechargeable IPG, rechargeable IPG, and external radiofrequency (RF) transmitter/receiver systems. Interestingly, the RF systems are on label for peripheral nerve indications. If voltage and current requirements are low during the trial, a primary IPG might be advantageous in the older patient group to reduce noncompliance from perceived complexities of periodic battery recharging.

Head Position

Although the prone position in a padded head holder is technically the most straightforward way to implant electrodes and tunnel extension wires (**Fig. 34.3**), many anesthesiologists are uncomfortable with airway control during sedation. Also, the IPG implant site would need to be posterior as well, usually in the upper buttock region, with long primary electrode or extension wires tunneled from the neck through a sometimes difficult cervicothoracic subcutaneous junction. The lead extensions may stretch for 3 inches or more with forward bending postoperatively, possibly contributing to a high lead migration rate. Either the lateral or supine position with head turned to the opposite side can be used to implant bilateral occipital electrodes tunneled to

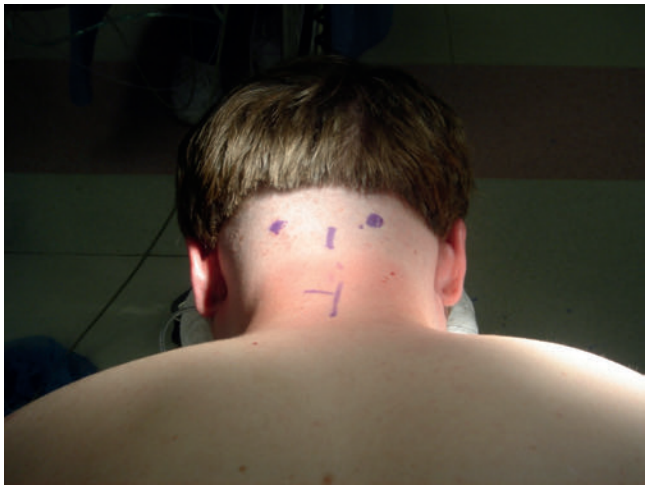

Fig. 34.3 Prone position with midline incision and maximal painful areas mapped bilaterally.

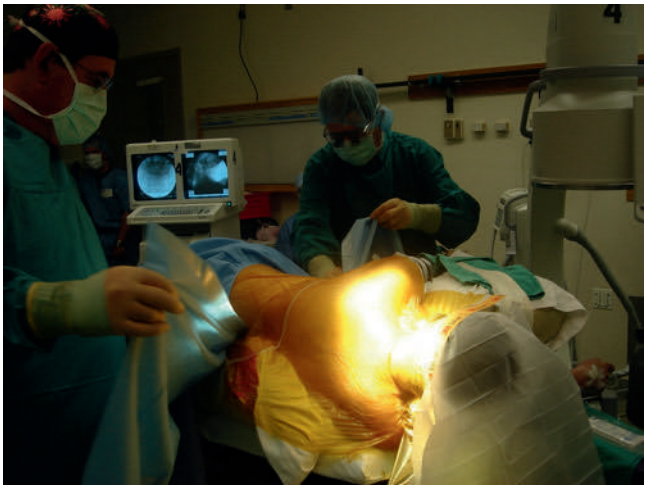

Fig. 34.4 Antibacterial draping.

an upper chest IPG placement with much less lead movement/migration potential depending on the anchoring technique.

Surgical Prepping and Draping

To minimize the risks of infection, the implanter must take great care to remain meticulous throughout the procedure, including the initial prep and draping techniques. Hibiclens (Mölnlycke Health Care, Norcross, GA, USA) showers the evening before surgery have been shown to be beneficial. Suboccipital hair should be shaved with clippers only. The use of razors has been shown in multiple studies to increase infection rates due to bacteria entering the minute skin abrasions produced by the razor. Alcohol-based preps with Steri-drape (3M, St. Paul, MN, USA) coverage of all skin surfaces is recommended (**Fig. 34.4**).

Generator Site

Generator placement influences patient positioning and the potential for postoperative electrode migration. Additionally, cosmetic appearance and IPG pocket comfort for chest and buttock placements, respectively, are important considerations. The following are typical implant locations:

1. *Upper chest.* Lateral or supine positions favor this location. Take special care when tunneling across the lateral neck region and over the clavicle to avoid possible accessory nerve, carotid artery or jugular vein injury, or inadvertent thoracic cavity puncture with subsequent pneumothorax. Women with large breasts may be a challenge in placing the IPG appropriately.
2. *Upper buttock.* This common area for placement facilitates electrode/extension tunneling to the IPG. Cautions include the need to avoid placing the IPG too low in the buttock; to avoid medial placement, which could damage the cluneal nerve; and to be aware that flexion tension on the electrode/extension appears to contribute to a relatively high incidence of lead migration.
3. *Abdomen*. The lateral position facilitates placement, probably with less risk of lead migration.
4. *Lateral thigh*. This location is useful for spinal cord stimulation but is not practical for ONS.

Electrode Tunneling and Fixation

Electrode migration has been reported in up to 24% of implants, no doubt due to the highly mobile upper cervical region, and is probably the most problematic part of the procedure. Various anchoring devices are available, which differ depending on the electrode manufacturer and achieve variable degrees of secure fixation. Some implanters prefer to tie sutures to looped electrodes as part of lead fixation without anchors, using the surrounding tissues to “squeeze” the electrode at the suture point. Strain relief loops, both proximal at the electrode incision site and distally with looped extension wires, have been used to minimize direct tension on the electrode contact array. Using medical-grade silicone glue can be helpful within certain anchor/electrode contact points. Newer “Chinese handcuff” and bumpy-type anchors offer improvement over traditional cuff anchors.

Minimizing electrode/extension lengths to the IPG pocket (i.e., chest placement or miniaturization of power sources placed closer to the electrodes) might significantly reduce the migration problem.

Intraoperative Stimulation Evaluation

The purpose of controllable short-acting sedation is to allow quick and accurate positioning of one or more electrodes into the subcutaneous tissues identified as subjacent to the maximal areas of pain/tenderness in the occipital scalp innervated by the occipital nerve system. This in turn allows direct patient feedback during stimulation testing intraoperatively to verify electrode placement in terms of depth and painful region. Patients should be queried as to whether the stimulation sensation is one of paresthesias as opposed to burning or grabbing discomfort. Feedback that the paresthesias cover the majority of their most painful areas allows for subsequent postoperative programming modes to be entered into the IPG for more complete pain coverage.

Stimulation Parameters

The following settings are a good starting point for intraoperative and postoperative programming with the cathode steering the polarity considerations:

- Lead polarity
- Voltage: 1 to 4 V
- Frequency: 30 to 60 Hz
- Pulse width: 120 to 240

It remains to be seen if ultra-high-frequency stimulation in the 10,000-Hz range will offer any advantages for long-term pain control as these devices become available for study.

Postoperative Management

ONS implantation surgery is usually an outpatient procedure; however, mitigating circumstances could include excessive postoperative pain from surgical dissection for paddle placements, and issues relating to operating on patients with long-term narcotic intake and tolerance problems. These patients might require a more extended hospital stay for pain stabilization. Many implanters will use cervical collars for several weeks to help minimize excessive neck movements postoperatively. Patient instructions, including recharging procedures. should probably be reiterated either in person or over the phone a day or two after the procedure because many patients have difficulty handling information following same-day sedation. Dry, sterile dressing changes are important to minimize wound infection.

Implant Technique

ONS surgical implant techniques have been described in multiple journal articles, textbooks, and monographs. An accompanying short video briefly shows some important aspects to electrode placement. In place of a step-by-step procedure, the following technical observations, gained from 20 years of experience by the author, might be of assistance to the implanter. The list is by no means exhaustive but merely represents some personal reflections.

1. The subcutaneous space in the occipital region usually accepts a tunneling electrode introducer (Tuohy needle or angiocatheter) without much difficulty at the right depth. Larger patients with greater subcutaneous fat are obviously easier to implant but may have a greater risk of migration. Consider ultrasound guidance for thinner patients.
2. When advancing the introducer within the subcutaneous tissues, follow the needle tip with finger palpation to be sure there is no dermal penetration, which could set into motion underlying tissue damage resulting in electrode erosion and infection. Do not underdrape the suboccipital region because an electrode could inadvertently poke through the skin during a lateral traverse under the drapes (**Fig. 34.5**).
3. Be meticulous with electrode anchoring to minimize migration.
4. Tunneling can be dangerous. Some of the supplied tunneling tools have very sharp tips and require careful handling. I am aware of a case of severe brain injury from a tunneling tool entering the foramen magnum during tunneling in a cephalad direction to connect an extension cable.
5. Prone positioning requires an experienced anesthesiologist and proper sedation to avoid airway difficulties or wound contamination from undersedation and excessive patient movements.
6. Chest IPG placement, when feasible, may be preferable over the other implant sites due to migration risk.
7. Always tunnel the electrode a centimeter or two beyond the area of maximal tenderness because trolling during on-the-table stimulation is only by electrode pullback.
8. Many patients with bilateral greater occipital nerve pain can be treated with a single 8-contact electrode placed across the midline using a single lateral incision.
9. Patient sedation can be challenging, especially in the presence of narcotic tolerance. IV ketamine can be quite effective in selected cases.
10. Counsel patients that ONS therapy is adjunctive and not curative to avoid misperceptions and disappointment.

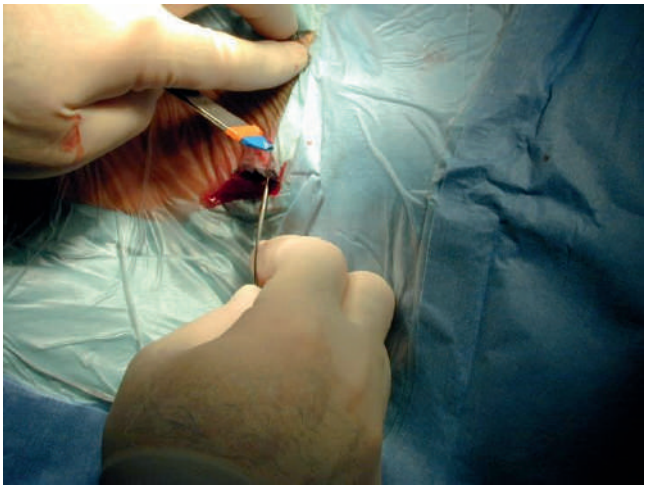

Fig. 34.5 Gentle subcutaneous needle insertion while using left index finger to monitor needle tip to avoid placing too superficially or too deep into the fascia.

Complications

Possible complications of ONS surgical implantation include:

- Migration, erosion
- Infection, hematoma
- Equipment malfunction/breakage
- Altered, attenuated, or failed response to stimulation
- Persistent incision site pain
- Wrong patient

Surgical complications for any procedure are multifactorial; however, better electrode and power source designs incorporated into the locally placed electrode with proper implantation technique should positively address most of these potential complications.

Outcomes

Numerous nonblinded, single-center studies in the literature claim a long-term success rate, defined as greater than 50% pain reduction in approximately 70 to 80% of implanted patients, concluding that ONS is a safe and effective therapy. Reduction in headache intensity and frequency has also been observed in multiple series. There have been three major device manufacturer–sponsored multicenter studies[12–14] to date that attempted to demonstrate the safety and efficacy of ONS in a migraine headache population for FDA device approval. None of these studies, however, achieved a statistically significant pain reduction endpoint of 50%. The best outcomes were from the St. Jude Genesis study[12]:

- 28% decreased headache days (7 d/mo) versus 4% (1 d/mo) placebo group
- 42% pain relief versus 17% placebo group
- 53% excellent or good pain relief versus 17% placebo group
- 67% improved quality of life versus 17% placebo group
- 51% satisfaction with headache relief versus 19% placebo group
- However, primary endpoint of 50% not met
- Difference between active and placebo groups statistically significant at 40% pain reduction level
- CE Mark achieved September 2011

It has been argued that statistical significance at 40% still represents a significant improvement for a group of chronic headache sufferers with little or no other treatment options who would benefit greatly from ONS. Unfortunately, most insurance companies will continue to avoid reimbursement for the devices and procedure due to its current off-label status. FDA approval following subsequent controlled studies is the goal of physicians, patients, and device companies.

Mechanisms of Action

Occipital nerve stimulation is actually the delivery of neuromodulatory electrical signals to subcutaneous tissues innervated by branches of greater, lesser, or third occipital nerves, either singly or in combination, unilaterally or bilaterally. When stimulation is applied, paresthesias are felt in the distribution of sensory representation of that nerve. The beneficial effects for occipitally mediated headache syndromes appear to involve the following elements:

- Subcutaneous electrical conduction
- Local innervation
- Dermatomal stimulation
- Myotomal stimulation
- Sympathetic stimulation
- Neurochemistry
- Blood flow alteration
- Trigeminocervical complex

Because the occipital nerves arise from the C2 and C3 nerve roots, it has been postulated that antidromic neurostimulation of these roots via the occipital nerve branches interacts with the descending tract of the trigeminal nerve into the upper cervical region with inhibition of interneurons in the trigeminocervical complex, and interrupts or decreases transmission of pain signals to the thalamic and frontal lobe recognition areas.[15,16]

Editor's Comments

Dr. Weiner is the pioneer not only of occipital nerve stimulation (ONS), but also of subcutaneous stimulation in general. In the United States ONS remains an off-label but otherwise viable treatment for occipital neuralgia. (See Chapter 20 for a discussion of this diagnosis.) I continue to have difficulty separating this diagnosis from "cervicogenic" headache, but given that ONS is a testable surgical therapy, I would not hesitate to conduct trial stimulation in a patient who complains of suboccipital pain, whether intermittent or constant.

ONS is 20 years old, but as Dr. Weiner points out, more data from a randomized prospective series will be necessary to fully legitimize this technique and potentially gain FDA approval. The lack of such approval is clearly hampering the application of this therapy.

There has been much speculation, and enthusiasm, about the use of ONS for other headache syndromes—migraine in particular. As reviewed in this chapter, results for headache have been disappointing, and thus far no randomized prospective trial has met its primary endpoint for success.

I thank Dr. Weiner for preparing a companion video to describe his surgical technique.

Conclusion

There continues to be significant interest and excitement throughout the pain management world in the utilization of ONS and other subcutaneous peripheral stimulation techniques to treat intractable pain conditions. The success of this treatment modality will require a combination of carefully designed and implemented outcome studies, clarification of appropriate implant indications, and a new generation of implant devices tailored to ONS and other peripheral sites.

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35 Trigeminal Neurostimulation for Neuropathic Facial Pain

Charles Nelson Munyon and Jonathan Miller

The face occupies only 4.5% of the body surface but is uniquely important for human identity, playing an indispensable role in basic survival functions like breathing and eating as well as complex communications involving vocalization and expression. Facial pain can interfere with all of these functions and is a source of considerable morbidity for patients affected by it. In particular, facial pain due to trigeminal nerve injury often does not respond adequately to medications and as a result can be particularly difficult to treat.[1] Neuromodulation techniques involving stimulation of the trigeminal nerve or its branches can be helpful to ameliorate certain types of neuropathic facial pain.

Trigeminal Neurostimulation: History and Reported Results

Stimulation of the gasserian ganglion as a means of treating trigeminal branch pain was first described in 1980 in a case series by Meyerson and Håkanson,[2] who published an expanded series in 1986.[3] Stimulation of distal trigeminal nerve branches was first described in 2002 in a report of two patients who underwent subcutaneous stimulator placement along the course of the affected nerve for postherpetic neuralgia with significant pain relief and reduction in medication requirements 3 years after implantation.[4] Johnson and Burchiel subsequently published a retrospective case series of 10 patients with posttraumatic trigeminal neuropathic pain (n = 5), postherpetic neuralgia (n = 4), or idiopathic trigeminal neuropathic pain (n = 1). At a mean follow-up of 27 months, all of the trigeminal neuropathic pain patients and 2 of the 4 postherpetic neuralgia patients reported a reduction in pain levels greater than 50%.[5] As part of a technical note in 2005 Slavin described a series of 8 patients that was expanded in 2006 to include 9 patients treated with trigeminal branch stimulation as part of a cohort of 22 patients undergoing trigeminal, occipital, or trigeminal and occipital nerve stimulator implantation.[6,7] More recent reports include a series of 10 patients who underwent neurostimulation for supraorbital neuralgia,[8] a series of 3 patients with posttraumatic trigeminal neuropathic pain,[9] and case reports of patients with posttraumatic trigeminal neuropathic pain or postherpetic neuralgia successfully managed via trigeminal peripheral nerve stimulation.[10,11] Finally, peripheral nerve field stimulation in the mandibular distribution has been described, with relief of pain at 1-year follow-up.[12] All of these reports indicate pain relief greater than 50% at last follow-up, which varied from 6 months to 3 years. There were no major complications reported in any of the reports, although several patients required revision or removal of their stimulator systems because of lead migration, skin erosion, or infection.

Indications

Selection of an appropriate treatment for facial pain requires accurate determination of the diagnosis. Since neurostimulation as a rule is more effective for neuropathic than for nociceptive pain syndromes, consideration should be given to possible sources of nonneuropathic pain, particularly in the distributions of the maxillary and mandibular nerves, where causes may include odontogenic pain and temporomandibular joint disease.[13] Once facial pain is confirmed to be neuropathic in etiology, it is often helpful to identify the precise subtype according to the framework first proposed by Burchiel in 2003 and expanded upon by Eller, Raslan, and Burchiel in 2005.[14,15] The patient's symptomatology and relevant medical history are used to differentiate two broad categories of pain: (1) trigeminal neuralgia pain due to idiopathic trigeminal neuralgia (types 1 and 2) or resulting from a central demyelinating process such as multiple sclerosis (symptomatic trigeminal neuralgia),

and (2) neuropathic pain due to nerve or ganglion injury from nerve trauma (trigeminal neuropathic pain), iatrogenic lesioning (trigeminal deafferentation pain), or herpes zoster (postherpetic neuralgia). Trigeminal stimulation is generally performed for the second category. Another important consideration is preservation of sensation because facial pain associated with significant sensory loss is unlikely to improve with trigeminal nerve stimulation, although some hypesthesia is not a contraindication.

Prior to consideration of any neuromodulation procedure, all potentially remediable causes of pain need to be investigated and excluded. Even if an appropriate workup has been completed, it remains essential that all relevant data be reviewed to ensure that nothing has been missed. Depending on the distribution and character of pain, referral to a neurologist, otorhinolaryngologist, ophthalmologist, or oral and maxillofacial surgeon may be indicated. The patient needs to have had an adequate trial of nonsurgical treatment, which may include a combination of opiates, anti-inflammatories, anticonvulsants, neuroleptics, or antidepressants as well as injection of local anesthetic or botulinum toxin. Therapies such as transcutaneous electrical stimulation, meditation, or psychological counseling may also play a useful adjunct role. All patients should be screened for psychological contraindications such as substance dependence, unrealistic expectations, or presence or pursuit of secondary gain. Medical contraindications include bleeding diathesis, immunodeficiency, and any condition for which the patient will likely require future magnetic resonance imaging of the head or neck.

The indications for consideration of trigeminal branch stimulation are otherwise similar to those for peripheral nerve stimulation elsewhere in the body: (1) pain should localize to the distribution innervated by the nerve(s) in question, and (2) the nerve must be in continuity proximal to the planned site of stimulation, with at least partial preservation of sensory function, although some hypesthesia may be present. Some authors advocate a trial of pharmacologic blockade or transcutaneous electrical stimulation prior to trial implantation, but the predictive value of these tests has not been definitively established.

Techniques

Supraorbital and Infraorbital Nerve Stimulation

Prior to implantation of a permanent stimulator, a trial period of stimulation should be undertaken to assess whether the patient derives adequate pain relief to justify implantation of the permanent system. The trial and permanent implantation are outpatient procedures and may be performed in either of two ways: (1) placement of a temporary externalized percutaneously located lead followed by subsequent implantation of an entirely new system, or (2) placement of an anchored lead with a temporary externalized extension that is discarded in a second operation when the generator is placed. The main advantage to the second approach is that the trial lead is also used for the permanent implantation, although the trial is considerably more invasive; removal in the case of an unsuccessful trial requires an additional operation, and it is necessary to use an extension cable with a bulky connector rather than connecting the lead directly to the generator. Therefore, we prefer to use the percutaneous trial method whenever possible.

Percutaneous trial placement is generally performed under local anesthesia with mild sedation to allow for patient feedback and ensure optimal coverage of the region of pain. Intraoperative fluoroscopy is helpful to confirm proper electrode placement. Once the patient is adequately sedated, the head is turned toward the contralateral side, in the case of unilateral implantation, or placed on a padded horseshoe head holder in the neutral position for bilateral implantation. The entry point is located above and lateral to the eyebrow for supraorbital nerve stimulation and just above the malar eminence for infraorbital nerve stimulation (**Fig. 35.1**). A stab wound is produced in the appropriate location. A Tuohy needle is prepared with a gentle convex curve away from the needle opening, and the needle is introduced with the stylet, with the convex curve outward to follow the contour of the skin. The skin surface overlying the needle should be carefully palpated to ensure that the needle is at the correct depth (**Fig. 35.2**). If it is placed too deep, stimulation will produce uncomfortable cramping or pulling due to muscle activation, and a course too shallow will produce unpleasant stinging instead of paresthesias. C-arm fluoroscopy is used throughout this process to verify electrode position. Once the needle has been advanced past the target nerve foramen, the stylet is withdrawn from the needle and the stimulation electrode is threaded into place through the needle (**Fig. 35.3**). Spinal cord stimulation electrodes with different numbers of contacts are available, but four contacts are adequate, as found on the Pisces Quad electrode from Medtronic, Inc. (Minneapolis, MN, USA). The needle is carefully withdrawn, leaving the lead in place, and the lead is connected to a stimulator to verify appropriate coverage of the area of pain without discomfort. If the electrodes are in the correct place, the patient should feel a pleasant tingling sensation that radiates along the course of the nerve. The electrode can be tunneled to an exit site above the ear by passing the stylet through the initial stab wound subcutaneously to a distal site from which

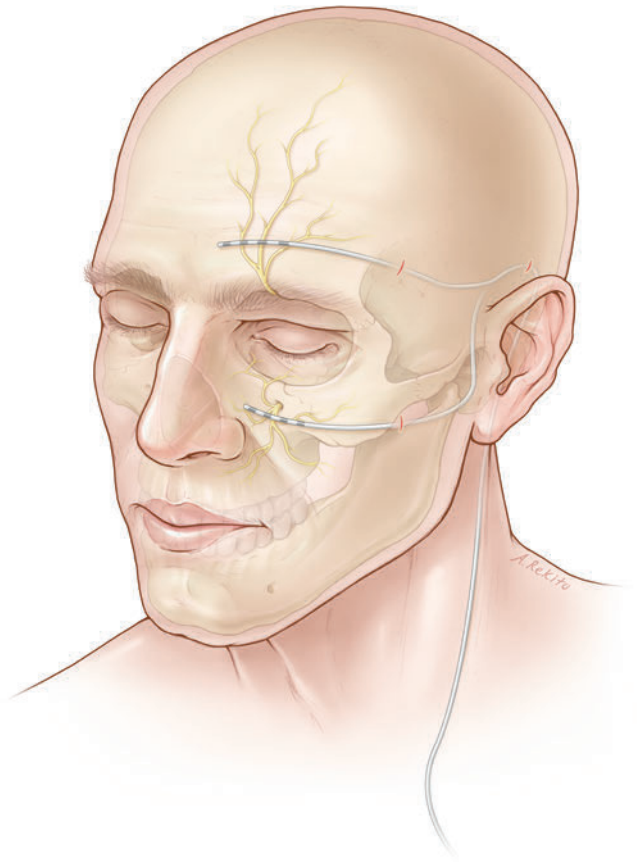

Fig. 35.1 Ideal subcutaneous location of supraorbital and infraorbital leads. Note the entry point lateral to the orbit and that each electrode spans the respective foramen.

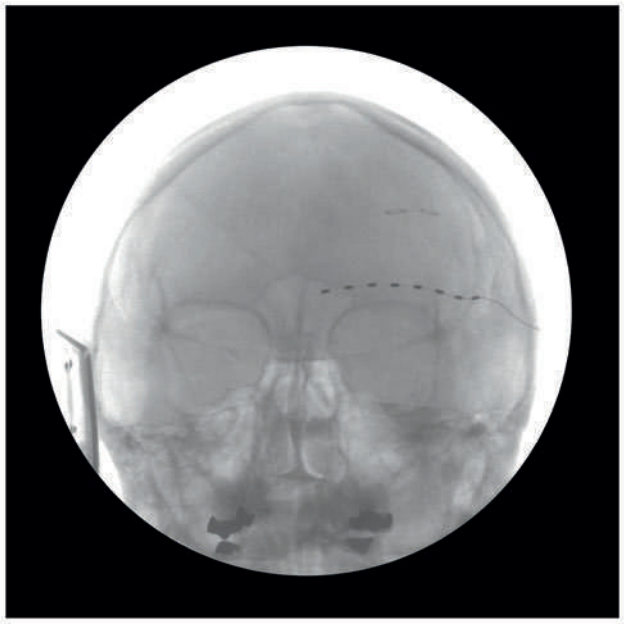

Fig. 35.3 Anterior-posterior radiograph demonstrating trial placement of an 8-contact lead for supraorbital stimulation.

the needle is passed backward around the stylet toward the initial stab wound. Removal of the stylet allows passage of the lead through the subcutaneous space to the site of exit. This process can be repeated to move the exit site further away. The externalized lead is secured to the skin at multiple locations and attached to the temporary stimulator for 3 to 10 days of trial stimulation as an outpatient procedure, after which the electrode is removed in the office.

If adequate relief is obtained during the trial, the permanent lead is placed in a separate operation (**Fig. 35.4**). The lead is placed using the same technique used during trial implantation. A 2-cm retro-auricular incision is then performed with the development of a subcutaneous pocket where the lead is securely anchored prior to tunneling to the site of subcutaneous implantation of the pulse generator. The generator is generally placed in an infraclavicular location,

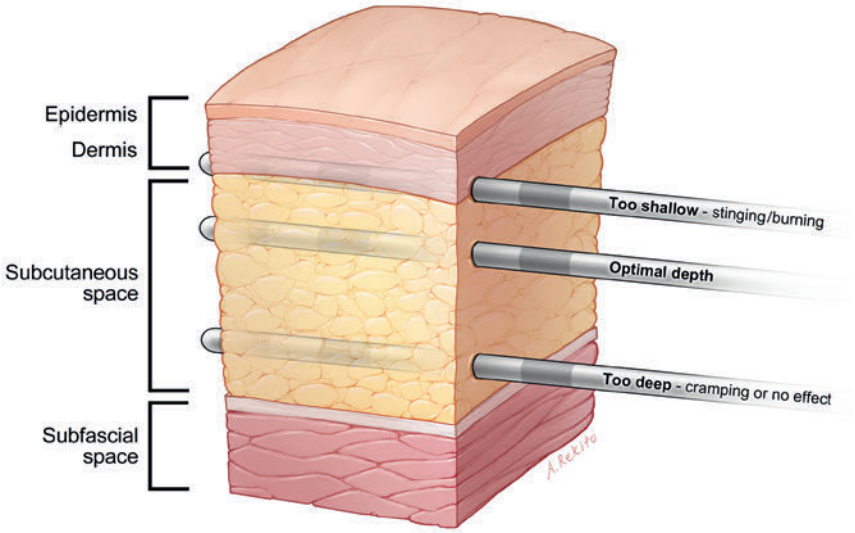

Fig. 35.2 Ideal depth of leads. The optimal depth is just deep to the dermis where paresthesias are similar to what is experienced dermatomally with epidural stimulation. A lead that is too shallow or too deep would produce different sensations and would require repositioning.

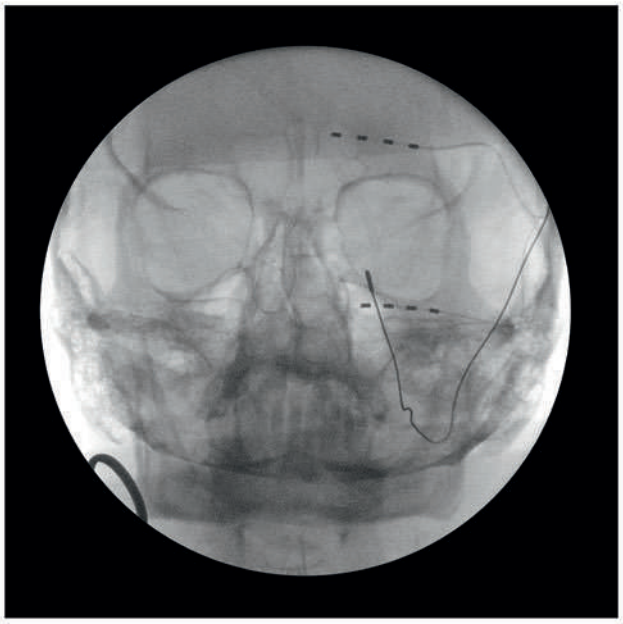

Fig. 35.4 Anterior-posterior radiograph demonstrating placement of supraorbital and infraorbital leads. There is a lead in the foramen ovale as well for stimulation of the trigeminal nerve at that location.

although other sites (e.g., abdomen) may be used if necessary for cosmetic reasons or for very thin patients. A subcutaneous pocket is developed, and the generator is attached to the lead and implanted in the pocket. Prior to closure of the pocket, the generator is interrogated to ensure that the system has been properly connected. The incisions are then closed, and the patient is allowed to awaken from anesthesia.

Gasserian Ganglion Stimulation

Implantation of a stimulating electrode directly into the gasserian ganglion may be used to produce diffuse stimulation of the entire trigeminal nerve distribution, which can be useful to treat neuropathic pain in distributions other than the supraorbital/infraorbital, such as the orbit or V3 distribution. A smaller electrode such as a Medtronic 3389 deep brain stimulation electrode may be used for this purpose. To place the electrode, a Tuohy needle is entered into the foramen ovale via the same technique used for percutaneous rhizotomy for trigeminal neuralgia. The patient is placed supine on the operating table with the head turned slightly to the contralateral side, and rapid-acting sedation is administered. The hemiface is prepped with iodine or chlorhexidine, and local anesthetic is instilled into a point 2 cm lateral to the corner of the mouth and 1 cm inferior to the occlusal line, where a stab wound is made. A Tuohy needle is advanced into the tissue of the cheek while the needle tip is guided toward the foramen ovale using one's finger inside the patient's mouth to prevent penetration into the oral cavity. Fluoroscopy using a modified submental vertex projection can be helpful, and lateral fluoroscopy is used to verify depth of insertion. At this stage, the stylet is withdrawn and the electrode is passed into the ganglion. Test stimulation, lead externalization, and permanent placement are performed as with the supraorbital and infraorbital leads. Rates of migration with subsequent loss of benefit are high with this approach, so careful anchoring is very important.

Conclusion

Intractable neuropathic facial pain can be challenging to treat due to the breadth of disorders that can cause orofacial pain and the relative resistance of many of these disorders to conventional pain management strategies. Evidence-based evaluation of these therapies has been hampered by the lack of a common classification system and marked variability in outcome measurement and length of follow-up. Standardized study is needed to better characterize

Editor's Comments

Drs. Munyon and Miller have written an overview of the techniques of trigeminal branch stimulation. Although direct trigeminal ganglion stimulation has been used in the past, it is rarely employed now due to the frequent complication of lead migration. Peripheral branch stimulation, particularly supraorbital and infraorbital, allows access to trigeminal distributions without the attendant high rate of lead movement or withdrawal.

We have yet to see a randomized prospective trial of implanted trigeminal leads, although a recent double-blinded, randomized, sham-controlled prospective trial of percutaneous supraorbital stimulation showed significant benefit of stimulation compared with sham for the number of 50% responders ($p = 0.023$), number of monthly headache days ($p = 0.041$), and monthly acute antimigraine drug intake ($p = 0.007$).[16] Whereas the therapeutic benefit of stimulation in this trial was modest (26%), it compared favorably with other nondrug and preventive drug therapies.

Trigeminal neuropathic pain is the clear indication for trigeminal branch stimulation. A prospective trial comparable to the one cited above for migraine would be a major contribution to the facial pain literature.

the relative efficacy and cost-effectiveness of treatment. However, for carefully selected patients with localized neuropathic facial pain and preserved sensation, electrical stimulation of the trigeminal nerve or along its nerve branches can be a valuable tool to provide long-lasting relief of symptoms.

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36 Motor Cortex Stimulation

Marc Sindou, Joseph Maarrawi, and Patrick Mertens

Motor cortex stimulation (MCS) was introduced in 1991 by Tsubokawa for the treatment of central neuropathic pain following stroke.[1] When Tsubokawa and his team started to examine the potentiality of chronic stimulation of the cerebral cortex in patients with central deafferentation pain, they realized that stimulation applied to the precentral gyrus, rather than to the postcentral gyrus, produced stronger pain inhibition both in animal models[2] and in post-stroke so-called thalamic pain.[3] The cortex area leading to strong inhibition of thalamic pain seemed to correspond to the motor cortex. Subsequently, the technique was popularized at several institutes as soon as the early 1990s to treat various kinds of neuropathic pain.[4–12]

Target Considerations

According to Tsubokawa's original results the target is precentral gyrus. It was, however, argued that premotor gyrus or central sulcus itself[13] could have better pain control. Nonetheless, it is the pre-central gyrus with its somatotopic representation of the motor homunculus that is actually the most currently targeted area. Briefly, the face is represented at the lower part of the gyrus, below the level of the inferior frontal sulcus. The hand is at the middle part, between levels of the inferior and superior frontal sulci. The leg is at its upper part, above the level of the superior frontal sulcus, and also into the interhemispheric fissure on the mesial aspect of the hemisphere, making this target to the lower limb theoretically largely inaccessible to extradural electrodes. However, because the lower limb is to some extent represented on the upper lateral surface of the hemisphere, the electrode may be put extradurally in a paramedian location lateral to the edge of the superior sagittal sinus. Because a large part of the primary motor cortex (Brodmann area 4) occupies the posterior wall of the precentral gyrus in the depth of the anterior buried part of the central sulcus as shown by cytoarchitectonic studies,[14,15] stimulation at convexity should theoretically be insufficient for stimulating the entire motor target. Actually, extradural stimulation at relatively high intensity seems to be able to reach the depth of the motor strip.

Not only motor cortex should be targeted, but in Tsubokawa's concept it is postulated that pain relief tends to be homotopic so that electrodes should be placed on the dura facing the cortical motor area corresponding to the territory of pain. Some neurosurgical teams share this concept and consider the precision of placement on strict motor mapping criteria crucial for the efficacy of MCS.[16,17]

Considering that intraoperative cortex mapping is important in that it helps to predict which electrode(s) should be used to get the best analgesic effect, Holsheimer et al advocate that monopolar stimulation be preferred for testing, because—in opposition to bipolar stimulation—the motor-evoked electromyograph (EMG) responses are unambiguous when related to a single stimulating electrode, their amplitude not being affected by the anode–cathode distance.[18] Further, since in monopolar stimulation amplitude of the EMG-evoked responses with an anode is 59% larger than with a cathode, anode (polarily +) should be preferred to cathode (polarity –) for testing conditions.[18] Conversely, for therapeutic application, cathodal stimulation should be preferred, because anodal stimulation results at low intensity to evoked responses of the corresponding muscles, whereas cathodal stimulation—at the same location—with a 60% lower intensity, leads to pain relief.[19] Based on these results, the authors advocate that the anode with the largest EMG-evoked motor response be replaced by a cathode, at the same location, for subsequent postoperative therapeutic stimulation.

Regarding mechanisms, Holsheimer et al postulate that anodal stimulation directly (i.e., not across a synapse) activates descending corticospinal fibers originating from primary large pyramidal cells

located in layer V of motor area 4, whereas cathodal stimulation activates the large myelinated fibers parallel to the cortical layers. They hypothesized that those parallel fibers constitute the link of the neuronal network that results in pain relief. These fibers parallel to the cortical layers include collaterals of the thalamocortical projections from the ventrolateral and ventral anterior thalamic nuclei, collateral projections from the postcentral and the premotor cortex, and the intrinsic cortical connections within cortical layers.[20]

Preoperative Technical Planning

Magnetic resonance imaging (MRI)-based image-guided navigation or, by default, stereotactic computed tomography (CT) scan is currently considered the standard for identifying central sulcus and neighboring frontal gyration. In most cases MRI is sufficient to define the precentral gyrus and to determine its somatotopic organization. However, this can be difficult in patients with pain resulting from encephalic origin where brain anatomy was significantly modified by the pathology. This is particularly true for patients harboring cortico-subcortical malacia after stroke; in these patients functional MRI (fMRI) might be of considerable help.[21]

Evoked electrophysiological testing is sometimes helpful for localizing the central sulcus but is not feasible for amputees because peripheral stimulation is not possible. In these patients and in patients with phantom pain in whom cerebral plasticity may have changed the location of limb representation, fMRI can help.[22–24]

Surgical Technique

The procedure is designed to ensure appropriate exposure of the motor cortex (**Fig. 36.1**).

The first step is to draw on the scalp the location of the central sulcus, estimated from conventional

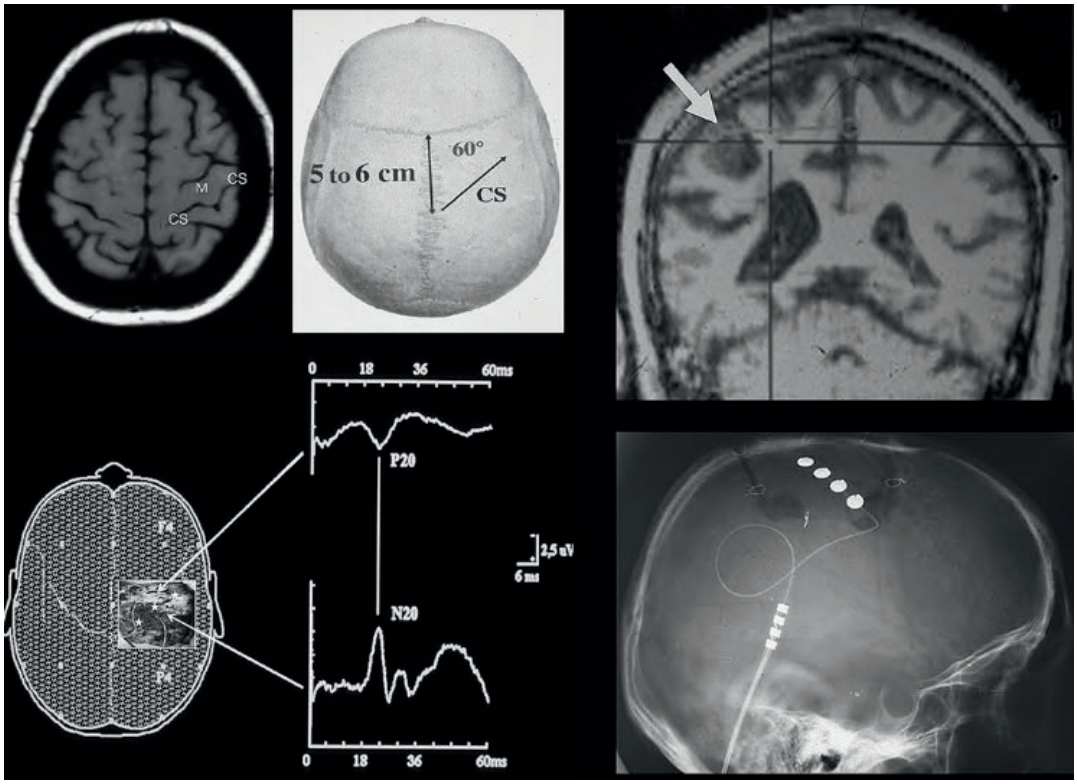

Fig. 36.1 Motor cortex stimulation (MCS): technical principles. The target for stimulation is the precentral gyrus, that is, the primary motor area (M), as shown on MRI (magnetic resonance imaging) (*upper left*). The skin incision and bone flap are centered according to classical bony landmarks (*upper middle*) and individual anatomic particularities* from image-guided neuronavigation (*upper right*). Identification of the central sulcus (CS) is confirmed by somatosensory evoked potential (SSEP) recordings, in this patient using platinum ball electrodes (*lower left*). The CS is drawn on the surface of the dura at the very sites of the reversal of the N20 (postcentral) wave into the P20 (precentral) wave (*lower left*). Postop lateral X-ray shows the implanted electrode (a 4-contact Resume from Medtronic) (*lower right*).

*The implanted patient had pain that developed in the left hemibody 1 year after a stroke in the right cortico-subcortical posterior parietal region, as shown on the neuronavigation MRI (*white arrow*). MCS achieved a complete and long-lasting (5 years of follow-up) pain relief.

bony landmarks and confirmed by the brain neuronavigation system. Then either a simple bur hole is made or a small craniotomy is performed over the precentral gyrus. A small bone flap is generally preferred because a bur hole limits the electrophysiologic testing and makes it difficult to secure the electrode(s) to the dura.

In most series intraoperative *somatosensory evoked potentials* (SSEPs) recordings (by stimulation of the median or, rarely, the tibial nerve) are performed to confirm the location of the central sulcus, using extradural electrodes. Location of the central sulcus and its orientation are confirmed by phase reversal of the (negative) N20 wave, recorded in front of the postcentral gyrus, into a (positive) P20 wave, recorded anteriorly in front of the precentral gyrus. When recordable, SSEPs are of valuable accuracy.

Motor mapping by direct cortical stimulation can indeed help to locate the electrode contact(s) where stimulation elicits motor responses at the lowest threshold in the painful area; this method is especially reliable when coupled with EMG recording. The method currently used is the same as the subdural cortical mapping popularized for brain tumor or epilepsy surgery. Technically it consists of delivering, with a bipolar probe in contact with the cortex, isolated square-wave pulses of 1 ms, at a frequency of 60 Hz, for 2 to 5 seconds. For sensibility and reliability, motor responses should be EMG recorded.

Monopolar (anodal) stimulation is preferred to bipolar because it decreases the risk of induced seizures.[17,25] In this context Nguyen and Lefaucheur claim that motor mapping improves the accuracy of electrode placement.[16,17,26] On the other hand, some other authors estimate that motor mapping gives little additional information because of the diffusion of the stimulation not only to the precentral gyrus but also to the postcentral and the premotor gyri, and also because of the risk of generating epileptic seizures during stimulation.[27]

For most neurosurgical teams *electrode implantation* is exclusively extradural, except for patients with pain in the lower limb, who may benefit from subdural electrode(s) along the falx inside the interhemispheric fissure.

Once the target has been determined, the electrode(s) is (are) secured epidurally to the dura. One currently used lead is the 4-contact Resume II, model 3986, plate electrode from Medtronic (Minneapolis, MN, USA). Implantation can be parallel or perpendicular to the central sulcus. Parallel implantation increases the chances of covering a large proportion of the homunculus. Perpendicular implantation enhances the probability that both the precentral gyrus and the central sulcus will be stimulated, and increases the chance of having one or more contacts in the motor area in case of error in localizing the central sulcus. Dual plates may be implanted with multiple possible orientations to enlarge the surface of stimulation.

A gentle bipolar coagulation of the superficial layer of the dura is advised to achieve its sensory denervation so as to avoid local pain at the stimulation site of the dura.

Subdural electrode positioning would offer the advantage of a better identification of the gyri and sulci anatomy and would allow a decrease in the intensity of stimulation, with a consequent economy in use of the battery. Another theoretical advantage is a better reach of the buried part of the motor area inside the central sulcus, especially in patients with brain atrophy. However, due to its higher risk of local complications, including epilepsy and cortex direct (mechanical) or indirect (hematoma) injury, subdural positioning has to be used with circumspection. Indications would include lower limb or atrophic cortex with an overlying thick layer of cerebrospinal fluid.

Internalization of the wires and battery can be done immediately or secondarily if the patient will benefit from an external stimulation trial. The battery is most often implanted in the subclavian region. The Itrel 3 pulse generator (model 7425, Medtronic) is designed for a 4-contact electrode, whereas the Synergy or Prime generator (model 7427, Medtronic) is made for those with more contacts. In addition, rechargeable generators are now commercially available for longer battery survival.

Optimal stimulation parameters vary in the literature, with no definite recommendations, based on experimental studies. Most often the advised settings are monophasic diurnal stimuli, at (low) frequency between 10 and 50 Hz, with a duration pulse width of 0.5 ms, applied continuously for no more than 10 to 20 minutes on each occasion, and at a restricted level of intensity that is slightly lower than the threshold for motor contractions (i.e., 3–8 V).[28] Publications cite different empirical settings.[29] In most series the stimulation has a bipolar configuration. In two series with electrodes implanted perpendicularly to the central sulcus, the negative pole (i.e., the cathode) is on the pre-central gyrus as advocated by Holsheimer et al on biophysical bases.[19]

After an initial benefit, which may last for several months or years, loss of efficacy may occur. The main hypotheses among the many are an increase in impedance by thickening of scar tissue and, more likely, neural plasticity rearrangements. Sometimes intensive reprogramming can reset the effectiveness of MCS in patients who have lost pain control, by using a structured step-by-step approach.[30] More rarely, efficacy can be restored by surgical retargeting of the electrode extradurally[17] or subdurally.[13,31]

Pain Outcome after MCS

In spite of mechanisms of action that are incompletely understood and somewhat puzzling, MCS has been reported as favorably controlling refractory chronic neuropathic pain in dozens of publications. However, as pointed out in a critical review of the literature, MCS effects are not consistently reproducible and sometimes disappointing.[29] MCS publications lack randomized studies with long-term follow-up, except for two small series.[32,33] In continuing medical education articles establishing guidelines on neurostimulation therapy for neuropathic pain,[34,35] the committees found only two studies classified as III, conferring only a level C of evidence for MCS effectiveness.[36,37]

For the preparation of this chapter, the following keywords were used to search the Medline database: "motor cortex stimulation and neuropathic pain" and "central pain and neurosurgery for pain," from 1993 to 2011 inclusive. Forty-five citations were found. Documented publications were reviewed in detail from the corresponding reprints. Series were considered when the following criteria were met: a minimum of five patients, clearly defined follow-up, and quantification of pain relief, mainly via the visual analogue scale (VAS). The 24 selected series, with a total of 345 patients, are summarized in **Table 36.1**. In this review MCS outcome was considered satisfactory when pain relief was more than 40%, in light of the fact that the cutoff percentage for MCS success varied in the revised studies from 30 to 50%.

Table 36.1 shows that MCS provided satisfactory effect (i.e., pain relief > 40%, range 23–93%) in 176 patients, that is, in 51% (range 23–92% according to series). Follow-ups were from 4 to 112 months with an average of 30 months. These figures are concordant with the other reviews. In the review by Fontaine et al, 55% of the 210 patients had greater than 40 to 50% pain relief.[29] In Lima and Fregni's meta-analysis, with 45% of the 152 patients with a postoperative follow-up of more than 1 year, the initial mean responder rate was 64.0% and the mean responder rate for the follow-up was of 54.6%, suggesting there was a decrease in analgesic effect of 9.4% with time.[38]

When etiology was mentioned (see **Table 36.2** and **Table 36.3**) (total 300 patients), pain was secondary to a brain lesion in 53.6% mostly after stroke, from trigeminal neuropathic origin in 19.3%, after brachial plexus avulsion in 15.3%, after amputation phantom limb pain in 8%, and from miscellaneous origin in 3.6%. Outcomes according to etiology are concordant with the ones reported by Fontaine et al, who found a satisfatory outcome in 54% of the 117 patients with chronic poststroke pain (CPSP) and in 68% of the 44 patients with trigeminal neuropathic pain (TNP),[29] and also concordant with the ones from the review by the Committee on Neuropathic Pain of the European Federation of Neurological Societies, who found a satisfactory outcome in 50% of the 143 patients with CPSP and in 60% of the 60 patients with TNP.[34]

Complications

Local complications are rare. Extradural hematomas (2%) were observed especially with the bur hole technique, and subdural hematomas (2%) only after subdural implantation of the lead. Seizures occasionally happened during the programming sessions, especially when high intensities were attempted (10%). Only one patient had fits for a prolonged time, which led to explantation of the system, followed by complete sedation of the seizures. Although development of epileptic activity was basically the greastest concern with the method, fortunately no such evolution resulted from chronic stimulation. In a few patients neurologic deficits were reported (2.5%), most often mild and transient. The most frequent complication by far was failure of the hardware (5.1%), as with the other neurostimulation procedures, requiring surgical revision of the implant. The infection rate varied from 2 to 5.7% of the patients according to the publications. Whatever the site of origin, the generator or the lead, the reporting authors proceeded to explantation with reimplantion later on. Only one case of meningitis, with arachnoiditis, was reported; it was in a patient who had a subdural implantation.

Outcome Predictive Factors

In the early period of MCS use, an intact corticospinal tract was considered mandatory for adequate analgesia. Katayama et al observed that pain relief was satisfactory in 73% of patients with absent or mild motor deficit versus only 15% when motor weakness was present.[10] Nuti et al found that neither preoperative motor status, pain characteristics, etiology or localization of the pathology, quantitative sensory testing, SSEPs, nor the interval between pain and surgery were predictive[37]; only the level of pain relief evaluated in the first months following implantation seemed to be a strong predictor of long-term relief ($p < 0.0001$).

In Hosomi et al's study no significant correlation was observed between improvement in the VAS score and age, gender, presence or absence of cerebral lesion, or treated painful region. Only the duration of pain before surgery was found significant when it constituted more than 5 years ($p = 0.013$).[13]

For Fagundes-Pereyra et al no differences in relation to age, gender, origin of the lesions—central

Table 36.1 Pain relief after motor cortex stimulation (MCS)

Author series*	Number of patients	Pain etiologies = *N*	Follow-up, in months: range (average)	Pain relief > 40% at latest follow-up, *N* (%)[a]	Complications[b]
Tsubokawa et al 1993[2]	11	BL = 11	> 24	6 (54.5%)	Revision of electrode = 3
Meyerson et al 1993[4]	10	BL = 3, TNP = 5, PNL =2	(12.7)	5 (50%)	Seizures = 1, hematoma = 1, skin ulceration = 1
Hosobuchi 1993[5]	6	BL = 6	9–30	3 (50%)	None
Herregodts et al 1995[6]	7	BL = 2, TNP = 5	(15)	5 (71%)	?
Ebel et al 1996[7]	7	TNP = 7	5–24	3 (43%)	Seizures = 1
Katayama et al 1998 (III, level C of evidence)[10]	31	BL = 31	> 24	15 (48.3%)	?
Nguyen et al 1999[16]	32	BL = 13, TNP = 12, SCL = 3, BPA = 2, PNL = 1, post-Hz = 1	3–50 (3,27)	23 (71.9%)	Epidural hematoma = 1, transient speech disorders = 1, infection = 1, wound dehiscence = 1
Saitoh et al 2001[65]	15	BL = 8, BPA = 4, PhL = 2, m.=1	(26)	7 (46.7%)	Infection = 2
Smith et al 2001[66]	12	BL = 7, BPA = 3, PhL = 1, m.=1	21–31	5 (41.6%)	Hematoma = 1, seizures = 1, infection = 3
Tirakotai et al 2004[67]	5	BL = 3, TNP = 2	4–24	4 (80%)	None
Nuti et al 2005 (III, level C of evidence)[37]	31	BL = 23, BPA = 4, SCL = 4	> 49	16 (51.6%)	Seizures = 3, transient deficit = 2, delayed wound healing = 2, infection = 1
Pirotte et al 2005[68]	18	BL = 6, TNP = 5, BPA = 3, SCL = 3, PhL=1	(29.7)	11 (61.1%)	Seizures = 1, infection = 2
Brown and Pilitsis 2005[69]	10	BL = 1, TNP = 9	(10)	6 (60%)	Infection = 1
Gharabaghi et al 2005[70]	6	BL = 4, TNP = 2	6–40 (18.5)	5 (83%)	None
Rasche et al 2006 (R)[32]	17	BL = 7, TNP = 7, PhL = 3	(49.7)	5 (29.4%)	?
Cioni et al 2007[71]	13	?	> 24	3 (23%)	?
Lazorthes et al 2007[72]	7	PhL = 7	6–7(42)	5 (71%)	?
Hosomi et al 2008 (subdural implantation)[13]	34	BL= 19, BPA = 7, PhL = 4	13–112(50)	12 (36%)	Infection = 3, paresis, numbness = 3, paresthesias with MCS = 2
Velasco et al 2008 (R)[33]	11	BL = 1, BPA = 3, post-Hz = 5, m. = 2	(12)	10 (92%)	None
Delavallée et al 2008 (subdural implantation)[31]	8	BL = 3, TNP = 3, BPA = 1, PNL = 1	19–69(54)	5 (62%)	Seizures = 3, infection = 2
Fagundes-Pereyra et al 2010[39]	26	BL =10, BPA = 12, PhL = 3, m. = 1	7–101(29)	15 (57.7%)	Seizures = 2, wound dehiscence =1, infection = 2
Tanei et al 2011[73]	11	BL = 5, SCL = 2, TNP = 1	6	9 (81%)	?
Raslan et al 2011[74]	8	TNP = 8	6–72(33)	5 (62.5%)	None
Sokal et al 2011[75]	9	?	36	4 (44%)	?
Total	345			176 (51%)	

Note: Series by chronological order; only the latest documented publication from a given team was retained. Pain etiologies (when mentioned) are indicated as follows: BL, brain lesion (mostly central poststroke pain, i.e., in 90% of BL cases); TNP, trigeminal neuropathic pain; SCL, spinal cord lesion; BPA, brachial plexus avulsion; PhL, phantom limb in amputees; PNL, peripheral nerve lesion; m., miscellaneous.

[a]Pain relief at latest follow-up of more than 40%, generally evaluated using reduction in verbal analogue scale (VAS) after MCS.

[b]Complications (when reported in details). (R) with randomized trials.

[c]III, publication classified as III according to the European Federation of Neurological Societies (EFNS), conferring level C of evidence.[34,35]

Table 36.2 Pain relief according to etiology

References of series	Total *N* of patients	Pain relief > 40% at latest follow-up, *N* (%)
Brain lesion (mostly chronic poststroke pain [CPSP]) 2, 4, 5, 10, 11, 13, 16, 31, 37, 39, 65, 68, 76	161	73 (45.3%)
Trigeminal neuropathic pain 4, 6, 7, 13, 16, 31, 68, 69, 74	58	37 (63%)
Brachial plexus avulsion 11, 13, 16, 33, 37, 39, 65, 68, 77	46	22 (47.8%)
Phantom limb 13, 36, 39, 65, 72, 76	24	12 (50%)
Spinal cord lesion 13, 37	6	4 (66%)
Postherpetic neuralgia 33	5	3 (60%)

Note: Differences in pain relief are not statistically significant.

or peripheral, area of the pain, presence of motor deficit, or duration of pain, were observed between patients with and without satisfactory pain control.[39]

Although some reports discussed the unfavorable role of certain factors—impaired corticospinal motor function, loss of sensory function, negative response to barbiturate, ketamine, propofol—those factors were not reproduced later and are no longer considered reliable. However, responsiveness to gabapentin might indicate a pain situation likely to be favorably influenced by stimulation.[40]

In recent studies a correlation between the efficacy of a rTMS (at 5 Hz) and that of MCS was reported,[13,41–45] so that preoperative rTMS could be helpful in selection of candidates for MCS. This finding, however, has to be confirmed in larger series.

Potential Mechanisms of Action

MCS was developed on the experimental hypothesis that hyperactivity in thalamic sensory relay neurons following spinothalamic tractotomy in cats, a typical model of central deafferentation pain, was inhibited by stimulation of the motor cortex.[2] However, the mechanisms whereby MCS controls pain still remain hypothetical.[46,47] As with every treatment against pain, the influence of a placebo effect must be considered. MCS—which does not induce any perceptible sensation in the patient—is particularly suited to a controlled, double-blind stimulation. Only two studies randomized "on" versus "off" stimulation blinded to the patient. In the first study, 6 of the 17 patients (35%) experienced a similar degree of pain relief in the two conditions, suggesting a placebo effect.[32] In the second study, pain levels evaluated after a period of 30 days were significantly reduced in the "on" and not influenced in the "off" condition.[33] But one confounding factor is that a marked posteffect was frequently noticed, which might have lasted for several weeks in the control group.[9,37] Such a prolonged effect may well be compatible with an opioid-mediated mechanism of MCS. Even more puzzling, patients were occasionally reported to have no recurrence of pain in spite of stimulation being definitively discontinued due to complications.[29]

In the mid-1990s electrophysiologic and rCBF positron emission tomography (PET) studies (**Figs. 36.2** and **36.3**) were launched to bring insights into MCS neurophysiologic mechanisms.[48] rCBF, which reflects synaptic activity, did not undergo under MCS any significant modifications in the motor or the somatosensory cortices directly underlying the stimulating electrodes. This is in accordance with the absence of SSEP alterations under MCS, suggesting no change in SI cortex excitability. rCBF studies also showed that MCS—applied to the hemisphere contralateral to the pain—produced a rapid and short-lasting activation of the thalamus ipsilateral to the stimulation, principally the ventrolateral nucleus, known to be richly connected to the precentral and premotor cortices.[48,49] It is important to recall, although classical, that the thalamus contralateral to pain is generally hypometabolic in the basal state in patients affected by chronic neuropathic pain.[50] This phasic activation of the lateral thalamus leads to a cascade of longer time course of activations in the pain matrix structures, namely the medial thalamus, anterior cingulate, and orbitofrontal cortices, and also the insula, and later on the periaqueductal gray (PAG). Activation of the latter structures, which is bilateral with a contralateral predominance to the stimulation, becomes maximal during the hours that follow the stimulation. Activation of cingular and orbitofrontal areas, and also of the insula, would modulate the emotional component of pain, rather than its intensity. Activation of the PAG, nucleus raphe magnus, and surrounding structures in the brainstem would exert descending inhibition toward the spinal cord, as demonstrated by recordings of the RIII polysynaptic withdrawal reflexes[51] and in experimental studies.[52] Patients with reflex attenuation experienced satisfactory effect, whereas none of the patients in whom the reflexes remained unmodified under MCS were satisfied with its clinical effect.[48] Changes in spinal reflexes support the implication of descending mechanisms leading to inhibition of pain impulses at the dorsal horn level and might explain efficacy in the allodynic components of the pain.[51,53,54] Such a schematization of mechanisms (**Fig. 36.4**), however,

Table 36.3 Pain relief in the various etiologies

Author series	Total *N* of patients	Follow-up (months)	Pain relief > 40% at latest follow-up, *N* (%)
Brain lesion (mostly central poststroke pain [CPSP])			
Tsubokawa 1990[2]	11	> 24	6/11 (54.5%)
Meyerson 1993[4]	3	12.7	0/3 (0%)
Hosobuchi 1993[5]	6	9–30	3/6 (50%)
Katayawa 1998 (III, level C[a])[10]	31	> 24	15/31 (48.3%)
Nguyen 1999[16]	13	(46)	10/13 (76.5%)
Mertens 1999[11]	16	(23)	10/16 (67%)
Saitoh 2001[65]	8	(26)	2/8 (25%)
Caroll 2000[76]	5	21–31	2/5 (40%)
Nuti 2005 (III, level C[a])[37]	23	> 49	10/23 (43.6%)
Pirotte 2005[68]	6	(29.75)	4/6 (66%)
Hosomi 2008[13]	19	13–112(50)	5/19 (25%)
Delavallée 2008[31]	3	(54)	2/3 (66%)
Fagundes-Pereyra 2010[39]	7	7–101(29)	4/7 (57%)
Total	**161**		**73/161 (45.3%)**
Trigeminal neuropathic pain			
Meyerson 1993[4]	5	4–28	5/5 (100%)
Herregodts 1995[6]	5	(15)	3/7 (43%)
Ebel 1996[7]	7	5–24	3/7 (43%)
Nguyen 1999[16]	12	(19)	9/12 (75%)
Pirotte 2005[68]	5	(29.75)	4/5 (80%)
Brown and Pilitsis 2005[69]	9	3–24	5–9 (55%)
Hosomi 2008[13]	1	13–112(50)	0/1 (0%)
Delavallée 2008[31]	3	(54)	3/3 (100%)
Raslan 2011[74]	11	31–76(33)	5/11 (45%)
Total	**58**		**37/58 (63%)**

does not explain the delayed and long-lasting clinical effects of MCS.

Recent data obtained from PET scanning with [11C]-diprenorphine, a nonselective opioid receptor (OR) ligand, suggest that MCS induces secretion/release of endogenous opioids in brain structures involved in pain processing.[55] The aim of the study was to compare OR availability in a group of eight patients with central poststroke pain before and after MCS. The main finding was a decrease in binding of the exogenous ligand after 2 months of chronic MCS. The decrease was significant in the anterior part of the middle cingular cortex (aMCC) and PAG; its magnitude was positively correlated with the degree of pain relief. The interpretation was that the regional decrease in exogenous binding was due to OR occupancy by the secretion of endogenous opioids triggered by MCS. These findings are consistent with the anatomical knowledge. PAG and aMCC correspond to regions with high density of OR.[56–59] PAG receives projections from the primary motor cortex and the dorsal premotor area, and is extensively interconnected with the middle and anterior cingular cortex.[60,61] It had also been shown by the same group that the long-lasting changes in rCBF after chronic MCS in aMCC and PAG were correlated with the clinical efficacy of MCS.[48,53] These data suggest that MCS induces an endogenous opioid secretion/release in the part of the pain matrix spared by the causal lesion that might have been made silent by a diaschisis-like phenomenon and/or histologic reorganization. These data are also concordant with animal experiments in which MCS elicited a substantial and selective (contralateral) antinociceptive

Author series	Total *N* of patients	Follow-up (months)	Pain relief > 40% at latest follow-up, *N* (%)
Brachial plexus avulsion			
Nguyen 1999[16]	2	(19)	1/2 (50%)
Mertens 1999[11]	4	(24)	2/4 (50%)
Saitoh 2001[65]	4	(26)	1/4 (25%)
Pirotte 2005[68]	3	(29.7)	1/3 (33%)
Nuti 2005[37]	4	(49)	3/4 (75%)
Hosomi 2008[13]	7	13–88	3/7 (43%)
Velasco 2008[33]	3	(12)	2/3 (66%)
Fagundes-Pereyra 2010[39]	12	7–101(29)	6/12 (50%)
Ali 2011[77]	7	12–112(47)	3/12 (25%)
Total	**46**		**22/46 (47.8%)**
Phantom limb			
Saitoh 2001[65]	2	20	1/2 (50%)
Caroll 2000[76]	3	21–31	2/3 (66%)
Katayama 2001[36]	5	24	1/5 (20%)
Lazorthes 2007[72]	7	6–76(42)	5/7 (71%)
Hosomi 2008[13]	4	13–88	1/4 (25%)
Fagundes-Pereyra 2010[39]	3	7–101(29)	2/3 (66%)
Total	**24**		**12/24 (50%)**
Spinal cord lesion			
Hosomi 2008[13]	2	(50)	1/2 (50%)
Nuti 2005[37]	4	(49)	3/4 (75%)
Total	**6**		**4/6 (66%)**
Postherpetic neuralgia			
Velasco 2008[33]	5	(12)	3/5 (60%)

Note: Differences in pain relief are not statistically significant.
[a]III, publication classified as III according to European Federation Neurological Societies (EFNS), conferring level C of evidence.[34,35]

effect, likely mediated by opioids because it can be reversed by naloxone.[62] Also, new animal models are under development to explore the cellular electrophysiologic mechanisms of the implicated anatomic structures.[63]

Further, recent studies, also using PET scan with [11C]-diprenorphine as the exogenous ligand, were launched to investigate in patients with neuropathic pain prior to surgical decision whether the magnitude and distribution of OR density could be a biological marker of the ability of MCS to relieve pain[64] (**Fig. 36.5**). The rationale for the study was that (1) OR density in structures involved in pain processing was found to be generally decreased in patients with neuropathic pain and that (2) MCS induces (as discussed above) secretion/release of endogenous opioids on the OR of the spared pain matrix structures, which is correlated with the degree of pain relief in key pain matrix and opioid-rich structures. The study showed that OR availability in receptor-rich brain regions was significantly decreased in patients not responding to MCS, as compared with either patient responders to MCS or normal volunteers. The level of availability was positively correlated with the degree of pain relief in improved patients. If these findings are confirmed in larger series, PET scan with [11C]-diprenorphine prior to surgical decision could become a valuable method for selecting patient candidates for the MCS procedure to treat refractory neuropathic pain, similar to the predictive potential of response to preoperative r-TMS. Such predictive factors could help clinicians avoid unnecessary and costly surgery and increase the percentage of patients responding to MCS.

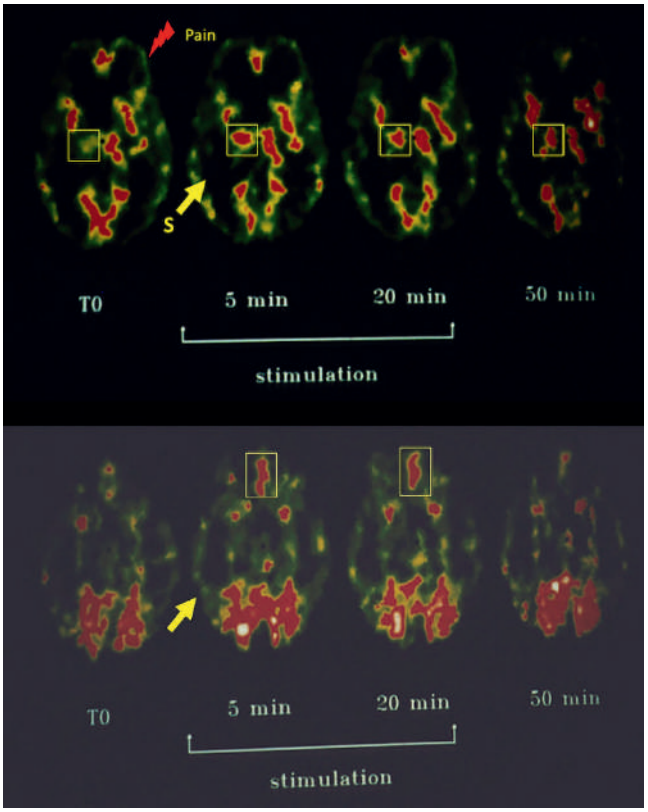

Fig. 36.2 Anatomic structures with increased metabolism after motor cortex stimulation (MCS). Positron emission tomography (PET) study of rCBF with IV injection of $^{15}OH_2$ 4 months after surgery. Left side of brain is on left side of image. The patient was a 72-year-old right-handed woman who presented 5 years previously with a left parietal infarct sparing the thalamus, and with a right hemiplegia and regressive aphasia, and who developed 2 years later a permanent right hemibody burning pain. Examination showed a right-sided hypoesthesia affecting all sensory modalities, with allodynia and hyperpathia. Somatosensory evoked potential (SSEP) exploration disclosed a 50% attenuation of the N20 wave and the presence of precentral responses P22 and N30, albeit of reduced amplitude; SSEPs after stimulation of the right tibial nerve were absent. An electrode was implanted extradurally on the left precentral region. Stimulation was at 50 Hz with a 1 V intensity. A lasting 70% decrease in pain was noted, but only in right upper limb and hemithorax; there was no relief in the lower limb. Quantitative analysis of rCBF before stimulation (T0) shows a decrease in rCBF in left thalamus. At T5 and T20 after MCS is "on," an increase in rCBF is observed in the left thalamus (*upper image*), orbitofrontal and anterior cingulate cortices (*lower image*), and also in the brainstem (*not shown*). The increase is progressively reversible after the end of the stimulating period—rapidly in the orbitofrontal and anterior cingulate regions, but slowly in the thalamus, as shown at T50 (which is 30 minutes after stimulation was discontinued), and also in the brainstem (*not shown*).

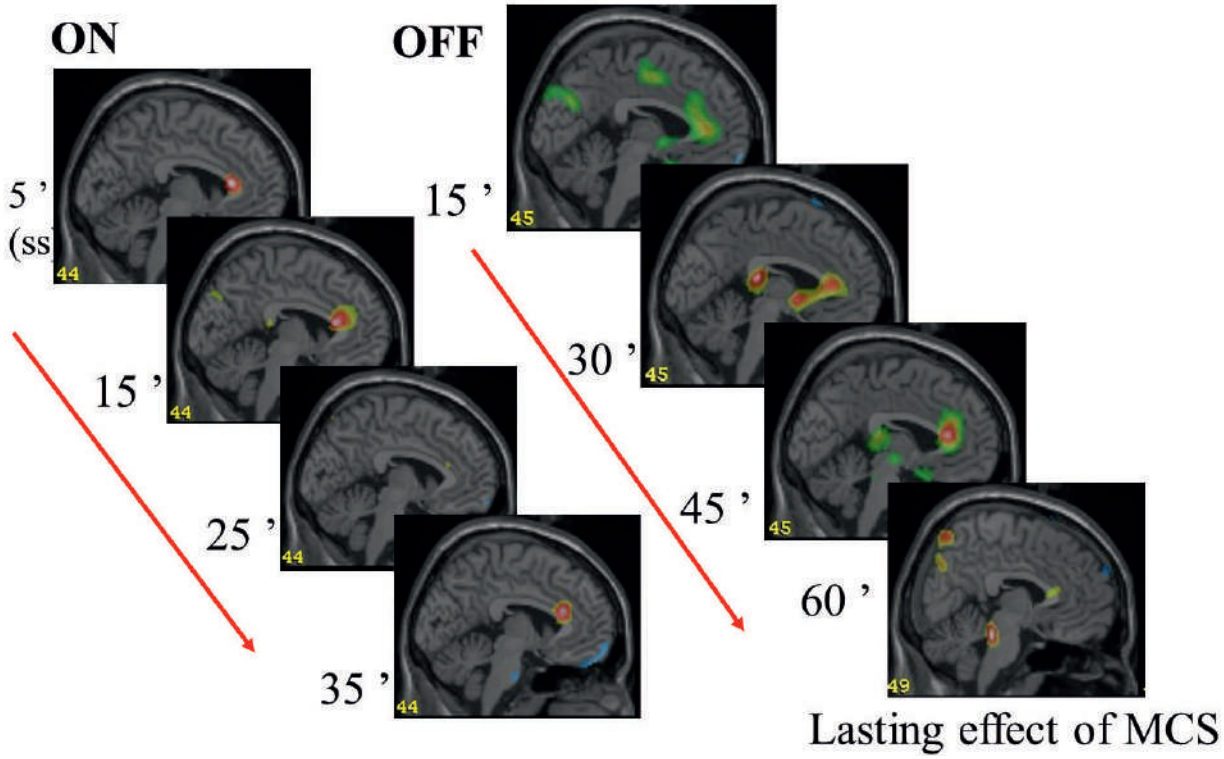

Fig. 36.3 Delayed effects of MCS. PET study of rCBF with $^{15}OH_2$ during (left: ON) and after discontinuing (right: OFF) MCS sessions, showing increased CBF in anterior middle cingulate cortex (aMCC) and periaqueductal gray (PAG). During the "on" sequence, rCBF in the aMCC starts to increase early after onset of stimulation (5 minutes), reaches a maximum after 30 minutes from the arrest of stimulation, and then diminishes after 45 minutes. rCBF has a delayed increase in the brainstem, and likely in the PAG; the increase appears 30 minutes after stimulation is discontinued and it lasts longer.

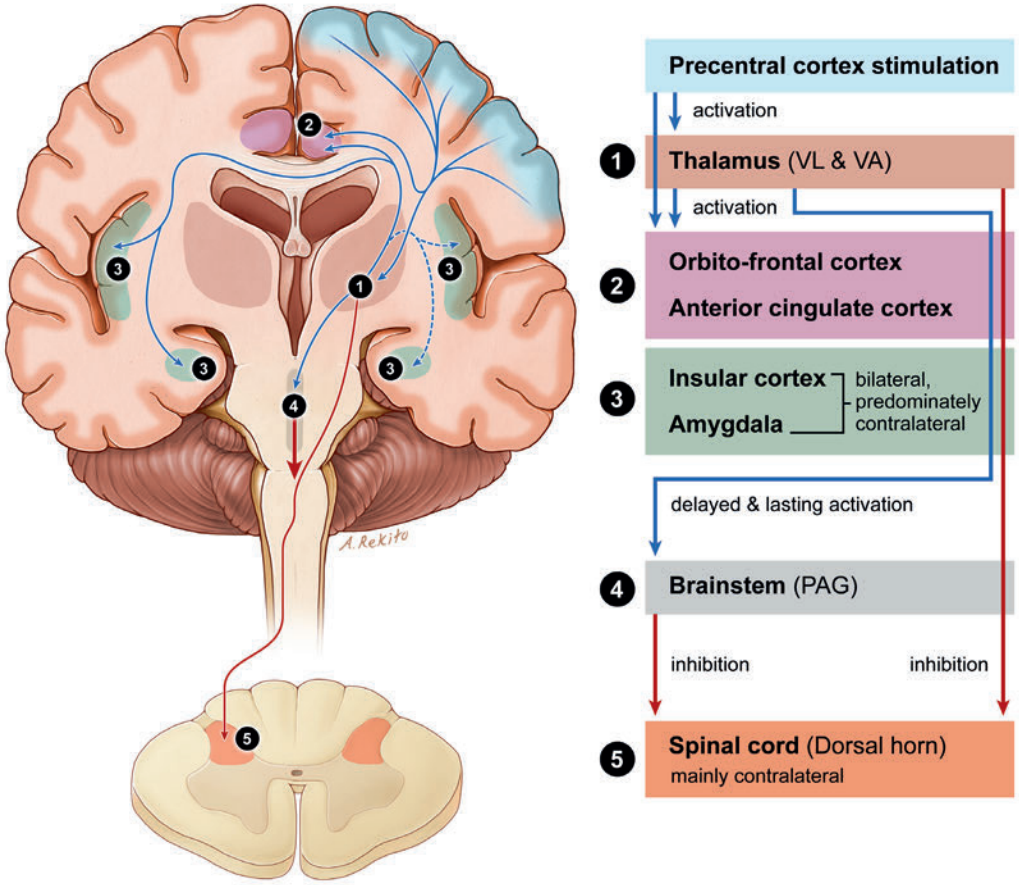

Fig. 36.4 Mechanisms of action of MCS: schematic representation. Stimulation of the motor cortex or, better said, the PCS activates, in step 1, the ipsilateral thalamus (likely its ventrolateral and ventroanterior nuclei), then the orbitofrontal and the anterior middle cingulate cortices, through direct projection or via the thalamus. Stimulation also activates the insula, likely its posterior part, as well as the amygdala, both bilaterally but predominantly on the contralateral side. Then, with a delayed and lasting effect, stimulation activates the brainstem, likely the periaqueductal gray (PAG). PCS also exerts a descending inhibitory effect on the dorsal horn circuitry of the spinal cord, predominantly on the contralateral side.

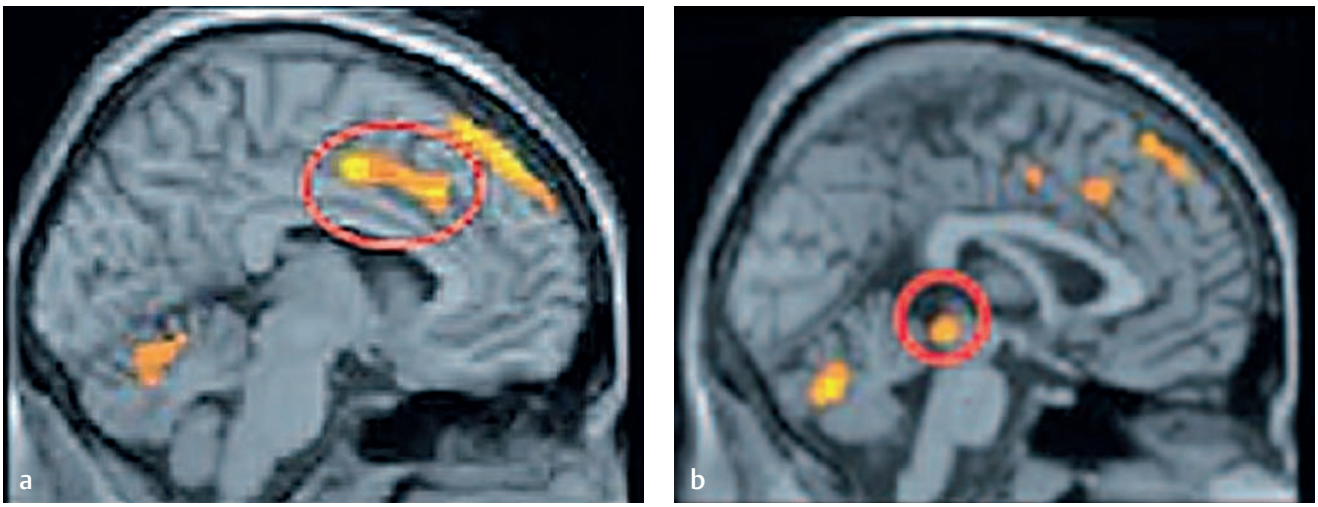

Fig. 36.5 (**a, b**) MCS (motor cortex stimulation) action through opioid secretion/release. PET study of fixation of the exogenous ligand of opioid receptors [11C]-diprenorphine after 7 months of chronic MCS. A study on eight patients shows a significant decrease of binding in the aMCC and the PAG. Significant decreases are marked in yellow/orange.[55]

Conclusion

Most literature reports over the past 15 years converge in estimating that approximately half of the patients with MCS benefited with more than 40% pain relief. But due to the lack of long-term follow-up surveys and solid selection criteria, the method has not obtained official approval to enter the current armamentarium of pain surgery. Hopefully in the near future, rTMS testing and PET scan with [11C] diprenorphine will be confirmed to be of value in selecting the candidates most likely to respond to the procedure.

The accumulation of neurophysiologic and PET scan imaging data on MCS's effects are strong arguments for considering the rationale valuable. This is all the more important as main potential indications are intractable pain syndromes not responding to the existing therapeutic arsenal, especially CPSP and TNP. Stimulation of the precentral cortex would increase, somatotopically, through reactiviation of the (lateral) thalamus, activity of the pain matrix structures made silent by diaschisis phenomena, and/or functional reorganization. Mechanisms of action would pass via opioid secretion/release. Because it is not known whether the motor cells and pyramidal fibers are implicated or not in MCS effects, the method would be better named precentral cortex stimulation (PCS) with regard to its principle, and further understood through investigations in patients and experiments in animal models.

Because the technique has been revealed over years of use to be reasonably safe, and because of its potential, MCS should be retained in the therapeutic regimen and further developed, especially once reliable selection criteria have been established.

Editor's Note

I am grateful to Professor Sindou and colleagues for taking on this difficult topic. There has been considerable skepticism expressed recently over the role of motor cortex stimulation (MCS) in the surgical treatment of neuropathic pain. In their review and analysis, the authors make a substantial contribution to our current understanding of this procedure.

MCS is perhaps the latest conceptual innovation in the surgical management of pain. Most other current neurostimulation technologies can trace their roots back to the late 1960s, when spinal cord and peripheral nerve stimulation were introduced. Deep brain stimulation (DBS) for pain began in the 1970s, flourished briefly in the 1980s, and now plays a dramatically reduced role in surgical pain management. By contemporary criteria, DBS for pain never achieved an evidence base that supported the technique. Twenty years after its inception, MCS finds itself in the same position that DBS for pain occupied two decades ago: Numerous case series attest to its efficacy, but there are no large definitive prospective, case-controlled, blinded studies.

The evidence for MCS from two large meta-analyses seems suggestive. Fontaine et al[29] searched the literature and came up with 14 series that passed minimal acceptance criteria. There were no controlled or blinded series on MCS identified by these authors. They found that these case series averaged a 45% favorable response rate for MCS at more than 1-year follow-up. Lima and Fregni[38] had similar results.

Professor Sindou and coauthors performed a new literature search, and found that out of 45 citations (1993–2011), 24 met the criteria of more than five patients, a defined follow-up, and quantification of pain relief (usually via VAS [visual analogue scale]). **Table 36.1** reveals that when success was defined as more than 40% pain relief, it was achieved in 30 to 50% of patients. None of the studies were randomized, and with the exception of two small studies, long-term follow-up was lacking. Perhaps most disturbing was the conclusion of the authors that no strong outcome predictors emerge from the MCS literature. Transcranial magnetic stimulation (TMS) or PET (positron emission tomography) imaging hold promise, but at present their respective roles for selecting patients for MCS remain unknown.

Based on the present review, and the extant literature, MCS remains an interesting, but as yet unproven, therapy for neuropathic pain. Although there have been notable attempts to assemble multi-institutional prospective, randomized, and controlled trials of MCS in both Europe and the United States, none have been completed, and none are currently planned. Promising or not, if no rigorous trials of MCS are mounted, MCS will join DBS as a minor footnote in the history of pain surgery.

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37 Deep Brain Stimulation for Chronic Pain

Suneil K. Kalia, Clement Hamani, Ali Rezai, and Andres M. Lozano

The chronic electric stimulation of cortical and subcortical brain targets is an increasingly used mode of therapy in stereotactic and functional neurosurgery. Intracranial neural stimulation can involve the use of cortical stimulators (e.g., motor cortex stimulation [MCS]) or implanted parenchymal electrodes in subcortical structures (e.g., deep brain stimulation [DBS]). The major advantage of intracranial neural stimulation in contrast to traditional lesioning procedures is that it is adjustable and reversible. These features allow for maximal clinical efficacy and titration of therapy as a disease or pain state changes over time, as well as minimizing complications.

Although chronic pain was one of the first conditions treated by intracranial stimulation, the most common current application of DBS is for the treatment of movement disorders. DBS for movement disorders such as Parkinson disease and essential tremor, with its improved safety and striking benefits, has paved the way for a reexamination of this mode of therapy for novel targets and indications.[1–8] The exact mechanism of action by which intracranial neural stimulation results in the modulation of functional pathways is currently unknown. Prevailing theories implicate a blockade of neuronal activity and an activation of axonal tracts. The effects of high-frequency (> 100 Hz) stimulation in areas populated by neuronal cell bodies often mimic those seen with lesioning of the same structure. The same parameters of stimulation in axonal projections such as the corticospinal or optic tracts, however, appear to activate these projections. Both anterograde and retrograde effects occurring locally or distant transsynaptic effects are possible. Whereas high-frequency stimulation is often necessary and routinely used in movement disorder surgery, lower frequency stimulation has been efficacious in pain surgery depending upon the target. Currently a wide range of neuropathic pain conditions are being treated by DBS, including neuropathic facial pain, centrally mediated thalamic pain syndromes, pain related to spinal cord injury, and phantom limb pain. This chapter provides an overview of the history of DBS in the treatment of pain, its proposed mechanism of action, current indications, clinical applications, and future prospects.

Historical Perspective

Based on the observation of positive reinforcement identified with brain stimulation in rodents,[9] neurosurgeons ventured into the field of electric stimulation of the brain for the relief of pain. Early efforts using temporarily implanted electrodes eventually were replaced by chronic brain stimulation through permanently implanted electrodes coupled to battery-powered pulse generators. The use of electrical stimulation for chronic pain dates back to the 1950s, when Heath[10] and Pool[11] implanted temporary electrodes in the septal region for psychosurgery in patients with schizophrenia and metastatic carcinoma. The electrodes were placed in the septum pellucidum in a region anterior and inferior to the foramen of Monro with successful pain relief. Pool et al in 1956[12] and Heath and Mickle in 1960[13] reported pain relief with septal stimulation in nonpsychiatric chronic pain patients. Ervin et al[14] reported analgesia induced by stimulation of the caudate nucleus in a patient with intractable facial pain secondary to carcinoma of the pharynx and skull base. The pain relief lasted for up to 6 to 8 hours after the stimulation was turned off. Gol[15] stimulated both the caudate nucleus and the septal region in six patients with intractable pain, but successful pain relief was obtained in only one patient.

Current application of intracranial neural stimulation for pain involves either DBS or MCS. Contemporary DBS targets include paresthesia-producing thalamic, medial lemniscus (ML), and internal capsule (IC) stimulation for neuropathic pain and periventricular gray (PVG)/ periaqueductal gray (PAG) stimulation for nociceptive pain. The concept of

thalamic stimulation arose from the Melzack–Wall gate theory of pain,[16] which holds that stimulation of large myelinated fibers of the peripheral nerves resulting in paresthesias would block the activity in small nociceptive projections. Thalamic stimulation for pain relief was envisioned within the spectrum of modulation of sensory and pain pathways in the neuraxis at the level of the spinal cord via dorsal column stimulation and more rostrally to the lemniscal pathways, thalamic sensory relay nuclei (ventralis caudalis [VC] or ventral posterior [VP]), and sensory portion of the IC.[17]

Thalamic stimulation for pain relief was first reported by Mazars et al,[18] who performed paresthesia-producing stimulation along the ventroposterolateral (VPL) nucleus to relieve chronic intractable deafferentation pain. Hosobuchi et al[19] reported the efficacy of chronic ventroposteromedial (VPM) stimulation using 100 Hz frequency in patients with refractory facial pain. Subsequently, Hosobuchi and Adams[19] and Mazars et al[20] reported long-term success using chronic implantable VP stimulators in patients with deafferentation pain.

At the same time that paresthesia-producing stimulation was being actively pursued, animal studies by Reynolds[21] demonstrated that stimulation of the lateral margin of the PAG in rats induced analgesia, enabling abdominal surgeries to be performed on awake animals without the use of anesthetics. Confirmation of this method's efficacy in humans was reported in 1977 by Richardson and Akil.[22,23] Hosobuchi et al[24] reported similar findings with PVG stimulation.

Mechanisms of Pain Modulation by DBS

The exact mechanism by which paresthesia-evoking thalamic stimulation results in pain relief is not known, but it is most likely not opioid mediated. One concept is that deafferentation causes an abnormal firing pattern in thalamic neurons and that thalamic stimulation inhibits this abnormal neural activity. Gerhart et al[25] showed that stimulation of the VPL, the primary somatosensory relay nucleus, in monkeys caused inhibition of evoked responses by spinothalamic neurons to noxious cutaneous stimulation.

In studies of chronic pain patients, an abnormal pattern of neuronal firing has been shown in the sensory thalamus in patients with central deafferentation pain.[26] Lenz et al[27] showed that areas in the somatosensory thalamus that had lost their normal innervation had abnormal spontaneous bursting activity, with electric stimulation inducing burning dysesthesias. Similarly, Rinaldi et al[28] demonstrated an increased number of bursting neurons in the medial and lateral thalamic nuclei in deafferented rats compared with controls, along with an increase in the number of nociceptive responsive neurons in the medial thalamus.

In contrast, the mechanism of pain modulation with PVG/PAG stimulation is most likely via an opioid-dependent pathway. Elevations of endogenous opioids, such as b-endorphin and metenkephalin, have been demonstrated in cerebrospinal fluid (CSF) samples from the third ventricle after PVG or PAG stimulation but not with VC stimulation.[29,30]

Indications

Pain Characteristics

Chronic pain can be generally characterized as nociceptive or nonnociceptive. *Nociceptive* or *somatic pain* is caused by direct activation of the nociceptors (mechanical, chemical, and thermal) found in various tissues. The afferent somatosensory pathways are intact in nociceptive pain. Examples include cancer pain from bone or tissue invasion and noncancer pain secondary to degenerative bone and joint disease.

Characteristics of Neuropathic and Nociceptive Pain

Nociceptive Pain
- Pain secondary to activation of nociceptors with intact somatosensory afferent pathways
- Most commonly described as sharp, dull, throbbing pain
- Responds to narcotic analgesics
- Responds to ablative/lesioning procedures

Neuropathic/Deafferentation Pain
- Pain secondary to a lesion, injury, or dysfunction of the central/peripheral nervous system (CNS/PNS)
- Most commonly described as constant, steady, burning, aching, dysesthetic pain
- Also neuralgic (sharp, shooting) and evoked (allodynia, hyperpathia) components
- Less responsive to narcotic analgesics
- Responsive to antidepressants
- Not responsive to ablative/lesioning procedures

Nonnociceptive pain, occurring in the absence of activation of peripheral nociceptors, also has been referred to as *neuropathic pain* or *deafferentation pain.* This type of pain results from an injury or dysfunction

Table 37.1 Chronic pain conditions treated with deep brain stimulation

Neuropathic/deafferentation	Nociceptive
Neuropathic facial pain syndromes	Failed back surgery syndrome
Thalamic pain syndromes	Osteoarthritis
Stroke pain	Cancer pain
Postherpetic neuralgia	
Traumatic brain and spinal cord injuries	
Iatrogenic brain and spinal cord injuries	
Brachial plexus avulsion	
Peripheral neuropathies	

of the central and/or peripheral nervous system. Examples include neuropathic facial pain syndromes such as anesthesia dolorosa, thalamic pain syndromes including thalamic stroke, traumatic or iatrogenic brain or spinal cord injuries, phantom limb or stump pain, postherpetic neuralgia, and various peripheral neuropathies.

Table 37.1 lists various chronic neuropathic and nociceptive conditions that have been treated by using DBS. In general, patients with refractory neuropathic pain should undergo paresthesia-producing stimulation, whereas those with nociceptive pain should undergo PVG/PAG stimulation. In reality, most pain syndromes have mixed components of nociceptive and neuropathic pain; thus, both paresthesia-evoking and PVG/PAG stimulation trials are performed at our center.

■ Techniques

Patient Selection

The initial choice for treating a patient with chronic pain is a conservative approach involving medications, physical therapy, biofeedback, and transcutaneous electrical nerve stimulation (TENS), as well as less conventional or alternative therapies. Once conservative approaches have been exhausted, more invasive procedures can be considered, such as blocks, neurolysis, other ablative procedures, and intrathecal opioid pumps. If a patient is not a candidate for these approaches, or if these measures fail and there is persistent incapacitating pain, neuromodulatory approaches such as spinal cord stimulation and intracranial neural stimulation including DBS may be considered.

Prior to proceeding with DBS, patients must satisfy general selection criteria and be treated by a multidisciplinary pain management team. Additionally, a minimum of 6 months should have passed after pain onset prior to consideration for brain stimulation. We generally reserve DBS for patients who have pain they regard as severe and incapacitating, that is, 6 or greater (of a maximum of 10) in intensity on a visual analogue scale (VAS) for pain. The pain should be the predominant problem causing disability and suffering for which the patient seeks relief and refractory to all other therapeutic modalities. Patients with long-standing pain complaints without a clearly defined etiology are usually not considered appropriate candidates for DBS.

Deep Brain Stimulation for Chronic Pain: General Selection Criteria

- Evaluation and treatment by a multidisciplinary pain team
- Persistent, severe, incapacitating pain
- Failure of all previous treatment modalities
- Pain is the predominant complaint.
- A clear understanding of the etiology of the pain
- Absence of major psychological or psychosocial overlay
- The patient must understand that the procedure is not curative.
- 50% or greater reduction in pain is a worthwhile improvement.
- Pain recurrence can be common.

Psychiatric evaluation by an experienced team is crucial to exclude patients with significant psychological or psychosocial overlay or motives of secondary gain. In general, patients with psychosis or a strong psychopathology should be encouraged to undergo further psychological treatment. It should be recognized, however, that most patients with refractory chronic pain may have an associated depressive and/or anxiety disorder.

Techniques

The initial steps in various stereotactic procedures are similar. We first describe the general stereotactic technique. Specific details pertaining to targeting and stimulation parameters are discussed subsequently.

Stereotactic Frame Application and Image Aquisition

Patients undergo application of a stereotactic head frame under local anesthesia. At our institutions, we use the Leksell model G frame (Elekta Instruments, Atlanta, GA, USA); however, any of the commercially available stereotactic systems can be used. After frame application, patients undergo either computed tomography (CT) or magnetic resonance imaging (MRI). MRI has higher anatomical resolution than CT, but it is more susceptible to distortions in spatial accuracy.

There are a number of different MRI acquisition sequences for the purposes of stereotactic planning, and they vary from institution to institution. A MRI-compatible localizer box is fitted to the stereotactic frame prior to obtaining imaging. Most commonly, a volumetric T1 scan (1 mm in thickness) is used to register the fiducial markers in the computer planning software of choice. A T2 image through the basal ganglia can be useful to help further visualize subcortical nuclei.

Anatomical Target Localization

Anatomical localization of the thalamic sensory nucleus VC, ML, IC, or PVG/PAG can be achieved by directly visualizing the structure on imaging studies as in the case of the IC or by selecting an appropriate final target by its relationship to the anterior commissure (AC) and posterior commissure (PC) using standardized anatomical brain atlases as in the case of thalamic nuclei. At our institution, we use commercially available planning software in which the program transcribes the patient's calculated AC–PC intercommissural line onto a digitized atlas-based map at the sagittal laterality of interest. On these maps, structures such as the VC and ML can be localized. The subsequently generated brain map is overlaid onto a millimeter grid ruled in stereotactic coordinates in the anteroposterior and dorsoventral scales with a corresponding diagram of the brain nuclei and tracts (**Fig. 37.1**). An entry point can be chosen that allows for optimal trajectory of the electrode. The corresponding stereotactic coordinates, including ring and arc angles, are then noted.

Surgical Procedure

Subsequent to the stereotactic CT/MRI acquisition and anatomical target localization, the patient is taken to the operating room. In our institution, the procedure is performed with the patient awake using local infiltrative anesthesia. A curved incision is planned such that the incision does not directly overlie the bur hole made at the planned entry site, which is usually anterior to the coronal suture. The dura is opened and fibrin glue is applied to minimize egress of CSF and entry of air into the cranial cavity. The stereotactic arc is then applied, and the X, Y, and Z coordinates for the anatomical target area are set. If the trajectory has been preplanned, the appropriate ring and arc angle are also set. A guide tube cannula with a blunt-tip stylet is then introduced into the brain parenchyma after ensuring that the systolic blood pressure is lowered to less than 150 mm Hg. A microelectrode assembly is inserted into the cannula and then attached to the frame with a microdrive apparatus.

Physiological Target Localization

Sole reliance on anatomical localization can be problematic because of the frequent discrepancy between the expected location and actual position of the stereotactic targets. Among the many possible contributing factors for this are MRI distortion and brain shift due to egress of CSF and entry of intracranial air following placement of the bur hole. Physiological corroboration can be achieved with microelectrode recording combined with stimulation, or macroelectrode stimulation alone. Macroelectrode stimulation is rapid but has low spatial resolution, and macroelectrodes are unable to discriminate between axons and neurons. Microelectrodes, however, provide exquisite physiological identification of receptive fields and neuronal firing patterns through direct measures of individual single-unit neuronal activity and are able to distinguish somatodendritic from axonal activity.

Paresthesia-Evoking Targets

Microelectrode recordings are useful for thalamic surgery because nuclei cannot be discriminated in imaging studies. The paresthesia-producing targets are the thalamic sensory relay nucleus (i.e., VC), the ML, and the IC. The target is typically 12 to 14 mm from the midline for facial pain, 14 to 15 mm for upper-extremity pain, and 15 to 17 mm for lower-extremity pain, although there is variation among centers. The ML can be targeted inferior to the intercommissural line 12 to 14 mm from the midline. Elec-

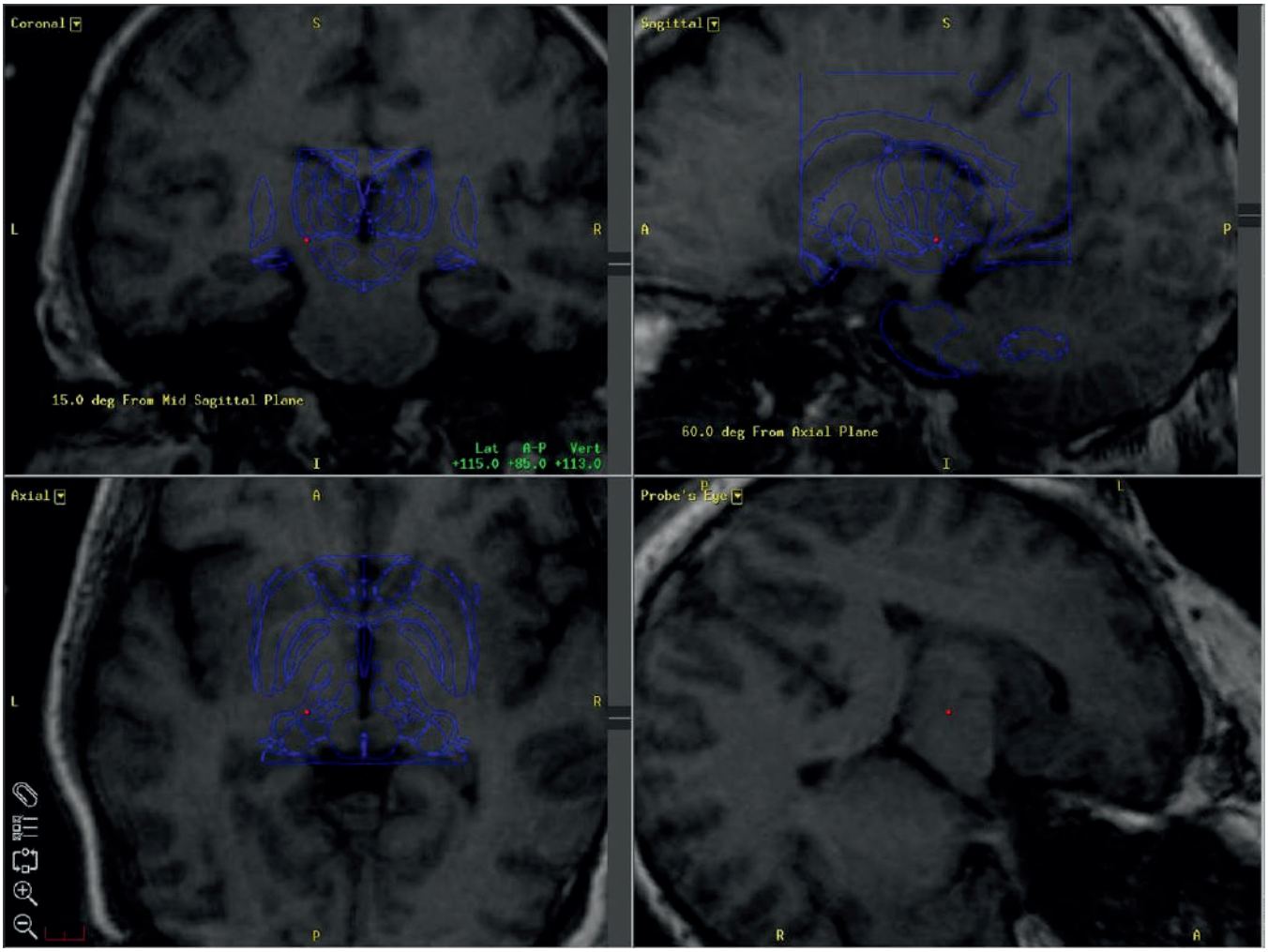

Fig. 37.1 Anatomical brain maps for targeting. Planning station screenshot showing digitized Schaltenbrand and Wahren atlas overlay on preoperative patient MRI (magnetic resonance imaging) with Leksell frame on. This image shows an example of target selection for VC (ventral caudalis).

trodes are generally placed contralateral to the area of pain. In patients with bilateral pain, electrodes are placed on both sides, usually in single or staged procedures. For focal neuropathic pain, the somatotopic representation of the patient's pain area in the VC is targeted. For more diffuse or hemibody pain, the ML or the IC is chosen to obtain more widespread coverage. With pain resulting from destructive thalamic lesions, microelectrode mapping of the thalamus may be of poor yield,[31] and thus the thalamic afferent or efferent projections (i.e., IC, ML) can be targeted for stimulation.[19]

Microelectrode recording in the VC reveals a somatotopic representation of body parts expressed with discrete tactile receptive fields. With microstimulation, patients experience somatotopically organized paresthesias, defining a projected field for these thalamic neurons. Technical aspects of microelectrode recording in the VC have been previously published in detail[32,33] and are beyond the scope of this chapter. As an alternative to micro-stimulation, macro-stimulation can be performed every 1 to 2 mm from about 10 mm above to 10 mm below the expected target.

Physiological mapping in patients with stroke or major deafferentation may vary from the normal observations as a result of neuronal loss, structural anatomical changes, or plasticity. These include an absence of neurons and their corresponding receptive or projected fields, mismatch between receptive and projected fields, somatotopic reorganization, widened or shrunken receptive fields, neuronal bursting activity, and projected fields that evoke burning or pain rather than paresthesias. In situations where physiological mapping does not provide a clear receptive field map definition, PVG/PAG stimulation can be an alternative option, particularly in patients with the evoked features of neuropathic pain.

PVG/PAG Targets

Although PVG and PAG are a continuous volume of neurons, they may be targeted separately. The anatomical targets for the PVG are typically 2 to 5 mm anterior to the PC, 2 mm lateral to the medial wall of the third ventricle, and at the level of PC.[22,23,34] The microelectrode recordings from the PVG region in humans are not well characterized. PVG stimulation can result in pleasant sensations of warmth and well-being with stimulation frequencies of 25 to 50 Hz. At higher stimulation intensities, PVG stimulation may evoke feelings of diffuse burning or, at times, anxiety. The typical stereotactic coordinates for the PAG are 2 to 3 mm lateral to the midline, just lateral to the aqueduct (1–2 mm), 1 to 2 mm behind the PC, and 2 to 3 mm below the AC–PC line.[24,35] With ventral PAG stimulation, sensations similar to those of PVG are experienced, but dorsal PAG stimulation typically evokes unpleasant sensations of fear, doom, anxiety, and agitation. Additionally, current spread from increased stimulation settings can cause vertical gaze or other gaze abnormalities. Furthermore, PAG stimulation can also modulate blood pressure.[36,37] In general, we prefer placement of the electrode in the PVG because of the decreased potential for adverse effects compared with PAG stimulation.

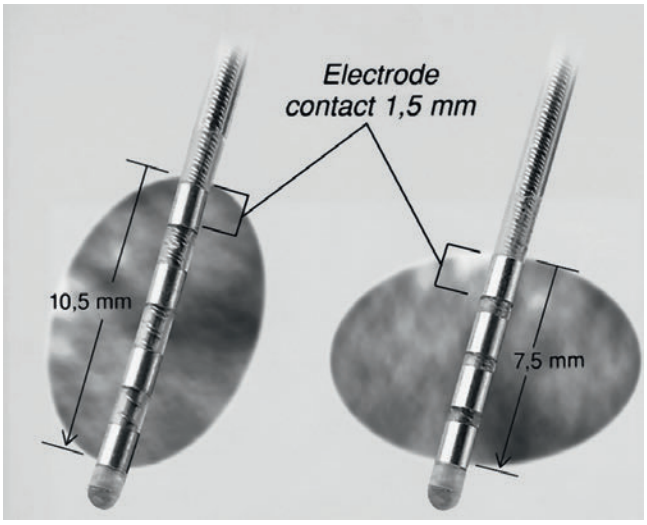

Fig. 37.2 The deep brain stimulation (DBS) electrode. The DBS electrode is a quadripolar electrode. Each pole/contact is made of cylindrical platinum/iridium alloy and is 1.5 mm long and 1.27 mm in diameter, separated from the other pole by an insulated distance of 1.5 mm or 0.5 mm, depending on the model and preference. (Reprinted with the permission of Medtronic, Inc. © 2007.)

DBS Electrode Implantation

The physiological mapping information obtained along each tract or trajectory is recorded, allowing simultaneous visualization and correlation of the physiological and anatomical findings. At this time, the optimal location for the placement of the DBS electrode is determined. General principles guiding the final implantation involve placement of the electrode at a region allowing for maximal efficacy while minimizing the undesired side effects. We currently use a quadripolar Medtronic (Minneapolis, MN, USA) electrode with a diameter of 1.27 mm. Each pole or contact is made of cylindrical platinum/iridium alloy and is 1.5 mm long, separated from the other contact by an insulated distance of 1.5 mm or 0.5 mm, depending on the model used (**Fig. 37.2**).

To confirm the position and trajectory of the actual DBS electrode, intraoperative stereotactic radiography or fluoroscopy is used (**Fig. 37.3**). Subsequent to insertion of the electrode into the target, a handheld pulse generator is used for intraoperative test stimulation. Various contact combinations and stimulation frequencies, pulse widths, and intensity levels are used to determine the thresholds for therapeutic and adverse effects. Once the optimal position is confirmed, the DBS electrode is fixed in position according to the manufacturer's instructions. At our institution, the proximal portion of the DBS lead is attached to a temporary transcutaneous extension wire for a trial

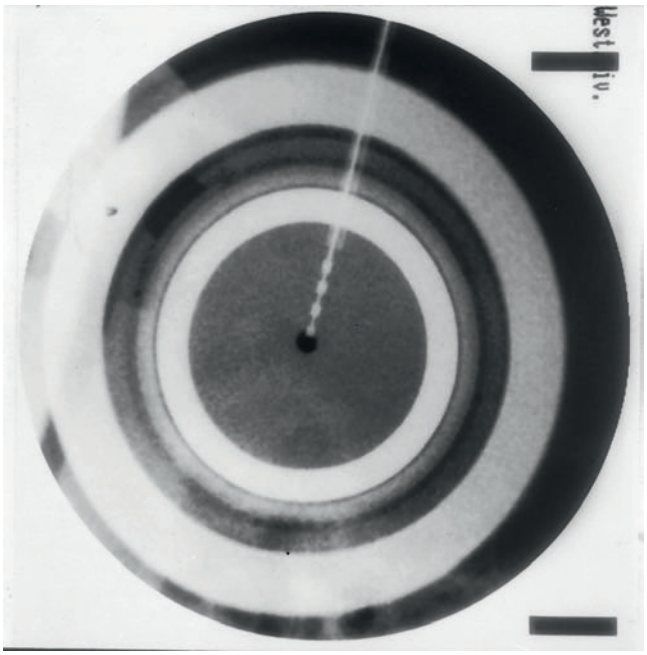

Fig. 37.3 Intraoperative target verification. Intraoperative stereotactic radiograph of the DBS (deep brain stimulation) electrode at the target. The electrode is introduced from a precoronal bur hole and directed posteriorly and ventrally. The position of the electrode is monitored via fluoroscopy. The crosshairs indicate the target, which is also the center of the stereotactic ring. Note the appearance of the four poles.

period to perform test stimulations. Postoperative MRI imaging confirms the electrode locations (**Fig. 37.4**).

Test Stimulation Trial Period

Patients undergo test stimulation for a trial period lasting 3 to 7 days. During this time, various stimulation parameters are used, and a detailed patient pain diary is compiled using visual analogue and verbal pain scores. Typical stimulation parameters include unipolar or bipolar stimulation, lower frequencies (25–75 Hz) for PVG/PAG and higher frequencies (> 100 Hz) for VC, pulse widths of 60 to 500 µs, and variable voltage intensities. A trial is considered successful if there is a greater than 50% reduction in the patient's pain with stimulation. A transient insertional effect resulting in pain reduction is observed in many patients at the time of implantation of the electrodes, which may complicate assessment of DBS benefit in this trial period. If a trial is clearly successful, the patient undergoes implantation of a pulse generator or radiofrequency-coupled receiver. If unsuccessful, the DBS electrode and the transcutaneous wires are removed.

Pulse Generator or Radiofrequency Receiver Implantation

This portion of the procedure is usually carried out with the patient under general anesthesia because it involves tunneling an extension cable from the frontal incision to the infraclavicular region. The patient position is similar to the position used for a ventriculoperitoneal shunt such that the head is turned away from the site of the externalized transcutaneous wires and there is clear visualization of the entire planned course of the subcutaneous extension wires to the infraclavicular region. A programmable implantable pulse generator (IPG) device compatible with the DBS electrodes is implanted in the subcutaneous tissue of the infraclavicular space (**Fig. 37.5**).

Outcomes

Although more than 600 cases of DBS for pain have been reported in the literature, a carefully designed scientific evaluation of DBS for pain has been a difficult task. This is due to several issues, including but not limited to (1) the variability in chronic pain patients for a given diagnosis, (2) the variability in conditions that may be suitable for DBS, and (3) differences in target selection and programming parameters used for a given diagnosis from center to center. Furthermore, postoperative evaluations for the most part were not standardized and definitions of success differed in the reported cases. Additionally, not all reports distinguished their outcomes between those undergoing an initial DBS trial and those who had permanent implants.

Most studies show a response in 30 to 60% of the patients treated.[6,23,35,38–43] In assessing long-term

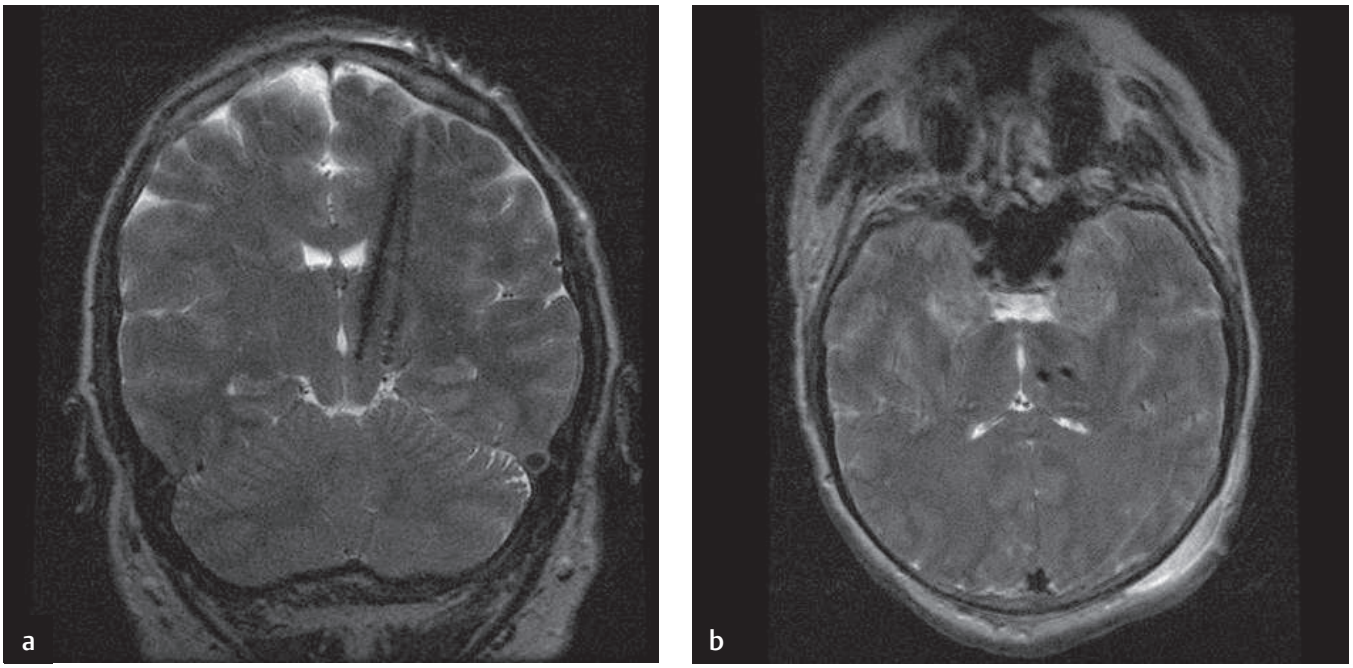

Fig. 37.4 (**a, b**) Thalamic and PVG (periventricular gray) DBS (deep brain stimulation). Axial T1-weighted MRI (magnetic resonance imaging) section demonstrating the location of thalamic sensory and PVG electrodes in a patient with chronic refractory facial neuropathic pain.

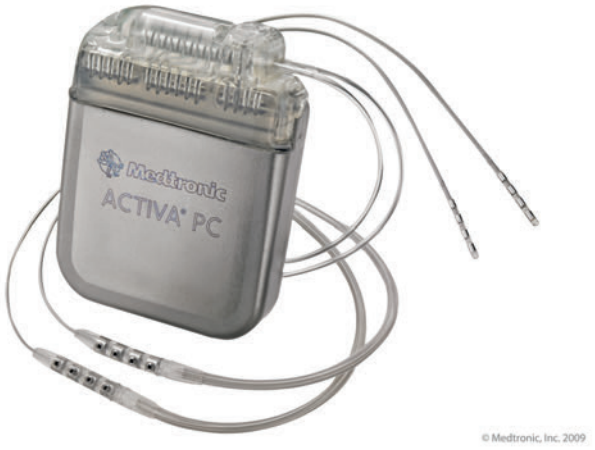

Fig. 37.5 An example of the quadripolar DBS (deep brain stimulation) electrode and the internal pulse generator (IPG). The IPG unit is powered by a lithium battery, which is fully programmable via telemetry. (Image © Medtronic, Inc. 2013.)

outcomes from previous published studies, the overall results seem to favor the treatment of nociceptive pain over neuropathic pain (63 vs. 47% long-term success).[44] However, no controlled trials comparing thalamic and PAG/PVG have yet been completed.[39,45–47] In general, PVG stimulation is optimal for nociceptive pain and the evoked feature of neuropathic pain, whereas paresthesia-producing stimulation works well for neuropathic pain but not nociceptive pain. **Tables 37.2** and **37.3** list some of the reported results of DBS for nociceptive and neuropathic pain, respectively.[6,23,35,38–41,47–50] Usually, the success rates decline with time. In general, the best results are in cancer pain, failed back surgery pain, cervical/ brachial avulsions, and peripheral neuropathy. On the opposite end of the spectrum, thalamic pain, post-herpetic neuralgia, and traumatic lesions of the spinal cord were among the poorest responders.[47,51–53]

Complications

Complications associated with DBS can be categorized as neurologic, implant related, and stimulation related.[6,23,35,38–41,47–50] The most significant neurologic complications include intracranial hemorrhage, infection, seizures, and pneumocephalus. The most significant complication associated with any DBS procedure is an intracranial hemorrhage. The incidence of hemorrhage from several series is reported as 2 to 3% and the incidence of infection ranges between 3 and 5%.[47] Levy et al[39] did not find any correlation between the duration of the test trial or externalization and the incidence of infection.

Implant-related complications have been reported at rates of 2 to 26% and include equipment failure, lead disconnection or breakage, and electrode migration.[47] The stimulation-related complications are for the most part transient and resolve with adjustments of the stimulator settings. These have included headaches, diplopia, nausea, vertical gaze palsies, blurred vision, horizontal nystagmus, uncomfortable paresthesias, and unpleasant stimulation side effects, particularly with PAG stimulation.

Perhaps the greatest challenge facing this treatment modality is the high rate of discontinuation of therapy. In our experience, more than 50% of those implanted with DBS systems for pain discontinue therapy within the first year of treatment. It is not clear why they experience loss of benefit; multiple factors may be involved, including adaptation due to neural plasticity and the possibility of patients initially overreporting benefits of stimulation during implantation trials. Two industry-sponsored, multicenter, prospective trials have failed to demonstrate effective long-term pain relief by DBS, resulting in the sponsor's not applying for FDA approval for DBS for pain.[52,53] Despite these results, we continue to offer DBS to appropriate candidates in whom all other options have been exhausted, given the fact

Table 37.2 Results of deep brain stimulation for nociceptive pain[6,22,23,29,34,35,39,40,50,54,55]

Series	Number of patients	Long-term success (%)	Follow-up (months)
Kumar et al 1997	49	71	84
Levy et al 1987	57	32	24–168
Hosobuchi 1986	65	77	24–168
Young et al 1985	31	81	2–60
Plotkin 1982	42	81	6–42
Ray and Burton 1980	19	74	14
Meyerson et al 1978	76	54	
Richardson and Akil 1977	20	70	1–46

Table 37.3 Results of deep brain stimulation for neuropathic/deafferentation pain[6,20,38,39,41,46,50,54,56–61]

Series	Number of patients	Long-term success (%)	Follow-up (months)
Hamani et al 2006	21	24	60
Owen et al 2006	34	52	18–19
Rasche et al 2006	41	20–24	42–44
Yamamoto et al 2006	18	78	12
Kumar et al 1997	16	44	45
Levy et al 1987	84	30	14–168
Young et al 1985	17	59	2–60
Dieckmann and Witzmann 1982	41	28	6–54
Turnbull et al 1980	18	72	1–47
Mazars et al 1979	99	84	
Meyerson et al 1978	160	26	

that long-term responders do demonstrate a greater than 60% decrease in VAS scores with DBS.[46,47]

Conclusion

DBS for chronic pain should be used only in patients who are incapacitated and have failed to respond to all other therapeutic modalities. Paresthesia-producing stimulation is indicated for the constant feature of neuropathic pain, and medial (PVG/PAG) stimulation is indicated for nociceptive pain and the evoked element of neuropathic pain. Patients with mixed pain syndromes should undergo implantation of both thalamic and PVG/PAG electrodes. Overall, results are better for nociceptive pain than for neuropathic pain. However, because evidence is limited, there is still a crucial need for carefully designed prospective studies assessing the role of DBS and the optimal target for nociceptive and neuropathic pain.

Editor's Comments

I appreciate the authors' treatment of this controversial topic, particularly since they are among the world's experts on the topic of deep brain stimulation (DBS). They provide us with a historical context for DBS for pain, and a scholarly discussion of its current status.

The published outcomes for DBS for pain are not compelling. The data are almost exclusively case series, and well-conceived prospective trials did not show efficacy. It is hard to imagine that randomized prospective trials would have been more successful, but these have not yet been accomplished. As a result, the technique remains unapproved by the FDA for pain in the United States.

The reader should absorb this discussion as part of the history, and potentially the future, of DBS. There is no doubt that the field of DBS continues to expand beyond movement disorders. Indications such as depression, obsessive compulsive disorder, and epilepsy have already been tested, and the acceptance of DBS for these indications may not be far off. Studies to potentially validate DBS for Alzheimer disease, and even intractable obesity, are either being planned or are under way. We will learn much from these studies, and the technology will continue to improve.

The history of functional neurosurgery has been one of discovery, retrenchment, and rediscovery. As our understanding of pathophysiology of chronic pain advances, it would not surprise me if DBS for pain becomes a focus of interest in the future.

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Section IV.A.3

Intrathecal Therapy

38 An Overview of the Rational Use of Intrathecal Analgesic Therapies

Elliot S. Krames and Tammy Penhollow

The need for the infusion of intrathecal (IT) agents should be determined by the diagnosis of the patient; the relevant patient history, including tried and failed medication management of the problem; physical examination; and imaging of the patient. It should be guided by an understanding of the appropriate indications[1,2] for placement of IT systems, the relevant spinal anatomy, and the technique. This chapter discusses the relevant anatomy of the epidural and IT space; indications for IT therapies; the rational use of the IT delivery of baclofen for central spasticity syndromes; and analgesic medications for pain control, including the FDA-approved analgesics morphine and ziconotide (Prialt) and other, non-approved analgesic medications, such as hydromorphone, methadone, fentanyl and sufentanil, the local anesthetic bupivacaine, and the α_2-agonist clonidine.

Relevant Anatomy

The spinal canal, containing the epidural space, the IT space, the dura, the spinal meninges, the spinal cord, fat, arteries, veins, lymphatics, nerve rootlets, nerves, and the dorsal root ganglion, is protected dorsally by the bony lamina and ligamentum flavum; ventrally by the posterior longitudinal ligament, the intervertebral disk, and the vertebral body; and laterally by the pedicles. Anatomy relevant to the placement of IT catheters for the IT delivery of opioids is that the spinal cord extends from C1–2 to L2, that the cauda equina extends from L1–2 to the sacrum, and that the dura envelops the exiting nerve roots to the dorsal root ganglia (DRG).

Cerebrospinal Fluid Dynamics and IT Catheter Fluid Flow Dynamics

Also relevant to the IT delivery of opioids is the cerebrospinal fluid (CSF) surrounding the brain and spinal cord within the subarachnoid space and produced by the ependymal cells of the choroid plexus of the brain. CSF is found in all intracerebral ventricles, spinal and brain subarachnoid spaces such as cisterns and sulci, and the central canal of the spinal cord. The rate of CSF formation in humans is about 0.3 to 0.4 mL/minute (about 500 mL/d). Total CSF volume is 90 to 150 mL in adults and 10 to 60 mL in neonates. It originates from the choroid plexus, parenchyma of the brain and the spinal cord, and ependymal lining of the ventricles.[3]

Agents delivered and diffused into and through the CSF are governed by the CSF circulation, CSF dynamics, cardiac output, the type of delivery of the agent into the IT space (bolus, continuous delivery, speed of delivery, where delivered, etc.), and the physical chemical properties of the agent infused (weight, hydrophilicity, etc.). It is known that CSF returns to the vascular system by entering the dural venous sinuses via the arachnoid granulations (or villi). However, it has been suggested that CSF flow along the cranial nerves and the spinal nerve roots and through the cribriform plate also seems to be important, especially in neonates,[4,5] since the villi in neonates is underdeveloped.

Flow of CSF is as follows: the portion of the fluid formed in the lateral ventricles escapes by the foramen of Monro into the third ventricle and then via the aqueduct into the fourth ventricle. A little CSF occurs in the central canal of the spinal cord and may be added to the intraventricular supply. From the fourth ventricle the fluid pours into the subarachnoid spaces through the medial foramen of Magendie and the two lateral foramina of Luschka. There is no functional communication between the cerebral ventricles and the subarachnoid spaces in any region except from the fourth ventricle.[6]

Two components can be distinguished in CSF circulation: (1) bulk flow (circulation) and (2) pulsatile flow (back-and-forth motion). In bulk flow theory, CSF is produced by choroid plexus and absorbed by arachnoid granulations. The force, which provides CSF movement from the ventricular system to arachnoid granulation and CSF absorption, is caused by a hydro-

static pressure gradient between the site of its formation (slightly high pressure) and its site of absorption (slightly low pressure). In pulsatile flow theory, movement of the CSF is pulsatile and results from pulsations related to cardiac cycle of the choroid plexus and the subarachnoid portion of the cerebral arteries.[7] Because very little CSF truly circulates through the subarachnoid space, pulsatile flow, rather than bulk flow, can be measured and demonstrated by phase contrast MRI (magnetic resonance imaging).[8]

It is important to know that CSF movement in the subarachnoid space of the spinal canal changes with position. The change from the supine to the prone position increases the movement of CSF in the dorsal subarachnoid space and decreases the movement in the ventral subarachnoid space; these findings may be attributed to change in the volume of CSF in the subarachnoid space after the positional shifts of the spinal cord.[9]

Prior knowledge of IT drug distribution was based on the literature regarding spinal anesthesia and factors that presumably increase drug spread, including morphological and technical factors.[10] However, because of the difference in the order of magnitude between the volume and flow rate (1 mL/30 s and 40 mL/d, respectively), most spinal anesthesia data are not applicable to chronic long-term IT drug administration. It was previously assumed that, upon its administration in the CSF, the drug would be transported by the flow of CSF and diffuse throughout the subarachnoid space to reach specific receptors in the spinal cord or the brain.

Biochemical, radiological, and experimental data refute the existence of a net CSF flow. In fact, the concentration gradient for normal small or large CSF constituent molecules is markedly rostrocaudal.[11,12] Early radiological findings from gated MRI have demonstrated that CSF moves in a to-and-fro oscillation[13] that is more marked in the cervical than in the lumbar region, but have not indicated the existence of a CSF bulk flow.[14,15]

CSF velocity and amplitude varies based on which part of the spinal cord is considered.[16] A pig model shows direct evidence that CSF does not circulate.[17]

Germane to IT catheter implantation, CSF drug distribution and spinal cord uptake are limited to the tip of the catheter and several centimeters distal to it; it does not wrap around the spinal cord, as evidenced by results from continuous IT low-flow-rate injections.[18–21] CSF pulsations are generated by the cardiac cycle, and this is responsible for IT drug diffusion from the fluid dynamic standpoint. These oscillations produce two diffusion-enhancing phenomena: (1) steady streaming, which is related to the perturbations created by obstacles such as ligaments and nerve roots present in an oscillatory flow; and (2) enhanced diffusion, which is caused by shear forces at the liquid–solid interface and is enhanced by geometric changes, whether cross-sectional or due to an intrinsic object such as a catheter.[22] Anatomical, functional, and fluid dynamic factors interact in a complex way whereby drug movements across and within nonhomogeneous spaces (IT and epidural) are difficult to predict and require different pharmacokinetic models.[17,23] In a study of laboring women receiving IT fentanyl, analgesia duration correlated not with CSF concentration but rather with blood pressure, emphasizing the link between the cardiovascular system, CSF oscillation, and drug spread.[24]

The CSF renewal throughout the day also has an impact, albeit unknown, on the pharmacokinetics of intrathecal drug delivery and dynamics. The clinical implications of wide variability in response to IT injections may account for a substantial portion of the discrepancies observed between single injections and continuous infusions.[25] A common assumption is that, for a given daily dose, the therapeutic effect is diminished with lower flow rate of higher drug concentrations. This intuitive belief is based on a number of anecdotal and mostly unpublished observations that are contradicted by two recently published randomized, controlled studies. In patients with complex regional pain syndrome (CRPS)-related dystonia, van der Plas et al[26] showed that, when the daily dose of baclofen was maintained, a fourfold increase in flow rate had no effect on dystonia or pain, but adverse event (AE) rates increased. Chronic pain patients given a fourfold increased flow rate in constant daily dose also showed negative effect: It did not result in improved pain scores but was associated with a significant decrease in EQ-5D quality-of-life scores.[27]

In summary, suffice it to say that the old and conventional wisdom that CSF moves from the spinal IT space to the ventricles by bulk flow is not supported by recent studies on the topic. CSF oscillations produced by the cardiac cycle are responsible for CSF fluid movement and for spread of IT delivered agents. Previous notions that agents spread in the CSF up and down are not supported by present knowledge, and the reality is that spread of slow delivery of agents is probably no more than at the tip and three levels above and below the tip. IT drug delivery is more complex than previously thought, and delivery and spread are governed by mode of delivery (bolus vs. continuous, slow vs. fast), the physical-chemical properties of the agent delivered (hydrophilic vs. lipophilic), cardiac output/heart rate, intrathecal obstructions such as membranes and tumors, position of the patient at any point in time, and position of the catheter within the IT space. See **Table 38.1** for the physicochemical properties of frequently delivered IT agents.

Table 38.1 Partition coefficients: the higher the coefficient, the greater the lipophilicity, and the lower the coefficient, the greater the hydrophilicity

Drug	Partition coefficient	References
Morphine sulphate	(Octanol/water), 1.42 @ pH 7.4	Infumorph 200-package insert, Baxter International
Hydromorphone HCL	(Octanol/water) 1.23	*Neural Blockade in Clinical Anesthesia and Management of Pain*, Issue 494 by Michael Cousins, Phillip O. Bridenbaugh, Lippincott Williams and Wilkins 1998
Clonidine	7.1	Hayek et al. Seminars in Pain Medicine 2003;1(4):238–253
Ziconotide	XLogP-10.3	Ragawski et al. Neurotherapeutics 2009;6(2):344–351
Bupivacaine HCL	*n*-Heptane/water 27.5	*Neural Blockade in Clinical Anesthesia and Management of Pain*, Issue 494 by Michael Cousins, Phillip O. Bridenbaugh, Lippincott Williams and Wilkins 1998
Baclofen	0.1	Hayek et al. Seminars in Pain Medicine 2003;1(4):238–253
Fentanyl citrate	813	*Neural Blockade in Clinical Anesthesia and Management of Pain*, Issue 494 by Michael Cousins, Phillip O. Bridenbaugh, Lippincott Williams and Wilkins 1998
Sufentanil citrate	1788	*Neural Blockade in Clinical Anesthesia and Management of Pain*, Issue 494 by Michael Cousins, Phillip O. Bridenbaugh, Lippincott Williams and Wilkins 1998

Source: Reprinted with permission of Deer.[50]

Technique

An implanted system for the delivery of IT medication consists of an implanted pump and catheter system, either a single catheter including the subarachnoid and subcutaneous portions or a two-piece catheter system including the subarachnoid portion and separate subcutaneous portion connected with an implanted connector. The choice of catheter system is determined by the preference of the implanter. Prior to placement of a permanent catheter and pump system a trial for IT delivery of either baclofen or analgesic medication is usually but not always performed. Trials for IT delivery of agents can be performed by single-shot CSF delivery of the agent, by continuous infusion of the agent via a temporary and externalized IT catheter, or by delivery of the agent through a permanent and internalized catheter subcutaneously connected to an externalized catheter and external pump.[28] There is no agreement as to how a trial should be performed; however, a recent expert panel recommends the following algorithm for trialing of patients for IT therapies, and also states that not all patients need to undergo a trial of IT therapy. These authors state, "trialing may not be appropriate for all patients. In some cases, socioeconomic factors may be involved in the decision of whether to forgo trialing. Furthermore, time constraints associated with terminal illnesses, such as cancer, can make trialing counterproductive and unnecessary. Trialing may also be unnecessary and/or detrimental in some nonmalignant conditions, such as cerebral palsy, or in patients who have had a stroke" (see **Fig. 38.1**).

Today there are several options for programmable pumps and catheters approved by the FDA, including Medtronic, Inc.'s (Minneapolis, MN) SynchroMed II pump, Flowonix's Prometra pump (Mt. Olive, NJ, USA), and Codman's Medstream pump (Depuy Orthopedics, Warsay, IN, USA) (see **Fig. 38.2**).

Positioning and Surgical Preparation of the Patient for Catheter Placement

Preoperative antibiotics covering skin flora are recommended for the prevention of perioperative infections.[29] If the trial for IT therapy was performed either by single-shot injection of an agent, continuous infusion of agent(s) using a temporary catheter, or continuous infusion of agent(s) using a permanent catheter, the patient, after induction of general anesthesia or regional anesthesia—depending on the preference of surgeon, the patient, or both—is placed in either the left or right lateral decubitus position for placement of the IT catheter and implantable pump, with the intended pump site toward the ceiling of the operating room. An axillary roll is placed

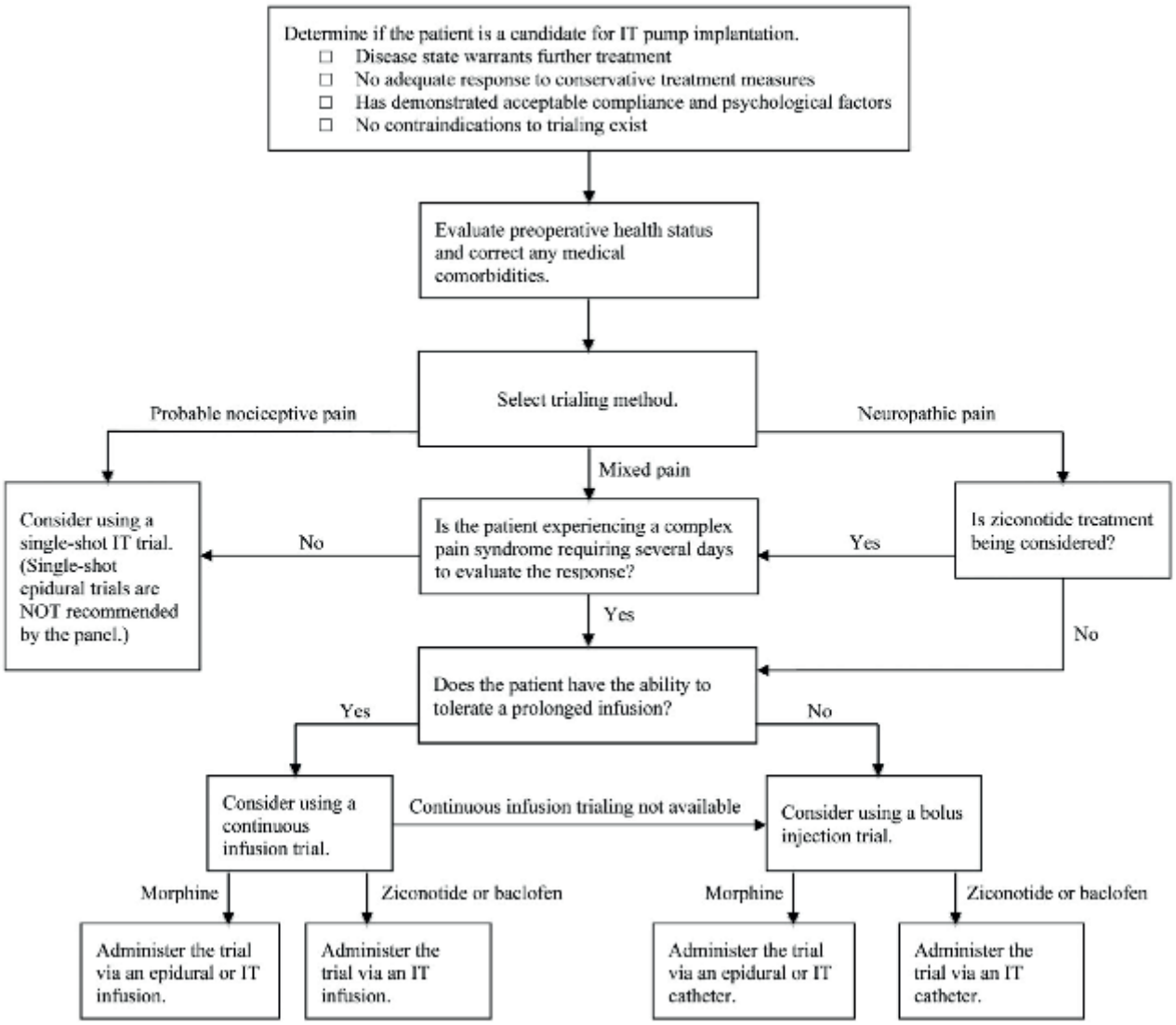

Fig. 38.1 Trialing algorithm for IT (intrathecal) analgesia. (Reprinted with permission of Deer et al.[28]

to relieve traction and pressure on the brachial plexus, and padding is placed under and between all bony protuberances. The arms are placed away from the surgical sites. The authors use the "praying mantis" position of the arms with a pillow between the upper and lower arms, paying careful attention to leave the endotracheal tube free for observation and emergency. Padding is placed beneath the lower knee and ankle, as well as between the legs. The patient is then secured to the table using either wide cloth tape or a "bean bag" security system. Either way, security must not encroach upon the surgical site.

Once secured to the table in the appropriate position, the patient is prepped and draped according to the customary process of the operating room and surgeon. Placement of the catheter system requires intraoperative fluoroscopy for both safety of the patient and to aid in identifying bony landmarks for catheter placement. Surgeons and operative personnel should take appropriate and recommended precautions for use of fluoroscopy. Using fluoroscopy, before prepping the patient, the skin is marked for intraoperative placement of incision for catheter placement and pump placement.

a b c

Fig. 38.2 Implantable programmable pumps. (**a**) Prometra from Flowonix. (**b**) Medstream (courtesy of Codman Neuro). (**c**) SynchroMed II by Medtronic (reprinted with the permission of Medtronic, Inc. ©2012).

If the trial used a temporary catheter, then that catheter should have been removed prior to the permanent operation and a new incision made in the midline or paramedian to the vertebral body, the apex of the incision being one level below the level of the dura that the needle will enter. If the trial used a permanent catheter, then the externalized portion of the trial catheter should be "prepped" out of the sterile surgical field. The surgical site for placement of the trial catheter is then opened to reveal the connection between the internalized and externalized catheter. The two catheters are disconnected and the internalized catheter end is clamped to prevent loss of CSF. The externalized catheter is gently pulled by a nonscrubbed staff member from under the drapes and discarded. The incision should be made large enough for anchoring of the catheter and carried down to the supraspinous fascia. A pocket is created by undermining the edges.

Care must be taken not to place the needle intraoperatively over the spinal cord to prevent needle placement into the spinal cord. If circumstance requires placement of an IT catheter directly over the spinal cord, then safety requires that the catheter be placed directly through a mini-laminotomy and visualization of the dura and cord. A narrow, greater than 60° angle, using a paramedian approach of the 17-gauge epidural needle, is recommended for ease of catheter placement and advancement and to prevent kinking and damage to the catheter within the IT space (see **Fig. 38.3**). **Fig. 38.4** shows a fluoroscopic technique introduced by Haddadan and Krames to prevent multiple attempts and failures of placement of the IT catheter.

Under fluoroscopic guidance, the catheter is threaded through the needle to the desired spinal level, determined by pain complaint and lipophilicity of agent used (see **Table 38.1**). The catheter should pass easily through the needle. If resistance to advancement is encountered, the catheter should be carefully retracted *slowly* through the needle to prevent injury or tearing of the catheter. If resistance to pulling the catheter back is encountered and the catheter is not in optimal position, the surgeon should weigh the risks and benefits of removing and replacing the entire catheter and needle, with full awareness that removal means an unnecessary hole in the dura with its attendant complications of dural leak.

There is no firm agreement as to where the catheter tip should be placed; however, Krames recommends that the catheter be placed as close to the area of the spinal cord that is processing the patient's pain as possible[30] to allow for the use of both lipophilic and hydrophilic agents (see **Table 38.1**). Good rules for catheter tip placement are that the catheter tip should be placed midspine for generalized pain as in multiple metastases from cancer pain, at the area of the spinal cord that is processing a single pain site, high in the cervical spine for head and neck pain, at midthoracic spine for spasticity of the lower extremities, high in the cervical spine for spasticity due to quadriparesis, and high in the cervical spine for dystonia.[31]

Once the catheter tip is placed in the optimal position, the needle is removed and the catheter is anchored to the fascia using the anchor of choice for the catheter selected by the surgeon. To prevent inadvertent removal of the catheter a strain loop should be created between the anchor and the pump in the pocket used for placement of the IT catheter. The authors use a permanent catheter trial; therefore, all old concentration of drug used during the trial is allowed to drain from the end of the catheter by allowing backflow of CSF. This usually amounts to less than 0.25 mL. The end of the catheter is again clamped to prevent further CSF leak.

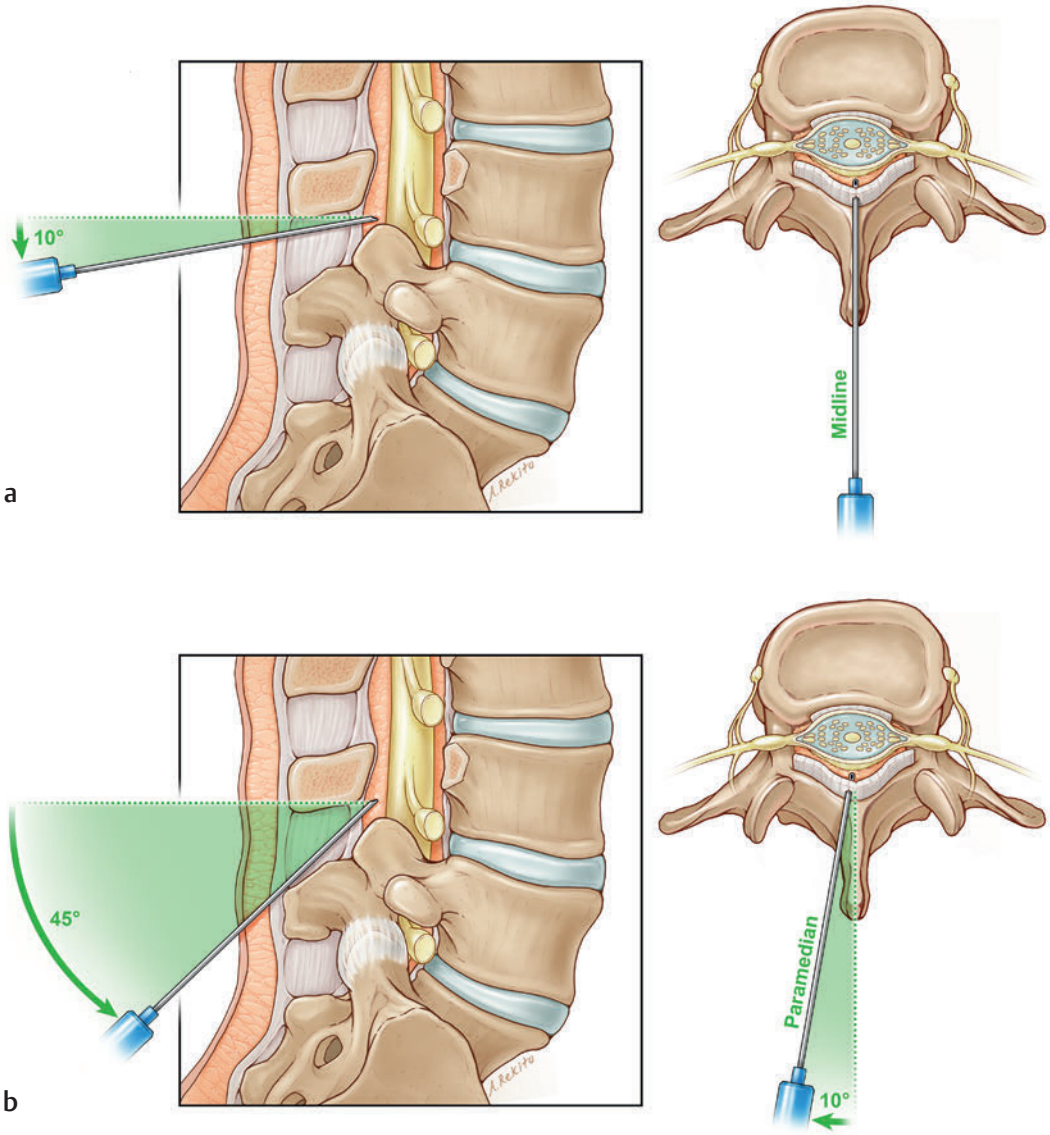

Fig. 38.3 (**a, b**) Paramedian approach to spinal canal.

Pump Placement

The pump is placed subcutaneously in the upper quadrant of the abdomen into a surgically created pocket and should be away from the iliac crest, the bladder, and previous incision sites. The choice of site for the pump, size of the pump, and cosmetic concerns should be discussed with the patient before surgery. There should be no surprises for the patient. The incision and created pocket should be just large enough for the pump of choice and no larger. These authors choose to use a pump with suture loops so that the pump can be anchored to the fascia within the pocket.

Once the pocket is created, a single-piece catheter is tunneled from the back incision to the pump pocket either using one pass in thin patients or via an intervening small, midflank stab wound in heavier patients. A provided catheter passer is used. If a two-piece catheter system is used, then the subcutaneous portion of the catheter system is tunneled from the pump pocket to the back pocket and connected to the IT portion of the system using a provided-for connecter and strain relief by the manufacturer used. The authors allow CSF

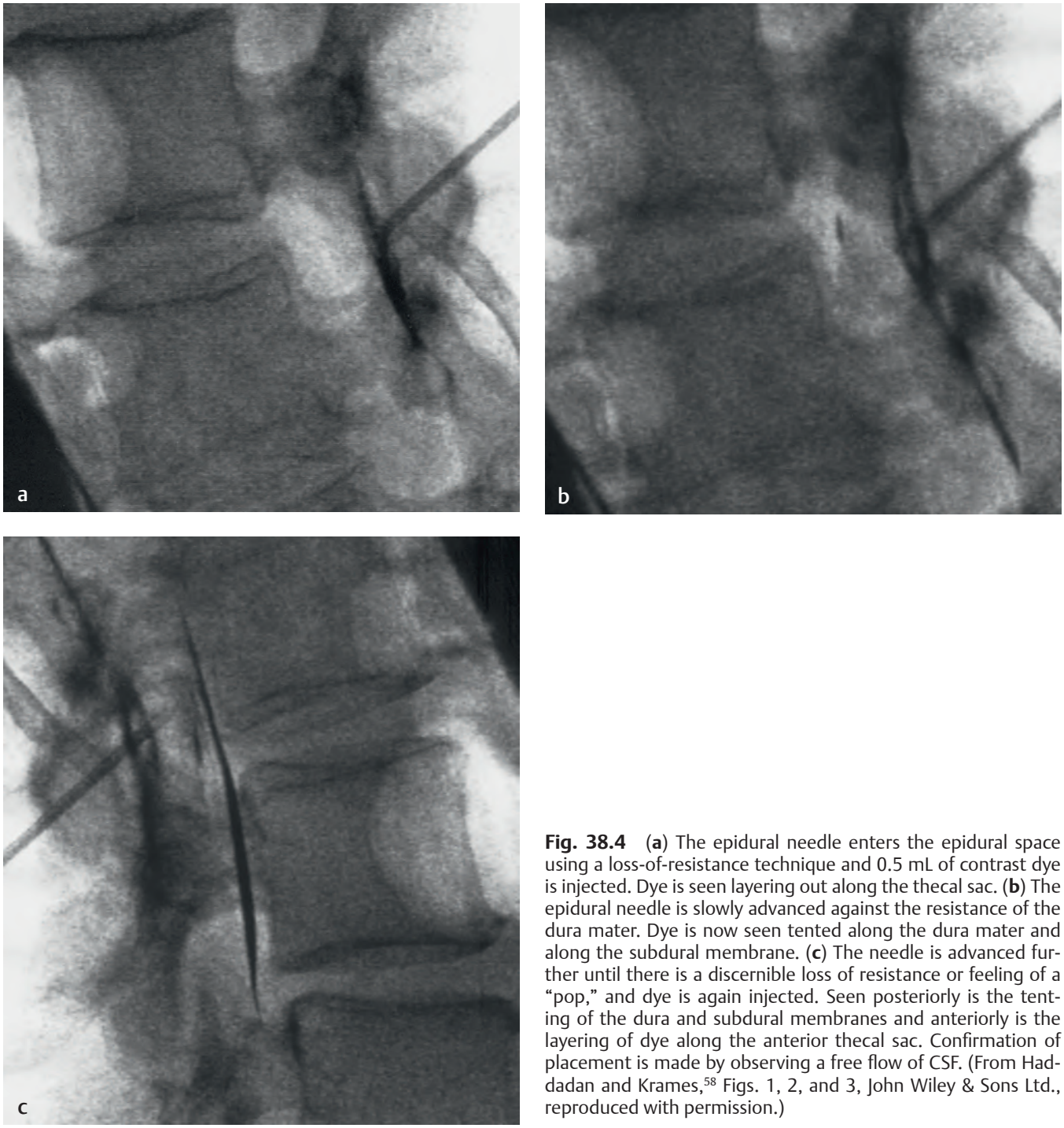

Fig. 38.4 (**a**) The epidural needle enters the epidural space using a loss-of-resistance technique and 0.5 mL of contrast dye is injected. Dye is seen layering out along the thecal sac. (**b**) The epidural needle is slowly advanced against the resistance of the dura mater. Dye is now seen tented along the dura mater and along the subdural membrane. (**c**) The needle is advanced further until there is a discernible loss of resistance or feeling of a "pop," and dye is again injected. Seen posteriorly is the tenting of the dura and subdural membranes and anteriorly is the layering of dye along the anterior thecal sac. Confirmation of placement is made by observing a free flow of CSF. (From Haddadan and Krames,[58] Figs. 1, 2, and 3, John Wiley & Sons Ltd., reproduced with permission.)

to drain to the end of the entire catheter system before connecting to the pump. The catheter system is then connected to the prepared (to manufacturer's specifications) pump before placement into the pocket.

Once the catheter is secured to the pump and the pump is placed into its pocket and the strain loop is created within the back pocket, both pockets are copiously irrigated with a sterile saline antibiotic solution and closed to the surgeon's specifications for closure. The incisions are appropriately dressed before leaving the operating room.

At this juncture, attention must be made to programming the pump, with consideration of CSF dead space within the catheter system according to recommendations of the manufacturer of the pump (see **Fig. 38.5**).

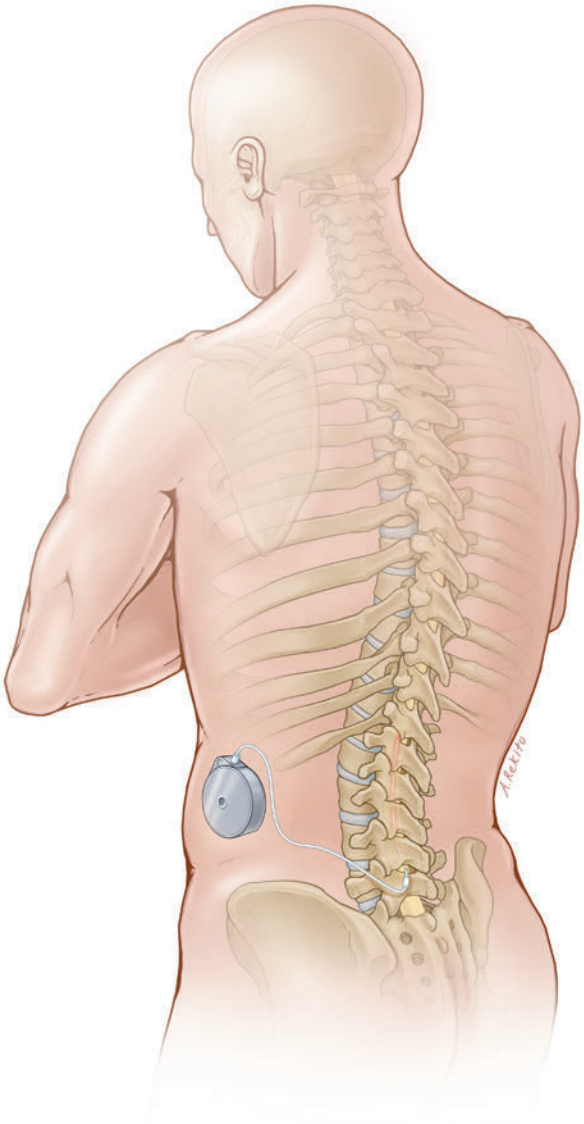

Fig. 38.5 A pump within its abdominal pocket and catheter tunneled to the intrathecal spinal space.

Risk Management and Complications of IT Therapy

Intraoperative risks include bleeding, damage to nerves and nerve rootlets, spinal cord damage and attendant neurologic sequelae, including paresis, bowel and bladder dysfunction, paralysis, neuropathic pain (including complex regional pain syndrome [CRPS]), postspinal headache, blindness, deafness, epidural hematoma, subdural hematoma,[32] epidural abscess, meningitis, wound infection, new back pain, and even death. These complications and risks should be discussed with the patient before proceeding with a trial, and informed consent should be obtained. Intraoperative management should be performed with the intent of minimizing the risk of intraoperative complications and postoperative complications of the implanted system and delivery of drugs, including programming complications, development of IT granuloma and neurologic sequelae of the granuloma, myelitis, and respiratory complications. For a more in-depth discussion of the problems and management of the risks and complications of IT therapy, see Follett et al,[29] Naumann et al,[33] Deer et al,[34] and Taira et al.[35]

The most-feared postimplantation complication of IT analgesic infusion is the development of IT granuloma, an intraspinal and nonmedullary granulomatous mass (see **Fig. 38.6**). Granulomatous masses, almost always at the tip of implanted IT catheters, are related to high doses and high concentrations of analgesic opioids, including morphine and other, nonmorphine opioids[36,37]; are found in large animals (e.g., dogs, sheep) and humans; are characterized as distinct, globular, or spheroid collections of macrophages, plasma cells, eosinophils, or lymphocytes[38–43]; are aseptic[44] as defined by staining or culture; and almost always arise from the arachnoid layer of the meninges and not from neuronal tissue of the spinal parenchyma. IT opioid-induced granulomas are not dependent on opioid receptor activation.[45] Instead, migration of inflammatory cells, most likely mast cells, from the local meningeal vasculature appears to be an important component of granuloma formation.[20] For a more in-depth discussion of the diagnosis and management of IT tip granuloma, refer to the recommendations regarding IT granulomas from the Polyanalgesic Conference 2012.[46]

The signs and symptoms of IT granuloma are listed in the accompanying box.

Signs and Symptoms Associated with Granuloma

- New or different sensory symptoms (e.g., numbness, tingling, burning, hyperesthesia, hyperalgesia, hypothesia, anesthesia)
- New occasional or intermittent bowel or bladder sphincter dysfunction
- New motor weakness, change in gait, or difficulty walking
- Any neurologic symptoms or signs that differ from baseline (e.g., reflex changes, clonus)
- Change in the character, quality, or intensity of pain
- The need for frequent or large escalations of the daily drug dose to maintain the analgesic effect
- Only temporary alleviation of increasing pain after rapid dose escalations
- Reports of new radicular pain, especially at or near the dermatomal level of the catheter tip

(Reproduced with permission of Deer et al.[46])

The recommendations of this panel for the prevention and detection of IT granuloma is presented in the next box. A treatment algorithm for IT granuloma is presented in **Fig. 38.7**. Present recommendations for dose and concentration limits are presented in **Table 38.2**.

Prevention and Screening for IT Granuloma

Prevention

1. Use the lowest effective concentration and dose of IT opioid agents, especially of morphine sulfate.
2. Use bolus dosing instead of continuous infusion for IT drug administration.
3. Consider placing the tip of the intraspinal catheter in the lumbar thecal sac, below the conus medullaris.
4. Implement adjuvant therapy with nonopioid analgesics if concerned about granuloma formation.
5. Switch from IT opioid therapy to ziconotide if concerned about a recurrence of granuloma.

Screening and Detection

1. Take a patient history and perform physical examinations on patients receiving IT opioid or baclofen therapy at least every 3 months.
2. Routinely monitor patients receiving opioids or baclofen for prodromal clinical signs or symptoms of granuloma.
3. Monitor the yearly rate of increase in drug dose.
4. Educate clinicians and radiologists about the radiological signs of granuloma.

(Reproduced with permission of Deer et al.[46])

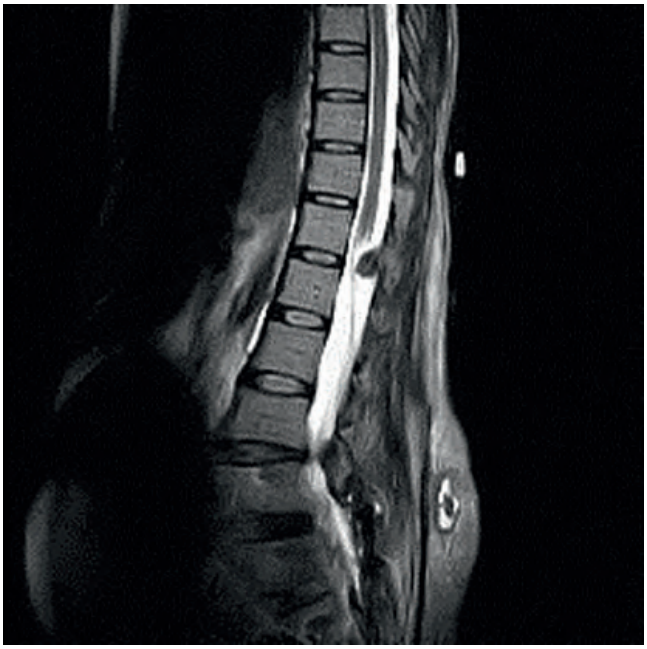

Fig. 38.6 Presence of IT granuloma. (Reprinted with permission of Deer et al.[46])

Table 38.2 Recommended maximum concentration and dose of IT agents to prevent IT granuloma

Drug	Maximum concentration	Maximum dose per day
Morphine	20 mg/mL	15 mg
Hydromorphone	15 mg/mL	10
Fentanyl	10 mg/mL	No known upper limit
Sufentanil	5 mg/mL	No known upper limit
Bupivacaine	30 mg/mL	10
Clonidine	1000 µg/mL	30–600 µg/d
Ziconotide	100 µg/mL	19.2 µg/d

Source: Reprinted with permission of Deer et al.[50]

Indications for IT Therapy

In 1993, because there were no published studies comparing systemic administration of opioids with the IT delivery of opioids, Krames stated that patients with nonmalignant pain or cancer pain who failed appropriate long-acting systemic administration of oral opioids (too many side effects) and who had greater than 50% reduction of pain during a trial of IT analgesic agents were candidates for a permanent IT administration as long as there were no contraindications, including psychological barriers, bleeding disorder, and failure to understand the therapy.[30] However, in 2002 Smith et al[47] performed a multicenter study comparing conventional medical management (CMM) of cancer pain with IT therapy of analgesic medication through and implantable drug delivery system (IDDS) for cancer pain. Sixty of 71 IDDS patients (84.5%) achieved clinical success compared with 51 of 72 CMM patients (70.8%, $p = 0.05$). IDDS patients more often achieved >20% reduction in both pain VAS (verbal analogue scale) and toxicity (57.7% [41 of 71] vs. 37.5% [27 of 72], $p = 0.02$). The mean CMM VAS score fell from 7.81 to

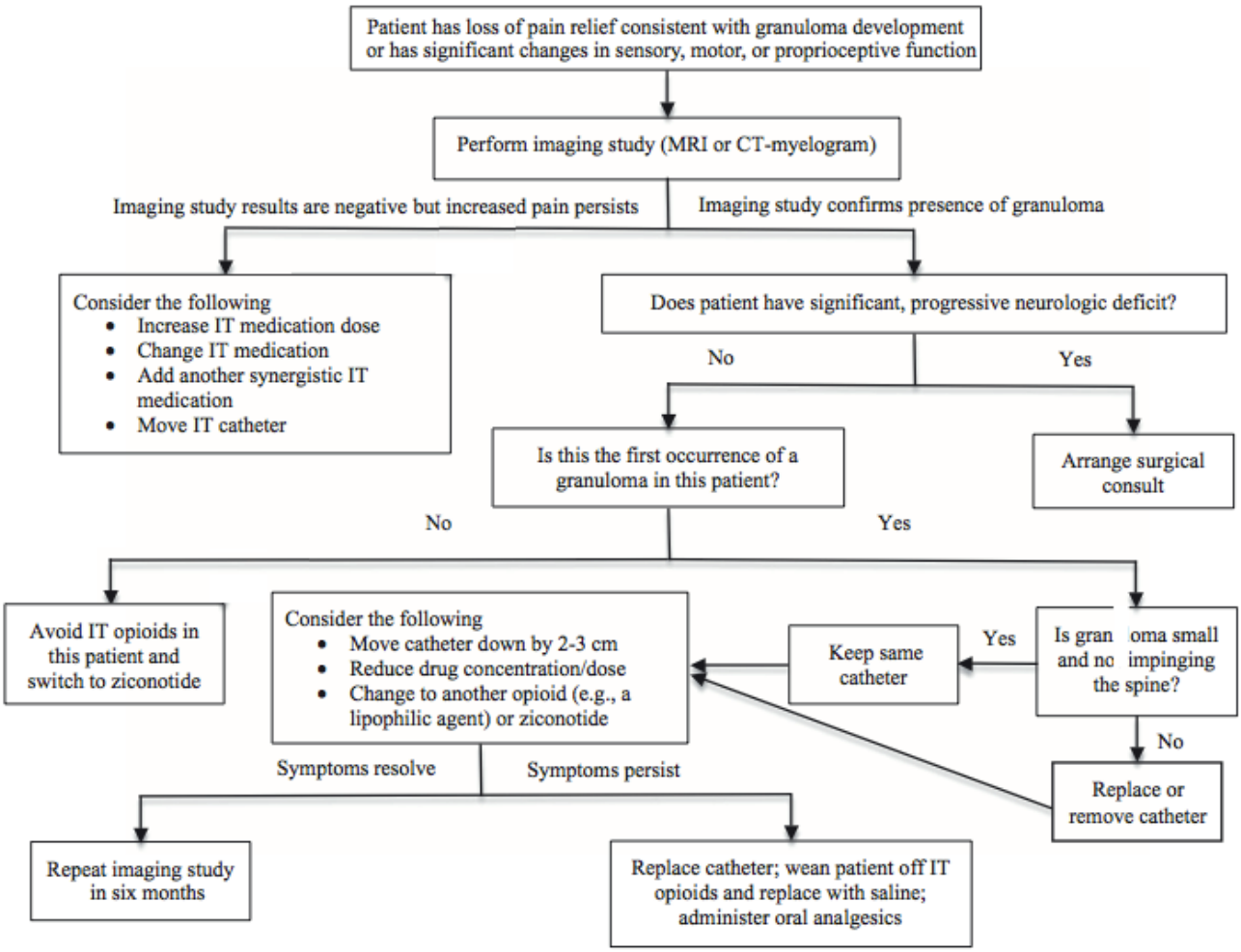

Fig. 38.7 Treatment algorithm for IT granuloma. MRI, magnetic resonance imaging; CT, computed tomography; IT, intrathecal. (Reprinted with permission of Deer et al.[46])

4.76 (39% reduction); for the IDDS group, the scores fell from 7.57 to 3.67 (52% reduction, $p = 0.055$). The mean CMM toxicity scores fell from 6.36 to 5.27 (17% reduction); for the IDDS group, the toxicity scores fell from 7.22 to 3.59 (50% reduction, $p = 0.004$). The IDDS group had significant reductions in fatigue and depressed level of consciousness ($p < 0.05$). IDDS patients had improved survival, with 53.9% alive at 6 months compared with 37.2% of the CMM group ($p = 0.06$). The authors concluded that IDDSs improved clinical success in pain control, reduced pain, significantly relieved common drug toxicities, and improved survival in patients with refractory cancer pain compared with CMM.

Today decisions on who is indicated for IT therapy must be made by the physician and patient, considering recommendations from the literature and reimbursement protocols of third parties. It is clear that good outcomes depend on good patient selection, and good patient selection should start with an appropriate psychological workup of the patient (see **Fig. 38.8**).

Opioid and Nonopioid IT Analgesia for the Control of Pain

Common chronic, nonmalignant disease states and diagnoses for which IT drug delivery is indicated include neuropathic pain syndromes (e.g., thalamic syndrome, spinal cord injury, diabetic neuropathy, postherpetic neuralgia), spinal stenosis, radicular pain from failed back surgery syndrome, complex regional pain syndrome, osteoporosis, compression fractures, pancreatitis, phantom limb pain syndrome, and other disorders caused by injury or irritation to the nervous system.[48] Unlike pain associ-

Fig. 38.8 Algorithm for psychological evaluation of patients for IT therapy. (Reprinted with permission of Deer et al.[50])

ated with terminal illness, noncancer pain patients tend to have longer life spans and require extended therapy that can range from months to years.[49]

Present IT analgesics approved by the FDA include morphine and ziconotide (Prialt) and the antispasmodic medication baclofen for central spasticity. Other analgesic opioid agents that have been used include fentanyl, sufentanil, methadone, hydromorphone, and meperidine/pethidine. Nonopioid analgesic medications used for IT therapy include ziconotide, the local anesthetics, bupivacaine, lidocaine, ropivacaine and tetracaine, the a_2-agonist clonidine, ketamine, droperidol, baclofen, gabapentin, midazolam, and various others. Agents that have shown neural toxicity and are not recommended for IT use include meperidine, methadone, tramadol, tetracaine, lidocaine, dexmedetomidine, and *N*-methyl-D-aspartate (NMDA) antagonists including ketamine, droperidol, midazolam, methylprednisolone, and ondansetron.[27] For a more complete discussion of this topic see Deer et al[50] and Penhollow et al.[48]

Opioids administered neuraxially act at receptors in the substantia gelatinosa of the spinal cord dorsal horn to yield dose-dependent analgesia. Opioids may act through multiple mechanisms, including inhibition of presynaptic neurotransmitter release from primary afferents via presynaptic inhibition of calcium channels. Furthermore, opening of G protein gates, K+ channels in the central nervous system (G protein–regulated inwardly rectifying K+ channels [GIRKs]) may lead to postsynaptic neuronal hyperpolarization.[48,51]

Ziconotide is an *N*-type calcium channel antagonist that is effective for the treatment of neuropathic, nociceptive, and mixed neuropathic–nociceptive pain. It is a synthetic derivative of a short peptide extracted from the venom of predatory cone snails (*Conus geographicus*, *Conus magus*) and is a member of a newly described chemical family called the conopeptides. Ziconotide blocks the *N*-type calcium channel located on the presynaptic terminal of dorsal horn C fibers. By blocking calcium entry into the presynaptic nerve terminal, ziconotide prevents the release of neurotransmitters into the synapse. Oxidized ziconotide is less active than ziconotide, so a pump containing a combination of ziconotide and another medication may need to be refilled more often. For this reason, the package insert for ziconotide does not recommend using the drug in combination with other drugs. However, a vast amount of clinical experience is surfacing on the use of ziconotide in combination with a variety of drugs with no adverse events reported.[48,50,52]

Baclofen reduces spasticity and spasms by binding to gamma-aminobutyric acid ($GABA_B$) receptors and inhibiting the release of excitatory neurotransmitters, thereby inhibiting monosynaptic and polysynaptic spinal reflexes.[15] Baclofen is not taken up into the brain tissue GABA system, and very little reaches the fourth ventricle to have any effect on respiratory centers.[53] Instead, IT baclofen has a selective effect on spinal neurons, which control reflex excitation of motor neurons, sparing other sensory and motor input.[54,55]

Present Recommendations for the Rational Use of IT Polyanalgesia

There have been four polyanalgesic conference recommendations for the rational use of IT agents based on a review of evidence from the literature and a consensus of expert opinion regarding the topic.[5,50,56,57] The present recommendations for the rational use of IT agents were presented in Polyanalgesic Conference 2012.[50] This panel of experts recommended different pathways for neuropathic and nociceptive pain with special considerations for cancer pain. Some recommendations have already been acknowledged. **Tables 38.3** and **38.4** outline the present recommendations for use of analgesic agents.[50]

Table 38.3 2012 polyanalgesic algorithm for IT therapies for nociceptive pain

Line 1	Morphine, ziconotide, morphine + bupivacaine
Line 2	Hydromorphone + bupivacaine, morphine or hydromorphone + clonidine
Line 3	Clonidine, ziconotide + opioid, fentanyl, fentanyl + bupivacaine or fentanyl + clonidine
Line 4	Opioid + clonidine + bupivacaine, bupivacaine + clonidine
Line 5	Baclofen

Line 1: Morphine and ziconotide are approved by the U.S. Food and Drug Administration (FDA) for IT therapy and are recommended as first-line therapy for nociceptive pain. Hydromorphone is recommended on the basis of widespread clinical use and apparent safety. Fentanyl has been upgraded to first-line use by the consensus conference.

Line 2: Bupivacaine in combination with morphine, hydromorphone, or fentanyl is recommended. Alternatively, the combination of ziconotide and an opioid drug can be employed.

Line 3: Recommendations include clonidine plus an opioid (i.e., morphine, hydromorphone, or fentanyl) or sufentanil monotherapy.

Line 4: The triple combination of an opioid, clonidine, and bupivacaine is recommended. An alternative recommendation is sufentanil in combination with either bupivacaine or clonidine.

Line 5: The triple combination of sufentanil, bupivacaine, and clonidine is suggested.

Source: Reprinted with permission of Deer et al.[50]

Conclusion

In this chapter we present the relevant anatomy of the spinal canal as it pertains to IT therapies, the indications for IT analgesia, the techniques of implantation, the risks and complications of IT analgesia, and up-to-date recommendations for the rational use of analgesic medications via the IT space. This chapter is meant as a short overview, and the reader is welcome to delve into the relevant literature of IT analgesia. Present knowledge is summarized by the Polyanalgesic Conference 2012 and the recent updates of prior conferences 2000, 2004, and 2007.

Table 38.4 2012 polyanalgesic algorithm for IT therapies for neuropathic pain

Line 1	Morphine, ziconotide, morphine + bupivacaine
Line 2	Hydromorphone + bupivacaine, morphine or hydromorphone + clonidine
Line 3	Clonidine, ziconotide + opioid, fentanyl, fentanyl + bupivacaine or fentanyl + clonidine
Line 4	Opioid + clonidine + bupivacaine, bupivacaine + clonidine
Line 5	Baclofen

Line 1: Morphine and ziconotide are approved by the U.S. Food and Drug Administration (FDA) for IT therapy and are recommended as first-line therapy for neuropathic pain. The combination of morphine and bupivacaine is recommended for neuropathic pain on the basis of clinical use and apparent safety.

Line 2: Hydromorphone, alone or in combination with bupivacaine or clonidine, is recommended. Alternatively, the combination of morphine and clonidine may be used.

Line 3: Third-line recommendations for neuropathic pain include clonidine, ziconotide plus an opioid, and fentanyl alone or in combination with bupivacaine or clonidine.

Line 4: The combination of bupivacaine and clonidine (with or without an opioid drug) is recommended.

Line 5: Baclofen is recommended on the basis of safety, although reports of efficacy are limited.

Source: Reprinted with permission of Deer et al.[50]

Editor's Comments

The use of intrathecal (IT) analgesic therapy has waned over the past few years, to the extent that few neurosurgeons are engaged in this activity. Despite this, the possibility of IT analgesia should still be entertained in select diagnoses. Although IT therapy is probably underutilized for pain related to cancer, most common clinical indications are in the domain of noncancer pain.

The indications for IT therapy vary with the agent infused. Opiates (morphine, hydromorphone, fentanyl, sufentanil) are generally recommended for nociceptive pain, whereas nonopiates such as clonidine and ziconotide would be preferable for neuropathic pain. Mixing agents within the pump reservoir, particularly at the inception of therapy, has the disadvantage of locking in a medley of drugs with a fixed concentration ratio; this leaves no possibility of altering the administration of one drug while holding another constant, at least until a new admixture can be injected into the pump reservoir.

The method of intrathecal trial is one area of variability in practice, as mentioned in this chapter. In my opinion, the potential for an intrathecal trial is one of the major advantages of this therapy, and should be conducted in every case. Our practice has been to use a "single-shot" trial for opiates, and this is certainly more expeditious than a prolonged intrathecal or epidural catheter trial, which requires hospitalization.

Intrathecal analgesic administration is a complex therapy, and it is easy to underestimate the potential for problems. For example, intrathecal opiate administration is almost universally accompanied by endocrinopathy in men and women, with decreased gonadotropins in both genders and, in particular, decreased testosterone in men. Withdrawal from intrathecal opiates can occur for a number of reasons, including pump or catheter malfunction, which occurs at a 10% rate every year. Intrathecal opiate withdrawal is painful and distressing but rarely fatal. Baclofen has been used intrathecally for pain control, as the authors mention, and withdrawal from this agent *has* been occasionally fatal.

Finally, every neurosurgeon should be familiar with the potential for catheter granuloma formation with IT opiate administration. This seems to be a sterile chemical irritation of the leptomeninges, related to the *concentration* of the delivered agent, particularly when the opiate is given in the range of hundreds of milligrams per day. Once a focal arachnoiditis develops, the distribution of the infused drug becomes even more limited, and the local concentration rapidly escalates in a regenerative process producing more chemical meningitis, and even more limited drug distribution, eventually leading to a frank granuloma. Drug concentration does appear to be the culprit, since delivery of drugs at levels of hundreds of micrograms per day (e.g., baclofen) essentially never produces catheter granulomas.

The authors outline the hallmarks of the development of a catheter granuloma. Neurosurgeons should know that once a diagnosis of a catheter granuloma has been made by MRI (magnetic resonance imaging), a complete resection is extremely ill-advised. Most of these granulomas occur in the thoracic area, where CSF (cerebrospinal fluid) flow is limited, and low-flow ("stagnant") areas are common. If the granuloma is producing a neurologic deficit, it can be decompressed by debulking, but should not be dissected off of the spinal cord or nerve roots. This can result in a severe neurologic deficit. Smaller, and minimally symptomatic, granulomas can be treated by simple withdrawal of the catheter from the granuloma, with or without replacement of the catheter at a different location. The granuloma will then regress, and the spinal cord will be decompressed. Due to the volume and flow of CSF in the lumbar theca, placement of the catheter in this area either primarily, if possible, or during catheter revision has a very low incidence of granuloma formation.

Intrathecal drug administration still represents a unique portal of entry into the blood–brain barrier, one that obviates both systematic parenteral administration and the enteral route. It is likely that some forms of advanced analgesic therapy will be able to leverage this modality to produce clinically significant analgesia. Neurosurgeons should continue to be involved in these procedures, particularly as the technology and pharmacology improve.

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39 Intrathecal Opioids: Patient Selection and Implant Technique

Daryoush Tavanaiepour and Robert M. Levy

As with most interventional therapies for chronic pain, in the administration of intrathecal opioids, careful patient selection appears to be the greatest and possibly the only significant predictor of success.

The precise variables that predict the success or failure of intrathecal opioids for the treatment of intractable pain remain poorly defined. Several factors that may indicate or contraindicate intraspinal analgesic treatment must be taken into account, and these are outlined in the accompanying box. In clinical practice, it is a valuable exercise to review these factors systematically for each patient before the decision is made to embark on chronic intrathecal opioid therapy.

Patient Selection Criteria for Chronic Intraspinal Opioid Administration

Absolute Indications
- Known physiological source of pain
- Failure of maximal medical therapy
- Favorable psychosocial evaluation
- Favorable response to intraspinal opioid trial

Relative Indications
- Nociceptive pain syndromes
- Axial/multifocal/diffuse pain syndromes

Absolute Contraindications
- Intercurrent infection
- Uncorrectable coagulopathy
- Allergy to agent to be infused

Relative Contraindications
- Intractable side effects
- Obstruction to cerebrospinal flow
- Severely limited life expectancy

Indications

Physiological Source of Pain

Prior to a trial of intraspinal opioids, it is important to ensure that a full diagnostic evaluation has been performed and that a cause for the pain has been established. If no reasonable cause for the pain is apparent after a careful history and physical examination have been performed, the probability of a significant functional component to the patient's pain becomes great, and the likelihood of long-term pain relief with intraspinal opioids falls significantly.

It is important to perform a careful pain diagnostic evaluation because many pain problems referred to the pain specialist are in fact treatable without the use of chronic interventional techniques. First, correctable causes of chronic pain must be established; direct therapy may result in pain relief. Thus, patients suffering from unrecognized peripheral nerve entrapment syndromes may have profound relief with decompression and transposition procedures; patients with neuromatous pain may benefit from neuroma excision and nerve stump implantation; and patients with significant spinal pathology may benefit from decompression or fusion procedures.

In addition to careful history taking, several features of the physical examination can aid in the diagnosis of chronic pain syndromes. Not only is it important to recognize and map regions of objective or subjective sensory loss, but it is also important to recognize abnormal sensory phenomena that accompany specific chronic pain syndromes. Thus, *allodynia,* the interpretation of a light touch stimulus as being painful, and *hyperpathia*, the interpretation of a mildly noxious stimulus as being significantly painful, are often hallmarks of neuropathic pain syndromes. The careful examination of skin temperature, sweating patterns, capillary filling time, hair growth, and possible trophic changes can indicate the presence of a sympathetically maintained pain

syndrome. The presence of focal muscle spasm with predictable patterns of referred pain on palpation may indicate a myofascial pain syndrome.

In the course of diagnostic evaluation, great value can be obtained from the use of specific local nerve blockade. It is vitally important for the surgeon either to perform the blocks or to know well the techniques used by the anesthesiologist performing the nerve blockade. By the use of small volumes of properly placed local anesthetics, the physician often can determine not only what nerves are involved in the perpetuation of the chronic pain syndrome, but also whether the somatic or sympathetic nervous system is involved and whether the pain is entirely peripheral or has a central component. These features can be remarkably important in predicting the efficacy of interventional pain procedures.

Numerous nonsurgically treated conditions are often overlooked by physicians referring patients for interventional pain therapy. Most commonly identified are myofascial pain syndromes, which may respond significantly to trigger point injections with local anesthetic, followed immediately by myofascial physical therapy directed at the affected muscle groups. Once the myofascial pain problem is appropriately treated, the residual chronic pain syndrome can be better characterized and more specifically addressed.

Failure of Maximal Medical Therapy

If a noninvasive regimen of analgesics provides satisfactory pain relief without intolerable side effects, intraspinal drug administration is not necessary. The World Health Organization (WHO) has published and widely distributed its schema for the management of pain secondary to malignancy.[1] Thus, patients with pain of malignant origin are seldom referred unless such a regimen has failed.

Failure to respect this patient selection criterion becomes an issue most often in the setting of pain of nonmalignant origin. Particularly relevant prior to the consideration of chronic intraspinal opioids is the consideration of the use of chronic oral or transdermal narcotics for pain of nonmalignant origin. Recommendations by the American Pain Society and the American Academy of Pain Medicine include the careful, regulated use of chronic narcotics for patients with pain of nonmalignant origin.[2] Thus, if oral or transdermal administration provides adequate pain relief without unacceptable side effects, intraspinal drug administration is not indicated. In routine clinical practice, oral or transdermal narcotics are given in a dose escalation paradigm until the patient achieves adequate pain relief or develops unacceptable side effects.

Thus, intraspinal narcotics should be reserved for patients in whom oral or transdermal narcotics either provide inadequate pain relief or produce truly unacceptable or uncontrollable side effects.

Favorable Psychosocial Evaluation

Although most investigators have highlighted the importance of a favorable psychosocial evaluation in the screening of potential implant candidates, wide agreement has not been reached in regard to the specific variables, their quantitation, and treatment. As part of this evaluation, most agree that both the patient and the patient's psychological and social support systems need to be evaluated. Clearly, acute psychotic illnesses and severe, untreated depression need to be diagnosed and effectively treated before consideration of surgery.

The presence or absence of medicolegal complications, such as worker's compensation or litigation, does not appear to predict outcome. Similarly, the number of prior pain-directed surgeries, the length of the chronic pain syndrome, the time away from work, or the patient's age or gender does not have clear predictive value.[3]

Pain Type: Predominance of Nociceptive Pain

Certain features of pain have been suggested as predictive of the efficacy of intraspinal morphine therapy. Intraspinal opioids are particularly effective in the presence of predominantly nociceptive chronic pain syndromes. Arner and Arner[4] placed in rank order the types of pain responding to epidural morphine administration in their experience. This ranking is presented in the designated box,

Whereas neuropathic pain syndromes may require higher doses of intrathecal opioids and ulti-

Ranking List of Different Cancer-Related Pain Types with Regard to the Likelihood of Relief with Epidural Morphine Treatment

1. Somatic, continuous
2. Visceral, continuous
3. Somatic, intermittent
4. Visceral, intermittent
5. Neurogenic, intermittent and continuous
6. Cutaneous (cancerous ulcer or fistula)

(From Arner and Arner.[4])

mately may be better treated with nonopioid intraspinal analgesics, the presence of neuropathic pain is not an absolute contraindication for evaluating intraspinal opioid therapy.

Pain Distribution: Predominance of Axial/Diffuse Pain

For axial pain syndromes, especially those involving the low back or neck, or for multifocal intractable pain syndromes, intraspinal opioids are particularly effective and should be considered. Regarding appendicular neuropathic pain states, spinal cord stimulation is particularly effective in this setting. Only after spinal cord stimulation has been attempted and failed should intraspinal opioids be investigated for solely appendicular pain syndromes.

Favorable Response to Intraspinal Opioid Trial

The response to acute intraspinal administration of analgesic agents is generally regarded as an excellent indicator of long-term efficacy.[5] The inability to achieve pain relief after such a trial is a contraindication to implantation. Several approaches to the trial of intrathecal narcotics have been advocated, including single versus multiple injections, administration by lumbar puncture versus indwelling catheter, epidural versus intrathecal routes, and bolus versus continuous infusion administration of the drug. Continuous epidural or intrathecal infusions are preferred over bolus administration trials because they better reflect the dynamics of chronic drug infusion and may predict the effective dose.

Attempts to control for patient bias by testing both morphine and saline and blinding the patient to which drug is being infused still do not control for the bias of the health care team. Another significant drawback to many attempts at preimplantation intraspinal opioid trials is their lack of objective measures. This subjectivity can negatively impact the validity and reliability of screening protocols.

To address these concerns, a quantitative, crossover, double-blind trial for the preimplantation screening of candidates for chronic drug infusion therapy for the control of intractable pain has been developed.[5] Application of this protocol resulted in the elimination of about 30% of potential implant candidates. Of patients whose screening trial was successful, about 70% have had good to excellent long-term pain relief. This screening paradigm appears to be both reliable and easily applied. Furthermore, the Polyanalgesic Consensus Conference (PACC) 2012, an expert panel of experienced physicians on intraspinal analgesics for chronic pain, has published a comprehensive analysis and algorithm for intraspinal opioid trials (see **Fig. 39.1** for details).[6]

Contraindications

Intercurrent Infection

Any local infection at the placement sites or the presence of systemic infection contraindicates the implantation of drug administration devices. A period of observation after completion of antibiotic therapy is recommended prior to the implantation of drug infusion devices. Furthermore, the use of perioperative and postoperative prophylactic antibiotics is recommended.

Uncorrectable Coagulopathies

Coagulopathies can complicate the procedure with the development of subcutaneous, epidural, or intradural hematomas. Significant uncorrectable coagulation disorders absolutely contraindicate the implantation of a drug infusion system.

Allergy to Infused Agent

Allergy to the analgesic agent to be infused obviously and absolutely contraindicates its use.

Intractable Side Effects

The most widely recognized side effects of intraspinal narcotics include urinary retention, pruritis, and, rarely, delayed respiratory depression. During intraspinal opioid screening, particularly with bolus administration, the clinician may observe these side effects. They are, however, only relative contraindications to chronic drug administration. With the use of lower opioid doses and chronic administration, these side effects usually resolve. The potential pain relief achieved by intraspinal opioids must be balanced against the severity of potential side effects.

Obstruction of Cerebrospinal Fluid Flow

Obstruction of cerebrospinal fluid (CSF) flow has been suggested as a relative contraindication to intraspinal drug delivery, depending on the size, location, and cause of the obstruction. In our experience, this has not been a significant problem, and patients have received excellent drug effects despite the presence of significant degrees of CSF flow obstruction. This is probably because the usual site of pain generation

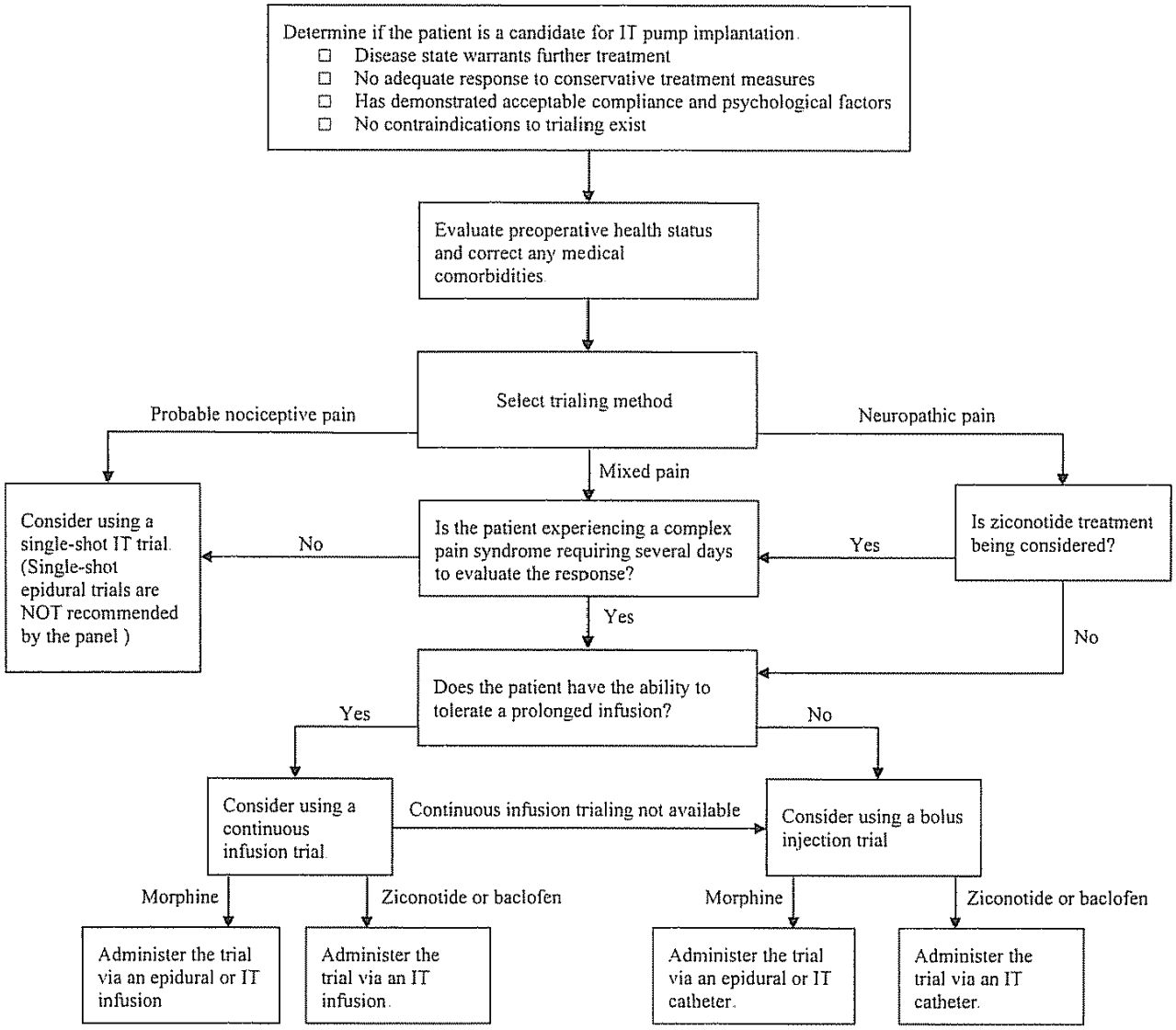

Fig. 39.1 The 2012 Polyanalgesic Consensus Conference algorithm on trialing for intrathecal (IT) drug delivery.[6]

is near the site of obstruction, so that sufficient CSF opioid concentrations are still reached at the target spinal cord site of pain transmission.

Severely Limited Life Expectancy

Whereas the expected length of life is not a contraindication to the intraspinal route of drug administration, it does bear greatly on the decision as to which method of administration to use. Thus, percutaneous epidural catheters attached to external pumps, internalized passive reservoirs and catheters requiring percutanous drug administration, patient-activated mechanical systems, constant-rate infusion pumps, and programmable infusion pumps are all options for intraspinal drug delivery.

For patients who are largely bedridden and whose life expectancy is only weeks, the expense and risk of surgical pump implantation are not indicated. Rather, these patients are well treated with a tunneled epidural catheter.

In patients with short life expectancy who are ambulatory and in whom a tunneled epidural catheter would significantly affect mobility, a subcutaneous reservoir attached to an intrathecal catheter is an excellent option

In patients with a life expectancy of greater than 3 months, implanted drug pumps become a viable option for intraspinal drug delivery. Nonprogrammable drug pumps, which deliver drug at a constant rate, are less expensive than programmable pumps and are well suited for patients in whom drug requirements are well defined and in whom frequent dose changes

are not anticipated. For patients in whom tailored drug delivery regimens are desired or in whom frequent dose changes are anticipated, the additional expense of implanted programmable drug pumps is warranted.

Surgical Technique

A detailed description of the surgical procedure can be found elsewhere.[7,8]

Preoperative Preparation

- Appropriate patient selection (see above)
- Pump preparation (programming, calibration, drug selection/preparation)
- Appropriate antibiotics
- Availability of fluoroscopy

Intraoperative Procedure

- *Patient positioning:* Lateral decubitus with right/left flank up (depending on abdominal pump insertion site), axillary role with pressure points padded
- *Pump pocket incision:* Lower right/left abdomen with consideration of iliac crest, ribcage, and patient's belt-line location. The incision should not directly overlay the final position of the pump. A subcutaneous pocket is fashioned above the rectus fascia large enough to accommodate the pump without undue tension to prevent wound dehiscence.
- *Lumbar incision:* Make a midline incision overlying the L3–4 region, approximately 4 cm in length with exposure of the lumbodorsal fascia. Develop a subcutaneous pocket sufficient to allow for anchoring and coiling of the catheter.
- *Insertion of intrathecal catheter:* Enter subarachnoid space with a Tuohy needle at a paramedian and shallow trajectory at the L2–3 or L3–4 level using fluoroscopy. Confirm CSF flow and with the bevel cephalad, advance the intrathecal catheter. Verify catheter position with fluoroscopy. With the introducer needle still in position, place a pursestring suture in the fascia and two additional sutures on opposite sides of the needle for anchoring the catheter. Carefully remove the needle and guide wire simultaneously, secure the catheter with the anchor system, and tie the pursestring suture to close the fascia around the catheter.
- *Install the pump:* Tunnel the catheter and connect the intrathecal catheter to the pump. Allow for a relaxing loop of the intrathecal catheter at the spinal fascia to accommodate for patient movement and to prevent kinking. Any excess proximal catheter is coiled beneath the pump (to prevent injury during refill or future revisions). The pump is placed within the subcutaneous pocket with the access port facing the skin. The pump is secured to the abdominal fascia using nonabsorbable sutures. The wounds are copiously irrigated with antibiotic solution and closed in layers.

A set of comprehensive and detailed recommendations to reduce morbidity and mortality related to intrathecal drug delivery system has been provided by the 2012 PACC.[9,10]

Conclusion

At present, the data concerning intraspinal opioids for pain secondary to cancer appear to be compelling and consistent, indicating a success rate of 70 to 80%. Data concerning their use in the setting of pain of nonmalignant origin are less clear and consistent, although recent unpublished findings suggest a similar efficacy of 65 to 75%. By ensuring that patient selection criteria are rigorously adhered to, the clinician may hope to expect similar rewarding outcomes.

Editor's Comments

Intrathecal drug administration holds substantial promise for the surgical management of pain, particularly in the areas of cancer-related pain and neuropathic pain.

Although the frequency of use of intrathecal opiates for cancer-related pain is unknown, my impression is that this technique is used very little. If 70 to 90% of cancer patients achieve effective pain relief using the WHO recommendations (see Chapter 28), that leaves 10 to 30% who do not. The principles of "by the mouth," "by the clock," "by the ladder," "for the individual," and "attention to detail" are sound and humane. The indications for more aggressive pain control, be it intrathecal agents or ablative surgery, would be fulfilled by the failure of that standard approach—the next step on the ladder. If even 10% of cancer patients have uncontrolled pain, why is it that the administration of intrathecal opiates has been so underutilized? There seems to be a cultural divide between oncology and surgical pain management that, in my opinion, represents a major disconnect and a major failure in our treatment of cancer.

Intrathecal opiates are still being used for the management of chronic pain not related to cancer. Their use remains somewhat controversial, and as with many surgical procedures, high-quality data to support their use is lacking. The use of opiates delivered by pump and intrathecal catheter has dwindled in the past decade, due largely to the problems of escalating doses in many patients, complications of the therapy such as catheter granulomas, and decreased funding by Medicare and other payers. Without better data, it is likely that the use of intrathecal opiates for "benign" pain will disappear entirely.

The effective treatment of neuropathic pain has been the "holy grail" of pain medicine over my entire career. Unfortunately, the pathophysiology of neuropathic pain must involve such fundamental properties of the nervous system (e.g., memory) that it has not yet been possible to develop oral analgesic agents that both relieve neuropathic pain and do not produce intolerable side effects. Intrathecal agents hold particular promise in this area. Candidate drugs will be discussed in Chapter 38.

Drs. Tavanaiepour and Levy outline patient selection and implant strategies for intrathecal drug delivery systems. The use of "pumps" for pain control is an important aspect of interventional pain management, which will only be amplified when cancer pain is more aggressively treated, and the appropriate intrathecal agent for neuropathic pain is discovered.

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Section IV.B

Procedures for Craniofacial Pain

40 Surgical Options for Facial Pain

Konstantin V. Slavin and Kim J. Burchiel

Much has been written about various surgical procedures developed to treat pain in the face. The list is long; there are at least 10 well-established surgical interventions that are commonly (or not so commonly) used to treat facial pain patients. And since surgical interventions are traditionally reserved for those who have failed medical management, the mere presence of these surgeries indicates the relative ineffectiveness of conservative (less invasive) treatments due to either unresponsiveness of the underlying condition to medications, development of eventual tolerance to initially effective regimens, or a high incidence of side effects that occur during required dose escalations.

However, it is rather obvious that if any condition has this many (surgical) treatments, and each of the surgical procedures is both effective and safe, there must be some rationale for choosing one procedure over all others in each specific clinical case. Ideally, such a rationale should be supported by high-level scientific evidence, perhaps through multiple independent, prospective, randomized, controlled studies comparing treatment modalities and weighing the benefits of each intervention against its risks and potential failures. But despite decades of widespread clinical use of most of these surgeries, the desired evidence is either weak or nonexistent, and the support for each intervention comes from anecdotal observations, retrospective (albeit quite large) case series, and uncontrolled, nonrandomized comparative evaluations.

Nevertheless, the main challenge in surgical management of facial pain is not in the overabundance of surgical approaches but in the matching of each individual patient with the most appropriate surgical intervention. The difficulty here lies in the wide variety of overlapping clinical syndromes that present with facial pain[1] and in the differential response of each syndrome to specific types of surgery. Therefore, any algorithm designed for the rational use of surgical interventions in the treatment of facial pain must start with establishing the correct diagnosis, and only after that may additional criteria be used to determine appropriate interventions and the order in which they should be offered to each patient. Ultimately, in those situations where more than one treatment option is available, the patient's preference should be taken into consideration, making the patient a part of the decision-making process.

Since our practical algorithm was published several years ago,[2] we have successfully applied it to facial pain patients presenting to us. Here we present an overview of surgical interventions and review the decision-making process used in selection of the appropriate approach.

Causes and Features of Facial Pain

Surgery for facial pain starts with establishment of the diagnosis, which may be the most difficult part of the entire treatment process. The face is the site of a wide variety of pain syndromes. Some are common, such as headaches and toothaches; some are relatively rare, like classic (typical) trigeminal neuralgia and posttraumatic trigeminal pain; and some are rarer still, for example, sphenopalatine neuralgia and glossopharyngeal neuralgia.

Central to the diagnosis of facial pain is obtaining a detailed history, with special attention to the character of pain, its distribution, triggering, the presence of remission, and response to medications. Unilateral sharp, lancinating pain limited to the territory of one or several divisions of the trigeminal nerve with short attacks and associated trigger points is characteristic of *idiopathic (typical) trigeminal neuralgia.* Other typical features of this condition are the absence of pain between attacks; frequent remissions, especially early in the course of the disease; normal neurologic examination; and a high degree of pain relief in response to oral carbamazepine.

Differential Diagnosis of Facial Pain

Trigeminal neuralgia (tic douloureux)
- Trigeminal neuralgia type I: idiopathic typical trigeminal neuralgia
- Trigeminal neuralgia type II: idiopathic atypical trigeminal neuralgia
- Secondary trigeminal neuralgia

Trigeminal neuropathic pain
- Posttraumatic trigeminal pain

Trigeminal deafferentation pain
- Anesthesia dolorosa
- Central deafferentation syndromes
  - Wallenberg syndrome
  - Thalamic syndrome

Postherpetic neuralgia

Other cranial neuralgias
- Glossopharyngeal neuralgia
- Geniculate neuralgia
- Sphenopalatine (Sluder) neuralgia
- Auriculotemporal neuralgia
- Nasociliary neuralgia

Paratrigeminal (Raeder) syndrome

Painful ophthalmoplegia (Tolosa–Hunt syndrome)

Petrous apex syndrome (Gradenigo syndrome)

Cancer-related pain

Atypical facial pain

Orofacial pain and temporomandibular joint–related pain

Headache and migraine syndromes

The cause of the idiopathic trigeminal neuralgia remains unknown; however, a great majority of patients have compression of the trigeminal nerve root by adjacent vessels, most commonly by the superior cerebellar and the anterior inferior cerebellar arteries.[3,4] This and the fact that pain was almost uniformly relieved after decompression of the root support the current belief in the importance of microvascular compression in the cause and pathogenesis of typical trigeminal neuralgia. The finding of focal demyelination in the intracranial trigeminal nerve root associated with prolonged vascular root compression further supports this theory and the surgical treatment of trigeminal neuralgia with microvascular decompression in the posterior fossa.[5] If the facial pain has some features of typical trigeminal neuralgia but differs from its classic description by the presence of hypesthesia in the trigeminal distribution, absence of response to carbamazepine, or additional constant pain that persists between classic attacks of the sharp, electric shocklike pain, then the diagnosis of *atypical trigeminal neuralgia* may be made.[6]

Typical and atypical trigeminal neuralgia may be difficult to differentiate since some patients may have features that change over time. As a matter of fact, the term *atypical trigeminal neuralgia*, indicating predominance or even the presence of a "permanent background of pain,"[7] has been largely replaced by the term *trigeminal neuralgia type II* and the typical trigeminal neuralgia is now referred to as *trigeminal neuralgia type I.*[1,8] Moreover, we theorized that trigeminal neuralgia may progress from type I to type II as the part of its natural history.[9]

The atypical features, especially sensory deficits and constant pain, should raise the possibility of the facial pain being a symptom of another pathologic process.

Causative Conditions of Secondary Trigeminal Neuralgia

Demyelinating disease
- Multiple sclerosis

Neoplasms
- Meningioma
- Trigeminal schwannoma
- Epidermoid
- Vestibular schwannoma
- Nasopharyngeal carcinoma
- Metastases
- Brainstem glioma

Vascular lesions
- Aneurysm
- Arteriovenous malformation
- Megadolichobasilar artery
- Persistent primitive trigeminal artery

Sarcoidosis

Connective tissue disorders
- Scleroderma
- Sharp disease (mixed connective tissue disease)

Syringobulbia

Pseudotumor cerebri

Paget disease

Acromegaly

Amyloidomas

Syphilis

Arnold–Chiari malformation

This is related primarily to various mass lesions in the posterior fossa (tumors and vascular malformations) or in the trigeminal ganglion and root that must be ruled out by using modern neuroimaging techniques, such as magnetic resonance imaging (MRI). Usually, the pain in these cases is referred to as *secondary trigeminal neuralgia,* although one may

argue that even idiopathic trigeminal neuralgia technically may be considered a secondary symptom of the primary pathologic process of neurovascular compression. Treatment of the secondary trigeminal neuralgias usually is aimed at elimination of the underlying problem; the symptomatic pain may resolve completely once the mass lesion or other offending process is removed or otherwise treated.[10,11]

If the neuroradiologic workup of trigeminal neuralgia type II does not show any underlying structural pathology, it is considered to be idiopathic. We believe that, in many instances, type II is a more severe or advanced form of typical, type I trigeminal neuralgia, and that it is seen in those cases in which vascular compression of the trigeminal nerve root is significant enough to produce not only mild demyelination with resulting paroxysmal pain but also a more overt neuropathy with sensory loss and chronic constant pain. In our opinion, surgical exploration and microvascular decompression are the definitive treatment for this pain syndrome.[7,9,12,13]

A syndrome resembling typical trigeminal neuralgia is encountered frequently in patients who have multiple sclerosis and in patients with brainstem infarction at the level of the trigeminal root entry zone.[14–16] The features of this "symptomatic" trigeminal neuralgia do not differ from the typical form of the disease, but treatment focuses on neuroablative interruption of the trigeminal nerve, retrogasserian root, or brainstem pathway rather than microvascular decompression.

Posttraumatic trigeminal pain or *trigeminal neuropathic pain* shares clinical features with other peripheral neuropathic pain syndromes; it is associated with constant dull, throbbing pain and paroxysms of sharp pain that may be burning in nature. The underlying mechanism of this type of pain is thought to be the injury of the trigeminal nerve or its branches, more distal than in cases presenting with typical trigeminal neuralgia.[17] What is not clear, however, is whether any trigeminal neuromata or other peripheral deafferentation can be found. Treatment of the posttraumatic trigeminal pain usually follows the same therapeutic algorithm as the rest of peripheral neuropathic pain syndromes: If conservative management fails, surgery on the peripheral trigeminal system is considered, followed by peripheral trigeminal stimulation and then by more central surgical interventions (e.g., ganglion, root, brainstem).[18–21]

As a part of effort to classify trigeminal pain syndromes based on etiology with a focus on subsequent simplification and standardization of treatment paradigms, the term *trigeminal neuropathic pain* is reserved for cases of pain due to unintentional trigeminal injury, such as facial trauma, oral or otorhinolaryngological surgery, posterior fossa operations not aimed at the trigeminal nerve, or stroke; cases of pain due to intentional trigeminal nerve injury such as neurectomy, gangliolysis, rhizotomy, and other peripheral or central denervating procedures are referred to as *trigeminal deafferentation pain.*[1,8]

Somewhat similar, but even more severe and frustrating, is pain associated with sensory loss in the face. This syndrome of *trigeminal anesthesia dolorosa* sometimes develops after brainstem and mesencephalic infarctions, but more commonly it is observed after destructive procedures on the trigeminal system that are used to treat trigeminal neuralgia, such as open or percutaneous rhizotomy, neurectomy, or tractotomy. In essence, trigeminal anesthesia dolorosa is an extreme case of either trigeminal neuropathic or trigeminal deafferentation pain, depending on the etiology of underlying trigeminal injury.

Pain in the distribution of one or more branches of the trigeminal nerve in association with herpetic eruption represents a separate subtype of facial pain. The acute herpetic pain is usually a self-limiting condition that starts with or just before the development of vesicular rash. Although quite severe, acute herpetic pain responds to narcotic medications and in most cases disappears without any long-term consequences; however, in some cases, especially in older patients, the acute pain transforms into a severe chronic pain condition called *postherpetic neuralgia*.[22,23]

Most commonly, postherpetic neuralgia involves the territory of the ophthalmic division of the trigeminal nerve. The pain has a burning and dysesthetic character, it is always associated with sensory loss, and allodynia may be a prominent feature. Treatment of postherpetic neuralgia is limited to central neurodestructive procedures, although stimulation of the thalamus and the motor cortex eventually may become an accepted way to manage it.[24,25] The peripheral nerve stimulation approach has also been tried for postherpetic neuralgia, but the results have been rather underwhelming.[18]

The trigeminal nerve is not the only nerve providing sensory supply to the face. Some parts of the face, especially around the ear, are supplied by the nervus intermedius, glossopharyngeal nerve, vagus nerve, occipital nerve, and autonomic afferent fibers that travel through the sphenopalatine ganglion or along the carotid artery. Disturbance of any of these nerves may produce pain in the face. The pain syndromes in these cases are named by their respective suspected pathologic substrates.

Geniculate (nervus intermedius) neuralgia presents with sharp pain deep in the external auditory canal and behind the ear, and may be associated with excessive salivation, tinnitus, and a bitter taste. The underlying mechanism of this pain syndrome is thought to be a vascular compression of the nervus intermedius, and so treatment usually consists of its surgical transection.

Sharp, shooting pain in the posterior part of the tongue, pharynx, tonsils, and ear, sometimes with trigger zones located in the ipsilateral half of the tongue and throat, is characteristic of the *glossopharyngeal* (or *vagoglossopharyngeal*) *neuralgia*.[26,27] In these cases, the pain may be provoked by swallowing, chewing, and talking. The glossopharyngeal and vagus nerves may be compressed by adjacent vascular structures; so the surgical treatment of this neuralgia resembles that of the typical trigeminal neuralgia and consists of either microvascular decompression of the affected nerve roots or, more commonly, section of the glossopharyngeal nerve and the superior fibers of the vagus nerve.

Pain localized primarily in the occipital area with radiation toward the ear and retromandibular region may represent a more common clinical entity, *occipital neuralgia.* This condition involves the greater or lesser occipital nerves that arise from the second and third cervical nerves, respectively, and somewhat resembles the peripheral neuropathic pain syndrome.[28,29] The treatment algorithm in this case starts from peripheral nerve procedures with gradual progression to stimulation and ablative procedures, if necessary.[30,31]

Infraorbital and retro-orbital pain that radiate toward the neck and are associated with lacrimation and conjunctival injection may represent the rare syndrome of *Sluder* (or *sphenopalatine*) *neuralgia,* whereas pain in the frontotemporal region with associated partial Horner syndrome may be caused by an injury to the sympathetic fibers that travel along the wall of the carotid artery (as in cases of carotid dissection) and is called *Raeder* (or *paratrigeminal*) *neuralgia*.[32] Other rare pain syndromes include auriculotemporal neuralgia, nasociliary neuralgia, and painful ophthalmoplegia in Tolosa–Hunt syndrome.[33]

Vascular headaches and migraines can usually be differentiated from the clinical syndromes mentioned above and are not considered under the rubric of facial pain; however, pain from temporomandibular joint dysfunction and from orofacial pathologic processes should always be a part of differential diagnosis in patients with atypical neuralgias. Neurosurgeons usually see these patients as they are filtered through a series of dentists, primary care physicians, and neurologists, so these patients only rarely reach neurosurgical attention. This, however, may change because peripheral nerve stimulation has now been tried with varying degree of success for both migraine headaches[34–36] and orofacial pain syndromes.[37]

The last group of patients does not fit into any of these categories. Their pain commonly does not follow anatomical boundaries, is usually bilateral and diffuse, and is associated with a normal neurological examination, except perhaps for some poorly localized tenderness and vague sensory loss in the painful region. This pain may be classified as *atypical facial pain* and usually represents a form of psychogenic pain disorder. The diagnosis of atypical facial pain may be made if other causes of facial pain have been considered, evaluated, and ruled out; if there is no subjective evidence for most facial pain syndromes; and if specific antecedent or ongoing psychological and behavioral factors can be identified. Obviously, this pain syndrome does not have a surgical treatment. The neurosurgeon's involvement in the management of these cases should end after the diagnosis is established.[1,2]

Nonsurgical Options

Nonsurgical treatment usually is offered to the patient first. In fact, most of these patients see a neurosurgeon for the first time when the conservative treatment fails.

Appropriate pharmacological treatment of facial pain depends on the nature of the pain. The sharp, shooting, electrical pains of trigeminal neuralgia usually disappear completely with oral carbamazepine or oxcarbazepine.[38,39] This anticonvulsant works so predictably well that pain relief after using it is considered one of the diagnostic criteria for typical trigeminal neuralgia. Over time, however, most patients may need to increase the dose of medication, or the medication may become increasingly less effective, causing the patient to be referred to a neurosurgeon. If, however, the patient develops adverse effects from carbamazepine/oxcarbazepine use, or becomes intolerant of the drug, it may be substituted or supplemented by other anticonvulsants, such as phenytoin, sodium valproate, and gabapentin; antispasticity agents (baclofen); benzodiazepines (clonazepam); or antidepressants (amitriptyline). None of these agents has the same high degree of success as oral carbamazepine or oxcarbazepine, but in some patients, pain may be significantly relieved.

Despite the high level of effectiveness of anticonvulsants, a prospective long-term cohort study of trigeminal neuralgia patients suggested that this effectiveness was rather short lasting, necessitating surgical intervention.[40] Based on this, the authors concluded that patients may benefit from having surgery earlier in the disease process to improve quality of life, freedom from medications, and the need for regular follow-up.[40]

Opioids may be used for short-term treatment, especially in critical circumstances, when facial pain becomes exacerbated and the definitive pain-relieving procedure cannot be performed immediately. Unfortunately, trigeminal neuralgia is classically resistant to opioids. Gabapentin also has been recommended for a variety of neuropathic conditions,

and it may suppress the burning and shooting component of pain in patients with atypical neuralgias and posttraumatic trigeminal pain.[41]

Topical ophthalmic application of local anesthetic has been suggested for temporary treatment of pain in first-division (ophthalmic) trigeminal neuralgia; however, a recent double-blind study showed no benefit of administrating proparacaine over administering placebo solution.[42] Topical application of a cream containing clonidine, an a_2-adrenergic agonist, in patients with different types of facial pain showed a better effect in neuralgic than in neuropathic pain,[43] but this agent is just entering the field of facial pain treatment and needs to be tested more thoroughly.

Nonpharmacological modalities include acupuncture, transcutaneous electrical nerve stimulation, and mechanical vibration. All these treatments were reported to decrease the level of facial pain in some patients, but they do not provide a long-lasting, definitive solution to the problem.[44–46]

Surgical Options

The goal of the surgical treatment of facial pain is to eliminate the pain with minimal morbidity and minimal, if any, new neurologic deficit. This goal can be accomplished by carefully reviewing the surgical indications in each case and by taking into consideration the patient's age and medical condition, presenting symptoms, underlying primary process, personal experience of the surgeon, and the patient's preferences.

Obviously, in cases of secondary trigeminal neuralgia, surgical attention should be directed toward elimination of the offending pathology. Resection of tumors and vascular malformations or systemic treatment of connective tissue disorders and infections may eliminate the pain and sometimes can reverse some of the presenting neurological deficits.

In cases of idiopathic typical trigeminal neuralgia, as well as in some cases of idiopathic atypical trigeminal neuralgia, the underlying pathology is thought to be neurovascular compression of the trigeminal nerve root. Specifically, for typical symptoms to develop, the compression apparently needs to involve the site of transition from peripheral myelin to central, known as *Obersteiner–Redlich zone*,[47] which is located in the retrogasserian root not far from its entry into the brainstem. Therefore, elimination of this vascular compression should bring complete relief. This theory has proven true with many thousands of patients, and the technique of microvascular decompression of the trigeminal nerve is widely accepted as the most definitive, and the longest lasting, surgical treatment for typical trigeminal neuralgia. It has a high success rate and usually does not cause a significant new sensory deficit in the trigeminal distribution.

This procedure, however, requires retromastoid craniotomy and general anesthesia, making microvascular decompression less desirable for patients who are in poor medical condition, who have short life expectancy, or who do not wish to undergo a major operation. For these patients, the most appropriate means of surgical treatment is a percutaneous procedure that can be done without the prolonged use of general anesthesia. Although neurovascular compression cannot be eliminated through this route, the neuralgic pain may be reliably relieved for several years with minimal morbidity, even though this relief may come with some degree of numbness in part of the trigeminal territory.

Peripheral neurectomies, chemical and thermal neurotomies, and nerve avulsions/exéresis are rarely used for trigeminal neuralgia these days.[48] Instead, attention is shifted to the gasserian ganglion and retrogasserian trigeminal root, which can be reached percutaneously through the foramen ovale. The three most accepted techniques of this approach are percutaneous radiofrequency trigeminal gangliolysis, percutaneous retrogasserian glycerol rhizotomy, and percutaneous balloon compression. All these procedures have their own advantages and disadvantages, but based on a meta-analysis of published studies, it is obvious that each of them is effective in relief of trigeminal neuralgia pain (**Table 40.1**).[49]

The percutaneous procedures are probably the most appropriate means of treatment of trigeminal neuralgia resulting from multiple sclerosis, in which neurovascular compression typically is not considered an issue. These procedures also may work for patients with trigeminal neuralgia secondary to the pontine infarction that involves the root entry zone of the trigeminal nerve.[14,16]

The next set of procedures involves transection of the trigeminal pathways proximal to the ganglion. This includes open trigeminal rhizotomy, trigeminal tractotomy/nucleotomy, mesencephalotomy, and, most centrally, thalamotomy. Other than rhizotomy, these ablative procedures are used infrequently. Open partial rhizotomy is used in cases of typical trigeminal neuralgia when posterior fossa exploration does not reveal convincing vascular compression of the trigeminal nerve root, or occasionally in patients with multiple sclerosis in whom repeated peripheral ablation has become ineffective. Other central neuroablative procedures are reserved for either atypical trigeminal neuralgia that is refractory to the medical treatment and does not respond to peripheral destructive procedures, for trigeminal neuropathic pain, for anesthesia dolorosa in patients after rhizotomy, or for postherpetic neuralgia.

Table 40.1 Results and complications of percutaneous procedures on gasserian ganglion and retrogasserian trigeminal root

Procedure	Radiofrequency thermocoagulation	Glycerol rhizotomy	Percutaneous balloon compression
Number of series	12	13	9
Number of patients	6,235	1,253	616
Immediate success rate	97%	91.5%	92.3%
Follow-up	6.2 y	2.7 y	2.5 y
Recurrence rate	23.2%	36.2%	17.7%
Anesthesia dolorosa	5.3%	2.6%	0.1%
Corneal anesthesia/keratitis	12.4%	7.6%	0.1%
Dysesthesia	18%	10.8%	8.4%

Source: Data from Tekkok and Brown.[49]

The last group of procedures includes various neuromodulation techniques, which can be considered in patients with facial pain other than trigeminal neuralgia, such as posttraumatic pain and atypical trigeminal neuralgia. Electrical stimulation, the most common means of neuroaugmentation, can be applied to the peripheral segments of the trigeminal nerve (e.g., the supraorbital nerve), the trigeminal ganglion, the sensory region of the thalamus (ventroposteromedial/ventroposterolateral), or the motor cortex. These procedures have been reported as having varying degrees of success in anecdotal reports or small series of patients with refractory pain. A comprehensive review of all kinds of neuromodulation procedures used for treatment of facial pain was recently published.[50] Based on this compilation of published studies, it appears that the level of any scientific evidence regarding the use of neuromodulation for facial pain is rather suboptimal.

The general algorithm for facial pain management is shown in **Fig. 40.1**. The most important thing to understand is that, although typical trigeminal neuralgia is a relatively straightforward condition with a well-established treatment strategy, other facial pain syndromes remain a major therapeutic challenge. Development of new surgical techniques and additional experience with existing nondestructive modalities may change this picture in the future, thereby improving the quality of life of many thousands of patients.

Conclusion

Among the existing therapeutic modalities for treatment of facial pain, none is uniformly successful and free of complications. Although typical trigeminal neuralgia has a relatively simple treatment algorithm, the treatment of other facial pain syndromes remains problematic and less satisfactory. The general trend toward less invasive nonablative procedures, a better understanding of pain mechanisms, and optimization of pharmacological therapy will continue to improve the neurosurgical approach to facial pain treatment in the future.

Editor's Comments

This chapter is a complete description of the diagnosis and surgical management of trigeminal neuralgia. Many of these "surgical options" are discussed in upcoming chapters. As we point out in this survey, the evidence to support surgical decision making in trigeminal neuralgia is somewhat lacking. We know what works; we know generally how long it works. We have a sense of which procedures might be appropriate, given the nature of pain, and the age and health of the patient. The algorithm suggested is merely a way to think about surgical care. Fortunately, we do have a number of surgical options for patients with trigeminal neuralgia who develop medical intractability.

This chapter points out as much about what we don't know about trigeminal neuralgia as it does about our current understanding of this disorder. We have by no means a complete and rigorous understanding of facial pain. I anticipate that progress in this area will continue, and much more is still to be recorded on this topic.

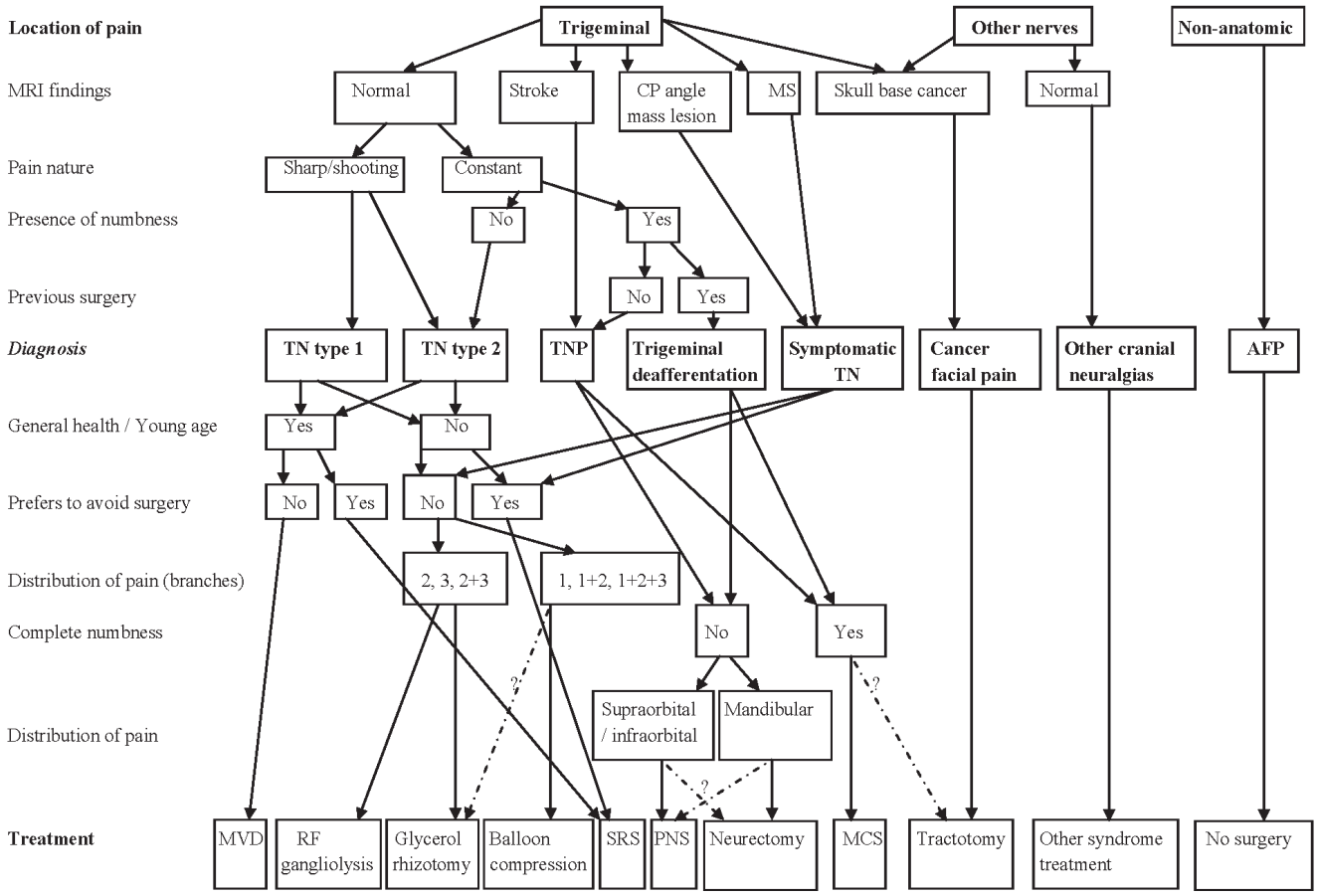

Fig. 40.1 Facial pain treatment algorithm. AFP, atypical facial pain; CP, cerebellopontine; MCS, motor cortex stimulation; MRI, magnetic resonance imaging; MS, multiple sclerosis; MVD, microvascular decompression; PNS, peripheral nerve stimulation; RF, radiofrequency; SRS, stereotactic radiosurgery; TN, trigeminal neuralgia; TNP, trigeminal neuropathic pain.

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41 Microvascular Decompression for Trigeminal Neuralgia

Kim J. Burchiel

In 1934 Dandy[1] first proposed that vascular compression of the trigeminal nerve was a cause of trigeminal neuralgia (TN). However, Dandy also pointed out that vascular contact occasionally occurs without the production of TN, and that TN may be present in the absence of trigeminal nerve compression. Contact of the trigeminal nerve by a blood vessel at or near the root entry zone[1–3] is still thought to be the most common anatomical association in patients with TN. Devor's "ignition theory" of TN relies on a focus of hyperactivity in the retrogasserian root, consistent with a focus of demyelination within the nerve, possibly caused by vascular compression. The theory holds that "nerve injury results in hyperexcitability of injured afferents, which results in after-discharges large enough to result in nonnociceptive signal being perceived as pain. This leads to windup and both peripheral and central sensitization."[4] Other etiologies such as multiple sclerosis,[5] central or peripheral demyelination,[6,7] root injury, and tumors may be associated with TN.[2,8]

It was Gardner who first suggested that vascular decompression of the trigeminal nerve could ameliorate TN.[9,10] Subsequently, Jannetta's extensive work established microvascular decompression (MVD) as one of the most important surgical approaches to TN and other cranial neuropathies.[3,11] Over more than four decades, MVD has established itself as a unique and durable treatment for medically intractable TN, a procedure that seemingly has dissociated the need for nerve injury, the attendant sensory loss, and a long-term successful outcome.

Vascular compression of the trigeminal nerve is also known to occur in patients who do not have TN, and TN is known to occur in patients who have no vascular compression. In 1982 Adams et al reported on "our failure to be convinced by vascular compression as a cause for the majority of our patients' pain."[12] He questioned the role of "microvascular compression" in the surgical treatment of TN, reviewing all the evidence at the time. He made the argument that there may be some other process involved.[13] In contrast, Jannetta and others have reported that essentially all patients with TN are found to have vascular contact with the nerve, at times from both arteries and veins.[14,15]

A review of autopsy studies reveals some degree of contact between the trigeminal nerve and a blood vessel in 90 to 100% of patients with TN, but also in 16 to 58% of patients without TN.[16–19] In 2009 Miller et al[20] evaluated neurovascular compression (NVC) in patients with and without TN and concluded that trigeminal NVC occurred in 17% of asymptomatic patients but was more severe and more proximal in patients with TN. A review of the literature reveals a wide range (4 to 89%) of TN patients with no demonstrable vascular contact.[1,12,19,21–25] For example, Leal et al[24] reported no NVC in 9% of patients by surgical exploration and imaging revealed no vessel in relation to the nerve in 12% of patients. Improvements in imaging technology resolution capabilities have further reinforced the proposition that TN can occur in the absence of vascular contact.[24–26]

Hamlyn in 1992 noted that an explanation for TN cases in which no vessel was found in contact with the trigeminal nerve at operation was needed, and that it should be possible to identify those cases preoperatively.[19] In 2009 Miller et al stated that "trigeminal NVC occurs in asymptomatic patients but is more severe and more proximal in patients with TN."[27] Although vascular compression of the trigeminal nerve by a blood vessel at or near the root entry zone[1–3] is the primary pathology of TN, there remains an unexplained subset of patients with TN without clear NVC. Improvements in surgical approaches and advances in imaging technology have only reinforced this discrepancy.[8,12,18,19,21,22,28]

A retrospective review of patients with TN type 1 (TN1) or type 2 (TN2)[29] at Oregon Health & Science University from July 2006 to February 2013 was recently undertaken.[30] Patients underwent preoperative high-resolution magnetic resonance (MR) imaging and analyzed MR angiograms with 3D reconstructions using OsiriX. MR imaging (BFFE

and MRA) using a 3-T MR scanner was as previously described.[25,27]

Our review yielded 257 patients with TN1 (219 patients) and TN2 (38 patients) who underwent high-resolution MRI/MRA with 3D reconstruction of combined images. Of the 257 patients, 33 had undergone previous MVD procedures, 26 TN1 patients and 7 TN2 patients. Of the 219 TN1 patients, 150 (68.49%) demonstrated unilateral compression, 6 (2.74%) had bilateral compression, and 63 (28.8%) had no NVC. The identity of the offending vessel was the superior cerebellar artery (SCA) in 121 cases (74.7%), venous in 20 (12.4%), anterior inferior cerebellar artery (AICA) in 13 (8%), vertebral artery in 5 (3.1%), basilar artery in 2 (1.2%), and a tumor in 1 (0.62%, meningioma).

Six TN1 patients had bilateral TN1 symptoms at some point in their history. Of these, 2 patients had bilateral compression, 1 patient had unilateral compression, and 3 patients had no compression as determined by imaging. Therefore, in patients with bilateral TN1, only 5 of 12 (41.67%) had visible NVC on imaging studies. Of the 38 TN2 patients, 31 (81.58%) had unilateral compression, and the vessel was the SCA in 26 (68.42%), a vein in 3 (7.89%), and AICA in 2 (5.26%). There were no patients with bilateral NVC and 7 had no NVC (18.4%).

Of the four TN2 patients with bilateral TN2 symptoms, no patient had bilateral compression, 3 patients had unilateral compression, and 1 patient had no compression. Therefore, in this group only 3 of 8 (37.5%) had visible compression on imaging studies. Sensitivity of imaging as a predictor of NVC for both TN1 and TN2 was 96%, and specificity of imaging findings for patients with TN1 and TN2 were 90% and 66%, respectively.

Thus, it appears that TN1 and TN2 can occur without NVC, and that preoperative imaging can, in most cases, determine if NVC is present.

Indications

When the diagnosis of TN is recognized, medical therapy should be attempted in essentially every patient. Occasionally, patients are so intolerant of anticonvulsant medications, due to either side effects or allergic reactions, that surgical therapy is considered at the outset of the disorder. More commonly, patients can be adequately treated with medications for several years, or even longer, given the sporadic nature of the disorder early on. Over time, TN becomes more persistent, and also becomes more medically resistant. At this point the diminished efficacy of medical management and emergent toxicity of anticonvulsant therapy can result in the clinical conclusion that the patient is approaching medical intractability.

The indications for an MVD for TN are: (1) medical intractability of the pain, (2) medical fitness for a posterior fossa craniotomy, (3) the presence of NVC demonstrated by imaging, and (4) patient choice of the procedure. In comparison to destructive procedures, MVD has the longest duration of pain relief,[31,32] and for this reason it is generally considered in younger patients, those with the greatest longevity. In the past, patients over age 70 have not been considered optimal candidates for the surgery, although this concept has been challenged by the demonstration of the relative safety of this procedure in an older patient cohort.[33] Clearly, destructive procedures can generally and adequately control TN in older patients over their life spans, given their reduced longevity. However, it is also clear that when older patients are subjected to destructive procedures they are more likely to develop complications of deafferentation, such as anesthesia dolorosa and its variants, in comparison with a younger population. These two facts may warrant a reconsideration of MVD for older patients with TN.

Techniques

MVD is performed under general endotracheal anesthesia, using a minimum of inhalational anesthetic and no chemoparalysis. A bipolar facial electromyogram (EMG) is recorded ipsilaterally from the orbicularis oris and orbicularis oculi. Brainstem auditory evoked responses (BAERs) are recorded bilaterally.

The patient is placed supine, with the head placed in the Mayfield head holder. The head is rotated away from the side of surgery, and the neck is slightly flexed and elevated (**Fig. 41.1**). **Fig. 41.2** shows the anatomical relationships of the retromastoid approach. After sterile preparation of the skin, a curved retro-auricular incision is made from approximately the top of the pinna to the mastoid notch (**Fig. 41.3**), and the skin edges are retracted using "fish hooks."

A small craniectomy is then created by drilling, initially taking care to stay inferior and posterior to the asterion. The craniectomy is then enlarged with Kerrison rongeurs to the point that the edges of the anterior transverse sinus, transverse–sigmoid junction, and the superior aspect of the sigmoid sinus are minimally, but definitively, exposed. Any bleeding points are controlled with small pieces of Gelfoam (Pfizer, New York, NY, USA) soaked in thrombin. The final size of the craniectomy should be 2.5 to 3.0 cm at its base and 3.0 to 3.5 cm at its surface to create a beveled edge (**Fig. 41.4**). Opened mastoid air cells should be fully waxed.

The dura is then opened in a curvilinear fashion paralleling the transverse–sigmoid junction, and the dura anterior to the incision is tacked up using three

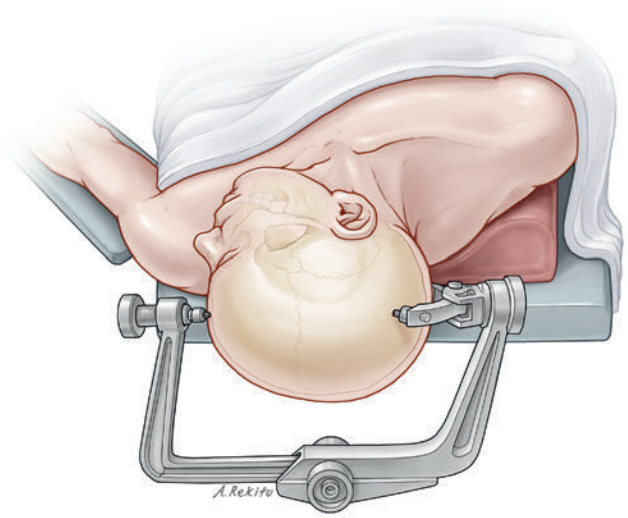

Fig. 41.1 Mayfield positioning.

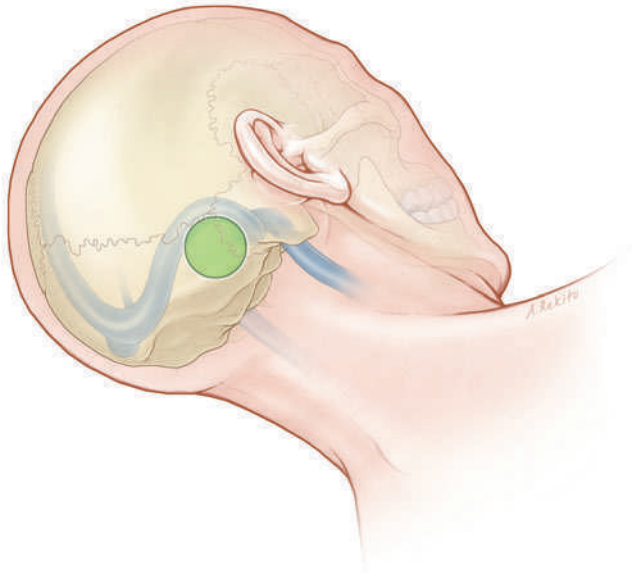

Fig. 41.2 View of the retromastoid region showing the relationships of the top of the pinna to the transverse sinus, the position of the transverse–sigmoid junction and sigmoid sinus to the asterion, and the relationship of the mastoid to the sigmoid sinus.

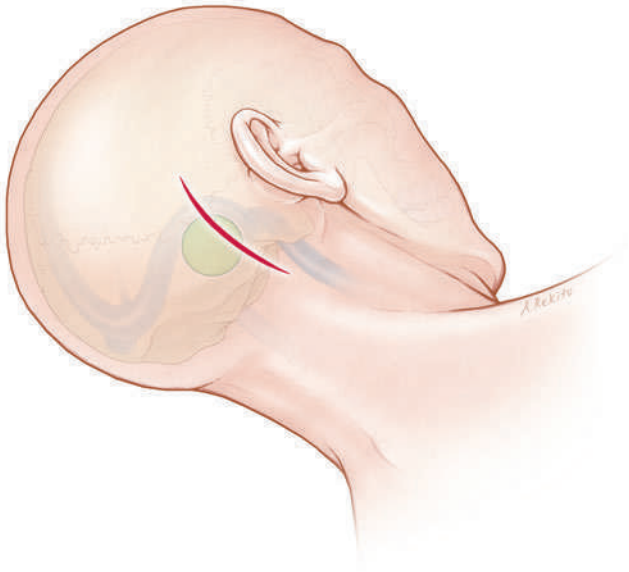

Fig. 41.3 Retroauricular skin incision, and relationship to planned craniectomy.

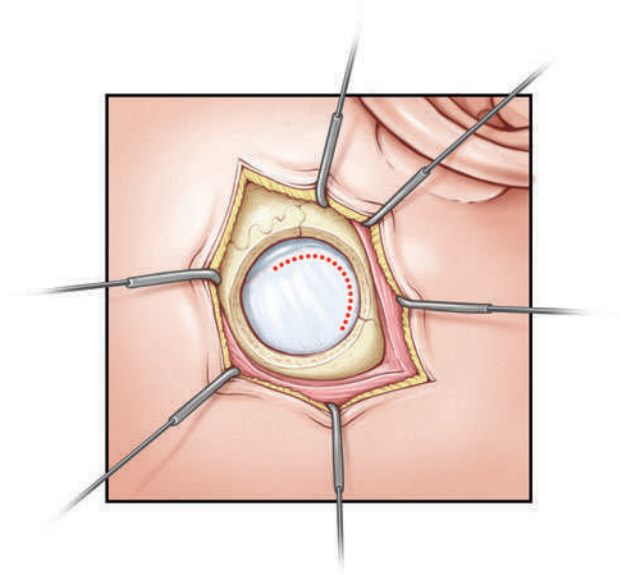

Fig. 41.4 The skin and underlying musculature are retracted using "fish hooks," and the 2.5–3.5 cm craniectomy is made to just expose the inferior margin of the transverse sinus, the transverse–sigmoid junction, and the posterior extent of the sigmoid sinus. A curvilinear durotomy is made to 3–4 mm posterior to the transverse–sigmoid junction, and its anterior margin is retracted using three or four dural sutures.

or four sutures. One or two small cottonoids are then inserted through the incision and over the cerebellum to facilitate cerebrospinal fluid (CSF) drainage. A flexible retractor is used to hold a small rounded brain retractor blade, and this is inserted to exert gentle pressure on the cerebellum and to augment CSF drainage. At this point the operating microscope is brought into position.

Under magnification, and under direct vision, the retractor blade is then inserted over the cerebellum pointing directly at the interval between the tentorium and the petrous ridge, taking care to not inadvertently injure any branches of the petrosal vein, which can be multiple and can be distributed anywhere along the tentorial–petrous junction

(**Fig. 41.5a**). Most commonly, when the petrous vein is encountered, an apparent trifurcation points to a common entry into the superior petrosal sinus. The entirety of the petrous vein is typically coagulated by bipolar cautery, with careful irrigation, and divided (**Fig. 41.5b**). The retractor is then inserted deeper over the cerebellum to eventually uncover the vestibulocochlear and facial nerves. More superiorly and at the apex of the exposure lies the trigeminal nerve, and its entry into the brainstem.

Once the trigeminal nerve is located and exposed, dissection of the offending vessel is begun. This is typically the superior cerebellar artery (SCA), and this vessel can usually be liberated from beneath the trigeminal nerve superiorly (**Fig. 41.6a, b**). The rare compression from the AICA is resolved inferior to the nerve. If the vertebral or basilar artery is the source of compression, mobilization of the artery is usually not completely successful.

During the procedure careful attention is paid to the ipsilateral BAERs. A latency change of less than 10% in waves IV and V is not unusual, and is almost immediately reversible at the conclusion of the procedure. If the BAER latency is delayed beyond 10%, or if amplitude changes in the BAERs are observed, the retractor is removed, and usually the decompression can proceed without additional retraction. If not, the retractor can be replaced once the amplitude changes have resolved, and BAERs can again be monitored for recurrent amplitude change.

Small pieces of Teflon (DuPont, Wilmington, DE, USA) fiber pledget, teased into small loose balls, are then placed in the interval between the nerve and artery, so as to securely and permanently separate the two structures (**Fig. 41.6c**). For highly redundant arteries, care must be taken to avoid kinking the artery during the placement of the Teflon balls. In the case of vertebral or basilar compression, usually the most that can be accomplished is the separation of the nerve and artery, although packing Teflon fibers between the nerve and these large arteries places the nerve under considerable tension.

Once the decompression is accomplished, hemostasis is ensured, and all retractors are removed. The dura is closed and sealed with fibrin glue, and the small skull defect is repaired with hydroxyapatite cement. The muscle and skin are closed in layers.

Outcomes

Despite the seeming complexity of MVD surgery, reported complication rates are low. CSF leakage can occur in 1.5% of patients,[31] hearing loss in 0.59%,[14] meningitis in 0.37%, cerebellar or supratentorial hematoma in 0.3%, permanent facial paresis in 0.15%, permanent extraocular palsy in 0.15%, and operative death in 0.15%.[31] With no complications, patients are usually able to return to full activities and employment within a month, although lingering effects of the surgery may last for several months.

Trigeminal neuralgia recurrence rates after an initially successful MVD have been reported from 1.7 to 75% (**Table 41.1**).[28,31,32,34–50] Van Loveren et al reported that of 50 TN patients treated by MVD 84% were pain free at 3 years.[48] Liao et al found that of 80 MVDs there were 5 cases of recurrence in 12 months.[41]

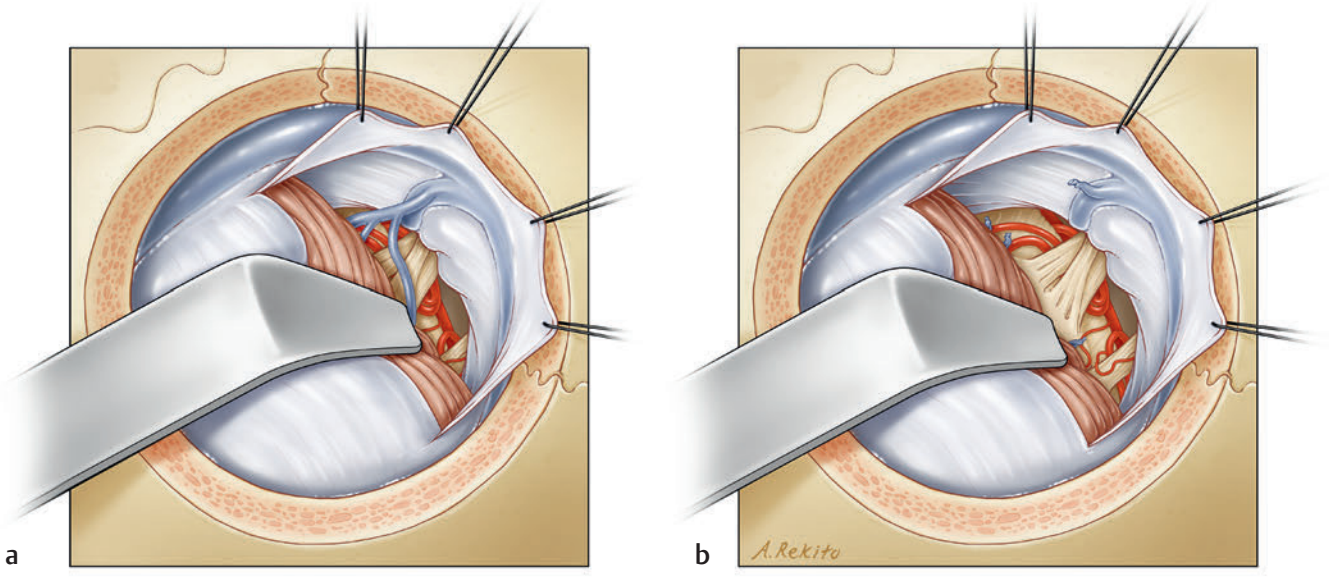

Fig. 41.5 (**a**) Retraction is used to facilitate CSF (cerebrospinal fluid) drainage and to expose the tentorial-petrosal angle with the petrosal vein(s). (**b**) The petrosal veins are typically coagulated and divided to facilitate exposure and retraction.

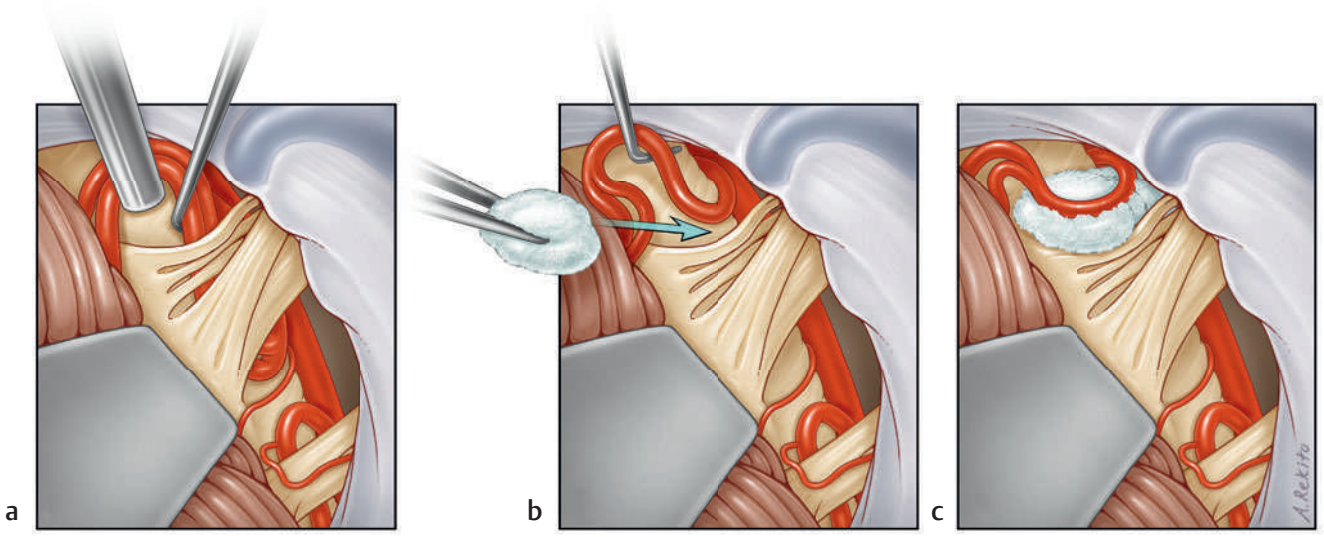

Fig. 41.6 (**a**) Vascular compression of the nerve is demonstrated, which in most cases is due to the superior cerebellar artery (SCA). (**b**) The artery is mobilized over the lateral surface of the nerve. (**c**) Teflon fiber packing is used to maintain the position of the artery away from the nerve.

Table 41.1 Summary: Lack of compression and recurrence rates for microvascular compression and radiofrequency lesioning procedures

Series	MVD (*N*)	RFL (*N*)	Follow-up	No compression (%)	MVD recurrence rate (%)	RFL recurrence rate (%)
Burchiel 2013	184		Mean 44.9 mo	16	22	
Van Loveran et al 1982	50	700	3–6 y		12 (at 3 y)	20 (at 6 y)
Liao et al 1997	80		9 mo–4 y		6.25 (at 1 y)	
Barker et al 1996	1,185		> 1 y		23.8	
Lee et al 2000	393		≤ 5 y		40.6 (≤ 3 mo); 15.6 (≤ 6 mo); 18.8 (≤ 12 mo); 12.5 (≤ 3 y); 3 (≤ 5 y)	
Zorman (Wilson) 1984	125		6 mo–13 y	20.8	16 (2.4 y)	
Bederson (Wilson) 1989	246		5.1 y	12.2	8.13	
Taha (Tew) 1997		1,200	7–9 y			20 (7–9 y); 25 (15 y)
Zakrzewska (Thomas) 1993	55	265	Mean 45 mo		13 (mean 45 mo)	29 (mean 45 mo)
Rath et al 1996	135		3 mo–5 y; mean 1.4 y	5	16.7 (5 y)	
Sun et al 1994	61		1.1–10.5 y		16 (≤ 2 y)	
Burchiel et al 1988	36	8*	Mean 8.5 y		47	50
Tronnier et al 2001	225	206	Mean 10.9 and 14.0 y		23.6 (2 y); 35 (10 y); 37 (20 y)	50 (2 y); 75 (4.5 y)
Kanpolat et al 2001		1,600	Mean 68.1 mo			7.7 (< 6 mo); 17.4 (> 6 mo)
Sindou et al 1990	120		41 mo			
Klun 1992	178	42*	12 y; mean 5.2 y		6	50
Cutbush (Atkinson) 1994	109		Mean 4.8 y		24	
Mendoza (Illingworth) 1995	133		6 mo–15 y; mean 5.3 y		16	
Kondo 1997	281		5–20 y; mean 10.1 y		16.7	
Lee et al 1997	146	235	Mean 5.7 y	2 pts	8.6	45.7 (glycerol)
Chen (Lee) 2003	114	127	≤ 2 y	4 pts	17.5	8.7

Abbreviations: mo, month; MVD, microvascular decompression; N, number; pts, patients; RFL, radiofrequency lesioning; y, year.
*Partial sensory rhizotomy.

Barker et al examined 1,185 patients who underwent an MVD for TN over a 20-year period. Patients were followed for 1 year or longer after surgery, with 91% having follow-up of at least 5 years. The SCA was the cause of compression in 75% of patients, and the AICA in 10%. A compressive vein was observed in 68% of patients, and in 12% a vein was the sole cause of compression. Recurrence of TN was found in 282 (23.8%) patients and reoperation was performed in 132 patients. They observed higher rates of recurrence: (1) in women, (2) in patients with 8 years of symptoms prior to surgery, (3) with decompression of a vein during surgery, and (4) in association with a lack of immediate postoperative relief.[31]

Bederson and Wilson reviewed 252 MVDs performed in 246 patients. Thirty patients (12.2%) had no observable compression and received a partial sensory rhizotomy (PSR), and 56 patients had vascular contact without distortion and received an MVD with a PSR.[34] Zakrzewska and Thomas evaluated 475 patients with TN. Sixty-five MVD procedures were performed in 55 patients; at 5 years 38% of the MVD patients had experienced a TN recurrence.[49] Rath et al reported on 135 MVDs with a follow-up interval of 3 months to 5 years (mean 1.4 years). Venous compression was seen in 9 patients and 7 patients had no venous or arterial compression (5%). Their recurrence rate was 16.7% at 5 years. They also commented that patients who had previous destructive procedures had worse outcomes.[43]

Sun et al reviewed 61 patients after MVD for TN with follow-up of 1.1 to 10.5 years (mean 6.7). There were 10 (16%) patients with recurrence within 2 years postoperatively.[45] Tronnier et al reviewed 225 MVDs and found that 63% of patients had 20 years of pain relief.[47] Sindou et al evaluated 120 patients after MVD, with a follow-up period of 41 months. They reported that 83.3% and 79% of patients had pain relief from sitting craniotomy and the lateral approach, respectively.[44] Cutbush and Atkinson evaluated 109 MVDs from a single surgeon. Their mean follow-up was 4.8 years and 83 (76%) of patients had resolution of their pain. They commented that most (66%) of the recurrences occurred within 12 months and the SCA was the vessel involved in over 70% of the cases.[28] Mendoza and Illingworth evaluated 132 patients who had 133 MVDs (1 patient with bilateral symptoms). Follow-up in this series was from 6 months to 15 years with an average of 5.3 years. There were 95 (71%) patients who were pain free and 21 (16%) patients with a minor recurrence. Operative findings of compression were statistically significant in giving long-term pain relief.[42] Lee et al evaluated 116 patients after MVD followed up 2 years postoperatively and there were 9 (8.6%) recurrences. There were at least 2 patients with no vascular compression who had pain recurrence.[39] Chen and Lee reviewed 114 MVDs with a follow-up of at least 2 years, with a recurrence rate of 17.5%. They noted that 4 patients (3.5%) did not have any compression visible at the time of surgery, and 9 patients had a prominent bone spur or acute angulation at the entry into Meckel cave as the proposed cause of compression.[35]

Burchiel et al[32] reported long-term results after MVD for TN, with an average follow-up of 8.5 years. In their series, during the first 2 years there was an approximately 25% recurrence rate, after which results remained stable until 5 years postoperatively, at which point recurrences began to mount. Over the course of follow-up pain recurrences averaged approximately 4% per year, and showed no trend toward plateauing (**Fig. 41.7**). In a later report, Miller et al[20] conclusively demonstrated what was widely believed to that point, that after MVD the outcome of TN1 was superior to that for TN2 (**Fig. 41.8**).

Long-term studies on the outcome from rhizotomy for TN are not as robust as those for MVD. Burchiel et al showed that after MVD or trigeminal rhizotomy (bipolar cautery of the lateral two thirds of the trigeminal nerve after crushing) recurrence occurred in 47% of the MVD group and in 50% in the trigeminal rhizotomy group, with a mean follow-up period of 8.5 years.[32] Zorman and Wilson evaluated 125 MVDs and PSRs. The mean follow-up was 26 months (6 months to 13 years). In 26 patients there was no compression seen at the root entry zone and each of those patients underwent a PSR. They reported a 91% success rate for pain relief.[50] Klun evaluated 178 patients after MVD and 42 patients after PSR with a follow-up period of up to 12 years (mean of 5.2 years). Eleven patients had tumors, 3 patients had MS, 4 patients had bilateral pain, and he excluded patients with "atypical pain." Five-year complete relief was 84% for both operations.[37]

It is important to note in most of the series mentioned above there was no differentiation of TN1 and TN2 symptomology, no confirmatory preoperative imaging, and no indication of the degree and severity of NVC.

From the studies cited above, two broad conclusions can be drawn. First, there seems to be a general consensus that some patients with TN do not manifest NVC at the time of surgical exploration. The mechanism for TN in these cases is unexplained. Second, despite initially effective MVD, the rate of pain recurrence may be as high as 4 or 5% per year.[1,12,19,21–25] There is no consensus as to the etiology of pain recurrence in these cases.

TN patients often experience a recurrence after an initially successful MVD procedure. A review of the literature reveals a wide recurrence range, 7.7 to 75%.[28,31,32,34–50] Surgical alternatives after recurrence include repeat exploration for recurrent vascular compression (MVD), internal neurolysis (IN), and radiofrequency lesioning (RFL). Alternatives for recurrent TN include partial or complete sensory rhi-

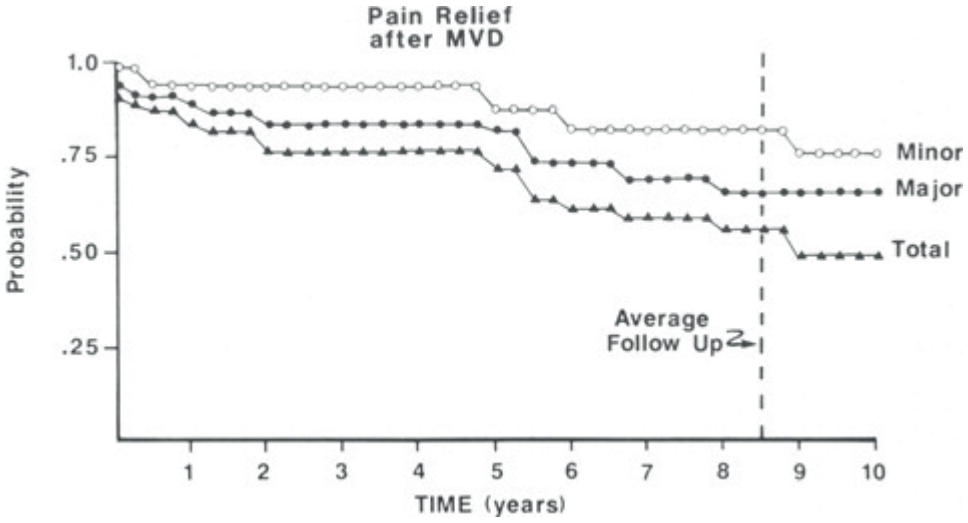

Fig. 41.7 Kaplan–Meier plot of probability of pain control over time after MVD (microvascular decompression). Major recurrences required additional surgical therapy, and minor recurrences required only medication for pain control. The total recurrence rate is approximately 4% per year.

zotomy, balloon rhizotomy, glycerol injections, and radiosurgery. Most experienced surgeons tend to favor less destructive approaches because anesthesia dolorosa (deafferentation pain) is a known, and feared, complication of destructive procedures of the trigeminal nerve.

Our results suggest that high-resolution MRI/MRA imaging can reliably detect NVC in patients with TN. Our imaging indicates that 28.8% of patients with TN1 *do not* manifest NVC. Further, post-MVD imaging can discern whether trigeminal NVC has been effectively relieved. A result of these postoperative studies is the recognition that *most* patients who exhibit clear imaging evidence of prior MVD of the nerve have recurrent TN *without* recurrent NVC. The main exception to this appears to be when the original NVC was either missed or inadequately decompressed at the time of the first MVD.

We have previously demonstrated that 17% of the general population manifests NVC of the trigeminal

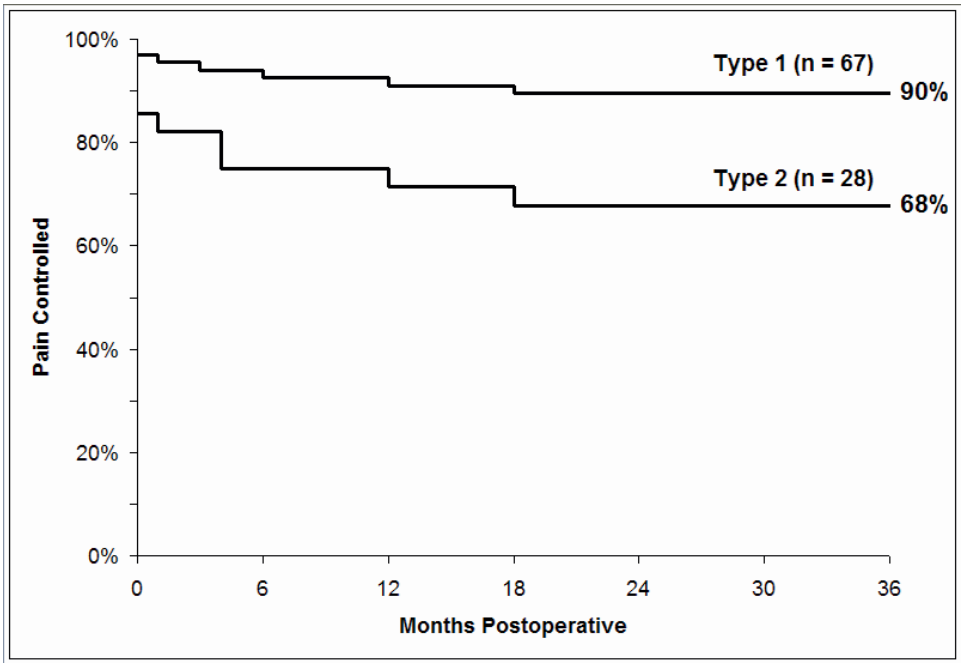

Fig. 41.8 Kaplan–Meier plot of pain control over time after MVD (microvascular decompression) in TN (trigeminal neuralgia) 1 and TN2.

nerve.[27] If, as has been estimated, the incidence of trigeminal neuralgia in the population is 1 in 10,000 (0.01%),[51] then 99.94% of individuals with trigeminal NVC *do not* have TN. Given these statistics, and the present evidence that TN can both occur and recur without NVC, the hypothesis that TN is reliably caused by neurovascular conflict must be challenged.

There is no serious debate that MVD is the most efficacious procedure for medically intractable TN. The question is why MVD works at all, when neurovascular compression may just be one element—and not an essential one—in the genesis of TN. Rather than "decompression," MVD may be effective because it creates chronic stretching and compression of the nerve, or it may be that in some way the arachnoiditis and scarring that accompany MVD either change the blood supply or otherwise alter the physiology of the nerve. These and other questions, including the possibility that genomic predisposition to the development of TN may play an important role, need to be addressed by clinical and laboratory research.

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42 Trigeminal Rhizotomy

Shih-Shan Lang and John Y. K. Lee

There are numerous surgical procedures used for the treatment of trigeminal neuralgia (TN), of which microvascular decompression (MVD) is the most common. This popular procedure is performed at the root of the trigeminal nerve (defined as the section of nerve between the gasserian ganglion and the brainstem). However, in a small population of patients, vascular compression is not seen at the time of surgical exploration.[1–8] These patients may benefit from an alternative procedure, partial sensory rhizotomy (PSR). The level of evidence for these procedures remains poor: All studies are Class III (retrospective case series or expert opinion only). Therefore, readers should recognize that the quality of the evidence for performing PSR is low.

History of Trigeminal Rhizotomy

Prior to the development of rhizotomy, multiple peripheral neurectomy procedures were performed in an effort to cure trigeminal neuralgia. Targeting the infraorbital sensory nerve or the mandibular nerve, for example, resulted in only temporary relief. Thus, surgeons explored more invasive alternatives to cure patients with intractable trigeminal neuralgia. In 1891 Sir Victor Horsley was the first to describe trigeminal rhizotomy as the sectioning of the trigeminal root between the brainstem and the gasserian ganglion.[9] He reported that complete removal of the gasserian ganglion was not possible without devastating outcomes. Therefore, he performed a trigeminal root sectioning (rhizotomy) in a patient suffering from TN through a subtemporal craniotomy. Throughout the next decade, several surgeons described the suboptimal results from gasserian ganglionectomy and proposed subtotal trigeminal neurectomy in order to preserve the motor root.[10–12] For example, Hartley and Krause independently modified the technique from an intradural operation to an extradural operation.[13,14] However, it was not until 1901 that the procedure of dorsal sensory root sectioning through a middle fossa approach was popularized by University of Pennsylvania neurologist and neurosurgeon Spiller and Frazier.[15] In 1925 Frazier further refined this procedure by describing a subtotal neurectomy approach that preserved not only the motor root, but also the ophthalmic division fibers that provide corneal sensation.[16,17] In the same decade, Stookey further advanced this procedure by differentiating the fibers in the dorsal root derived from the mandibular division from those derived from the maxillary division.[6] Thirty years later Stookey described his experience with over 700 trigeminal rhizotomies and reported 92% pain-free outcomes.[18] However, overall complications were high: 8% of patients had facial weakness, 29% had mild paresthesias, and 10% had severe parasthesias. Also, in the 1950s, Peet and Schneider reported their 10-year experience on 553 patients who underwent trigeminal rhizotomies.[4] Similar to the Stookey study, a subtemporal craniotomy was performed under local anesthesia and the majority of these operations were performed in the sitting position. Similarly, pain relief was high, at 95%; however, the majority of patients had some type of significant parasthesias, and facial paralysis occurred at a rate of 6.5%.[4]

The subtemporal approach was the most popular craniotomy during this premicroscope era. However, in the 1920s Walter Dandy proposed the retromastoid/posterior fossa approach to the trigeminal nerve. He sectioned the sensory root at the level of the pons.[19] He reported the hypothesis that, due to the position of the pain fibers running in the posterior portion of the trigeminal nerve, he could spare the normal facial sensation via a posterior fossa approach. Dandy reported outcomes in 250 patients with this approach, only 4 of whom had recurrences.[20] In his series, there were no cases of keratitis, or facial nerve or motor root injury. In addition, he found 18 cases of posterior fossa tumors that were the cause of the TN, which would not have been

found during a subtemporal approach. Despite these successful results, neurosurgeons during his era did not or could not adopt this approach. Walter Dandy is often credited for having incredible skill and keen vision, operating in the posterior fossa without the advantage of microscope or modern illumination. Few surgeons in that era were able to adopt Dandy's technique with the same success rate, and thus the subtemporal route remained the approach of choice.

Over the next few decades, trigeminal rhizotomy via subtemporal or retrosigmoid craniotomy became less popular with the advance of antiepileptic medications as well as the innovation of less invasive, percutanous techniques described in other chapters. In addition, the arrival of the microscope led to an alternative, nondestructive technique. In 1967 Peter Jannetta confirmed observations of Walter Dandy in the posterior fossa, describing the etiology of trigeminal neuralgia as being vascular compression.[1] With the advantage of the microscope and electrocautery, Jannetta achieved high success rates with vascular decompression using Teflon (Pfizer, New York, NY, USA) implants to displace the artery/vein away from the nerve.[1] With the gradual success of Jannetta's microvascular decompression, craniotomy for trigeminal rhizotomy became virtually a salvage operation.[1,5,7,21,22] In the current era, trigeminal rhizotomy is typically reserved for the patients who have undergone a MVD with no evidence of a compressing vascular structure or recurrent TN with poor outcomes.

Literature Review

We conducted a PubMed search for the following terms: "trigeminal neuralgia, microvascular decompression, partial sensory rhizotomy." We defined the search to include both microvascular decompression (MVD) and partial sensory rhizotomy (PSR) because in current practice, patients are typically offered the Jannetta MVD, and PSR is usually performed only during a negative posterior fossa exploration. Thus, it is unusual to schedule a patient for primary upfront PSR without knowledge of the status of vascular compression or without having performed a microvascular decompression previously. We also excluded studies on patients with multiple sclerosis and studies performed before 1989, which was the approximate date marking the entrance of magnetic resonance imaging (MRI) scans into routine clinical practice. We identified 33 papers and included 13 in our analysis. All studies were retrospective case series—Class III evidence. This is summarized in **Table 42.1**. The overall rate of performing a PSR during posterior fossa exploration for trigeminal neuralgia was 28% (438 of 1,538 patients). Hence, among surgeons who keep PSR in their armamentarium for surgical procedures, approximately one quarter of the patients will undergo a partial sensory rhizotomy at the time of surgery. This practice obviously excludes surgeons such as Dr. Jannetta himself,

Table 42.1 Literature review of studies including microvascular decompression (MVD) and partial sensory rhizotomy (PSR)

	Patients (*N*)		Pain-free outcome: 1 year (%)		Pain-free outcome: 2 years (%)		Pain-free outcome: 5 years (%)	
	MVD only	MVD + PSR	MVD only	MVD + PSR	MVD only	MVD + PSR	MVD only	MVD + PSR
Zhang et al 2012[37]	142	68	90.6	92.5	90.2	97.8	–	–
Pollock et al 2011[34]	59	8	87*	87*	–	–	78*	78*
Ma et al 2009[33]	86	10	–	–	–	70 (3 yrs)	–	–
Zakrzewska et al 2005[36]	245	60	–	–	–	–	79	72
Liu et al 2004[3]	0	40	–	80	–	–	–	–
Delitala et al 2001[25]	34	14	–	–	87.5	12.5	–	–
Howng et al 1998[26]	0	8	–	–	–	–	–	62.5
Walchenbach et al 1994[35]	51	5	–	–	–	–	71*	71*
Cho et al 1994[31]	376	24	86*	86*	–	–	–	–
Young et al 1993[30]	152	102	–	58	–	56	–	50
Jamjoom et al 1992[32]	49	11	–	–	88*	88*	–	–
Klun et al 1992[27]	178	42	–	–	–	–	94	51
Bederson et al 1989[24]	166	86	–	–	–	–	75*	75*

*Equal percentages due to outcomes not distinguished between the two groups.

who published on 1,185 patients in 1996 and did not report having performed a partial sensory rhizotomy on any of them.[23]

Technique for Partial Sensory Rhizotomy

Because PSR is not typically the first-line surgical treatment, there are limited literature reports describing PSR in the current era.[3,24–37] In all the literature reports, the choice of performing partial rhizotomy instead of traditional MVD was done on a case-by-case basis depending on whether a significant vascular structure was encountered during posterior fossa exploration. The variability in technique is described as follows. In a large series by Young et al 102 patients underwent a PSR.[30] The authors used intraoperative brainstem auditory evoked responses (BAER) and somatosensory evoked potentials (SSEP). In 74 patients who underwent PSR, one third to one half of the cross-sectional area of the sensory root was incised from its caudolateral part approximately 2 to 5 mm from the pons. In the other 9 patients, approximately two thirds of the nerve root was sectioned. No patients underwent a complete neurectomy. Klun reported his experience with partial sensory rhizotomy in 42 patients with a mean follow-up of 5.2 years.[27] His surgical technique consisted of sectioning one third or less of the portio major, with consideration of the distribution of trigeminal branches. The rhizotomy was performed as close as possible to the brainstem. Similarly, Zhang et al performed a PSR by cutting one fifth to one quarter of the breadth of the sensory root with scissors as close as possible to the brainstem using no coagulation.[37] In both case series by Liu and Apfelbaum[3] (40 patients) and Pollock et al[34] (8 patients) a partial rhizotomy of the trigeminal nerve consisted of sectioning approximately one third to one half of the nerve next to the brainstem, starting at its posterior inferior margin. They describe first scoring the pia with microscissors and then lengthening this resection using a microhook. They did not alter this technique based upon the locality or division of the patient's TN. Delitala et al reported on 14 patients who underwent a partial sensory rhizotomy; up to half of the inferolateral "portio major" was sectioned.[25] In another series of 8 patients, rhizotomy was performed with a microdissector and the extent of rhiztomy was determined by the patient's pain involvement, ranging from approximately one quarter to three quarters of the nerve[26] (**Fig. 42.1**).

In summary, the technique of partial sensory rhizotomy varies among different surgeons. Most surgeons perform partial sectioning using microscissors. The anatomical positions of the fibers that

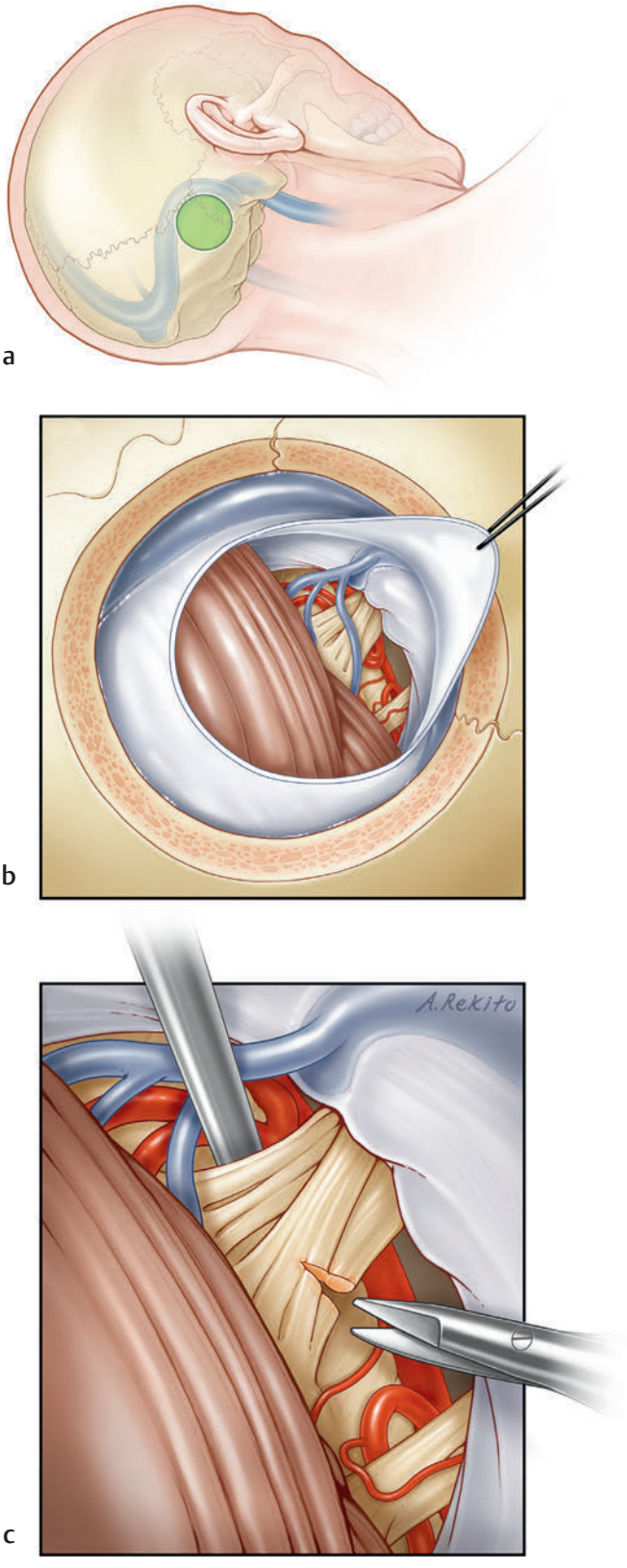

Fig 42.1 (**a**) Keyhole microvascular decompression craniotomy at the junction of the transverse and sigmoid sinuses. (**b**) Dural retraction showing the cerebellopontine angle and cranial nerve 5. (**c**) Inferocaudal partial sensory rhizotomy with microscissors.

innervate each branch of the trigeminal nerve have been studied.[38,39] The fibers from the mandibular division are found ventral-lateral throughout the length of the ganglion to the pons, the ophthalmic division fibers dorsomedial, and the maxillary division fibers in between. Thus, a partial sensory rhizotomy is usually performed by cutting the ventral (caudal) -lateral portion of the trigeminal nerve, although there is some variability, especially because the nerve (and its somatotopy) may rotate slightly upon exiting the pons and entering Meckel cave. In addition to direct sectioning techniques, Ma et al reported a different technique termed "nerve combing."[33] This technique resembles neurolysis in that a "microneedle" is used to separate individual fascicles of the trigeminal nerve. In personal communication with Dr. Michael Lim from Johns Hopkins University and in the senior author's (JYKL) own experience, alternative techniques have included direct injection of glycerol into the cisternal portion of the nerve. The efficacy of these different techniques cannot be compared directly.

Results and Outcomes

Overall, mixed results have been reported with PSR. **Table 42.1** shows our analysis of the literature review, depicting a trend toward poorer outcomes in the PSR group. Many series reported combined outcomes for the MVD-only group and the MVD + PSR group because a significant difference between the two groups could not be accounted for.[24,31,32,34,35] In one of the largest case series, Zakrzewska et al described 245 patients who underwent MVD only and 60 who underwent PSR.[36] Interestingly, the PSR group experienced the lowest satisfaction rate, with 4% of MVD patients reporting themselves as "not satisfied" versus 20% of PSR patients. Complications from PSR were the leading cause of poor outcomes in the PSR group. However, one can also speculate that the patients who required PSR have a different etiology of pain that may lower the potential success of any particular technique.

In the series by Young and Wilkins,[30] 83% of their 102 patients were pain free at 1 year follow-up, with no or mild sensory deficits in 82% of patients. The two main variables they reported as predictive of a poor pain outcome included reoperations and lack of preoperative involvement of the mandibular division. Bederson and Wilson performed a PSR on 30 patients in whom no vascular structures were encountered.[24] In addition, both a MVD and rhizotomy were performed for 56 patients in which vascular compression did not cause nerve indentation or distortion. Overall, about 75% of patients had an excellent result and 8% had good results. They reported increased sensory loss and dysesthesias in the rhizotomy group, particularly those with a history of prior lesioning or lysis procedures. At 5-year follow-up, they found a nonsignificant trend toward a better outcome in patients who underwent both a MVD and rhizotomy and a worse outcome for rhizotomy alone.

In Klun's series, immediate pain relief was achieved in 86% of the PSR patients; however, this rate dropped to 84% during the follow-up period.[27] The recurrence rate difference between the MVD group and rhizotomy group was dramatic because only 6% of the MVD group recurred versus 49% in the rhizotomy group. Complications were uncommon and consisted of hearing loss, corneal reflex impairment, and lesioning of the portio minor. The degree of parasthesias among those in the rhizotomy group varied widely; however, painful dysesthesias or anesthesia dolorosa was not encountered. One interesting point from his series was that labial herpes occurred in about half of the MVD patients and in virtually all of the PSR patients.

Lui and Apfelbaum described their experience with partial sensory rhizotomy of 40 patients[3] and reported complete pain relief in 32 of the patients (80%). In the 8 patients who did not have complete resolution of their pain, either medical treatment or additional percutaneous lesioning procedures helped control all but 1 patient's pain. Delitala et al reported immediate complete pain relief in 88% of their 42 patients.[25] During a 2-year follow-up this rate dropped to 72%; however, no patient had significant parasthesias. The authors recommended that venous compression and arterial compression that did not distort the nerve be considered a negative exploration and these patients should undergo partial sensory rhizotomy. In the small series of eight patients, five had complete pain relief without recurrence.[26] Two patients recurred at 2 and 3 years, respectively, and the pain was controlled medically. One patient had pain greater than was experienced preoperatively, and one patient developed anesthesia dolorosa. No hearing loss, corneal reflex deficits, or facial weakness was noted. In the "nerve combing" series of 10 patients, the overall pain-free outcome at 3 years was 70%, lower than the expected MVD pain-free outcome rate.[33]

Indications and Technique

Since 2011 the senior author has modified the standard microscopic MVD and has performed a fully endoscopic MVD.[40–42] We believe the use of the neuroendoscope for posterior fossa pathology may reduce complications from traditional microscopic surgery, leading to improved outcomes. With the endoscope,

minimal retraction on the cerebellum is needed for visualization, and the neuroendoscope allows superior panoramic visualization compared with a traditional microscope. In addition, the endoscope provides an unobstructed view of the Obersteiner–Redlich zone at the brainstem as well as at the entry into Meckel cave, and may provide additional detail of vascular compression (**Figs. 42.2, 42.3, 42.4**). This panoramic view may also be useful for evaluating which trigeminal nerve fascicles to incise during a rhizotomy.

In a quick review of patients of the senior author undergoing microvascular decompression within a 1-year span (May 2012–May 2013), 41 patients underwent posterior fossa exploration. Of these, 6 patients underwent microscopic surgery because of lack of endoscope sterilization at time of procedure. The vast majority, 85.3% of patients (35 of 41), underwent purely endoscopic surgery. Eleven of the 41 patients (27%) underwent a neurolysis with a round knife along the fascicles of the nerve similar to the "nerve combing" technique described above. Neurolysis (a variant of partial sensory rhizotomy) was performed when no compressive vessel was identified or when the senior author felt that the degree of compression by artery or vein was not great enough to be the sole cause of pain. Short-term pain-free outcomes are encouraging. The similar rates of neurolysis in our fully endoscopic series and in the PSR series in the literature review may suggest that even with angled endoscopes, there is no increase in the ability to identify additional vascular compression. However, longer term studies are needed.

For other facial neuralgias that require a neurectomy, such as geniculate neuralgia, our experience is that the endoscope allows a much greater appreciation of the anatomy and identification of the nerve. For geniculate neuralgia, the classic microscopic maneuver is to retract at the flocculus below the eighth nerve near the ninth nerve and to search

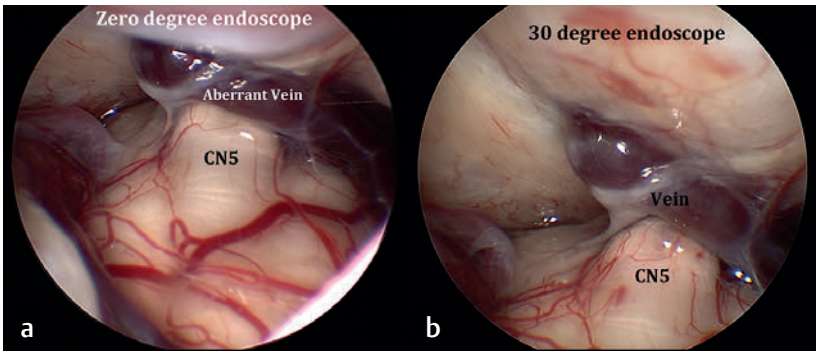

Fig. 42.2 Venous compression. This is a right-sided microvascular decompression for trigeminal neuralgia. One of the benefits of the angled endoscope is that it can help the surgeon appreciate anatomy that is not visible with a microscope. (**a**) In this case, the 0-degree endoscope (standard microscopic view) provides only a head-on view of the trigeminal nerve at the root entry zone. (**b**) A 30-degree up-angled endoscope can be used to carefully delineate the petrosal vein crossing the distal aspect of the trigeminal nerve. CN, cranial nerve.

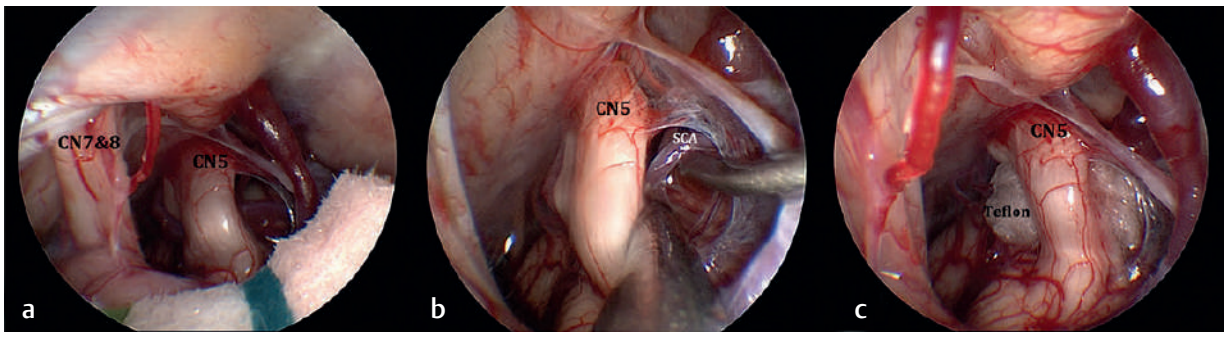

Fig. 42.3 SCA (superior cerebellar artery) compression. This is a left-sided microvascular decompression of trigeminal neuralgia. (**a, b**) This is an example of an endoscopic view of the classic vascular compression by the SCA, resulting in lateral and inferior deformation of the trigeminal nerve (CN 5) . The Dandy petrosal vein is not sacrificed in the great majority of fully endoscopic procedures because the panoramic view of the endoscope allows the vein to be visualized throughout the procedure. The degree of stretch on the vein can be monitored at all times. (**c**) Notice the improvement in the coloration of the nerve after the Teflon is placed in between the trigeminal nerve and the superior cerebellar artery. CN, cranial nerve.

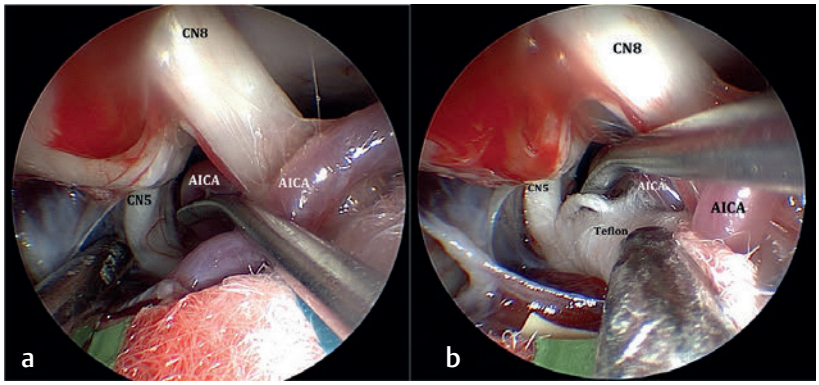

Fig. 42.4 AICA (anterior inferior cerebellar artery) compression. This is a right-sided microvascular decompression for trigeminal neuralgia. In this case, the vascular compression is easily identified. (**a**) The fifth nerve is deformed from the caudal side by a branch of the AICA. (**b**) A single piece of Teflon is placed between the trigeminal nerve and AICA. CN, cranial nerve.

for a distinct geniculate nerve. However, using a 30-degree endoscope facing medially eliminates the need for a retractor. **Fig. 42.5a** shows that using a 0-degree endoscope allows visualization of the seventh nerve but not the nervus intermedius. The 30-degree angled-down endoscope (**Fig. 42.5b, c**) allows much better appreciation of the anatomy and identification of the nervus intermedius. In the senior author's experience, occasionally the endoscope has illuminated vascular compression that could not be visualized using a traditional microscope. In these cases, the endoscope was essential in avoiding a sensory rhizotomy.

Conclusion

In the advancement of the surgical treatment of trigeminal neuralgia there have been a number of improvements of surgical technique. The history of trigeminal rhizotomy ranges from the complete removal of the gasserian ganglion, to complete sectioning of the dorsal root, to preserving the motor and ophthalmic fibers as well as differentiating between the mandibular and maxillary branching fibers. The current practice involves posterior fossa exploration with performance of a standard Jannetta MVD procedure if the vascular contact appears to be significant. The partial sensory rhizotomy is performed at a rate of approximately 28%. The rhizotomy is generally performed on the infero-caudal-lateral portion of the nerve using a range of techniques. From the literature reports, a large proportion of patients who undergo this procedure have good pain relief with only partial sensory loss. The lack of "satisfaction" of patients undergoing partial sensory rhizotomy may be a reflection of sensory complications or a reflection of underlying difference in pain etiology. Fully endoscopic techniques may identify additional points of vascular contact, but outcomes remain preliminary. Partial sensory rhizotomy of the trigeminal nerve continues to be a tool in the armamentarium of surgeons treating patients with trigeminal neuralgia. Although the level of evidence is Class III, PSR procedures should be used in a judicious manner.

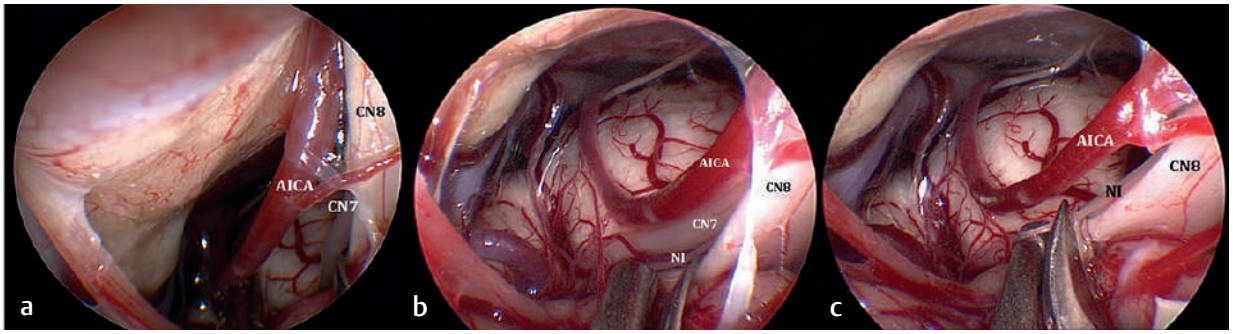

Fig. 42.5 Geniculate neuralgia. The geniculate nerve can be very difficult to find. (**a**) The 0-degree endoscope is the standard microscopic view, which allows visualization of the 7th nerve, but not of the nervus intermedius (NI) . (**b**) However, a 30-degree endoscope eliminates the need for a retractor and allows much better appreciation of the anatomy and identification of the nervus intermedius. (**c**) The sectioning of the nervus intermedius. AICA, anterior inferior cerebellar artery; CN, cranial nerve.

Editor's Comments

Partial sensory rhizotomy (PSR) is an important aspect of the surgical treatment of trigeminal neuralgia (TN). It has not gotten nearly as much attention as microvascular decompression (MVD), but if 28% of patients who undergo surgery for planned MVD have PSR due to the absence of convincing vascular compression, then it should have. Parenthetically, we have found almost *exactly* the same rate of no vascular compression in our series of posterior fossa surgery for TN (Chapter 41).

Doctors Lang and Lee have outlined the history of PSR and the current state of the outcome data. Loyalty to their university tradition, and to the contributions of Spiller and Frazier, may have prevented them from acknowledging the seminal contribution of Harvey Cushing to the development of trigeminal rhizotomy.[43] They have summarized the literature on rhizotomy, although, as they point out, the evidence derives only from case series (Class III).

Whether a PSR is performed by microscopic or endoscopic techniques is a matter that could easily be subject to a randomized trial, at centers adept at both techniques. In my view, our principal goal should be a randomized prospective trial of MVD versus PSR for trigeminal neuralgia.

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43 Trigeminal Neurectomy

Richard K. Osenbach

Painful conditions involving structures of the face and teeth have been recognized for more than 10 centuries. Indeed, early in the previous millennium, the Persian physician and philosopher Avicenna wrote about painful disorders involving the face. Facial pain is, in fact, a common affliction that affects many people. In most cases, the symptoms are acute and transient and resolve with minimal medical intervention. In some patients, however, facial pain may persist and evolve into a disabling chronic pain syndrome that can be quite refractory to conventional pain therapies.

The best-known chronic facial pain syndrome is classic trigeminal neuralgia. Although John Locke has been credited with the description of this malady in 1677, the first clear description actually was given in 1671 by Drs. Johannes Michael Fehr and Elias Schmidt, who elucidated the details of the ailment as it affected Johannes Laurentius Bausch, a physician, philosopher, and municipal counselor of Schweinfurth, Franconia.[1]

Although trigeminal neuralgia is the most-recognized and best-studied of the facial neuralgias, it is by no means the only cause of facial pain. Indeed, many conditions can result in chronic facial pain of such severity as to warrant medical intervention. Some of these conditions may cause damage or injury to one or more peripheral branches of the trigeminal nerve and lead to a condition known as *trigeminal neuropathic pain*.[2] For example, surgery on the maxillary sinus can be complicated by damage to the infraorbital nerve, which in turn can lead to neuropathic pain in the corresponding cutaneous distribution of the nerve. Facial fractures involving the supraorbital ridge can lead to damage to the supraorbital and/or supratrochlear nerves. Also, dental procedures such as root canal and tooth extractions can damage the peripheral nerve endings and lead to chronic intractable pain in the jaw and mouth.

The treatment of facial pain in general and trigeminal neuralgia in particular has undergone considerable evolution in terms of both medical and surgical therapy. Currently, an array of procedures can be performed for medically refractory trigeminal neuralgia as well as for other selected facial neuralgias. This chapter is devoted to examining the indications for, techniques of, and results from peripheral trigeminal neurectomy, the oldest recorded treatment for trigeminal neuralgia. These particular techniques are currently more of historical than practical interest, given the alternatives such as the minimally invasive percutaneous needle techniques (radiofrequency gangliolysis, glycerol rhizolysis, and balloon microcompression) and stereotactic radiosurgery, especially for the treatment of trigeminal neuralgia. Moreover, the surgical treatment of trigeminal neuropathic pain has evolved with the increasing application of nonablative techniques such as peripheral trigeminal branch stimulation and epidural motor cortex stimulation. Regardless, even though these techniques are rarely if ever utilized in contemporary neurosurgical practice, they still have an important place in the history of neurosurgical treatment trigeminal neuralgia and other facial pain disorders.

History of Peripheral Trigeminal Branch Ablation

The destruction of peripheral branches of the trigeminal nerve as a treatment for trigeminal neuralgia goes back more than two centuries. Schlichting was originally credited with performing the first peripheral nerve operation for trigeminal neuralgia in 1748. As it turns out, the first peripheral destructive operations for tic douloureux were carried out, albeit unsuccessfully, by Maréchal, surgeon to King Louis XIV, in 1730 and 1732.[3] In the second patient, pain relief was achieved temporarily, but it lasted only 2 months. Temporary pain relief from peripheral destructive procedures would prove to be a common, recurring theme. André reoperated on Maréchal's second patient by exposing the mandible and then

applying a hot iron to exfoliate the bone. He then enlarged the mandibular foramen with a trephine, presumably to expose the inferior alveolar nerve, which he destroyed by applying a liquid caustic.

Following Maréchal and André, others performed a variety of procedures on peripheral branches of the trigeminal nerve for the treatment of trigeminal neuralgia. Lizars and Warren cut the inferior alveolar nerve within its bony canal of the mandible. Malgaige, in 1849, and Langenbeck, some two decades later, devised a method of sectioning the infraorbital nerve on the floor of the orbit. Presumably because of the transient pain relief with the more distal procedures, attempts were made to divide the nerve(s) as close to the trigeminal ganglion as possible. Indeed, Kronlein devised a series of procedures for exposing the maxillary and mandibular divisions at the foramen rotundum and foramen ovale, respectively. Kronlein's technique involved making a U-shaped incision extending from the ear to the molar prominence and then resecting the zygoma and coronoid process of the mandible. He then reflected the temporalis muscle superiorly to expose the second and third divisions exiting the cranial base.[4]

During the same period, it was discovered that injection of a destructive liquid into branches of the trigeminal nerve was not only effective but also simpler than open ablative procedures. Numerous substances were tried, including chloroform, osmic acid, 2% cocaine followed by 60% ethanol, chromates, formolized glycerine, carbolized gylcerine, alcoholized metholated gylcerine, ether, antipyrene, salicylate of soda, and quinine salts in various proportions and doses.[1] Sicard, in 1918, having tried many of these agents, concluded that alcohol was the best compound. In addition to chemical neurolysis, several surgeons attempted peripheral trigeminal ablation using radiofrequency electrocoagulation.

Ultimately, as experience accumulated, it became clear that the relief provided by peripheral branch ablation was only temporary and that developing procedures that could produce more successful long-term relief was desirable. Although more sophisticated procedures currently exist (as discussed in other chapters), peripheral branch destruction remains a useful procedure in the appropriate clinical setting (see subsequent discussion).

Clinically Relevant Anatomy of the Peripheral Trigeminal Nerve

A thorough understanding of the anatomy and sensory distribution of the peripheral trigeminal nerve is essential when considering any type of ablative procedure on one or more of these nerves. Indeed, failure to recognize correctly the neural distribution of the patient's nerve consists of three major divisions: the ophthalmic (V-1), maxillary (V-2), and mandibular (V-3) nerves. Phylogenetically, the trigeminal nerve is the main cutaneous sensory nerve of the head and face. As the phylogenetic ladder is ascended, the sensory distribution of the trigeminal nerve is expanded, whereas those of the facial, glossopharyngeal, and vagal nerves (of which the afferent inputs enter the spinal trigeminal tract and nucleus) are reduced. In addition to providing most of the somatic sensory input from cutaneous structures, the trigeminal nerve supplies sensation to the cornea, most of the mucous membrane surfaces of the oral and nasal cavities, the mucosa of the paranasal sinuses, the intracranial dura, periodontal structures, and portions of the large intracranial arteries.[5] The pertinent anatomy of each division of the trigeminal nerve is described later in this chapter. The cutaneous innervation of the head is illustrated in **Fig. 43.1**.

Ophthalmic Nerve

The ophthalmic nerve, or first division, is a flat band, approximately 2.5 cm long, that exits the anterior superior portion of the gasserian ganglion and enters the orbit through the superior orbital fissure. The ophthalmic nerve is purely sensory, providing sensation to the globe, conjunctiva, lacrimal gland, mucous membranes of the nose and paranasal sinuses, and the skin of the forehead, scalp, eyelids, and nose. The ophthalmic nerve sends a small recurrent filament to supply the tentorium and dura of the anterior fossa and then, before passing through the superior orbital fissure, divides into three branches: frontal, lacrimal, and nasociliary.

Frontal Nerve

For all practical purposes, the frontal nerve, which is the largest of the three branches, can be considered a continuation of the ophthalmic nerve. The nerve passes forward and, at approximately the midpoint from its origin to the superior orbital rim, divides into the larger *supraorbital* and smaller *supratrochlear* nerves. The supraorbital nerve leaves the orbit through the supraorbital foramen, providing filaments to the upper eyelid in the process. It then divides into medial and lateral branches beneath the frontalis muscle. The smaller, medial branch pierces the frontalis muscle and supplies cutaneous innervation to the scalp posterior to the parietal bone. The larger, lateral branch penetrates the galea and supplies the scalp all the way back to the lamb-

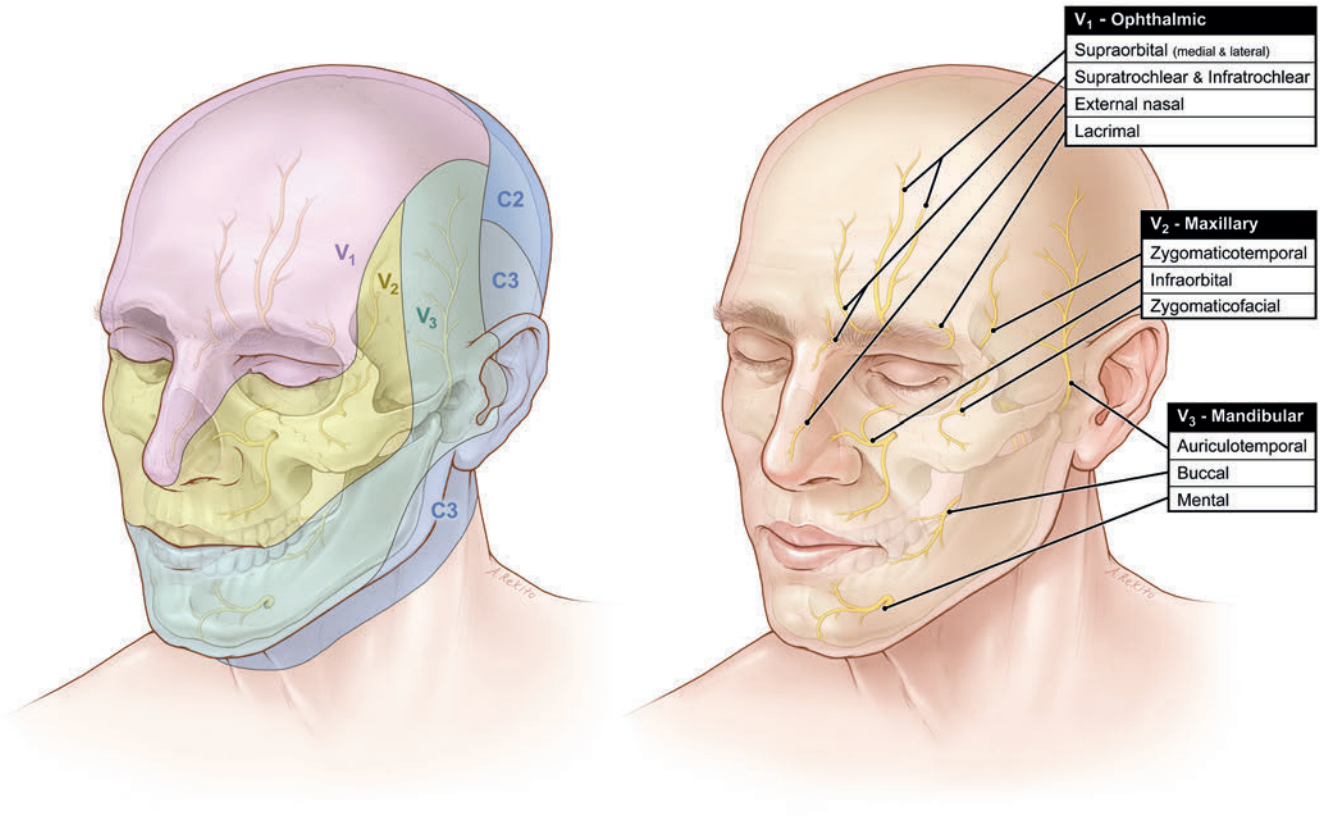

Fig. 43.1 The cutaneous innervation of the head and neck. The cutaneous branches of the major divisions of the trigeminal nerve are indicated. Note that the supraorbital, infraorbital, and mental nerves all lie in the vertical plane of the pupil.

doidal suture. Occasionally, the supraorbital nerve branches proximal to its foramen, in which case the lateral branch generally occupies the foramen and the medial branch exits through a separate foramen.

The supratrochlear nerve turns medially within the orbit above the pulley of the superior oblique muscle, where it produces a filament that communicates with the infratrochlear branch of the nasociliary nerve. After piercing the orbital fascia, branches are given off to supply the skin and conjunctiva of the medial upper lid. After exiting its foramen, it divides into branches that supply the lower and medial portions of the forehead.

Lacrimal Nerve

The *lacrimal nerve* is the smallest of the three branches arising from the ophthalmic nerve. It passes anteriorly, entering the orbit through the narrowest portion of the superior orbital fissure. Within the orbit, it runs along the superior border of the lateral rectus muscle and enters the lacrimal gland to supply the gland and the adjacent conjunctiva. The nerve then pierces the orbital septum and terminates in the skin of the upper eyelid.

Nasociliary Nerve

Intermediate in size between the frontal and lacrimal nerves, the *nasociliary nerve* occupies the deepest position in the orbit of the three branches. The nerve enters the orbit between the heads of the lateral rectus muscle and between the superior and inferior divisions of the oculomotor nerve. The nasociliary nerve runs obliquely through the orbit, crossing above the optic nerve and below the superior rectus and oblique muscles approaching the medial wall of the orbit. At this point, it exits the orbit through the anterior ethmoidal foramen as the anterior ethmoidal nerve and enters the intracranial cavity just above the cribriform plate, following which it penetrates the bone at the side of the crista galli to enter the nasal cavity, where it supplies branches to the mucous membranes of the nose.

The nasociliary nerve gives rise to several branches. The *long ciliary nerves* emerge as the nasociliary nerve crosses the optic nerve. The long ciliary branches pass through the ciliary ganglion and accompany the short ciliary nerves, pierce the posterior sclera, and, running between it and the choroid, supply sensation to the iris and cornea. The *ethmoidal branches* supply the mucosa of the sinuses.

These consist of a *posterior ethmoidal branch,* which supplies the posterior ethmoid and sphenoid sinuses, and *anterior ethmoidal branches,* which arise as the nerve passes through the anterior ethmoidal foramen; the latter supply the frontal and anterior ethmoid sinuses.

The infratrochlear nerve arises from the nasociliary nerve just proximal to the anterior ethmoidal foramen. After running anteriorally along the upper border of the superior rectus muscle, it is joined by a branch of the supratrochlear nerve and then passes to the medial angle of the eye to supply the skin of the eyelids and side of the nose, the conjunctiva, lacrimal sac, and caruncula lacrimalis. Finally, internal and external nasal branches are given off: The *internal nasal branches* supply the mucosa of the anterior part of the septum and lateral wall of the nasal cavity; the *external nasal branches* supply the skin of the ala and apex of the nose.

Maxillary Nerve

The *maxillary nerve,* which is entirely sensory, arises from the midportion of the trigeminal ganglion. It initially passes rostrally in the inferior portion of the lateral wall of the cavernous sinus, continues beneath the dura, and exits the skull through the foramen rotundum. Henceforth, it courses through the pterygopalatine fossa, enters the orbit through the inferior orbital fissure, and then runs along the floor of the orbit (roof of the maxillary sinus). In the posterior portion of the orbit, it becomes the infraorbital nerve, which then continues in the infraorbital groove and ultimately emerges onto the face through the infraorbital foramen. The maxillary nerve provides cutaneous innervation to the middle of the face, lower eyelid, side of the nose, and the upper lip. It also supplies sensation to the mucous membranes of the nasopharynx, maxillary sinus, soft palate, tonsil, and roof of the mouth as well as the upper gums and teeth. There are five sets of branches of the maxillary nerve: intracranial, pterygopalatine, posterior superior alveolar, infraorbital, and facial.[5]

Intracranial and Pterygopalatine Branches

The *middle meningeal nerve* is an intracranial branch of the maxillary nerve, which arises just distal to the gasserian ganglion. The nerve accompanies the middle meningeal artery and supplies the dura. There are multiple branches within the pterygopalatine fossa, including the zygomatic nerve, pterygopalatine nerves, and posterior superior alveolar branches. The *zygomatic nerve* originates in the pterygopalatine fossa, enters the orbit through the inferior orbital fissure, and divides into temporal and facial (malar) branches. The *temporal branch,* after running in the groove within the zygoma along the lateral orbital wall, pierces the zygoma and enters the temporal fossa, where it penetrates the temporalis muscle and is distributed to the skin of the side of the forehead. The *facial* or *malar branch* emerges from the inferolateral angle of the orbit, pierces the orbicularis oculi muscle, and supplies the skin of the malar eminence.

The *pterygopalatine nerves* are divisible into four groups: orbital, palatine, posterior superior nasal, and pharyngeal. The *orbital (ascending) branches* enter the orbit through the inferior orbital fissure to supply the periosteum, along with the posterior ethmoid and sphenoid sinuses, through filaments that pass through the frontoethmoidal suture. The *greater (anterior) palatine nerve* exits the fossa through the pterygopalatine canal and enters the hard palate to supply the gums and mucosa of the hard palate nearly as far as the incisors. The greater palatine nerve has two sets of branches: the *lesser palatine nerves,* which emerge from their corresponding foramen and supply the soft palate, uvula, and tonsil; and the *posterior inferior nasal branches,* which are distributed to the inferior nasal turbinate. The *posterior superior nasal branches* enter the posterior nasal cavity through the sphenopalatine foramen and supply the superior and middle turbinates, the mucosa of the posterior ethmoid sinuses, and the posterior nasal septum. The *pharyngeal branch (pterygopalatine nerve)* passes through the pharyngeal canal to supply the mucosa of the nasopharynx posterior to the meatus of the eustachian tube.

Posterior Superior Alveolar Branches

The *posterior superior alveolar branches* arise from the trunk of the maxillary nerve just before it enters the infraorbital groove. These branches radiate several twigs, which supply the gums and adjacent mucosa before entering the posterior alveolar canals. They then traverse the bony maxilla and provide innervation to the molar teeth along with branches to the maxillary sinus. The posterior superior alveolar branches communicate with the middle superior alveolar nerve (discussed later).

Branches in the Infraorbital Canal

The maxillary nerve has two main branches within the infraorbital canal: anterior and middle superior alveolar branches. The *middle superior alveolar branch* supplies the two premolar teeth; the *anterior superior alveolar branch* supplies the incisor and canine teeth. After giving rise to these branches, the infraorbital nerve emerges into the face through the infraorbital foramen.

Facial Branches

The *inferior palpebral branches* pass superiorly and supply the skin and conjunctiva of the lower eyelid, anastomosing with the zygomaticofacial nerves at the lateral angle of the orbit. The *external nasal branches,* which communicate with the terminal twigs of the nasociliary nerve, innervate the skin of the nose and the cartilaginous septum. The largest facial branches in both size and number are the *superior labial branches,* which pass deep to the levator labii superioris muscle and supply the skin of the upper lip, the mucous membranes in the mouth, and the labial glands.

Mandibular Nerve

The *mandibular* or *third division* is the largest of the peripheral trigeminal branches. In addition to the large sensory root, the mandibular nerve contains a small motor root. The afferent portion of the nerve supplies the skin of the temporal region, auricula, external meatus, cheek, lower lip, and lower part of the face. The mucous membranes of the cheek, tongue, and mastoid air cells along with the lower teeth and gums are also supplied by the third division, along with the mandible and temporomandibular joint. Portions of the dura and skull also receive sensory supply from this division. The sensory and motor roots emerge separately from the skull base through the foramen ovale, but they unite just outside the skull, forming a common trunk for a distance of 2 or 3 mm. The main trunk gives off a meningeal branch and the medial pterygoid nerve before bifurcating into a smaller anterior and larger posterior division.

Anterior Division

The *anterior division* of the mandibular nerve contains a small number of sensory fibers along with all the motor fibers except for those carried in the medial pterygoid and mylohyoid nerves. The *masseteric nerve* passes laterally above the lateral pterygoid to enter the masseter muscle and then provides a twig to the temporomandibular joint. The *buccal nerve* passes between the heads of the lateral pterygoid muscle and eventually emerges from beneath the inferior border of the masseter. It supplies the skin of the cheek over this muscle along with penetrating branches, which supply the mucosa of the mouth and gums in this area.

Posterior Division

The *posterior division* of the mandibular nerve has three major branches: the auriculotemporal, lingual, and inferior alveolar nerves. The posterior division is chiefly sensory, although a small number of motor fibers also travel in the branches.

The *auriculotemporal nerve* typically originates from two roots, which encircle the middle meningeal artery in the vicinity of the foramen spinosum. It passes posteriorly, deep to the lateral pterygoid muscle along the medial aspect of the mandible, and then it turns superiorly and runs with the superficial temporal artery between the auricula and mandibular condyle. After it emerges from beneath the parotid gland, the nerve passes over the root of the zygoma and divides into superficial branches. The small branches of the auriculotemporal nerve provide afferent innervation to the skin of the temporal region (superficial temporal branch), the skin of the anterior auricula (primarily the helix and tragus), the external auditory meatus, and the temporomandibular joint.

The *lingual nerve* initially lies deep to the lateral pterygoid muscle and runs parallel to the inferior alveolar nerve, with which it has an anteromedial relationship. It then runs between the mandible and medial pterygoid muscle and crosses obliquely above the superior pharyngeal constrictor and styloglossus to reach the lateral aspect of the tongue. After passing between the hyoglossus and the submandibular gland, the lingual nerve runs along the undersurface of the tongue, providing somatic sensation to the anterior two thirds of the tongue and the adjacent mucous membranes of the mouth and gums.

After arising from the posterior division of the mandibular nerve, the *inferior alveolar (inferior dental) nerve* accompanies its corresponding artery, running deep to the lateral pterygoid and then passing between the sphenomandibular ligament and ramus of the mandible to enter the mandibular foramen. It travels anterior within the mandible in the mandibular canal to the mental foramen and divides into two terminal branches: the *mental* and *incisive nerves.* The dental branches arise from the main trunk of the inferior alveolar nerve within the bone and supply the lower molar and premolar teeth. The incisive branches form a plexus, which supplies the lower canine and incisor teeth. After exiting through the mental foramen, the mental nerve divides into three branches, which supply the skin on the chin and the skin and mucous membrane of the lower lip.

■ Indications for Peripheral Trigeminal Neurectomy

It is a well-known fact that destructive procedures on the peripheral branches of the trigeminal nerve—in particular, peripheral branch neurectomies—are effective in producing pain relief from trigeminal neuralgia. Once common, these procedures currently

are rarely if ever performed for trigeminal neuralgia because of the popularity of microvascular decompression and percutaneous retrogasserian techniques, such as radiofrequency thermocoagulation, glycerol injection, and balloon microcompression. Additionally, it seems as though stereotactic radiosurgery continues to play an ever-increasing role in the treatment of trigeminal neuralgia. Indeed, some surgeons now advocate stereotactic radiosurgery as primary treatment for trigeminal neuralgia. Nevertheless, the reason that peripheral neurectomy is effective is it eliminates the nociceptive afferent input to the spinal trigeminal nucleus and tract. In addition, there is evidence that trauma to peripheral branches of the trigeminal nerve produce temporary degenerative changes in trigeminal ganglion cells, which may contribute to the pain relief that occurs following neurectomy. The principal reason that peripheral neurectomy is not as popular as it once was is that it is only a temporary solution to the problem.

Although purely palliative, peripheral neurectomy has a number of advantages. The fact that peripheral neurectomy is capable of producing pain relief is unquestionable.[6–11] Peripheral neurectomies are generally technically simple as long as one has an understanding of the pertinent anatomy. These procedures can be performed under general or local anesthesia. One of the most important advantages is that peripheral neurectomy is a low-morbidity procedure that can be especially beneficial in an older and infirm patient who might not tolerate a more involved procedure. It is particularly useful in patients who suffer from trigeminal neuralgia involving the first division because there is no risk of producing corneal anesthesia, as there is with retrogasserian procedures, especially radiofrequency lesions. Peripheral neurectomy also may prove beneficial in the treatment of selected patients with trigeminal neuropathic pain syndromes caused by dental surgery, surgery on the paranasal sinuses, or injury to peripheral branches from facial trauma.

In patients with trigeminal neuropathic pain, several factors may have prognostic value in selecting patients who might benefit from a neurectomy. These factors are similar to those used to select appropriate candidates with peripheral nerve neuropathic pain for neurectomy or neuroma resection. These factors include pain related to trauma, pain within a single nerve distribution, the presence of Tinel sign, and complete pain relief with local anesthetic nerve blockade.[12,13] If all these conditions are satisfied, neurectomy is 50 to 60% effective in relieving pain. One final advantage is the lack of need for any special intraoperative imaging such as biplane fluoroscopy, which is essential in performing retrogasserian procedures. As with any surgical procedure being considered for intractable pain, all patients who are candidates for peripheral neurectomy should have completed an exhaustive course of pharmacological therapy that failed to bring relief.

Peripheral Neurolysis Using Injection Techniques

Injection techniques play an important role in the management of patients with refractory facial pain syndromes, especially when a peripheral ablative procedure is contemplated. Indeed, local anesthetic nerve blocks can have excellent predictive value in determining whether a neurectomy will be beneficial. An alternative to surgical neurectomy is the injection of neurolytic substances into the nerve. The most commonly used agent has traditionally been alcohol, although within the last decade, there have been reports regarding the use of other agents such as streptomycin.[14,15]

Peripheral trigeminal branch blocks also can assist in illuminating the exact neural distribution of pain. In the performance of diagnostic blocks, several practical points should be kept in mind. The first is the choice of local anesthetic. Generally, an agent such as 0.5% lidocaine or 0.25% bupivacaine is satisfactory. My preference is to use a 50:50 mixture of 1% lidocaine and 0.5% bupivacaine *without* epinephrine. Under normal circumstances, primary afferent neurons do not exhibit catecholamine sensitivity, and their activity is unaffected by catecholamines or sympathetic outflow.[16] Afferent neurons that have been injured, however, exhibit up-regulation of catecholamine receptors and develop hypersensitivity to catecholamines. Under these circumstances, injection of a local anesthetic containing epinephrine around an injured nerve actually may potentiate pain and conceivably produce a false-negative (no pain relief when pain relief may have occurred) result from the block. Another important point is that a diagnostic nerve block should be as precise and specific as possible such that accurate information is gained. This is accomplished by having a thorough understanding of the anatomy and by using as little volume of anesthetic as possible. Injection of large amounts of anesthetic may result in anesthesia in the desired nerve distribution but may also diffuse and result in blockade of other nerves and thereby skew the information. The following section outlines the techniques for somatic blockade of the peripheral trigeminal branches of the head.

Ophthalmic Nerve Branches

Supraorbital and Supratrochlear Nerves

Local anesthetic blockade of the supraorbital and supratrochlear nerves is a simple procedure. The supraorbital nerve and foramen lie in the vertical place occupied by the pupil with the patient looking straight ahead.[17] The block is achieved most easily above the eyebrow after the nerve has exited its foramen. The

supratrochlear nerve runs parallel and approximately one fingerbreadth medial to the supraorbital nerve. The nerve can be blocked as it emerges from the eyebrow or by medial extension of an anesthetic wheal used to block the supraorbital nerve **(Fig. 43.2**).

Infratrochlear and Anterior Ethmoidal Nerves

The terminal branches of the nasociliary nerve can be blocked by inserting a 27-gauge needle 1 cm above the inner canthus and directing it backward and slightly medially to a depth of approximately 1 inch (**Fig. 43.2**). This trajectory allows the needle to pass just lateral to the medial wall of the orbit but medial to the globe and medial rectus muscle. Once positioned, 1 mL of local anesthetic is slowly injected as the needle is withdrawn. The most significant complication is related to intraorbital hemorrhage from damage to the orbital veins, which can result in proptosis. Therefore, a small-gauge needle should be used, and repeated insertion should be avoided.

Maxillary Nerve and Branches

Main Trunk

The main trunk of the maxillary nerve can be blocked within the pterygopalatine fossa using a lateral approach (**Fig. 43.3**). Blockade of the nerve at this point will produce profound analgesia of the ipsilateral upper jaw, teeth, and overlying skin and soft tissues. The point of needle insertion is at the midpoint of the zygoma overlying the coronoid notch of the mandible. The needle is introduced and directed medially until contact is made with the lateral pterygoid plate along the medial wall of the infratemporal fossa, usually at a depth of about 5 cm. The needle then is "walked" along the lateral pterygoid plate anteriorly until the pterygopalatine fossa is encountered, and then it is advanced a centimeter deeper.[17] A few milliliters of local anesthetic are instilled to produce the desired effect. Incidentally, this technique also can be used for blockade of the sphenopalatine ganglion, although selective blockade of the ganglion without involving the maxillary nerve is difficult if not impossible. The major morbidity of maxillary nerve block is a hematoma in the infratemporal or pterygopalatine fossa, which can spread into the orbit and produce a black eye. Treatment is according to symptoms. The other possible complication is related to temporary blindness due to diffusion of local anesthetic. Because of the proximity of this region to the orbit, this procedure probably should be avoided for permanent neurolytic blockade.

Infraorbital Nerve

Blockade of the infraorbital nerve can be performed at the junction of the medial and middle thirds of the inferior orbital rim. The landmark for the infraorbital nerve is again the pupillary line. The infraorbital foramen is configured such that its long axis is directed medially and caudally. Therefore, cannulation of the foramen requires that the needle be directed laterally and cephalad (**Fig. 43.2**). The block can be accomplished by injecting 1 to 2 mL of anes-

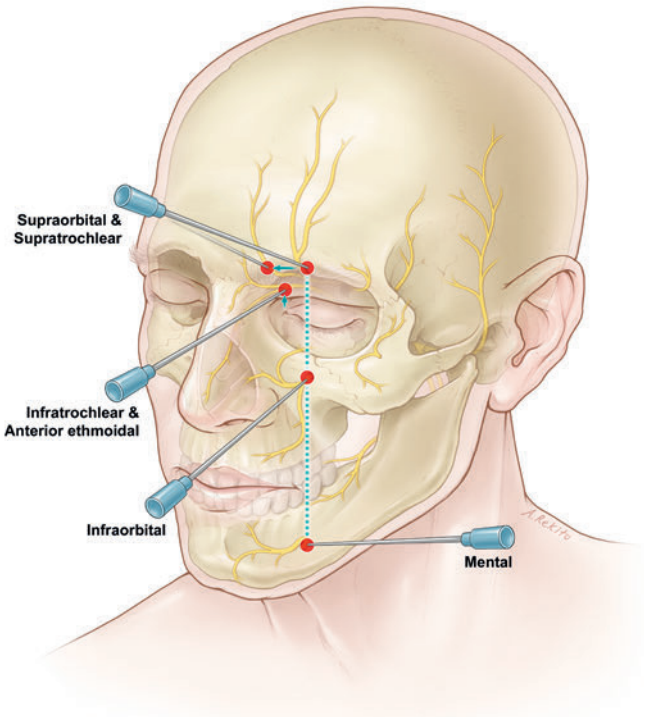

Fig. 43.2 The entry sites and needle trajectories for blockade of the superficial branches of the trigeminal nerve.

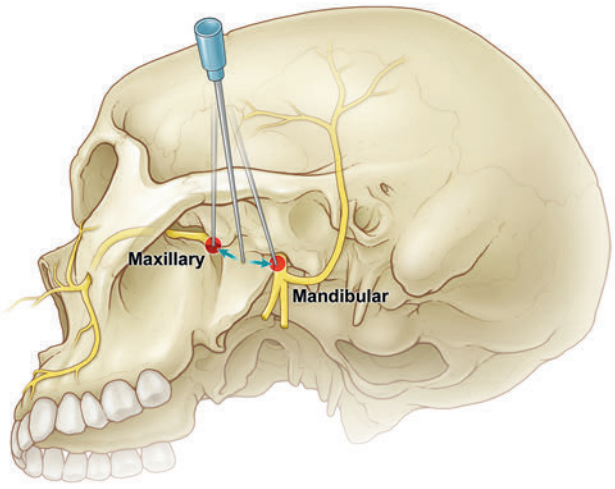

Fig. 43.3 The technique for blockade of the maxillary and mandibular nerves from a lateral approach.

thetic using a small-gauge needle at the point where the nerve exits the foramen.

Mandibular Nerve and Branches

Main Trunk

The main trunk of the mandibular nerve can be accessed using the same approach as that described for the maxillary nerve in the pterygopalatine fossa. The technique differs once the medial wall of the infratemporal fossa is encountered. The needle is "walked" *posteriorly* along the lateral pterygoid plate until paresthesias in the third division are elicited (**Fig. 43.3**).[17] Once paresthesias are obtained, several milliliters of local anesthetic are instilled. If a high enough concentration of local anesthetic is used (1% lidocaine or its equivalent), motor blockade will likely occur. Although this is not particularly problematic with temporary blockade, permanent neurolysis can result in a lack of coordination of jaw movements, which can be extremely distressing to the patient. Another consideration is the proximity of the otic ganglion, which supplies secretomotor fibers to the parotid gland to the mandibular nerve. Mandibular blockade cannot be accomplished without anesthetizing the otic ganglion. Thus, permanent mandibular neurolysis would result in permanent impairment of parotid secretion. One final word of caution regarding third-division blockade: Once the needle has been "walked" posteriorly off the lateral pterygoid plate, it should never be inserted deeper because it can penetrate the superior constrictor muscle and enter the pharynx.

Mental and Auriculotemporal Nerves

The mental foramen lies in the same vertical plane as do the pupil and the supraorbital and infraorbital foramina. The position varies depending on age and dentition, lying more caudal on the mandible in younger people and nearer the margin of the mandible in older and edentulous patients. To perform an extraoral block of the mental nerve, the needle is directed anteriorly and caudally.[17] The auriculotemporal nerve can be blocked as it ascends over the posterior root of the zygoma accompanied by the superficial temporal artery, which lies anteriorly.

Nerve Avulsion (Neurectomy) Procedures

Supraorbital Neurectomy

Supraorbital neurectomy is indicated for patients with trigeminal neuralgia limited to the first division or for patients with posttraumatic neuropathic pain within the distribution of an accessible nerve. The technique of supraorbital neurectomy is illustrated in **Fig. 43.4**. My preference is to perform the procedure under local anesthesia, although if it is tolerated, general anesthesia also can be used. The patient is positioned supine with the head supported on a padded headrest and the back of the table is raised to a position of comfort. The eyebrow should *never* be shaved because the hair may not grow back. After the area is prepared and draped, the skin of the eyebrow is infiltrated with local anesthetic, and an incision is made through the hair of the eyebrow. The incision is slowly and carefully deepened until the branches of the supraorbital and supratrochlear nerves can be identified. The supraorbital nerve usually can be readily identified exiting the supraorbital foramen as a fairly robust bundle composed of several fascicles. The nerve is isolated by using a nerve hook, ensuring that all fascicles have been identified and isolated. The nerve often is accompanied by the supraorbital artery, which can be either spared, if possible, or ligated and divided. By using a fine rongeur to remove a small lip of bone over the supraorbital foramen, a longer segment of nerve can be isolated. Once the nerve has been isolated, it can be removed using a number of different techniques.[18]

Classically, a hemostat grasps the nerve, sharply divides it, and then twists to avulse a portion of the nerve from within the foramen. The technique used by the author differs somewhat (**Fig. 43.4**). Once a generous length of the nerve has been exposed, it is placed on stretch and doubly ligated with ligatures of 3–0 silk as far proximal as is technically feasible. The bipolar unit then is used to cauterize the epineurium between the two ligatures, taking care not to violate the epineurium. The nerve then is divided distal to the second ligature and allowed to retract into the foramen. The foramen can then be plugged with bone wax. The supratrochlear nerve also can be removed in a similar fashion through the same incision. This procedure is similar to that used for peripheral neurectomy in the extremities, except that in the extremity the proximal stump is placed into the muscle or a hole that has been drilled in a nearby bone.

Persing and Jane described a slightly different technique, which may be slightly more cosmetic.[19] They place the incision in the supratarsal fold of the upper eyelid, about 9 to 11 mm above the border of the upper eyelash (**Fig. 43.5**). An incision is made and carried through the orbicularis oris to the level of the orbital septum, which consists of a thin layer of fascia just above the levator oculi muscles. The dissection then is carried out in an avascular plane above the orbital septum to the supraorbital rim, dividing the superior leaf of the corrugator muscle in the process. The supraorbital nerves then are identified and avulsed and the incision closed with an intradermal 6–0 suture.

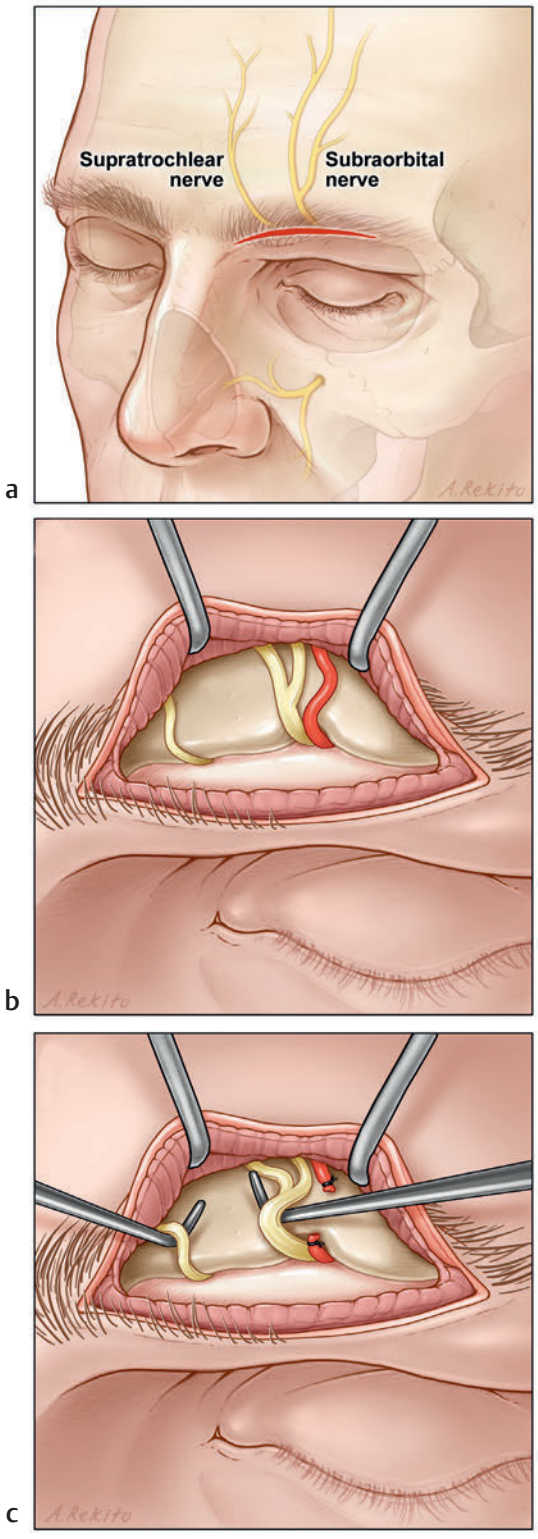

Fig. 43.4 Exposure of the supraorbital and supratrochlear nerves for the purpose of neurectomy via avulsion or ligation/division. (**a**) Skin incision through the eyebrow relative to surface anatomy and underlying nerves. (**b**) Dissection through orbicularis oculi muscle to expose supraorbital nerve and artery exiting the supraorbital foramen and the supratrochlear nerve more medial along the orbital rim. (**c**) Ligation and division of the artery and mobilization of the nerves in preparation for avulsion or division.

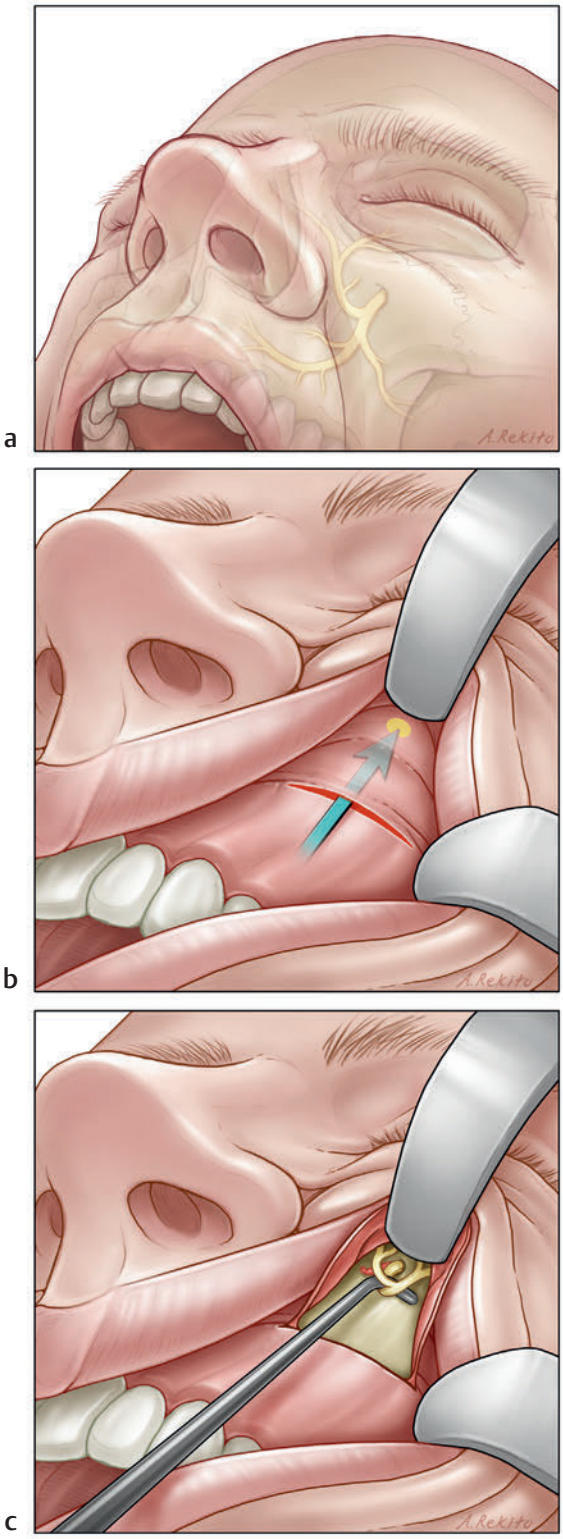

Fig. 43.5 Intraoral exposure of the infraorbital nerve for the purpose of neurectomy via avulsion or ligation/division. (**a**) Position of infraorbital foramen and nerve in relation to surface anatomy. (**b**) Intraoral incision at the gingivolabial margin and dissection trajectory toward infraorbital foramen. (**c**) Infraorbital artery cauterized and infraorbital nerve branches mobilized for avulsion/ligation.

Infraorbital Neurectomy

Infraorbital neurectomy may be of benefit in patients with trigeminal neuralgia involving the second division and in patients with trigeminal neuropathic pain who have sustained an injury to the nerve during surgery on the maxillary sinus or from periodontal surgery. Infraorbital neurectomy is most effective for pain confined to the cheek and upper lip. It is not nearly as effective for pain involving the roof of the mouth. Pain involving the roof of the mouth and the upper teeth requires an approach to a more proximal portion of the infraorbital nerve or even to the main trunk of the maxillary nerve in the pterygopalatine fossa.

There are several options for infraorbital neurectomy.[18] The infraorbital nerve can be approached extraorally through a skin crease or intra-orally. To approach the nerve extraorally, an incision is planned over the infraorbital rim in a skin crease at approximately the junction of the lower eyelid and skin of the cheek. After local anesthetic infiltration, the incision is made and carried deep to the infraorbital rim. The infraorbital nerve is identified exiting its foramen and is removed in the manner described for the supraorbital nerve.

Alternatively, the infraorbital nerve can be approached through an intraoral technique (**Fig. 43.6**). Although this approach is not quite as direct, it has the advantage of not leaving a surgical scar on the face. The patient is positioned supine with the head slightly extended. This should be done carefully in older patients, who often suffer from cervical spondylosis. The upper lip is retracted and the gingivolabial margin is identified. The incision is placed in the gingivolabial margin, beginning with the medial edge starting at the level of the canine tooth and then extending laterally for approximately 2 cm. The incision is deepened to expose the bony maxilla. A periosteal elevator is used to dissect the soft tissues off the maxillary bone superiorly until the infraorbital nerve is identified emerging from the foramen. Because the anterior wall of the maxillary sinus can be quite thin, caution should be exercised in exposing the bone to avoid entry into the maxillary antrum. The nerve is accompanied by an artery, which should be cauterized and divided to avoid it being torn and retracting into the bone. Because exposing a length of nerve sufficient to ligate may be difficult, the nerve can simply be divided. Then a nerve hook can be inserted into the infraorbital foramen and the stump cauterized. The foramen then is obliterated with bone wax.

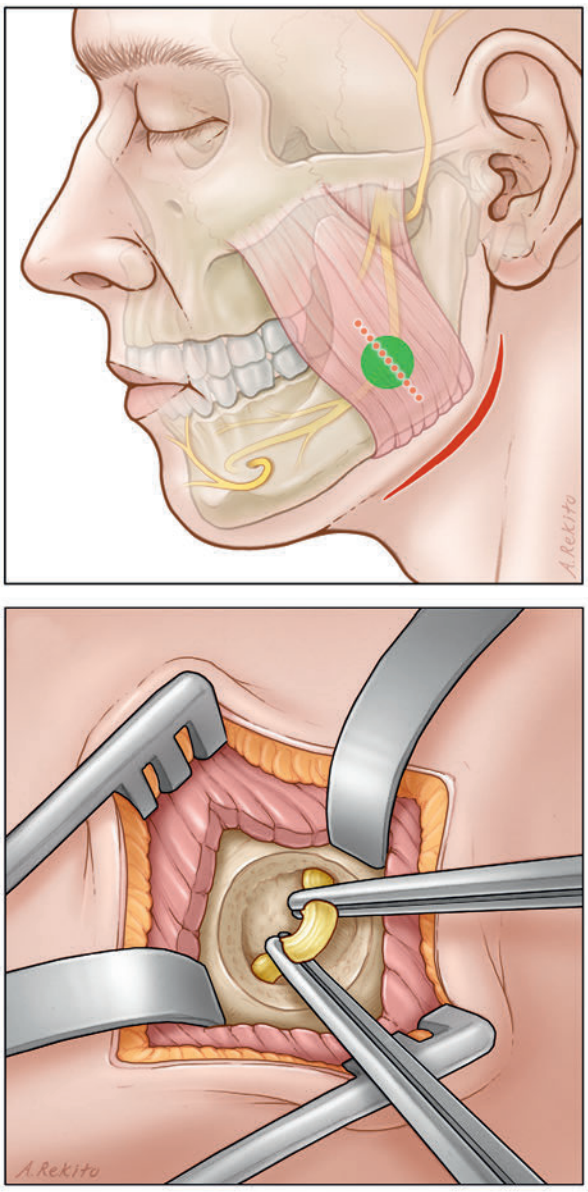

Fig. 43.6 Exposure of the inferior alveolar nerve for the purpose of neurectomy via avulsion or ligation/division. (**a**) Relevant anatomy: skin incision (*red curvilinear line*), masseter muscle incision (*dotted line*), and the area of bone removal (*green circle*). (**b**) Completed exposure with masseter muscle retracted, and inferior alveolar nerve exposed and mobilized in preparation of ligation/avulsion.

Maxillary Neurectomy

In some patients, the distribution of pain may be such that infraorbital neurectomy will not be effective. The maxillary nerve can be accessed using a Caldwell–Luc approach through the maxillary antrum.[20,21] Once in the maxillary antrum, the posterior wall of the sinus is removed to expose the periosteum, which covers the retroantral space. The operating microscope then is used for the remainder of the dissection. The first step is identification of the maxillary artery, which is defined and ligated and divided between vascular clips. The infraorbital nerve can be indentified running in the roof of the sinus and traced

Special Consideration

After performing a trigeminal neurectomy, obliteration of the bony foramen from which the nerve had previously exited may enhance the efficacy and duration of pain relief by preventing regrowth of the nerve into the cutaneous and subcutaneous tissues.

posteriorly to the maxillary nerve. The maxillary nerve then is followed proximally to the foramen rotundum, which represents the safe proximal limit of dissection. The nerve or any of the branches can be ligated and divided between hemoclips, depending on the distribution of the patient's pain. As an alternative to an open procedure, a minimally invasive endoscopic transantral approach also can be performed to gain access to the same anatomical structures.

Inferior Alveolar Neurectomy

Inferior alveolar neurectomy generally is performed for third-division trigeminal neuralgia involving the lower jaw. It is not effective for pain that is located in the tongue. In the latter case, the lingual nerve must be sectioned.[22] The inferior alveolar nerve may be approached either intraorally or extraorally.[7] The extraoral exposure can be performed aseptically and is somewhat easier from a technical standpoint than the intraoral approach. On the other hand, the intraoral approach offers the possibility of simultaneously exposing the lingual nerve in patients who have a significant component of pain involving the tongue.

The extraoral approach is accomplished most easily with the patient under general anesthesia. The patient is placed supine with the head turned to the opposite side. A curvilinear incision is made below and parallel to the angle of the mandible. The incision should be sufficiently below the mandible to avoid injury to the cervical branch of the facial nerve. The skin and subcutaneous tissue are undermined and the masseter muscle identified. The muscle is split in line with its fibers and retracted to expose the lateral surface of the mandible. A bony opening then is made exactly in the center of the mandible using a high-speed drill. Almost immediately after the outer table of bone has been removed, the inferior alveolar nerve will come into view, covered by a layer of fibrous tissue. The nerve is isolated and removed. Hemostasis is obtained and the incision closed in layers in the usual fashion. Inferior alveolar neurectomy can be expected to produce anesthesia of the skin and soft tissues of the lower jaw as well as the lower teeth.

Results

It is somewhat difficult to get an accurate handle on the true efficacy of peripheral trigeminal neurectomy. Most of the literature regarding this topic was published in the 1970s and earlier. Indeed, since the early 1990s, articles concerning trigeminal neurectomy have been rare compared with the number that have appeared in the literature concerning microvascular decompression and various percutaneous retrogasserian procedures. Moreover, there have never been any randomized trials regarding the use of neurectomy.

Despite the fact that peripheral neurectomy is a purely palliative procedure, the results would seem to justify its use in carefully selected patients. Indeed, a properly performed peripheral neurectomy almost never fails to produce anesthesia in the desired distribution. It is important to make the patient aware that, despite profound anesthesia, the pain may not resolve completely for several days, and the presence of some immediate residual pain should not be taken as an indication of failure. In most cases, the residual pain is considerably less severe than the pain before the procedure.

In general, most of the larger series that have been published report the average duration of pain relief to be on the order of 2 to 3 years.[7–11] In 1952 Grantham and Segerberg reported on 55 patients who had undergone peripheral neurectomy and were followed from 6 months to 8 years.[10] The average duration of pain relief in this group was slightly longer than 33 months. Freemont and Miller reported pain relief on the average of about 2 in 26 patients who underwent excision of a total of 43 nerves.[23]

Quinn performed a total of 112 neurectomies on 63 patients whose follow-up ranged from several months to 9 years.[8] The average duration of pain relief ranged between 24 and 32 months. In 1975 Quinn published a supplemental report that included the patients previously reported plus an additional 25 patients.[9] In all, 162 neurectomies had been performed on 88 patients with trigeminal neuralgia between 1956 and 1971. The operation was successful in providing pain relief in all 88 patients; however, slightly more than 50% (48 of 88) of the patients experienced some immediate residual pain, which persisted for an average of about 6 days (range, 1 to 21 days) before resolving. The median pain-free period among the 88 patients was 41 months (mean, 52 months). There was no significant difference in the pain-free intervals when patients with mental (37.5 months), inferior alveolar (38 months), and infraorbital (38.5 months) neurectomies were compared; however, lingual neurectomy provided a slightly longer pain-free interval (44 months), which Quinn postulated was related to the slower regeneration of nerve lying completely within soft tissue.

Mason reported the results of 47 neurectomies performed in 36 patients, including 32 infraorbital and 15 inferior alveolar neurectomies.[7] Twenty-one of infraorbital and all the inferior alveolar neurectomies were carried out as primary procedures; 11 patients underwent infraorbital neurectomy for at least the second time. Mason defined failure as the point where further medical or surgical treatment was required to achieve pain control. The failure rate at the end of 1 year was 36% and at the end of 4 years, 74%. There was no difference in the pain-free incidence between those patients undergoing primary and secondary procedures. In general, infraorbital neurectomy was more effective than inferior alveolar neurectomy. Mason noted that in patients who underwent infraorbital neurectomy, failure to occlude the bony foramen resulted in a statistically higher failure rate.

More recently, Murali and Rovit examined the efficacy of trigeminal neurectomy performed in 40 patients.[11] They performed a total of 69 neurectomies, including 28 on the supraorbital and supratrochlear nerves, 40 on the infraorbital nerve, and a single inferior alveolar procedure. The series included 28 patients who had previously undergone trigeminal ganglion radiofrequency thermocoagulation 6 weeks to 5 months before the neurectomy. The results were stratified in terms of pain relief into three categories: *excellent* (total pain relief without the need for pharmacological therapy, e.g., carbamazepam); *good* (residual pain requiring "modest" amounts of carbamazepam); and *poor* (no significant pain relief despite adjunctive treatment with carbamazepam). The best outcomes occurred in the group who had previously had a radiofrequency gangliolysis. Twenty-two patients (79%) in this group were judged as having excellent pain relief, which persisted in excess of 5 years; the other 6 patients had a good result. In the group who underwent neurectomy as a primary procedure, 7 (58%) had excellent pain relief and 5 (42%) were classified as good. Six (15%) of the 40 patients experienced pain recurrence after a mean period of 24 months and were treated with an additional neurectomy. All these patients had complete pain relief with an average follow-up of 2 years.

Conclusion

Although peripheral trigeminal branch neurectomy has largely been supplanted by other surgical procedures that provide better long-term pain relief, it can still be a considered a valuable option in selected patients. Peripheral neurectomy is especially useful in treating older debilitated patients who suffer from trigeminal neuralgia and who cannot undergo a more substantive procedure. It also may offer pain relief to persons with trigeminal neuropathic pain and even highly selected patients with atypical facial pain. The procedures are relatively easy to perform and are associated with low morbidity. However, as is always the case in treating patients with facial pain disorders, it is imperative to establish the correct diagnosis right from the outset to make good clinical decisions.

Nonetheless, in spite of all the newer procedures currently available, peripheral branch trigeminal neurectomy can still be a valuable modality of treatment in the overall armamentarium of the surgeon who is involved in treating patients with chronic refractory facial pain syndromes.

Editor's Comments

Dr. Osenbach has provided an excellent review of the peripheral anatomy of the trigeminal nerve, and established techniques for trigeminal nerve block and neurectomy.

I would have to disagree with his opening statement:

> *These particular techniques are currently more of historical than practical interest, given the alternatives such as the minimally invasive percutaneous needle techniques (radiofrequency gangliolysis, glycerol rhizolysis, and balloon microcompression) and stereotactic radiosurgery, especially for the treatment of trigeminal neuralgia.*

What he has demonstrated is that these procedures are low morbidity and relatively straightforward to accomplish, and that they should be preserved in the surgical armamentarium to combat facial pain. He presents two case series with excellent results in 79 to 100% of patients from 41 months to in excess of 5 years. These outcomes compare very favorably to those of both trigeminal radiofrequency gangliolysis and radiosurgery.

Pain surgery, like all of medicine, can sometimes be needlessly "trendy." Older techniques, with demonstrated efficacy, fall out of favor and are sometimes lost to future generations of surgeons simply because the practices are not passed along. I would hope that this chapter, and the continuing attention of surgeons who deal with facial pain will promote the preservation of a wide spectrum of surgical options for facial pain.

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44 Stereotactic Radiosurgery for Trigeminal Neuralgia

Douglas Kondziolka and L. Dade Lunsford

Trigeminal neuralgia is described by patients as one of the most severe pain disorders. When medical management fails to control the pain of trigeminal neuralgia, patients require surgical intervention. Effective surgical procedures include craniotomy and microvascular decompression, percutaneous ablative procedures,[1] and stereotactic radiosurgery. All surgical procedures have variable but definite rates of risk and pain recurrence.

Gamma Knife (Elekta, Stockholm, Sweden) stereotactic radiosurgery (GKSR) is a minimally invasive surgical approach for managing trigeminal neuralgia. In 1951 Lars Leksell advocated radiosurgery for trigeminal neuralgia using a prototype guiding device linked to a dental X-ray machine.[2,3] During the next 50 years, new radiosurgery devices were developed and used for this indication.[4–9] This report evaluates the effectiveness of GKSR for pain relief, the time until relief occurs, the durability of pain relief, and clinical factors associated with success or complications. When the current technique of trigeminal neuralgia radiosurgery that targets the nerve just anterior to the pons using high-resolution magnetic resonance began in 1992, it was not long before the concept was widely adopted. A literature search (3/8/2013) noted 117 articles under "trigeminal neuralgia, gamma knife" (www.world-sci.com). Other radiosurgery techniques using modified linear accelerators have also been used for trigeminal neuralgia.

Considering Gamma Knife Radiosurgery versus Other Surgical Options

The role of GKSR in the management of medically refractory trigeminal neuralgia has evolved. It is important to place this surgery in the context of other therapeutic modalities for this disorder.[10] By the end of the 20th century, craniotomy and microvascular decompression had emerged as the "gold standard" surgical interventions for medically refractory trigeminal neuralgia in eligible patients; at 10 years 64% of patients had complete relief (defined as the absence of lancinating facial pain, or a reduction in pain of at least 98% off medication—Barrow Neurological Institute, or BNI, outcome grades I and II). Nine percent noted partial relief (defined as a 75% reduction in pain with or without medication [BNI grade IIIb]).[11] Unfortunately, many patients with trigeminal neuralgia are unsatisfactory craniotomy candidates because of the associated risks of advanced age or the presence of medical comorbidities.[12] Stereotactic radiosurgery is the least invasive modality for such patients.

There are different ways to report pain relief. These include outcomes that separate relief into complete (no pain), partial (significantly improved but occasional or less severe pain), and inadequate (failure). In addition, whether or not patients can reduce or eliminate medical therapy is important. The BNI score is one such approach that includes these different outcomes: Grade I is complete relief off all medication; grade II is partial relief off medication; grade IIIa is complete relief with medication; and grade IIIb is partial relief with medication.[13] These four groups constitute "successful" pain relief, although some consider only outcome grades I to IIIa as successful. BNI scores IV and V are usually considered treatment failures because they represent limited or even no pain relief.

The goal of trigeminal neuralgia (TN) surgery is complete elimination of pain and the need for medication. Achieving this entails a balance between surgical risk, maintenance of trigeminal nerve function, and acceptable rates of pain relief. Not all procedures relieve pain and not all patients may be able to eliminate medication. For patients who have failed one or more surgical procedures, the expectation of complete relief by additional procedures is reduced. For many patients, pain reduction may be an acceptable outcome, particularly if medication-related side effects are reduced and performance of daily activities is

improved and more comfortable. In addition, in view of the vagaries of pain assessment and the periodic nature of pain associated with trigeminal neuralgia, a patient may report having no pain at one assessment (grade I), only to have it recur at various levels in the future. There is a need to report not only pain outcomes but outcomes that describe the effect of pain on daily living and quality of life.

It is important to compare stereotactic radiosurgery with other minimally invasive surgical strategies such as percutaneous rhizotomy. Kanpolat et al[15] reported on 1,600 TN patients who underwent RFL. At 5-year mean follow-up, 58% were pain free but 42% had partial or complete recurrence. At an average of 20 years, the pain-free rate decreased to 41%. Other studies showed that the pain-free rate following RFL varied from 20 to 82% and recurrence or failure varied from 20 to 80%.[15–19] With RFL, an increased rate of facial sensory dysfunction has been correlated with longer pain relief, but also with various degrees of sensory dysesthesias. Tatli et al[20] reported a meta-analysis including microvascular decompression (MVD) and RFL from a total of 28 studies. They concluded that MVD had superior outcomes compared with RFL. Although RFL provided a high rate of initial pain relief, the average pain-free rate was 50.4% at mean follow-up of 5 years.

Gamma Knife Radiosurgery Technique for Trigeminal Neuralgia

Patients with trigeminal neuralgia are evaluated with high-resolution magnetic resonance imaging (MRI); computed tomography (CT) may be substituted in patients who cannot undergo MRI scans. Prior imaging is important to rule out a compressive tumor or vascular malformation. Gamma Knife radiosurgery begins with rigid fixation of an MRI-compatible Leksell stereotactic frame (model G, Elekta) to the patient's head. Local anesthetic scalp infiltration (5% Marcaine and 1% Xylocaine) is used, supplemented by mild intravenous sedation as needed. High-resolution images are acquired with a fiducial system attached to the stereotactic frame. For trigeminal neuralgia radiosurgery, a three-dimensional (3D) volume acquisition MRI using a gradient pulse sequence (divided into 28 to 36 1-mm-thick axial slices) is performed to cover the entire region and surrounding critical structures. A T2-weighted 3D volume sequence is performed to visualize the cranial nerves and can be helpful in certain patients, particularly after prior microvascular decompression. The entire cranial vault is assessed with a 3-mm T2 study to exclude other, unrelated pathologies in addition to providing a volumetric rendering of the head for dose planning. Planning is performed on narrow-slice-thickness axial MR images with coronal and sagittal reconstructions. The sagittal view provides excellent identification of the course of the nerve in that plane.

Radiosurgical Dose Planning

Dose planning is a critical aspect of radiosurgery, and image-integrated software (GammaPlan, Elekta) provides the platform for reliable and accurate nerve irradiation. Specific Gamma Knife radiosurgery techniques include accurate definition of the nerve anterior to the pons using small collimation (one or occasionally two 4-mm isocenters)[14] (**Fig. 44.1**).

After optimizing the plan, a maximum dose to the nerve target is determined. The treatment isodose, maximum dose, and dose received by any adjacent structures are jointly selected by a neurosurgeon, radiation oncologist, and medical physicist. In Gamma Knife radiosurgery a dose of 80 to 90 Gy is typically prescribed by most centers to the 100% (maximum) isodose line. The dose fall-off at the 20 or 30% line is also examined. It is prudent to keep the brainstem dose low, but this is achieved with small beam collimation without beam channel or sector blocking. Dose prescriptions for trigeminal neuralgia evolved in the mid-1990s (with a range of 60 to 90 Gy) and now are consistent at most centers. A maximum dose of 80 Gy is associated with a low rate of facial sensory dysfunction (about 10%) with an approximate 80% success rate for significant pain relief. Some centers have used 85 or 90 Gy as the maximum dose to increase the radiobiologic effect. Clinical trials that compared one- and two-isocenter radiosurgery (where a longer segment of nerve would be irradiated) were performed. These showed that the rate of sensory dysfunction increased but that pain relief was not significantly affected.[21]

After radiosurgery, patients are followed up with serial clinical assessments that are commonly requested at 3 months and then annually or as needed. If an MRI with contrast is obtained within the first 2 years, contrast enhancement within the nerve target site is commonly seen (**Fig. 44.2**).

Other centers, using modified linear accelerators, have reported clinical results in relatively small patient case volumes. Frame-based stereotactic radiosurgery (SRS) facilitates accurate delivery of dose to the target while sparing adjacent pontine and temporal lobe structures. Subsequent experience with linac-based radiosurgery has provided additional concern. A commercially available product that links two technologies led to radiation injury to the brainstem and concomitant neurological deficits

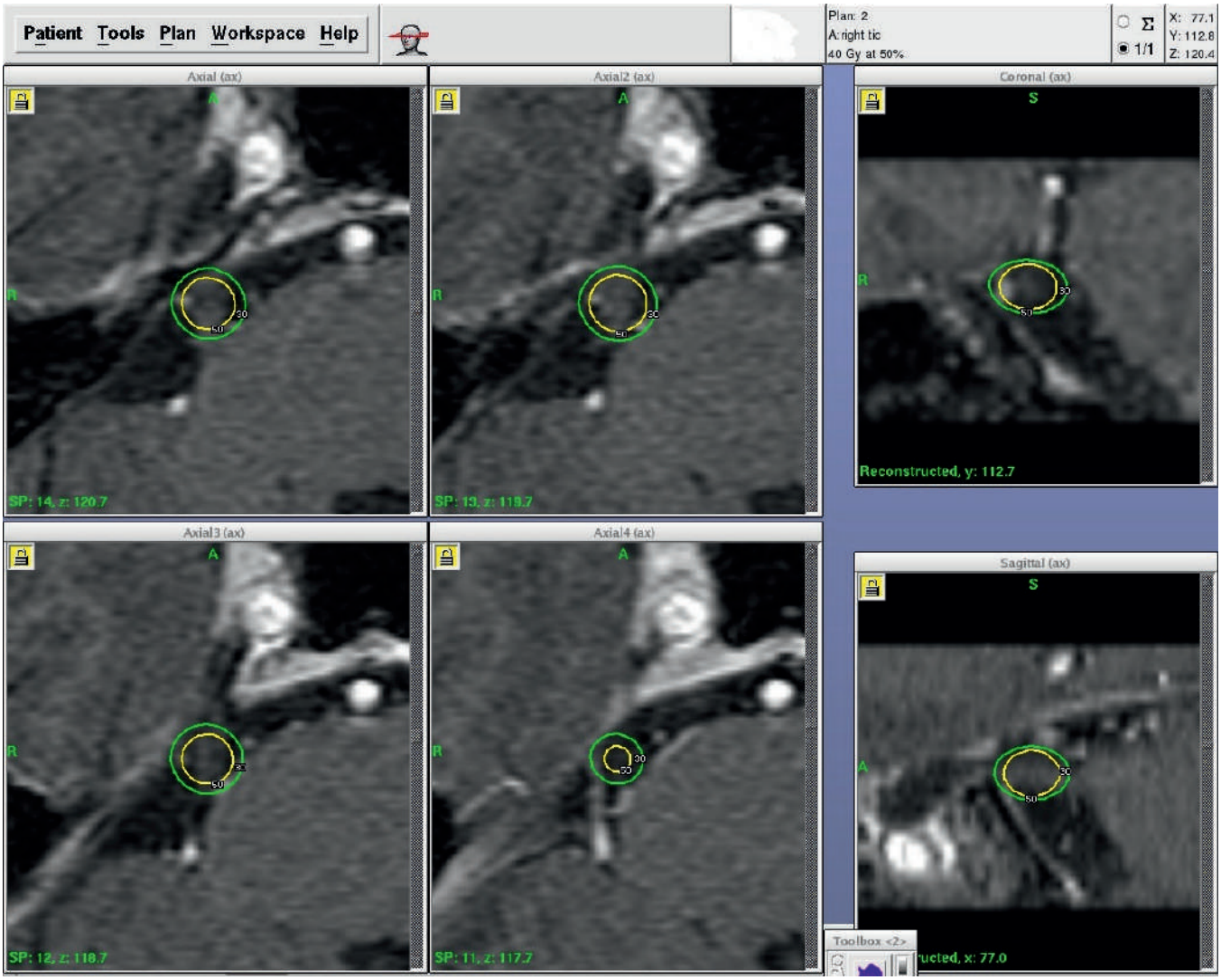

Fig. 44.1 Trigeminal neuralgia radiosurgery dose planning. A single 4-mm isocenter is targeted at the nerve. The 30% isodose line is at the brainstem surface. The sagittal image (*lower right*) shows the horizontal course of the nerve.

(New York Times, 12/28/2010; http://www.nytimes.com/2010/12/29/health/29radiation.html?_r=0). A recent report from Italy described 23 patients who underwent linac (i.e., linear accelerator) radiosurgery (margin dose of 40 Gy) and compared outcomes with 22 patients who underwent hypofractionated radiation (fractionated total dose of 72 Gy) using a mask and bite block immobilization system.[22] The authors reported that patients obtained better pain relief after radiosurgery. Radiosurgery is designed to obtain a limited radiobiologic effect that includes nerve demyelination at a specific site and via a specific volume. Fractionation provides no radiobiologic advantage in lesion generation, but for technologies that have poor dose fall-off beyond the target volume (poor selectivity), it may provide less risk of collateral damage. Quality radiosurgery is dependent on reliable technology, rigid target immobilization, high-resolution imaging, proper dose selection, and delivery in a single treatment session.

Gamma Knife Radiosurgery: Clinical Results

Achievement of Pain Relief

Most centers report an average latency to pain relief after radiosurgery of approximately 1 to 2 months.[14,23–26] In our own study we found that 89% of patients responded to treatment at a median of 1

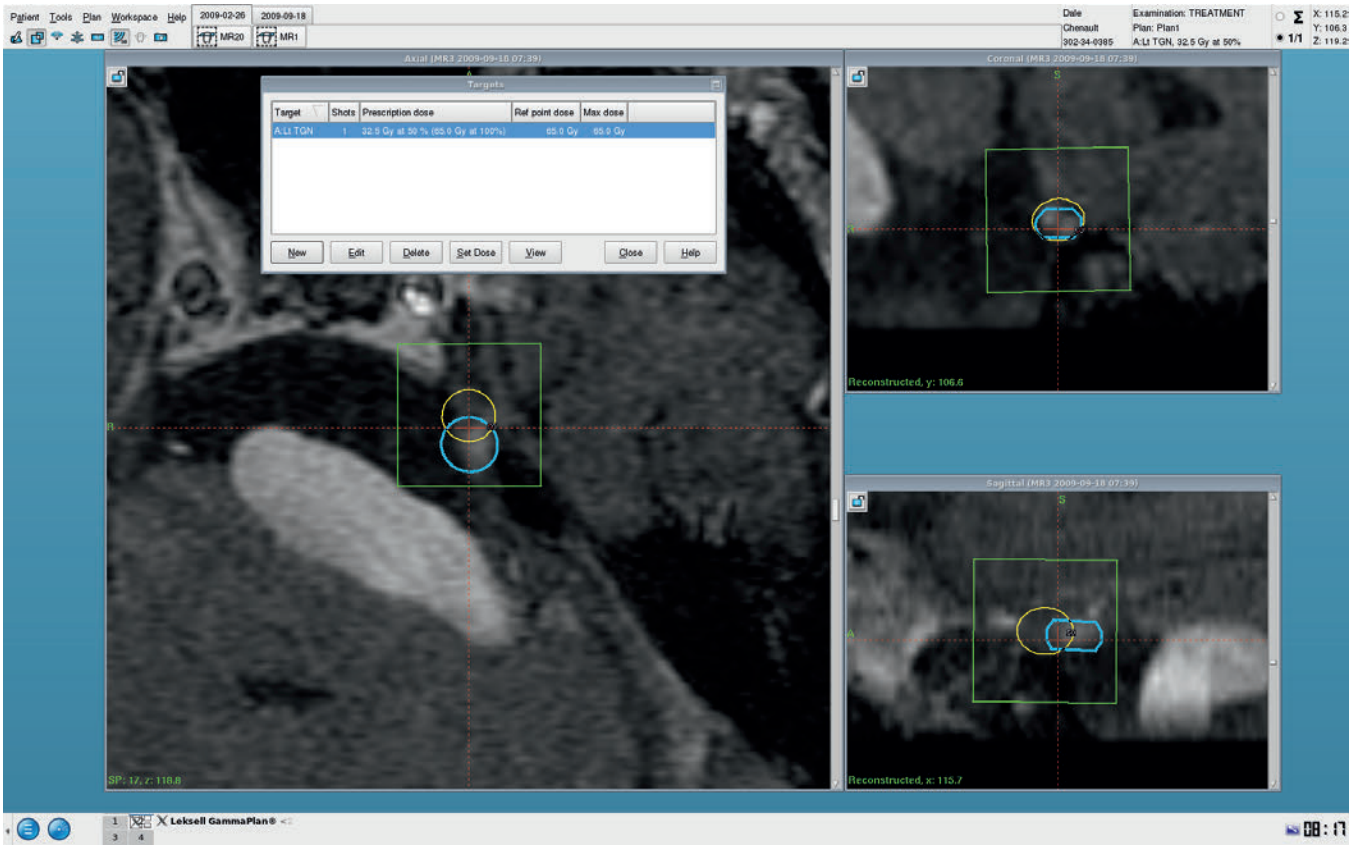

Fig. 44.2 Repeat trigeminal neuralgia radiosurgery. The original dose plan on the proximal nerve shows contrast enhancement at that target. The first dose was 80 Gy and the second, 65 Gy. The patient had pain from dolichoectatic vascular trigeminal nerve compression.

month.[27] We found that patients with typical trigeminal neuralgia, patients who underwent GKSR as their initial surgical procedure, and patients who underwent earlier GKSR (< 3 years) after pain onset had faster pain relief (grades I–IIIb). The median time to achieve complete pain relief (grade I) was 5 months. By 12 months after GKSR, 11% of patients still had pain. Patients who continued to suffer disabling pain required an additional surgical procedure. We advocate repeat GKSR only if complete pain relief had been achieved initially, with subsequent recurrence.[25] A recent analysis by Park et al is the largest series of repeat Gamma Knife radiosurgery with outcomes similar to a first procedure.[28] Typically, results are not as good as after a first procedure, with fewer patients reaching complete pain relief. Still, many patients are improved after repeat radiosurgery (**Fig. 44.2**).

In a large recent series from Wake Forest University with 777 Gamma Knife radiosurgery procedures performed between 1999 and 2008 (448 evaluable patients), the authors found that 83% of patients achieved pain grades of I to III, with 43% achieving grade I.[6] Twenty-six percent developed some postradiosurgery facial numbness, which they correlated with the nerve entry zone dose; however, their mean dose was 88 Gy. Increasing sensory loss correlated with pain relief.

Maintenance of Pain Relief

Our experience indicates that the majority of patients experience lasting, satisfactory pain reduction with few complications after GKSR. In our series, 75% of patients achieved or maintained pain control (BNI grades I–IIIb); 59% had pain relief at 3 years; 43% maintained relief at 5 years; and 29% were still controlled with or without medications at 10 years.[27] We found that younger patients (< 65 years), those with atypical pain features, and those who had undergone more than three prior surgical procedures were more likely to suffer earlier pain recurrence. The best result, BNI grade I (pain free, off medication), was achieved in 28% of patients. Of those with a significant pain recurrence, 60% underwent further surgery and 40% were maintained on medication alone. These findings are consistent with the results reported by other centers.[13,27,29–32]

Villavicencio et al reported that 95 TN patients who underwent CyberKnife (Accuray, Sunnyvale, CA, USA) radiosurgery had an initial pain relief rate of 67%. Fifty percent maintained complete pain relief, defined as > 90% pain relief without medication (BNI grades I and II), but 47% developed postradiosurgery sensory loss. Sensory loss did correlate with better pain relief.[33] In addition this report noted that 18% of patients developed other side effects such as masticator weakness, diplopia, and decreased hearing. Such avoidable complications are related to excessive dose delivery to adjacent structures, poor target definition (often based on CT rather than MRI nerve definition), or selection of the trigeminal ganglion as the target. The median length of nerve irradiated was 6 mm (range, 5–12 mm), which is longer than the typical GKSR target length using a single isocenter. In our previous prospective randomized study for TN patients who underwent GKSR using one or two isocenters, longer nerve irradiation resulted in a higher complication rate with no difference in efficacy.[21] The common Gamma Knife radiosurgery technique utilizes one isocenter and a limited target nerve segment that lies between the ganglion and the pons.

Sensory Dysfunction after Gamma Knife Radiosurgery

Postrhizotomy paresthesias or sensory loss of varying degrees is observed in 6 to 70% of patients after thermal rhizotomy, glycerol rhizotomy, or balloon microcompression, depending on the technique.[22,23,25,29,30,34–36] Some investigators believe that the onset of sensory loss is associated with longer term pain relief. In our report, sensory dysfunction was found in 11% of patients, a lower incidence than noted in the Wake Forest series, perhaps related to the average higher dose used at that center.[6] Only one patient in our experience (0.19%) has developed deafferentation pain. Ten of 53 patients who later developed facial sensory dysfunction reported pain recurrence after GKSR. The 1-, 3-, and 5-year rates for maintenance of pain relief in patients who later developed facial sensory symptoms were 91, 82, and 78%, respectively. These data suggest that patients who developed facial sensory symptoms had a reduced rate of recurrent pain ($p < 0.0001$). Pollock et al reported a significant association between higher radiation dose and increased risk of trigeminal neuropathy; 45% of the patients had received a maximum dose of 90 Gy and reported a trigeminal deficit as opposed to 15% who received less.[37,38] They reported a lower rate of pain recurrence in patients with sensory symptoms (15% versus 41% in those without), but this did not reach significance ($p = 0.08$).

Consistent with our own findings, Brisman reported a 5% complication rate in patients irradiated to doses between 70 and 80 Gy.[29,30] Henson et al reported that 54% of patients who underwent percutaneous retrogasserian glycerol rhizotomy (PRGR) and 30% of patients who underwent GKSR later developed facial sensory symptoms. A higher morbidity rate was found after PRGR ($p = 0.018$).[39]

Comparison of Gamma Knife Radiosurgery with Other Surgical Approaches: Level 2 Studies

The outcomes of Gamma Knife radiosurgery can be compared with those from other surgical options (**Table 44.1**). There has not been a randomized controlled trial to compare radiosurgery with any other treatment.

Henson et al[39] reported on a series of 36 patients who underwent PRGR and 63 patients who underwent GKSR for trigeminal neuralgia. They found that 86% of patients who underwent PRGR and 92% of patients who underwent GKSR achieved a successful treatment outcome, defined as BNI grades I to IIIb ($p = 0.49$). Fifty-three percent of patients who underwent PRGR and 41% of patients who underwent GKSR experienced pain recurrence or no pain relief at median recurrence times of 5 and 8 months, respectively ($p = 0.30$). Although PRGR worked faster on average, GKSR lasted longer. Thus, radiosurgery appears to have a lower rate of pain relief in longer term follow-up (5–10 years), but it also has the lowest morbidity or associated sensory dysfunction. To date no longitudinal assessment of quality of life exists after any of the surgical procedures for TN. Most agree that the three key indicators of such quality are pain relief, new sensory symptoms, and medication tolerance if used.

Pollock and Schoeberl reported results from 91 patients who underwent MVD and 49 who had GKSR.[7] The patients having MVD were younger (mean, 58 vs. 67 years; $p < 0.001$). Although both groups did well, those who underwent MVD were pain free off medication at a higher rate (84 vs. 66% at 1 year; 77 vs. 56% at 4 years). Complications after MVD included cerebrospinal fluid leakage ($n = 3$), hearing loss ($n = 2$), wound infection ($n = 1$), pneumonia ($n = 1$), and deep vein thrombosis ($n = 1$). The only morbidity after GKSR was facial sensory dysfunction ($n = 20$), which was also seen after MVD ($n = 19$). Thus, MVD had a higher rate of complete pain relief but more general morbidity and was performed in younger patients.

In a similar study to compare GKSR and MVD, Brisman reported 61 patients after GKSR and 24 after MVD.[30] No significant difference was found between pain outcomes. After MVD, 68% were pain

Table 44.1 Studies comparing gamma knife (GK) radiosurgery with other surgeries

Author	Number of patients: GK	Number of patients: other*	Improved (%): GK	Improved (%): other	Other surgery
Henson[39]	63	36	92	86 (BNI I–IIIb)	Glycerol rhizotomy
Pollock[7]	49	91	77	84 (BNI I)	MVD
Brisman[30]	61	24	58	68 (BNI I)	MVD
			75	90 (BNI I–IIIb)	

*Glycerol rhizotomy or microvascular decompression (MVD).

free, and the result was 59% after GKSR (p = 0.09). For pain improvement, the results were 90 and 75%, respectively (p = 0.17).

In summary, radiosurgical pain relief results appear similar to the results reported by patients who undergo initial microvascular decompression.[30,40] Microvascular decompression is designed to obtain relief by solving one particular etiology of pain for many patients: vascular cross-compression of the root entry zone of the trigeminal nerve. We continue to advocate craniotomy and microvascular decompression for younger patients suitable for invasive surgery. The benefit of decompression is less if pain recurrence requires a second MVD. GKSR as an alternative minimally invasive procedure designed to reduce patient risk is clearly well tolerated, has a strong safety profile, and pain outcomes that are consistent between Gamma Knife centers.

Editor's Comments

Few question whether stereotactic radiosurgery (SRS) has a role in the management of medically intractable trigeminal neuralgia (TN). The only serious debate is over the question of the outcome from SRS, and how that compares with other interventions. Part of this discussion is how to define pain relief after interventions for TN.

The Barrow Neurological Institute (BNI) scale defines six grades of facial pain relief: I, no pain, no medications; II, occasional pain, no medications required; IIIa, no pain, medication; IIIb, pain, medication controlled; IV, pain, not well controlled; and V, no pain relief. Drs. Kondziolka and Lunsford mention that " some consider only outcome grades I to IIIa as successful." For the record, I count myself as one of those "some."

I submit that the goal of surgery for TN is pain relief. To label "pain, medication controlled (but not gone)" as successful is generous at best. In fact, Dr. Kondziolka has tacitly acknowledged this in an article in which he refers to "significant" pain relief. In that series[27] significant pain relief (BNI grades I–IIIa) after GKSR (gamma knife stereotactic radiosurgery) was achieved in 73% at 1 year, 65% at 2 years, and 41% at 5 years. In that series, which included grade IIIb, a BNI grade of I to IIIb was found in 80% at 1 year, 71% at 3 years, 46% at 5 years, and 30% at 10 years—a substantial difference. From these data I would estimate that the median pain-free survival after SRS is between 3 and 4 years.

Direct comparisons of SRS and microvascular decompression (MVD) have been conducted. Linskey and colleagues[41] looked prospectively at a nonrandomized cohort of patients with TN who underwent either MVD or SRS. Initial and follow-up pain-free rates were 100 and 80.6% for MVD and 77.3 and 45.5% for GKSR. The median time to the maximal benefit after GKSR was 4 weeks (range, 1 week–6 months). The initial, 2-, and 5-year actuarial pain-free rates were 100, 88, and 80% for MVD and 78, 50, and 33% for GKSR (p = 0.0002). The relative risk of losing pain-free status by 5 years post-treatment was 3.35 for patients in the GKSR group compared with the MVD group. The respective rates of permanent mild and severe sensory loss were 5.6 and 0% for patients in the MVD group, and 6.8 and 2.3% for patients in the GKSR group. In this series, MVD was distinctly superior to SRS for the management of TN.

SRS is an important strategy for managing TN. It is a destructive procedure, and it is a form of noninvasive trigeminal rhizolysis. In terms of outcome assessment, it probably compares most favorably with radiofrequency rhizolysis (Chapter 45). MVD is still the "gold standard," but another destructive procedure, posterior sensory rhizotomy (PSR), must be better studied. Ultimately, excellent and durable outcomes should determine which procedures should be used on patients with TN, in whom medication has failed to relieve their pain. I respect the pioneering efforts of Drs. Kondziolka and Lunsford in this innovative therapy, and the integrity required to report their results in a rigorous manner.

Conclusion

Gamma Knife radiosurgery has become a well-documented management option for patients with trigeminal neuralgia. It is both safe and effective and is the least invasive surgical option. Reports from centers worldwide show consistent outcomes, and longer term data are now available from numerous centers. Outcomes data are consistent because methods of targeting and radiosurgical delivery have been consistent.

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45 Percutaneous Radiofrequency Trigeminal Gangliolysis for Trigeminal Neuralgia

Kim J. Burchiel

Denervation of the receptive fields of the triggering zones has long been known to be a successful strategy to control the pains of trigeminal neuralgia (TN). Initial procedures involved either peripheral surgical neurectomy or neurolytic injection into relevant trigeminal branches.[1] In the 19th century it was also recognized that subtemporal trigeminal rhizotomy, or ganglionectomy, could produce long-lasting pain relief.[2–4] In fact, Cushing was one of the first innovators of the subtemporal approach.[5]

The first electrocoagulations of the trigeminal ganglion using radiofrequency (RF) diathermy were performed by Kirschner in 1932.[6] These lesions were made with a large (1-cm uninsulated tip) electrode. Damage to adjacent cranial nerves from the procedure, and the associated neurologic deficits, limited the usefulness of this approach. Percutaneous gangliolysis did not advance until White and Sweet[7] refined the RF technique by: (1) the use of short-acting anesthetic agents to produce brief and intermittent analgesia, immobility, and amnesia; (2) electrical stimulation for localization of the electrode within target roots; (3) a reliable RF generator; and (4) a thermistor within the RF electrode to monitor temperature during the lesion process. Following these improvements, the RF technique became the procedure against which subsequent percutaneous techniques for TN were compared.

The complications of trigeminal deafferentation continue to challenge the practice of RF gangliolysis. Advances in electrode and RF generator technology have helped to minimize the dreaded outcome of anesthesia dolorosa (or its lesser variants) and "neuroparalytic keratitis." Nevertheless, much of the morbidity associated with this procedure is dependent on the sensory loss objective, and experience, of the neurosurgeon. Despite early suggestive evidence, damage to the trigeminal rootlets by RF heating does not appear to be selective to smaller pain-conducting axons (C and Ad fibers).[8] Damage to trigeminal afferents appears to be a *quantitative* phenomenon, but preservation of touch sensation, and currrent hypalgesia, can be achieved by carefully graded lesions with contemporaneous testing of the patient's facial sensation during the procedure.

Principles

Trigeminal rhizotomy, by any form, stands out in the treatment of a neuropathic pain in that sensory loss, up to a critical point, reliably stops the characteristic and "classic" triggerable lancinating, stabbing, or shocklike pains of type 1 TN (TN1). For almost every other neuropathic pain syndrome, the production of sensory loss is ineffective in alleviating the pain, and has a substantial chance of making it worse. Arguably, TN1 is not a "typical" neuropathic pain,[9] which is typified by a constant burning or otherwise unpleasant sensation. It is the brief nature of trigeminal neuralgia and the typical sensory triggers that set it apart. Most probably, it is the consequential blunting of the triggering input that allows remission from TN after rhizolysis or gangliolysis that is the basis for its efficacy.

Devor et al have proposed the most coherent physiological theory of TN.[10] They hypothesized that a triggering stimulus, touch or proprioceptive, within large trigeminal afferent fibers sets off an abnormal discharge in the retrogasserian root. This discharge, in turn, antidromically invades the gasserian ganglion, thereby "igniting" a wave of depolarization within the ganglionic cell bodies produced by a chain reaction of incremental extracellular release of excitatory neurotransmitters. Direct human observation by microelectrode recordings supports this proposed mechanism.[11]

Therefore, as our neurosurgical predecessors consistently advised, denervation of the trigger areas of TN should be the goal of these destructive procedures. If this can be accomplished, then triggering stimuli will fail to produce the abnormal retrogasserian after-discharge, and no ignition will occur in

the ganglion. The majority of trigeminal afferents terminate in the perioral area, so it should be no surprise that most trigger areas surround the mouth, and that most denervating procedures, including percutaneous radiofrequency trigeminal ganglionlysis (PRTG), target the mandibular (V3) and maxillary (V2) divisions.

Practice

Patient Positioning

The patient is brought to the operating room and an appropriately sized nasopharyngeal airway is selected based on the patient's nasal passages.

The patient is positioned to obtain an image of the foramen ovale, by either the submental vertex or oblique fluoroscopic projection, and the entry point on the face is sterilely prepared and draped. After an initial amnestic dose of propofol is given, the nasopharyngeal airway, which has been lubricated with lidocaine jelly, is inserted into the nostril. Once this is accomplished, a second bolus of propofol is then administered to induce brief general anesthesia. Respiration can be supported through the nasopharyngeal tube, if necessary, by combining occlusion of the opposite nares with forward displacement of the mandible ("jaw thrust"), using the anesthesia circuit. If the patient is made briefly apneic by the propofol bolus, respirations will promptly resume after a few breaths are administered via the nasopharyngeal tube.

Placement of the Electrode

Once the patient is surgically anesthetized as evidenced by the loss of the eyelash reflex, a no. 11 blade is used to make a stab incision approximately 2.5 cm lateral to and 1 cm inferior to the labial commissure (**Fig. 45.1**). The TEW cannula with the stylet is then inserted toward the foramen ovale, with one finger placed within the oral cavity to prevent violation of the oral mucosa. The line of insertion is the junction of two planes from the insertion site: to a point 3.0 cm anterior to the ipsilateral tragus, and to a point at the medial border of the ipsilateral pupil (Hartle technique) (**Fig. 45.2**). The cannula is advanced until it contacts the skull base, radiographically anterior to, and in line with, the foramen ovale. The cannula is then gradually redirected posteriorly until the foramen is acquired. Commonly, entering the foramen ovale is accompanied by a jaw jerk.

Once the foramen ovale is entered, the fluoroscope is moved into the lateral position, and the cannula is advanced until an appropriate depth is reached. For V1 or V2 trigeminal neuralgia, a curved electrode is often needed. Generally, the, curved electrode will not need to be positioned beyond the

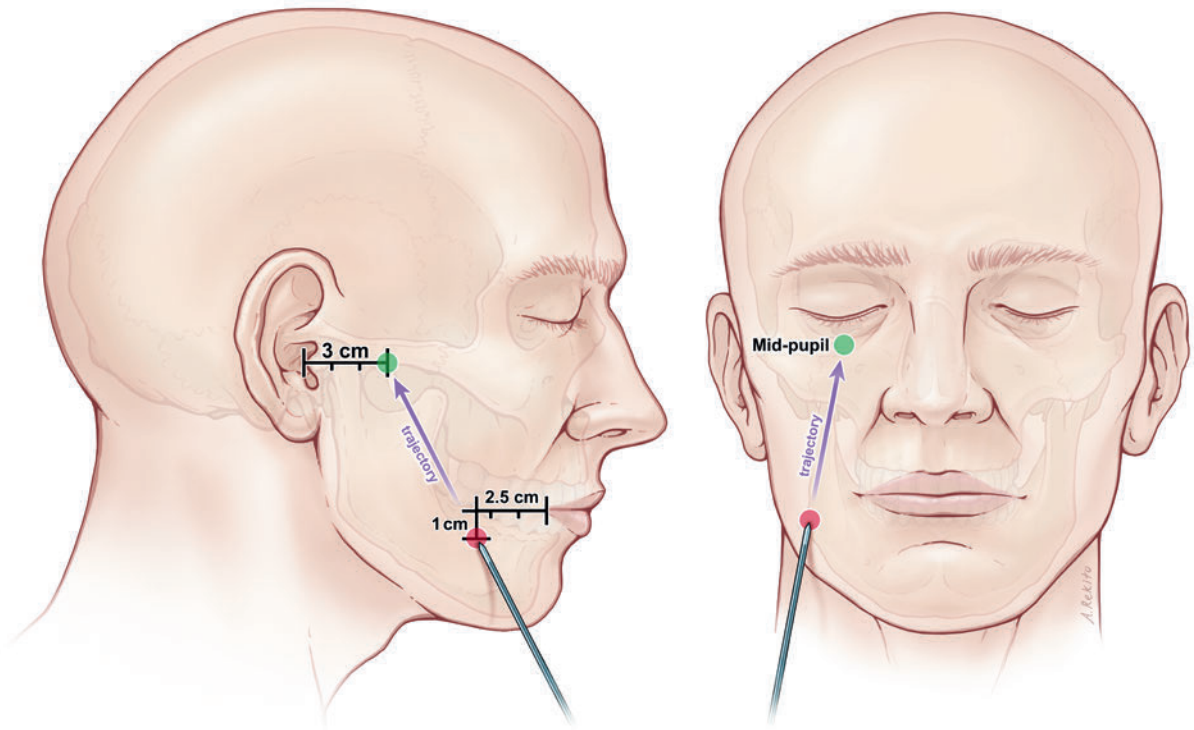

Fig. 45.1 Once the patient is surgically anesthetized a no. 11 blade is used to make a stab incision approximately 2.5 cm lateral to and 1 cm inferior to the labial commissure.

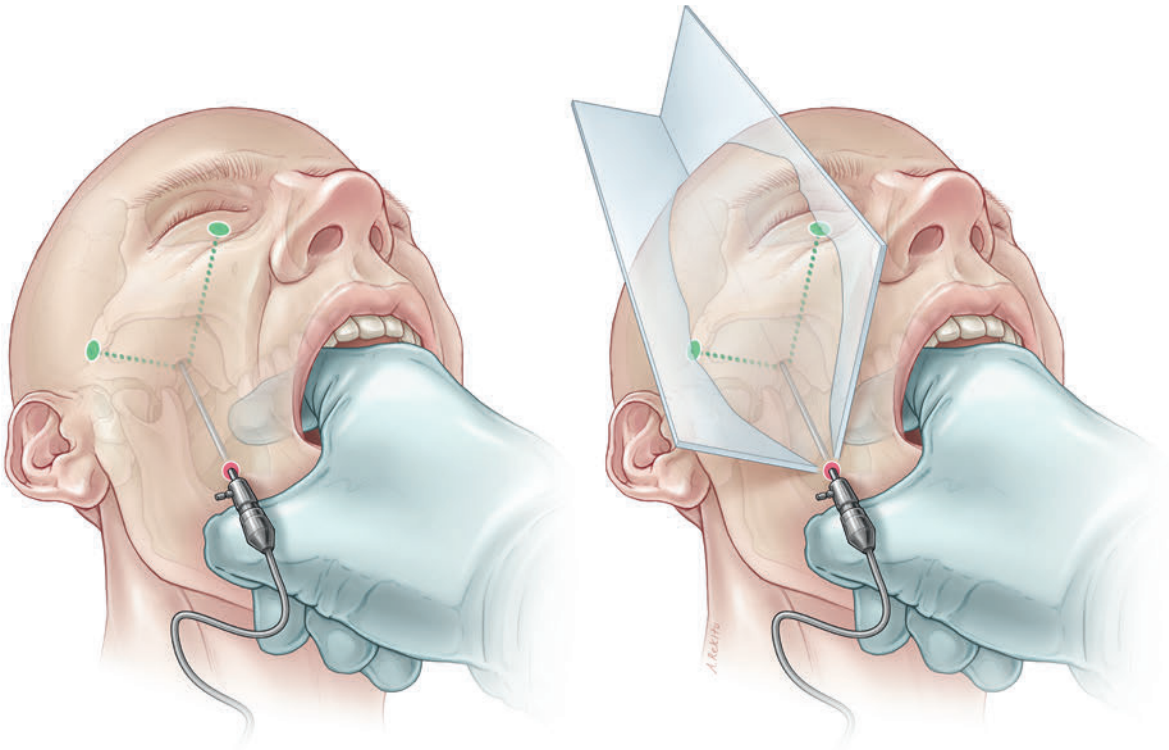

Fig. 45.2 The cannula with the stylet is inserted toward the foramen ovale, with one finger placed within the oral cavity to prevent violation of the oral mucosa. The line of insertion is the junction of two planes from the insertion site: to a point 3.0 cm anterior to the ipsilateral tragus, and to a point at the medial border of the ipsilateral pupil.

clival line on lateral fluoroscopy. For V3 trigeminal neuralgia, a straight electrode can be used, and the cannula is positioned well anterior to the clival line. The trigeminal cistern lies just anterior to the nexus of the clivus and the petrous bone on lateral fluoroscopy. Positioning of the electrode tip such that it points more toward the posterior clinoid allows acquisition of the more medial V1–2 divisions, as deeper advancement of the electrode transits this part of the retrogasserian roots (**Figs. 45.3** and **45.4**). **Fig. 45.5** shows the sequential appearance of the procedure on lateral fluoroscopic imaging from electrode penetration of the foramen ovale (**Fig. 45.5a**), followed by straight electrode (**Fig. 45.5b**) and curved electrode (**Fig. 45.5c**) placement.

Stimulation and Lesion Generation

Once the radiofrequency electrode is in a radiographically satisfactory position, the patient is allowed to awaken. Stimulation testing is then performed (rate of 50 Hz and a pulse width of 1 ms) with the awake and cooperative (but still sedated and usually amnestic) patient to ascertain that the desired divisions of the trigeminal nerve are being targeted. Once this has been accomplished, another bolus of propofol is given for sedation and to allow the creation of the first lesion. For V2 and V3 lesions, the first lesion is often made at 75 to 80°C for 90 seconds. For V1 trigeminal neuralgia, a lesion at 70 to 75° may be advisable to minimize the risk of corneal anesthesia.

Once the lesion has been made, the patient is again awakened and several minutes are allowed to pass such that the patient demonstrates reliable and consistent responses to testing. A facial sensory examination is performed, with the patient asked to discriminate between pin prick and light touch sensation. The goal of the lesion is the loss of the patient's ability to differentiate sharp and dull sensation. Stimulation testing (50 Hz at 1 ms pulse duration) can again be performed to ensure that the RF electrode is targeting the desired division of the trigeminal nerve. Once this is confirmed, the patient is re-sedated with a bolus of propofol, and further cycles of lesion production can be completed, raising the lesion temperature by 5°C each time, followed by repeat sensory testing. With progressive thermal neurolysis, these further lesion cycles can be facilitated by the administration of an analgesic (sufentanil or alfentanil) and often further propofol boluses will not be necessary. The process of sensory testing and lesion generation can be repeated until the desired level of hypalgesia is achieved.

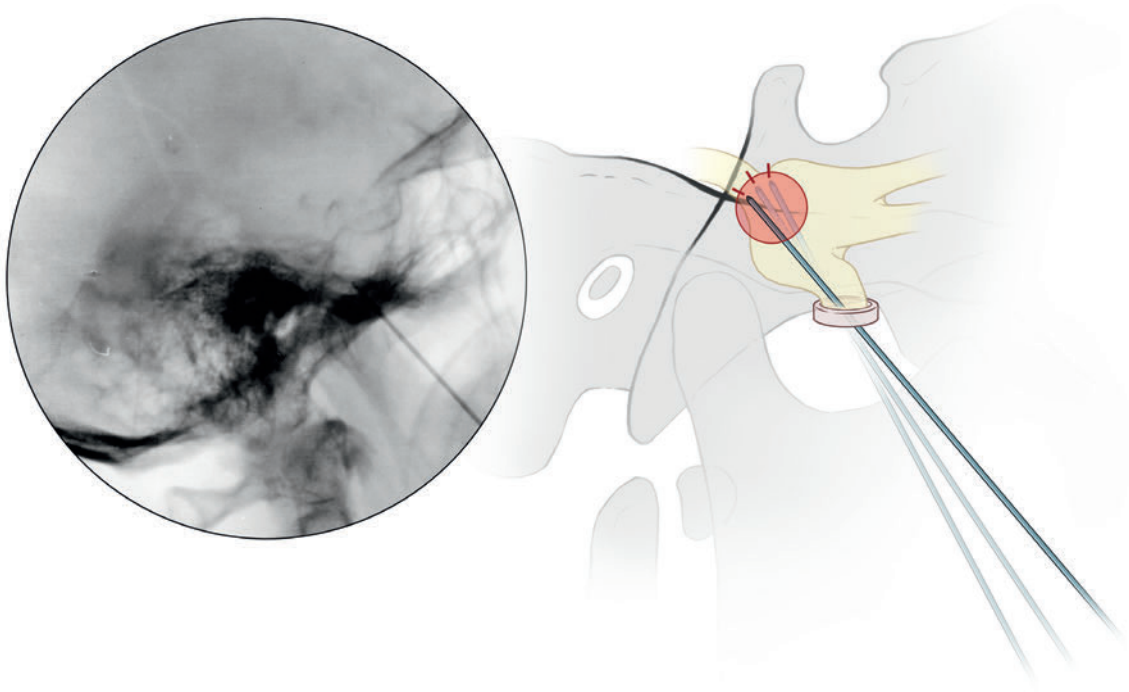

Fig. 45.3 Once the foramen ovale is acquired on the submental vertex or oblique view of the skull base, the fluoroscope is moved into the lateral position, aligning the internal auditory canals to attain a true lateral view. The cannula may then be advanced, first through V3, then sequentially through V2 and V1. Deeper penetration is needed to reach V2 and V1, and a more superior trajectory is more likely to achieve access to V1. The retrogasserian cistern (*red circle*) is generally located just anterior to the nexus of the petrous bone and clivus on lateral fluoroscopy.

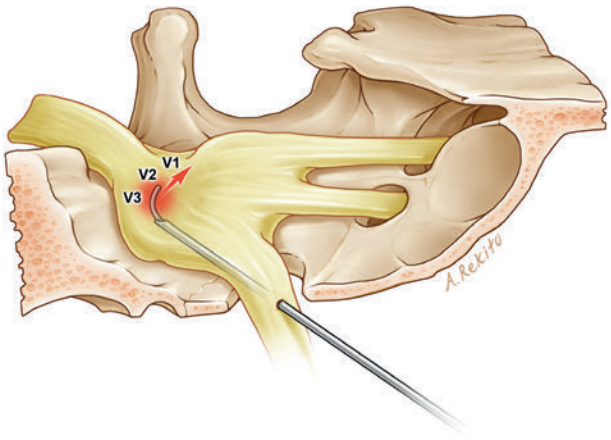

Fig. 45.4 As the cannula penetrates the ganglion from lateral to medial, it should pass from V3 to V2, and eventually to V1. Based on the angle of attack, and the geometry of the patient's petrous bone and ganglion, a straight cannula can pass from V2 directly through the dura propria and become subtemporal. A curved electrode, introduced into V3, can help to reduce this possibility.

Outcomes

There seems to be wide variation in the literature concerning the outcome of PRTG. Numerous reports describe what appear to be extended excellent outcomes after PRTG for TN.[12–20] Many of these studies rely on the range and mean duration of follow-up to describe the patient population. Tew and Taha reported on a group of 1,200 patients followed up from 1 to 20 years (average follow-up of 9 years), and 93% had an excellent or good result, 4% were fair, and 1% rated poor.[13] In contrast, Haridas et al[21] have also reported their long-term results in 77 patients after PRTG for TN, and found that their 3-year success rate was 70.7%. In their series of 256 patients, this was compared with a 54.8% 3-year pain-free survival in 77 patients after glycerol injection, and 85.6% in 95 patients after MVD (microvascular decompression). Some authors have seen as much as a 53 to 80% recurrence rate when patients were followed long term.[22,23]

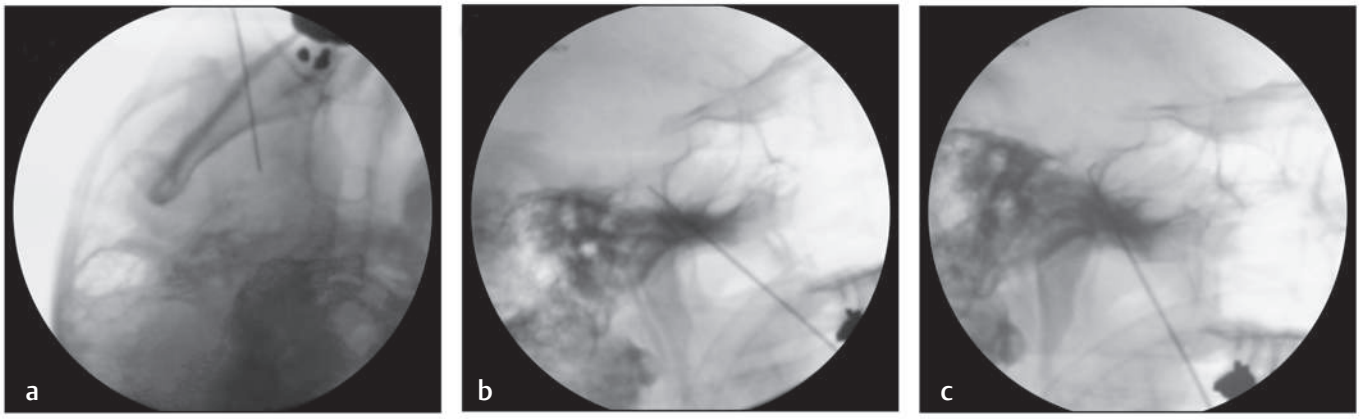

Fig. 45.5 (**a**) Submental vertex fluoroscopic view showing acquisition of the foramen ovale by the cannula. When the cannula is first inserted, a "safe zone" anterior to the foramen, on a trajectory to intercept it, is first encountered, and then the electrode is gradually directed posteriorly under fluoroscopic control until the foramen is entered, typically accompanied by a jaw jerk. (**b**) Lateral fluoroscopic view showing the straight electrode in a position at which stimulation should produce V3, and possibly V2, paresthesias. (**c**) Lateral fluoroscopic view showing the curved electrode in a position at which stimulation would likely produce V2 and possibly V1 paresthesias.

The outcome from any pain surgery, including one for trigeminal neuralgia, can be measured by Kaplan–Meier statistics and reported as "pain-free survival." This allows a prediction, over time, of the longevity of pain relief. In our experience, this method of analysis of the outcome of PRTG, and other procedures for trigeminal neuralgia, yields a somewhat less optimistic view of the durability of pain relief over time after PRTG.

"Pain-free survival" using Kaplan–Meier statistics was first described in 1981,[24] and since that time a number of investigators have followed suit for a wide range of pain procedures. The original report indicated that about 80% of patients were pain free immediately after PRTG, and that at 3 years postoperatively about 50% of patients experienced a full or partial recurrence (**Fig. 45.6**). In this series we saw a 15% incidence of nonbothersome paresthesias, a 4% incidence of anesthesia dolorosa, and a 3% rate of corneal anesthesia and keratopathy. This review involved contemporaneous follow-up of patients whose procedures had been performed up to 6 years previously, during the 1970s. What sets this series apart somewhat from the rest of the reported literature on this topic was the lower initial success rate (less than 80%), which may have skewed the pain-free survival period somewhat lower than subsequent case series reports have found.

Taha et al[18] employed Kaplan–Meier statistics in a series of 154 consecutive patients with trigeminal neuralgia treated by PRTG. Of the patients, 99% were pain free after their initial PRTG. They defined the sensory outcomes as analgesia (loss of pain perception without loss of touch perception), dense hypalgesia (loss of ≥ 75% of pain perception, without loss of touch perception), and mild hypalgesia (loss of < 75% of pain perception, without loss of touch perception). Dysesthesia occurred in 23% of patients: 7% with mild initial hypalgesia, 15% with dense hypalgesia, and 36% with analgesia. Keratitis developed in 3 patients, and 14.3% had trigeminal motor weakness. The 14-year recurrence rate was 25% in the whole group: 60% in patients with mild hypalgesia, 25% in those with dense hypalgesia, and 20% in those with analgesia. The timing of the pain recurrence clearly varied according to the degree of sensory loss. All pain recurrences in patients with mild hypalgesia occurred within 4 years of surgery. The median pain-free survival rate was 32 months for patients with mild hypalgesia, and more than 15 years for patients with either analgesia or dense hypalgesia.

In comparing these results[18] with our series,[24] it seems likely that our goal for the production of facial sensory loss from the PRTG procedure was closer to what these authors termed "mild hypalgesia" rather than to either "dense hypalgesia" or "analgesia."

Lopez and colleagues have published a systematic review of ablative neurosurgical techniques for the treatment of trigeminal neuralgia, including PRTG.[25] Incorporating detailed and explicit inclusion criteria, this article is probably the best review of ablative procedures for TN to date. By their analysis, the success rate for PRTG was between 53 and 69% at 3 years, between 56 and 60% at 4 years, and between 51 and 56% at 5 years. In this survey, masticatory weakness occurred in 11.9%, cranial nerve deficits in 0.9%, meningitis in 0.2%, troublesome dysesthesias in

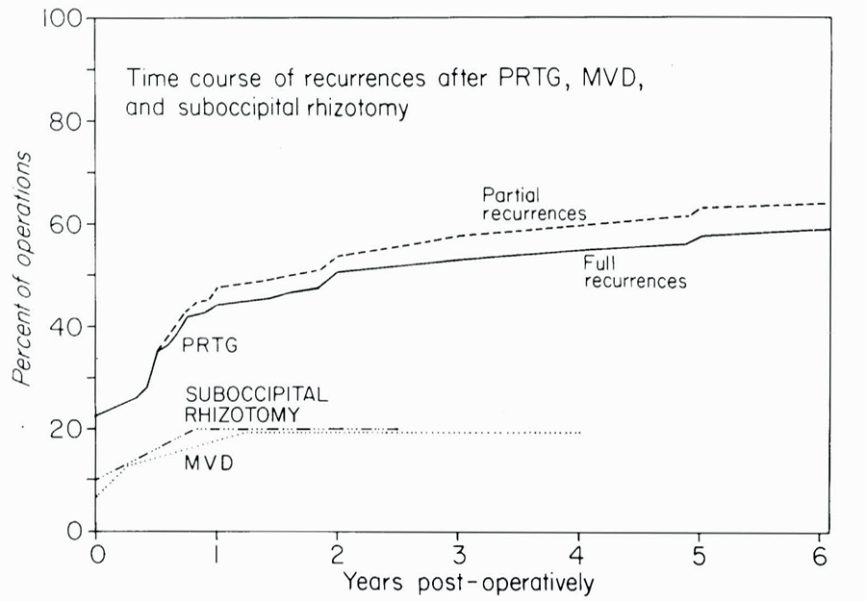

Fig. 45.6 First implementation of a Kaplan–Meier curve to describe "pain-free survival" after a surgical procedure. This graph shows the percentage of pain-free survival after PRTG (percutaneous radiofrequency trigeminal gangliolysis), MVD (microvascular decompression), and trigeminal rhizotomy, over time. (Reprinted from Burchiel et al.[24])

3.7%, anesthesia dolorosa in 1.6%, corneal numbness in 9.6%, and keratitis in 1.3%.

More recently, Udupi and colleagues[26] have reported on 39 patients after PRTG for TN, using the Kaplan–Meier method. They found that the pain-free survival probability at 54 months was 45.3%.

There seems to be no question that the amount of sensory loss produced by PRTG is directly related to the longevity of the pain relief, but also directly related to the incidence of facial dysesthesias or frank anesthesia dolorosa.[18] The density of hypesthesia produced by the procedure may account for some of the variability in outcomes in both duration of pain-free survival and painful dysesthesias, but some of the variance is also likely due to the reporting method.

Without quantitative sensory testing, it is difficult to gauge exactly how much sensory loss has been produced by a PRTG procedure, or how that is communicated in the literature on the topic. It seems clear that an increased rate of dysesthesia is the price to be paid for an increased duration of relief from trigeminal neuralgia. It appears that there is considerable variability in what constitutes the goal of sensory loss among centers. Based on the most recent data using appropriate statistical reporting, the pain-free survival after PRTG with the goal of facial hypalgesia, but not analgesia, seems to be approximately 50% at 5 years postoperatively.

Conclusion

PRTG is an important option for pain control in trigeminal neuralgia. Although the pain-free outcome from surgery is less durable than for MVD, serious complications occur in less than 10% of procedures. It can be performed on outpatients, and it can be repeated, if necessary. The training and experience necessary to perform these procedures effectively and safely should be preserved in our residency training programs.

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46 Percutaneous Retrogasserian Glycerol Rhizolysis

Neal Luther, Douglas Kondziolka, and L. Dade Lunsford

The goals of surgical intervention for trigeminal neuralgia are rapid and long-lasting pain relief together with preservation of trigeminal nerve function. Percutaneous retrogasserian glycerol rhizotomy (PRGR) is a safe, minimally invasive approach that has been well established in the treatment of trigeminal neuralgia. In this chapter, we review our experience using glycerol rhizotomy in 1,174 patients to evaluate procedural technique, results, and complications. We further discuss the role of PRGR in the management of trigeminal neuralgia, along with other therapeutic options including medication, microvascular decompression, and Gamma Knife (Elekta, Stockholm, Sweden) radiosurgery for idiopathic or multiple sclerosis–related trigeminal neuralgia.

Trigeminal neuralgia is a challenging pain syndrome with numerous medical and surgical therapeutic options. The pain is pathophysiologically related to direct vascular compression of the trigeminal nerve in the majority of cases, with multiple sclerosis the next most common underlying etiology. Surgery is usually considered for patients who do not tolerate or respond adequately to medical treatment. Surgical interventions include microvascular decompression, which may directly remove the vascular etiology of pain if present, and ablative procedures that address nerve irritability. The ablative techniques include nerve balloon microcompression, thermal-induced axonal degeneration by radiofrequency rhizotomy, radiation-induced degeneration produced by stereotactic radiosurgery, and chemical ablation via percutaneous retrogasserian glycerol rhizotomy (PRGR). Injection of chemical agents to peripheral nerve targets (for example, alcohol injections to the supraorbital and infraorbital nerves) may also be performed. Radiosurgical ablation to the anatomical location of vascular compression may also work to "treat the cause." However, it is believed that the effect is more likely a result of selective axonal degeneration of the nerve.

Approaching the trigeminal nerve less invasively through the face has a long history. Härtel is given credit for the accepted technique of spinal needle placement into the trigeminal cistern.[1] When absolute alcohol was injected into this location, multiple severe cranial neuropathies could be seen. Jefferson advocated the use of phenol mixed with glycerine rather than absolute alcohol.[2] Lars Leksell had long been interested in the use of focused radiation for the management of trigeminal neuralgia. His initial work in the early 1950s coupled an orthovoltage X-ray tube to a stereotactic frame to irradiate the trigeminal ganglion. The first-generation Gamma Knife was built in 1967. Leksell and Håkanson injected tantalum dust mixed with glycerol into the trigeminal cistern as a marker to localize the nerve for radiosurgery.[3,4] When the targeting solution was injected prior to performing radiosurgery, patients noted pain relief. It was in this manner that PRGR was discovered as a therapeutic option.

In the care of patients with trigeminal neuralgia, we seek the goals of rapid onset and long-lasting pain relief together with preservation of trigeminal nerve function. PRGR offers distinct advantages over the aforementioned other percutaneous procedures. These include the lack of need for intraoperative confirmatory sensory testing (patient cooperation is not necessary) or for a radiofrequency generator. Precise anatomical localization of the target is established using intraoperative cisternography rather than having the patient describe radiofrequency-induced sensory changes. The patient does not need to participate during the procedure and, as a result, can be more deeply anesthetized. Glycerol is associated with a lower risk of facial sensory loss compared with either radiofrequency rhizotomy or balloon microcompression. This feature significantly reduces the risk of deafferentation pain. The choice of this procedure is in part related to the factors of patient age, medical condition, symptom severity, and personal preference. Finally, glycerol rhizotomy remains our preferred primary surgery for patients with multiple sclerosis–related trigeminal neuralgia.[5,6]

Patient Selection

All surgical interventions for trigeminal neuralgia patients are decidedly more effective in patients without features of atypical facial pain. The correct diagnosis of trigeminal neuralgia is validated by a careful history that elucidates the quality, character, and distribution of pain. Patients with atypical trigeminal neuralgia may complain of a lingering, dull, or aching pain without triggers. In these patients, rhizotomy may be used to manage any severe lancinating component, but will likely have little effect on more constant pain. We rarely perform rhizotomy in this setting unless it is for patients who have undergone a successful procedure for prior typical trigeminal neuralgia symptoms.

We recommend initial medical treatment with appropriate doses of carbamazepine, oxcarbazepine, gabapentin, phenytoin, baclofen, or perhaps lamotrigine. Selected additional medications also may be used. High-resolution brain imaging should be performed to exclude a skull base lesion, a vascular anomaly, or a basal tumor that might change the regional anatomy or be the cause of trigeminal neuralgia. PRGR can be offered as first-line therapy in patients with idiopathic trigeminal neuralgia. However, we typically recommend Gamma Knife radiosurgery first unless the patient cannot eat or drink and requires more rapid pain relief. For such patients the possible latency interval associated with radiosurgery is less acceptable.[7] As a minimally invasive strategy, PRGR is used as a second-line approach in patients who have not responded adequately to radiosurgery. Finally, PRGR is an excellent first choice for patients with trigeminal neuralgia in the setting of multiple sclerosis,[5,6,8] which can occur at an earlier age than in patients without idiopathic neuralgia. It is an appropriate second-line therapy in those who have failed other surgical options such as microvascular decompression.

The technique of glycerol rhizotomy can vary from institution to institution. Some surgeons do not perform a contrast cisternogram, and others do not directly visualize the injection of glycerol into the trigeminal cistern with a metallic marker such as tantalum. Thus, if a prior attempt at PRGR failed elsewhere due to technical difficulties, we may repeat the procedure in an attempt to confirm that glycerol was in fact injected in the appropriate location. Injection of contrast to identify the trigeminal cistern is the most conclusive way to know that the appropriate target has been reached.

Preoperative testing to rule out a bleeding diathesis, electrocardiogram, and chest X-ray are obtained as indicated. All antiplatelet agents (such as aspirin and ticlopidine) must be discontinued at least 1 week before PRGR. If patients must remain on warfarin or other anticoagulants, then radiosurgery is a better option.

Anesthetic Technique

At our institution, PRGR is performed with the patient under continuously monitored deep intravenous sedation in the operating room setting. The anesthesiologist monitors vital signs, provides adequate sedation, and is asked to quickly respond to any cardiovascular changes that might occur during the procedure. Patients generally receive propofol or another rapidly acting agent together with a narcotic. Some patients, especially younger men, may benefit from preadministration of 0.4 mg of atropine sulfate, which serves to blunt the occasional vasovagal response that may be seen during the procedure. Most of the discomfort during the procedure occurs when the 20-gauge spinal needle is passed through the foramen ovale, and it is thus important that patients are adequately sedated during this time. A deep injection of local anesthetic is as important as making sure that the skin surface is anesthetized.

Both the surgeon and anesthesiologist should be aware that up to 20% of patients can have a vasovagal response to transovale needle penetration or to the glycerol injection. Administration of an intravenous anticholinergic agent is important at the first sign of bradycardia. Other patients may have a hypertensive response to needle placement, usually due to pain or anxiety. Such a response can be lessened by the administration of hydralazine or beta-blockers. The systolic blood pressure should be kept below 160 mm Hg: higher blood pressures can be associated with facial hematomas from needle placement. Because the procedure is started with the patient supine but completed with the patient in the semisitting position during glycerol injection, a balance of pain control, blood pressure management, and respiratory care must be maintained by the surgeon and anesthesiologist.

Surgical Technique

The patient is placed supine on an operating room table that allows control of head, leg, and body position. The patient's head is suspended in a Mayfield cerebellar headrest (Mayfield Clinic, Cincinnati, OH, USA) so that the arm of the rest does not interfere with fluoroscopic imaging in the lateral or anterior-posterior (AP) direction. Initially, a C-arm fluoroscopic image intensifier is positioned in the AP projection. The head is aligned such that the petrous ridge is at the same level as the inferior orbital rim. The foramen ovale can often be visualized just inferior and lateral to the junction of the inferior and medial orbital rims. The face is sterilized with 70% ethanol solution, and towels are placed around the neck and upper chest as the area is draped.

The entry point, located 2.5 cm lateral to the corner of the mouth on the side of pain, is marked. From this point, straight-line trajectories toward the medial ipsilateral pupil and to a point 2.5 cm anterior to the external auditory canal are marked. Intradermal injection of lidocaine 1% with a 25-gauge needle is performed, and then a 21- or 23-gauge needle is used to inject lidocaine into the deep structures of the cheek. A gloved finger is paced inside the patient's oral cavity to prevent penetration of the mucosa either by the anesthetic needle or by the 20-gauge spinal needle used for the rhizotomy.[9] The 20-gauge spinal needle is then inserted along the marked trajectory under fluoroscopic guidance toward the skull base. In the AP projection, the needle is guided toward the medial aspect of the inferior orbital rim (**Fig. 46.1**). Proper lateral positioning of the C-arm can be ensured by confirming that the auditory canals overlap (**Fig. 46.2**). Using the lateral projection, the desired trajectory is one directed toward the angle created by the clivus and petrous ridge (**Fig. 46.3a**).

Penetration of the foramen ovale can be uncomfortable for the patient, and thus administration of a short-acting barbiturate or propofol is administered immediately prior to puncture. Penetration of the needle through the foramen ovale can be felt by the surgeon. The stylet of the needle should be removed to check for flow of cerebrospinal fluid (CSF). If no CSF is encountered, then the needle with the stylet replaced is advanced at 1-mm increments under fluoroscopic guidance until the trigeminal cistern is entered. CSF flow should then be confirmed. If the needle has passed the clival line without flow of CSF, it may require adjustment; the most common problem is that the needle is either too lateral in the cistern or too medial. If too lateral within the foramen ovale, the tip of the needle may be in the subdural or subtemporal space. Although the finding of CSF flow is desirable, its absence does not always preclude identification of the trigeminal cistern (particularly in repeat cases). If CSF flow is identified or the needle is believed to be within the trigeminal cistern, the patient is placed in the sitting position for a contrast cisternogram. Cisternography is required to assess the volume of the trigeminal cistern and to select the proper amount of glycerol. With the needle in the cistern, the head of the bed is elevated to put the patient in the semisitting position with the neck slightly flexed. We use a tuberculin syringe to inject sterile iohexal in 0.05-mL increments and fluoroscopic guidance until the contrast is seen to overflow out of the cistern. The average volume of the trigeminal cistern is 0.25 mL, and the volume rarely exceeds 0.4 mL (**Fig. 46.3b**). The characteristic appearance of the cistern is of a bowling pin on its side. The contrast is then allowed to evacuate from the cistern by spontaneous drainage (which may require that the patient be placed again in the recumbent position). If full evacuation of the contrast is desired, particularly for patients with lower division pain, the patient can be returned to the supine position.[9] It should be noted that some surgeons do not inject contrast,[6] relying on fluoroscopic findings and CSF return. We

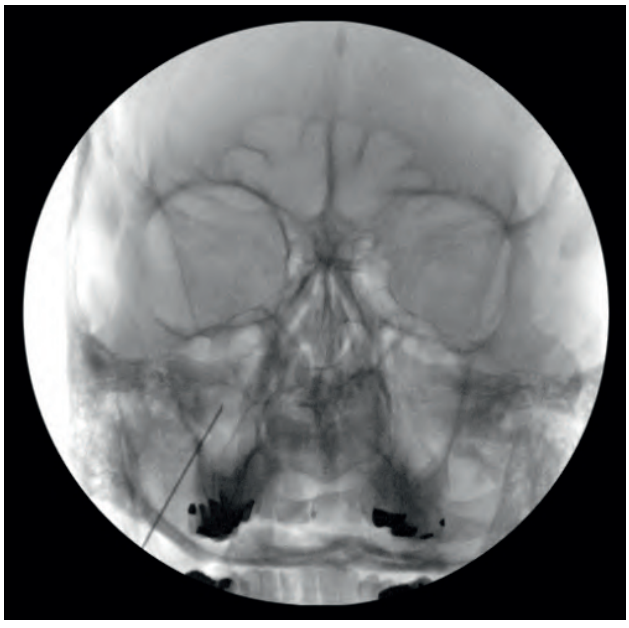

Fig. 46.1 Intraoperative AP (anterior-posterior) projection demonstrates spinal needle directed toward the inferomedial aspect of the orbit.

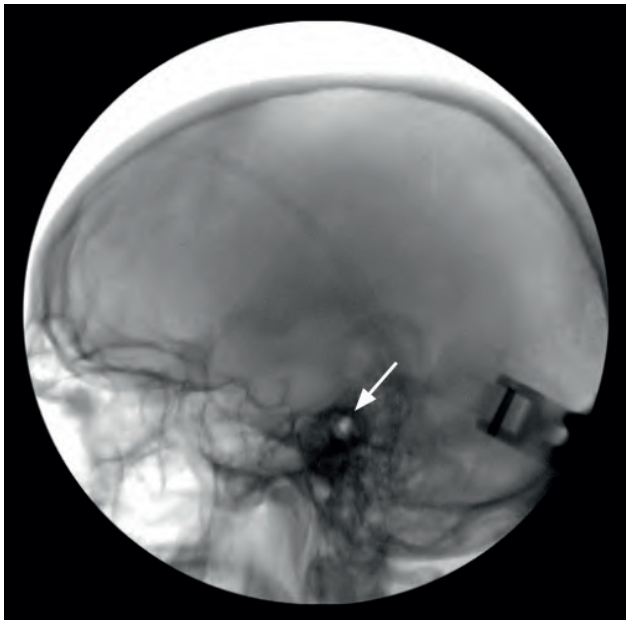

Fig. 46.2 Proper lateral position of the C-arm is confirmed by overlap of the auditory canals (*arrow*).

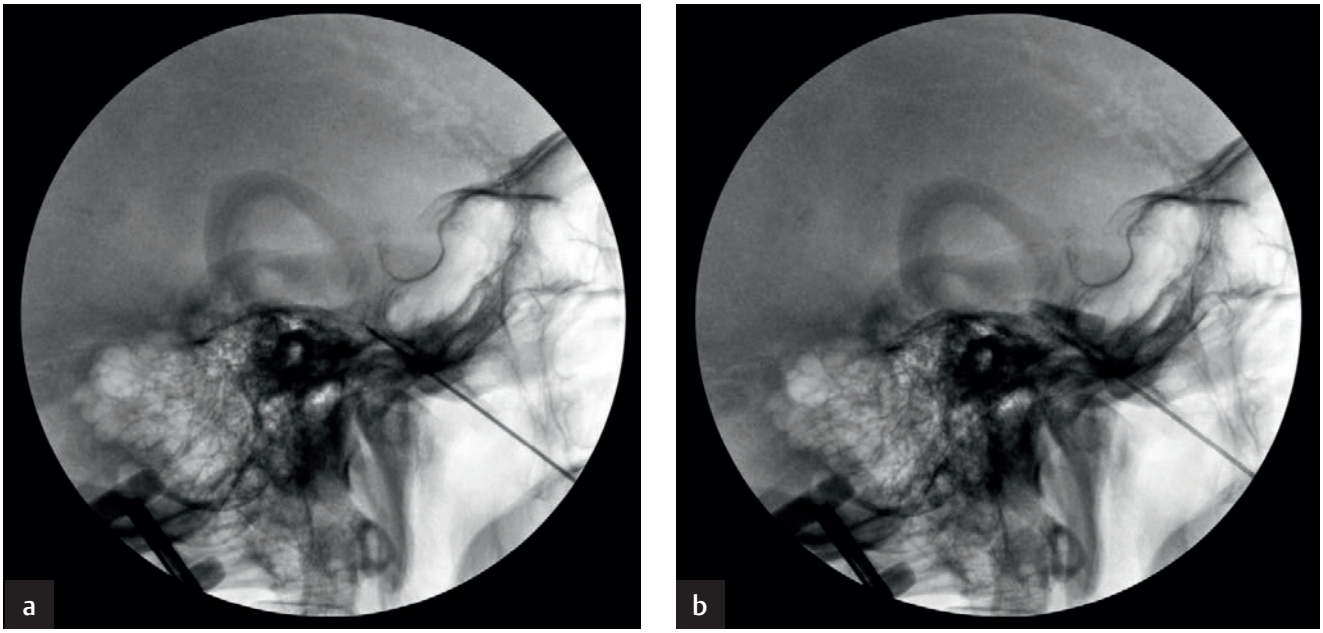

Fig. 46.3 (**a**) Intraoperative lateral projection shows spinal needle inserted into foramen ovale at the angle of the clivus and petrous bone. (**b**) Accurate placement is confirmed following injection of contrast, which fills the cistern in a characteristic pattern.

continue to advocate contrast injection because it is the only way to directly confirm that the trigeminal cistern has been entered.

The glycerol injection is performed in the same manner as injection of contrast medium under fluoroscopic guidance. Again, the patient is placed in a semisitting position. The mixture used for ablation is 99.9% anhydrous glycerol with radiopaque tantalum powder. The final volume of glycerol injected is dependent upon the cisternal volume measured and the nerve distributions affected. There are different techniques for glycerol injection that vary from filling the entire cistern for patients with multi-division pain to leaving approximately one third of the contrast material still in the cistern and "floating" the glycerol on top of the contrast in patients with isolated V1 pain. Because of its lighter density, the glycerol mixture floats above the residual contrast medium, exerting its effect mainly on upper-division fibers. During the injection, some patients experience ipsilateral periorbital discomfort and facial flushing. Bradycardia is often seen and is further confirmation that the target has been localized. After the glycerol is injected, the needle is removed, and a small sterile adhesive strip is placed on the skin entry point. The patient remains in the semisitting position for 2 hours to prevent the escape of glycerol into the posterior fossa. Most patients are kept in the hospital overnight because of the slight possibility they may experience headache from aseptic meningitis, and are discharged home the next day.

Many patients have chronic herpes simplex perioralis virus dormant in the gasserian ganglion. With percutaneous therapies, the subsequent development of cold sores is common. Patients with cold sore history are placed prophylactically on acyclovir and given acyclovir ointment in the perioperative interval. Early aseptic meningitis (1 or 2 days) is an extremely rare event, occurring in approximately 2 out of 1,000 cases. Although spinal fluid analysis should be repeated on an urgent basis to confirm the absence of bacterial meningitis, patients can be placed on corticosteroids if the CSF Gram stain is negative. The pleocytosis may be profound when it occurs, and can be very hard to differentiate from true bacterial meningitis. The risk of bacterial meningitis is minimized by making sure the spinal needle does not penetrate the oral mucosa.

■ Outcomes

There have been numerous studies that confirm the value of PRGR in the management of trigeminal neuralgia.[4,6,8–16] Variations in surgical techniques do somewhat compromise efforts to compare the efficacy of PRGR with that of other treatment modalities. As previously mentioned, some centers do not perform cisternography, whereas others inject larger glycerol volumes. Most centers report that initial pain relief is seen in the majority of patients, with the rate of improvement in the range of 90%. We usually tell patients that half of those who respond will do so within the first day of the procedure, and in half it may take up to 2 or 3 weeks for the full effect.

Some complexities exist as to the definition of recurrence rates depending on the time frame of evaluation, the need for concomitant medication, and the degree of pain control.

At the University of Pittsburgh, glycerol rhizotomy had been performed in 1,174 patients up to 2004. Immediate or early complete pain relief occurred in 90% of patients. An initial report that evaluated 112 patients demonstrated 90% pain relief at 2 years. Of these patients, 60% had complete relief after glycerol rhizotomy alone and 23% required additional (reduced) drug therapy. A subsequent analysis of 376 patients with follow-up to 7 years found a long-term pain control rate of 85%.[10] Sixty percent had complete relief after glycerol rhizotomy alone, although in some patients repeat procedures were necessary. A longer term assessment up to 11 years found long-lasting relief of pain in 77% of patients, with 55% off all medications and 22% requiring some drug usage.[10]

It should be emphasized that trigeminal neuralgia is not a static disease but is characterized by remissions and recurrences, some mild and some severe. This challenge is known and expected at all experienced centers. Pollock recently reported on 98 patients and found that 73% were without pain at some point after surgery, with the chances of remaining pain free off medications found to be 61 and 50% at 1 and 3 years, respectively.[13] Mild paresthesias or numbness was noted in 53% of patients, and 12% developed herpes simplex perioralis with full recovery.

Treatment of trigeminal neuralgia in the setting of multiple sclerosis poses a greater challenge. In these cases, microvascular decompression is not a viable option. A newly published report from Johns Hopkins of 822 patients with trigeminal neuralgia directly compared the efficacy of PRGR with that of radiofrequency ablation in those with and without multiple sclerosis. Multiple sclerosis was present in 67 patients. This study did not find any significant difference in pain control outcomes (both rate of control and time to failure) between the two techniques in either setting. In patients with multiple sclerosis, pain control was achieved by PRGR in 68% of cases. Median time to failure was 25 months.[16] Patients who underwent radiofrequency ablation were more likely to experience postoperative numbness than those who had PRGR.

Other than the perioperative blood pressure or cardiac changes noted above, other complications are relatively rare. Days after their first procedure, approximately 10 to 20% of patients will have detectable but usually mild reduction in light touch or pin

Editor's Comments

As the authors acknowledge, there are several options for the surgical treatment of trigeminal neuralgia. Percutaneous retrogasserian glycerol rhizolysis (PRGR) has some advantages and some disadvantages.

The procedure is fairly straightforward, although proper analgesia requires experience and coordination on the part of the surgeon and anesthesiologist. Bradycardia can occur during the penetration of the foramen ovale. During the injection of glycerol, the patient can experience severe burning pain in the ipsilateral trigeminal distribution. Profound bradycardia—even asystole—can also occur at this point. As the authors point out, prophylactic treatment with either atropine or glycopyrolate can prevent a crisis of bradycardia and hypotension.

The authors have a great deal of experience with PRGR, but for the uninitiated, the procedure can prove fairly daunting. Placement of the spinal needle with the patient in the supine position, under fluoroscopic control, using the Härtel technique can become routine with practice. However, at the point of cisternography and the glycerol injection, a fairly sedated patient is now placed in the sitting position with the head flexed forward, to allow first the contrast, and then the glycerol, to fill the cistern, and not pass immediately into the posterior fossa. If this sounds like a challenge, it can be!

I do agree that cisternography is important to verify the position of the needle tip in the cistern. Spinal fluid can be obtained from the subtemporal subarachnoid space, but this becomes apparent when the injected radiocontrast layers out in a thin stream along the floor of the middle fossa. Glycerol will work only if injected into the cistern and left in place for several hours while the patient remains sitting.

Finally, I am not quite as optimistic as the authors about the long-term relief of trigeminal neuralgia after PRGR. The literature generally supports a "half-life" of between 2 and 3 years. For multiple sclerosis, the results are even less durable. In our series, pain relief in these patients was for about 1 year.[1]

The advantages of this procedure are that it does not require specialized equipment, pain relief is usually immediate or has a short latency, and the incidence of deafferentation pain is very low. Disadvantages include the need for technical expertise on the part of the surgeon and anesthesiologist, the potential for bradycardia and hypotension during the procedure, and the limited duration of pain relief.

As a tool, PRGR will remain solidly in the toolbox of neurosurgeons who treat trigeminal neuralgia.

prick perception. This still compares favorably with a roughly 30 to 40% likelihood of hypesthesias associated with radiofrequency ablation.[16] With repeated glycerol procedures, the incremental sensory dysfunction assessment goes up, so that after two or three procedures, 50 to 70% of patients will have detectable sensory changes of a mild to moderate degree. Deafferentation pain in our experience has been extremely unusual and most likely occurs in the context of a complication noted below. The risk of developing delayed corneal dysfunction is extremely low, especially with an initial procedure.

In our experience with more than 1,000 patients with PRGR, we have had 1 perioperative death. This patient sustained a myocardial infarction about 1 hour after the procedure. This 0.1% surgical mortality risk should also take into account the consideration that this procedure was often undertaken in a higher risk population. For this population and others with this chronically debilitating pain syndrome, PRGR represents a safe and effective, minimally invasive treatment option.

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47 Percutaneous Balloon Compression for Trigeminal Neuralgia

Jeffrey A. Brown, Nathaniel D. Stetson, and Cletus Cheyuo

Three decades ago Sean Mullan published the results of his first 50 patients' treatment with "percutaneous microcompression of the trigeminal ganglion."[1] Although the operation is no longer considered to be either a "micro" compression or trigeminal "ganglion" compression, it has become a worldwide mainstay for the treatment of trigeminal neuralgia.

The purpose of this chapter is to review the indications for treatment, the nature of the injury caused by the procedure, the results and complications of treatment across many centers, and our recommendations regarding the technique for performing the procedure.

Nature of the Injury and Indications

Balloon compression selectively injures the myelin of large myelinated axons. It selectively preserves from injury small ganglion cells and fine-caliber primary efferent fibers.[2] Because the unmyelinated fibers that mediate the blink reflex are preserved, there is less chance of injuring the corneal reflex with balloon compression than with radiofrequency rhizotomy.[3]

The operation is effective because the trigeminal nerve is compressed within the anatomical confines of the porus trigeminus. The body of the balloon lies on the trigeminal ganglion. The ganglion is not a contained anatomical site; it is an open box demarcated by the temporal bone ventrally, and the subarachnoid and subdural spaces dorsally. When properly inflated, the balloon elevates the arachnoid and dura off of the ganglion. This requires some pressure, but it is not sufficient to effectively injure myelin or ganglion cells.[2] Histopathological studies of the ganglion in New Zealand rabbits after balloon compression show preservation of the ganglion cells at pressures sufficient to cause injury to large and medium-size myelinated fibers.[2]

When the balloon is inflated within the porus trigeminus, the trigeminal nerve root is compressed against the ventral petrous bone and the lateral and superior firm edge of the tentorial dura that splits to allow passage of the trigeminal root to the prepontine cistern. This forms the tip of the pear shape (**Fig. 47.1**). If the balloon is inserted farther, the fluoroscopic image seen will be a dumbbell shape wherein the balloon tip lies in the prepontine cistern.

Indications

Balloon compression is uniquely indicated for the ablative treatment of trigeminal neuralgia with first-division pain. Other indications are consistent with those of other percutaneous procedures. When constant dysesthetic pain predominates, balloon compression may not be indicated. The additional sensory loss caused by compression may aggravate the dysesthetic pain. Many clinical series have been published using balloon compression for the neuropathic facial pain associated with multiple sclerosis.[4] Balloon compression may be done bilaterally, although not during the same anesthetic.

Preoperative Evaluation

Preoperative MR or CT imaging will show any associated tumor or arteriovenous malformation. These may not be a contraindication to balloon compression. An acoustic neuroma or tentorial meningioma may cause trigeminal neuralgia pain by compressing a vessel against the trigeminal nerve. The presence of tumor in the pontine cistern usually will not interfere with completion of the procedure. A trigeminal schwannoma will likely cause dysesthesias and not paresthesias and may contraindicate balloon compression, although it will be technically possible to perform it. However, a tumor in Meckel cave will

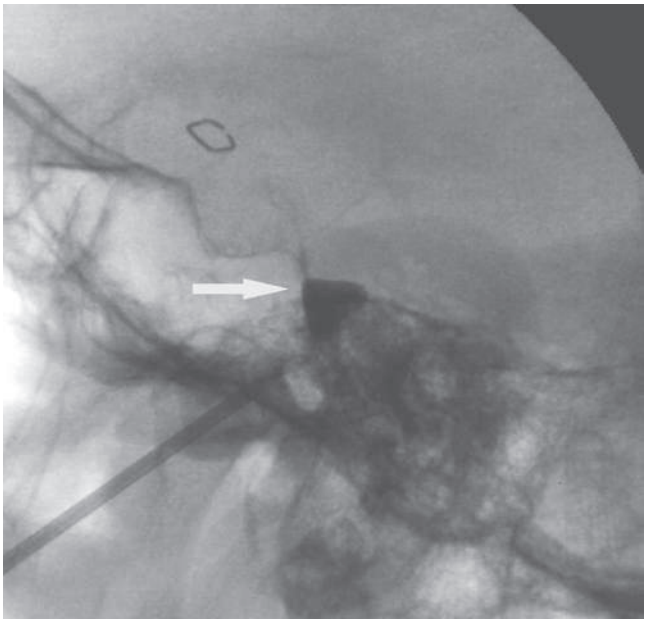

Fig. 47.1 Lateral radiograph of the skull. Arrow points to a properly inflated balloon. The tip forms the pear shape and is located within the entrance to Meckel cave, the porus trigeminus.

preclude successful compression. The balloon will not pass to the porous trigeminus.

Often older patients are on blood thinners such as warfarin, Lovenox, Plavix, or aspirin. Balloon compression is an intracranial procedure and has associated mortality. The medications must be stopped and their effect normalized before surgery. Often the decision to do this must be made in consultation with a cardiologist to learn the appropriateness of doing so and how soon after surgery a medication should be re-started.

Balloon compression causes brief but significant bradycardia and potential hypotension or hypertension.[5] These changes can be rapidly limited, but patients should be able to tolerate brief variations. If a patient has a permanent pacemaker, its effectiveness should be confirmed preoperatively and it should be on during the surgery to provide protection from the bradycardia.

Technique

Many articles on balloon compression speak about using the technique first described by Mullan and Lichtor. This is no more appropriate than attempting to do a microvascular decompression using the technique first described by Walter Dandy. Many advances in technique have been made in the ensuing decades. The original article may be of historical interest, but need not now be a technical reference.

The operation is done using general anesthesia, most commonly propofol and an inhalation agent. We do not give anticholinergic medications. The brief bradycardia that occurs during insertion of the cannula at the foramen ovale and during compression of the trigeminal nerve can be blocked with an external pacemaker once it occurs. It is helpful to obtain the feedback of the trigeminal depressor response that occurs during trigeminal nerve injury.[5] This confirms that the nerve has been adequately compressed and does not endanger the patient. The pacemaker should be set to capture at 40 beats/minute and should be tested after induction with anesthesia. A patient with a functioning implanted pacemaker will not need the external pacer. Patients taking a beta-blocker as an antihypertensive may not develop bradycardia, but they should still be fitted with the external device. It is not necessary to insert an arterial catheter to monitor blood pressure changes. The blood pressure can be monitored with an inflatable cuff at 1-minute intervals during the period surrounding the compression. If bradycardia persists, then intravenous (IV) anticholinergic reversal can be given.

Preoperative antibiotic coverage is given intravenously, usually cephazolin. Patients with multiple sclerosis are given intravenous steroids. We have not seen a benefit from treating potential postoperative cold sores with acyclovir. We do not recommend muscle relaxants. This allows a feedback twitch to occur in the jaw muscles when the foramen is engaged by the introducing cannula.

This is usually an outpatient procedure. The patient is positioned on his back with a supportive roll behind the neck, which is in the neutral position. The anesthesiologist is positioned on the side opposite the planned surgery. The anesthesiology equipment is positioned at chest level, leaving room for the fluoroscopy unit at the head of the bed and the digital monitor at waist level.

The operation can be done in the operating room or imaging suite using biplane fluoroscopy. Before starting, obtain confirming images in the lateral, modified submental, and anterior-posterior positions so that the images can rapidly be obtained when the surgery starts. The equipment required is manufactured by Cook Medical (Bloomington, IN, USA) and called the Brown Percutaneous Trigeminal Ganglion Microcompression Set. It consists of a 14-gauge cannula, a blunt obturator, a sharp obturator, straight and angled guiding stylets, a no. 11 blade, a short angled ruler, a no. 4 F catheter, and a latex balloon (**Fig. 47.2**).

We use an insufflation syringe and a digital monitor to measure intraluminal pressure. Many physicians perform the operation “according to the

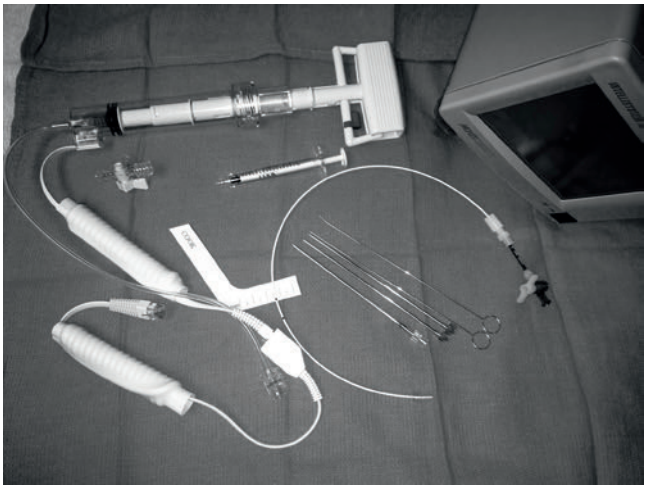

Fig. 47.2 Disposable equipment used in performing percutaneous balloon compression. There is a no. 4 balloon catheter, a tuberculin syringe, a straight and ab angled guiding stylet, a sharp and a blunt obturator, and a 14-gauge cannula.

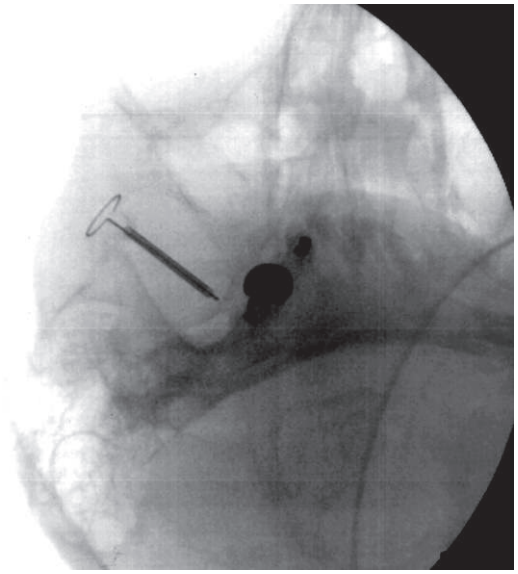

Fig. 47.3 Modified submental fluoroscopic image. The stylet just penetrates the foramen ovale, which is seen superior to the petrous ridge, medial to the head of the mandible and lateral to the maxillary sinus.

technique of Mullan and Lichtor." This is volume- and image-controlled balloon inflation, not pressure-controlled. The volume of dye injected into the balloon and catheter is usually 0.75 to 1.0 mL. Some physicians vary the volume to adjust the fluoroscopic image of the inflated balloon to their concept of the "ideal" appearance of the "pear shape." We find it more reasonable to control the intraluminal pressure while monitoring the inflated balloon appearance. During the period of inflation, adjustments must be made to the inflation volume to maintain the pressure. One may, however, develop a sense of the intraluminal pressure from the pressure needed to inflate the balloon with the tuberculin syringe. We find it more repeatedly accurate to measure the pressure digitally in atmospheres. Our goal is to achieve 1.5 to 1.6 atmospheres of pressure for 1 to 1½ minutes.

Position the fluoroscopy unit so that the target screen is on the side opposite to the surgeon. The surgeon stands on the side of compression. First, obtain a pure lateral view by aligning the floor of the frontal fossa on the image. Second, obtain a modified submental view (**Fig. 47.3**). Set the screen of the fluoroscopy unit almost on the chest of the patient and rotate the neck about 15 degrees away from the side of surgery. Find the foramen ovale just above the petrous ridge, medial to the mandibular head and lateral to the maxillary sinus. Third, rotate the fluoroscopy unit to obtain a modified anterior-posterior view (**Fig. 47.4**). This view centers the petrous ridge in the orbit as viewed radiographically. By maintaining the 15-degree rotation of the neck it is possible to see the dip in the petrous ridge that represents the porus trigeminus or the entrance to Meckel cave.

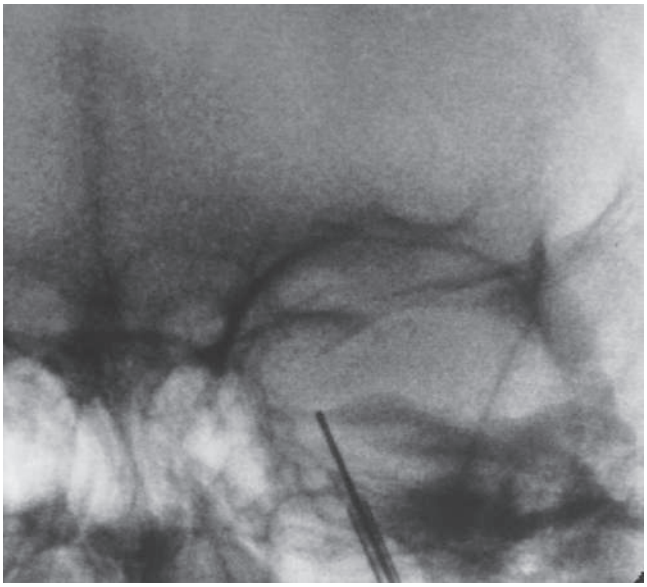

Fig. 47.4 Modified anterior-posterior radiograph of the skull with the petrous bone aligned in the center of the orbit as viewed radiographically. The balloon tip is positioned in the center of the dip for optimal compression of second-division trigeminal pain.

Return to the lateral view, prepare the face with sterile solution, and mark a point 2.5 cm lateral to the angle of the lip for placement of the cannula. Surround this entrance point with sterile plastic drapes and put a drape across the body. The 14-gauge cannula with a sharp obturator is inserted at a point in the cheek that places it along the line extending from the floor

of the petrous ridge. That may require adjusting the point of insertion above or below the standard Haertel point lateral to the angle of the lip. If the target is the first division, then the cannula is inserted just below and lateral to Haertel point. This allows direction of the balloon tip more superomedial so that the fibers of the first division are selectively compressed. This angle makes it more difficult to engage the foramen ovale with the cannula, however.

Make a stab incision with the no. 11 blade. Insert the cannula and inner sharp obturator through the cheek skin using the lateral fluoroscopic guidance. Once the cannula has penetrated the cheek skin, switch from the sharp to the blunt obturator. The cannula need not engage the foramen ovale at this point and should be positioned at the level of the skull base. By using the blunt obturator, the risk of arterial injury is eliminated.

Switch to the modified submental view to see the foramen ovale. Direct the cannula to the center of the foramen ovale, but only to engage it. A brief drop in heart rate will occur when the foramen is engaged and the mandibular branch stimulated. There may be a twitch from the masseter muscle also.

Remove the blunt obturator and insert a straight guiding stylet. Switch to the modified anterior-posterior view. For second-division pain direct the guiding stylet to the midpoint in the dip in the petrous bone representing the entrance to Meckel cave, then 2 mm beyond. For isolated third-division pain it may be useful to direct the stylet slightly more lateral. For first-division pain, the stylet is directed lateral to medial. On the lateral view the angle away from the petrous bone will be wider. Usually it is simplest to direct the stylet and balloon to the midpoint in the dip. Remove the stylet and place the balloon catheter in the same location. The kit is designed so that the second mark on the catheter is within a millimeter of the desired distance from the foramen ovale (17 mm). There is a slight give when the catheter enters the porus trigeminus.

The AP (anterior-posterior) view is essential to obtain. It is possible to believe that the catheter is within the porus when it is actually more lateral and positioned beneath the temporal lobe rather than adjacent to the trigeminal nerve. In that situation, the balloon will not achieve the pear shape that is the most significant association with a successful operation. The "pear" is the portion of the balloon within the tunnel created by the split in the tentorium to allow the nerve to pass from the middle to the posterior fossa through the prepontine cistern. A more medial position of the catheter is possible also. In this situation the catheter passes through the inferior orbital fissure. If inflated, it may injure the optic nerve (**Fig. 47.5**). By combining the use of these three images, the likelihood of successful balloon compression is increased.

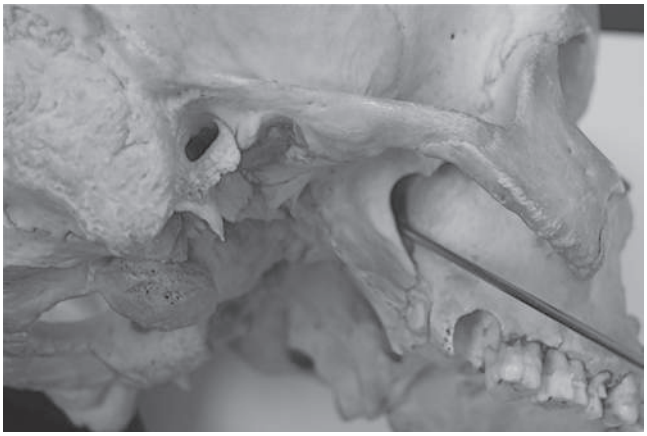

Fig. 47.5 Photograph of a skull with the 14-gauge cannula inserted into the inferior orbital fissure instead of the adjacent foramen ovale. If only a lateral radiograph is used during surgery, it may seem that the cannula is properly positioned at the foramen ovale when it is not.

Switch to the lateral view. Confirm the balloon catheter position and that the tip of the balloon is posterior to the clival line. Remove the inner stylet. Attach a three-way stopcock. Fill the insufflation syringe with radiopaque dye. Make sure that there are no air bubbles in the insufflation syringe line. Attach the syringe to the balloon and remove air from the catheter with the tuberculin syringe. Attach the insufflation syringe to the digital monitor and allow the reading to stabilize.

Switch the blood pressure cuff to stat mode. Ask the anesthesiologist to control the rise in blood pressure expected during compression. While using intermittent lateral fluoroscopic imaging, slowly inflate the balloon to a pressure of 1.5 atm (atmosphere of pressure) and observe for the "pear" shape. Patients requiring repeat compression or who have severe pain may need 1½ minutes of compression at 1.6 atm rather than 1.5 atm compression for 1 minute. The latter will almost always lead to mild sensory loss and preserve corneal sensation.

If the pacemaker is triggered, it is usually for only a few beats. Prolonged bradycardia can be treated with intravenous anticholinergic injection. It is rare for it to be required, but the injection should be readied.

After compression, deflate the balloon completely and remove it along with the cannula to prevent the creation of a tear in the balloon. If the balloon is removed before the cannula, slightly bloody cerebrospinal fluid (CSF) will drip and then clear. CSF will not drip when the cannula is first positioned because it does not penetrate the subarachnoid space at the level of the foramen ovale.

Compress the incision against the maxilla for 5 minutes to prevent bleeding in the cheek and place a

simple bandage. In the recovery room use an ice pack to reduce swelling.

Technical Problems

Rarely (e.g., when there is Paget disease), the foramen ovale will not accommodate the 14-gauge cannula or allow penetration by the balloon catheter. Repeated balloon compression can make it difficult to inflate the balloon. Scar tissue may form and thicken the dura, increasing the pressure required to open the balloon. If inserted too far, the balloon may either inflate in the prepontine cistern or form a dumbbell shape from partial inflation in the cistern and partial inflation in the porus trigeminus. Neither of these configurations is likely to lead to adequate nerve compression. Repeated inflations that fail to lead to a pear shape require reconsideration of the balloon position. If the balloon is placed over Meckel cave, but not within the porus, inflation will elevate the dura off of the ganglion; there will be no pear shape. This requires some pressure, but it is insufficient to achieve lasting pain relief. If the guiding stylet tracks lateral or medial to the porus trigeminus after repeated attempts, the cannula should be removed and repositioned. Sometimes there will be venous bleeding when the cannula is positioned at the foramen ovale. This is usually from a venous complex at the skull base. The bleeding can be abated if the cannula is held against the foramen ovale.

Morbidity

Jaw weakness almost always occurs and almost always resolves within 1 month (**Table 47.1**). The incidence of painful dysesthesia/numbness in our series is 6%.[6] Corneal anesthesia is reported. Because compression selectively preserves the small myelinated and unmyelinated fibers that mediate the blink reflex, the corneal reflex is preserved. Meningitis has occurred, but is rare. Several unusual complications have been reported. Cavernous sinus injury has occurred with injury to vision. Most likely this was because of placement of the cannula in the inferior optic fissure. The procedure should be done using the multiple views described above so that misplacement of the cannula does not occur. Bleeding is more likely if a kit that has a sharp pointed obturator is used. The Brown access kit has a blunt obturator for use after the skin of the cheek is penetrated. Balloon rupture is possible, but no complications have been reported because of it. Allergy to dye could be pretreated with steroids, if it is known to be present. The volume of dye leaked by a ruptured balloon is small, however. There has been a death when the inflated balloon ruptured an undiagnosed fistula present after a previous microvascular decompression (MVD) but not seen on preoperative magnetic resonance imaging (MRI). Although "simple" to perform, the compression is intracranial and there is still significant risk to be considered.

Results

Published series dating from 1983 indicate a range of initial success rates from 64 to 100% (**Table 47.1**).[6–24] Recurrence rates vary from 0%, in an early series, to 59% (in a series that used a compression time of 60–90 seconds and had a lower initial success rate of 83%). The lower initial success rate also occurred in an earlier series in which only 48% of patients had sensory loss from the compression. Skirving's series from 2001[20] had more than 500 compressions that were evaluated. The initial success rate was 96%. The recurrence rate was 32% when compression was done for a range of 2 to 7 minutes. This series achieved 89% sensory loss. Montano focused on a series of patients with multiple sclerosis. He had only 81% initial success in 21 patients, achieved only a 10% incidence of sensory loss, and had a 57% recurrence rate in a mean of 15 months.[11] Masseter and pterygoid muscle weakness, when reported, varied from 4 to 100%. Asplund et al demonstrated a significant correlation of success with the presence of a pear shape during compression ($p < 0.001$). There was no association with the presence of hypesthesia.[7] Depression of the corneal reflex, when reported, was usually 2 to 3%. Chen et al reported an incidence of 16% when they compressed for an average of 4 minutes; however, these patients were all undergoing repeat compression.[10] Only two series used pressure monitoring.[6,14] Corneal anesthesia did not occur in these series.

Balloon compression for trigeminal neuralgia is a standard percutaneous treatment that is simple to perform. It is best indicated for treatment of first-division or multidivision trigeminal neuralgia when a percutaneous procedure has been selected. It is also applicable to patients with multiple sclerosis and it may be repeated when recurrence occurs. Care should be taken to adhere to technical guidelines when performing balloon compression to limit the potential morbidity and maximize the potential of successful pain alleviation.

Table 47.1 Published results of treatment of trigeminal neuralgia by balloon compression

A.	Author (year)				
	Chen et al (2012)[10]	**Montano et al (2012)[11]**	**Baabor et al (2011)[12]**	**Chroni et al (2011)[13]**	**Stomal-Słowińska et al (2011)[14]**
No. of patients/no. of PBCs	32/32[a]	21/21	206/206	15/15	59/92
Demographics					
Age range	26–79	30–75	20–80	65–80	29–87
Gender (men:women)	14:18	10:11	74:132	10:5	23:36
Pain distribution: no. of patients					
V1	0	8	5	0	–
V2	18.7	10	25	26.7	–
V3	25	3	25	53.3	–
Multiple	56.3	0	151	20	47
Bilateral	0	0	–	0	0
Classification of TN: no. of patients					
Typical	32	0	–	–	42
Atypical					
TN2	0	0	–	–	7
Trig. neuropathic	0	0	–	–	2
TN in MS	0	21	2	–	3
Postherpetic	0	0	–	–	3
Trig. pain + complex etiology	0	0	–	–	2
No. of patients who had prior operation(s)					
MVD	–	0	22	–	6
RFT	–	2	9	–	9
GR	–	3	14	–	2
AR	–	0	–	–	3
SRS	–	1	–	–	5
PBC	32	1	–	–	0
Others (periph. block, etc.)	–	2	–	–	0
Surgical parameters					
Balloon shapes: no. of patients					
Typical pear	–	0	–	–	–
Others (pearlike, dumbbell, elliptical, etc.)	–	21	–	–	–
Duration of compression (seconds)	240	120–720	78–180	120–300	60–90
Outcome measures					
Initial success rate (%)	93.8	80.95	93	100	83
Recurrence rate (%)	43.3	57.14	15	20	59
Mean time to recurrence (months)	–	15	–	6	–
Follow-up range (months)	60.96–105	30.71–72.46	1–48	1–12	3–48
Morbidity (%)					
Defined postoperative period (months)	< 3	None specified	> 2	< 1	12–82
Corneal anesthesia/decreased reflex	15.6	0	–	0	0
Masseter/pterygoid weakness	18.8	0	–	100	11.9
Trigeminal depressor response	0	0	–	0	0
Dysesthesia	0	0	–	0	1.7
Hypesthesia	0	0	–	0	0
Hypoesthesia	62.5	9.5	–	0	90
Diplopia					
CN VI palsy	0	0	–	0	3.4
CN IV palsy	0	0	–	0	0
CN unspecified	0	0	–	0	0
Hearing loss/CN VIII	0	0	–	0	0
Blindness/CN II	0	0	–	0	0
Anesthesia dolorosa	0	0	0	0	1.7
Meningitis	–	–	–	0	0
Vascular complication					
Hematoma	0	0	0	0	0
CC fistula	–	–	–	0	0
IC hemorrhage	40.6	0	–	–	–
Herpes simplex oralis	0	0	–	0	0
Failure due to technical difficulties	0	0	–	0	0
Other	–	–	–	0	0
Mortality (%)	0	0	0	0	0

(Continued)

B.	Author (year)				
	Campos et al (2011)[8]	Chen et al (2011)[9]	Kouzounias et al (2010)[4]	Kouzounias et al (2010)[15]	Asplund et al (2010)[7]
No. of patients/no. of PBCs	39/39	130/130	47/66	61/66	69/87
Demographics					
Age range	62.3 ± 12.5	26–83	34–91	60–80	43–88
Gender (men:women)	18:21	63:67	26:35	43:57	1:2.2
Pain distribution: no. of patients					
V1	2	3.8	3	26	–
V2	10	20.8	11	74	–
V3	8	19.2	23	72	–
Multiple	19	54.7	62	–	–
Bilateral	0	1.5	8	–	–
Classification of TN: no. of patients					
Typical	39	130	35	–	49
Atypical					
TN2	0	0	0	–	0
Trig. neuropathic	0	0	4	–	0
TN in MS	0	0	17	17	20
Postherpetic	0	0	0	–	0
Trig. pain + complex etiology	0	0	0	–	0
No. of patients who had prior operation(s)					
MVD	–	32	13	13	6
RFT	–	7	0	0	1
GR	–	0	51	50	18
AR	–	0	0	0	0
SRS	–	9	7	7	0
PBC	–	0	19	20	23
Others (periph. block, etc.)	–	14	0	0	0
Surgical parameters					
Balloon shapes: no. of patients					
Typical pear	–	117	18	–	46
Others (pearlike, dumbbell, elliptical, etc.)	–	13	43	–	41
Duration of compression (seconds)	–	70–90	65–180	60–120	60–180
Outcome measures					
Initial success rate (%)	79.5	93.8	85	85	–
Recurrence rate (%)	20	37.7	60.5	50	–
Mean time to recurrence (months)	36	–	17.28	21	–
Follow-up range (months)	≤ 50	96–121.2	5.5–50.5	0.5–48	4–73
Morbidity (%)					
Defined postoperative period (months)	–	≤ 3	≤ 4	–	–
Corneal anesthesia/decreased reflex	2.6	2.3	2	3	–
Masseter/pterygoid weakness	17.9	6.2	–	7	–
Trigeminal depressor response	0	0	–	0	–
Dysesthesia	0	0	4.3	5	–
Hypesthesia	0	0	–	62	–
Hypoesthesia	84.5	30.7	–	0	–
Diplopia					
CN VI palsy	0	1.5	–	–	–
CN IV palsy	2.5	0	–	–	–
CN unspecified	0	0	–	–	–
Hearing loss/CN VIII	0	0	2	5	–
Blindness/CN II	0	0	–	0	–
Anesthesia dolorosa	0	0	–	0	–
Meningitis	0	0	–	0	–
Vascular complication					
Hematoma	2.5	2.3	–	0	–
CC fistula	0	0	2	3	–
IC hemorrhage	–	–	–	–	–
Herpes simplex oralis	43.6	33.1	–	7	–
Failure due to technical difficulties	0	0	–	0	–
Other	0	0	2	0	–
Mortality(%)	0	0	0	0	0

C.	Author (year)					
	Park et al (2008)[16]	Omeis et al (2008)[17]	de Siqueira et al (2006)[18]	Brown and Pilitsis (2005)[6]	Lee and Chen (2003)[19]	Skirving and Dan (2001)[20]
No. of patients/no. of PBCs	50/50	29/41	105/105	56/65	80/80	496/531
Demographics						
Age range	27–83	26–90	35–85	37–92	45–86	18–86
Gender (men:women)	22:28	14:15	45:60	23:33	33:47	279:217
Pain distribution: no. of patients						
V1	4	7	5	10	0	–
V2	32	25	31	25	0	–
V3	18	23	31	30	80	–
Multiple	46	–	38	0	0	146
Bilateral	0	0	1	0	0	0
Classification of TN: no. of patients						
Typical	50	29	–	–	–	496
Atypical						
TN2	0	0	–	–	–	0
Trig. neuropathic	0	0	–	–	–	0
TN in MS	0	0	–	6	–	11
Postherpetic	0	0	–	–	–	0
Trig. pain + complex etiology	0	0	–	–	–	0
No. of patients who had prior operation(s)						
MVD	5	2	–	4	–	7
RFT	4	15	–	–	–	11
GR	1	1	–	–	–	–
AR	0	0	–	–	–	–
SRS	1	1	–	–	–	–
PBC	0	10	–	–	–	–
Others (periph. block, etc.)	6	0	–	30	–	–
Surgical parameters						
Balloon shapes: no. of patients						
Typical pear	33	29	105	56	–	–
Others (pearlike, dumbbell, elliptical, etc.)	17	0	0	0	–	–
Duration of compression (seconds)	60–120	30–90	30–60	60–90	60–180	120–420
Outcome measures						
Initial success rate (%)	92	83	99	92	100	99.8
Recurrence rate (%)	16	45	16.2	16	2.5–5	31.9
Mean time to recurrence (months)	18	17	2.5	12.6	12	128.4
Follow-up range (months)	12–82	1–101	1–6	3–38	1–12	1–204
Morbidity (%)						
Defined postoperative period (months)	–	–	< 3	–	< 12	–
Corneal anesthesia/decreased reflex	0	52	–	0	0	0
Masseter/pterygoid weakness	4	6.9	50.5	24	100	3.4
Trigeminal depressor response	34	–	–	–	0	–
Dysesthesia	0	6.9	5.2	4	0	3.8
Hypesthesia	0	–	–	0	0	–
Hypoesthesia	–	–	–	83	90	89
Diplopia						
CN VI palsy	–	–	–	0	0	–
CN IV palsy	–	–	–	0	0	–
CN unspecified	–	–	–	0	0	–
Hearing loss/CN VIII	–	–	7.6	0	0	–
Blindness/CN II	–	–	–	0	0	–
Anesthesia dolorosa	–	3.4	–	0	0	0
Meningitis	–	–	1	0	0	0
Vascular complication						
Hematoma	–	–	32.3	0	0	0.01
CC fistula	–	–	–	0	0	–
IC hemorrhage	–	3.4	–	2	0	–
Herpes simplex oralis	26	–	44.6	–	0	–
Failure due to technical difficulties	8	–	–	0	0	–
Other	–	–	–	0	0	–
Mortality (%)	0	0	0		0	0

(Continued)

D.	Author (year)				
	Abdennebi et al (1995)[21]	Lichtor and Mullan (1990)[22]	Lobato et al (1990)[23]	Fraioli et al (1989)	Belber and Rak (1987)[24]
No. of patients/no. of PBCs	150/150	100/100	144/164	159/159	25/33
Demographics					
Age range	24–84	–	30–90	–	48–86
Gender (men:women)	73:77	–	58:86	–	15:10
Pain distribution: no. of patients					
V1	0	–	5	–	–
V2	19	–	33	–	–
V3	14	–	39	–	–
Multiple	117	–	67	–	–
Bilateral	2	7	4	–	–
Classification of TN: no. of patients					
Typical	–	–	–	143	21
Atypical					
TN2	–	–	–	0	0
Trig. neuropathic	–	–	–	0	0
TN in MS	–	–	3	3	4
Postherpetic	–	–	–	0	0
Trig. pain + complex etiology	–	–	–	13	0
No. of patients who had prior operation(s)					
MVD	–	–	3	–	–
RFT	–	1	43	3	–
GR	–	–	–	10	–
AR	–	20	–	–	–
SRS	–	–	–	–	–
PBC	–	–	–	–	–
Others (periph. block, etc.)	–	–	27	–	–
Surgical parameters					
Balloon shapes: no. of patients					
Typical pear	–	100	117	–	–
Others (pearlike, dumbbell, elliptical, etc.)	–	0	27	–	–
Duration of compression (seconds)	300	300–420	60–180	60–420	240–600
Outcome measures					
Initial success rate (%)	96	100	100	89.9	100
Recurrence rate (%)	30.6	28	9.7	9.8	24
Mean time to recurrence (months)	–	–	10–35	–	–
Follow-up range (months)	1–48	12–120	6–54	42	6–84
Morbidity (%)					
Defined postoperative period (months)	–	–	–	–	–
Corneal anesthesia/decreased reflex	2.6	0	–	–	–
Masseter/pterygoid weakness	6.6	–	12	10	48
Trigeminal depressor response	–	–	–	–	–
Dysesthesia	10.6	–	–	–	12
Hypesthesia	–	17	4.1	–	–
Hypoesthesia	93.4	–	40	76.7	100
Diplopia					
CN VI palsy	1.5	–	–	–	–
CN IV palsy	–	1	1	–	–
CN unspecified	–	–	–	–	–
Hearing loss/CN VIII	6.6	–	–	–	–
Blindness/CN II	–	–	–	–	–
Anesthesia dolorosa	–	0	0	0.6	–
Meningitis	–	–	1.4	–	–
Vascular complication					
Hematoma	–	–	–	–	–
CC fistula	6.6	–	3.5	–	16
IC hemorrhage	–	–	–	–	–
Herpes simplex oralis	–	–	–	–	–
Failure due to technical difficulties	–	–	11	–	48
Other	–	–	6.2	0.6	–
Mortality (%)	0	0	0	0	0

E.	Author (year)			
	Brown et al (1989)	**Meglio et al (1987)**	**Esposito et al (1985)**	**Mullan et al (1983)**
No. of patients/no. of PBCs	22/24	47/47	50/50	50/50
Demographics				
Age range	36–83	–	48–82	16–88
Gender (men:women)	16:6	–	19:31	28:22
Pain distribution: no. of patients				
V1	–	–	–	–
V2	–	–	–	–
V3	–	–	–	–
Multiple	–	–	13	–
Bilateral	–	–	–	–
Classification of TN: no. of patients				
Typical	22	–	–	48
Atypical				
TN2	0	–	–	0
Trig. neuropathic	0	–	–	0
TN in MS	0	–	–	2
Postherpetic	0	–	–	0
Trig. pain + complex etiology	0	–	–	0
No. of patients who had prior operation(s)				
MVD	2	–	0	5
RFT	–	–	0	2
GR	–	–	0	0
AR	–	–	0	16
SRS	–	–	0	0
PBC	–	–	0	6
Others (periph. block, etc.)	11	–	0	1
Surgical parameters				
Balloon shapes: no. of patients				
Typical pear	22	–	–	50
Others (pearlike, dumbbell, elliptical, etc.)	0	–	–	0
Duration of compression (seconds)	60–180	240–360	300	180–600
Outcome measures				
Initial success rate (%)	100	100	64	–
Recurrence rate (%)	14	54.5	0	12
Mean time to recurrence (months)	9.5	–	6	16.5
Follow-up range (months)	3–53	36	6	6–54
Morbidity (%)				
Defined postoperative period (months)	≤ 3	–	–	1–4
Corneal anesthesia/decreased reflex	0	–	0	–
Masseter/pterygoid weakness	14	4.25	–	–
Trigeminal depressor response	–	–	–	–
Dysesthesia	14	8.5	0	–
Hypesthesia	23	–	–	6
Hypoesthesia	23	–	48	8
Diplopia				
CN VI palsy	5	–	–	–
CN IV palsy	0	–	–	2
CN unspecified	0	–	–	–
Hearing loss/CN VIII	0	–	–	–
Blindness/CN II	0	–	–	–
Anesthesia dolorosa	0	–	–	–
Meningitis	5	–	–	–
Vascular complication				
Hematoma	0	–	–	–
CC fistula	0	–	–	–
IC hemorrhage	0	–	–	–
Herpes simplex oralis	–	–	–	8
Failure due to technical difficulties	0	–	–	4
Other	14	–	–	–
Mortality (%)	0	0	0	0

Editor's Comments

Balloon compression continues to be an option for patients with refractory trigeminal neuralgia (TN). When performed properly, as described by Dr. Brown and colleagues in this chapter, the procedure should be safe and painless for the patient. The outcome is determined by the technique used, in that if the balloon is inflated and the characteristic "pear shape" is not seen on lateral fluoroscopy, the balloon can compress other structures within the cavernous sinus (e.g., CN VI) and produce neurologic complications.

In the correct radiographic position, filling of the balloon to produce nerve compression must be carefully accomplished and monitored. In the early days of this procedure, the balloon was filled to higher pressures than are currently employed, and held at pressure for longer times. This resulted in good relief of TN, but also a higher rate and density of facial hypesthesia, which resulted in a higher incidence of uncomfortable dysesthesias and even frank anesthesia dolorosa. The trend has been for the balloon inflation times to diminish, which has reduced consequent numbness, but also decreased the median time to recurrence of TN after the procedure.

Review of the table in this chapter shows that the median time to recurrence after balloon compression generally runs 1 to 2 years. Longer intervals of pain relief are seen in centers using longer compression times, and are associated with higher incidences of facial hypesthesia. The results of balloon compression from most centers compare favorably with those of glycerol injection, but are generally inferior to results from radiosurgery or radiofrequency lesions in terms of time to pain recurrence.

I would agree that balloon compression is a "mainstay" therapy for medically intractable TN, if the correct technique is used, and the expectations of the duration of pain relief are explained to the patient.

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48 Intracranial Procedures for Nontrigeminal Neuralgias

Nicholas Barbaro and Jason D. Hill

This chapter aims to examine the causes and surgical treatments of one small but not insignificant outpost within the landscape of pain disorders: nontrigeminal pain. We begin with a brief discussion of the relevant anatomy, followed by an overview of some of the more common nontrigeminal pain disorders. We then conclude with a survey of ablative and nonablative intracranial surgical techniques.

It is important to remember that pain in the distribution of a given cranial nerve or nerves may be due to extrinsic factors such as tumors, compression by adjacent intracranial structures, inflammation, and mass effect secondary to infection, or intrinsic factors such as ischemia. A thorough workup, including dental examination and ear, nose, and throat (ENT) evaluation, as well as appropriate imaging, should be undertaken to rule out other causes of nontrigeminal pain.

Keep in mind that a patient should exhaust all medical options prior to undergoing surgery. Common medications used to treat chronic and/or neuropathic pain include, but are not limited to, gabapentin, pregabalin, carbamazepine, amitriptyline, narcotic medications, as well as agents used in headache management, such as verapamil and the triptans.

Anatomy

The pain system is a complex biochemical and cellular environment, where noxious stimuli are first apprehended and reacted to via reflex pathways in the lower nervous system, are transmitted centrally where processing and reflex refinement take place, and are only then consciously felt by the individual. The conscious recognition of noxious stimulation we might term *pain*, whereas the continued psychic distress elicited by these pain signals might be termed *suffering*. At times, as in the case of chronic pain, the pain pathways may continue to fire in the absence of the original stimulus, resulting in continued suffering following the resection or removal of a clear anatomic lesion.

Pain signals travel through the dorsal horn/Lissauer tract and ascend to the thalamus via the anterolateral and lateral spinothalamic tracts.[1] The lateral spinothalamic tracts originate from lamina I and primarily transmit C fiber signals, whereas the antrolateral tracts have their origin in lamina IV and V and transmit Aδ and Aβ signals.[1] The lateral spinothalamic tract may be further subdivided into paleospinothalamic and neospinothalamic divisions,[2] with the paleospinothalamic tract involved in the emotional dimension of pain.[2] These synapse in the lateral thalamus in the case of the neospinothalamic and anterolateral tracts (VPL/VPI), and the intralaminar nuclei and medial thalamus (mediodorsal nucleus/medial nucleus of the posterior group) in the case of the paleospinothalamic tract. Although there is evidence that these neurons may also send terminations to the VPL/VPM/VPI, others hypothesize projections to a distinct nucleus termed VMpo.)[1] VPM and VPL signals then travel to SI, whereas VPI signals transmit to SII. Mediodorsal signals that have their origin in the lateral spinothalamic tract project to the anterior cingulate; the medial nucleus of the posterior group transmits to the insula. Procedures such as medial thalamotomy and cingulotomy have sought to arrest chronic pain at these levels of processing.

Pain disorders often involve discrete cranial nerves, resulting in neuralgias of the trigeminal or glossopharyngeal nerves, as well as the nervous intermedius/geniculate ganglia. The nervus intermedius is a component of cranial nerve (CN) VII and is formed when fibers from the superior salivatory nucleus join fibers from the nucleus of the solitary tract.[2] Fibers from the facial nucleus then join nervus intermedius as they emerge from the pons. Nervus intermedius projects to the geniculate ganglion and is situated between cranial nerve VII motor fibers and cranial nerve VIII.[2] Of clinical relevance, the nervus intermedius contains parasympathetic as well

as sensory fibers from the external auditory meatus, and is a target in the treatment of otalgia.

The glossopharyngeal nerve is also associated with a variety of pain syndromes and therefore is a surgical target. The glossopharyngeal nerve receives fibers from the inferior salivatory nucleus, nucleus ambiguous, nucleus of the solitary tract, and spinal trigeminal nucleus. It emerges from the medulla, and its sensory functions include sensation to the pharynx, soft palate, posterior tongue, tonsils, and ear (including the tympanic membrane, Eustachian tube, and some components of the outer ear and ear canal). Fibers of the glossopharyngeal nerve pass through the superior ganglion just proximal to the foramen magnum, and the inferior ganglion distal to the foramen magnum, where it begins to branch.[2]

The first branch of the glossopharyngeal nerve, the tympanic nerve, carries sensory fibers (spinal nucleus of trigeminal nerve) from the tympanic cavity and Eustachian tubes. The glossopharyngeal nerve also supplies branches to the carotid sinus, pharyngeal plexus, the stylopharyngeal muscle, and the pharyngeal tonsils and posterior one third of the tongue.

Cranial nerve X may itself be implicated in a variety of pain syndromes. The vagus nerve is composed of fibers from several brainstem nuclei: dorsal nucleus of the vagus, nucleus ambiguous, nucleus of the solitary tract, as well as the spinal trigeminal nucleus.[2] The vagus nerve exits the brainstem at the level of the medulla, passes through a superior ganglion proximal to the jugular foramen and an inferior ganglion distal to the foramen magnum. The vagus has a number of branch points in the neck, including pharyngeal branches, the superior laryngeal nerve, recurrent laryngeal nerve, and cervical cardiac branches. The sensory role of the vagus includes transmitting sensory information from the dura of the posterior fossa, from the external auditory canal, and from a region posterior to the auricle. Sensory information is also transmitted from the lower pharynx and the larynx, from receptors in the aortic arch and aortic body, and from visceral organs.[2]

Both the glossopharyngeal nerve and the vagus nerve exit the skull via the jugular foramen. The vascular structures passing through the foramen—the jugular vein, inferior petrosal sinus, and the posterior meningeal artery—are in general posterior to the neural structures passing through the foramen. The spinal accessory nerve is the most lateral and posterior of the cranial nerves as they enter the foramen, and is just antromedial to the posterior meningeal artery. The vagus nerve is antromedial to CN XI, and the glossopharyngeal nerve is antromedial to the vagus, traversing through the most anterior aspect of the foramen.[2] Often, the glossopharyngeal nerve is separated from the other two nerves by a fibrous or bony band.

The pterygopalatine, or sphenopalatine, ganglion as well as the vidian nerve (nerve of the pterygoid canal) may be implicated in one of several pain disorders. The vidian nerve is formed where the greater superficial petrosal nerve joins the deep petrosal nerve. It traverses the pterygoid canal to enter the pterygopalatine ganglion.[3] The ganglion itself acts as a relay station for a number of motor, sensory, and autonomic pathways.[3] The ganglion is located in the pterygopalatine fossa, which is inferior to the sphenoid sinus, anterior to the medial plate of the pterygoid process, and posterior to the maxillary sinus and middle turbinate.[3] There are six routes via which neurovascular structures enter the fossa: foramen rotundum, pterygoid canal, greater palatine canal, lesser palatine canals, sphenopalatine foramen, and the inferior orbital fissure.[2] Sensory fibers originate from the maxillary nerve and supply sensation to the nose, throat, and sinuses.[3] Synapsing parasympathetic fibers originate with CN VII/nervus intermedius, pass through the geniculate ganglion and ultimately reach the pterygopalatine ganglion via the greater superficial petrosal nerve-come-vidian nerve; sympathetic fibers from the internal carotid plexus join the deep petrosal nerve-come-vidian nerve, pass through the ganglion without synapsing and join the maxillary nerve.[2,3]

Pain Syndromes and Surgical Approaches

Chronic Neurogenic Pain, Central Pain, and Poststroke Pain

Syndromes

Chronic neurogenic pain is a condition that may arise from a lesion along the pain system axis, from abnormal signaling in the absence of a clear lesion, or after the removal of the inciting lesion. The International Association for the Study of Pain Task Force on Taxonomy has defined central pain as "pain due to a lesion or dysfunction of the central nervous system."[4] According to an article by Nurmikko in 2000, a significant number of stroke patients (8%), spinal cord injury patients (50%), as well as syringomyelia/syringobulbia (80%) patients complain of some degree of pain.[5] Furthermore, poststroke pain often affects the thalamus (61%), most often the ventroposterior region, but 39% of cases do not demonstrate clear thalamic injury.[5] Inversely, stroke may place the patient at decreased risk of central pain, as in the case of brainstem stroke involving the bilateral quintothalamic tracts.[4] Studies suggest that dysfunction of the spinothalamocortical tract is a necessary but in some cases not a sufficient cause of central pain.[4]

Although stroke is believed to be the most common cause of central pain, this is most likely due to the fact that stroke is much more common than other etiologies, rather than possessing a greater predilection to cause central pain.[4] Central pain itself may present in a variety of different ways and involve disparate locations. Most commonly, poststroke pain is described as having a cold, burning quality, and there is often (72%) a component of allodynia.[4] Stroke patients may also describe novel sensations which, although not painful, are exceedingly unpleasant.[4] In contrast, patients with spinal cord involvement often describe dysesthesia, or "pins and needles" sensations.[4] Multiple sclerosis (MS) patients may describe aching pain, stabbing pain, or burning sensations.[4,5] It should be noted that although some causes of central pain are of brainstem origin and may mimic CN neuralgias, central pain often manifests with other signs or symptoms of brainstem dysfunction.

Central pain has been hypothesized to occur due to deafferentation and resultant overactivity of neural elements upstream from an insult, or to damage and subsequent disruption of previously homeostatic signaling pathways.[4] Nurmikko points out that these two hypotheses assume that higher levels of processing and perception haven't been disrupted, either directly via insult or indirectly via alterations in downstream circuitry; nor do they account for the neuropsychiatric changes that may arise amid a maelstrom of chronic suffering.[4]

In a series of publications, Jeanmonod et al demonstrated the presence of abnormal calcium spike bursts that they hypothesized result in "self perpetuating thalamic cell membrane hyperpolarization, similar to the one seen in slow wave sleep."[6] They go on to hypothesize that this hyperpolarization of thalamic cells may be responsible for other positive symptoms following central insult, such as "tinnitus, abnormal movement, epilepsy and certain neuropsychiatric disorders."[6] In another report by the same group, they describe microelectrode analysis of the medial thalamus in 45 patients undergoing medial thalamotomy for pain, and found that the most effective therapeutic results correlated to regions in and around the central lateral nucleus demonstrating low-threshold calcium spike bursts. They hypothesize that central pain involves an imbalance and overinhibition of central lateral and ventroposterior nuclei by the reticular nucleus.[7] The hypothesis states that after a lesion occurs involving the lateral spinothalamic tracts, there is a preferential decreased excitation of VP as compared with CL. The spared excitation of CL results in overactivation of the reticular nucleus and subsequent inhibition of VP. This inhibition causes low-threshold spikes, activation of the reticular nucleus, and inhibition and subsequent generation of low-threshold spikes involving CL, giving rise to a positive feedback loop[7] (**Table 48.1**).

Surgical Approaches

Deep brain stimulation (DBS) has been used for the management of chronic pain as well as phantom limb pain. The traditional target has been the periaqueductal gray/periventricular gray region, although the mechanism of action remains unknown.[8] Cortical stimulation is another modality that has been used to treat a variety of pain disorders, from poststroke pain[9] to cranial neuralgias.

Radiofrequency ablation has been used for many years to target the thalamus in the treatment of neuropathic pain.[10] Central pain was first hypothesized in 1911 by Head and Holmes, but the ability to perform medial thalamotomies for central pain was realized with the emergence of stereotactic techniques in the 1950s.[11] The procedure was initially embraced as low risk and with minimal side effects, but symptomatic recurrence was frequent.[11] Classically, caudal regions in the intralaminar complex, such as the centromedian/parafascicular complex, central lateral nucleus, posterior complex, and medial pulvinar, were targeted.[11] In the *Textbook of Stereotactic and Functional Neurosurgery,* Jeanmonod and Morel discuss targeting of the posterior central lateral nucleus "based on recent multiarchitectonic studies [due to integration of] the nucleus in a large thalamocortical network responsible for the multiple sensory, cognitive, and affective components of the neuropathic pain condition."[11]

In advocating the targeting of the central lateral nucleus, Jeanmonod and Morel make four points: (1) afferents from the spinothalamic tract to the nucleus are known, in contrast to the lack of data establishing afferents to the central median/parafascicular complex or medial pulvinar; (2) fibers from layer I and layers III–IV passing through the central lateral nucleus project to regions governing a wider array of pain processing than other targets, such as the "discriminative (SI, SII), affective-motivational (ACC, insula), cognitive (PFC), and motor (motor cortex)"[11]; (3) the central lateral nucleus is farther from the primary somatosensory nuclei, reducing the risk of sensory deficits as compared with CM lesioning; (4) there is low anatomic variability in this target.[11]

The procedure itself is performed using a magnetic resonance imaging (MRI)-compatible frame, and under local anesthetic. Localization is achieved via stereotactic MRI. Axial images parallel to the intercommissural plane are derived. The lead is placed with the assistance of impedance monitoring in the posterior portion of the central lateral nucleus via a prefrontal approach, anterior to the coronal suture. The target is located at the level of the intercommissural plane, 2 mm posterior to the posterior commissure, and 6 mm lateral to the thalamo-ventricular border.[11] A lesion 1 to 2 mm above the intercommissural plane may be made to avoid lesioning

Table 48.1 Surgical options for nontrigeminal pain

Etiological site	Pain location	Surgical approaches
Central pain/poststroke[8,9,11–13]	Throughout the body	1. Medial thalamotomy—radiofrequency 2. Medial thalamotomy—radiosurgical 3. Medial thalamotomy—focused U/S (experimental) 4. Cortical stimulation 5. Periaqueductal gray DBS 6. Focused U/S
Vagoglossopharyngeal[12,14,16–18]	Lancinating pain in posterior oropharynx, base of the tongue, below the angle of the jaw; may involve the ear; may be accompanied by hemodynamic instability/syncope	1. Microvascular decompression 2. Case reports of epidural sensory cortex stimulation 3. Gamma Knife
Geniculate/nervus intermedius[19–22]	Lancinating paroxysmal pain within the ear	1. Microvascular decompression 2. Nerve sectioning
Pterygopalatine neuralgia (Sluder syndrome)[3,19,23,25]	Retro-orbital, zygomatic, nasal pain; may have numbness of the nose, soft palate, pharynx; parasympathetic overactivity	1. Blocks 2. RF stimulation 3. RF ablation
Vidian neuralgia (Vail syndrome)[25]	Variant of Sluder. Pain may radiate into the shoulder, neck or ear, and may be accompanied by vertigo or tinnitus	Block
Cluster headache[13,18,23,24,26]	Paroxysmal unilateral attacks centered on temple, cheek, eye; accompanied by autonomic dysfunction	1. Pterygopalatine blocks or stimulation 2. DBS of posterior hypothalamus 3. RF ablation of pterygopalatine ganglion
Superior laryngeal neuralgia[27]	Unilateral paroxysmal pain centered around hyoid bone, thyroid cartilage; may radiate to jaw or ear	Block

Abbreviations: DBS, deep brain stimulation; RF, radiofrequency; U/S, ultrasound.

the pretectum. The medial-lateral angle is between 5 and 10 degrees, and the antroposterior (AP) angle between 60 and 65 degrees. This AP angle may be less than 60 degrees in some patients, necessitating a 1 mm posterior correction in some cases. Partial lesioning of the CL is adequate in most cases.[11]

Microelectrode recording is performed while the patient is asked to carry out various motor tasks. Additionally, tactile, nociceptive, and proprioceptive stimuli are applied and monitored. Once recording is complete, the microelectrode is replaced with a blunt pencil tip macroelectrode, and stimulation is applied to assess for any motor, cognitive/emotional, or sensory responses. Most patients experience paresthesias or dysesthesias localized to the affected region, but may experience full-body responses. Radiofrequency lesioning of 10 to 12 mm length by 4 mm diameter is then performed.[11]

Ninety-six patients between the ages of 18 and 84 with chronic, medically refractory central or peripheral pain underwent lesioning in the study. Over 60% of the patients had undergone previous transcutaneous electrical nerve stimulation (TENS), dorsal column or thalamic stimulation, or ablative procedures such as sympathectomy, neurotomy, cordotomy, or rhizotomy.[11] Follow-up was from 2 weeks to over 10 years. Close to 20% of patients experienced complete pain relief, whereas 53% demonstrated over 50% pain relief. Paroxysms were reduced by 65% and the duration of pain episodes was reduced by 90%.[11]

Radiosurgical ablation offers a less invasive technique for performing medial thalamotomy. Frighetto et al propose linear accelerator thalamotomy as an alternative to more invasive techniques. In the series of three patients, two presented with poststroke pain and the third with malignant pain secondary to invasion of the brachial plexus.[12] In the study, 150 to 200 Gy were administered to the target for 55 to 85 minutes using a 5-mm collimator. A BRW frame was first fitted parallel to the AP commissure plane.[9] The centromedian-parafascicular nuclei were targeted using MRI imaging and the Schaltenbrand and Warren atlas, where the atlas was sized to the patient's MRI at the AP commissure plane.[9] Patient 1 was treated for refractory pain following an MCA stroke and demonstrated immediate pain relief that lasted 4 months.[9] She subsequently required motor cortex stimulation for refractory pain. Patient 2 presented with small cell carcinoma with invasion of the brachial plexus. He had previously deferred

brachial plexus ablation. Due to comorbidities and a trial of medically induced coma for pain relief, it was felt that stereotactic thalamotomy was the best and safest option. He was able to return home following the procedure with good pain relief and decreased requirement of pain medication.[9] Patient 3 presented with refractory pain of the face, hand, and foot following a right posterior cerebral artery infarct with right thalamic lacunar infarct. She demonstrated an immediate decreased pain medication requirement and decreased allodynia, and at 3 years was taking pain medication only twice a week.[9]

Ultrasound therapy is an older modality, which is nonetheless experiencing a reemergence as localization technology becomes more sophisticated. Jeanmonod et al reported the use of MRI-guided focused ultrasound for central lateral thalamotomy. The procedure was performed on 12 patients with a variety of medically refractory neuropathic pain disorders, including postherpetic neuralgia, traumatic trigeminal nerve injury, lumbar radiculopathy, thalamic infarct, and brachial plexus avulsion.[9] Using 3T MRI-guided focused ultrasound via the ExAblate 4000 (InSightec, Haifa, Israel), the authors completely shaved the patient's head, covered it with a special fenestrated silicone membrane, and placed the patient's head into an MRI-compatible stereotactic frame. The silicone membrane was used to circulate water at 15 to 20°C around the head. MR imaging was obtained and the target—the posterior portion of the thalamic central lateral nucleus—was identified. The target was then heated to between 39 and 42 degrees for 10 to 20 seconds with sublesioning pulses. This allowed the targeted tissue to be confirmed with MR thermography. Once confirmation was achieved, a series of higher sonifications were applied, with a target tissue temperature of 51 to 64°C. The authors noted that although thermocoagulation effects may be seen at a temperature of 50°C, tissues must reach 55 to 57°C to ensure a 100% lesioning effect.[13] Sonications were of 10 to 20 seconds in duration, with up to 12,000 J per sonication.[13] Mean pain relief at 3 months was 47% (of 9 patients) and 57% at 1 year (8 patients). The potential for ultrasound therapy to supplement radiofrequency ablation or radiosurgical ablation seems promising, particularly in those patients for whom a more invasive procedure is prohibitive. However, more work needs to be done in this arena before the technique can enjoy a wider acceptance (**Table 48.1**).

Glossopharyngeal Neuralgia

Anatomy and Syndrome

Chronic pain involving the cranial nerves may be due to tumor compression, compression from normal or abnormal vascular structures, postinfectious chronic nerve irritation, or demyelinating disorders. Glossopharyngeal neuralgia (or vagoglossopharyngeal neuralgia, as some have proposed[14,15]) describes a condition where the patient experiences paroxysmal attacks of lancinating pain in the posterior oropharynx, the base of the tongue, beneath the angle of the jaw, and possibly the ear.[14,15] Attacks may be triggered by oropharyngeal maneuvers, raising the arm, or turning the head, and may be accompanied by hemodynamic instability resulting in syncopal episodes (suggesting vagal involvement).[16] Most cases present between the ages of 40 and 60, and often involve the left side. It is rare; reported incidence varies among studies, but has been cited as between 0.2 and 0.7 per 100,000 per year,[14] with slight predominance of men at 0.9 per 100,000 per year versus women at 0.5 per 100,000 per year.[15] It has been noted that 10% of cases copresent with trigeminal neuralgia.[11]

Glossopharyngeal neuralgia may be subdivided into pharyngeal, otalgic, and vagal neuralgias, depending upon the predominant constellation of symptoms.[14] In a case series of 19 consecutive patients treated for glossopharyngeal neuralgia, Gaul et al found that although 3 patients presented with concomitant vagal neuralgia, all patients were found to have vascular compression of the vagus nerve at the time of surgery.[14] Compression of the nerve by posterior inferior cerebellar artery (PICA) was the most common finding at the time of surgery, although compression by PICA and the vertebral artery, or the anterior inferior cerebellar artery (AICA) and the vertebral artery was also observed.[14] In a series of 31 patients, Ferroli et al found that the vertebral artery or the AICA alone could act as an offending vessel, and documented 1 case where the offending vessel was a vein[16] (**Table 48.1**).

Surgical Interventions

Microvascular decompression (MVD) has been successfully used to treat trigeminal neuralgia for many years. Dandy was the first to note compression of the trigeminal nerve by a vascular loop in 1934,[16] and 2 years later Lillie and Craig reported on a patient with glossopharyngeal neuralgia (GN) thought to be caused by a compressive vessel loop.[16] But it wasn't until the 1960s that microvascular decompression for cranial neuralgias was articulated and popularized by Dr. Jannetta.[16] Given the rarity of glossopharyngeal neuralgia, as well as the hazards of operating upon the lower cranial nerves, there are scant long-term outcome studies of patients undergoing MVD for GN.

In a study published in 2009, Ferroli et al looked at 31 patients over 18 years (1990–2007) who underwent MVD for GN.[16] Surgical technique involves exploration of the cerebellopontine angle via a ret-

romastoid approach. In this particular approach, the authors identified the "margin of the sigmoid sinus from its beginning to the region behind the mastoid tip."[16] The dura was incised parallel to the margin of the sigmoid, and the cerebellomedullary cistern was opened to allow for access to the lower cranial nerves as well as for cerebrospinal fluid (CSF) drainage.[16] The authors describe use of the endoscope in 4 of the cases to fully visualize the root entry zones of cranial nerves IX and X.[16] Compressive vessels were identified and microvascular decompression accomplished using Teflon (3M, Minneapolis, MN, USA) or muscle fragments of fibrillar Surgicel (Ethicon, Cincinnati, OH, USA).[16] If venous structures were thought to be the etiological culprit, these were coagulated and cut. In their series, 18 cases were left sided, and the remaining right sided. Twenty-two cases demonstrated compression by the PICA, 7 due to vertebral artery compression, and 1 each due to AICA and a compressive vein.[16] Immediate pain relief was noted in 28 cases, with the other 3 patients experiencing gradual relief over the span of a few weeks.[16] Two patients required reoperation for medically refractory recurrence, and were found to have incomplete decompressions at the time of surgery.[16]

In 2011, Gaul et al published a series of 19 consecutive patients (18 of whom underwent surgery, and 1 of whom was excluded due to medical control of pain) from 1994 to 2009 referred for refractory glossopharyngeal neuralgia. Patients were subdivided into vagal, pharyngeal, and otalgic subtypes based upon clinical presentation. All patients underwent preoperative MRI with 3D (three-dimensional) reconstructions. In this series, the authors used a retrosigmoid approach with extension into the foramen magnum. The cerebellopontine cistern was opened for CSF drainage, and cranial nerves IX and X were identified. Offending vessels were dissected free and isolated using Teflon.[14] Twelve cases were left sided and 7 right sided. Although all patients presented with pharyngeal pain, 12 patients demonstrated additional otalgic symptoms, and 3 suffered vagal symptoms.[14] Of the 18 surgical patients, 16 were pain free and 2 demonstrated a decrease in their pain.[14]

In the rare case that a patient is refractory to medical and conventional surgical management, there are other options. A 2010 case report by Anderson et al described cortical stimulation in a patient with medically and surgically refractory glossopharyngeal neuralgia, trigeminal neuralgia, and dysphagia.[17] Signs and symptoms included left-sided facial pain, throat pain, nausea/vomiting, and dysphagia due to the pain. She had previously undergone multiple open and percutaneous procedures, to no avail. The patient underwent an initial awake craniotomy for placement of an epidural trial electrode across the central sulcus. The electrode position was then adjusted to elicit lower facial and tongue responses using a pulse generator set at 5 Hz and 250 µs. Once the desired location was found, the electrode was attached to the dura. After the trial week, in which the patient's pain went from 10/10 to 6 to 7/10 with stimulation, the lead was tunneled and attached to a subclavicular generator. In the postoperative period, the patient required adjustments and generator replacement, but experienced pain relief as well as decreased dysphagia and nausea/vomiting.[17]

For patients who are not good surgical candidates, or have refused open surgery, radiosurgical intervention is an option. In a 2010 report, Williams et al described the case of a 47-year-old woman who presented with medically refractory, lancinating left throat pain.[18] She declined MVD, so was offered GK therapy. A dosage of 80 Gy was administered to the nerve as well as the glossopharyngeal meatus, and the patient remained neurologically intact and pain free at 12 months' follow-up[12] (**Table 48.1**).

Geniculate/Nervus Intermedius Neuralgia Syndrome

Geniculate neuralgia (nervus intermedius) describes a condition where patients experience lancinating, paroxysmal pain within the ear. Pressure upon the tragus, sound, cold, or swallowing may trigger pain.[19] The diagnosis is one of exclusion; that is, a full otolaryngological examination must be performed, including vestibular examination; audiogram; evoked potentials; full examination of the mouth, nose, nasopharynx, pharynx, larynx, and paranasal sinuses; as well as MRI of the brain, to rule out other etiologies.[20] Because there is some overlap in the sensory distribution of cranial nerves V, VII, IX, and X, diagnosis may be difficult, or may point to involvement of two or more nerves[19] (**Table 48.1**).

Surgical Interventions

Nervus intermedius (NI) neuralgia has classically been treated with nerve sectioning. Using a standard retrosigmoid approach, the nerve is identified and dissected as it exits the brainstem between CNs VII and VIII, and it may be sectioned using standard techniques. A 2005 article published by Ashram et al described intraoperative electrophysiologic identification of the NI.[21] Although this report describes identification in the context of various CP angle procedures, it could prove useful for procedures specifically targeting NI neuralgia. The study was a retrospective case review of 33 patients who underwent facial nerve monitoring using electrodes placed in the orbicularis oculi and orbicularis oris. They found that stimulation produced a long-latency,

low-amplitude response in the orbicularis oris electrode at a mean threshold of 0.4 V, a mean latency of 11.1 ms, and a mean amplitude of 11.1 mV.[21] These responses were found to be distinct from facial nerve responses.[21]

Microvascular decompression has also been proposed as a treatment for otalgia, or NI neuralgia. In a case report published in 2011 in the *Journal of Laryngology and Otology*, Saers et al report upon a 24-year-old with a 9-year history of otalgia.[22] The patient presented with a deep lancinating pain within the left ear refractory to a variety of medications and blocks. Hearing and cranial nerve function were preserved. Imaging demonstrated anomalous AICA between the facial and vestibulocochlear nerves, in the region of the NI.[22] Surgical exploration was performed, and several blood vessels as well as arachnoid adhesions were noted overlying the facial and vestibulocochlear nerves.[22] The adhesions were removed and the vessels were carefully dissected away and isolated from the nerve complex using Gelita-Spon (Gelita Medical, Eberbach, Germany) and Tissucol Duo 500 (Baxter, Vienna, Austria).[22] The patient awoke without deficit and remains pain free. Whereas sectioning of the NI remains a popular option for NI neuralgia, MVD may be considered in certain cases (**Table 48.1**).

Pterygopalatine/Sphenopalatine Neuralgia, Vidian Neuralgia, and Cluster Headaches Syndromes

Pterygopalatine/sphenopalatine ganglion neuralgia, or Sluder syndrome, is a particular pain disorder that manifests with gustatory, motor, and sensory abnormalities in addition to pain,[3] which may be due to previous inflammation/infection of the posterior ethmoid and sphenoid sinuses.[19] The condition may involve paroxysmal attacks of parasympathic overactivity, causing tearing, nasal congestion, eye infection, and alteration in taste along with retroorbital, zygomatic, and nasal pain, and accompanied by numbness of the nose, soft palate, and pharynx.[3] There is some speculation that the sphenopalatine ganglion is involved in cluster headaches, and therefore it has been proposed as a target in the treatment of cluster headaches.[23,24]

Vidian neuralgia, or Vail syndrome, may be considered a variant of sphenopalatine neuralgia, and occurs when the nerve is irritated in the pterygoid canal due to trauma or inflammation/infection. It is paroxysmal and unilateral, with pain radiating into the shoulder, neck, or ear, and may be accompanied by vertigo and tinnitus.[25]

The term *cluster headache* describes paroxysmal unilateral attacks centered around the temple, cheek, or eye that are accompanied by autonomic dysfunction such as ocular swelling, tearing, and nasal congestion.[26] Although the etiology is poorly understood, a variety of targets have been proposed for therapy, including the posterior hypothalamus and sphenopalatine ganglion.[23,26] Cluster headaches may occur in bursts for up to 12 weeks followed by periods of remission, or may be chronic in up to 10% of sufferers, occurring for a year or more without remission.[26] There are known triggers, such as bright lights and alcohol ingestion, but studies have demonstrated a circadian relationship as well, suggesting an endocrinologic role in the generation of cluster headaches.[26] Prevalence has been quoted as between 0.006 and 0.24%, depending upon geographic location[26] (**Table 48.1**).

Surgical Interventions

Sphenopalatine blocks may be performed using the fluoroscopic-guided percutaneous technique described below. A needle is advanced inferior to the zygomatic arch, advanced through the coronoid notch onto the pterygoid plate, and anteriorly along the plate and into the fossa.[23] Anesthetic may then be injected into the ganglion.

Vidian neuralgia may be treated with a block, by entering the pterygoid canal via the greater palatine foramen and advancing the needle into the canal. Local anesthetic may be instilled or neurolysis performed with alcohol.

Both radiofrequency ablation and radiosurgery have been proposed as treatments for sphenopalatine neuralgia and cluster headaches, by targeting the sphenopalatine ganglion or the trigeminal nerve. A 2007 article by Lad et al followed a patient with medically refractory cluster headaches who had undergone two successful block trials prior to undergoing radiosurgery. A single fraction of 45.5 Gy was administered to the 78% isodose line to a maximum dose of 65 Gy.[24] At 12-month follow-up, the patient demonstrated a decrease in the number and severity of attacks, as well as a decrease in medication usage.

Radiofrequency ablation of the sphenopalatine ganglion involves an infrazygomatic arch approach. Ruiz-Lopez et al describe a technique where the clivus, sella, petrous bone, and pterygopalatine fossa are identified on a lateral film.[25] The needle is inserted perpendicular to the skin in the upper region of the mandibular arch and advanced to the fossa until the patient experiences paresthesias in the jaw.[25] An AP film is then used to advance the needle medially, 1 to 2 mm above the vomer, until the tip is adjacent to the lateral wall of the nasal cavity.[25] Upon stimulation, paresthesias should occur

in the nasal region and the palate, and no maxillary contraction should be observed.[25] If the paresthesias are noted in the palate only, the electrode should be slightly advanced.[25] Inject 1 ml of 2 percent lidocaine prior to lesioning. Single lesioning may be performed via pulsed radiofrequency for 4 minutes.[25] Pulsed RF may also be used to create 3 lesions—one in the PPF, one located 1–2 mm medially, and one located 3 mm medially—though the duration of each is 1 minute rather than 4.25. Alternately, conventional RF at 80°C may be used to create the above three lesions (PPF, 1-2 mm medial, and 3 mm medial), with a duration of 1 minute for each lesion.[25]

Radiosurgical targeting of the trigeminal nerve has also been proposed as a treatment for cluster headaches, although a 2006 study by McClelland et al does not bear this out. The study followed 10 patients who had undergone Gamma Knife (Elekta, Stockholm, Sweden) surgery of the trigeminal nerve. They found poor pain relief in 9 patients immediately following radiosurgery.[13] Although 6 patients improved between 2 weeks and 2 years, they ultimately regressed. Half of the patients experienced facial numbness following the procedure.[18]

In 2010 Ansarinia et al published a paper targeting the sphenopalatine ganglion (SPG) for the treatment of cluster headaches via radiofrequency stimulation. The authors followed 6 patients treated with up to 1 hour of sphenopalatine stimulation during a cluster headache attack. These attacks were spontaneous or were triggered using pungent smells, bright lights, IV nitroglycerin, or alcohol ingestion.[23] The treating physicians used a fluoroscopically guided percutaneous infrazygomatic transcoronoid approach, placing the electrode into the pterygopalatine fossa, adjacent to the sphenopalatine ganglion.[23] A 20-gauge foramen needle was used to enter inferior to the zygomatic arch and advance through the coronoid notch and onto the pterygoid plate, where it was then advanced anteriorly into the pterygopalatine fossa.[23] Next, a single-contact temporary electrode was placed into the needle and advanced toward the ganglion. Paresthesias in the root of the nose and posterior nasopharynx were induced via stimulation of various intensities (less than 2 V) at 50 Hz and 300 µs to confirm physiological placement of the electrode.[23] Treatment was initiated when patients rated their pain as 8 (out of 10) or greater, and stimulation parameters were adjusted so as to effect pain relief. When the cluster headache resolved it was reinduced with known triggers and allowed to reach its maximum intensity prior to restimulation.[23] This cycle was repeated for a total of 1 hour per patient.[23] Of the 18 attacks investigated in the study, 61% (11 of 18) demonstrated full resolution, whereas 4 attacks demonstrated no resolution and 3 demonstrated partial resolution.[23] Autonomic features such as ocular swelling and nasal congestion also demonstrated resolution with stimulation.[23] The authors concluded that the SPG may offer a reasonable target for permanent neuromodulation in the treatment of cluster headaches, although the investigation is ongoing.

In 2002, Franzini et al published a study targeting the posterior hypothalamus for the treatment of cluster headaches. The study followed 5 patients who had undergone long-term, high-frequency stimulation via implantable electrodes. Electrodes were placed 2 mm lateral to midline, and 3 mm posterior and 5 mm inferior to the midcommissural point.[26] At 2 to 22 months follow-up period, all patients were pain free, 2 patients were pain and medication free, while 3 required continued low-dose medication (methysergide and verapamil).[26]

Electrodes were implanted using the Leksell stereotactic frame and under local anesthetic and/or low-dose benzodiazepine or propofol.[26] High-resolution MRI was used to determine the anterior commissure–posterior commissure line, and was fused with a computed tomography (CT) scan obtained under stereotactic conditions.[26] A precoronal paramedian bur hole was used to advance a cannula up to 10 mm from the target.[26] The microrecording electrode followed by the definitive electrodes were advanced to the target. Macrostimulation was used to elicit potential side effects, and adjustments were made until these were minimized. After a trial period of 7 to 10 days, the leads were connected to a subclavicular generator (**Table 48.1**).

Superior Laryngeal Neuralgia Syndrome

Superior laryngeal neuralgia is a very rare disorder, which may manifest with unilateral paroxysmal pain centered around the hyoid bone or thyroid cartilage, although it may radiate to the jaw or ear.[27] Other causes for pain, such as mass lesion, must be ruled out with imaging and full ENT examination (**Table 48.1**).

Surgical Intervention

Superior laryngeal nerve blocks may be performed by injecting high-dose local anesthetic into the region where the nerve enters the hyothyroid membrane.[27] The block tends to be short acting, although in an article published by Sato et al, they reported long-term pain relief over the course of many sessions using high-dose lidocaine.[27] Care must be taken to avoid injection of anesthetic into the superior thyroid artery.[27] Of benefit, this procedure avoided the side effects of neurolysis with alcohol or phenol[27] (**Table 48.1**).

Editor's Comments

The host of diagnoses that are included here make this chapter a difficult assignment, both for the authors and the reader. Whereas trigeminal neuralgia is a relatively common and reasonably definable entity, a listing of other, more uncommon cranial neuralgias quickly becomes somewhat obscure. I congratulate Drs. Barbaro and Hill for producing this readable review.

Given the rarity of these conditions, careful prospective series with well-described outcomes are a rarity. In some instances, even the diagnoses are controversial. For example, there is not a consensus concerning the distinction between sphenopalatine neuralgia and cluster headache. Other conditions such as vidian neuralgia and superior laryngeal neuralgia are so obscure and indeterminate that their mere existence may be supported solely by comprehensive lists of historical diagnoses in chapters such as this. In these instances, it is certainly possible that these "named" diagnoses may simply be unusual variants of more common conditions, referable to their anatomical region.

What we can glean from the evidence and the published experience is that there does seem to be a distinct entity that we call glossopharyngeal neuralgia (GPN). This condition refers to episodic lancinating or stabbing pain in the tonsillar region or the posterior tongue. Pain can be referred to the throat just behind the angle of the jaw. It is usually triggerable by swallowing. In the past it was referred to as vagoglossopharyngeal neuralgia because sufferers could experience syncope, apparently due to bradycardia and hypotension from vagal nerve activation. In my experience, this accompaniment to the pain is rare to nonexistent.

The evidence to support a surgical approach to a patient with medically intractable GPN is based on case series, but these results do comport with my experience, as well. Using high-resolution MRI and MRA, we have found that essentially every patient with this clinical diagnosis has demonstrable vascular compression of the 9th and 10th cranial nerves, usually from the posterior inferior cerebellar artery (PICA), sometimes from the anterior inferior cerebellar artery (AICA), and rarely from the vertebrobasilar complex. Microvascular approach to these nerves is the most effective strategy, particularly when vascular decompression is combined with complete section of the glossopharyngeal nerve and partial section of the vagus nerve (section of the most superior one or two rootlets).

In my opinion, geniculate neuralgia (intermedius neuralgia) may or may not be a legitimate syndrome. Because it is so rare, it is difficult for any one surgeon to mount much of an experience base. When a patient tells me that he has paroxysmal stabbing pain deep in the ear only ("an ice pick in the ear"), this diagnosis comes to mind. The diagnosis is based solely on the patient's complaint because, at least in our center, imaging has not yielded any consistent results. I have personally operated on around a half dozen patients in whom I thought the diagnosis applied. I have performed section of the one or two rootlets of the nervus intermedius. This can be a somewhat daunting task; these rootlets lie between the 7th and 8th cranial nerves and potential complications can include facial weakness and hearing loss. In my small case series, the results have been mostly gratifying, but I am still unsettled as to the nature and diagnosis of this syndrome.

The evidence to support radiosurgical treatment or radiofrequency ablation of the sphenopalatine ganglion for sphenopalatine neuralgia or cluster headache is simply too meager to recommend these options at this time. Other treatments for neuropathic pain, such as deep brain stimulation and medial thalamotomy, are discussed in other chapters. These are not potential treatments exclusively for cranial neuralgias, and the data to support them must be comprehensively evaluated for each diagnosis in which they are applied.

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49 Percutaneous Computed Tomography–Guided Trigeminal Tractotomy and Nucleotomy

Yücel Kanpolat

The pain sensation reaches the central nervous system via a transmission system. Therefore, surgical destruction of this transmission pathway has been considered as a treatment method in pain surgery. Concepts regarding destruction of the pain transmission system emerged as a result of clinical observations based on the destruction of this system due primarily to accidents, injury, trauma, or tumor.[1] Cordotomy emerged as a result of such a coincidental observation, and was suggested by a meticulous neurologist, Spiller, before the functional structure of the lateral spinothalamic tract had been described.[2–4]

Stereotaxic destruction of the pain-transmitting system is the basis of stereotaxic pain procedures. Stereotaxy can be described as a technique that utilizes a three-dimensional coordinate system to locate a specific region in the body with the reference of instruments such as needles or electrodes.[5] In my experience, stereotactic pain surgery is performed in three stages: (1) direct morphological localization of the target point with stereotaxic methods, which can be performed with computed tomography (CT) or magnetic resonance imaging (MRI) in today's facilities; (2) measurement of the resistance of the target point using the impedance method and confirmation of the functional status with stimulation; and (3) controlled, selective destruction of the target point or tissue. This can be done with radiofrequency (RF) energy of a specific size or temperature. Operations in which these three basic principles are applied can be referred to as stereotaxic. These applications are surgeries in essence, and they should be performed by an experienced neurosurgeon.

The stereotaxic pain procedures, which require specific knowledge and experience, have had quite encouraging outcomes. Unfortunately, these procedures, which are applied to relieve intractable pain mostly in cancer patients, have been prevented from attaining popular use due to the complication and mortality rates reflected in data from obsolete literature.[6] Today the majority of patients experience difficulty in finding a physician who can relieve their pain. According to a study in the United States, one in four patients has had to change physicians at least three times because of persistent pain. This is also a reflection of the generally insufficient knowledge and experience of physicians in the field of pain management.[7]

Today fundamental procedures in pain surgery have been developed by neurosurgeons, and these valuable and important techniques are being proffered on golden trays to other medical occupational groups. We live in a time commonly accepted as the science and information age. In my opinion, physicians in this century are guided by company dogmas. The use in developed Western countries of numerous procedures that are of no medical value supports this opinion. Unfortunately, today the benefit of some procedures is extremely debatable but their efficacy or popularity is not. A patient's sleep quality, pain-free status, appetite, and defecation habits are important parameters in the practice of pain management, especially in cancer patients, and shape their quality of life. Many physicians today use arguable algorithms and scoring systems rather than evaluate these fundamental parameters. Today, using the analgesic ladder recommended by the World Health Organization (WHO) in the late 1980s[8] as a gold standard is inappropriate with respect to treatment realities. Despite the reliance on guidelines, persistent pain problems have been identified at rates of up to 40% in some studies.[9,10] Cancer pain is usually managed at a suboptimal level.[11,12] Rana et al emphasized that pain management is still not an essential component of oncological care.[13] The addition of a fourth step consisting of interventional procedures to the WHO's three-step analgesic ladder has been suggested.[14,15] It should be recognized that intractable pain is a humanitarian as well as a medical problem, and especially in cancer patients, this problem can be solved with rational treatment alternatives. Pain-free survival has been defined as a human right by both the WHO and the International Association for the Study of Pain (IASP)[16]; however,

it is a sad fact that this right is not recognized adequately in the present day. Human beings should be given the right to die with the same dignity with which they are accorded by law to live.

The first attempt at destructive procedures for intractable pain treatment was originally performed in 1912 using open surgical techniques in the spinal cord.[2] In 1963 Sean Mullan described the percutaneous approach for performing cordotomy. Beginning in 1965, RF energy was used to make controlled lesions.[17,18] Later, the RF generator and electrode systems provided information regarding use of the impedance of the tissue and electrical stimulation to evaluate the function of the target.[19] These procedures, called "stereotactic," were classically performed using radiographic guidance; however, it was determined later that it was impossible to visualize the spinal cord and the target using such conventional visualization methods.[20] Finally, in response to the necessity of a dynamic visualization system, we started to use CT guidance in percutaneous procedures.[21–23]

The descending trigeminal tract is an excellent target for controlling intractable facial and oronasopharyngeal pain. Destruction of the descending trigeminal tract in the medulla is known as a trigeminal tractotomy.[1] Lesioning of the nucleus caudalis is known as trigeminal nucleotomy, and lesioning of the whole substantia gelatinosa of the nucleus caudalis is known as the nucleus caudalis dorsal root entry zone (DREZ) operation.[24–26] The pain-transmitting fibers of the 7th, 9th, and 10th cranial nerves join and descend with the spinal tract of the trigeminal nerve into the upper spinal cord.[27,28] Lesioning of this tract was first performed by Sjöqvist in 1938.[1] In 1965 Kunc successfully used the procedure to relieve glossopharyngeal neuralgia.[29] Sweet observed special hypoalgesia in the dermatomes of the 7th, 9th, and 10th cranial nerves after trigeminal tractotomy.[30] Crue et al and Hitchcock, with the aid of RF thermocoagulation, independently performed the first stereotactic trigeminal tractotomies.[31,32] Schvarcz, who has used the technique since 1971, suggested lesioning the oral pole of the nucleus caudalis, and designated the procedure as trigeminal nucleotomy.[24,33,34] Hosobuchi and Rutkin used evoked potentials to delineate the descending trigeminal tract during the procedure.[35] In 1990 Nashold's group[36] described a special open technique to destroy the substantia gelatinosa of the nucleus caudalis, and named the procedure the trigeminal nucleus caudalis DREZ operation.[25,26] In 1989 we developed a percutaneous technique for trigeminal tractotomy-nucleotomy (TR-NC), guided by CT, to facilitate topographical localization of the electrode tip in the spinal cord.[23]

In this chapter, our vast experience with trigeminal TR-NC with CT guidance is presented in conjunction with the knowledge gained from our patients and colleagues.

Pertinent Anatomy and Rationale

The descending trigeminal tract is the caudalward branch of the trigeminal afferents at the medulla after its bifurcation upon entry into the pons. These fibers terminate in the spinal trigeminal nucleus.[1,37] The tract overlies the spinal trigeminal nucleus in the posterolateral part of the spinal cord at the cervicomedullary junction. All three divisions of the trigeminal nerve have a specific topographic organization in the tract: fibers from the mandibular dermatome (V-3) are located in the dorsal part of the tract; ophthalmic fibers (V-1) are located ventrolaterally, and maxillary fibers (V-2) are located between them. Primary sensory fibers from the 7th, 9th, and 10th cranial nerves also enter the tract.[38,39] These fibers lie slightly medially, behind the tract. The trigeminal sensory nucleus consists of three nuclei: (1) spinal, (2) principal, and (3) mesencephalic trigeminal nuclei. Afferent fibers that carry the sensations of pain and temperature descend in the spinal trigeminal tract in the medulla and terminate in the spinal trigeminal nucleus.

The spinal trigeminal nucleus has three distinct subdivisions along its pontospinal extent: (1) the nucleus oralis, located rostrally between the pons and medulla; (2) the nucleus interpolaris, located intermedially; and (3) the nucleus caudalis, located at the medullospinal junction and extending down to the level of the C-2 segment.[40] The nucleus caudalis represents the substantia gelatinosa, and there is an extensive overlap between facial and high cervical afferents, where the 7th, 9th, and 10th afferents also end. From a neuropathological basis, the secondary caudalis neurons begin to fire like those in an epileptogenic area after deafferentation, as in anesthesia dolorosa, postherpetic pain, and trigeminal dysesthesia.[40] Schvarcz attributed particular importance to the destruction of the oral pole of the nucleus caudalis, which probably acts on the pathology site, removes the pool of neuronal hyperexcitability, eliminates convergence, and severs the ascending intranuclear polysynaptic pathways.[24,34] The nucleus caudalis of the trigeminal nerve lies between a point 5 mm above the obex at the posterolateral part of the bulbus and spinal cord and the dorsal root of the C-2 segment (approximately 20 mm below the obex). At the medullobulbar junction, it is located between the lateral border of the dorsal column (fasciculus cuneatus) and the rootlets of the spinal cord in the axial section.[26–28,37]

There is a topographic representation of the ipsilateral face on the spinal tract of the trigeminal nerve; that is, the most central areas of the face terminate highest on the nucleus caudalis and the most peripheral areas of the face end lowest. Called onion-skin organization, this causes the central area of the

face to be spared from hypoalgesia after the nucleus caudalis DREZ operation if the lesions do not extend above the obex.[25,27,28,37,40]

The dorsal spinocerebellar pathway is located immediately lateral to the descending trigeminal tract and nucleus caudalis, and the external arcuate fibers cover the tract posteriorly; thus, ataxia of the ipsilateral extremities usually accompanies extensive tractotomy and nucleotomy.[25,26,38,40] The lateral spinothalamic tract is located anteriorly to the descending trigeminal tract and the nucleus caudalis. Anterior lesions may produce analgesia on the contralateral body. The funiculus cuneatus is located just posteromedially to the descending cranial nociceptive tract and the 7th, 9th, and 10th fibers, and a lesion involving the funiculus may produce loss of proprioceptive sensation in the lower extremities.[40,41]

Indications

Destructive procedures on the descending cranial nociceptive tract and the trigeminal nucleus caudalis are indicated in patients with craniofacial paroxysmal, dysesthetic, or deafferentation pain, especially in anesthesia dolorosa; postherpetic dysesthesia; atypical facial pain; dysesthetic sequelae after previous trigeminal surgery; posttraumatic neuropathy; geniculate-glossopharyngeal neuralgias; and head, neck, or facial pain from malignancy.[1,28,29,32–34,41–45] Patients with head, neck, or facial pain due to malignancy may be the best candidates for such operations.

Technique

Patients should be fasted for 5 hours before the operation. If required, neuroleptic anesthesia should be given at a dose that will not affect patient cooperation during the procedure.[40] In each case, a cranial CT scan must be taken to rule out a mass lesion due to metastasis because this would be a contraindication to performing TR-NC. It is important to stress that all patients should be well informed regarding the possibility of a midprocedure cancellation if they are unable to tolerate the operation. In our series, such cancellations were necessary in four patients (4.9%).

Target

The target is the descending trigeminal tract and the nucleus caudalis, located at the medullospinal junction at the occiput–C1 level (**Fig. 49.1**). The descending trigeminal tract and nucleus caudalis are located laterally and anteriorly to the fasciculus cuneatus in the posterolateral part of the upper spinal cord, and the posterior spinocerebellar tract lies just outside the descending trigeminal tract.[40] The nucleus caudalis is located medially to the descending trigeminal tract, and the trigeminal tract is located laterally. Within the tract, the facial, glossopharyngeal, and vagal fibers are located posterolaterally, whereas the trigeminal fibers are located anterolaterally. The target is 3 mm deep from the posterior aspect of the spinal cord and in the lateral third of the transverse diameter of the semicord. Because of the close proximity between the nucleus caudalis and descending trigeminal tract, any lesion usually affects both structures; thus, we use the term TR-NC.[40]

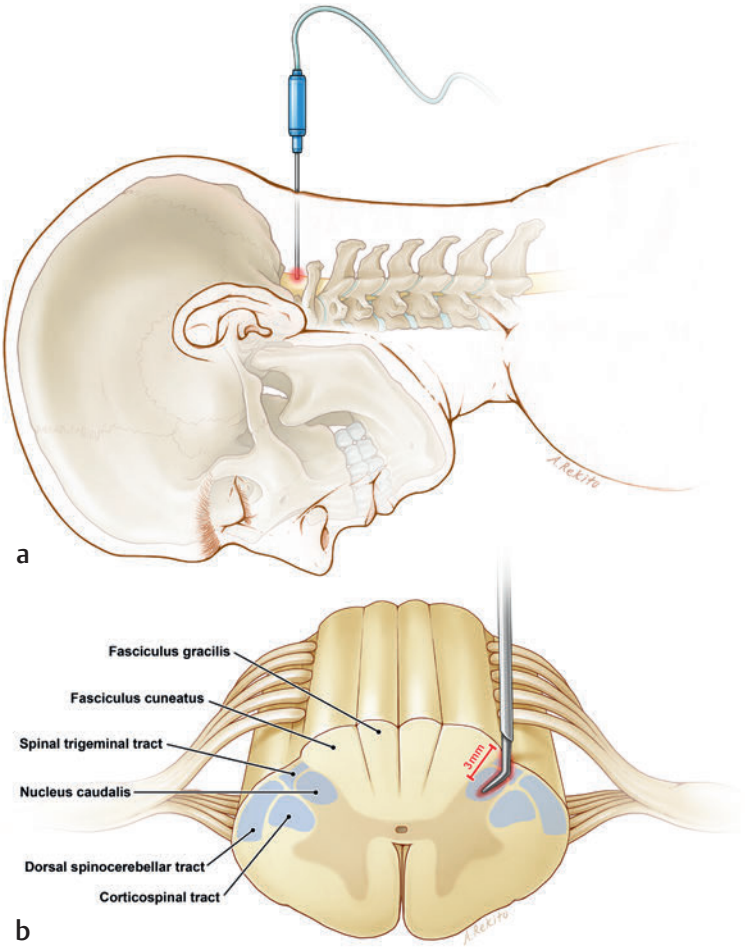

Fig. 49.1 Schematic representation of the trigeminal tractotomy-nucleotomy (TR-NC) procedure. (**a**) Insertion of the needle into the occiput–C1 level in prone position. (**b**) Final position of the electrode tip in the target and pertinent anatomical structures.

Needle and Electrode System

The Kanpolat cannula and electrode system are recommended for this procedure (Cosman, Burlington, MA, USA). Straight and curved electrodes with a 0.4-

mm diameter and 2-mm open tip are usually used; rarely, 0.3-mm-diameter, 2-mm open-tip straight and curved electrodes are chosen.[40,46]

Injection of Contrast Material

Generally, contrast material is administered into the subarachnoid space of the spinal cord by lumbar puncture 20 to 30 minutes before the procedure. A lateral scanogram is obtained, axial CT scans using a 1-mm slice thickness are taken, and the spinal cord diameters at the occiput–C1 level are measured.[40]

Positioning

The patient is placed on the CT table in the prone position. With the help of the head support of the CT table, the patient's head is kept in slight flexion. The chest must be elevated and supported with soft pads, the head is fixed with a fixation band, and nasal oxygen tubing is fixed to the patient's nostrils.[40]

Insertion of the Needle Electrode System

The needle is inserted at the occiput–C1 level, 7 to 8 mm lateral to the midline. Local anesthetic is administered before the initial puncture. Special attention must be given to ensuring the cannula is kept straight during the puncture. Placement of the needle at the occiput–C1 level can be seen in the lateral scanogram (**Fig. 49.2a**). The distance between the dura and the skin has been measured with CT scans and ranges from 40.5 to 56.5 mm (mean, 49 mm).[40,47] This critical range must be kept in mind during the procedure. The dura is punctured, and the cerebrospinal fluid (CSF) gradually emerges. The needle must be positioned in the posterior aspect of the spinal cord, one-third lateral to the semicord (**Fig. 49.2b**). The adjusted active electrode tip is inserted into the spinal cord using the needle (**Fig. 49.2c**). The inserted part of the active electrode is adjusted in accordance with the spinal cord diameters measured at the beginning of the procedure. The puncture should be done as gently as possible; even so, the patient must be warned that the puncture will be painful. Impedance measurements are taken and should be less than 400 ohms when the electrode system is in the CSF, and greater than 1,000 ohms when the electrode system is inside the spinal cord.[40]

Stimulation

Electrical stimulation with low (2–5 Hz, 0.1–0.3 V) and high (50–100 Hz, 0.2–1.0 V) frequencies is used. We recommend starting the stimulations in low frequencies. Observation of paresthesia of the face is a good indication that the electrode is located in the trigeminal fibers. If the 5th, 9th, and 10th fibers are the targets, slight withdrawal of the tip and restimulation usually cause a dysesthetic sensation in the throat or inside the ear, indicating that the tip is in the nociceptive fibers of these cranial nerves (9th and 10th).[40]

Lesioning

It must be kept in mind that TR-NC lesioning is painful. At this stage, if the surgeon is certain, according to the CT slices, that the electrode is in the correct position, and stimulation confirms these findings, neuroleptic anesthesia is administered. The temperature of the electrode is increased gradually. The

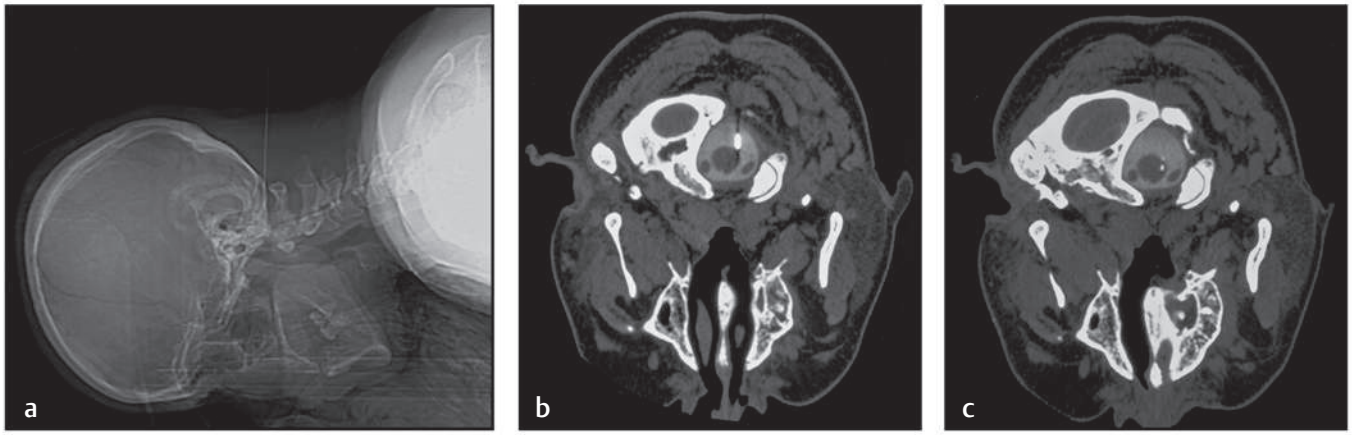

Fig. 49.2 The CT-guided trigeminal tractotomy-nucleotomy (TR-NC) procedure. (**a**) Position of the needle at the occiput–C1 level in the lateral scanogram. (**b**) Final position of the needle in the axial CT scan. (**c**) Final position of the electrode.

first lesion is made at a temperature of 50 to 60°C to 80°C for 60 seconds. One or two additional lesions are made if necessary.[40]

Outcomes

Eighty-one patients who underwent 96 CT-guided TR-NC procedures were followed for 1 to 216 months (mean, 64.8 months). Patients were followed via telephone calls or direct visits, and the period was ended in the event of any change in their contact information or their death. The distribution of their primary diseases is shown in **Table 49.1**. The term *mixed craniofacial pain* was attributed to the situation of trigeminal neuralgia, which evolved later into glossopharyngeal neuralgia in one case and into geniculate neuralgia in another. Complete pain relief indicated maintenance of a pain-free status in the patient without the use of any medication. Partial pain relief indicated positive response to the procedure, with the pain controlled with a lower medication dose than previously necessary. The last group consisted of those cases that responded to the procedure poorly or not at all.

In 4 patients (4.9%), the procedure was terminated due to patient intolerance. Complete or partial satisfactory pain control, which was accepted as success, was obtained in 66 patients (85.7%). Patients who responded to the procedure poorly or not at all were classified as failure (14.3%). The majority of the patients had glossopharyngeal neuralgia, with a success rate of 90%. The results of the TR-NC procedure immediately afterward and in the early follow-up period (up to 1 month after the procedure) are shown in **Table 49.1**. The best results were obtained in patients with geniculate neuralgia; complete pain relief was achieved in 5 of 6 patients, and the remaining patient required the NC-DREZ operation additionally to obtain the same result. The worst results were determined in patients with anesthesia dolorosa.

At the conclusion of the follow-up period, complete pain relief was obtained in 55 patients (71.4%), partial pain control in 13 (16.9%), and failure in 9 (11.7%).

In the total series, additional procedures were required after the TR-NC due to intractable pain in 14 patients during the follow-up period (DREZ lesioning operation, $n = 10$; neurotomy, $n = 2$; microvascular decompression, $n = 1$; RF rhizotomy, $n = 1$). Complete pain relief was obtained in all patients who had additional procedures except in the DREZ group. One patient who suffered from intractable facial pain due to invasive pituitary tumor did not respond to either the TR-NC or the DREZ operation and later committed suicide. Of the remaining 9 patients who underwent DREZ, partial pain relief was obtained in 2 and complete pain relief in the remaining 7. One patient who suffered from intractable pain due to geniculate neuralgia responded partially to the TR-NC procedure and underwent the NC-DREZ operation. He was pain free following the DREZ operation, but was lost due to pulmonary embolism prior to discharge.

Complications

CT-guided TR-NC is an effective and safe procedure, with a low risk of complications. In tractotomy and nucleus caudalis DREZ lesioning, the most important complication is ataxia, caused by lesioning of the dorsal spinocerebellar tract.[25,26,48] Contralateral hypoalgesia is observed as a complication in cases of lesioning of the lateral spinothalamic tract if the lesion is made

Table 49.1 Distribution of patients according to their primary pathologies and the status after the TR-NC procedure in the early follow-up period

Pathology	*n* (%)	Not tolerated *n*	Complete pain relief, *n* (%)	Partial pain relief, *n* (%)	Failed pain relief, *n* (%)
Atypical facial pain	16 (19.7%)	1	8 (53.3%)	3 (20%)	4 (26.7%)
Atypical trigeminal neuralgia	12 (14.8%)	–	11 (91.7%)	1 (8.3%)	0 (0%)
Geniculate neuralgia	6 (7.4%)	–	5 (83.3%)	0 (0%)	1 (16.7%)
Glossopharyngeal neuralgia	20 (24.7%)	–	17 (85%)	1 (5%)	2 (10%)
Malignancy	17 (21.0%)	3	10 (71.4%)	2 (14.3%)	2 (14.3%)
Bilateral trigeminal neuralgia	2 (2.5%)	–	2 (100%)	0 (0%)	0 (0%)
Anesthesia dolorosa	2 (2.5%)	–	0 (0%)	1 (50%)	1 (50%)
Postherpetic neuralgia	4 (4.9%)	–	2 (50%)	1 (25%)	1 (25%)
Mixed craniofacial pain	2 (2.5%)	–	2 (100%)	0 (0%)	0 (0%)
Total patients	81 (100%)	4 (4.9%)	66 (81.5%)		11 (13.6%)

Abbreviation: TR-NC, trigeminal tractotomy-nucleotomy.

anterior to the target.[48] In our series, temporary ataxia was the only complication; it was observed in 4 cases (4.2%), and all cases resolved within 2 weeks.[40] Within the series of the author spanning the past 20 years, the procedure-related mortality rate is zero.

Conclusion

Descending trigeminal tractotomy, the nucleus caudalis DREZ operation, and trigeminal nucleotomy are different operative techniques for destruction of the descending trigeminal tract, the substantia gelatinosa of the nucleus caudalis, and a special, limited part of the nucleus caudalis.[26,31,32,34,38] These procedures may involve open surgical techniques, that is, craniectomy or upper cervical laminectomy and dural opening, or percutaneous lesioning with a needle-and-electrode RF system. We prefer to call the technique TR-NC because there is still a lack of anatomical and physiological data as to which anatomical part of the involved structures, the nucleus or the tract, is destroyed and which part is the cause of pain relief.

Using CT guidance allows direct visualization of the upper cervical spinal cord at the occiput–C1 level. Theoretically, the nucleus caudalis should be destroyed in patients with neuropathic pain, and the descending trigeminal tract should be destroyed in patients with neuralgic pain. Therefore, the aim is slightly lateral to the nucleus–tract complex when the intention is to destroy the tract and slightly medial for destruction of the nucleus.

For medically intractable cases in which typical trigeminal neuralgia is present but has not been managed with customary surgical techniques, CT-guided TR-NC is not the operation of choice.[42] Cases classified as failed trigeminal neuralgia, which present great problems in their management, may be treated with this procedure. Most of these patients have been managed previously with operations such as microvascular decompression, RF rhizotomy, and intragasserian glycerol injection, and they usually have neuropathic pain or even anesthesia dolorosa. CT-guided TR-NC should be performed in these patients before the trigeminal nucleus caudalis DREZ operation, which is a much riskier and more invasive procedure.[25,26,48,49]

In my practice, distinguishing facial pain as type II or atypical facial pain depends on my years of experience. In other words, this is still a controversial issue.[50] Clarification is possible with the use of a multidisciplinary approach between the neurosurgeons and neurophysiologists. Comparable with the chronicity of a craniofacial disease, it is notable that the pain character may change in time, from neuralgic to neuropathic or vice versa.

I believe that trigeminal neuralgia is a lifelong disease. As with its main cause, the causes of its recurrence are unknown. The incidence of bilateral cases was 2.95% in our series.[51] Patients with bilateral trigeminal neuralgia who are older (6th decade or more) or who have a medical problem that presents a relative contraindication to a more invasive surgical procedure with general anesthesia, may be candidates for CT-guided TR-NC. Usually, these patients have undergone RF rhizotomy on one side and may have moderate or severe hypoesthesia on that side.[4] A contralateral RF rhizotomy may cause severe difficulties in mastication, and CT-guided TR-NC, which preserves sensory modalities other than pain, may be performed on that side.

Microvascular decompression[52,53] is effective for treating glossopharyngeal, vagal, or geniculate neuralgias, but its mortality and complication rates are worth regarding as important risk factors. In our series, CT-guided TR-NC was effective in relieving pain in most cases with glossopharyngeal and geniculate neuralgia.[54] Combined neuralgic involvement of the 5th, 7th, 9th, or 10th cranial nerve presents a serious problem as to surgical treatment, and we propose that CT-guided TR-NC may be the most suitable choice.

Patients with craniofacial malignancies may have severe, intractable cranial neuralgic or neuropathic pain, and may be especially difficult to manage. CT-guided TR-NC is the ideal procedure in such cases.[55] Tissue changes attributable to previous surgical procedures or applied radiation may present some difficulties for CT-guided TR-NC.

CT-guided TR-NC is also effective in the treatment of patients with atypical facial pain. Such patients should be observed carefully before any kind of surgical intervention is done.[6]

The indications for CT-guided TR-NC are similar to those for the nucleus caudalis DREZ operation, but the effectiveness of the former procedure is quite high and the complication rate is extremely low.[25] TR-NC is safe and effective for repeated applications. The DREZ operation may be performed only if TR-NC is not sufficiently effective. With its advantages of minimal invasiveness, high success rates, and low complication rates, percutaneous CT-guided TR-NC should be considered as a rational alternative to other pain-relieving procedures.

Acknowledgments

I express my gratitude to Eyyub S.M. Al-Beyati, M.D. (graduate, Ankara University Faculty of Medicine, Ankara, Turkey) for his contributions to this chapter; Ahmet Sinav, MD (professor, Department of Anatomy, Trakya University School of Medicine, Edirne, Turkey) for his creative drawings; Andy Rekito, who adapted and drew the illustration used in this chapter; Mrs. Corinne Logue-Can for her language editing; and Mrs. Mukaddes Kurum Yucel for her assistance in writing the manuscript.

Editor's Comments

Professor Kanpolat has made major contributions to the field of pain surgery, not the least of which is his creative and staunch support of percutaneous ablative procedures. His innovations have been solidly based in anatomy, and this chapter highlights that approach. He has shown us that a superior understanding of neuroanatomy and readily available technology can combine for high-quality outcomes, opposing the most difficult pain syndromes and enhancing patient comfort. No one in the world deserves more credit for maintaining the flame of knowledge and experience in this area.

The TR-NC (trigeminal tractotomy-nucleotomy) procedure appears, in his hands, to be a highly effective option for patients with medically intractable craniofacial pain. He includes in the indications for the procedure "paroxysmal, dysesthetic, or deafferentation pain, especially in anesthesia dolorosa; postherpetic dysesthesia; atypical facial pain; dysesthetic sequelae after previous trigeminal surgery; posttraumatic neuropathy; geniculate-glossopharyngeal neuralgias; and head, neck, or facial pain from malignancy." Each of these conditions poses unique challenges. If TR-NC can be successfully passed on to the next generation of pain surgeons and helps even 50% of these patients, it would represent a major breakthrough.

My hope is that through this chapter, and accessible video documentation linked to it, other pain surgery practitioners will come to adopt this technique, and determine if it is equally successful in their hands and for their patient populations.

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Section IV.C

Procedures for Back Pain

50 Lumbar Spine Disorders: Natural History, Surgical Outcome, and Treatment Failure Management

Elizabeth Emily Abbott and Edward C. Benzel

The term *failed back surgery syndrome* encompasses myriad, often heterogeneous diagnoses, with multiple and varied interventions and both expected and unexpected complications in a diverse patient population. Pain is not itself a pathophysiological entity; it is a poorly understood secondary response associated with a primary pathologic process. Therefore, at best, its treatment can only be indirect.

Failed Back Syndrome

As medical knowledge continues to expand, an improved understanding of back and leg pain should similarly develop. One must exercise caution when applying proven strategies or techniques for known pathologic entities to less clearly defined treatment and pathological relationships. If surgeons do not heed this conservative maxim, failure may be inevitable. Two distinct diagnostic symptom categories have been recognized consistently as being associated with good surgical outcomes: (1) symptoms referable to neural tethering or compression, and (2) symptoms associated with spinal instability. Radiculopathy is the major clinical manifestation of the former group, whereas mechanical back pain is the clinical expression of the latter.

Among patients presenting with acute low back pain, 85% cannot be given a definite diagnosis.[1] Only 1% of patients with low back pain have radicular symptoms and only 1 to 3% will have a herniated lumbar disk (HLD).[2] It is assumed that most of these patients suffer some minor musculoligamentous injury that heals regardless of therapy. The natural history of this particular idiopathic back pain patient population is clinically favorable. More than 90% of these patients return to work within 6 weeks[3]; however, the recurrence rate is high. Traditional therapies for these patients include nonsteroidal anti-inflammatory medications, muscle relaxants, and active strengthening and stretching regimens. Low back pain relief from exercise diminishes with the discontinuation of exercise, and there is also evidence that decreasing the number of days of bed rest results in fewer workdays missed without compromising functional or clinical outcome.[4]

Finally, depression and chronic pain are interrelated, but this relationship is not well understood. Patients with endogenous unipolar depression and back pain do indeed respond to antidepressant medication; however, patients with chronic back pain lacking the diagnostic criteria of depression do not benefit from trials of antidepressant therapy.[5]

Preoperative Diagnosis

Radicular Pain

The most common etiology of back pain encountered by patients with radicular pain is the HLD. Typical HLD causes compression of the nerve root existing at the level below the disk herniation. Symptoms may begin with back pain; however, this usually yields to more prominent radicular leg pain. Patients often describe relief of their pain with flexion of the knee or thigh and aggravation of their pain with sitting, standing, or lying in a particular position. Further exacerbation may occur with coughing, sneezing, or straining. This "cough effect" has been reported in up to 87% of cases in one series.[6]

Herniated Nucleus Pulposus

The aforementioned history is extremely specific for the diagnosis of herniated nucleus pulposus (HNP); however, the physical examination can add important information as well. For example, sciatica is a particularly sensitive finding. The likelihood of a clinically significant HNP without sciatica is less than 1 in 1,000.[7] Exceptions include central disks with resultant

stenosis and cauda equina syndrome. Moreover, in one neurosurgical series of 280 patients referred to outpatient clinics for radiating leg pain, 28% had motor weakness, 45% had sensory disturbances, and 51% had reflex changes.[8]

A positive straight leg raise test (SLR) is observed in up to 83% of cases.[9] The ipsilateral SLR is more sensitive, but the crossed SLR exhibits more specificity.[9] A positive femoral stretch test or reverse leg raise is seen more frequently with L2–L3 or L3–L4 HNPs.[9]

Computed tomography (CT) identifies most spinal pathology with 80 to 95% sensitivity for HLDs and 68 to 88% specificity.[10,11] Despite its poor bony detail, magnetic resonance imaging (MRI) generally has supplanted myelography for the evaluation of spinal stenosis, secondary to its noninvasive nature and its high sensitivity for detecting HLD.

Spinal Stenosis

The second major diagnostic subset responsible for symptoms of nerve root tethering or compression encompasses the constellation of features attributable to spinal stenosis. Spinal stenosis can be classified as central canal stenosis, foraminal stenosis, or lateral recess stenosis.[12] Concomitant symptomatic cervical and lumbar stenosis is reported in 57% of patients[13,14] and is most commonly observed at the L4–L5 level, followed by the L3–L4 level. Spinal stenosis is frequently associated with short pedicles, calcified central disk herniation, and spondylolisthesis. Patients typically complain of symptoms known as *neurogenic claudication* or pseudoclaudication; still, these symptoms are only 60% sensitive but highly specific for spinal stenosis.[15] This is unilateral or bilateral buttock, hip, thigh, or leg discomfort precipitated by standing or walking. It is characteristically relieved by sitting, squatting, or lying down, which all increase lumbar lordosis and subsequently the diameter of the central canal. The etiology of these symptoms is attributed to local metabolic changes in the nerve roots secondary to compression from spinal canal structures and results in reversible ischemia initially, but persistent neural compression can result in permanent deficits. Furthermore, paresthesias may predominate over pain in the lower extremities and the physical examination may be normal in a significant number of patients; however, absent or diminished knee and ankle jerks are observed most commonly.[16]

Lumbar spine radiographs may reveal a pars defect or spondylolisthesis and confirm that the restabilization process is ensuing. CT is specific for spinal canal diameter assessment; the evaluation of hypertrophied ligaments, facets, and calcified herniated disks; and assessment of the patency of the lateral recesses and foramina. The latter is especially important to address after the central canal has been decompressed. MRI is excellent for demonstrating spinal nerve impingement, other soft tissue pathology, and loss of CSF signal on T2WI.[12]

Lateral Recess Stenosis

An important group of patients with spinal stenosis have clinically significant lateral recess stenosis, with or without central stenosis. Symptoms of radicular pain are produced when the hypertrophied superior articular facet impinges on the nerve root before entering into the neural foramen. These patients tend to have more prominent lower extremity complaints as opposed to back and buttock pain. They usually find some relief by bending forward while ambulating, the so-called shopping cart sign. L4–L5 is the most commonly affected level.

Mechanical Back Pain

Another group of patients who may benefit from surgical intervention are those with symptoms referable to chronic spinal instability. The pathoanatomical correlation of chronic instability and mechanical back pain is divided into two processes: glacial instability and the dysfunctional motion segment.

Glacial Instability

Glacial instability is defined as chronic spinal instability that is not overt and where significant forces do not cause substantial movement or progression of kyphotic, scoliotic, or translational deformities (**Fig. 50.1**). Various etiologies have been associated with glacial instability, including spondylosis, trauma, tumor, congenital defect, and infection. Excessive mobility and progressive slippage (deformity progression) may be present. This implies, along with glacial instability, dysfunctional segmental motion.[17]

MRI does not demonstrate evidence of acute soft tissue injury. Serial spine radiographs, however, may demonstrate deformity progression over time (usually months or years). This type of instability may take the form of a progressive translational, rotational, or angulation deformity (**Fig. 50.1**). Treatment may range from no treatment at all to surgical stabilization.

Dysfunctional Motion Segment

Dysfunctional segmental motion is defined as a type of instability related to disk interspace or vertebral body degenerative changes, tumor, or infection that results in the potential for pain of spinal origin. A characteristic pain pattern (usually worsened by

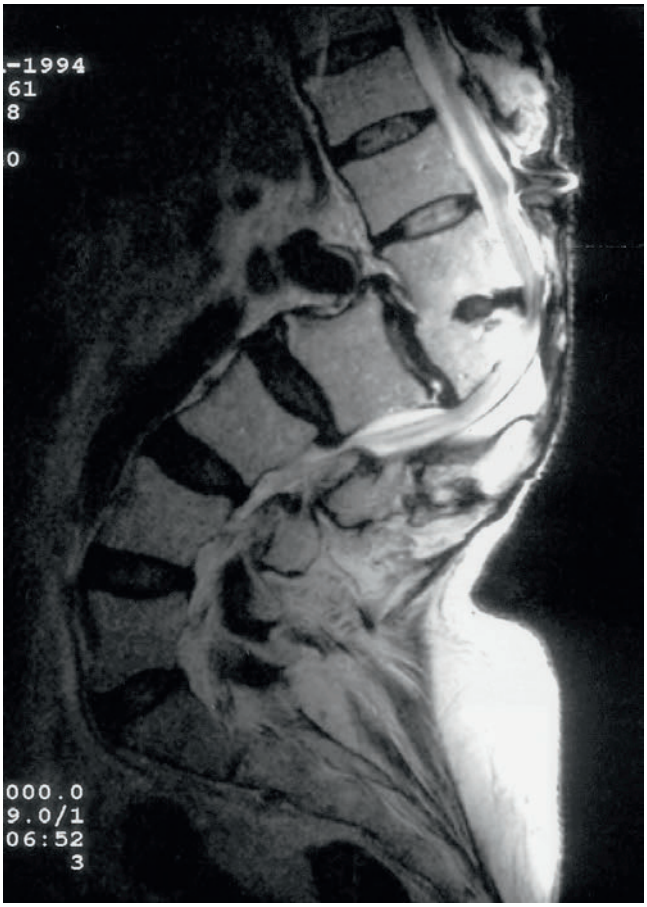

Fig. 50.1 An older patient with "old" trauma. The initial deformity progressed gradually over time to a 90-degree deformity. Now progressive myelopathy is present.

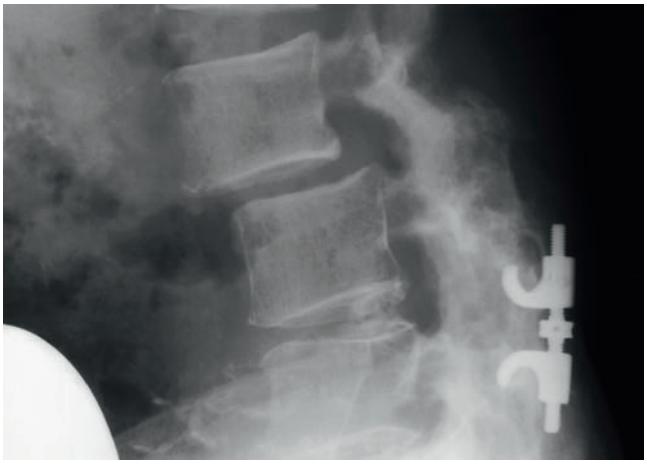

Fig. 50.2 Patient with postoperative instability above the level of spinal fusion and mechanical back pain. This is an example of glacial instability. The fusion placed the spine in a fixed kyphotic posture, creating a flat back, and most certainly exacerbated the patient's pain.

activity and improved by rest, along with the positioning of the torso to minimize spinal stresses) suggests the diagnosis. This pain pattern is similar to that associated with glacial instability and is termed *mechanical pain.* The pain pattern implicates an exaggeration of reflex muscle activity that is enlisted to maintain an acceptable amount of spinal stability (implying that adequate intrinsic stability is not provided by the spine proper).

Plain radiographs, MRI, and discography have been touted as useful for the diagnosis of a spine pain generator (harbinger of the symptoms associated with dysfunctional segmental motion). A lack of objective data, however, impugns these techniques. Plain radiographs provide the greatest advantage for clearly assessing potentially dysfunctional motion segments (**Fig. 50.2** and **Fig. 50.3**). If excessive movement is not present on dynamic imaging (flexion and extension), the absence of instability cannot be assumed. Pain and guarding may result in a protection from movement that might have been demonstrated if the pain and guarding were not present.[17]

It cannot be overemphasized that the lack of objectivity makes the diagnosis of dysfunctional segmental motion often controversial and, simultaneously, subject to abuse. Fusion and instrumentation operations are lucrative for the surgeon. Likewise, the diagnostic algorithm used is often lucrative for the diagnostician. These factors, combined with the inability to assess objectively either operative indications or surgical results, enhance the potential for abuse regarding the establishment of this diagnosis.[17]

■ Expectations

Herniated Nucleus Pulposus: Natural History, Surgical Outcomes, and Complications

The natural history of herniated disks and lumbosacral radiculopathy has been conclusively documented.[18–22] Surgery should predominantly be performed in those who have persistent or severe symptoms because symptoms may improve with time, as extruded disk material is reabsorbed. Furthermore, only patients subjected to surgery are at risk of suffering complications of intervention.

A recent systematic review of surgery for radiculopathy with HLD analyzed four trials comparing surgical and nonsurgical therapy.[23] All of these trials

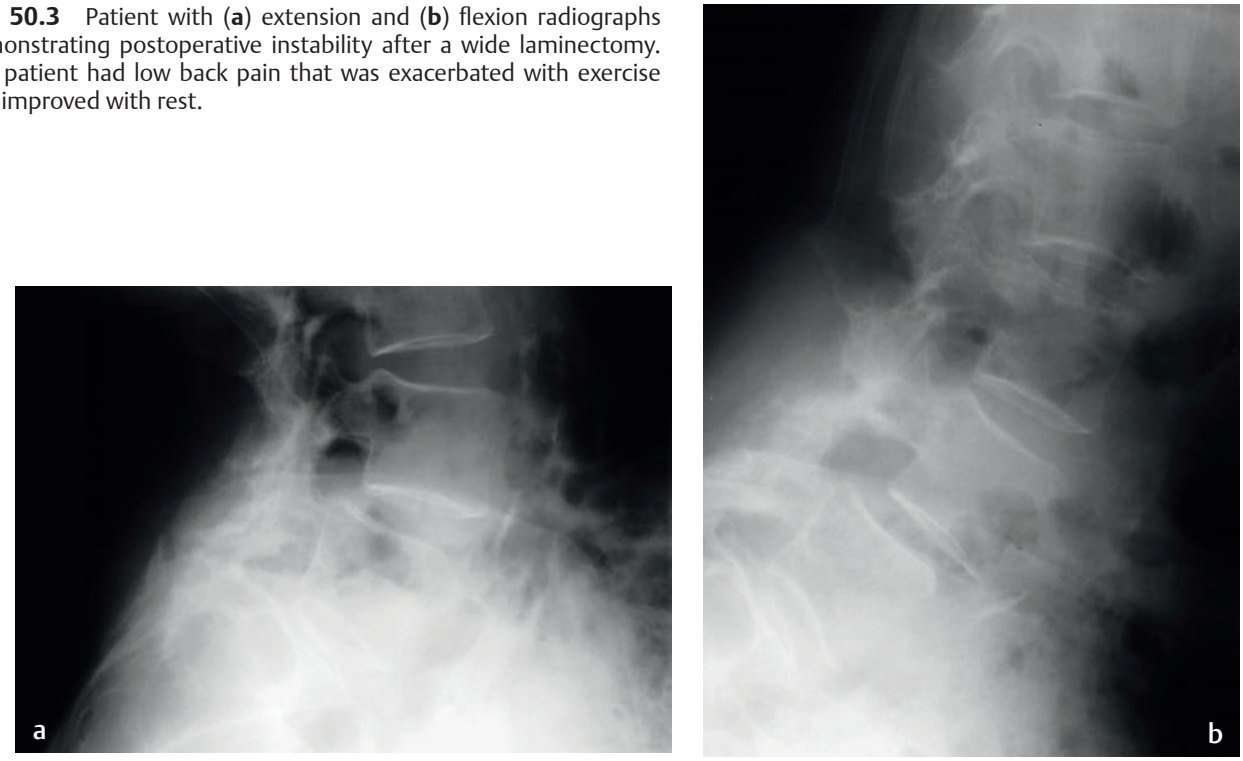

Fig. 50.3 Patient with (**a**) extension and (**b**) flexion radiographs demonstrating postoperative instability after a wide laminectomy. The patient had low back pain that was exacerbated with exercise and improved with rest.

found short-term benefit in undergoing surgical, as compared with nonsurgical, treatments; however, in general, these differences were not maintained past 26 weeks in some instances. In the higher quality Spine Patient Outcomes Research Trial (SPORT), however, significant benefits of surgical intervention persisted through 4 years when they analyzed only patients who did not cross over from original treatment groups.[24] In conclusion, it is clear that the benefit of surgery lies in the short-term improvement; long-term improvement remains uncertain.

Moreover, improvement with surgery in the short term is neither assured nor complete. In the literature, reoperations generally occur in 3 to 7% of patients within 1 year and 9% within 2 years of initial surgery.[23] Atlas et al reported results on 389 patients with sciatica treated either surgically or nonsurgically.[25] Despite having worse functional status and symptoms at baseline, surgical patients were more satisfied with their current state and functional status from baseline for low back pain, leg pain, sciatica index, and modified Roland scale at all follow-ups. Still, disability, work status, and improvement of symptoms were similar between groups. Patients undergoing reoperation or nonsurgical patients undergoing surgery (25% of patients) had inferior outcomes to the original group who underwent surgery. It should be obvious that despite the current level of understanding of HNPs and sciatica, surgical outcomes are far from perfect.

Spinal Stenosis: Natural History, Surgical Outcomes, and Complications

The natural history of spinal stenosis has not been as extensively documented as sciatica. Historically, surgery has been reserved for patients with documented progression of symptoms despite medical management. The traditional goals of surgery have been to decrease the patient's pain, halt symptom progression, and possibly reverse some neurological deficits.

Similar to the discectomy series, high initial satisfaction is followed by a decline. In the 2005 Maine Lumbar Spine Study, the long-term outcomes of 148 patients with spinal stenosis who underwent either surgical or nonsurgical treatment were reported.[26] Outcomes at 1 and 4 years favored surgical treatment, but at 8 and 10 years there was no difference in lower back pain improvement, predominant symptom improvement, or satisfaction in current status. Surgical patients, however, did have significantly better improvement of bothersome leg pain, symptom index, and improvements in back-specific functional status at 8 and 10 years (both $p < 0.05$). Furthermore, at 10-year follow-up, 23% of surgical patients had undergone one or more further lumbar spinal surgeries. After adjusting for a 39% crossover rate to surgery, actual treatment analysis demonstrated no significant differences between surgical

and nonsurgical interventions. Overall, it appears difficult to predict who will have a good outcome.

The reoperation rates with long-term follow-up are in the range of 17 to 29%.[27,28] A trend observed with longer follow-ups reveals higher reoperation rates. These patients develop not only a recurrence of symptoms referable to the original level of decompression, but may also develop progressive stenosis at other levels,[29] especially above a fusion, if one was performed. Series vary regarding the incidence of postoperative instability, particularly with preoperative spondylolisthesis patients.[27]

Third, the complication rate of spine surgery increases with the patient's age. In a review of more than 18,000 patient discharges after laminectomy, Deyo reported an 18% complication rate for patients more than 75 years old.[1] He also noted more frequent complications and longer hospitalizations with patients undergoing fusion.[1]

Finally, because there is no clear consensus comparing the outcome of conservative treatment with surgical intervention, one should intervene only in cases of incapacitating pain or progressive loss of function. Furthermore, the routine performance of lumbar fusion after laminectomy cannot be recommended, based on existing data. Randomized, prospective trials are needed to justify this excessive, expensive, and risky treatment alternative.

Spinal Instability: Natural History, Surgical Outcomes, and Complications

The natural history of patients with mechanical back pain secondary to chronic spinal instability remains unknown. Some patients respond to aggressive weight loss and exercise regimens, but no prospective randomized trials are available to assess outcomes. This is primarily a result of the heterogeneity in opinion concerning the definition of instability and the heterogeneity of the patient population itself. The indications for surgery have not been clearly elucidated, which leaves the surgeon with little concrete evidence for any intervention, let alone surgical intervention. The etiology of instability-related back pain obviously requires further investigation.

Persistent Postoperative Pain and Revision Surgery

In general, persistent postoperative symptoms can result from inappropriate diagnosis, inadequate intervention, or a surgical complication, whether expected or unexpected (see the accompanying box).

A large series by Burton et al in 1980 addressing the etiology of failure of lumbar spine surgery (excluding spondylolisthesis) provides a useful list of common pitfalls. An underappreciated lateral recess stenosis was found in 58% of patients with persistent spinal stenosis and was responsible for 7 to 14% of failures.[30] Recurrent or persistent disk material was evident in 12 to 16% of patients. Arachnoiditis (6–16%) and epidural scar (6–8%) were also prominent offenders. Neural injury, mechanical pain, pseudarthrosis, and opera-

Differential Diagnosis for Failures of Lumbar Spine Surgery

Diagnostic Error
- Tumor: osseus or neural, retroperitoneal malignancy
- Referred pain
- Hip disease
- Rheumatologic disease
- Metabolic disease: diabetic neuropathy, neuropathy, herpes zoster
- Meningeal cyst
- Conjoined nerve root
- Recurrent disk: residual disk/far lateral disk
- Vascular disease: aortic aneurysm, vascular claudication, spinal cord arteriovenous malformation (AVM)
- Tethered cord
- Lateral recess stenosis
- Concomitant cervical/lumbar pathology
- Thoracic pathology: diastematomyelia, tumor, syrinx
- Recurrent stenosis
- Malingering, litigation, worker's compensation
- Unrealistic expectations
- Psychiatric disease: depression, personality disorders

Interventional Error
- Wrong level, wrong side
- Inadequate decompression: lateral recess/foraminal stenosis
- Unrecognized second disk herniation
- Wrong operation

Surgical Complications
- Infection: diskitis, osteomyelitis
- Pseudomeningocele
- Nerve root injury
- Peridural/epidural scar
- Arachnoiditis
- Postoperative instability
- Pseudarthrosis
- Instrumentation failure
- Misplaced instrumentation in canal or impinging upon nerve root at exit from foramen
- Migration of instrumentation, such as threaded fusion cage migrating into spinal canal

tion on the wrong side or level all were implicated (< 5% of failures).[30] An additional 7 to 14% of patients may have a conjoined nerve root. If this is not appreciated preoperatively, it not only may lead to an operation on the incorrect level but also may result in inadvertent nerve root damage. Finally, instability after diskectomy remains infrequent (up to 3%), but may be more common after laminectomy with patients with spondylolisthesis (2–10%) (**Fig. 50.3**).[31]

Patients who undergo fusion for instability are also subject to both acute and chronic complications. In the immediate postoperative period, new radicular pain may be secondary to a misplaced pedicle screw. Also, the reduction of high-grade spondylolisthesis (grade III or IV) has been observed to produce new-onset radiculopathy or a cauda equina syndrome, whereas the risk of these neurologic outcomes with reduction of low-grade spondylolisthesis is low. This has been used as an argument for in situ fusion without deformity reduction.

Flat-back syndrome or progressive lumbar degenerative kyphosis can occur following lumbar fusion. No definitive criteria exist for flat-back syndrome, but generally, patients have chronic postoperative pain and are younger (< 60 years old) and therefore are more likely to have undergone surgery for lumbar disk herniation or lateral recess stenosis.[32] The pain in flat-back syndrome can be mechanical, neuropathic, poorly defined, or secondary to coexisting musculoskeletal or orthopedic-related conditions (**Fig. 50.4**). Several causes have been suggested, including residual nerve root compression, spinal instability, neuropathic injury, and "fusion disease."[32]

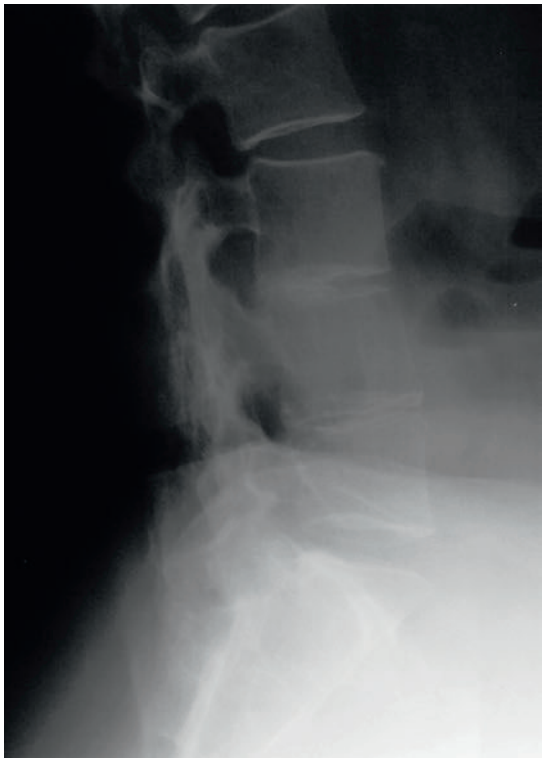

Fig. 50.4 Patient with flat-back syndrome. Patient manifested chronic back pain after fusion that was not mechanical in nature. Presumably, this was caused by the abnormal kyphosis, with resultant chronic muscle spasm of the paraspinous gluteal and hamstring muscle groups.

Alternative Surgical Interventions

The failed back surgery syndrome has given way to the "end-stage" chronic back pain patient. Treatment of a secondary response to a pathologic condition—pain—has become the primary objective (to this end) in treating these patients. Two adjunctive procedures are spinal cord stimulation and intrathecal morphine administration. Spinal cord stimulation (SCS) is generally considered in younger patients with unilateral symptoms, whereas intrathecal morphine pump therapy (IMT) is indicated for those with the more disabling and chronic conditions because it is more of a palliative measure to assist with long-term narcotic administration.[32]

Spinal Cord Stimulation

SCS is not a new technique. Introduced by Shealy et al in the 1960s,[33] SCSs are minimally invasive and an alternative to other, more permanent pain treatments, such as nerve ablation.[32] Melzack and Wall's "gate control" theory of pain, proposed in 1965, which initially inspired these therapies, has fallen out of favor.[34] Recent data show that SCS affects both spinal and supraspinal circuits. Convincing evidence is emerging to support the concept that its mechanism is partially exerted by neurotransmitters released from the dorsal horn in response to electric stimulation.[35] Furthermore, recent animal and human studies have found a potentiating effect of adenosine$_A$ receptor agonist on SCS.[36] Lastly, SCS may also rebalance the ratio of oxygen supply and demand, thereby preventing or dampening peripheral ischemic pain.[36]

North et al in 2005 conducted a randomized, controlled trial comparing SCS versus reoperation alone in patients with persistent or recurrent radicular pain after lumbosacral spine surgery.[37] SCS was found to be significantly more successful based on self-reported pain relief and patient satisfaction compared with reoperation ($p < 0.01$). Furthermore, patients assigned to SCS were significantly less likely to cross over to the reoperation group. Activities of daily living and work status, however, did not differ significantly between groups.

The complexities lie in patient selection and the frequent need for reoperation, up to 45% in one series.[38] The selection criteria for implantation have not been established. Even patients who have an initial poor response may benefit substantially from pain relief later. This subset, although increasing the cost-benefit ratio initially, may demonstrate the benefit of SCS at long-term follow-up. Despite refinements in both techniques and indications, SCS is a modality that requires much further investigation before it is broadly applied in the chronic low back pain population.

Intrathecal Morphine Therapy

IMT is another surgical intervention with the specific goal of pain control. This concept has been applied for years in cancer patients with medically intractable pain syndromes. Recently, Grider et al retrospectively reviewed 22 patients with failed back surgery syndrome who underwent IMT and found IMT improved function as assessed by the visual analog scale (VAS).[39] Also, patients tended to gradually discontinue their oral opioid regimen, but authors note that at least 30% of patients continued to require systematic opioids with the intrathecal morphine.

The indications for this procedure have been neither elucidated nor (generally) universally agreed on; but using the experience from cancer patients, it seems safe to infer several obvious features. First, the patient will require a test dose, with or without a placebo, during prescreening. Second, although the surgical implantation carries relatively little significant morbidity, complications can be frequent. Examples include subdural hematoma, implant infection, hormonal disturbance, and catheter migration, all of which affect ultimate cost and success. Furthermore, effectiveness is usually limited to 1 year.[40] Unlike systemic opioids, however, IMT offers less sedation and/or confusion, decreased constipation, and likely less nausea or emesis.[40] Finally, the pump will require frequent initial adjustments and constant refilling over time. The complexities of this approach probably dictate a dedicated evaluation and intervention team. Most of the postoperative manipulation may be done at home, however, saving clinic or hospital fees. The ultimate utility of this intervention, like SCS, should become evident over time with the reporting of more clinical trials.

Conclusion

Echoing the major themes presented herein, this discussion closes with a general philosophical algorithm to use when caring for patients with chronic back or

Editor's Comments

Why include a chapter on back surgery in this textbook? My rationale is that for the most part, back surgery *is* pain surgery. Although we do spinal procedures for other neurological problems, such as weakness and numbness, the main impetus for back surgery is the relief of back and leg pain. Further, as we explore in this and other chapters, one of the main chronic pain problems we deal with in pain medicine is the failed back surgery syndrome (FBSS). There is little argument that FBSS is mostly attributable to improper patient selection for spine surgery, or to inadequate surgery. Thus this discussion is highly relevant to our understanding of pain surgery.

This chapter provides a sober reminder of the limitations of back surgery. Low back pain is one of the most common pain diagnoses, second only to headache. If 85% of back pain sufferers cannot be accurately diagnosed, the way is open for a large variance in surgical practice. Even the classic herniated lumbar disk (HLD) is poorly understood, and the results of surgery for this entity appear somewhat short term.

Lumbar spinal stenosis is another entity that is commonly diagnosed, but also not well understood. In my view lumbar stenosis is chiefly a clinical, not a radiographic, diagnosis. Patients who have neurogenic claudication, with either narrowing of the entire spinal canal or the more limited lateral recess stenosis, seem to do well from surgery, and this has been borne out in outcome studies. As Drs. Benzel and Abbott point out, relief from surgery for spinal stenosis includes improvement in leg pain, other leg symptoms (numbness and weakness), and the functional status of the patient with respect to the back. The fact that long-term results from spinal stenosis surgery deteriorate somewhat is not surprising, given that this is a disorder of the aged spine; osteoarthritis and "wear and tear" effects will continue, even after surgery.

I think it would be instructive for the reader to review this chapter and compare it with Chapter 14, which is specifically devoted to the FBSS. In the case of spine surgery, *more* care is not clearly predictive of *better* care. The prevention of FBSS by appropriate patient selection, and technical excellence in the performance of indicated spine surgery, would be a major advancement in the care of patients with spinal disorders.

leg pain. Primarily, only two categories of symptoms consistently respond to surgical intervention: tethering or compressive spinal pathology and spinal instability. Despite an appropriate diagnosis and surgical technique, success, however it may be defined, cannot be ensured. For many reasons, not the least of which is the inadequate current medical understanding of pathophysiological relationships, there will always be "failures." Therefore, surgeons must be conservative, use parsimony in both diagnosis and intervention, and expect "realistic" outcomes. Not to discount personal observation, but one must use the literature liberally and carefully, relying heavily on controlled clinical trials to assess specific therapeutic indications and their respective outcomes. Only in these ways might we limit the number and complexity of future patients who would otherwise fall prey to the diagnosis of failed back surgery syndrome.

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Section IV.D

Destructive Procedures

51 Overview of Destructive Neurosurgical Procedures for Pain

Daniel R. Cleary and Justin S. Cetas

Targeted lesions made in the nervous system can provide pain relief when medical management and neuromodulation are no longer sufficient. Destructive techniques are primarily used to treat medically intractable cancer pain, where life expectancy is limited, but in some cases they are also useful for long-term relief from nonmalignant pain. Before proceeding with any ablative procedure, medical and neuromodulatory options should be thoroughly explored. Destructive procedures should be used selectively and with careful consideration of patient circumstance because neuroablation has the potential to worsen pain or cause permanent disability. Ablative techniques are best suited to cases where neurological deficiencies are already present, where new deficits will have less of an impact on quality of life, or where the potential benefit strongly outweighs the potential adverse effects. With late-stage malignancy, destructive procedures are used because a shortened life expectancy decreases the potential harm from a surgical complication or adverse effect. In contrast, with nonmalignant pain, destructive techniques should be considered only when drastic improvements in quality of life and few adverse effects are expected.

Destructive neurosurgical techniques produce analgesia by destroying overactive areas of the nervous system or by blocking nociceptive signaling pathways. Attempts have been made with varying success to disrupt nociceptive signaling at nearly all levels of the nervous system, from peripheral nerves to selected regions of cerebral cortex (**Fig. 51.1**). Few rigorous clinical studies have been done on destructive procedures for pain management, and reported short-term success rates range from as low as 20% of patients receiving pain relief to greater than 90% patient satisfaction. Outcomes vary depending on patient selection, the indications for the procedure, and the experience of the surgeon with the technique, but the percentage of patients who continue to

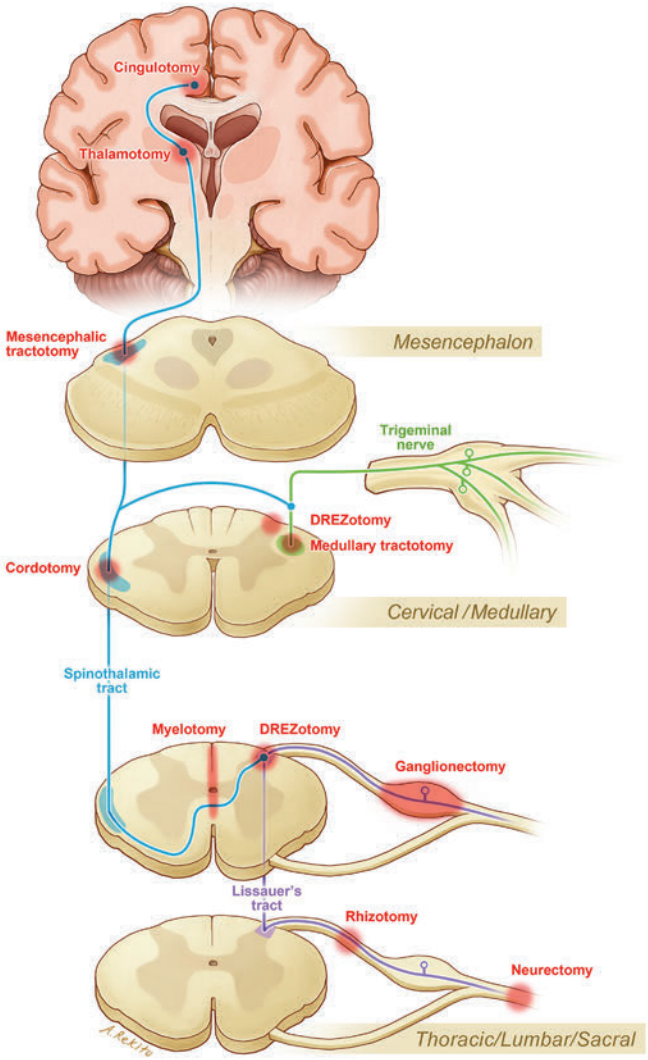

Fig. 51.1 Common ablative sites for the treatment of intractable pain. Lesions can be made along all levels of ascending nociceptive transmission, from peripheral neurectomy to cingulotomy, with varying degrees of success.

experience relief consistently declines in the months to years after the procedure. Patient evaluation is a critical factor for a successful surgery, and the procedure should be well matched to the mechanism, quality, and distribution of the pain. Somatic or cancer pain that responds to opioid therapy is likely to be helped by ablation of sites in the canonical nociceptive pathways, as with cordotomy or rhizotomy, whereas little improvement in neuropathic path is seen with lesion to these same sites. Similarly, lesion to the dorsal root entry zone is highly effective for deafferentation pain from brachial plexus avulsion, but performs poorly for postherpetic neuralgia.

Techniques and Outcomes

To combat chronic pain, neurosurgical procedures have been developed to target nearly every level of the nervous system, from peripheral nerves to frontal cortex. This overview of techniques and outcomes follows the transmission of nociceptive signals from peripheral to central, with discussion emphasis on procedures more commonly used.

Destruction of First-Order Neurons: Neurectomy, Rhizotomy, and Ganglionectomy

Destruction of sensory nerves and ganglia produces immediate anesthesia and pain relief, but patients often have poor long-term outcomes and worsening of pain due to the regrowth of nerves or the development of alternative afferent pathways.[1–4] Destruction of first-order neurons also often results in such adverse effects as dysesthesias, loss of proprioception, and occasional loss of motor function,[5] so these procedures should be selectively applied.

Neurectomy, the destruction and removal of a peripheral nerve, provides reasonable short-term pain relief with variable long-term results.[6,7] Common long-term side effects include the development of deafferentation syndromes or neuromas; boundary pain; recurrence of pain; and loss of motor, sensory, or proprioceptive function. Because of these adverse effects, this procedure is not usually performed for pain in the extremities, but instead is primarily used for facial pain, trigeminal neuralgia, and some postsurgical pain syndromes.[8–11]

Rhizotomy, the partial or complete destruction of the dorsal nerve root, has similar outcomes as those that occur with neurectomy and ganglionectomy. Complete rhizotomy is rarely used due to frequent adverse effects and poor pain control, but partial rhizotomy, specifically lesion of the medial branch of the dorsal root, is used for a variety of pain syndromes. Medial branch lesion is not recommended for extremity pain, but has been successfully used for trigeminal neuralgia, lumbar facet syndrome, cervical pain, cluster headache, and malignant pain.[12–14] Sufficient evidence exists to recommend medial branch ablation for select patients because greater than half of patients usually receive therapeutic benefit.[6,15,16] As with other destructive procedures, the high success rates seen early after the procedure may decline over time.[10]

Ganglionectomy, the removal of the entire dorsal root ganglion, has been advocated as an improvement upon rhizotomy with more complete pain control. This idea is based on observations of sensory and unmyelinated afferents entering the spinal cord via the ventral root, which could explain why some patients obtain only minimal pain relief after complete rhizotomy.[17,18] Ganglionectomy has been tried for many of the same indications as rhizotomy, including both malignant and nonmalignant pain syndromes. In one of the few randomized, double-blinded trials for surgical pain control, ganglionectomy produced no better pain control than placebo for nonmalignant back pain, so the procedure is strongly discouraged for treatment of lumbosacral radicular pain.[5,19] Other outcome reports for ganglionectomy are mixed, and it is unclear whether the procedure offers clear improvement over partial rhizotomy.[6,16,20] Overall, ganglionectomy is a relatively safe procedure with low morbidity and fair pain relief, but few patients have prolonged pain relief.[10,21]

Lesion of Dorsal Root Entry Zone (DREZotomy)

Among destructive neurosurgical procedures for pain control, lesion of the dorsal root entry zone (DREZ) is one of the most recently developed and most effective. The basic technique was first described by Sindou[22] and later modified by Nashold to include a greater area of ablation.[23] The modern DREZotomy procedure destroys the central portion of the dorsal rootlets, the most superficial layers of the dorsal horn, and the superficial band of fibers transmitting nociceptive inputs (Lissauer tract). It is typically done as an open procedure using a hemilaminectomy, and multiple lesions are made in a rostral-caudal distribution.

In selecting patients for DREZ ablation, their pain should be unilateral and with a limited distribution because this technique does not provide pain relief above or below the region affected by the lesion. DREZotomy is highly efficacious in the treatment of deafferentation pain from brachial plexus avulsion, spinal cord injury, or tumor invasion, and has also successfully been used with malignant pain and pain from hyperspasticity, albeit with less success.[13,24] The procedure has poor to moderate out-

comes for treatment of phantom limb pain, stump pain, and postherpetic neuralgia. In cases of deafferentation pain with brachial plexus injury, DREZ ablation should be considered as a first-line treatment because more conservative management is less frequently successful. Case studies exist with reports of greater than 90% of patients having excellent relief at discharge, and the majority of patients continue to have acceptable pain relief several years after surgery.[6,25–27] Side effects of DREZotomy are infrequent and often transient, but can include permanent motor deficits, dysesthesias, and loss of bowel or bladder function.[28]

Myelotomy

The commissural myelotomy is a destructive technique that blocks signal transmission at the spinal decussation of the ascending nociceptive afferents. Second-order nociceptive neurons from the dorsal horn extend axons ipsilaterally for one to two spinal levels, and then these fibers cross the midline at the median commissure. Selective disruption of these fibers provides bilateral pain relief covering a broader area than DREZ lesion, although the coverage is not as extensive as with cordotomy. The commissural myelotomy is used less frequently than other destructive methods because the requisite laminectomy is not well tolerated by sick patients, and neurologic complications are common.[29] The most common adverse effects are loss of bowel and bladder function, and loss of motor, sensory, and proprioceptive function. Recurrence of pain frequently occurs in the months after surgery, and so commissural myelotomy is not recommended for nonmalignant pain. Clinical studies on commissural myelotomy are limited to case reports, but usually greater than half the patients report adequate pain relief from the procedure.[6,16]

The limited midline myelotomy and the punctate midline myelotomy were modifications of the commissural myelotomy made in an effort to improve outcomes and reduce complications.[30–33] These techniques are particularly effective at relieving midline or visceral pain, possibly by targeting a previously unrecognized ascending visceral nociceptive pathway deep in the midline of the dorsal columns.[34,35] The midline myelotomy and modifications provide pain control for bilateral or visceral pain syndromes, such as with abdominal malignancy, but the technique does not often improve somatic pain and so is limited in the scope of application. Only a relatively small laminectomy and spinal lesion are required, which are generally well tolerated by most patients. Fair to good pain control is often achieved with few adverse effects, but evidence is largely limited to case reports.[36–38]

Cordotomy

Unilateral lesion to the ascending nociceptive afferents in the spinothalamic tract (STT) provides more effective and widespread pain relief than myelotomy, although complications can also be more severe. Cordotomy targets the STT at the cervical level, thereby providing effective pain relief for thoracic, lumbar, and lower cervical regions without compromising sensory function. It is primarily indicated for pain limited to a unilateral distribution, but a bilateral procedure can be used for midline, visceral, or otherwise broadly distributed pain. Cordotomy is most often performed for pain from malignancy or spinal cord injury and is most effective in cases where the pain has a clear nociceptive origin. Although it is occasionally performed for nonmalignant pain, cordotomy often does not provide adequate relief for persistent neuropathic pain and can have life-threatening complications.[39] The most significant risk of cordotomy is central apnea (Ondine curse) due to the proximity of the STT to descending fibers controlling respiration. This complication occurs more frequently and tends to be more severe following bilateral ablation. Nearly all patients who receive cordotomy will temporarily have Horner syndrome, and a lower number will have unilateral motor dysfunction, loss of bowel and bladder control, dysesthesias, and, more rarely, unmasking of contralateral pain. Most of these problems are transient, but the potential remains for permanent dysfunction.

Percutaneous cordotomy is now one of the most commonly used destructive techniques for intractable pain, and it has some of the highest levels of patient satisfaction and longest durations of effect—as long as 35 pain-free years in one case.[16,40,41] The percutaneous technique is less invasive than prior methods and requires only the introduction of an electrode into the cervical spinal cord at the level of C1–C2. The STT can be accurately targeted using myelography with fluoroscopy, impedance measurements, or intraoperative stimulation. The recent introduction of intraoperative computed tomography (CT) guidance for electrode localization has led to significant improvements in targeting and thus fewer complications.[38,41,42]

Outcomes of cordotomy stand out among other destructive procedures for pain control, and patient satisfaction with the use of CT guidance is reported to be as high as 98%, with significant improvements in pain, in activities of daily living, and with sleep.[6,40] No randomized, controlled trials have been done on cordotomy, but case studies frequently show complete pain resolution in a high percentage of patients.[42–44] With a carefully selected cohort, cordotomy is a highly efficacious technique for the treatment of intractable pain.

Medullary Lesions

Destructive procedures to treat chronic facial pain target nociceptive-specific structures within the medulla, including the nucleus caudalis and the descending trigeminal tract. The nucleus caudalis is primarily involved in processing nociceptive input from the trigeminal (gasserian) ganglia, but it also receives some sensory and nociceptive input from cranial nerves VII, IX, and X. The descending trigeminal tract is a group of afferent fibers from the gasserian ganglion that enter at the pons and transverse caudally to synapse within the nucleus caudalis.

Two similar techniques targeting these regions are commonly used with moderate to good results. Stereotaxic trigeminal tractotomy/nucleotomy targets the descending trigeminal tract and/or the nucleus caudalis, and is done as a percutaneous procedure using CT guidance or microendoscopy.[45–47] Nucleus caudalis DREZ ablation is a similar procedure that targets the second-order nociceptive neurons of the nucleus caudalis, although the caudalis DREZ ablation is an open microsurgical procedure and uses numerous small lesions to destroy the entire nucleus caudalis.[48,49] Both operations have been used for cancer pain, postherpetic neuralgia, intractable trigeminal neuralgia, anesthesia dolorosa, and atypical facial pain, all with varying degrees of success. The most frequent complication is ataxia due to damage to the nearby spinocerebellar tract.

A clear indication does not exist for one procedure over the other, although the less invasive percutaneous technique may be better tolerated by patients with late-stage malignancy. Because the nucleus caudalis is primarily involved in nociceptive processing, patients typically have analgesia without anesthesia. As with other ablative procedures, pain control often lessens in the months to years after the procedure.[10,50] With careful selection, most patients see some improvement in pain control, although evidence is limited mostly to case reports and a small number of controlled studies. With some forms of atypical and neuropathic facial pain, earlier intervention correlates with greater benefit, and so with nerve injury these procedures should be considered before extensive deafferentation occurs.

Mesencephalic Tractotomy

Similar in concept to cordotomy, lesions to ascending STT fiber tracts within the mesencephalon have been used to treat intractable pain. Mesencephalic tractotomy has been tried for nociceptive, deafferentation, and central pain syndromes, including poststroke pain, thalamic syndrome, facial pain, and cancer pain.[51] Although studies are limited, the procedure has high reported success rates for treating nociceptive and malignant pain (upwards of 85%) but poor outcomes with neuropathic and deafferentation pain.[6,51,52] The ablative target is in close proximity to the medial lemniscus, so sensory loss and dysesthesia are common side effects, and ocular palsies and diplopia can also occur. This technique has some advantages over cordotomy because it offers pain control at the facial and high cervical levels, has a lower risk of motor and respiratory side effects, and can be more safely performed bilaterally. Although with recent improvements in outcomes with cordotomy, mesencephalotomy now is rarely indicated over cordotomy.

Thalamotomy

Ascending nociceptive fibers terminate in the medial and lateral thalamus, which respectively project to areas involved in the affective and somatosensory aspects of pain.[54–56] Lesions of both the medial and lateral thalamus have been tried for multiple forms of pain, but only lesions of the medial thalamic nuclei reliably provide pain relief.[21] The therapeutic mechanism of thalamotomy is unclear, but the projections of the medial thalamus to the prefrontal and anterior cingulate cortices may be involved in therapeutic effect. Medial thalamotomy is effective for the treatment of malignant, central, neurogenic, and deafferentation pain, although outcomes vary and reemergence of pain frequently occurs over time. Evidence in favor of this technique for pain control is largely limited to case series, but reports consistently show a majority of patients receive pain relief for a few months to a few years after surgery.

Thalamic lesions are typically made using a stereotaxic approach and radiofrequency coagulation, but they can also be successfully performed noninvasively using Gamma Knife (Elekta, Stockholm, Sweden) or high-intensity focused ultrasound.[57–59] Regardless of the method used, medial thalamotomy is among the safest of the destructive neurosurgical procedures for pain.

Cingulotomy

Stereotaxic ablation of the cingulate cortex does not produce analgesia or decreased sensory function, but instead appears to decrease the affective component of pain. The cingulate cortex is involved in the perception and affective processing of pain, and the region has connections to the medial thalamus, the midbrain periaqueductal gray, and other areas of the cortex.[60,61]

The beneficial effects of cingulotomy on pain were first noted in patients with “unbearable pain” who subsequently received prefrontal lobotomy.[62] Since that time, cingulotomy has been performed

for many pain-related conditions, and the procedure has uses in the treatment of central pain, malignant pain, and some forms of neuropathic pain. About half of patients receiving the procedure will see lasting therapeutic improvement, including decreases in reported visual analog pain scale ratings, decreased use of and craving for opioids, and pain becoming less bothersome.[6,16,63] These benefits tend to fade in the years following the procedure, so repeat cingulotomies or additional synergistic surgical procedures can be performed to prolong and improve the therapeutic effect.[64–66]

Despite the destructive nature of cingulotomy, adverse neurological effects are infrequent and rarely permanent. Immediately after surgery, patients most commonly experience headache, bladder dysfunction, seizures, and postsurgical confusion. Long-term changes in attention, learning, organization, and motivation have also been observed, although these latter changes are often subtle.[63,67] Because this procedure involves irreversible destruction of an area of the forebrain, it should be considered only when conventional treatments have failed.

Sympathectomy

In complex regional pain syndrome (CRPS), abnormal sympathetic activity causes burning pain (causalgia), hyperalgesia, and abnormal vascular function. These symptoms are poorly responsive to opioid analgesics but can be effectively relieved by medical or surgical sympathetic blockade.[68,69] Interruption of sympathetic activity by division of the paravertebral sympathetic ganglion chain can permanently relieve chronic pain, especially when treatment is initiated early in the disease process.[70,71] Sympathectomy is one of the few destructive neurosurgical techniques for nonmalignant pain that is indicated early in the disease process and consistently offers a high degree of success. Studies on sympathectomy include well-controlled trials and case reports, and strong evidence shows sustained improvements in pain for a high percentage of patients with CRPS.[72] In light of the high rate of definitive improvement following sympathectomy for CRPS, misdiagnosis should be considered in cases of poor outcome following surgery. The procedure also has some utility in the treatment of malignant pain from pancreatic and upper abdominal visceral malignancies, but tends to be poorly efficacious for the treatment of neuropathic pain and nonsympathetically mediated pain syndromes. Common complications include hyperhidrosis, Horner syndrome, vascular injury, and the reemergence of pain over time.[73]

Conclusion

Destructive neurosurgical procedures for pain control target nociceptive neural pathways and dysfunctional elements of the nervous system. When medical therapies are no longer sufficient, neurological lesions offer long-lasting pain relief, although the potential for permanent neurological dysfunction is often high. In-depth discussion with the patient should be made prior to any destructive neurosurgery, and care should be taken to ensure the surgery is appropriately matched to the pain syndrome. Patient outcomes are often mixed, with some patients seeing no improvement, whereas others may have a dramatic decrease in pain. For nearly all destructive procedures for pain, the therapeutic effect will decrease over time. Improved outcomes and lower complication rates have been seen in recent years through refinements of technique and an increased use of intraoperative imaging, but a strong need still exists for randomized and well-controlled clinical trials.

Editor's Comments

The history of pain surgery virtually begins with procedures that intentionally damaged "pain pathways" to control pain. To some extent, this approach was based on a "labeled line" theory of pain sensation; that is, there are tracts and central nervous system (CNS) centers that are specific to nociception, and that by interrupting these sites, analgesia can be achieved. That this worked at all is a tribute to our early understandings of nociception.

As we have come to understand the nociceptive system, it is clear that pain perception is a highly complex phenomenon, and that there are no "pain centers" in the brain that can be destroyed or removed, akin to resection of an epileptogenic focus to alleviate a seizure disorder. Despite this, a completely nihilistic approach to destructive operations for pain control is unwarranted.

Anterolateral cordotomy is probably the best example of the power of disruptive surgery to achieve pain relief. During the mid-20th century, open surgical cordotomy proved to be an important method of surgical pain control, and the procedure became even more practical when the technique of percutaneous cordotomy was developed and popularized. Attaining somatic analgesia from cancer pain caudal and contralateral to a spinal cord lesion, using a technique that could be performed without incision, was clearly a breakthrough. As Drs. Cleary and Cetas point out, similar success for noncancer pain has never been routinely achieved,

although interest in minimally invasive interruption of pathways and nuclei for these pains does remain (Chapter 49).

Likewise, dorsal root entry zone (DREZ) lesions proved highly effective for pain syndromes in which dorsal roots had been traumatically avulsed from the spinal cord, often when a phantom pain was experienced. This was perhaps the first, and last, example of durable analgesia from a destructive lesion in the CNS for noncancer pain. In this case pain relief from DREZ appears to be durable.

A further successful example of a destructive surgical approach to pain is trigeminal rhizotomy. This can be performed on the peripheral trigeminal branches by open surgical technique, percutaneous lesion by radiofrequency thermal injury, glycerol injection or balloon compression, radiosurgery, or open surgical rhizotomy by a posterior fossa approach. In this case, it is probably the triggering stimulus that is affected, rather than the pain mechanism itself, and the results are often not permanent.

Apart from these few examples, predictable pain relief from surgical disruption of primary afferents, deep nuclei (medial thalamus), or neocortex (cingulate gyrus) has been elusive. The same can be said for sympathectomy, which seems to have almost disappeared from the pain surgeon's toolbox.

Each destructive procedure for pain control is unique, and requires both experience and skill. My concern is that a generation of neurosurgeons have been exposed to few such procedures, sometimes to none of them. The knowledge and expected outcomes of our mentors and teachers are receding on the horizon. Unless we identify these procedures and subject them to study, by contemporary standards of evidence, we risk losing valuable insights and approaches that can benefit patients with cancer and noncancer pain. My hope is that the next generation of pain surgeons will take up this cause and will convincingly demonstrate what works and what does not work—certainly for cancer pain, and particularly for neuropathic pain.

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52 Facet Blocks and Denervations

Sunil Panchal and Allan J. Belzberg

Each spinal segment from C2 caudal possesses three joints: anteriorly, the disk and associated uncovertebral joint; and posteriorly, the paired facet joints. For almost a century, the lumbar facet (zygapophyseal) joint has been considered a significant source of low back pain. Ghormley was the first to describe the *facet syndrome,* which he defined as a lumbosacral pain with or without radiculopathy, occurring most often after a sudden twisting or rotary strain of the lumbosacral region.[1] Hirsch et al injected hypertonic saline in the region of the lumbar facet joints, which resulted in pain in the sacroiliac and gluteal regions with radiation to the greater trochanter.[2] Mooney and Robertson performed saline intraarticular facet injections that resulted in a similar pain referral pattern; however, they noted that the pain was relieved by intra-articular local anesthetic injection.[3] Similar findings were produced in the cervical spine. Cervical facet injection with hypertonic saline by Pawl resulted in neck pain and headache.[4]

Although the "slipped disk" has commanded the spotlight as the principal cause of low back pain, surgical removal of the disk usually does not afford relief from axial back pain. A spinal fusion, which stops the motion of the facet joint, often is required for adequate control of back pain. The pathophysiology of low back pain is a complex issue, with various soft tissues and bony structures of the spine vying for the distinction of pain generator. Among these, the facet joint likely plays a significant role.

Anatomy

Facet Joints

The facet joints are paired diarthrodial synovial joints formed by the inferior articular process of one vertebra and the superior articular process of the vertebra below.[5] They are present from the C1–C2 junction to the L5–S1 junction. A tough fibrous capsule is present on the posterolateral aspect of the joint. There is no fibrous capsule on the ventral aspect of the facet joint. Instead, the ligamentum flavum is located ventrally, in direct contact with the synovial membrane. Adipose tissue surrounding the spinal nerve is in direct contact with adipose tissue located in the superior recess of the facet joint, allowing direct spread of injectate from the joint to the epidural space and potentially to the spinal nerve.[6,7] The capacity of the joint space averages only 1.0 to 2.0 mL in total volume. Communications between ipsilateral or contralateral facet joints do occur, often via defects in the pars interarticularis. These account for some of the spread of anesthetic that can occur during facet injections.

Facet Innervation

Each spinal nerve root divides into a posterior and an anterior ramus. The *posterior ramus,* also known as the *sinuvertebral* nerve of von Luschka, divides approximately 5 mm from its origin into *medial, lateral,* and *intermediate* branches. In turn, the medial branch divides into two branches that supply both the facet joint at the same level and the joint at the level below.[8] Therefore, each joint has a dual innervation supply (**Fig. 52.1**). The location of the medial branch and its divisions vary from the lumbar, cervical, and thoracic regions in relation to the bony structures.

In the lumbar region, the medial branch is located in a groove at the base of the superior articular facet, where it crosses the transverse process posteriorly and inferiorly. It then divides, sending a branch medially and cephalad to the joint at the same level and a branch inferiorly to the joint below. The medial branch also supplies the multifidus and interspinalis muscles as well as the ligaments and periosteum of the neural arch.[2] Therefore, neural blockade of the medial branch is not specific for facet joint pain. There is some evidence of joint innervation from a

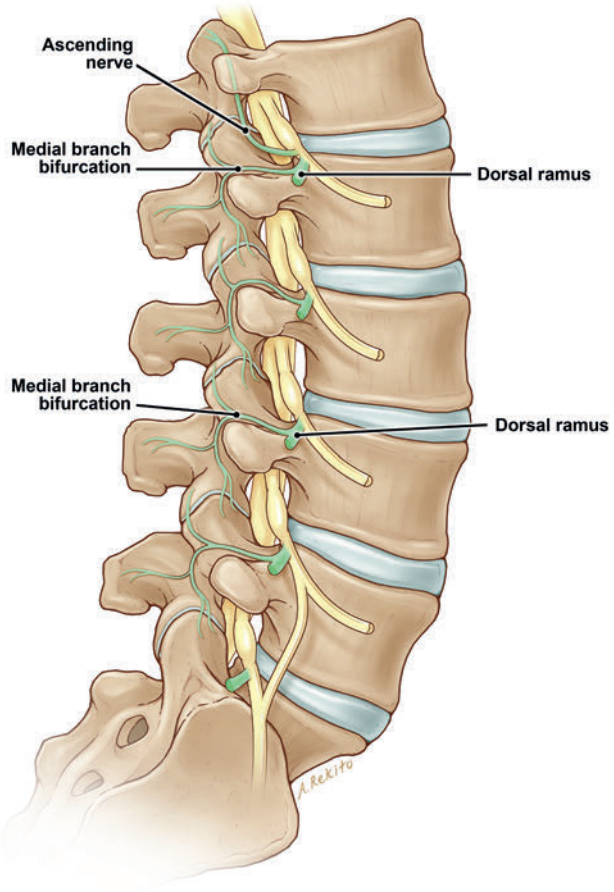

Fig. 52.1 Illustration of the lateral view of the lumbar spine with corresponding facet joint dual innervation patterns of the dorsal rami. The medial branch indicated demonstrates bifurcation after crossing the transverse process, with one branch terminating in the inferior pole of the adjacent facet joint, and the other branch descending to the superior pole of the facet joint below. Additionally, a third ascending nerve directly from the spinal root provides innervation to the facet joint above.

third ascending branch, which originates directly from the mixed spinal nerve (**Fig. 52.1**).[5,9,10]

Innervation of the cervical facet region differs in that the medial branch predominantly supplies the facet joints, with minimal innervation of the posterior neck muscles.[11] The C3–C4 to C7–T1 facet joints are supplied by the medial branches from the same level and the level above.[12,13] These branches wrap around the waist of each articular pillar bound to periosteum by investing fascia and the tendons of the semispinalis capitis.[4] The medial branch of C8 crosses the T1 transverse process, similar to the orientation of lumbar facet innervation. The C3 medial branch divides earlier in its course into a deep, superficial (third occipital nerve) branch. The deep C3 medial branch descends to innervate the C3–C4 facet joint; the superficial medial branch (third occipital nerve) traverses the lateral and dorsal surface of the C2–C3 facet joint before entering the joint capsule.[11,13,14] The atlantooccipital and lateral atlantoaxial joints receive innervation from the C1 and C2 ventral rami (**Fig. 52.2**).

The thoracic facet joint innervation has a pattern similar to that of the lumbar region, except for the T5–T8 levels. The medial branches at these levels travel lateral from the foramen, cross the superior lateral border of the transverse process, and course medial to innervate the corresponding facet joint and level below.[15]

Pathophysiology

Intervertebral disk space narrowing occurs as the disk degenerates and loses hydration. The change in segment height can cause subluxation of the facet joints, resulting in abnormal stresses on the joint and nerve root impingement. Other sequelae, such as capsular irritation and local inflammation, may result in reflex spasm of the erector spinae muscles. As degeneration proceeds, abnormal motion leads to osteophyte production, exacerbating the symptoms.[16]

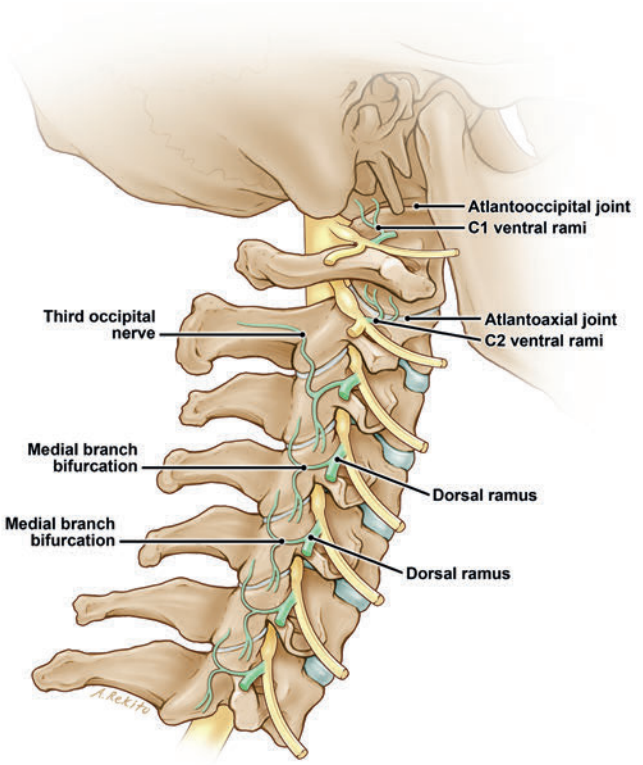

Fig. 52.2 Illustration of the lateral view of the cervical spine with corresponding facet innervation patterns. Each medial branch courses along the lateral surface of each articular pillar, and then bifurcates for a dual innervation pattern for the facet joints. Also shown is the location of the atlantooccipital joint, atlantoaxial joint, the C2 ventral ramus, and the third occipital nerve.

That the facet joint is a source of nociception has yet to be universally accepted. Opponents submit that local anesthetic blockade of the facet joint with subsequent pain relief lacks validity. This position is supported by observations of contrast injection spilling over into the epidural space or intervertebral foramen.[7] Pain elicited with hypertonic saline or relief with local anesthetic administration may be due to action on neural structures or on other pain-sensitive tissues.

Proponents for the facet joint as a site of nociception point to the presence of substance P in facet capsule neurons.[17] In addition, most of the mechanosensitive somatosensory units in the facet joint are group III high-threshold, slow-conduction units, which are thought to mediate nociception.[18–20] Chronic inflammation may lead to fluid accumulation and distension, stimulating the richly innervated synovial villi inside the capsule, resulting in pain.

Facet Block: Diagnostic or Therapeutic Tool?

Lumbar facet arthropathy is characterized by low back pain, unilateral or bilateral, with or without radiation. The pain is described usually as a deep, dull ache; is difficult to localize; and frequently is referred into the buttock, groin, hip, or posterior thigh to the knee (**Fig. 52.3**). Fukui et al described referral patterns for thoracic facet joints.[21]

Some patients describe a sudden onset of pain, usually associated with twisting or bending. There is no exacerbation of the pain with Valsalva maneuver. In contrast to discogenic pain, sitting does not severely aggravate pain secondary to facet arthropathy.

The cervical facet joints also cause pain described as deep and aching. Referral patterns vary, depending on which level is of concern. The C1–C2 facet joint may refer pain to the occipital and postauricular region.[22] The C2–C3 facet joint may cause pain referred to the occiput, ear, vertex, forehead, or eye.[23,24] The C3–C4 facet joint refers pain over the posterolateral cervical region, following the course of the levator scapulae. The lower cervical facet joints refer pain to the base of the neck and down to the scapulae (**Fig. 52.4**).[23]

Physical examination often reveals tenderness over the facet joints and involves associated muscle spasm. The pain is exacerbated by extension or lateral bending as opposed to flexion as well as prolonged sitting. A few patients may exhibit mechanical hyperalgesia over the associated innervated skin. Although range of motion in all directions may be reduced, extension and rotation are most uncomfortable. Straight leg raise is usually negative.

To make the diagnosis of a painful facet joint requires the typical history and physical findings already described in combination with diagnostic blocks. The use of facet block for diagnosis is hampered by certain pitfalls. There is a lack of a corresponding cutaneous innervation to the facet joint and thus an inability to determine when complete

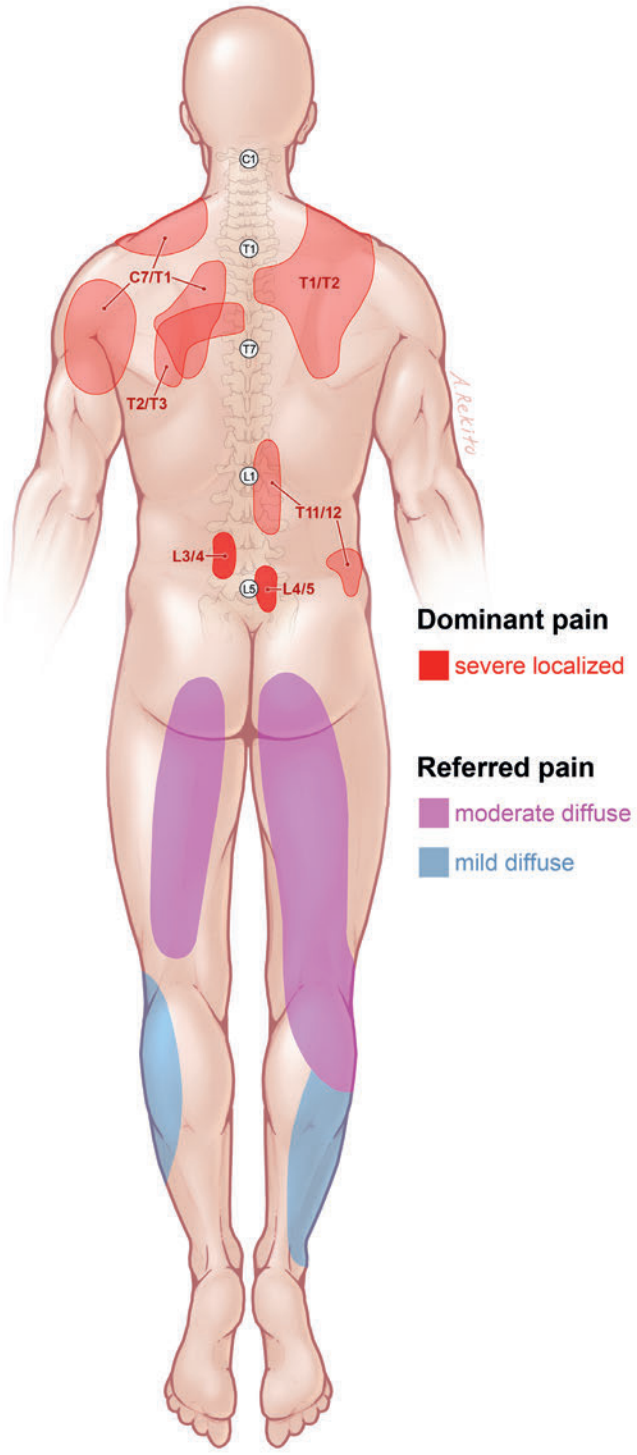

Fig. 52.3 A composite map of distribution of thoracic and lumbar facet syndrome pain, from volunteers who had undergone intra-articular needle placement.

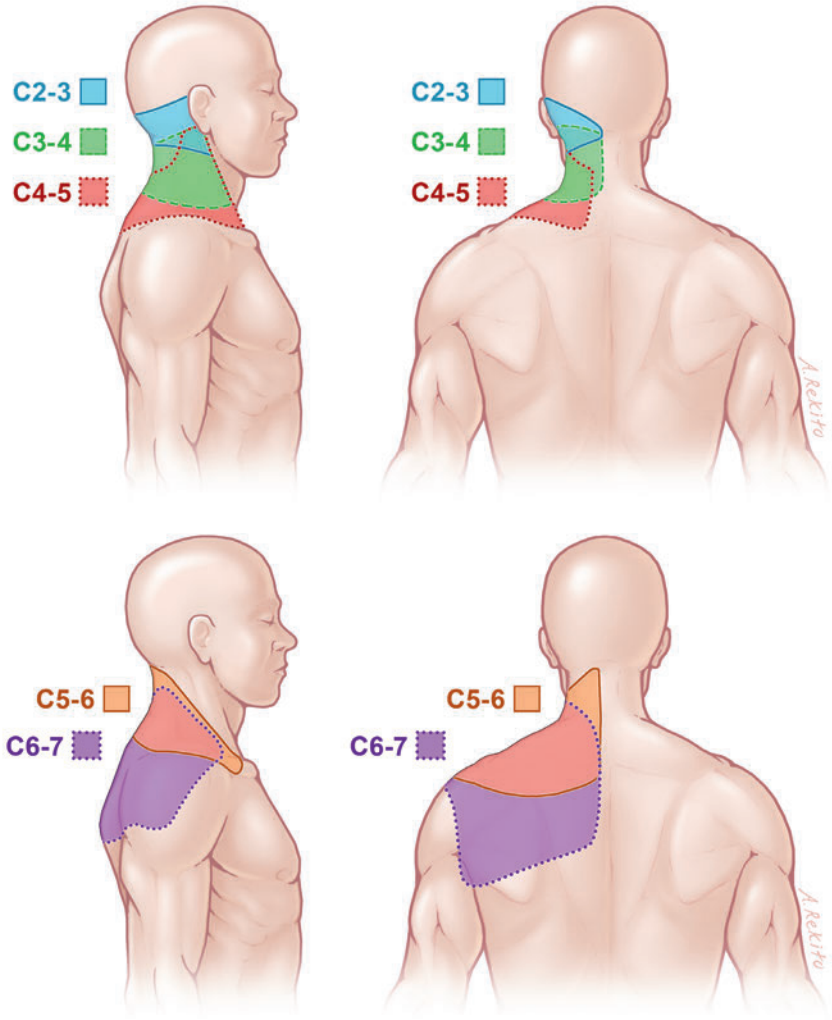

Fig. 52.4 A composite map of cervical facet syndrome pain referral patterns after intra-articular needle placement.

blockade has occurred. Injection into the joint often results in joint capsule rupture and spillage of local anesthetic into the epidural space or intervertebral foramen, which can interrupt nociceptive impulses from alternative sites.[20,25–27] The medial branch nerve innervates muscles, ligaments, and periosteum in addition to the facet joints, again limiting specificity of the test. Facet blocks should be avoided in patients with systemic infection, infection at the site, or coagulopathies, or in patients who refuse the procedure.

Needle placement for facet injection as well as local anesthetic delivery can result in pain provocation. A provocative response that is concordant with the patient's ongoing complaints lends further support to the notion that the facet joint is the pain generator.

Facet injections are commonly used for both therapeutic and diagnostic interventions. Intra-articular steroid injection often produces significant pain relief that outlasts the action of a local anesthetic.[26,28–30] Although therapeutic benefit from steroid has been demonstrated, long-term outcomes have been disappointing.[31–33] Intra-articular block also does not correlate well with the success of radiofrequency (RF) denervation (only 64%); therefore, medial branch block is the preferred procedure as a trial prior to facet denervation.[34]

■ Technique

Lumbar and Thoracic Facet Blocks

For facet joint injection, the patient is positioned prone, with an abdominal cushion to reduce lumbar lordosis. Sterile preparation and draping of the back are performed. Intra-articular injection requires oblique fluoroscopic views. Best results are achieved at a 30- to 45-degree plane to "open" the joint. Either the table or the C-arm can be rotated for optimal viewing.

The entry point through the skin then is identified and marked with the aid of a radiopaque instrument. The skin is infiltrated with 1% lidocaine using a 25-gauge needle. A 22-gauge, 3.5-inch spinal needle then is introduced via the skin wheal and advanced into the joint using a trajectory parallel to the fluoroscopy beam. Local anesthetic alone or with steroid (0.25% bupivacaine and 20 mg Depo-Medrol [methylprednisolone acetate]) is delivered in a volume of 1.0 to 1.5 mL. Volumes in excess of 2 mL will rupture the capsule and spill over into the epidural space.

For medial branch block, the patient is positioned prone, and the transverse process for each branch to be blocked is identified using fluoroscopy. Approximately 5 cm from the midline, a skin wheal is raised, and a 22-gauge 3.5-inch spinal needle is advanced to the medial end of the transverse process, contacting the dorsal surface of the process near the superior edge. The L5–S1 medial branch is blocked at the groove between the ala of the sacrum and the superior articular process of the sacrum (**Fig. 52.1**). A total volume of 1.0 mL of 0.5% bupivacaine is delivered at each site, and the patient is questioned for concordance compared with the original pattern of referred pain. For the T5–T8 levels, the ideal site of placement is the superolateral aspect of the transverse processes.

The patient is ideally positioned prone in order to reduce potential injury to the vertebral arteries, but lateral position as well as supine for the upper levels have been described. Sterile technique and needles are used as previously outlined. Needles are introduced 1 to 2 cm lateral to the waist of the articular pillar, guided by a posteroanterior view on fluoroscopy. The needle then is advanced to the centroid of the articular pillar as seen on a lateral view. Again, 1.0 mL of local anesthetic is delivered (**Fig. 52.5**).

Intra-articular injection at the cervical level is not favored for several reasons. Cervical joint spaces are small and narrow. Further, the epidural space is immediately medial to the joint, and the vertebral artery is just lateral to the joint. Therefore, direct injection into cerebral circulation or blockade of cervical nerve roots is of great concern.

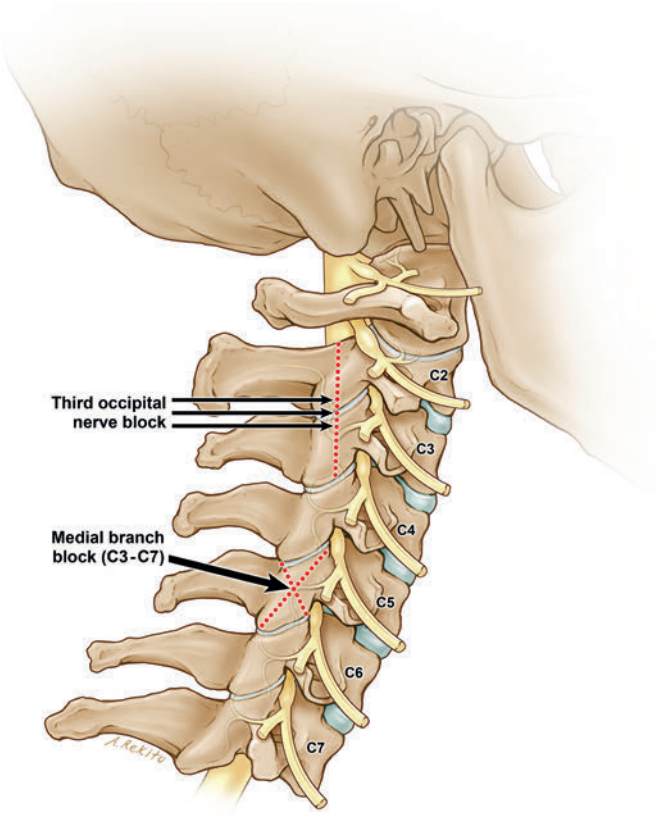

Fig. 52.5 Illustration of a lateral view of the cervical spine demonstrating correct needle placement for medial branch blocks at levels C3–C7. The desired target is the centroid of the articular pillar as seen at the intersection of the superimposed dotted lines. Also, the third occipital nerve for block of the C2–C3 facet joint is targeted at three positions (*arrows*). The upper arrow is above the subchondral plate of the inferior articular facet of C2, the middle arrow is over the joint line, and the lower arrow is below the subchondral plate of the superior articular facet of C3.

Facet Joint Denervation

Denervation of the medial branch can be accomplished by using either radiofrequency ablation or cryoneurolysis. Each method is described here in terms of its mechanism of action, followed by the results of long-term outcome studies.

Conventional Radiofrequency Ablation

The radiofrequency lesion generator has the following critical functions: (1) continuous online impedance measurement; (2) nerve stimulation; (3) monitoring of voltage, current, and wattage during radiofrequency lesioning; and (4) temperature monitoring. Electric impedance is measured to confirm the continuity of the electric circuit and to detect short circuits. Impedance is usually 300 to 600 ohms in extradural tissue. The nerve stimulator is used to detect proximity to sensory or motor fibers of the segmental root. Stimulation at 50 Hz is used to detect sensory fibers; 2 Hz is used to detect motor fiber stimulation. Ford et al demonstrated that if the electrode is resting on the nerve, 0.25 V will be required to produce discharge, whereas 2 V will be required to produce discharge at a distance of 1 cm.[35] Therefore, monitoring voltage is important in determining proximity.

Temperature monitoring occurs at the tip of the electrode only, with a thermocouple technique, producing a thermodionic voltage that is proportional to temperature.

Bogduk et al performed lesions in egg whites and meat and found that radiofrequency lesions do not extend distal to the electrode tip. Instead, lesions extended radially around the electrode tip in the shape of an oblate spheroid with a maximal effective radius of 2 mm using a 21-gauge electrode with a 3-mm exposed tip.[36] **Table 52.1** demonstrates a survey of varying tip sizes and temperatures with the corresponding lesion sizes. The first visible signs of coagulation occur at 62°C, but neural destruction begins at 45°C. The maximal lesion size is attained once the "working" temperature is maintained for 20 to 40 seconds. Maintaining the temperature for longer periods did not result in any discernible increase in lesion size.[37] Although initial reports indicated selectivity for small fibers, Uematsu conclusively showed that radiofrequency indiscriminately damages both small and large fibers.[38]

Retrospective studies demonstrate similar success rates of lumbar denervation. Goupille et al and others showed a 38.4% success rate at 2 years, and North et al showed a 45% success rate with a mean follow-up of 3.2 years.[39–41] North et al went further, concluding that there was no difference in success for bilateral denervation for bilateral pain compared with unilateral denervation for unilateral pain.[41] Goupille et al reported that patients who did not have prior spine surgery had better success with denervation, whereas North's group did not show any statistical difference (**Table 52.2**). Van Kleef et al performed a lumbar facet RF denervation double-blinded randomized, controlled trial (RCT) in 31 patients with 80 C lesions at L3–L4, L4–L5, and L5–S1 with a sham control. At 8 weeks, the mean visual analog scale (VAS) score was 4.8 for controls and 2.8 for the treated group. This was statistically significant for both differences in VAS, and for Oswestry scores as well. In the treated group, 10 of 15 patients were successfully treated (at least a 2-point reduction on VAS and greater than 50% pain relief) at 8 weeks, and of these patients, 7 were still a success at 12 months.[42] Nath et al performed a sham-controlled RCT of lumbar facet RF denervation in 40 patients after at least 80% pain relief was documented from controlled medial branch blocks. The RF group had multiple lesions performed at each level. At 6 months, the RF group had statistically significant improvement in VAS scores and in the patients' global assessment in comparison with the sham group. There was also significant improvement in secondary measures such as spine range of motion, quality-of -life measures, and physical exam findings posttreatment.[43] A 10-year prospective clinical audit of lumbar facet RF denervation in 209 patients was able to maintain 2-year follow-up data on 174 of the patients. Of these individuals, 119 (68.4%) had good (> 50%) to excellent (>80%) relief at 6 months. At 12 months, 81 patients still had good to excellent relief, and this was maintained in 36 patients at 24 months.[44] See **Table 52.2**.

Stolker et al reported on 40 patients who underwent thoracic facet denervation with a mean follow-up of 31 months.[45] They found that 44% were pain free and 39% had greater than 50% relief. Stolker and coworkers also performed a cadaver study, with fluoroscopic guidance, in which radiofrequency denervations were performed bilaterally at T1–T12. They found that 61% of the lesions hit neural tissue, but *none* hit the medial branch stem (the "target").[46]

The nerve stimulator should be used in an attempt to reproduce the patient's usual pain complaints and achieve better localization of the thoracic medial branch.

A randomized, double-blind trial of 24 patients with cervical facet pain after a motor vehicle accident was performed to compare percutaneous radiofrequency denervation of multiple lesions at 80°C with controls. Patients were selected for study after confirmation of cervical facet syndrome by use of double-blinded, placebo-controlled diagnostic local anesthetic blocks. Follow-up assessment was per-

Table 52.1 Survey of tip sizes and temperatures

Investigators	Electrode diameter (mm)	Exposed electrode tip length (mm)	Tip temperature (°C)	Transverse lesion size (mm)	Test medium
Cosman et al 1988[75]	216	3	65	2–4	Egg
Bogduk et al 1987[36]	186	5	80	2.2 ± 0.4	Egg
	226	4	80	1.1 ± 0.2	Egg
	226	4	90	1.6 ± 0.2	Egg
Moringlane et al 1989[76]	216	2	60	3.7	RC
	216	2	70	5.5	RC
	216	2	80	7.2	RC
Vinas et al 1992[37]	206	4	80	4.9	RC

Abbreviation: RC, rabbit cortex.

Table 52.2 Long-term outcome of radiofrequency (RF) denervation

Investigator	Type	No. of patients	Length of follow-up	Success (> 50% relief)	Failure	Outcome with history of previous back surgery
Goupille et al 1993[40] (RF)	R	10	24 mo	38.4%	61.6%	Worse
North et al 1994[41] (RF)	R	42	Mean, 3.2 y	45%	55%	No difference

Abbreviation: R, retrospective.

formed to determine the time until pain returned to 50% of the preprocedural level.

Radiofrequency patients had a median duration of relief of 263 days compared with 8 days in the control group.[47] In a separate study, psychological distress was measured by the McGill Pain Questionnaire and the SCL-90-R psychological questionnaire in patients with whiplash injury. A significant resolution of psychological distress was associated with pain relief from cervical facet radiofrequency denervation.[48]

A prospective study was performed to assess for differences in outcomes of cervical facet RF denervation for treatment of whiplash symptoms based on litigation status. Patients with pain that persisted after 20 weeks were referred for RF treatment and followed for 1 year (N = 46). There was significant improvement in pain immediately after treatment and at 1 year follow-up, but no statistical difference between litigants and nonlitigants. Pain scores for nonlitigants were reduced by 2.0 immediately and by 2.9 at 1 year, and by 2.5 and 4.0, respectively, for litigants.[49]

In regard to recurrence of pain and repeat treatment, two reports of small (20 and 24 patients) retrospective studies of repeat procedures after successful RF were identified for cervical and lumbar facet denervation. In both series, more than 80% of patients had > 50% relief from repeat RF treatment, and mean duration of relief from subsequent RF treatments was comparable to the initial treatment.[50,51]

Pulsed Radiofrequency Ablation

Pulsed radiofrequency (PRF) treatments involve the application of short pulses of RF energy to neural tissue ranging from 5 to 50 ms with a frequency ranging from 1 to 10 Hz. The most common setting described is 2 Hz and 20 ms, with the goal of keeping the tissue temperature below the denaturation threshold of 45°C. This method has been theorized to be nonablative, and to provide relief by inducing intracellular changes, but has not been determined to have either of these benefits in a definitive manner.[52–54] In vitro studies suggest that PRF may change morphology of mitochondria and alter axonal structures, and it has been demonstrated to reduce neuropathic pain behavior in the rat Chung model as well as a sciatic nerve ligation study in rabbits.[54,55] The clinical experience for utilization of PRF for lumbar facet pain has been positive, but PRF does not appear to enjoy the same duration of effect as conventional RF. Tekin et al performed a randomized trial of PRF versus conventional RF, with similar rates of improvement at 6 months, but only the RF group had maintained benefit at 1 year.[56] Van Zundert et al randomized 23 patients to PRF versus sham treatment and results were better immediately, but not significantly different at 6 months.[57]

Cryoanalgesia

The application of cold temperatures for pain relief has been used for centuries. Trendelenburg noted that freezing caused nerve damage with loss of function, but regeneration always occurred without formation of scar or neuroma. Neural damage from freezing is possibly secondary to the hypertonicity of intracellular and extracellular fluids, physical damage from ice crystals, cell protein damage, or ischemic necrosis.[58–63] If freezing occurs slowly, crystals form mostly in the extracellular space, and neurons may not be completely injured. If freezing occurs rapidly, large intracellular crystals form and destroy the cell. The critical temperature for cell injury is –4°C or lower, but may be variable. Below –20°C, cells are irreversibly damaged. Slow thawing leads to recrystallization (smaller crystals melt, whereas large crystals grow temporarily) and greater cellular damage.[64] Also, the longer the freeze time, the greater the diameter of the ice lesion.

Cryolysis probes function based on the Joule–Thompson effect (**Fig. 52.6**), which states that gas under pressure emitted from a small orifice will expand and with expansion cools significantly. Probes are made of stainless steel with a coaxial design. Those with thermocouples allow control of the target temperature. The probe tip may be either hemispherical or shaped like a needle bevel. A hemispherical tip will create a circular ice lesion with the tip at the center, whereas the beveled tip will create an ice lesion proximal to the tip. Large (14-gauge) probes have electrical nerve stimulation and temperature-monitoring capability, but smaller probes do not. With the

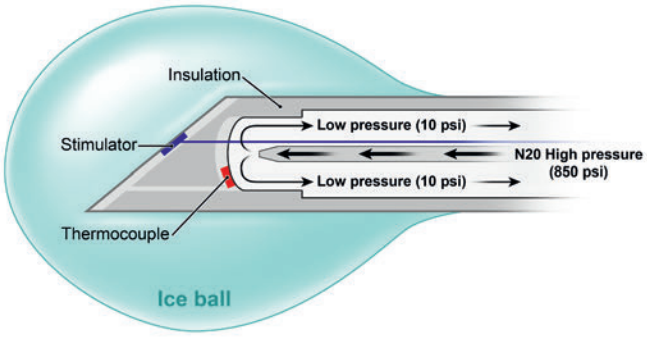

Fig. 52.6 Illustration of a cryoprobe with electrical stimulation capabilities. The probe is insulated except at the distal end, with a coaxial shaft designed to circulate N_2O under high pressure, which then expands as it enters the larger outer canal. Expansion of the gas leads to a decrease in temperature, which is measured by the thermocouple. N_2O, nitrous oxide; psi, pounds of pressure per square inch.

use of N_2O or CO_2, one can achieve a temperature of –50°C to –70°C at the tip. The temperature gradient from the probe tip will change 10°C/mL of distance. It has been noted that lesion size can be increased by freeze–thaw cycles.[65] Brechner demonstrated that cryoprobe application for facet block did not result in a significant change in the temperature of cerebrospinal fluid (CSF) (**Table 52.3**).[66]

Histopathologic analysis reveals that, after cryolysis, wallerian degeneration occurs, but the perineurium and epineurium remain intact. Duration of relief is dependent on the distance the axon must cross during regeneration. Regrowth averages 1 to 3 mm per day.[67,68]

The success rate of cryolysis is optimistic. Ross et al reported on 23 patients who underwent medial branch cryoneurolysis for facet syndrome; these patients had follow-up of 6 months to 2 years. During this time, 2 patients had recurrence of pain (at 6 and 8 months) and had good response to repeat treatment.[69] Schuster monitored 52 patients over 13 months. Significant relief was reported by 47 patients, and only 1 patient had recurrence requiring repeat denervation, which occurred at 9 months.[10]

Complications

Complications from facet block are infrequent and transient. A brief exacerbation of pain may occur and last a few days to a few weeks. Intrathecal injection has been reported, as well as one case of chemical meningitis.[70] Epidural blockade has occurred, and vertebral artery puncture and strokes have been described at the cervical level.

Radiofrequency denervation resulted in postprocedure pain in 13% of patients in one study; the pain resolved spontaneously over 2 to 6 weeks. No persistent motor or sensory deficits were reported.

Table 52.3 Temperature changes (°C) at various sites with cryoprobe at ventral surface lamina

	Control	Postfreeze
Intrathecal	37.5	36.4
Dorsal surface lamina	36.8	36.4
Ventral surface lamina	36.5	28.9

Systematic Literature Reviews

A 2007 systematic review of facet joint interventions utilizing AHRQ (Agency for Healthcare Research and Quality) criteria found that the evidence for pain relief with RF denervation is moderate for short- and long-term pain relief at the cervical and lumbar levels, but was indeterminate for thoracic facets.[71] A 2009 systematic review of diagnostic utility and therapeutic effectiveness of cervical facet joint interventions by Falco et al found level II-1 or II-2 evidence (controlled trials without randomization, and cohort or case control studies from more than one center) for RF neurotomy in the cervical spine using U.S. Preventive Services Task Force (USPSTF) quality ratings.[72] Using the same rating system, Datta and colleagues found level II-2 and level II-3 (cohort or case control studies from more than one center, and multiple time series with or without the intervention) evidence for lumbar radiofrequency neurotomy.[73] Van Boxem and colleagues, in a review of evidence for continuous and pulsed RF, note that RF at the cervical and lumbar levels has produced the most solid evidence, and differences in outcome among RCTs can be attributed to differences in patient selection and/or inappropriate technique.[74]

Conclusion

The facet joints are increasingly accepted as a source of axial spine pain with common referral patterns, but methods for diagnosis remain underutilized. Specificity of local anesthetic injection is limited, but clearly medial branch block is preferred compared with intra-articular injection when attempting to prognosticate relief from denervation.

Local anesthetic injections as well as denervation, with either radiofrequency or cryoneurolysis, are performed easily, are well tolerated by patients, and are extremely safe. Pain relief can be achieved in about 50% of patients for a reasonable duration.

Directions for future study include investigation of outcomes of thoracic facet RF denervation, and for patients with multiple areas of degenerative changes, outcomes of combined denervation treatments across targets are desirable.

Editor's Comments

The data to support facet denervation is modest and the benefits short-lived, probably measured in months at best. Drs. Panchal and Belzberg present the anatomical case for facet rhizolysis. What we do not have is an explanation of why these procedures fail so quickly. The short-term relief in 50% of patients may well fall within the placebo response range. In fact, it is known that the original Shealy lumbar facet rhizotomy knives were of inadequate length to access the sinuvertebral nerve, yet the procedure was still effective in many cases.

It is likely that the multilevel nature of the innervation of the facet joints is in part to blame. It is also likely that there are multiple anatomical contributors to neck and back pain: Anterior and posterior longitudinal ligaments, the interspinous ligament, the dura, the annulus fibrosus, putative pathologic innervation of the degenerated nucleus pulposus, and the paraspinous musculature are all possible candidates. Segmental localization of neck and back pain is also notoriously difficult, particularly in patients with multilevel disk degeneration and osteoarthritis.

To some extent, the odds are against the procedure from the outset. We still lack the diagnostic specificity and precision to diagnose the origin of neck and back pain. It is possible that even this goal is a "fool's errand," and it may be that *all* the aforementioned structures involved in the spinal motion segment contribute to pain when the segment has degenerative change. To attack just one of the constituents is almost certain to fail.

As pointed out in this chapter, one of the most effective and durable methods to address axial pain is spinal fusion, yet this drastic step cannot be effectively tested preoperatively, and cannot be reversed. It is unfortunate that this major procedure has supplanted more minor palliative procedures like facet denervation.

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53 Dorsal Rhizotomy and Dorsal Root Ganglionectomy

Feridun Acar and Selçuk Göçmen

From the beginning of the 20th century, destructive procedures targeting different locations in the pain pathway have been used.[1,2] Despite their value and efficacy, newer neuromodulation techniques and current medications have diminished in prominence as approaches in the surgical management of pain. However, in some cases, more contemporary neuromodulation approaches are inadequate to control a particular pain. Moreover, neuromodulation techniques are typically expensive and need both follow-up and maintenance. With this perspective, a pain surgeon should know the indications for destructive procedures and skills to perform these procedures.[3,4]

Otfrid Foerster was the pioneer who described dorsal rhizotomy to control spasticity.[5] In 1966 Scoville described the technique of spinal dorsal root sectioning,[6] and in 1970 Smith[7] reported combined dorsal rhizotomy and sectioning of sympathetic rami communicans. In 1974, Uematsu reported on percutaneous radiofrequency rhizotomy.[8] Osgood et al[9] introduced dorsal root ganglionectomy in 1976.

Anatomical Background

Each spinal nerve is attached to the spinal medulla by two roots: posterior (afferent) and anterior (efferent) (**Fig. 53.1**). The posterior root is larger than the anterior root because it contains a larger number of radicular fibers and the individual fibers are of larger size. The posterior rootlets have a vertical linear attachment to the posterolateral sulcus of the spinal medulla. The fibers of the posterior rootlets are in close proximity and in some instances overlap. The posterior root separates as it passes away from the spinal medulla into two bundles, both of which become connected with the proximal end of a spinal ganglion. From the distal end of this ganglion, the posterior root proceeds to its junction with the anterior root in the intervertebral foramen. The spinal ganglia are found on the posterior roots of all the spinal nerves. In the case of the first cervical segment the spinal ganglion may be rudimentary or

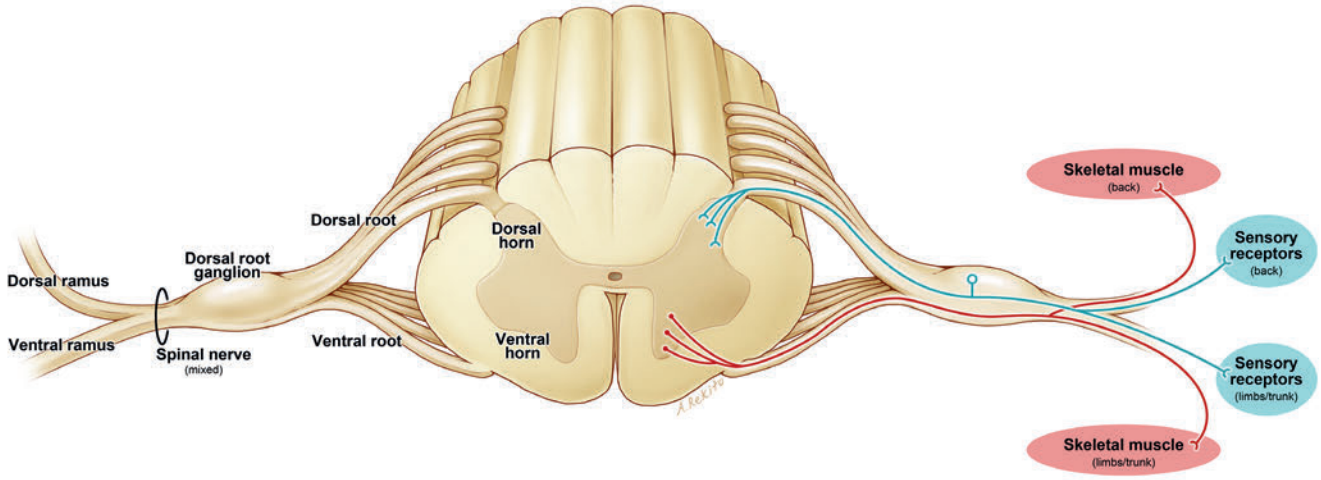

Fig. 53.1 The anatomical organization of the spinal nerve. Each spinal nerve is attached to the spinal medulla by two roots: posterior (afferent) and anterior (efferent). The afferent fibers carry the sensory input and efferent fibers innervate the skeletal muscles.

absent and the posterior root itself may be derived from the accessory nerve. The posterior roots occupy the intervertebral foramina except in the case of the sacral and coccygeal nerves, where the ganglia lie within the vertebral canal, and the first and second cervical nerves, where the ganglia lie upon the vertebral arches of the atlas and axis, respectively. The ganglia are of ovoid form and bifurcated in some cases at the proximal end.[10]

The anterior root arises from the anterior surface of the medulla in the anterior root exit zone by means of bundles of nerve fibers, which occupy a greater horizontal area and are more irregular in their arrangement than the radicular fibers of the posterior root. It possesses no ganglion in its course. The nerve fibers sometimes overlap and are sometimes connected with neighboring radicular fibers above and below.[10]

From their attachment to the spinal medulla the dorsal and ventral roots proceed laterally in the vertebral canal toward the intervertebral foramina, where they unite to form the spinal nerve. The direction of the first two cervical spinal nerve rootlets is superior and lateral; the rootlets of the remaining spinal nerves course obliquely inferiorly and laterally, the obliquity gradually increasing from the cervical area to the inferior conus medullaris.

The dorsal and ventral rami of the spinal nerves contain fibers from both posterior and anterior roots. Indeed, each root can be seen on removal of its sheath to divide into two portions, one of which enters into the formation of the dorsal ramus and the other into the formation of the ventral ramus. With the exception of the first two spinal nerves, the dorsal rami are uniformly smaller than the ventral rami.

Indications for Dorsal Rhizotomy and Ganglionectomy

The indications for dorsal rhizotomy and ganglionectomy can be divided into two broad categories: those pains related to cancer and those pains unrelated to cancer. Both procedures produce irreversible changes of the peripheral and central nervous systems. Thus, the evaluation of the patient prior to surgery is paramount. A detailed clinical workup will help the physician to determine the proper level and the number of roots and ganglia to be sectioned. The determination of level can vary between a single root or ganglion and multilevel procedures. The level of surgery also depends on intradural root anastomosis and the rich interplay of the sympathetic system and ventral root sensory fibers.

Preoperative local anesthetic blocks can be helpful in determining the levels for surgery. However, diagnostic blocks can also be misleading due to the block technique or to a placebo effect. The outcome of diagnostic blocks is one factor in surgical decision making, and cannot be used as the sole determinant.

Cancer Pain

In patients with malignancies involving the brachial plexus such as invasive breast carcinoma, multilevel cervical dorsal rhizotomy to denervate a functionally impaired limb can be successful in controlling pain.[11] In patients with intact upper extremity motor function, this procedure can result in severe functional loss of the involved limb.

In patients with malignancies of thorax and chest wall, thoracic ganglionectomy and rhizotomy can be good surgical options.[11] There is a segmental overlap of dermatomes in the thoracic area that mandates multilevel rhizotomy or dorsal root ganglionectomy in these patients. A three- to five-level ganglionectomy and/or rhizotomy centered on the target dermatome(s) should be considered to completely denervate one or two segments.

A successful outcome can be achieved with dorsal rhizotomies in cases with pain secondary to pelvic neoplasms.[9,12–14] The most important disadvantage of this surgery is the destruction of S2 and S3 sensory innervation, which will lead to neurogenic bladder, neurogenic bowel, and also impotence.

Noncancer Pain

The most common indication for ganglionectomy and rhizotomy in noncancer pain is the treatment of occipital neuralgia.[15–17] Occipital neuralgia can be successfully treated with C2 and C3 ganglionectomies.[15–17] C2 and C3 ganglionectomies can also be considered for medically resistant cervicogenic headache.

In patients with pain syndromes presenting with allodynia, ganglionectomy of the corresponding level can be considered. The allodynia-dominant pain is often seen in postthoracotomy, postlaparatomy, and postherpetic pain syndromes.[3,17–19]

Technique

Cervical Dorsal Rhizotomy and Ganglionectomy

Intradural cervical rhizotomy is rarely performed, but can be achieved by identifying the roots by their exiting foramina. The roots can be cut dorsal to the denticulate ligament to preserve the anterior rootlets. For C2 ganglionectomy, the ganglion is exposed through a midline incision between the inion and the

transverse process of C3, and dissection of the paravertebral musculature to expose the C1–C2 interspace is completed.[20] The venous complex surrounding the root and ganglion is cauterized dorsally using bipolar electrocautery. The root exiting from the C2 space is identified and followed distally until the ganglion is identified. The nerve should be cut just proximal to the ganglion, allowing it to retract slightly, and the proximal stump cauterized to prevent bleeding. The nerve is then followed distally and removed (**Fig. 53.2**). The C3 ganglionectomy is performed in a similar fashion with the addition of a foraminotomy to expose the C3 nerve root and ganglion (**Fig. 53.3**). Once the ganglion is identified, it is removed as in C2 surgery.

Thoracic Dorsal Rhizotomy and Ganglionectomy

Dorsal rhizotomy can be performed through an intradural or extradural approach. The dorsal rhizotomy is performed similarly to cervical rhizotomy. The larger feeding segmental arteries that can enter along the posterior roots must be protected.[21] A multilevel laminectomy is a standard for intradural rhizotomy. In general, the roots of (at least) three segments should be destroyed to accommodate overlap innervations.[22] In this approach, the correct sensory roots are identified by opening dura at their respective intervertebral foramina. They then are cut after coagulating. The procedure for extradural rhizotomy is comparable to that of extradural ganglionectomy without resection of the ganglion.

A thoracic ganglionectomy may be used to relieve the thoracic neuropathic pain, such as intercostal neuralgia. The patient is placed in a prone position under general anesthesia and the relevant transverse process is confirmed by fluoroscopy. After midline incision, the paravertebral muscles are displaced from the spinous process and from the laminae and the lateral edge of the facet joints until the transverse processes are exposed. The surgeon can perform a small lateral bone resection of the laminae, lateral facetectomy, and foraminotomy with a small Kerrison rongeur or a high-speed drill. Under a surgical microscope, the dural cuff

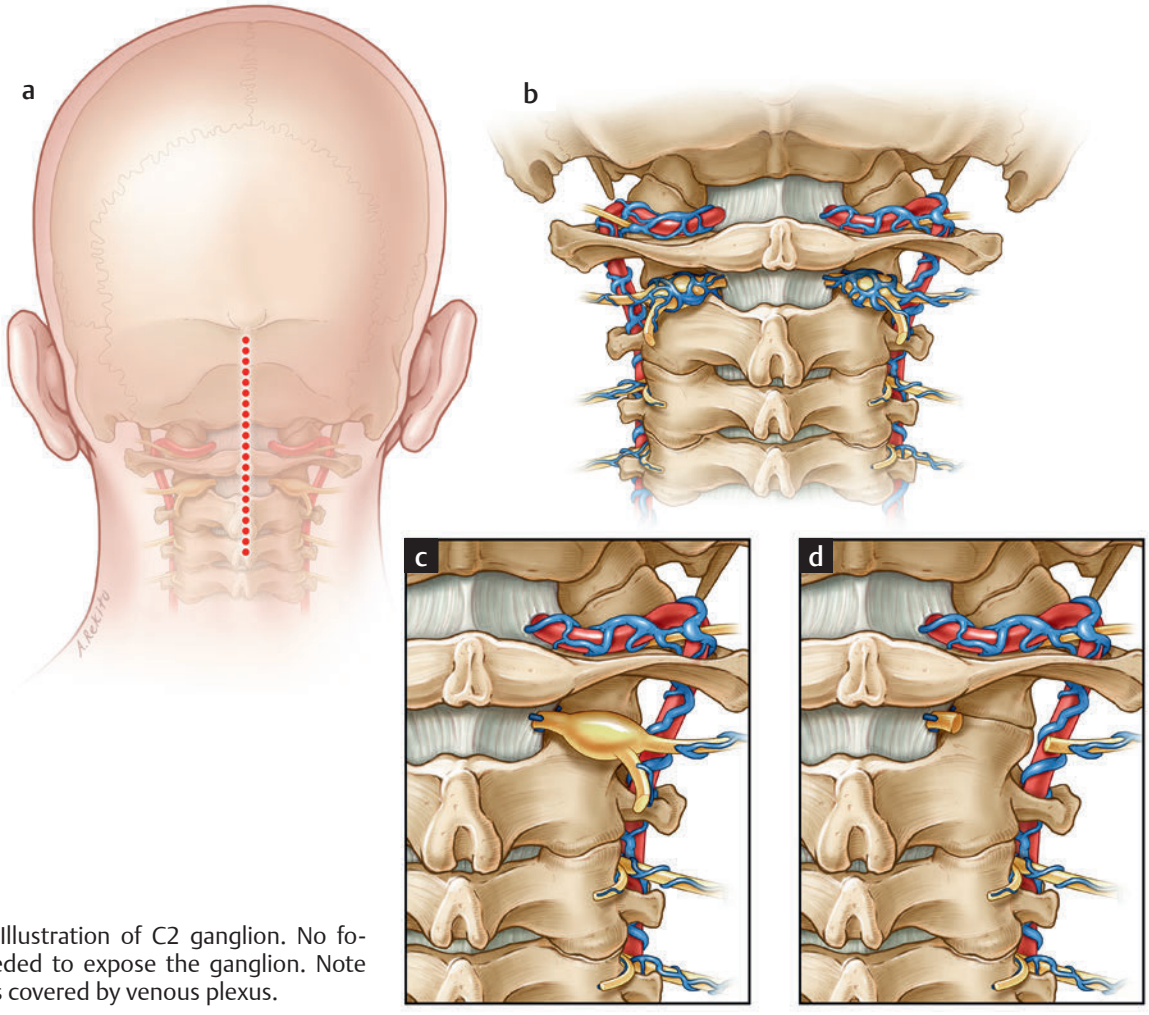

Fig. 53.2 (**a–d**) Illustration of C2 ganglion. No foraminotomy is needed to expose the ganglion. Note that the ganglion is covered by venous plexus.

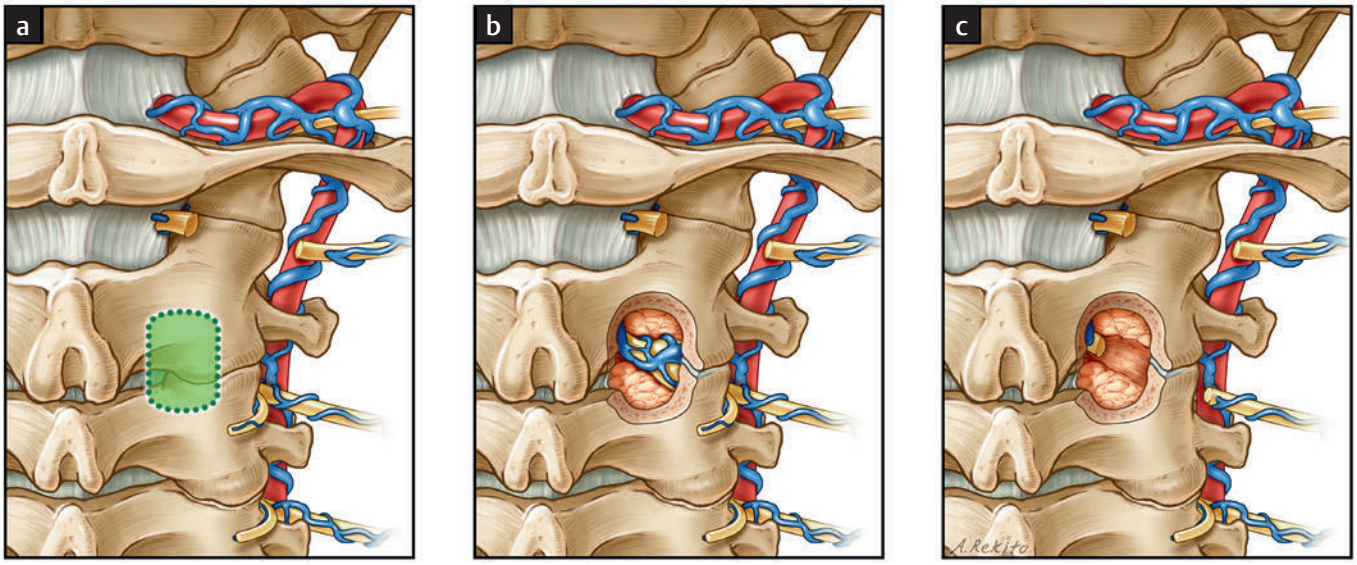

Fig. 53.3 (**a–c**) Illustration of C3 ganglion. Note that a foraminotomy is needed to expose the ganglion. This ganglion is also covered by venous plexus. Careful coagulation is necessary before the ganglion excision.

of the root is identified and followed through a foraminotomy, exposing the root in both directions, and the ganglion identified. The dorsal and motor roots usually are enclosed within the same dural sheath, but occasionally are contained within separate dural sheaths. The feeding segmental arteries that pass through the foramen should be protected. The dural cuff is exposed further laterally to the bifurcation of the spinal nerve, exposing the intercostal nerve originating from the ventral branch and allowing identification of the radiculomedullary artery originating from the intercostal artery. A proximal ligature of the proximal sensory root is necessary to prevent CSF (cerebrospinal fluid) leakage. The ganglion is grasped, elevated, and bluntly dissected off the fibrous septum. Distally, the ganglion is cut after coagulating and sectioning its distal connection to the spinal nerve.[11]

A posterior paraspinal approach may be used for a radiofrequency rhizotomy in the thoracic region. The theory behind radiofrequency lesions of the dorsal roots and dorsal root ganglia was developed by Letcher and Goldring,[23] who noted that the action potentials of nociceptive fibers (Aδ and C fibers) are blocked at lower temperatures compared with the larger tactile fibers (Aα and Aβ fibers). With fluoroscopic guidance a 2-mm uninsulated-tip electrode is placed within the neural foramen. Proper placement is confirmed and sensory stimulation is then performed at less than 1 V with 50-Hz stimulation to ascertain paresthesia in the region of the patient's pain. Motor stimulation is then tested at 2 Hz to elicit contraction in the paraspinal muscles. A test lesion is made at 42°C for 15 seconds. A permanent radiofrequency lesioning is performed at 65 to 90°C for 60 to 90 seconds.[11]

Lumbar intradural dorsal rhizotomy is performed similarly to cervical dorsal rhizotomy. In the sacral region, Crue and Todd reported on the technique of extradural rhizotomy.[12] In brief, the S1 and S2 roots are exposed after a bilateral upper sacral laminectomy. The thecal sac is then ligated with 0-silk suture. One tie is passed around the thecal sac just caudal to the S1 nerve root axilla, and a second tie is passed around thecal sac just rostral to the S2 nerve root axilla. The thecal sac is sharply cut with its contents between the two ties, preserving the S1 nerve roots.

For lumbar ganglionectomy, the ganglion is exposed within the intervertebral foramen. Resection of the lateral margin of the facet joint and the medial aspect of the inferolateral margin of the pars interarticularis is required. For S1 ganglionectomy,[24] the standard L5–S1 hemilaminectomy and foraminotomy are performed. After the dural sheath of the S1 root is identified, the dorsal root is sectioned proximal and distal to the ganglion. The ganglion is elevated, and bluntly dissected off the fibrous septum, which separates it from the ventral motor root. Finally, the root is ligated proximally, and then the ganglion is cut distally.

Outcome

Despite the fact that the history of destructive procedures for the treatment of pain dates back to the beginning of modern neurosurgery, there are relatively few clinical papers in peer-reviewed journals that contain detailed descriptions of long-term outcomes of dorsal rhizotomy or dorsal root ganglionec-

tomy, employing validated outcome measures and standardized follow-up.

Only a few studies meet Class I evidentiary criteria. Cetas et al reviewed 146 articles about destructive procedures for the treatment of nonmalignant pain.[25] In general, these studies showed either a modest treatment effect (in the case of radiofrequency neurotomies for facet pain), consistent with earlier case series, or no effect (in the case of ganglionectomies), despite the positive results reported from uncontrolled studies.

Published studies are confounded by both reporting and observer bias. The subjective nature of pain and the frequent absence of an objective treatment effect marker further complicate the assessment of the literature on this topic.[25] Almost all of the reviewed studies demonstrated an early, dramatic response to treatment that tended to deteriorate over long-term follow-up.[26]

Dorsal Rhizotomy

A total of 24 dorsal rhizotomy studies have been published concerning spinal and other pain syndromes (**Table 53.1**). In the majority of the studies (14 of 24) the data reported were relevant to lumbar facet syndromes (LFS) (**Table 53.1**, first section; 14 studies).[4,6,22,27–37,48] The remainder examined the effects of rhizotomy on a variety of truncal and extremity pains (**Table 53.1**, third section; 9 studies).[38–46]

The effects of dorsal root rhizotomies on a variety of localized pain syndromes were published between 1966 and 1973.[4,6,22,29,32] Echols[29] and White and Kjellberg[4] reported a success rate (variably defined) of just over 60% in two reports on 62 patients. Loeser,[22] Scoville,[6] and Onofrio and Campa[32] reported encouraging early success rates, but long-term results were modest (25–50%). Despite the variability in the pain syndromes treated, number of sectioned roots, out-

Table 53.1 Literature review of rhizotomy: grouped according to disorder treated

Lumbosacral pain					
Author(s) and year	**Study design**	**Diagnosis**	**No. of patients**	**Follow-up**	**Outcome**
Bärlocher et al 2003[27]	Case series	LFS	50	1 y	1-y VAS scores and work capacity assessment: 62% w/ good response, 38% not successful
Dreyfuss et al 2000[28]	Prospective audit	LFS	15	1 y	~ 60% w/ 90% relief of pain at 12 mo, 87% w/ at least 60% relief
Echols 1969[29]	Case series	Chronic UE and LE pain after ≥ 1 ops for ruptured intervertebral disk	62	Not stated	40% w/ op failure, 60% dramatically and probably permanently relieved of pain by section of one or two sensory roots
Gallagher et al 1994[30]	RCT	LFS	41	6 mo	At 1- and 6-mo FU, statistical difference between placebo and rhizotomy (33% VAS score reduction at 1 mo; 13% at 6 mo)
Leclaire et al 2001[31]	Prospective double-blind RCT	LFS	70 pts w/ LBP lasting > 3 mo w/ good response after intra-articular facet injections under fluoro (36 pts w/ perc RF articular facet denervation under fluoro, 34 w/o denervation [placebo])	4 and 12 wk	At 4 wk, Roland–Morris score improved by a mean of 8% in neurotomy group and 2.2% in placebo group; Oswestry or VAS scores not significant per tx; at 12 wk no tx effect based on the three scales
Loeser 1972[22]	Case series	İntractable LBP	33 NM/46 total	3 mo–10 y	63% w/ overall initial success, 28% w/ overall long-term success; 29 pts w/ initial excellent/good results, but 19 w/ long-term failure

come measures, and follow-up, the results were apparently discouraging enough that the procedure was effectively abandoned and replaced with modified rhizotomies directed at facet denervation for the treatment of facet syndromes.[22]

Radiofrequency rhizotomies of the medial branch of the dorsal root were compared with sham or intrafacetal versus extrafacetal rhizotomies in blinded RCTs (randomized controlled trials).[25] Outcome measures and patient selection differed sufficiently between the groups to preclude a meta-analysis.[47] The treated group showed modestly improved pain scores in the long term. They found that the intrafacetal rhizotomies were superior to extrafacetal procedures.[25] Complications were minimal in all blinded RCTs. Patients with "good outcomes" varied from 41 to 75% in long-term follow-up of prospective studies. The success rates for Class III studies ranged from 40 to 60% at long term (see **Table 53.1**, first section).[25]

Oh and Shim evaluated the effects of treatment of chronic discogenic back pain using radiofrequency lesions of the ramus communicans.[48] After a failed intradiscal electrothermal procedure, patients were screened using a good response by local nerve blockade of the ramus communicans as an endpoint. Patients with other identifiable causes of back pain, such as lumbar facet syndrome and radiculopathy, were excluded. At 1 and 4 months of follow-up, the treated group showed significant improvement on the VAS and the 36-Item Short Form Health Survey (SF-36).

Radiofrequency rhizotomies were compared with sham procedures for the treatment of cervical pain[40,44] or cervicogenic headache.[43] Patients were carefully selected based on their response to repeated nerve blocks with local anesthetics and followed for a period from 8 weeks to 3 years. Two of the RCTs demonstrated a significant effect of the radiofrequency

Lumbosacral pain					
Author(s) and year	**Study design**	**Diagnosis**	**No. of patients**	**Follow-up**	**Outcome**
Pevsner et al 2003[33]	Case series	Mechanical back pain	122	18 mo	12-mo FU: 63% w/ good results, 37% w/ no effect; 18-mo FU of 22 pts: all had significant pain relief; 22% w/ minor complications
Onofrio and Campa 1972[32]	Case series	İntractable LBP	286 pts total, 218 available for FU	Not stated	25–50% relief for group w/ pain of unknown origin, other groups not stated directly ("many groups had no success")
Sanders and Zuurmond 1997[34]	Randomized blinded?	LFS	34	3 mo	VAS and Oswestry Disability Index used: intrafacet injections better than extrafacet
Scoville 1966[6]	Case series	Various	10 NM/12 total	Not stated	40% w/ good results
Staender et al 2005[35]	Case series	LFS	76	Median 22.5 mo	VAS score 6.7 preop and 2.9, 3.2, and 3.4 at 3 d, 3 mo, and 6 mo postop, respectively; in 40% of pts, pain reduced for ≥12 mo
Tzaan and Tasker 2000[36]	Case series	LFS	118	Mean 5.6 mo	41% had > 50% pain reduction
van Kleef et al 1999[37]	RCT/ prospective double-blind	LFS	31	12 mo	8 wk postop, tx successful in 10 pts in tx group and 6 in control group; unadjusted OR 3.3 ($p = 0.05$, NS) and adjusted OR 4.8 ($p < 0.05$, significant); differences in effect on the VAS scores, global perceived effect, and Oswestry Disability Index were statistically significant; and at 3, 6, and 12 mo postop there were significantly more tx successes in pts in the RFL compared w/ the sham group
White and Kjellberg 1973[4]	Case series	Mixed	62	Unclear (1 mo–17 y?)	Overall 64.5% w/ "permanent success"
Oh and Shim 2004[48]	RCT	Chronic discogenic LBP	49	4 mo	VAS significantly lower in lesion group

(continued on page 546)

Table 53.1 *(continued)* Literature review of rhizotomy: grouped according to disorder treated

Cervical pain					
Author(s) and year	**Study design**	**Diagnosis**	**No. of patients**	**Follow-up**	**Outcome**
Barnsley 2005[38]	Case series	Cervical zygapophysial joint pain	35	2 y	36 of 45 ops achieved significant pain relief, w/ mean duration of pain relief of 36 wk
Govind et al 2003[39]	Prospective trial	3rd occipital HA	49	90–900 days	88% w/ initial successful outcome, median duration of relief 297 d
Lord et al 1996[40]	Randomized double-blind trial	Pain in ≥ 1 cervical zygapophysial joints after auto accident	24 pts: 12 w/ perc RF neurotomy w/ multiple lesions and temperature of lesion-making electrode raised to 80°C; 12 w/ identical op except RF current off	263 d	Median elapsed time before pain returned to at least 50% of preop level: 263 d in active tx and 8 d in control group (p = 0.04); at 27 wk, 7 pts in active tx and 1 in control group were free of pain
McDonald et al 1999[41]	Case series	Cervical zygapophysial joint pain	28	Up to 730 d	Complete pain relief in 71% of pts
Sapir and Gorup 2001[42]	Case series	Cervical whiplash	46	1 y	Significant overall reduction in cervical whiplash symptoms and VAS score post tx and at 1 y
Stovner et al 2004[43]	Randomized double-blind trial	Cervicogenic HA	12 pts: 6 w/ RF neurotomy of facet joints C2–C6	2 y	No difference after 3 mo
van Kleef et al 1996[44]	Prospective double-blind randomized trial	İntractable chronic cervico-brachial pain	20 pts: Group I, 67°C RFL adjacent to DRG, and Group II, no RFL	8 wk	Significant no. of successfully treated pts in Group I compared w/ Group II (p = 0.0027); significant reduction in VAS score (p < 0.01) and also in parameters measured w/ MPQ-DLV and MPI-DLV in Group I—therefore, 67°C RFL adjacent to DRG can result in a significant alleviation of chronic cervicobrachial pain
van Suijlekom et al 1998[45]	Case series	Cervicogenic HA	15	16.8 mo	VAS and VRS used; RF neurotomy of cervical zygapophysial joints significantly reduced HA severity in 80% of pts at short- and long-term assessment
Wallis et al 1997[46]	Randomized double-blind trial	Cervical zygapophysial joint pain	17	3 mo	

Abbreviations: DRG, dorsal root ganglia; fluoro, fluoroscopy; FU, follow-up; HA, headache; LBP, low back pain; LE, lower extremity; LFS, lumbar facet syndrome; MPI-DLV, Multidimensional Pain Inventory, Dutch Language Version; MPQ-DLV, McGill Pain Questionnaire, Dutch Language Version; NM, nonmalignant; NS, not significant; OR, odds ratio; perc, percutaneous; RCT, randomized controlled trial; pts, patients; RF, radiofrequency; RFL, RF lesioning; tx, treatment; UE, upper extremity; VAS, verbal analog scale; VRS, 7-point verbal rating scale.

lesions,[40,44] although one study did not.[43] Based on a single Class II study, a pain score reduction was durable.[39] One study failed to demonstrate any effect, but was underpowered.[43] Both studies with long-term follow-up demonstrated similar median times to recurrence[39,40] (**Table 53.1**, third section).

Dorsal Root Ganglionectomy

A total of 17 articles related to ganglionectomy studies. Two of these studies were RCTs. In one,[49] radiofrequency lumbar ganglionectomy was compared with sham surgery for sciatica, and in the other, radiofre-

quency lesions made at two different temperatures were compared.[50] The remaining articles were Class III case series ranging in size from 3 to 102 patients (**Table 53.2**).[7,15,16,19,34,49–61]

Geurts et al reported on 83 patients who had either radiofrequency lesion (45 patients) or needle placement without radiofrequency lesion (38 patients) of a selected lumbar ganglion.[49] All the cases were adult patients with clear radicular pain symptoms. Patients were further selected by their response to repeated local nerve blocks. No statistical difference was found between groups. Slappendel et al also found no difference in outcomes between brachialgia patients receiving radiofrequency lesions directed at the ganglion.[50]

Jansen reported the efficacy of C2 ganglionectomies for occipital neuralgia.[53] Eighty percent of patients had significant relief of symptoms, but long-term follow-up data were less compelling. The next largest series of patients compared ganglionectomies performed in patients with occipital pain described as either "sharp, burning, jabbing, electrical, or exploding" (Group I) or "dull, aching, throbbing, or pressurelike" (Group II).[55] Patients in Group I had a higher prevalence of a traumatic history (74%) and had the best response: nearly 80% improved. Overall, Group II patients had a poor response. Ganglionectomy articles are listed in **Table 53.2**.

Acar et al performed ganglionectomy procedures in 20 patients (50% men) with occipital neuralgia.[20] Pain was localized to the C2, C3, or both distributions in 8 (40%), 9 (45%), and 3 patients (15%), respectively. They studied three groups of patients: C2 ganglionectomy (4 patients), C3 ganglionectomy (5 patients), and C2 and C3 ganglionectomies (11 patients). Consecutive C2 and C3, or C3 and C2 ganglionectomies were performed due to failure of an initial single-level ganglionectomy. Although 95% of patients had significant relief from pain, the long-term follow-up results showed excellent relief (pain free) in only 4 patients (20%), moderate relief (50–90% relief) in 8 (40%), and poor relief (< 50% relief) in 8 (40%). There was no statistically significant predictor of favorable outcome. Diagnostic ganglion blocks had strong correlation with short-term favorable outcomes ($p < 0.005$) but no influence on long-term pain relief ($p > 0.5$).

Conclusion

Destructive surgeries such as ganglionectomy and rhizotomy may still have a role in the treatment of some pain syndromes mentioned in this chapter. Destructive procedures for the treatment of pain have played an important role in the history of neurosurgery, but their efficacy has not been well established based on contemporary standards.

How should future studies be designed and conducted? The answer is clear: RCTs (single blinded) in patients with standardized and well-documented diagnoses should be conducted. Well-designed studies with appropriate control groups will be necessary to provide evidence that meets contemporary standards.

Editor's Comments

Dorsal rhizotomy is one of the oldest procedures performed for pain relief. As with many historical procedures, the contemporary evidence to support its use needs to be strengthened.

Doctors Acar and Göçmen have described the surgical technique at length. Although it appears simple, the procedure can be quite daunting, particularly at C2 or C3, given the venous plexus that surrounds the root and ganglion. In my experience, time devoted to bipolar coagulation of this plexus, and its careful dissection, saves considerable time and blood loss.

The present chapter is an excellent review of the current state of the evidence on the topic of dorsal rhizotomy and dorsal root ganglionectomy. The procedures are straightforward, and it should certainly be possible to conduct randomized crossover trials that compare surgical and nonsurgical therapy over a reasonable follow-up period. Long-term follow-up of the same study group could answer the question of how durable pain relief is after surgery. Indications can also be refined in the design of such a study.

The authors do not discuss the theoretical advantage of dorsal root ganglionectomy over dorsal rhizotomy, given the presence of "ventral root afferents," which are known to over-represent small myelinated and unmyelinated axons. Removing the ganglion would disrupt all pain fibers, whereas dorsal rhizotomy would spare only ventral root afferents. There has been no high-quality trial of dorsal root ganglionectomy since these afferents were discovered, more than three decades ago.

In my opinion, neurosurgeons will continue to use these procedures in the future for selected indications, and it is important that our trainees gain some familiarity with these operations. It will be up to those of us who practice surgical pain management to generate the data that support or reject this modality for long-term pain control.

Table 53.2 Literature review of ganglionectomy

Author(s) and year	Study design	Diagnosis	No. of patients	Follow-up	Outcome
Dubuisson 1995[15]	Case series	Occipital neuralgia	11	Unclear	71% w/ likelihood of improvement
Fedder 1990[51]	Case report	Minor causalgia	4	6–12 mo	All w/ relief and decreased narcotic use
Geurts et al 2003[49]	Multicenter double-blind RCT	Chronic lumbosacral radicular pain	83 total: 45 w/ RFL, 38 control	3 mo	At 3 mo, 16% of treated pts and 25% of control had successful tx; lumbosacral RFL of DRG showed no advantage over control tx w/ local anesthetics
Hosobuchi 1980[52]	Case series	İntractable chest pain	3	3 y	2 of 3 developed total anesthesia, including loss of dysesthesia, hyperesthesia, and original pain
Jansen 2000[53]	Case series	Cervicogenic HA	102	Unclear	80% improved
Kato et al 1990[54]	Case report	Neuropathic pain	3	1–32 mo	1 w/ complete pain relief, 2 w/ partial pain relief
Lozano et al 1998[55]	Case series	Medically refractory chronic occipital pain	39	19–48 mo	19 pts w/ excellent results; pts w/ pain from trauma or Group I criteria responded best to ganglionectomy (80% good or excellent response), but pts w/ nontraumatic pain or Group II did not have favorable results
Murphy 1969[56]	Case series	Occipital neuralgia of various origins	30	< 1 y–5 y	18 w/ excellent; 7 w/ good, 3 w/ fair, 2 w/ poor results (unclear what criteria were used to determine outcome measurements)
North et al 1991[57]	Case series	Failed back surgery syndrome	13	Mean 5.5 y	2 w/ success at 2 y postop, 0 w/ success at 5.5 y postop; 1 w/ equivocal success at 2 y postop, 2 w/ equivocal success at 5.5 y postop
Osgood et al 1976[58]	Case series	Lumbosacral pain, BPA, amputation	18	Mean 7 mo	10 w/ "good" results, 4 w/ fair
Sanders and Zuurmond 1997[34]	Case series	CHA	66	Mean 29.1 mo (Group A), 24 mo (Group B)	İntermittent CHA (Group A): 60.7% w/ complete relief; chronic CHA (Group B): 30% (3 of 10) w/ complete relief
Slappendel et al 1997[50]	Prospective double-blinded RCT	Cervicobrachialgia	Group 1 (32 pts): RFL at 67°C; Group 2 (29 pts, control): RFL at 40°C	3 mo	İdentical outcome in two groups
Smith 1970[7]	Case series	Postthoracotomy, herpes	10 NM/12 total	Unclear	Per authors: "all had some degree of relief"
Stechison and Mullin 1994[16]	Case series	Greater occipital neuralgia	5	Mean 24 mo	5 w/ immediate postop relief of pain; 1 w/ recurrence of pain at 26 mo underwent ganglionectomy; all w/ nausea and dizziness postop, and 1 w/ a CSF leak
Taub et al 1995[59]	Case series	Sciatica	61	< 1 y–15 y	59% w/ pain markedly reduced or eliminated
Wetzel et al 1997[60]	Case series	Postop chronic lumbar radiculopathy	51	6 mo, 2 y	55% good or excellent at 6 mo, the rest w/ poor or failed outcomes; at final FU (2-y minimum) 19% of 37 pts w/ good or excellent outcome
Wilkinson and Chan 2001[61]	Retrospective chart review	Various origins	19	Mean 22 mo	74% reported > 50% reduction, only 1 pain free

Abbreviations: BPA, brachial plexus avulsion;CSF, cerebrospinal fluid; CHA, cluster headache; DRG, dorsal root ganglia; FU, follow-up; HA, headache; NM, nonmalignant; pts, patients; RCT, randomized controlled trial; RFL, radiofrequency lesioning; tx, treatment.

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54 Percutaneous Computed Tomography–Guided Cordotomy for Pain

Ahmed M. Raslan and Ashwin Viswanathan

Anterolateral cordotomy is a spinothalamic tractotomy. It was one of the first central nervous system (CNS) ablative procedures to be done to control pain in humans.[1] The term itself was coined by Schüller.[2]

Cordotomy has a history that in itself tells the story of pain surgery over the last century. When cordotomy was introduced, it was a very popular procedure and a frequently performed operation up until the 1970s and early 1980s. The early iteration was an open procedure that involved a laminectomy and sectioning of the anterolateral cord, with an associated morbidity and mortality.

In the 1960s, a second iteration of the procedure was introduced that was percutaneous. Several destructive methods were tried, and eventually experts settled on a radiofrequency (RF) thermolysis.[3,4] This iteration was a significant improvement on open cordotomy because it eliminated much of the morbidity related to open surgery. The percutaneous procedure was widely used for pain control for both cancer-related and noncancer-related pain.

By the early 1980s oral opioids, in many formulations, were being widely used for the control of pain. This, and a general aversion to surgical procedures for pain, led to a significant reduction in the number of cordotomies being performed. In that environment, a third iteration of cordotomy was developed by Kanpolat[5] in Turkey. This cordotomy, whereas still percutaneous, introduced computed tomography (CT) as a method of direct visualization of the radiofrequency electrode within the spinal cord prior to and during the radiofrequency lesion—an addition that would render the procedure safer and more effective. CT-guided cordotomy did not gain traction in North America initially but was employed in other parts of the world, particularly those areas where the technology of intrathecal drug delivery was cost prohibitive. Only recently has there been a renewed interest in cordotomy in North America. It is this most advanced form of cordotomy, and refinements of this technology,[6] that is the focus of this chapter.

Anatomy

The spinothalamic tract carries nociceptive signals, temperature and nondiscriminative touch, from the contralateral side of the body. The spinothalamic tract axons migrate ventrally as they ascend the length of the spinal cord. In segments rostral to the cervical enlargement, axons do not migrate farther ventrally but continue in a position ventral to that in which they ascend through thoracic segments.[7] There is a somatotopic organization of axons within the spinothalamic tract; fibers entering from rostral and caudal segments are located in the medial and lateral parts of the tract, respectively. The spinothalamic tract terminates mainly in the ventroposterolateral nucleus, the ventroposteromedial nucleus, the intralaminar nuclei (mainly the central lateral nucleus), and the posterior complex. Spinothalamic tract projections to the central lateral nucleus of the thalamus play a part in the motivational-affective responses to pain, and the projection to the lateral thalamus (the ventrobasal complex) is involved in sensory-discriminative aspects of pain.[8] The corticospinal tract lies posterior to the lateral spinothalamic tract (LST) with white matter (the safety zone) in between (**Fig. 54.1**). The ventral spinocerebellar tract overlies the LST and a lesion that eliminates the spinocerebellar tract may cause ipsilateral ataxia of the arm. Human autonomic pathways for vasomotor and genitourinary control in addition to the reticulospinal tract that controls ipsilateral automatic respiration are also part of the anterolateral quadrant of the spinal cord. Therefore, sleep apnea (Ondine curse), incontinence, and hypotension are possible undesirable cordotomy effects. There is considerable variation in the size and location of the ventral corticospinal tract; absence of decussation is also possible. Motor decussation may extend from the obex to the C1 level; contralateral leg weakness may also occur if a lesion is too high.

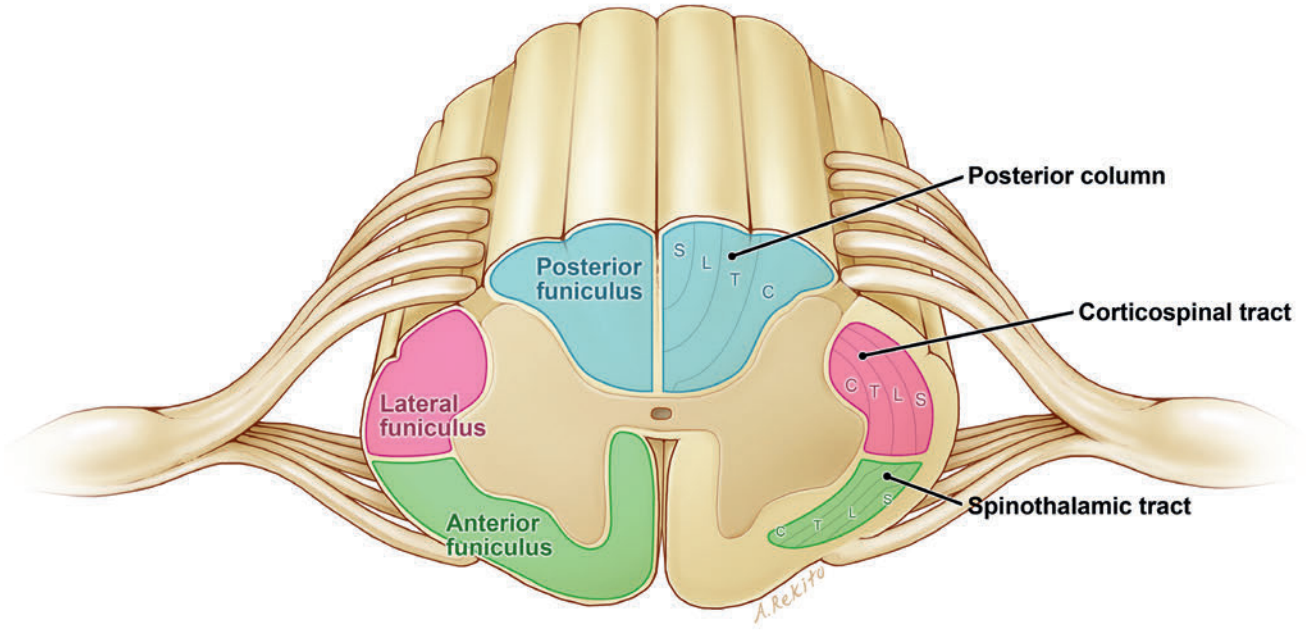

Fig. 54.1 Somatotopic organization of spinothalamic and corticospinal tracts in the cervical spinal cord.

Candidacy

The indications for cordotomy have also evolved over time. Early in its history it was used mainly for pain unrelated to cancer. Over time, it has come to be used primarily for cancer-related pain. The ideal candidate is a cancer patient with unilateral somatic pain with a life expectancy of under a year. Bilateral pain is more difficult to treat, and midline pain generally does not respond to cordotomy. Further, pain above the dermatome of C5 is generally not well controlled by cordotomy. Pulmonary function tests demonstrating an forced expiratory volume at one second (FVC1) and forced expiratory volume (FEV) > 50% are generally the minimal standards for the procedure.[9]

Pain due to mesothelioma represents the prototypic cancer-related pain that is responsive to cordotomy given its unilateral nature and the somatic type of pain resulting from involvement of the pleura and ribs. Pulmonary involvement is usually a late development in mesothelioma, as is impairment of pulmonary functions beyond the minimal cutoff.[10]

Evidence

The evidence for cordotomy stands almost alone among other ablative spinal cord procedures. It is the most studied and has the highest number of dedicated publications and the highest number of patients reported, and is second only to sympathectomy in terms of the quality of data.

In a recent structured review of all percutaneous ablative procedures, 3,601 patients were reported in 47 publications between 1966 and 2010; many reports involved more than 200 patients, with follow-up exceeding 6 months.[3,11–15] The most recent cordotomy literature has originated outside the United States, where the economic environment has favored ablative over neuromodulation procedures. There were no Class I reports of cordotomy found in this review. One prospective trial was identified.[16] This trial used standardized outcome measures: the visual analog scale (VAS), the Karnofsky performance scale (KPS), activities of daily living (ADL), and total sleeping hours. The author reported a statistically significant improvement in all outcome measures that compared post-procedure and baseline pain levels. Three reports were retrospective cohorts with survival analysis of pain relief of the entire cohort until death.[17–19] Many other reports were retrospective cohorts with large numbers (> 100) of patients and 6 months of follow-up.

GRADE is a system that separates the strength of recommendation from the underlying quality of evidence. When we applied the GRADE system of evidence to cordotomy, it received a 1C grade—a strong recommendation for the use of cordotomy in cancer pain, but based on a low level of evidence.[20]

Technique

Equipment

The needle, stylet, and electrode we use is the KCTE kit provided for CT-guided spinal cord radiofrequency lesioning (Cosman Medical, Burlington, MA, USA). A RF lesion generator that is capable of stimulation and impedance monitoring is needed.

The procedure is generally performed in the CT scanner in the radiology suite, however, with the recent availability of wide-bore mobile intraoperative CT scanners, the procedure may also be done in the operating theater.

Preoperative Preparation

Patients are usually admitted the same day. Anticoagulant or antiplatelet agents are stopped at least 1 week prior to the procedure.

Thirty minutes prior to the procedure, a lumbar injection of 12 mL of Omnipaque 300 mg/mL (GE Healthcare, Princeton, NJ, USA) is performed and patients are then kept in the Trendelenburg position.

Surgical Positioning

Cordotomy is done in the supine position and the head is immobilized in the CT gantry. It is important to maintain the head in a straight, neutral position to facilitate the three-dimensional orientation during needle placement. The shoulders are pulled down to ensure adequate access to the side of the neck to allow placement of the electrodes. The area around the mastoid tip is prepped and draped.

Imaging and Data Acquisition

Parallel, preferably zero-gantry-angle, 1.0 to 1.25-mm cuts are scanned spanning from the foramen magnum down to the bottom of C2 with a wide field of view (FOV) to allow imaging of the skin. The FOV can be adjusted to avoid dental artifact. The cut of choice to perform the procedure is between C1 and C2, where there is a lateral space to allow introduction of the needle. The laser beam of the scanner is used to guide the entry point into the skin. The skin dura thickness and the anteroposterior and lateral diameter of the cord are all determined from the slice through which skin entry will be accomplished (**Fig. 54.2**).

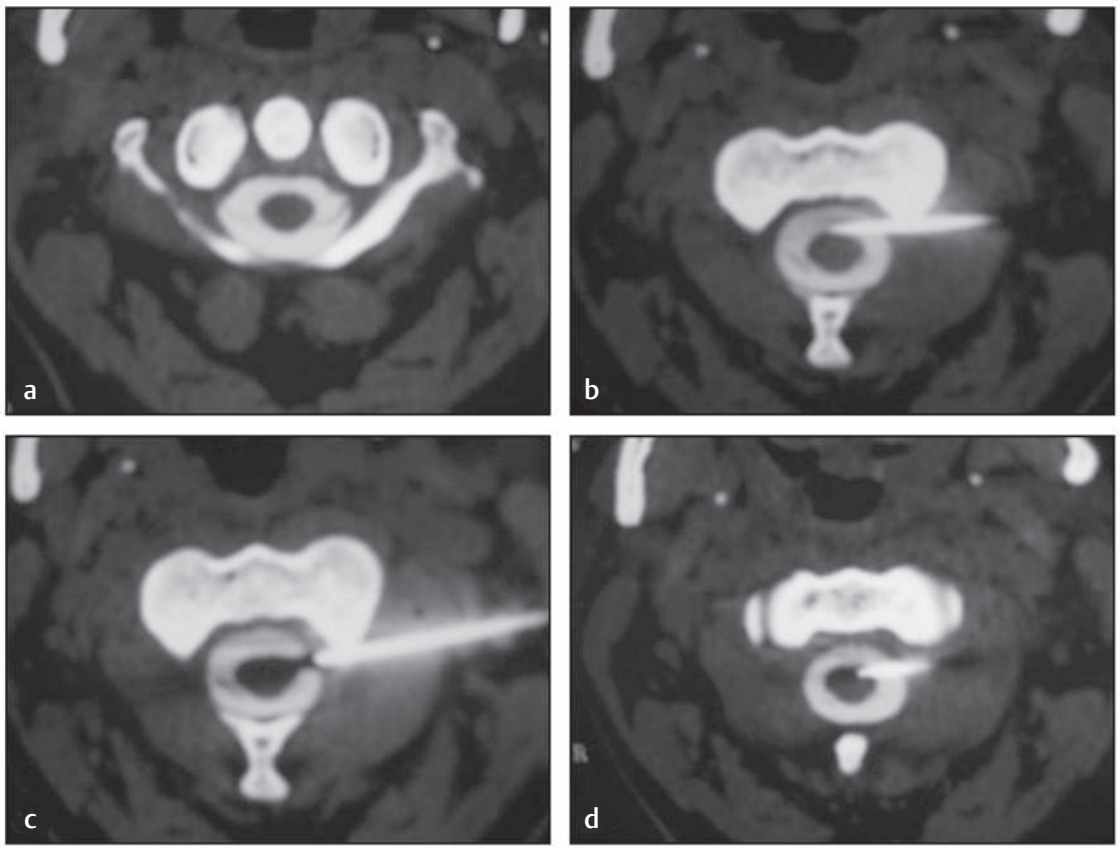

Fig. 54.2 (**a**) CT (computed tomography) myelography revealing the dentate ligament and the upper cervical spinal cord; the cord diameter and skin dura thickness are obtained from the image. (**b**) The needle introduced to a trajectory anterior to the cord. (**c**) The needle trajectory is adjusted to proper targeting of the anterolateral quadrant. (**d**) The electrode is inserted through the needle into the spinal cord.

Needle Placement

After local infiltration with lidocaine 2%, the cannula of the KCTE kit is introduced through the skin to a length that is shorter than the skin dura thickness in a direction mostly perpendicular to the skin at the level of the mastoid tip in the anteroposterior plane. CT is used frequently to check the position of the cannula until the dura is punctured. Before puncture of the dura 2 mL of xylocaine 2% can be injected to avoid pain due to contact with the sensitive C2 ganglion and dura. After free flow of CSF (cerebrospinal fluid) is obtained, a CT check is always performed, then according to the previously determined lateral diameter of the cord, the length of exposed tip of the electrode is adjusted on the hub of the electrode and the electrode is introduced through the cannula. Cord penetration is signaled by a sudden increase in the impedance of the CSF values (< 400 ohms) to approximately 1,000 ohms. Typically at this point the patient experiences a mild pain and/or electric sensation.

Target Verification

Radiological

By CT, the position of the electrode is confirmed in relation to the geometry of the cord (the opposite anterolateral quadrant of the cord in relation to the side of pain). The electrode placement can also be confirmed through the relation of the area of maximal pain intensity and the somatotropic arrangement within the spinothalamic tract: more anteromedial for the arm, and more posterolateral for the leg.

Clinical

Usually cord penetration produces a brief somatotopic-specific pain, which can also be confirmed by stimulation of the electrode.

Electrophysiological

Impedance Monitoring

Impedance monitoring is useful in identifying the degree of cord penetration only, and not the location of the electrode within the spinal cord.

Macrostimulation

The electrodes we use for lesioning allow us to stimulate the spinothalamic tract (the target) in both high (sensory) and low (motor) frequencies to verify the targeting.

All patients are stimulated with 100-Hz pulses of duration 0.1 ms, producing a sense of warmth and/or painful sensation in the opposite half of the body at < 0.15 V, covering the painful region. Motor stimulation at 2 Hz and pulse duration 0.1 ms is then performed up to 1.0 V. There should be no motor response in the extremities with stimulation.

Lesion Making

We begin with one test lesion (60 s, 60°C) and then check the contralateral half of the body for hypothesia and any pain relief. The test lesion is completed with the ipsilateral leg of the patient elevated off the table to detect any subtle change of the motor power during the lesion process. If adequate hypothesia or pain relief is not obtained from the test lesion (which is the case in most patients), a second lesion at 75°C for 90 seconds is performed.

The benchmark of a successful lesion is the abolition of the patient's ability to differentiate a sharp pin prick and a dull sensation. Once a successful lesion is accomplished, the cannula is removed from the patient and the puncture site is dressed.

Postoperative Care

Overnight observation with continuous pulse oximetry is needed for cordotomy patients to monitor for possible sleep apnea. Opioids can be weaned on the first postoperative day, but in most cases, this is deferred to a week after the procedure.

■ Results

Since cordotomy is rarely done for non–cancer-related pain, the results of cordotomy in this group are from older studies and are generally inferior to the results of cordotomy for cancer-related pain.[21] However, this general notion has been challenged by case reports of prolonged pain relief after cordotomy for non–cancer-related pain.[6]

Table 54.1 summarizes the results of percutaneous cordotomy in cases of cancer-related pain published in English between 1966 and 2010.[3,11–15] The results aggregate all cordotomies published, only a small fraction of which were done using CT guidance. CT-guided cordotomy is categorically different from fluoroscopic cordotomy because CT allows direct visualization of target-electrode relationship, leading to higher safety and precision. In a series of 41 patients,[16] the immediate postoperative results of CT-guided cordotomy ranged between 92 and 98% pain relief, or satisfactory pain relief, declining to

Table 54.1 Results of percutaneous cordotomy for cancer pain from 1966 to 2010 in all English-published peer-reviewed manuscripts, redundancy eliminated

Author(s)	Year	Study design	Diagnosis	Patient number	Follow-up	Outcome
Kanpolat et al[22]	2009	Retrospective cohort	Cancer pain	193	Up to 6 mo	Significant reduction of VAS in > 90% of patients
Raslan[16]	2008	Prospective open-label	Cancer pain	41	6 mo	Significant improvement in VAS, KPS, ADL, sleeping h at 6 mo
Raslan[23]	2005	Case series	Cancer pain	8	6 mo	Improvement of VAS, NRS, anterior transdiscal
Crul et al[24]	2005	Case series	Cancer pain	43	Up to 4 y	Significant and persistent reduction of NRS
Yegul and Erhan[25]	2003	Case series	Cancer pain	9	Short	Safe bilateral cordotomy after 1 wk
Jones et al[26]	2003	Case series	Cancer pain	9	Up to 830 d, median 107	Open cordotomy effective in pain reduction
McGirt et al[27]	2002	Case series	Cancer pain	6	5–11 mo, mean 6 mo	Effective significant reduction of VAS, using MRI-guided cordotomy
Jackson et al[10]	1999	Case series	Cancer pain	52	1–52 wk	83% of patients had substantial pain relief initially
Sanders and Zuurmond[28]	1995	Case series	Cancer pain	80 (18 bilateral)	3–18 mo	87.1% with satisfactory pain relief initially, then gradually faded
Fenstermaker et al[29]	1995	Case series	Cancer pain	6	Short	Satisfactory pain relief in 5/6 patients; this is mainly a technical note
Nagaro et al[30]	1994	Case series	Cancer pain	10	94.7 d ± 71.1 d	Significant reduction of VAS from 8.5 to 3
Lahuerta et al[31]	1994	Case series	Cancer pain	146	Up to 9 mo	Complete or satisfactory pain relief in 89% of patients
Krol and Arbit[32]	1993	Case series	Cancer pain	13	Short	Good pain relief in the short term
Stuart and Cramond[33]	1993	Large retrospective cohort	Cancer pain	273	Long term	Satisfactory pain relief in 89% of patients
Amano et al[34]	1991	Case series	Cancer pain	161 (mostly cancer)	> 6 mo	76% showed good pain relief
Högberg et al[35]	1989	Case series	Cancer pain	24	> 6 mo	79% pain relief
Palma et al[36]	1988	Case series	?	?	?	?
Ischia et al[17]	1985	Retrospective cohort of prospectively collected data (survival analysis)	Cancer pain	119	Till death (survival analysis)	92% initial pain relief declines to as low as 30% at the time of death (around12 mo)
Ischia et al[18]	1984	Retrospective cohort of prospectively collected data	Malignant vertebral pain	69	Median 5 mo	71% pain relief, some patients may be included elsewhere
Ischia et al[19]	1984	Retrospective cohort of prospectively collected data	Cancer pain	36	Till death	Bilateral cases only, 47% complete pain relief and 12.5% pain relief; patients might be included in other studies

(continued on page 556)

Table 54.1 *(continued)* Results of percutaneous cordotomy for cancer pain from 1966 to 2010 in all English-published peer-reviewed manuscripts, redundancy eliminated

Author(s)	Year	Study design	Diagnosis	Patient number	Follow-up	Outcome
Cowie and Hitchcock[37]	1982	Case series	Cancer pain	33	Up to 1 y	95%, 73%, 55% pain relief at immediate postop, 6 mo, and 1 y, respectively
Meglio and Cioni[38]	1981	Case series	Cancer pain	52	15 wk	73% and 63% had excellent results after 1 and 15 wk, respectively
Lipton[39]	1978	Case series	Cancer pain	650	Till death	95% initial pain relief, drops to 75% near death; 6.2% mortality
Rothbard et al[40]	1972	Case series	Cancer pain (gynecologic)	10	Up to 3 y	Pain-free interval 6–29 mo
Batzdorf and Weingarten[41]	1970	Case series	Cancer pain	41/47 total	Up to 12 mo	27 excellent or good pain relief, 11 fair pain relief
O'Connell[42]	1969	Case series	Cancer pain (rectal)	56	6 wk–2 y	63% had complete pain relief until death
French[43]	1974	Case series	Cancer pain	177/200	Up to 1 y	90.6% had no pain or good pain relief, up to more than 1 y; open surgical cordotomy
Rosomoff[44]	1969	Case series	Cancer pain	71 cancer pain/ 100 total	Till death	Initial 93% pain relief that fades to about 60% at 2 y; this is a bilateral series
Lin et al[45]	1966	Case series	Cancer pain	38	2 wk–7 mo	74–86% adequate (no pain or good pain relief) depending whether it is anterior or posterior
Mullan et al[3]	1965	Case series	Cancer pain	47	Short	36 good outcome, 1 death
Esposito et al[46]	1985	Case series	Cancer pain	8	6 mo	Cordotomy worked for 2–3 mo only
Grote et al[47]	1978	Case series	Cancer pain	138	Unclear	Initial relief in 114 (106 complete, 8 partial), dysesthesia in 9, 1 anesthesia dolorosa
Tasker[9]	1976–1977	Case series	Mostly cancer pain	264 mixed	Unclear	Initial 96%, 83% pain relief unilateral and bilateral; decreased to 89% and 66% at the time of last follow-up; 3% permanent complications
Crue and Felsoory[48]	1974	Case series	Mixed	29/48	Short	31% pain relief even in the short term
Fox[49]	1973	Case series	Mixed	14/18	Unclear	11/14 had adequate pain relief
Tasker and Organ[50]	1973	Case series	Mixed, mostly cancer pain	78 total	Till death, survival generally 3–6 mo	84% had pain relief till death
Smith[51]	1972	Case series	Mixed, mostly cancer pain	19 total	Around 6 mo	In cancer pain patients, 100% complete or satisfactory pain relief
Foer[52]	1971	Case series	Cancer pain	21/30	Unclear	90% had partial to complete pain relief; 1 death
Salmon[53]	1969	Case series	Mixed	34 total	Unclear	25/34 had good pain relief, minor transient ataxia in 3, no mortality
Fox[54]	1969	Case series	Mixed	50	Not reported	Not reported
Uihlein et al[55]	1969	Case series	Cancer pain	45/50	Unclear	80% with either complete (52%) or satisfactory (28%) persistent pain relief

Author(s)	Year	Study design	Diagnosis	Patient number	Follow-up	Outcome
Acosta and Grossman[11]	1969	Case series	Cancer pain	12/15	3 mo–2 y	Adequate pain relief in all patients; 2 required redo
Kelly and Alexander[12]	1966	Case series	Cancer pain	14/17	1–10 mo	13/14 had pain relief
Rosomoff et al[4]	1966	Retrospective cohort	Cancer pain	82/100	Mostly 24 wk; by that time only 39/100 survived; the 61 deaths were cancer pain	Initial 92% pain relief, 82% at 24 wk
Rand et al[13]	1965	Case report	Cancer pain	2	Short	One case had pain relief; it is a report about cooling electrode
Gildenberg[14]	1976–1977	Retrospective cohort	Cancer pain	288	6 mo	82–85% had pain relief till 6 mo, depending on whether anterior or posterior
Raskind[15]	1969	Case series	Mixed	30/237	Not stated	60% good pain relief, not requiring narcotics

Abbreviations: ADL, activities of daily living; KPS, Karnofsky performance scale; MRI, magnetic resonance imaging; NRS, numeric rating scale; VAS, visual analog scale.

80% at 6 months, with a persistent clinically and statistically significant reduction in the VAS (**Fig. 54.3**). Kanpolat et al also reported an initial success of 97%, which declined to 84% at 6 months' follow-up.[22]

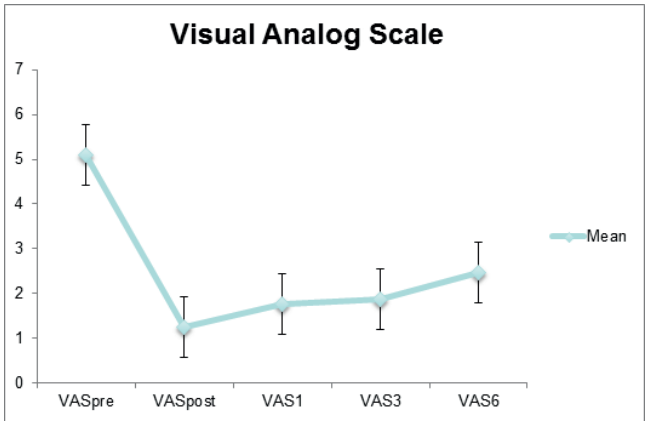

Fig. 54.3 Persistence of statistically and clinically significant reduction in visual analog scale after cordotomy at 6 months.

Complications

There have been no mortalities reported in the literature for CT-guided cordotomy, although a 6.25% mortality rate has been reported for the older fluoroscopic cordotomy.[56]

Ondine curse can result from cordotomy when pulmonary function is impaired or the only functioning lung is the lung ipsilateral to the cordotomy (a contraindication for cordotomy). True Ondine curse is universally fatal; however, no cases of Ondine curse have been reported so far using CT-guided cordotomy.[16,22]

Postcordotomy dysesthesias affect 5% of patients and usually develop in long-term survivors who either have a significant component of neuropathic pain or had received a large lesion.[56,57]

With direct visualization of the electrode in the spinal cord and proper electrophysiological verification, ipsilateral weakness should be a very rare occurrence. Ataxia and urinary incontinence have been reported by some authors, but not in modern cases of CT-guided cordotomy.[22,56]

One rare, troubling, and unpredictable consequence of cordotomy is what is called mirror pain, which either can be attributed to a bilateral pain syndrome that is masked by marked severity on one side, or is potentially due to the bilateral projection of dorsal roots into both spinothalamic tracts.

Local anesthetic can be inadvertently injected into the CSF if mistaken for the water-soluble radiocontrast. This can lead to respiratory cessation, especially if a cisternal injection is performed. This underscores the need for clear marking of injection syringes and segregation of local anesthetic syringes from the surgical field.

Bilateral Cordotomy

Bilateral cordotomy has been reported by both Kanpolat et al and Yegul and Erhan.[22,25] It relies on a superselective lesion of the dorsal part of the spinothalamic tract close to the equator of the cord to avoid damage to the respiratory fibers that are in close proximity to the ventral component of the spinothalamic tract. The two sides should not be disrupted at the same session, and an interim interval of 2 weeks is recommended. Even with these restrictions, bilateral cordotomy can benefit bilateral lower extremity pain given the known somatotopic organization of the spinothalamic tract.

Future of Cordotomy

In medicine, historic procedures are sometimes reborn: What is old is new again. Cordotomy is one procedure that is poised to be utilized again for many reasons: (1) the increasing costs to maintain and manage the complications of intrathecal opioid systems; (2) the realization that pharmacological neuromodulation is not always reversible (e.g., weaning a patient from intrathecal opioids has in many instances proved impossible); (3) an increased recognition of opioid-induced hyperalgesia; (4) a need for the development of cost-effective procedures; and (5) the potential for increased safety, accuracy, and precision of a cordotomy procedure using technology such as intraoperative monitoring and neuronavigation.

Intraoperative imaging is making significant inroads in neurosurgery, and cordotomy may also benefit from this technology. A report of O-arm (Medtronic, Minneapolis, MN, USA) -guided cordotomy was recently published. The author has been using the intraoperative CereTom CT scanner (NeuroLogica, Danvers, MA, USA) for CT-guided tractotomy and myelotomy. With wider bore intra-operative CT scanners, cordotomy will move back to the surgical theater from the radiology suite. Endoscopic cordotomy has been introduced recently, and this technique presents the potential of improved visualization during the placement of the lesion electrode.[58]

Conclusion

Cordotomy is a very effective pain-relieving procedure that is most appropriate for patients with unilateral somatic cancer pain, who have a life expectancy of 1 to 2 years. It can be performed with the patient awake using CT guidance and myelography. It is a rather classic procedure that has a place in today's pain surgery practice.

Editor's Comments

Cordotomy may be the exemplar for procedures that have proven effective in the past, were then lost to practice, and have been resurrected judiciously. Medicine, particularly pain medicine, is a trendy business. During the past several decades, neuromodulation has dominated the care of patients with chronic pain. When trainees never see a particular procedural option, those procedures tend to disappear; they are lost to future generations. This is not to say that we should uncritically adopt past practices, but more to reflect on what might be gleaned and improved on from older techniques.

CT-guided cordotomy applies established principles, and takes advantage of newer technology that can make the procedure safer and more effective. If cordotomy is to undergo a renaissance, it will be in the area of cancer-related pain. As I have pointed out in previous comments, the fact that at minimum 10% of cancer patients experience uncontrolled pain despite maximum tolerable medical therapy indicates that there is a role for surgical pain control in these individuals. Ablative procedures, when done properly by experienced clinicians, can provide effective pain control while preserving health care resources. As Drs. Raslan and Viswanathan mention, this conclusion is supported by evidence that the practice of cordotomy has been reinvigorated in countries that do not have the health care resources of the United States. As the proportion of our economy devoted to health care in the United States comes more into alignment with that of other countries, there will be more pressure to implement cost-effective pain-relieving procedures like cordotomy in patients with cancer-related pain.

As cordotomy re-emerges as a viable procedure, there will be a need to define its role, if any, in the treatment of pain not related to cancer. Several generations of neurosurgeons have passed since cordotomy was attempted for chronic "benign" pain. Careful and cautious inquiry may yield some instances when ablative lesions might produce durable pain relief.

Our first steps will be to reeducate a generation of neurosurgeons in the technique of cordotomy, probably CT-based. I am grateful to Drs. Raslan and Viswanathan for initiating that process.

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55 Midline Myelotomy and the Interruption of the Postsynaptic Dorsal Column Pain Pathway for the Treatment of Visceral Pain

Haring J. W. Nauta, Karin N. Westlund, and William D. Willis

This chapter attempts a synthesis of three topics: visceral pain, the surprising discovery of robust pain pathways in the dorsal columns of the spinal cord, and a body of knowledge around an old operation, midline myelotomy, now used only rarely. Each topic could provide material for a separate chapter, but they are discussed together here because the evolution of their understandings is closely intertwined so that each informs the other. Better understanding of the midline myelotomy operations used clinically and how they were effective (Hirshberg et al[1]; see also **Fig. 55.1**) inspired laboratory studies in animals that led to a better understanding of the anatomy and physiology of the pain pathways that ascend in the dorsal columns. An improved understanding of visceral pain characteristics, in turn, and their differences from somatic pain (see **Table 55.1**) clarifies why visceral pain pathways and mechanisms might be different from those for somatic pain, and why in the past visceral pain seemed so difficult to treat. And finally, with an improved understanding about the postsynaptic dorsal column pathway and the properties of visceral pain, it has been possible to refocus the older myelotomy operations on the aspects that make them more effective and safer. The story has an almost circular quality of discovery and was laid out in great detail in the first edition of this text,[2] wherein the conclusions were still so novel that they were presented as tentative. Since then, further work in both the basic science laboratory and the clinical application has reinforced the conclusions. This is a process still in evolution and our increasing knowledge from the laboratory suggests that further clinical refinements may still be possible.

Clinical Implications

What we are successfully doing clinically today is treating intractable visceral pain of pelvic origin by interrupting an ascending postsynaptic pathway in the dorsal columns that conveys more visceral than somatic pain. For the pelvic and lower abdominal organs, the pathway runs in a juxta-midline direction, so the ascending axons there can be easily located and interrupted either by making a short transverse cut, or crush (see **Fig. 55.2a, b**), as we do it today in the punctate midline myelotomy (PMM) operation; or we can use "collateral damage" from a sagittal cut in the traditional midline myelotomy operation[3] originally intended as a commissural myelotomy proposed by Greenfield in 1926. The PMM operation we perform today might more properly be described as a limited transverse dorsal column myelotomy or transection centered on the midline, to distinguish it from the traditional midline myelotomy in which the cut in the spinal cord is in the sagittal plane. **Fig. 55.3** highlights this comparison.

The Anatomy and Physiology of the Postsynaptic Dorsal Column Visceral Pain Pathway

Fig. 55.4 (modified from Willis et al[4]) summarizes what is now understood about the anatomy of the postsynaptic dorsal column pathways as these relate to visceral pain. The information comes from physiological localization studies as well as from retrograde and anterograde labeling studies in rats. **Table 55.2** highlights the differences between the long-recognized presynaptic dorsal column pathway and the more recently characterized postsynaptic dorsal column pathway.

Postsynaptic dorsal column axons have their cell bodies in the gray matter of the spinal cord (see review by Willis and Coggeshall[5]). Many are concentrated in laminae III and IV of the dorsal horn, although they are found in other laminae as well.[6–9]

Retrograde labeling of axons in the dorsal columns of the cervical spinal cord has demonstrated the presence of a large population of postsynaptic

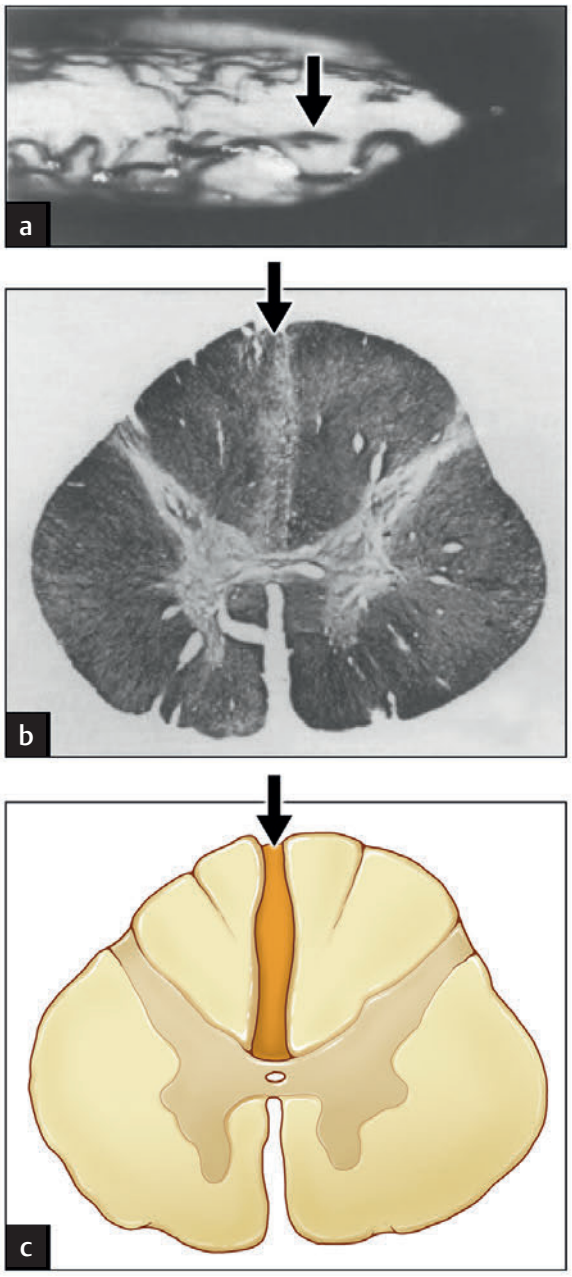

Fig. 55.1 Limited midline myelotomy as performed by Hirshberg with a short sagittal cut in the midline at the T10 level. (**a**) Intraoperative photograph. (**b, c**) The extent of the lesion when analyzed at autopsy (*arrows*). Note that although the myelotomy produced dramatic relief of chronic, medically intractable visceral pain, the extent of the lesion does *not* interrupt either the dorsal or ventral commissures. This observation was pivotal in inspiring further analysis into how the lesion could have been so effective when it clearly did not interrupt the bilaterally crossing fibers of the classically understood spinothalamic pathway. (Modified from Hirshberg et al.[1])

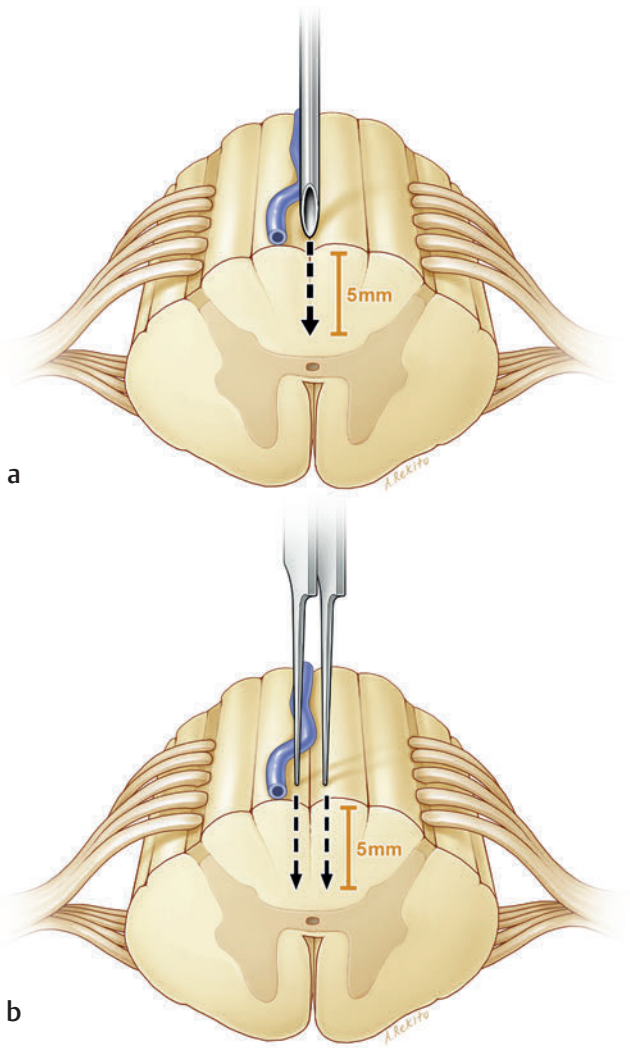

Fig. 55.2 (**a**) The transverse cut interrupting the medial millimeter of the dorsal columns on either side of the midline was originally made using the point of a 16-gauge needle as a knife. The needle tip was inserted to a depth of 5 mm precisely centered on the midline. No standard scalpel blade was narrow enough to produce the depth and width required. (Modified from Nauta et al.[41]) (**b**) The lesion was later made using a jeweler's forceps inserted as shown. (Modified from Nauta HJW, Hewitt E, Westlund KN, Willis WD. Punctate myelotomy for the relief of visceral cancer pain. J Neurosurg Spine 2000; 92:L25-L30.)

Table 55.1 Comparison of visceral and somatic pain

	Visceral pain	Somatic pain
Primary pathway	Postsynaptic dorsal column	Spinothalamic tract
Injury required?	No	Yes
Referral	Yes	No
Sensation	Continuous burning	Sharp
Localization	Poor	Good
Hyperalgesia	Yes	Yes
Adequate stimulus	Stretch, traction, inflammation, ischemia	Damage, infection
"Emotional valence"	Higher	Lower
Input to spinal cord	5–8%	95–98%
Central terminals	Highly arborized; end in laminae I, II, V, X, some on contralateral side	Discrete termination in superficial laminae
Somatotopic	No	Yes
Viscerosomatic convergence	Yes	Yes
Location in dorsal column	Midline dorsal column, intermediate septum	Majority of the dorsal column
Crossed pathway	No	Yes
First spinal cord relay	Neurons in laminae III–VII, X	Neurons in laminae I, IV, V
Second relay	Second dorsal column nuclei Third medial and intralaminar thalamic nuclei	Thalamus, ventral posterolateral (VPL) nucleus
Cortical termination	Limbic—cingulate, prefrontal, insular	Sensory neocortex—SI, SII cortex

dorsal column neurons in the area around the central canal of the sacral spinal cord (see **Fig. 55.5**).[1] It is known that visceral primary afferent fibers project to this region.[10–14] Injection of an anterograde label into the same region of the spinal cord showed that neurons in this region project to the medial part of the gracile nucleus.[1,15,16] Thus, there is anatomical evidence of a postsynaptic dorsal column pathway that originates from a part of the spinal cord gray matter that is known to contain neurons that respond to somatic and/or visceral stimuli.[17–20] The axons of these neurons in rats ascend in the fasciculus gracilis near the midline in a homologous position to the lesion made by Hirshberg,[1] as demonstrated after autopsy in his last clinical case (see **Fig. 55.1**).

Retrograde tracing experiments have confirmed the observation of a large population of post-synaptic dorsal column neurons in the central gray region of the sacral spinal cord (**Fig. 55.5**) that project to the medial nucleus gracilis.[1,21,38] Anterograde tracing experiments using *Phaseolous vulgaris* leuko-agglutinin (PHA-L)[16] confirm that axons of postsynaptic dorsal horn neurons in the central gray region of the sacral spinal cord ascend in the fasciculus gracilis near the midline (**Fig. 55.4**). However, at least in rats, the axons of comparable neurons in the midthoracic spinal cord ascend more laterally, in the vicinity of the dorsal intermediate septum,[15,16] which separates the fasciculus gracilis from the fasciculus cuneatus (also shown in **Fig. 55.4**). Many of the terminals of these axons are in the lateral gracile and medial cuneate nuclei, whereas others continue rostrally to higher brain areas.

Evidence from Neurophysiological Studies in Animals

To determine if this postsynaptic dorsal column pathway carries visceral nociceptive information, it was necessary to demonstrate the response properties of neurons affected by this pathway. The first indication that cells present in the brain were visceral nociceptive neurons whose responses depended on information conveyed by the dorsal columns came from recordings of the activity of neurons in the ventral posterolateral (VPL) nucleus in rats.[22] The neurons that were selected responded to noxious colorectal distension (CRD),[23] as well as to stimulation of a cutaneous receptive field. A lesion of the dorsal column at T10 was shown to dramatically reduce the responses of the VPL neurons to CRD and to weak mechanical stimulation of the skin, whereas a lesion

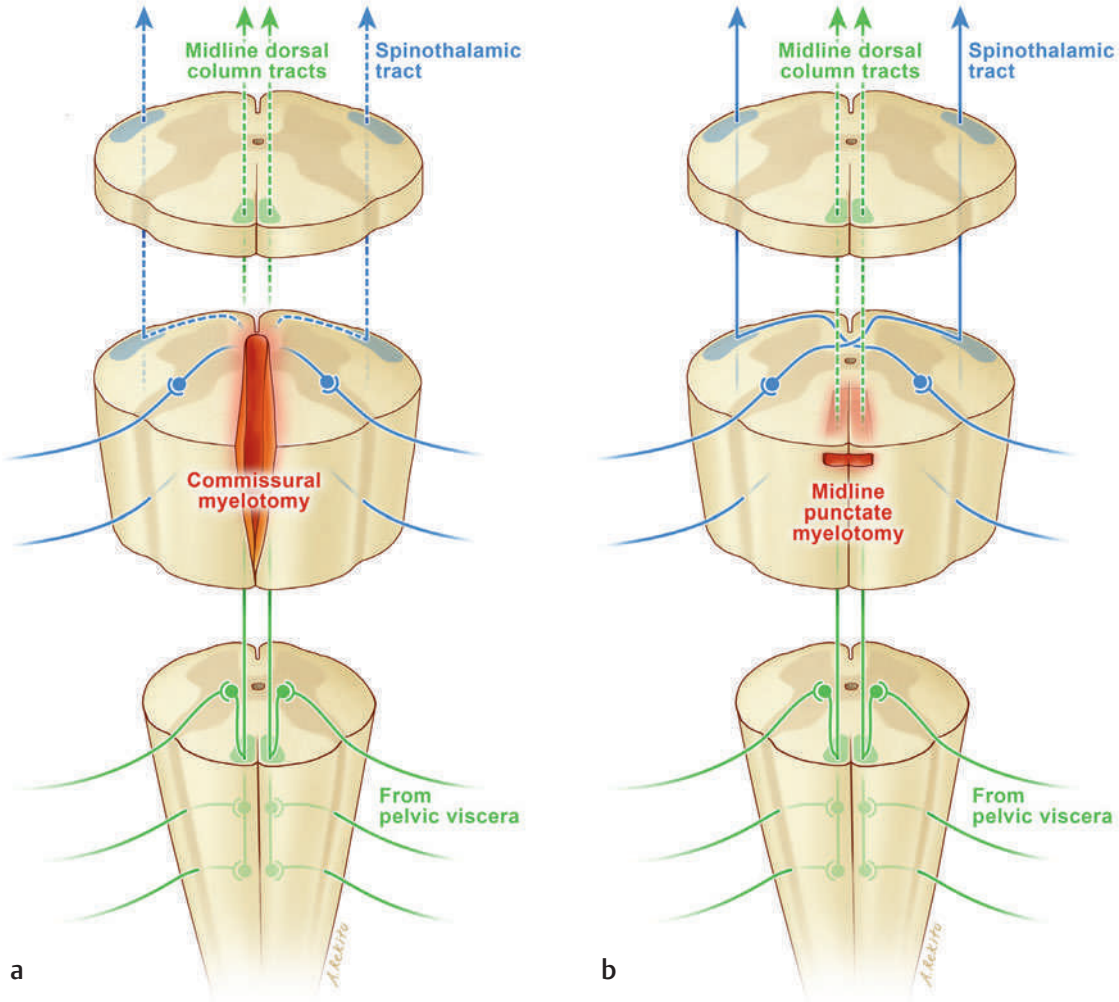

Fig. 55.3 Comparison of the effects of commissural myelotomy with punctate midline myelotomy (PMM). The commissural myelotomy (left) requires a sagittal cut deep enough to reach the commissures so that the bilaterally crossing fibers of the spinothalamic tracts will be interrupted. Somatic pain should thereby be affected over an area coextensive with the segmental levels involved. However, in doing so, the medial fibers of the dorsal columns will also be injured, interrupting the postsynaptic dorsal column pathway subserving predominantly visceral pain for all levels caudal to the lesion. In PMM, shown at right, only the postsynaptic dorsal column pathway is interrupted with a very short transverse incision centered on the midline, affecting mostly visceral pain caudal to the level of the lesion.

of the lateral funiculus (and presumably of the spinothalamic tract) eliminated the responses to noxious mechanical stimulation of the skin (**Fig. 55.6**). By contrast, a lesion of the spinothalamic tract blocked the responses to noxious cutaneous stimulation but not those to CRD (**Fig. 55.7**). Comparable effects were also observed when acute inflammation of the colon by injection of a chemical irritant, mustard oil, was used instead of CRD to elicit a response. To ensure that it was the dorsal column projection that was involved in the responses of VPL neurons to CRD, a lesion study was done in which a radiofrequency or a kainic acid lesion was made *in* the nucleus gracilis.[24] A small, incomplete lesion of the nucleus gracilis resulted in a substantial reduction in the responses of VPL neurons to CRD, indicating that the pathway involved did relay in the nucleus gracilis.

Another question was whether the responses of VPL neurons to CRD depend on primary afferent axons in the dorsal column that project directly to the nucleus gracilis or on the axons of postsynaptic dorsal column neurons. The approach used to answer this question was to administer either morphine or the non–*N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) into the gray matter of the sacral spinal cord by microdialysis to interfere with synaptic excitation of postsynaptic dorsal column neurons following CRD[25] (**Fig. 55.8**). The responses of neurons in the nucleus gracilis to CRD were used to assay the

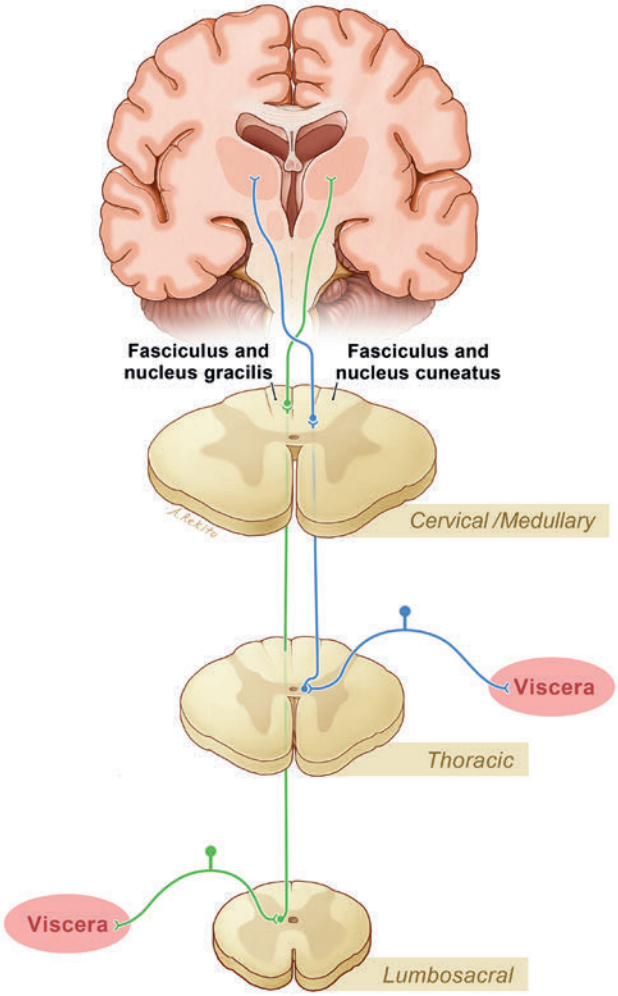

Fig. 55.4 Course of the axons of postsynaptic dorsal column neurons whose cell bodies are located in the central, visceral processing region of the spinal cord around the central canal. The projection from the sacral spinal levels ascends near the midline of the fasciculus gracilis. The projection from the midthoracic spinal cord levels ascends near the dorsal intermediate septum and ends in the lateral nucleus gracilis and medial nucleus cuneatus.

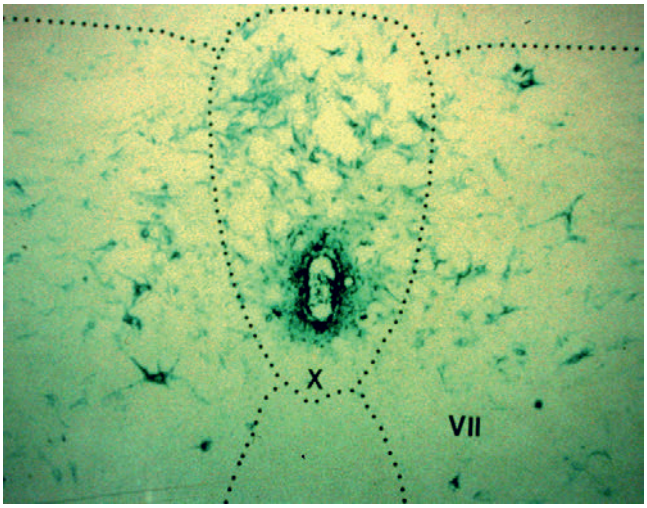

Fig. 55.5 Cells of the central, visceral processing region of the spinal cord around the central canal, retrogradely labeled by HRP injection into the dorsal column nuclei. These are the cells of origin of the postsynaptic dorsal column pathway. (From Hirshberg et al.[1])

effects of the drugs. Because drugs given by microdialysis are likely to affect only about one segment of the spinal cord,[26] the hypogastric nerves were sectioned prior to the experiment so that the responses of nucleus gracilis neurons to CRD depended on input to the spinal cord just through the pelvic nerves. The open dialysis membrane of the microdialysis fiber was placed in the gray matter of the sacral spinal cord. If the responses of neurons in the nucleus gracilis depended entirely on the activity carried there directly by primary afferent fibers, then morphine or CNQX administered by microdialysis into the sacral spinal cord gray matter would presumably not have any effect.[27,28] However, administration of either

Table 55.2 Comparison of presynaptic and postsynaptic dorsal column pathways

	Dorsal column pathways	
	Presynaptic: first order	**Postsynaptic: second order**
Nomenclature	Dorsal column pathway	Postsynaptic dorsal column pathway
Modality	"Epicritic," vibration, discriminative touch, position sense, pressure	Visceral pain
Cells of origin	Dorsal root ganglia (DRG)	Spinal neurons in laminae III–VII, X Second order
Location in dorsal column	Majority of the dorsal column	Midline dorsal column–intermediate septum (fasciculus interfascicularis)
Myelinated	Yes	No
Termination site	Dorsal column nuclei	Dorsal column nuclei
Effect of midline lesion	Little or none	Reduces pelvic visceral pain

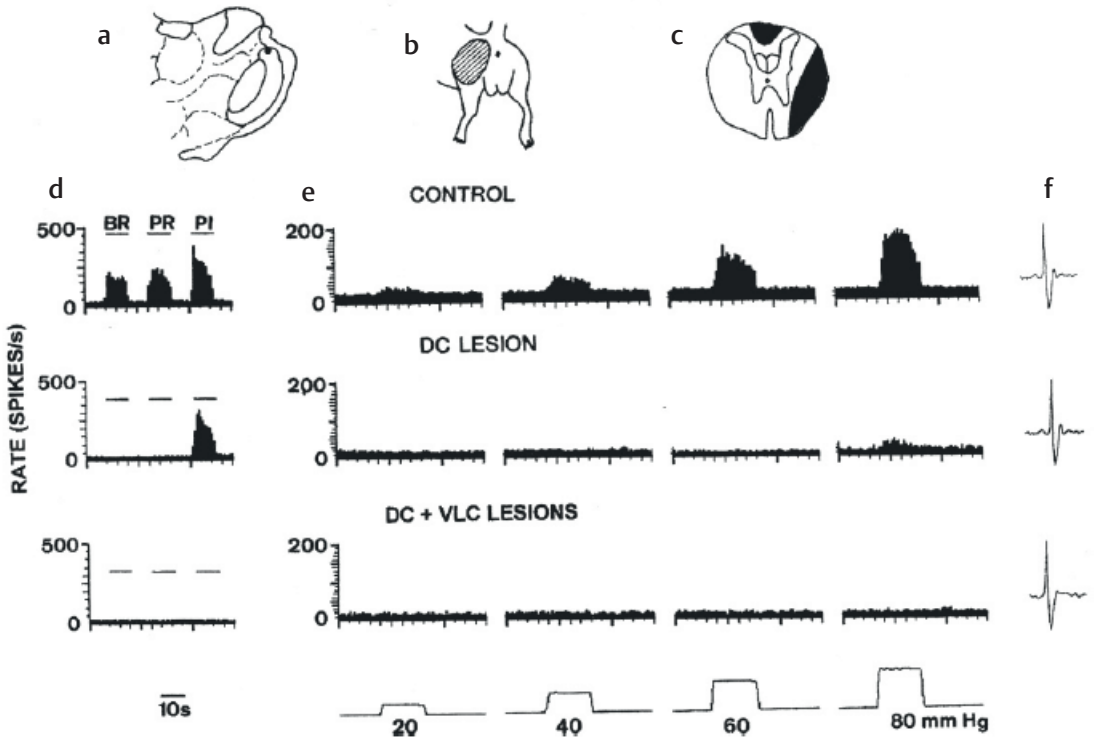

Fig. 55.6 Effects of spinal cord lesions on the responses of a neuron in the ventral posterolateral (VPL) thalamus of a rat to visceral and cutaneous stimulation. (**a–c**)The recording site, cutaneous receptive field, and locations of the lesions. (**d**) Responses to mechanical stimulation of the skin (brushing, BR, pressure, PR, and pinch, PI, due to application of arterial clips to a fold of skin). (**e**) Responses to graded intensities of colorectal distension (CRD), at bottom. The responses in the upper rows of (**d**) and (**e**) were recorded in the control condition; those in the middle rows followed a lesion of the dorsal column (DC); and those in the lower rows followed an additional lesion of the ventral lateral column (VLC). Note that the majority of the responses are eliminated by the dorsal column lesion, with the small remainder disappearing as well after the additional VLC lesion. The monitor traces below (**e**) show the pressures applied to the colon wall with intensities of 40 to 80 mm Hg considered noxious. (**f**) The spikes show that the recording conditions remained unchanged throughout the experiment. (Al-Chaer et al.[22])

morphine or CNQX did indeed block the responses of neurons in the nucleus gracilis to CRD, but not the responses to cutaneous input, which were presumably transmitted directly by ascending collaterals of primary afferent fibers. The action of morphine depended on activation of opiate receptors because this action was reversed by systemic administration of the opiate receptor antagonist naloxone. Thus, this study confirmed the hypothesis that visceral nociceptive information is relayed through postsynaptic dorsal column neurons in the spinal cord.

Recordings from postsynaptic dorsal column neurons in the central gray region of the sacral spinal cord confirmed that many of these cells could be excited by CRD and that their responses to CRD are blocked by microdialysis administration of morphine or CNQX. The axons of these postsynaptic dorsal column neurons could be followed by antidromic stimulation and mapping of the nucleus gracilis. Morphine administered locally into the sacral spinal cord by microdialysis showed a powerful effect on the responses of postsynaptic dorsal column neurons to noxious visceral stimuli. In contrast, morphine showed a weaker action on the responses of these same neurons to somatic stimuli. This differential action may be relevant to the effectiveness of epidural or intrathecal morphine administration in relieving visceral pain in many patients.

A related study was done in which distension of the duodenum in rats was employed rather than CRD.[29] Both behavioral responses (writhing responses) and electrophysiological responses of VPL neurons were employed to evaluate the effects of dorsal column lesions in their studies. A lesion placed at the midline of the dorsal column was without effect. However, lesions placed bilaterally at the position of the dorsal intermediate septum resulted in a dramatic reduction in writhing responses and in the excitation of VPL neurons in response to duodenal distension. The failure of a midline lesion and the success of more lat-

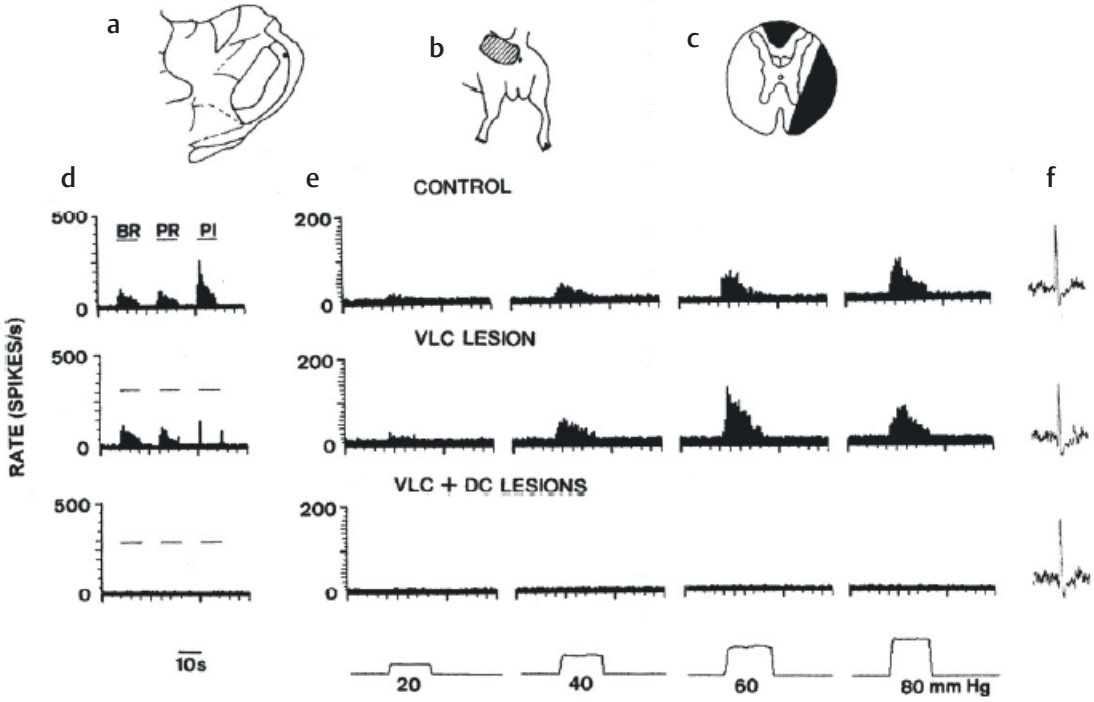

Fig. 55.7 Effects of spinal cord lesions on the responses of a VPL (ventral posterolateral) neuron to cutaneous and visceral stimuli. The abbreviations and arrangement of data are the same as in **Fig. 55.6**. However, the sequence of the spinal cord lesions was reversed, so that the VLC (ventral lateral column) was interrupted first and then the dorsal column lesion. Note that only about a 5 to 10% reduction in the responses occurs after the VLC lesion whereas the responses are eliminated completely after the additional dorsal column lesion. Again, as shown in (**f**), the recording conditions remained constant throughout the experiment. (From Al-Chaer et al.[22])

erally placed lesions of the dorsal column are readily understandable based on the observation by Wang et al[16] that the axons of postsynaptic dorsal column neurons originating from the central gray region of the midthoracic spinal cord ascend near the dorsal intermediate septum, rather than near the midline (see **Fig. 55.4**). Lesions that have included *this* region have also been effective in restoring behavioral exploratory activity in a pancreatitis model in rats.[30] These findings, if applicable to humans, suggest that surgical elimination of visceral pain that is relayed through the midthoracic spinal cord would require placement of lesions bilaterally near the border between the gracile and cuneate fasciculi. However, the situation in humans may be different because both Hwang et al[31] and Kim and Kwon[32] report good results treating upper abdominal visceral cancer pain with PMM at upper thoracic levels, but the lateral extent of their lesions is not fully known.

Responses of neurons in the VPL nucleus in macaque monkeys can also be evoked by CRD.[33] A lesion of the dorsal column at T10 reduced the responses by about half. Additional lesions of the dorsal parts of the lateral funiculi caused a further reduction in the responses to CRD, but lesions of the ventrolateral white matter were not effective in changing the responses. The effectiveness of lesions in the dorsal part of the lateral funiculus in monkeys can be explained by the presence of axons of the lamina I component of the spinothalamic tract[34,35] and some postsynaptic dorsal column neurons in this location.[6] A comparable dorsal lateral funiculus projection of postsynaptic dorsal column neurons of the lumbosacral spinal cord does not occur in rats.[8]

A survey of postsynaptic dorsal column neurons and of spinothalamic tract neurons in the sacral spinal cord of monkeys revealed that the two types of neurons had similar stimulus-response functions following different intensities of CRD.[36] However, the sample included many more postsynaptic dorsal column neurons than STT cells. It was suggested that the greater effectiveness of the postsynaptic dorsal column pathway compared with the spinothalamic tract in conveying information to the brain about visceral pain could be based on the number of neurons available for activation by CRD in the two pathways.

Regional cerebral blood volume changes following CRD were mapped in the brains of four monkeys.[37,38]

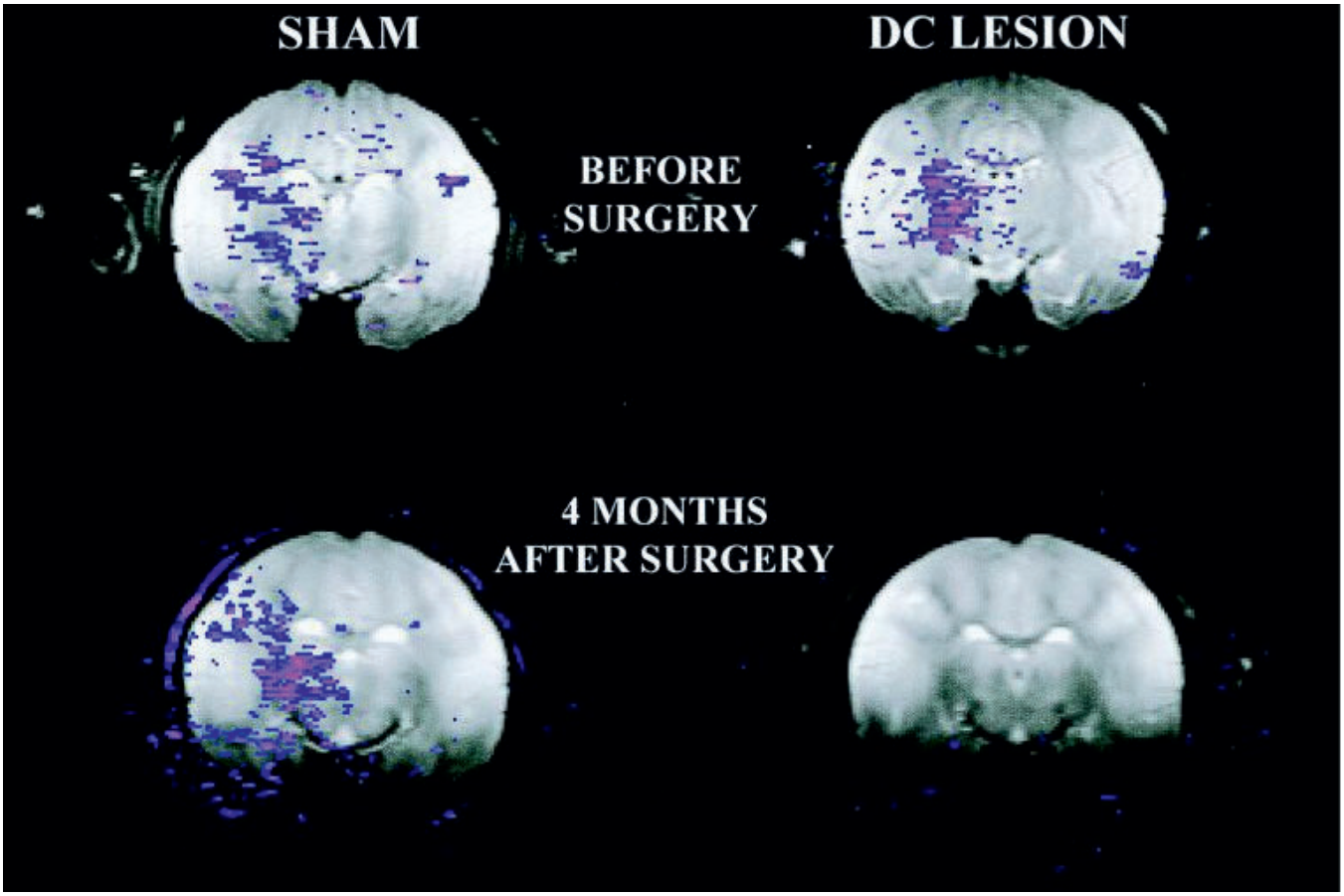

Fig. 55.8 Regional cerebral blood volume in response to noxious colorectal distension before and after a lesion of the dorsal column or sham surgery in anesthetized monkeys. The colored areas in the upper images represent voxels showing an enhanced regional blood volume in the brain of a monkey following noxious CRD (colorectal distension) as determined by functional magnetic resonance imaging (MRI). The transverse sections are taken through the posterior thalamus. The lower images were taken at approximately the same level and in the response to the same stimulus 4 months following sham surgery (left) or a lesion of the dorsal column (DC) at T8 (right). (Willis et al.[38])

A lesion was made in the dorsal column at T8 in three of the animals, and sham surgery was done on the others. Before surgery or after sham surgery, CRD distension produced increases in regional blood volume in many regions of the brain, including the lateral thalamus in the region of the VPL nucleus. Following the lesion of the dorsal column, CRD resulted in no regional blood volume changes (**Fig. 55.8**), suggesting that the lesion eliminated the neural connections necessary for activation of higher brain centers by nociceptors supplying the colon.

Multiple Pain Pathways: Some General Considerations

From the above review of anatomy and physiology, it seems clear that there are several pathways in the spinal cord white matter transmitting information about pain. This redundancy probably reflects at least two principles. First, visceral pain is different from somatic pain at the functional and perceptual levels (see **Table 55.1**), and it should therefore not be surprising that these two broad pain categories are mostly segregated into different anatomical systems. Second, redundancy and a degree of overlap between systems may reflect the importance of pain to survival generally from both a phylogenetic and an evolutionary perspective. Even nonmammalian vertebrates appear to have a postsynaptic dorsal column pathway in addition to the spinothalamic pathway as demonstrated in a reptile.[39]

A closer look reveals several functional differences among the routes taken by these separate pain pathways. The spinothalamic tract pathway transmits precise body map information about pain arising from somatic structures (i.e., skin, muscles, bones) to higher brain centers. Many spinothalamic tract neurons are located in deep laminae IV, V, and

VII of the dorsal horn and send their axons through the well-known ventral or "anterolateral" white matter pathway. The integrated information carried can arise from both somatic and visceral structures, and is likely responsible for transmission of referred pain and chronic pain states. Information about temperature and acute somatic pain is primarily carried by axons located in the lateral white matter from spinothalamic tract neurons in the superficial lamina I.[35,40] However, pain arising from visceral structures is relayed in large part by the dorsal horn postsynaptic dorsal column cells in lamina III and situated medially in laminae IV–VII and X. The visceral pain information is transmitted by way of the dorsal column–medial lemniscus pathway. Despite this association with the dorsal column–medial lemniscus pathway carrying discriminitive sensory information, visceral pain is diffuse and poorly localized. This is probably explained by the widely divergent extent of the visceral afferent terminal endings that can communicate with numerous spinal cord neurons. In comparison, the terminal endings in the superficial spinal cord convey the discrete, somatotopic information in the spinothalamic tract that allows the precise body map localization of painful input through the lateral thalamus to the sensory cortex. The visceral pain information is also transmitted to the medial and intralaminar nuclei of the thalamus. Thus, the visceral sensory and pain pathways are biased toward limbic cortical areas, where they are potentially better able to influence behavioral and emotional response mechanisms.

Initial Clinical Application with the Intention to Interrupt an Ascending Visceral Pain Pathway by Making a Short Transverse Cut across the Midline of the Dorsal Columns

In the late 1990s our group began a prospective study to determine the usefulness of making a small *transverse* cut in the dorsal columns for the treatment of intractable pelvic visceral pain. This represented a significant departure from the usual midline myelotomy procedure, where the incision in the spinal cord had always been made in the midsagittal plane, and any damage to the dorsal columns had been unintentional but fortuitous. We undertook this departure because: (1) convincing laboratory evidence had accumulated demonstrating that there is an important visceral pain pathway in the dorsal columns; (2) for the pelvic visceral organs this pathway runs in an identifiable place along the dorsal midline of the spinal cord; (3) there is historical clinical evidence in humans that limited dorsal column lesions do not produce disabling deficits; and (4) many past published clinical observations about midline myelotomy were consistent with the conclusion that functional deficits were minimal and that the benefits in visceral pain control were substantial.

The first case[41] was a 39-year-old diabetic woman who had been successfully treated for cancer of the uterine cervix by radiation. However, although her tumor was well controlled, she had severe pain apparently due to radiation damage of the bowel, bladder, and ureter. The pain was not controlled by high doses of opiate analgesics, and she had excruciating pain during bowel movements. Her weight had decreased from 96 to 75 lbs, a life-threatening problem. She described herself as either in severe pain or drowsy from overmedication with less severe pain. She had withdrawn socially, and saw no end in sight since her tumor appeared to be well controlled. She requested surgery after full disclosure and institutional review board (IRB) and ethics committee criteria were met. At operation, after T8 laminectomy, a small transverse cut was made across the midline of the dorsal columns ending 1 mm to each side of the midline. The transverse cut was so short an ordinary scalpel blade was too large to allow it. Instead, we made it by using the sharp edge of a 16-gauge needle as a microknife, inserting it vertically into the midline of the spinal cord to a depth of 5 mm as shown in **Fig. 55.2a, b**. Also, for this reason we initially called the procedure "punctate midline myelotomy (PMM)," but it differs from past midline myelotomy procedures because it is made in the transverse rather than in a sagittal direction. When performing the operation with such a narrow cut, we considered it extremely important that the patient and microscope be positioned so that the midline view is perfectly vertical (see **Fig. 55.9a**) and that the cut or crush not deviate from the midline at the depth. We also observed that the usually midline dorsal vein may meander quite extensively off midline (see **Fig. 55.9b**), and the guide to true midline should be determined by the shallow sulcus seen in a position midway between the dorsal root entry zone on each side.

Immediately postoperatively the pain that led to the operation was relieved completely. As expected, the patient's operative-site pain was initially difficult to control, consistent with her chronic opiate usage leading to down-regulated opiate receptors. However, within a few days the patient's narcotic medication could be reduced dramatically, and she soon thereafter regained her appetite and part of her lost weight. She resumed social interactions. About a year later, she developed a fistula between the rectum and bladder and then another fistula between the bladder and peritoneal cavity. To treat these complications of her radiation, a colostomy was required

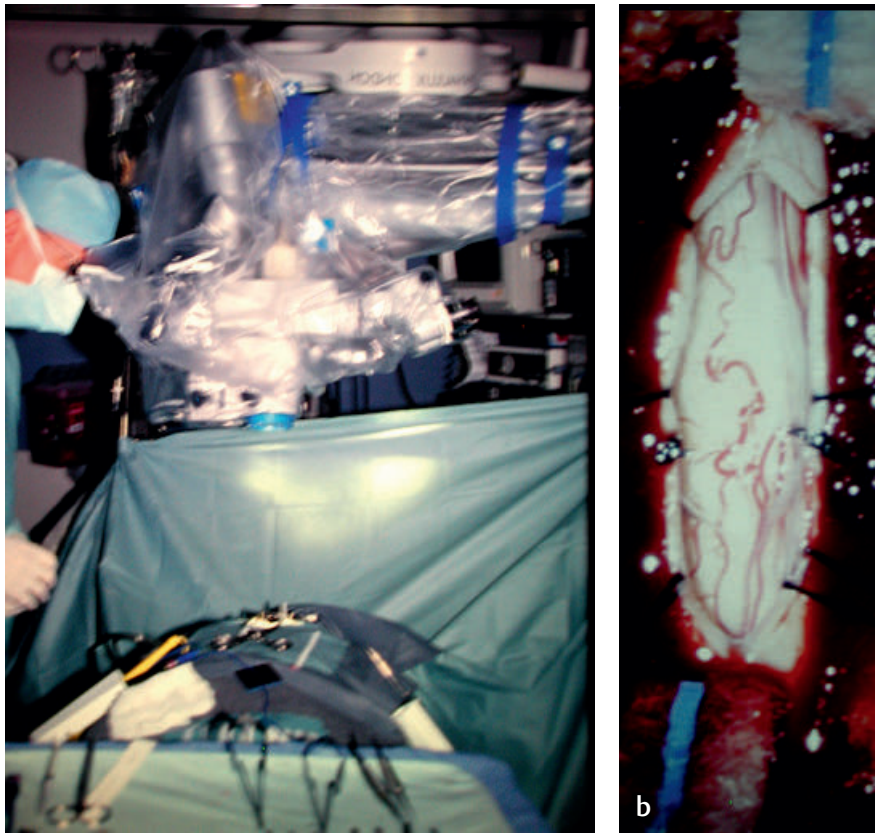

Fig. 55.9 (**a**) The operative alignment of the microscope should be as close to the patient's vertical midline as possible to optimize the narrow vertical lesion along the midline of the dorsal columns. Every effort should be made to lesion only the tissue of the exact midline extending 1 mm to either side. (**b**) An example of a meandering midline dorsal vein, emphasizing that the localization of the midline should be based primarily not on the location of the vein, but on the midline contour of the dorsal columns, measured halfway between the dorsal root entry zone on either side.

as well as later insertion of nephrostomy tubes bilaterally. She had postoperative pain of the abdominal wall at the colostomy site that was managed by an increase in opiate medication. She also later experienced pain in her upper abdomen from peritonitis, but none below the umbilicus. Pain from the nephrostomies and sacral pain that developed later from a decubitus ulcer also could be managed with opiates. She eventually died 31 months after the punctate midline dorsal column myelotomy. During the postsurgical survival period, she never again experienced the severe pelvic pain refractory to high-dose opiates that led to the midline myelotomy.

Following that first case, we reported on PMMs performed on an additional five patients.[42] The procedure was modified by using microforceps for blunt crushing of the juxta-midline dorsal column tissue to 1 mm on each side of the midline to a depth of 5 mm (see **Fig. 55.2b**). The modification was designed to minimize the chances that the procedure would result in bleeding within the spinal cord.

The procedure resulted in a significant reduction in patient ratings of "worst pain" and in daily narcotic use. Postoperative pain from the laminectomy, as well as opiate withdrawal symptoms, were transient and managed with gradual withdrawal of opiates. All but one of the patients became at least temporarily independent of narcotic analgesics before other complications of the underlying disease intervened. There was no evidence of sensory deficits, motor weakness, gait disturbance, or sphincter dysfunction, although one patient had transient bilateral tingling in her toes and transient incomplete bladder emptying. Four of the patients died of tumor progression after survival times of 3 to 9 months. The remaining patient enjoyed 18 months of dramatic relief of pain due to a presacral lesion treated with radiation after biopsy. The tumor then progressed with spread into the sacrum, leading to the recurrence of pain attributable to compression of the sacral plexus and nerve roots within the sacral spinal canal. An aggressive resection of the tumor was then carried out with a combined anterior and posterior approach that included colostomy and resection of the sacrum from S3–S5 and of the coccyx, as well as an epidural dissection of the caudal nerve roots. Three months after the resection, the pain was diminished and narcotic analgesics again could be discontinued.

The results of "punctate midline myelotomy" in our series of six patients indicate that this procedure can result in a significant reduction in visceral pain and in the requirements for narcotic analgesics in

patients with pelvic and abdominal cancer. The benefits are uncertain for components of pain of somatic origin. Placement of the lesion transversely across the midline of the posterior columns l mm to each side would be expected to interrupt axons carrying pain signals from visceral organs that are relayed in the sacral spinal cord.[1,16,22,25] However, we initially expected that more lateral lesions would probably be required to interrupt axons carrying pain signals from visceral organs that have primary afferent fibers that relay in the midthoracic spinal cord.[16,29] Soon after these observations, Kim and Kwon[32] reported relief of pain from stomach cancer by PMM at a high thoracic level. Hwang et al[31] also reported success with PMM at the T3 level to treat intractable visceral cancer pain of hepatobiliary or pancreatic origin.

The visceral pain that led to the midline myelotomy did not recur within the 3- to 31-month survival periods of this series of patients, although pain from other sources did develop in some of the patients. There were no long-lasting sensory, motor, or autonomic changes as a result of the procedure, although one patient had transient sensory changes and urinary retention.

Since the original case was published by Nauta et al,[41] several other series have reported good results with minimal or no deficits with the PMM procedure.[31,32,43–45] In addition, an excellent review article has appeared by Hong and Andrén-Sandberg.[46] The reports of Kim and Kwon[32] and Hwang et al[31] are particularly interesting because they performed the myelotomy at high thoracic levels for the treatment of pain derived from upper abdominal viscera and still were successful despite evidence in rats that axons of the postsynaptic dorsal column pathway for these organs might begin to ascend in a more lateral position in the dorsal columns.[29,30]

Is It Safe to Transect Part of the Dorsal Columns?

The sensory modalities in humans that depend on information ascending in the dorsal columns are said to include discriminative touch, vibration sense, and proprioception.[47–49] The idea of intentionally transecting part of the dorsal columns was, and remains, a strategy accepted only with great caution. This issue needs to be addressed with some emphasis because many clinicians are unlikely to accept an ablative procedure of even a small part of the dorsal columns without considerable reassurance. The evidence comes from both clinical observations in humans and experimental studies in animals that even large incomplete lesions of the dorsal columns do not appear to produce major disabling deficits. Qi et al,[50] from experiments in squirrel monkeys, point out that part of this phenomenon may come from reorganization in the somatosensory cortex, with reactivation based on remaining secondary afferents from other sensory pathways originating in the spinal cord. McKenna and Whishaw[51] report that in the rat, in the absence of dorsal columns, other sensory-motor pathways support a surprising degree of preserved function. Especially pertinent to this, in humans, Cook and Browder[52] performed dorsal column cordotomy at a midthoracic level in five patients and in the upper cervical area in three patients. They concluded that deficits were transient and did not include the expected major loss in proprioception. Noordenobos and Wall[53] also noted a remarkable degree of preservation of diverse sensory functions, including proprioception, in a clinical case of spinal cord transection with complete transection of both posterior columns and preservation of only part of one anterolateral quadrant.

Certainly any neuroablative procedure prompts concern about loss of function, but for small lesions of the dorsal columns, with preservation of other sensory systems, the deficits are not likely to be disabling, if they are detectable at all. This realization permits us to balance the benefits of pain control from a very limited transection of the dorsal columns against drawbacks that include minor demonstrable deficits, if any occur at all. This comes as something of a surprise to the neuroscience community because dorsal column lesions have long been equated with the disabling proprioceptive loss once seen commonly in tabes dorsalis. But that disorder is more properly considered to result from a loss of dorsal root ganglia neurons all up and down the spinal cord bilaterally. Witness the profound loss of deep tendon reflexes seen in tabes dorsalis as evidence of a more widespread sensory loss than would be suggested by the focal dorsal column loss seen in the Weil–Weigert stained histology of the postmortem spinal cord. Because most axons in the dorsal columns are presynaptic, with cell bodies of origin in the dorsal root ganglia, the dorsal columns will show significant axonal loss in the case of advanced tabes dorsalis, whereas the major deficits probably come mostly from other connections of the missing dorsal root ganglion neurons that function also at segmental and propriospinal levels, and trans-synaptically through other ascending pathways such as the spinocerebellar tracts and the anterolateral quadrant system. Further reassuring is the general agreement that, unlike the anterolateral quadrant pathways, there are no major commingled descending motor pathways in the dorsal columns, and effects on respiration and sphincter control are not reported as a problem with dorsal column lesions.

How Historical Midline Myelotomy Operations Suggested the Presence of Pain Pathways in the Dorsal Columns

For unilateral somatic cancer pain, the development of anterolateral cordotomy was a logical choice. The procedures could be performed minimally invasively at the C1–C2 level with fluoroscopic guidance and physiological confirmation, and the clinical results matched the understanding of the anterolateral-quadrant spinothalamic pathway's role in the conduction of pain from the body wall and extremities. However, for midline or visceral abdominal pain, the anterolateral cordotomy was difficult to apply for two reasons. First, bilateral lesions would be required, and these resulted in unacceptable complications stemming from collateral damage to commingled descending pathways in the anterolateral quadrant related to respiration ("Ondine curse") and loss of sphincter control. Second, even when efforts were made to stagger the lesions at different segmental levels, the results of midline or visceral pain control were often disappointing. In retrospect, we can now understand these observations because for visceral pain, the dominant ascending pathway is the post-synaptic dorsal column system (see **Figs. 55.4, 55.6, 55.7**).[1,21,22]

In 1926 the neuropathologist G. Greenfield proposed a solution[3] to the problem of side effects from bilateral anterolateral cordotomies: interruption of the crossing axons of spinothalamic tract neurons on both sides by a longitudinal incision placed along the midline of the spinal cord. This procedure, originally intended to be a commissural myelotomy, was first performed by Armour[3] in 1926 (reported in 1927) and later by many others. The success rate for the relief of cancer pain was relatively good, although reports of side effects limited enthusiasm for the procedure. If one performs the procedure with the goal of commissural myelotomy, then the first obstacle to clinical application is determining the functional segmental levels involved, something that might be difficult to discern from the description of a patient distraught with pain. Next, a multilevel laminectomy would be required and a similarly long sagittal incision made in the spinal cord, something that could easily result in vascular damage to the cord. Even with modern surgical instrumentation and techniques there is still a significant incidence of new postoperative deficit.[54] Although the results for visceral pain relief remain good, and if there is coexisting somatic pain, the commissural myelotomy procedure might still hold some advantages in affecting both anterolateral quadrant somatic and dorsal column visceral pain pathways.

The demonstration by Hirshberg et al[1] that midline myelotomy could be dramatically successful without any damage to the commissures (see **Fig. 55.1**) certainly inspired renewed interest by laboratory researchers receptive to the idea that a pain pathway exists in the dorsal columns.

Seen now in retrospect, many reports by different authors can be reinterpreted in light of the knowledge that there is a pain pathway predominantly carrying visceral pain ascending near the midline of the dorsal columns. Many clinicians have reported successful pain control with operations on the spinal cord that traversed the dorsal midline in order to reach some intended deeper target. They attributed the successful pain control to the destruction of the target at that depth and made every effort to avoid damage to the dorsal columns in reaching this target. They worked with the understanding that the dorsal columns conveyed only "epicritic" sensory modalities and that any damage to them should be minimized to the extent possible. Furthermore, they reasoned that damage to the dorsal columns could not be expected to contribute to pain control because at that time they were not aware of any information about pain pathways ascending in the dorsal columns or their location specifically in the midline area they were traversing. Thus, they failed to appreciate that the even minimal damage they produced to the midline of the dorsal columns was possibly the dominant factor in determining the operation's success. Hitchcock[55] made a percutaneous lesion traversing the posterior midline at the C1 level and produced the intended pain relief in the bilateral upper extremities as well as an unexpected loss of pin prick pain in both lower extremities. He eventually seemed to prefer the explanation that stereotactic myelotomy at C1 interrupted a "central multisynaptic pain pathway" separate from the spinothalamic tract. Schvarcz[56–58] also made lesions at the midline in the C1 segment to treat pain. Stimulation before lesion production caused sensations in the legs or over wider areas of the body and even the face. In addition to paresthesias, stimulation sometimes caused "bilateral burning truncal sensations.[56,57] The lesions were made at a depth of 5 mm below the posterior surface of the spinal cord. Neuropathic pain (causalgia, postherpetic neuralgia, brachial plexus avulsion, and spinal cord lesions) was relieved in 64% of 14 patients who were followed for 0.5 to 4 years. No neurologic side effects of the surgery were seen. In a later report, the results in 79 cases of patients with intractable pelvic cancer pain who underwent the procedure were described. Satisfactory pain relief was obtained in 76% when defined as no pain or infrequent pain relieved by nonnarcotic analgesics. The patients were followed for 0.5 to 30 months, although most died of their malignant disease in the first 6 months.

Clinical Indications for PMM

We now appreciate that punctate or other limited posterior column myelotomies interrupt an ascending pain tract largely subserving visceral pain. There have already been several additional series reported from around the world, but it remains to be seen whether this operation will actually gain wider clinical acceptance and use. The six patients in our original series took over 2 years to acquire. At least in part because of our scientific interests, we limited our indications narrowly to patients with pure or predominantly pelvic visceral pain (as best as we could determine). However, when the visceral pain component is the most troubling to the patient, and its severity appears to be the source of inadequate response to opiates, it makes sense to treat the patient with midline myelotomy even if other somatic pain components are present because these likely could be managed by conventional medical means postoperatively. Such patients might remain dependent on opiates because of their residual somatic pain and might therefore be classified as treatment failures of midline myelotomy, but their overall status would likely be improved. By this reasoning, the indications for midline myelotomy might legitimately be broader than those used in our originally focused study. Hwang[31] and Kim and Kwon[32] have also demonstrated that it may be reasonable to broaden the indications for PMM to include patients with cancer pain from upper abdominal organs, including those of gastric, hepatobiliary, and pancreatic origin.

Patients suffering from cancer typically have already had surgery of one sort or another before being considered for myelotomy, and they typically are reluctant to undergo further open surgery for pain if there is any reasonable alternative. To address this limitation, there is room for future refinements of the posterior column myelotomy procedure, and following Hitchcock's[55] and Schvarcz's[56–58] examples, a percutaneous method at the C1 level may be reasonable, especially now that advances in medical imaging are finding more widespread use in guiding therapeutic interventions. Toward this goal, Vilela Filho et al[44] have already described successful application of a computed tomography (CT)-guided percutaneous technique for PMM in two patients. Also, CT-guided percutaneous techniques for extralemniscal myelotomy, as described by Kanpolat,[59] may have direct applicability with only minor modification to PMM. A percutaneous method at a thoracic level, however, may be problematic because at thoracic levels the interlaminar space is typically small (making needle entry difficult), whereas the septum posticum of the arachnoid and its associated midline dorsal vein is typically well developed,[60] tending to divert a needle off the targeted midline. Regardless of the rostrocaudal level, there may be a hazard of subarachnoid hemorrhage with the percutaneous techniques using a 16-gauge needle as originally described,[41,42] and it may be appropriate to transition to a fine-tip probe with less chance of vascular injury. However, even if a convenient percutaneous method for PMM could be developed, the bias against surgical ablative interventions for pain may persist. For example, percutaneous C1–C2 anterolateral cordotomy is not commonly performed today, although the technique has been well worked out for decades, it is minimally invasive, and the scientific rationale seems well established. The oral or transdermal medical alternatives or opiate infusion remains more attractive for many patients who are well controlled and who do not envision a long survival with the serious side effects of chronic opiates. For these reasons, it remains likely that the PMM procedure will find its use limited to exceptional circumstances, such as a patient with predominantly visceral pain refractory to opiate management, who is otherwise in good enough medical condition, and who has good enough tumor control that the side effects of chronic high-dose opiate therapy are anticipated to be a serious long-term problem—including drowsiness, which frustrates the enjoyment of any remission.

In some settings, the advantages of PMM over high-dose medication may also include cost concerns and independence from medical attention required with long-term high-dose oral, transdermal, or neuraxis infusion for opiate therapy.

Conclusion

There appears to be a clinically significant pain pathway that ascends in the dorsal columns. The pathway appears to subserve mostly visceral pain with a relatively minor role in somatic pain. Punctate midline myelotomy (PMM) interrupts components of this pathway related to the pelvis and lower abdomen and has also been modified successfully to treat visceral pain derived from upper abdominal viscera. PMM can be useful for reducing otherwise intractable visceral pain due to cancers of the pelvis and abdomen in cases where these are not relieved by opiate analgesic drugs or where prolonged opiate therapy with major side effects is anticipated. The relief from posterior column "punctate" midline myelotomy has been observed to last for periods of up to 31 months after surgery without sensory, motor, or autonomic complications, and with no proprioceptive dysfunction. A growing appreciation of the anatomy, physiology, pharmacology, and results of clinical manipulations of the dorsal column visceral pain pathway may continue to contribute to better methods for pain control. It may also be possible to adapt PMM to CT or other image-guided percutaneous methods that would increase its applicability and attractiveness in more clinical settings.

Editor's Comments

Dr. Nauta and his colleagues have developed a procedure based on a new anatomical substrate, the postsynaptic dorsal column pain pathway. In many ways, this represents a model of how new surgical procedures should be developed. The clues to its potential efficacy came from the analysis of the results of more historic procedures, such as midline myelotomy and midline C1 lesions. The implications of these older results were then taken as impetus to unravel the neuroanatomy of the dorsal columns, resulting in the discovery of a previously unrecognized tract in the medial ventral dorsal column. From this discovery, a procedure was developed to disrupt this tract in patients with pelvic visceral pain. In this case, the "bench" informed the "bedside"—a surgical approach based on solid basic research. Would that all surgical procedures had this pedigree!

The potential generalizability of their results will depend on data from other practitioners taking notice of this, and similar, procedures and publishing results. This will also require a change on the part of oncologists, who have proven very difficult to convince that surgery for pain secondary to malignancy is *ever* indicated. Clearly, as Nauta and colleagues point out, minimally invasive adaptations of the punctate myelotomy must be developed, if this procedure is to become more than a footnote in the surgical management of pain. It is my hope that reiteration of their approach in this book will both perpetuate these insights and promote the appropriate expansion of this procedure for the benefit of patients with intractable pain.

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56 Dorsal Root Entry Zone Lesions

Marc Sindou

In the 1960s the "gate control" theory drew the attention of neurosurgeons to the dorsal horn as the first important level of pain modulation. This theory also suggested that it could be a target for pain surgery.[1] It gave rise to a popular method of electrostimulation of the primary afferents to the spinal cord, the spinal cord stimulation (SCS),[2] and also to destructive surgery in the dorsal root entry zone (DREZ) for very selected cases.[3]

The DREZ region was defined as an entity including the central portion of the dorsal rootlet, the medial part of the tract of Lissauer (TL), and layers I to V of the dorsal horn (DH), where the afferent fibers terminate and synapse[3,4] (**Fig. 56.1**).

The first attempts of DREZ lesioning, using microsurgical coagulations, were performed at the University Neurological Hospital in Lyon, France, first for pain due to thoracic apex tumors (March 1972), then for neuropathic pain after spinal cord injury (December 1972), postamputation pain (July 1973), and brachial plexus avulsion pain (January 1974). Soon after, in September 1974, Blaine Nashold at Duke University, Durham, NC, started to develop DREZ lesioning using radiofrequency (RF) thermocoagulation,[5,6] especially for pain related to brachial plexus avulsion. Other lesion makers were also used: the laser by Levy et al[7] and Powers et al,[8] and the ultrasound probe by Kandel et al[9] and Dreval,[10] again for pain caused by plexus brachial avulsion. More recently, based on the greater softness of the dorsal horn bordered by the tougher columns of the white matter tracts, Spaic et al proposed the aspiration of the gray matter over several metameres of the spinal cord through a single-level laminectomy.[11,12]

Indications

The main indications for DREZ surgery correspond to clear-cut etiologies and mechanisms. Pain after brachial plexus avulsion is the most appropriate indication because it is predominantly linked with a deafferentation mechanism, and the same applies for pain after lumbar–sacral plexus injury. A similarly appropriate indication is pain after spinal cord injury, especially the one located at the conus medullaris/cauda equina, when pain is predominantly "segmental," that is, corresponding to the segments injured. Pain after peripheral nerve lesions, amputation, or herpes zoster may be considered only if the predominant components of pain are of the paroxysmal and/or allodynic types, and only if spinal cord stimulation tried as the first option has failed. The same applies for complex regional pain syndrome (CRPS). Pain related to a malignancy may also be an indication, but only if of limited extent and in patients with a life expectancy measured in years. Separately, pain linked to intense spasticity in severely disabled patients can also be considered for DREZ surgery.

Principles of Microsurgical DREZotomy

My preference is to perform DREZ surgery using the microsurgical techniques, since lesioning can be done relatively safely under direct vision after opening the dorsolateral sulcus.

Working with DREZ requires knowledge of the microsurgical anatomy of the spinal roots and cord,[13,14] as well as of the internal morphology of the cord, to avoid damaging neighboring anatomical structures (**Fig. 56.2**).

Microsurgical DREZotomy (MDT) consists of a longitudinal opening of the dorsolateral sulcus performed ventrolaterally at the entrance of the rootlets into the sulcus, then of continuous microbipolar coagulations inside the sulcus down to the dorsal horn, along all the selected spinal cord segments to be lesioned. The lesion penetrates the lateral part of the DREZ and the medial part of the tract of Lissauer, and extends to the dorsal horn, which can be recognized

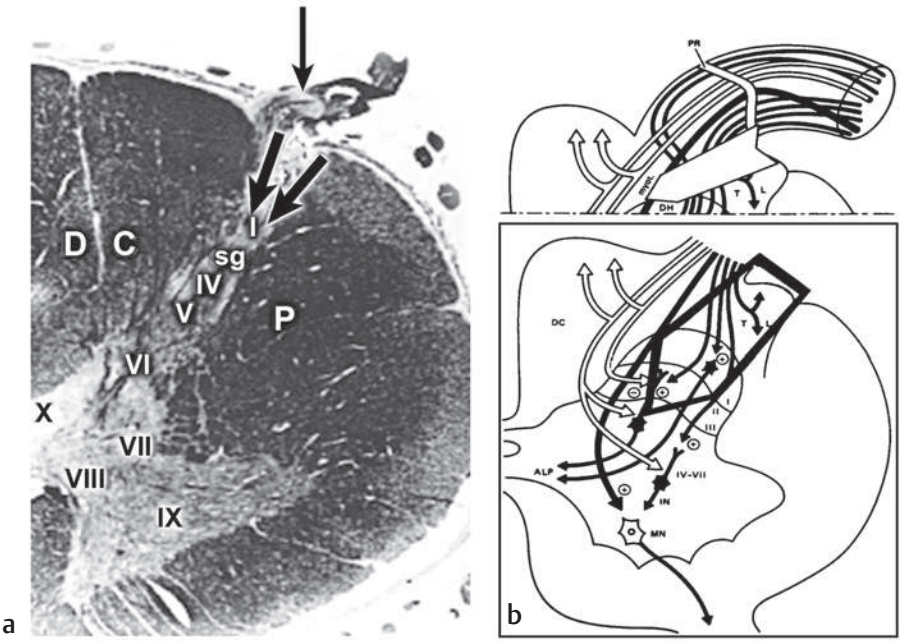

Fig. 56.1 Anatomical organization of the dorsal root entry zone (DREZ). As shown in the upper right diagram, each rootlet is divided owing to the transition of its glial support into a peripheral and a central segment. The transitional zone between the two segments is at the pial ring (PR). (**a**) Transverse hemisection of the spinal cord (at lower cervical level) with myelin stained by luxol-fushine, showing dorsal horn (DH) Rexed lamination (I–VI). *Thinner arrow* designates the transitional zone. (**b**) Organization of fibers (*arrowheads*). The microsurgical DREZotomy (MDT) target includes the lateral bundle of the fine (nociceptive) fibers, the medial (excitatory) part of the tract of Lissauer (TL), the five dorsal-most layers of the DH where the primary afferents terminate and whose neurons become hyperactive if deafferented. MDT attempts to spare the maximum of the large (likely inhibitory) fibers of the medial bundle that reach the dorsal column (DC). P, pyramidal tract; sg, substantia gelatinosa.

Fig. 56.1 Considerations

Each dorsal root divides into 4 to 10 rootlets according to metameres.[13,14] Each rootlet, of 0.25 to 1.50 mm in diameter according to levels, can be considered an anatomical–functional entity, that is a root in miniature.[3,4] Each rootlet is divided owing to the transition of its glial support into a peripheral and a central segment. The transitional zone between the two segments is at the pial ring (PR), which is located approximately 1 mm outside the penetration of the rootlet into the dorsolateral sulcus. Peripherally, the fibers are mixed together. As they approach the PR, the fine fibers (considered nociceptive) move toward the rootlet surfaces. In the central segment, there is a spatial segregation of the afferent fibers according to their size and destination, with the fine fibers regrouping in the lateral region of the DREZ (dorsal root entry zone) to enter the dorsal horn (DH) through the tract of Lissauer (TL), and the large fibers in its medial region to reach the dorsal column (DC). The large myotatic fibers (myot.) are situated in the middle of the DREZ to project onto the motoneurons (MN) in the ventral horn. The DH is segmented according to Rexed lamination (I–VI). The TL is situated dorsolaterally to the DH apex, and includes two parts. (1) Its medial part—which the small afferents enter and where they trifurcate to reach the DH, either directly or through a few metameres ascending or descending pathway—transmits the excitatory effects of each dorsal root to the adjacent metameres.[52,53] (2) Its lateral part—through which a large number of longitudinal endogenous propriospinal fibers interconnect different levels of the substantia gelatinosa (sg)—conveys the inhibitory influences of the sg to the neighboring metameres.[53] Most of the fine nociceptive afferents, which convey excitatory input, enter the DH through the TL medial part and the dorsal aspect of the sg. The Ramon y Cajal's recurrent collaterals of the large primary afferent fibers[54] approach the DH through the ventromedial aspect of the sg to exert inhibitory effects on the DH neurons.[55] Because a number of dendrites of the cells of origin of the spino-reticulo-thalamic tract, that will form the contralateral anterolateral pathways (ALP), make synaptic connections with the primary afferents inside the sg layers, the sg exerts a strong segmental modulating effect on the nociceptive input.[56]

by its pink-brown-gray color. Lesions are 2 to 3 mm deep, oriented medially and ventrally in the axis of the gray matter (**Fig. 56.3**).

The procedure is intended to preferentially interrupt the (nociceptive) fibers grouped in the lateral bundle of the dorsal rootlet and the (excitatory) medial part of the tract of Lissauer. The dorsal-most layers of the dorsal horn, which harbor hyperactive neurons in the cases with deafferentation[15–18] (**Fig. 56.4**), are destroyed if microcoagulations are performed deep inside the dorsal horn. The procedure is presumed to partially preserve the (inhibitory) medially located structures of the DREZ, namely the fibers reaching the dorsal column and their recurrent collaterals to the

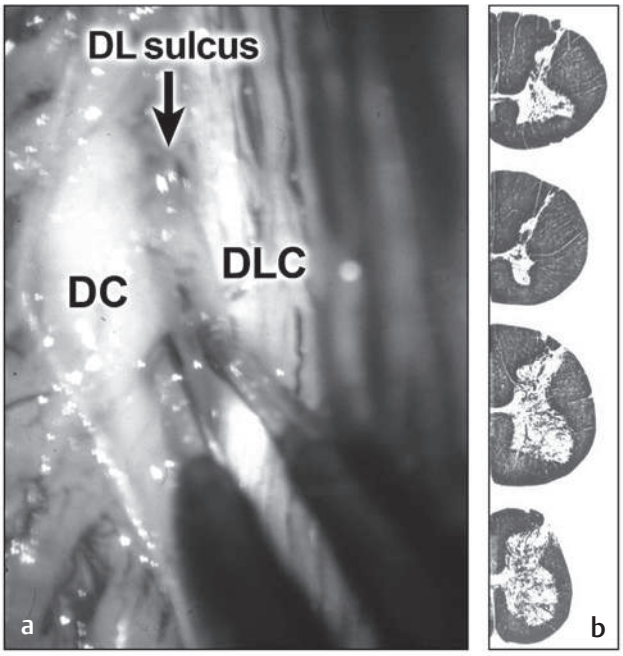

Fig. 56.2 (**a**) Microsurgical operative view of the dorsal horn (DH) after opening of the dorsolateral sulcus. Note the gelatinous aspect of the DH gray matter, in between the dorsal column (DC) and the dorsolateral column (DLC) white tracts. (**b**) Variations of shape, width, and depth of the DREZ (dorsal root entry zone) area according to spinal cord level (from top to bottom: cervical [7], thoracic [5], lumbar [4], sacral [3]). Note how at the thoracic level the Lissauer tract is narrow and the dorsal horn deep, so that DREZ lesioning, especially at that level, can be dangerous for the corticospinal tract and the dorsal column.

dorsal horn. MDT was conceived to avoid total abolition of tactile and proprioceptive sensations when preoperatively present, as well as further deafferentation.[19] The depth and extent of the lesion are tailored depending on the degree of the desired therapeutic effects and on the patient's preoperative sensory and functional status.

Pain after Brachial Plexus Injuries

The incidence of pain after brachial plexus injury is reported at less than 30% for postganglionic location of the neural disruption, as opposed to 90% when the location is preganglionic.[20,21] Pain is so intense that patients almost constantly resort to opioid consumption, frequently attempt suicide or commit self-mutilations to call caregivers' attention to their dramatic situation. From study of the effects of DREZ lesioning on an animal model of cervical plexus avulsion, we observed that after deafferentation rats performed self-directed mutilations of the autotomy type in the forelimb, and that this behavior was reversed in the group that benefited from microsurgical DREZotomy, which was not the case for those in the sham control group ($p = 0.01$).[22]

A valuable preoperative appraisal of the radicular lesions can be achieved with high-resolution T2 spinal magnetic resonance imaging (MRI), electro-

Fig. 56.3 Considerations for MDT at the Cervical Level

The prone position with the head and neck flexed in the « Concorde » position with three-pin head holder has the advantage of avoiding brain collapse caused by cerebrospinal fluid depletion. The level of laminectomy is determined after identification of the prominent spinous process of C2 by palpation. For unilateral DREZ-operation, a hemilaminectomy with preservation of the spinous processes is sufficient to access the posterolateral aspect of the spinal cord. Laminectomy from C3–C7 included, allows exposure of the rootlets of C5–T1. After opening the dura and arachnoid, the exposed roots are dissected free by separating the tiny arachnoid filaments that bind them to each other to the arachnoid sheath and to the cord pia. Identification of roots can be verified by electrical stimulation at their corresponding foramen, and their functional value checked. Stimulated ventral roots have a motor threshold at least 3 times lower than the dorsal roots. Responses are in the diaphragm for C4 (the response is palpable below the lower ribs), in the shoulder abductors for C5, in the elbow flexors for C6, in the elbow and wrist extensors for C7, and in the muscles intrinsic of the hand for C8 and T1. Microsurgical lesioning is performed at the selected levels according to the preoperative program. The dorsal rootlets are displaced dorsally and medially with a hook or a microsucker to access the ventrolateral aspect of the dorsolateral. Then, an incision 2 mm in depth at 35 degree angle is made with a microknife, currently an ophtalmologic microscalpel, at the ventrolateral border of the DL sulcus. Then microcoagulations are made in a *chain*, that is, dotted manner, down into the dorsal horn. Each microcoagulation is performed—under direct magnified vision—by short-duration (a few seconds), low-intensity, bipolar electrocoagulation, with a specially designed graduated sharp bipolar forceps incremented in millimeters (graduated bipolar forceps ref: 12-30179, DREZotomy Set, Stryker Leibinger GmbH & Co.KG). The depth and extent of the lesion depend on the desired therapeutic effect and the preoperative functional status of the limb (3 mm in depth). If the laxity of the root is sufficient, the incision is performed—continously—in the dorsolateral sulcus, thus accomplishing a sulco-myelotomy. If not, successive incisions are made ventrolaterally at entry of each of the rootlets of the root after the surgeon has isolated each one by separating the tiny arachnoid membranes that hold them together.

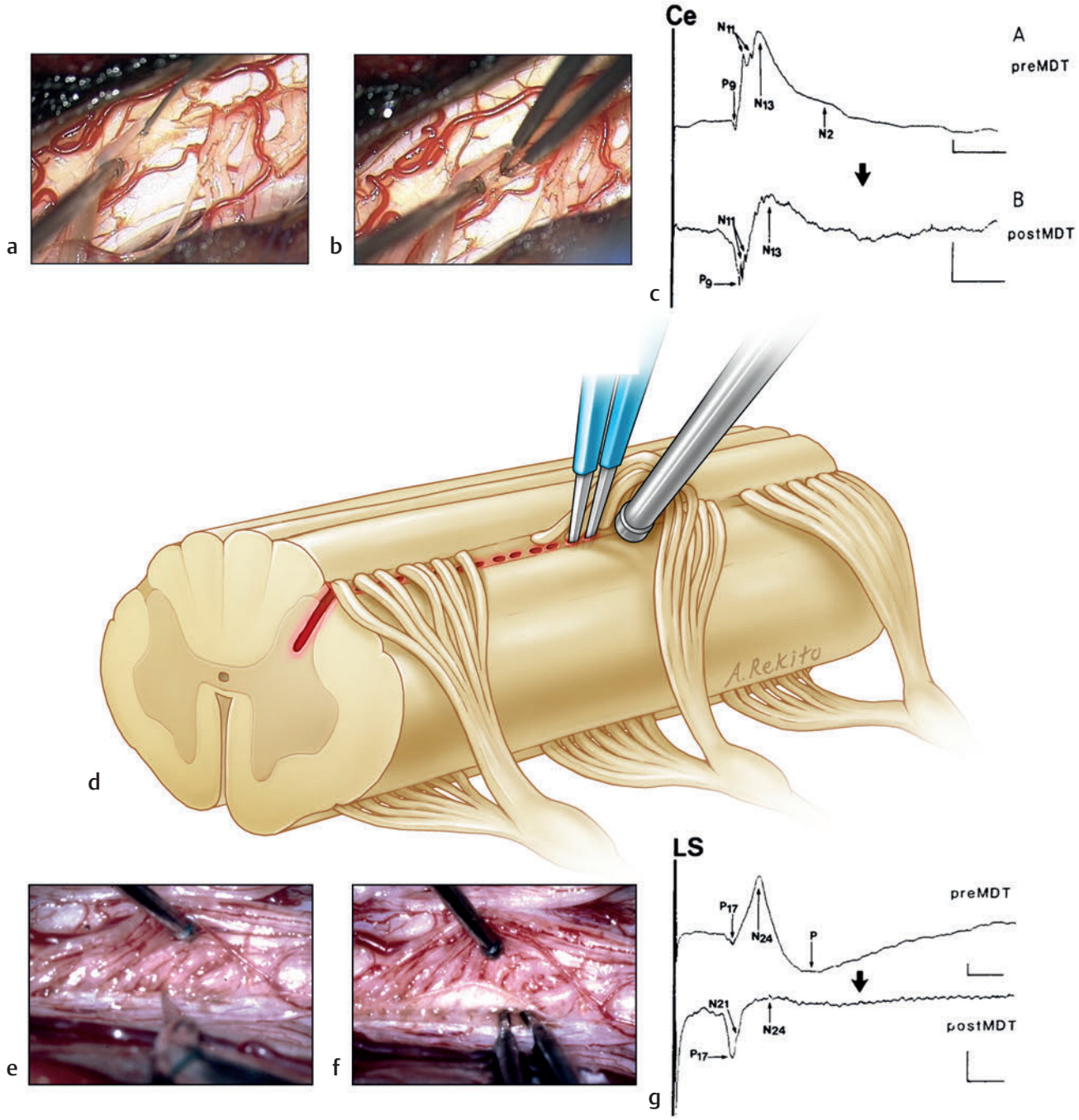

Fig. 56.3 Technical principles of microsurgical DREZotomy (MDT). (**a–c**) Operative procedure at the cervical (Ce) level, when roots are intact (**a, b**: microsurgical operative views at C7 level on right side through right hemilaminectomy). (**a**) Exposure for incision in dorsolateral (DL) sulcus. (**b**) Microcoagulations inside DL sulcus. (**d**) Drawing of MDT at cervical level. (**e–g**) Operative procedure at the lumbosacral (LS) level, when spinal cord and roots are intact (**e, f**: microsurgical operative views at L5–S1 segments on left side). Exposure of conus medullaris through a T11–L1 laminectomy and approach of the dorsolateral sulcus, on the left side in this example, by displacing the dorsal rootlets dorsally and medially. (**e**) The rootlets are held with a specially designed ball-tip microsucker used as a hook to access the ventrolateral part of the DREZ and make incision with a micro knife. (**f**) Lesioning is performed by doing microcoagulations under direct magnified vision +++. (**c, g**) Effects of MDT on the evoked electrospinogram (EESG) recorded from the surface of the dorsal column medially to the DREZ at the C7 cervical (Ce) and the L5 lumbosacral (LS) segments, ipsilateral to the stimulation of the median and the tibial nerve, respectively, before (pre-MDT) and after (post-MDT) MDT.[57] The initial positive event P9 (for cervical), P17 (for lumbosacral) corresponds to the nearfield presynaptic successive axonal events, generated in the proximal portion of the dorsal root, the dorsal funiculus, and the large-diameter afferent collaterals to the dorsal horn. After MDT, all these presynaptic potentials remain unchanged. The larger, slow negative wave N13 (N24) corresponds to the postsynaptic activation of the dorsal horn by groups I and II peripheral afferent fibers of the median (tibial) nerves. They are diminished after MDT, in the order of two thirds. The later negative slow wave N2 (just visible in the cervical recording) corresponds to postsynaptic dorsal horn activity consecutive to the activation of group II and III afferent fibers. N2 is suppressed after MDT.

Fig. 56.3 Considerations for MDT at the Lumbosacral Level

The patient is positioned prone on thoracic and iliac supports and the head placed 20 cm lower than the level of the surgical wound to minimize CSF loss. Vertebral levels are identified with lateral X-ray from the S1 vertebra. To access the conus medullaris, a laminectomy is performed from T11 to L1 (or L2). After opening the dura and arachnoid longitudinally, the filum terminale is isolated. Identification of roots can be checked by electrical stimulation. The L1 and L2 roots are easily identified at their penetration into their respective dural sheaths. Electrical stimulation of L2 produces a response of iliopsoas and adductor muscles. Identification of L3–L5 is difficult for several reasons: (1) their exit through their respective dural sheaths is caudal to the exposure; (2) their dorsal rootlets enter the sulcus in an uninterrupted way; (3) their ventral roots are hidden in front of the dentate ligament. Stimulation of L3 produces a preferential response in the adductors and quadriceps, of L4 in the quadriceps, and of L5 in the anterior tibialis and gluteal muscles. Stimulation of the S1 dorsal root produces a motor response in the gastrocnemius-soleus group. Stimulation of the S2–S4 dorsal roots (or better, directly, the corresponding spinal cord segments at the DREZ) can be assessed by recording the bladder or more easily the anal responses by use of electromyography of the anal sphincter (or simply with a gloved finger into the rectum). Because intraoperative neurophysiologic investigations are time-consuming, we found that measurements at the conus medullaris can be sufficient in the patients who already have severe preoperative impairment of the versicoanal functions. These measurements, based on human postmortem anatomic studies, showed that the landmark between the S1 and S2 segments is situated approximately 30 mm above the exit from the conus of the tiny cocygeal root.[3,13,14]

MDT at the lumbosacral level has the same principles as the ones at the cervical level. But at the lumbosacral level, MDT is difficult and potentially dangerous because of the rich vasculature of the conus. The dorsolateral spinal artery courses ventrally along the dorsolateral sulcus. Its diameter is 0.1 to 0.5 mm; it is fed by the posterior radicular arteries and joins caudally with the descending anterior branch of the Adamkiewicz artery through the conus medullaris anastomotic loop of Lazorthes. This artery should be preserved by being freed from the sulcus. The conus medullaris is approached through a T11–L1 laminectomy and sulcus by displacing the dorsal rootlets dorsally and medially. The rootlets are held with a specially designed ball-tip microsucker used as a hook to access the ventrolateral part of the DREZ. The main arteries running along the dorsolateral sulcus are preserved. A continuous incision is performed with a microknife. The cut is at a 45 degree angle and to a depth of 3 mm. Then, lesioning is performed by doing microcoagulations under direct magnified vision at a low intensity, in the sulcomyelotomy, down to the dorsal horn. These microcoagulations are made all along the segments of the cord selected to be operated on by means of the special sharp bipolar forceps, gradauted every millimeter over 6 mm.

neuromyography (EMG), somatosensory-evoked potentials (SSEPs), and motor-evoked potentials (MEPs) investigations. Pseudomeningoceles on MRI are classically considered to be indirect signs of root avulsion. In our series pseudomeningoceles were present in 31% of the patients, and almost always corresponded to total or partial avulsion of the contained roots. However, surprisingly, 50% of the partially or even totally avulsed roots were not associated with any observable pseudomeningocele; the risk of underestimating avulsed roots on imaging only should be taken into account before making a surgical decision.[23] For those patients who benefited from surgical repair after injury, the lesions described in the operative record are of major help in defining the plexus anatomical pathology.

Anatomical Findings at Surgery

Our patients referred for pain surgery all had severe radicular lesions, at least two markedly affected root levels. Altogether, 78% of the total brachial dorsal roots were impaired, 79% of which were totally avulsed and 21% either partially avulsed or atrophic. The extent of the sensory deficit corresponded to the dorsal root lesions at the intradural level in only half of the patients, indicating coexisting extrarachidian lesions, well explained by the intense stretching of the entire plexus.[23]

Additional abnormalities of the spinal cord were found in 49% of our patients.[23] They consisted of marked deviation/distorsion of the cord fixed by strong adhesive arachnoiditis, a more or less nota-

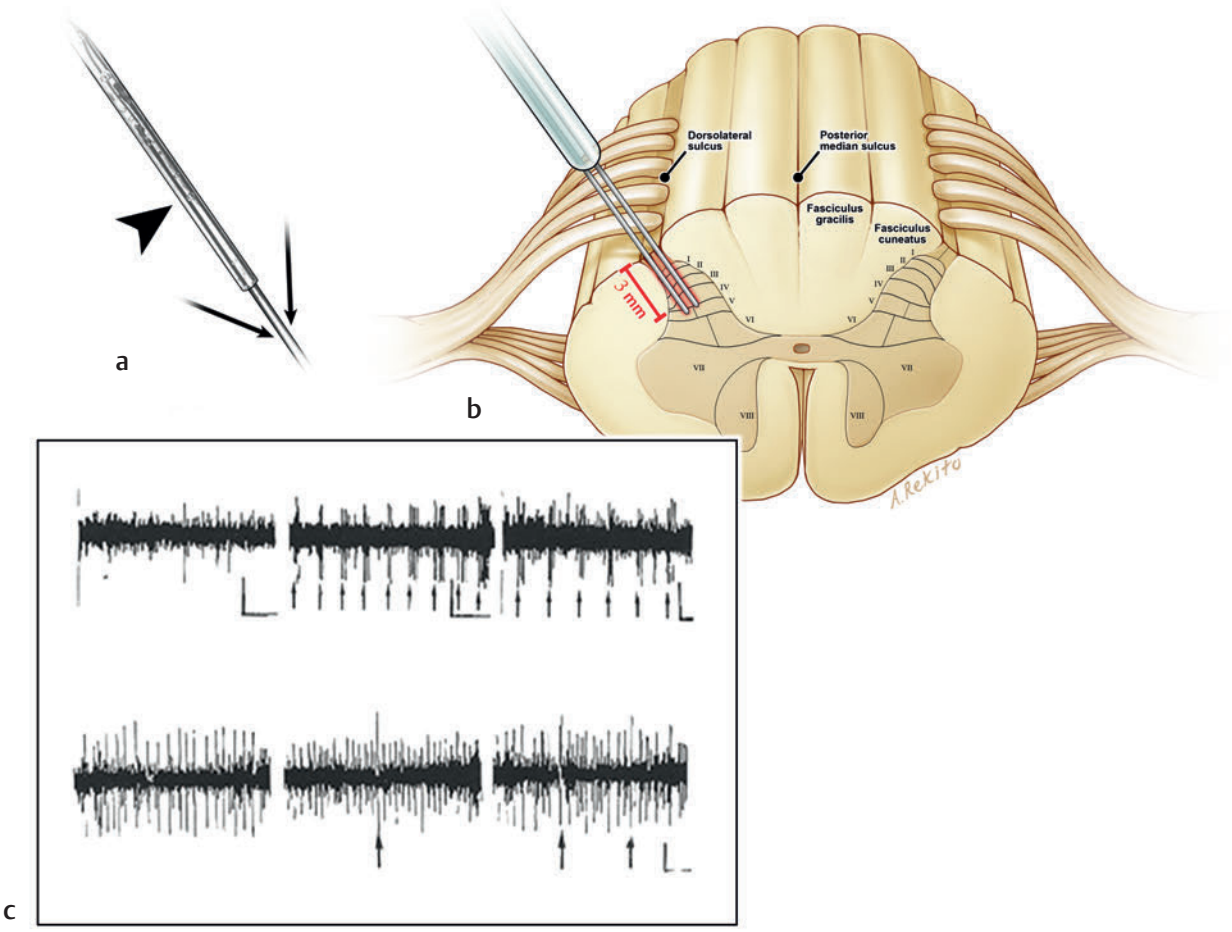

Fig. 56.4 Microelectrode recordings of deafferentation hyperactivity. (**a**) Photograph showing the floating dual, tungsten-in-glass, microelectrode of the Ainsworth-Guenot type designed to obtain unitary recordings in the human dorsal horn. The two independant tips are separated by a distance of 300 µm, allowing for distinguishing spikes (recorded on one tip) from artefacts (recorded simultaneously on the two tips).[17] The protective silicon sleeve (*arrowhead*) is 5 mm away from the tips, allowing them to reach the deeper part of the dorsal horn. (**b**) Schematic drawing of the microelectrode implanted into the dorsal horn following its axis. (**c**)Traces of dorsal horn microelectrode recordings in humans. *Upper trace:* normal activity. Recordings in a nondeafferented dorsal horn at the lumbosacral level (in a spastic patient). *Left:* almost no spontaneous activity (three spikes at random). *Middle:* spike discharges evoked by regular light tactile stimulation in the corresponding dermatome. *Right:* spike discharges evoked by electrical stimulation of the corresponding peripheral nerve. *Lower trace:* deafferentation hyperactivity manifested by continuous regular discharges that remain unaltered.[16] Recordings in the L5 cord segment of a patient with pain due to traumatic section of the hemicauda equina from root L4–S4. *Left:* spontaneous activity of the recorded unit: continuous, regular, high frequency discharge. This activity is not influenced by tactile stimulation of the L4–S1 dermatomas (*middle arrow*), nor by electrical stimulation of the tibial nerve. The vertical bars are 50 µV; the horizontal bars are 100 ms. These spontaneous hyperactivities, as well as the ones observed in patients after brachial plexus avulsion (*not shown*),[16,18] are thought to be at the origin of so-called deafferentation pain, with its neurochemical substrate.[58] Such abnormalities can be reproduced in animal experiments;[22,59,60] the clinical and electrophysiological expression of this experimental deafferentation pain can be suppressed by DREZ lesioning.[16–18,22]

ble degree of cord atrophy on the side of the avulsion, which makes identification of the dorsolateral sulcus difficult. Therefore, freeing the spinal cord and roots prior to performing DREZ lesioning is of prime importance. Furthermore, it contributes to relief of the components of pain induced by the neck movements. Under high magnification of the surgical microscope, focal gliosis and microcysts can be found inside the dorsal horn. Such abnormalities, observed in 36.4% of our patients, were reported to be similarly important by others.[10] Formation of scar and gliotic tissue at the avulsed root segments is assumed to play a role in the genesis of pain, likely by facilitating hyperactivity in the local DH neurons.

Surgical Procedure

DREZ lesioning should not be limited to the avulsed segments but extended to the remaining roots corresponding to the painful territory especially if found to be atrophic or of a grayish color (**Fig. 56.5**).[23]

Under general anesthesia with tracheal intubation and short-lasting curarization, the patient is placed in the prone position, the neck flexed in the so-called Concorde position with the head maintained in a three-pin holder. This position has the advantage of avoiding brain collapse caused by cerebrospinal fluid (CSF) depletion. Through a median cutaneous aponeurotic posterior incision and unilateral paravertebral muscle division a hemilaminectomy, with preservation of the spinous processes but with ronging of their base to have enough working space, is performed ipsilaterally to the avulsion. For unilateral DREZ surgery hemilaminectomy is sufficient and lowers the risk of painful kyphotic deformity of the neck. For a total plexus avulsion, including C5–T1 roots, the hemilaminectomy is performed from C3–C7. The dura mater and arachnoid membrane are longitudinally opened. Opening is often difficult because of strong fibrotic adhesions to the cord. Pseudomeningoceles with fragile membranes are frequently found at the level of the avulsed roots.

Under the surgical microscope, the aspect (normal, grayish and atrophic, partially or totally avulsed) of all roots—both ventral and dorsal—is carefully noted. The functional status of the remaining roots can be checked by observing the muscular responses of the limb to direct electrical stimulation at 1 mA (Icare NIMBUS stimulator, Newmedic/Hemodia, Toulouse, France). Important for level identification, stimulation of the C4 ventral root causes a response in the diaphragm, palpable at the abdomen. If the dorsolateral sulcus is not clearly visible, identification should start from the intact remaining rootlets above and below the avulsed segments. The presence of tiny perforating capillaries entering the sulcus helps to determine its location. Yellow areas corresponding to old hemorrhages on the cord surface, and microcavities and gliotic tissue within the dorsal horn provide guidance for tracing the dorsolateral sulcotomy. Intraoperative monitoring of the dorsal column SSEPs and the pyramidal tract can be helpful,[23] at least until one has reached a good level on the learning curve.

As shown in **Fig. 56.5**, the first step of the procedure is dorsolateral sulcus opening. An incision is made with a microknife, of the ophthalmologic type, in the axis of the DH, 2 mm in depth and oriented 35 degrees medially and ventrally. Under magnified vision and with a sharp graduated bipolar forceps (model 12-30179, DREZotomy set, Stryker Leibinger GmbH, Freiburg, Germany, and Kalamazoo, Michigan, USA), dotted microcoagulations are performed every millimeter inside the DH, 3 mm in depth from the surface of the cord. Each coagulation is performed under direct vision, approximatively for 2 seconds, at low intensity of the bipolar generator. Special care is taken to locate these microcoagulations inside the limits of the dorsal horn, between the cuneate fasciculus of the dorsal column medially and the corticospinal tract laterally, to avoid impairing the sensory and motor pathways, respectively.

The same surgical principles apply for the less frequently encountered lumbar–sacral root avulsions at the conus medullaris.

Outcome

Good long-term outcome (i.e., pain relief of more than 75%) was obtained in 42.7 to 85% of the patients according to the literature review (**Table 56.1**). From our Kaplan–Meier (KM) analysis at 8 years of follow-up, a good outcome allowing withdrawal of the opioids was achieved in 85.9% of our 84 patients, of whom three fourths had a complete cure—that is, no pain and no medication.[23]

Using microsurgical coagulation, RF thermal or ultrasound probes for making lesions obtained similarly good results, whereas a laser beam showed poor efficacy, likely because its lesion does not reach the deeper DH layers.

Failures and recurrences were not found to be statistically correlated with the time elapsed between injury and onset of pain or, surprisingly enough, with the duration of pain prior to surgery.[23,24]

DREZ lesioning produced a more pronounced and complete effect on the paroxysmal than on the continuous pain component (63 vs. 26%, $p = 0.01$) in the series of Ali et al,[25] as well as in our study with KM analysis at 10 years of follow-up (76.2 vs. 43.1%, $p = 0.03$).[26] We think, nevertheless, that the presence of a continuous background of pain must not be considered a contraindication for DREZ surgery.

Pain after Spinal Cord/ Cauda Equina Lesions

Chronic pain after spine injuries can be related not only to persisting compression or bony instability, but also to spinal cord/root nerve lesions that may generate so-called neuropathic pain, the incidence of which varies overall from 10 to 25%, according to a literature review,[27] and reaches 35% for the conus medullaris/cauda equina location. Classification of the pains as segmental and infralesional (that is, below the lesion) is of practical importance. As a matter of fact, regarding segmental pain, which is the type that resides in the territories

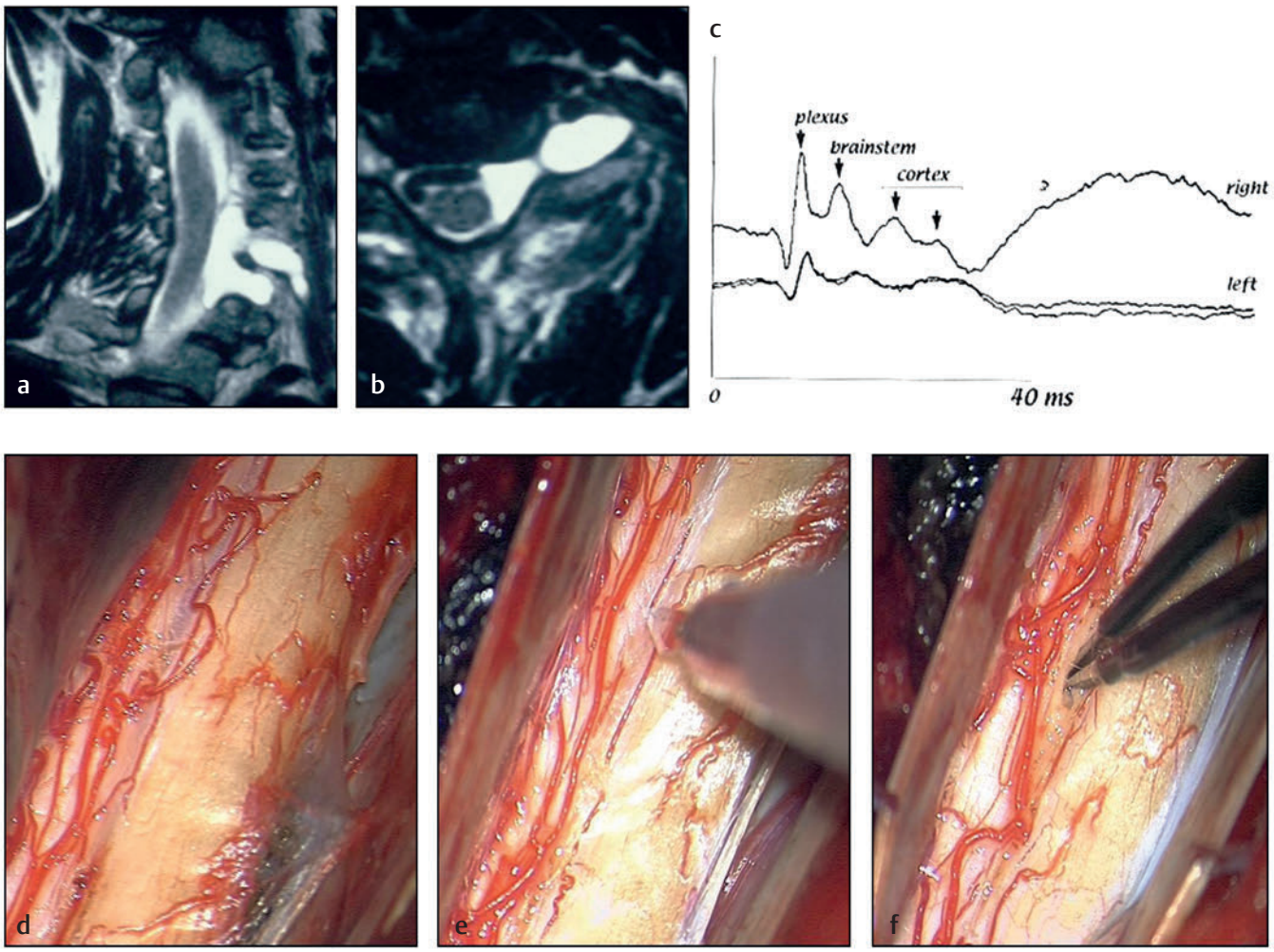

Fig. 56.5 Microsurgical DREZotomy (MDT) for brachial plexus avulsion. MDT at the cervical level for C6–T1 brachial plexus avulsion on left side. (**a, b**) T2-weighted MRI (magnetic resonance imaging) shows pseudomeningoceles at the lower cervical spine on left side. (**c**) Somatosensory-evoked potentials (SSEPs) after median nerve stimulation are abolished from cervical spinal cord up to cortex on left side, compared to right side. (**d–f**) Operative views show total avulsion from C6–T1 on the left side. (**d**) Dorsolateral sulcus (DLS) can be easily identified. (**e**) Incision into the DLS is made with a microknife. (**f**) Dotted microcoagulations into the dorsal horn, which has a gliotic aspect, are performed 3 mm inside the sulcus with the graduated bipolar microforceps.

corresponding to the injury and altered neighboring segments, mechanisms may result from nerve root contusion, entrapment, or scarring, and also from the development of central dysfunction due to deafferentation or direct damage to the spinal cord neurons. These disturbances, likely due to release of the neurons from their normal inhibitory impulses or to an increase in their intrinsic excitability, lead to abnormal spontaneous patterns of discharge in the dorsal horn.[28] Such hyperactivities could be recorded during surgery in patients with deafferented segments of the spinal cord.[15–18] A related hypothesis, based on the fact that cordectomy improves pain only if performed rostral to the level of the lesion,[29,30] suggests that the origin of pain comes from the spinal cord segments just rostral to the site of injury.

When the diagnosis of neuropathic pain is retained and medical therapies have failed, DREZ surgery can be the recourse, but only if the pain is considered segmental. According to our experience, MDT has revealed effectiveness only in patients in whom pain corresponded with the level and extent of the spinal cord lesions, in contrast to the pain located in the territory below the lesion. In our series pain "below the lesion," especially the one located in the perineosacral region, was not influenced even when DREZ lesioning was performed at the lower medullary segments.[27]

Pain caused by lesions in the cauda equina can also be favorably influenced by MDT performed at the corresponding spinal cord segments.

Table 56.1 DREZ lesioning for brachial plexus injury: Literature reports

Reference	Technique	Number of patients	Follow-up, in years: range (mean)	Percentage of patients having > 75% relief
Nashold and Ostdahl[6]	RF-Th	18	1–4 (1.8)	72.3
Garcia-March et al[61]	RF-Th	11	1–5 (1.5)	54
Thiebault et al[62]	RF-Th	18	(6)	83
Campbell et al[63]	RF-Th	10	1–5	80
Ishijima et al[64]	RF-Th	19	(1.7)	82.4
Friedman et al[65]	RF-Th	39	1–10	67
Young[48]	RF-Th/CO_2 laser	18/4	1–5 (4)	RF, 75; laser, 50
Kumagai et al[66]	RF-Th	7	(4.2)	42.7
Dreval[10]	Ultrasound	124	(4)	87
Thomas and Kitchen[67]	RF-Th	44	1–12 (5)	79
Rath et al[68]	RF-Th	14	3–12 (6.2)	76
Samii et al[24]	RF-Th	47	2–18 (14)	63
Prestor[69]	Microsurgery	21	2–10 (5.6)	80.9
Sindou et al[23]	Microsurgery	55	1–27 (6)	85
Tomás and Haninec[70]	RF-Th	21	1–8	62
Chen and Tu[71]	Microsurgery	40	3–10	80
Kanpolat et al[72]	RF-Th	14	> 1	69
Aichaoui et al[26]	Microsurgery	29	1–10 (5)	76.9
Ali et al[25]	RF-Th	10	1–5 (3)	70
Taira (p.c.)	Microsurgery	53	> 1	65

Anatomic/Pathologic Data

The segmental levels to operate on are not only those injured, but also the adjacent ones if modified by consecutive pathologic processes—cavitation, gliosis, arachnoiditis, and others. The most frequent pathologic alterations due to spinal cord injuries have been well summarized by Nashold: Blunt injury to a segment of the spinal cord by a spinal dislocation results in a relatively localized spinal cord injury, whereas a gunshot wound may produce an injury that involves numerous segments above and below the injury. The initial insult is followed by central hemorrhage. After the hemorrhage resolves, small microcysts may form larger necrotic cavities which can be seen on the MRI-Scan. As a result of the spinal injury, not only the spinal cord is damaged, but also the adjacent tissues including the dorsal and ventral roots and the arachnoidal tissue. The arachnoidal scarring at the site of the spinal injury may be enough to tether the cord (personal communication).

Surgical Procedure

In paraplegic patients with complete motor sensory and sphincterian deficits, MDT can be done extensively on the selected segments. In patients with incomplete paraplegia, DREZ lesioning should be performed more restrictively to avoid creating additional neurological deficits. In patients with spine fractures not previously treated, surgery must start with liberation of the neural structures from the bony fragments that may occupy the intrarachidian and sometimes the intradural spaces. Frequently there may be a need for an intradural freeing from an adhesive arachnoiditis. Such a preparatory approach may be long and bloody; in that eventuality, surgery may be stopped and MDT performed in a second stage, around 2 weeks later.

Outcome

Outcome varies essentially according to the distribution of pain. As shown in **Table 56.2**, good long-term outcome (i.e., more than 75% relief) was achieved in 68 to 73% of the patients who had a predominantly segmental distribution of pain, compared with none of the patients with predominantly infralesional pain in spite of DREZ lesioning being performed down to the lower part of the cord. The clinical key for indication is the ability to differentiate the segmental from the infralesional part of the pain, which may be difficult but is of practical importance. Pain below the lesion is likely related to interruption of the ascending sensory tracts, with degeneration of fibers up to the brainstem and induction of pain generators at the supraspinal level. With regard to pain characteristics, a good outcome is better achieved on the paroxysmal and/or the allodynic components than on the permanent, often burning component. Good relief was obtained in 88 versus only 42% of our patients, respectively,[27,31] which is similar to other studies.[32,33] This discrepancy, which we also observed when dealing with pain after brachial plexus avulsion, is in accordance with the likely dorsal horn origin of the paroxysmal/allodynic components, and the hypothesis that the continuous component is the clinical expression of the degeneration of the spinothalamic, spinoreticular fibers.[23,31]

Pain Resulting from Peripheral Nerve Lesions or after Herpes Zoster Infection

Pain resulting from peripheral nerve pathologies and complex regional pain syndrome (CRPS) are rare indications for lesioning surgery in the DREZ, as these pains are most often relieved by SCS.[34] However, in refractory situations, when the predominant component of pain is of the paroxysmal type (electric flashes) or corresponds to allodynia/hyperalgesia, MDT can be indicated because it may be effective on those components. In CRPS, the pain manifestations and the vasomotor disturbances can be favorably influenced. MDT may also be indicated for severe occipital neuralgias[35]; the procedure can be easily performed at the C2–C3 spinal cord segments through a limited C2 hemilaminectomy. After limb amputation, two main types of pain may occur that often coexist: pain in the stump and pain in the phantom limb. DREZ surgery can be considered if SCS (and motor cortex stimulation, when phantom pain is predominant) has failed.[36] The existence of root avulsion should prompt recourse to DREZ surgery as a first option.

In patients who do not have important neurological deficits, lesioning must not be too extensive in depth so that the tactile and proprioceptive sensory capacities are at least partially preserved, and uncomfortable paresthesias avoided.

Table 56.2 DREZ lesioning for spinal cord injury: Literature reports

Reference	Technique	Number of patients	Follow-up, in years: range (mean)	Percentage of patients having > 75% relief
Weigand and Winkelmüller[73]	RF-Th	20	1–2	50
Friedman and Nashold[74]	RF-Th	56	0.5–5	Segm., 78; below lesion, 20
Young[48]	RF-Th/CO_2 laser	20	1–5 (4)	55
Edgar et al[75]	Rh-Th	46	2–7 (3.5)	92
Sampson et al[76]	RF-Th	39	0.1–12 (3)	54
Rath et al[68]	RF-Th	22	1–13 (5)	55
Spaić et al[77]	Microsurgery	26	0.5 (0.8)	Segm., 100
Sindou et al[27]	Microsurgery	44	1–20 (7)	Segm., 68; below lesion, 0
Falci et al[78]	Rh-Th	41	1–6	80
Kanpolat et al[72]	Rh-Th	17	> 1	69
Chun et al[32]	Microsurgery	38	2–6 (3.5)	Segm., 82.6
Taira[33]	Microsurgery	4	> 1	57

Postherpetic pain, well known to originate from sequelar lesions located in both the dorsal root ganglion and the corresponding dorsal horn, complicates herpes zoster infection in approximately 10% of the patients, mostly older ones. The pain syndrome is characterized by three types of algias that may be associated: permanent, burning, deep ache; electric, shootinglike paroxysms; and allodynia/hyperalgesia in the affected hypoesthetic dermatomas. There is a general agreement that DREZ surgery alleviates only the latter two components; the deep, aching pain is generally unrelieved and may even be aggravated.[36–38]

Determination of the spinal cord segments involved may be difficult. Observation at surgery of atrophic and grayish root(s) is most helpful for their identification. When the thoracic spinal cord is the target, because at this particular level the dorsal horn is narrow and deeply situated as shown in **Fig. 56.2**, encroachment of the corticospinal tract laterally and of the dorsal column medially might occur if lesioning is not prudently performed. The literature review is summarized in **Table 56.3**.

Pain in Malignancies

Only a few patients with malignancies are potential candidates for DREZ surgery. Mechanisms are often mixed: somatogenic due to cancer invasion and neurogenic linked to compression/destruction or (surgical, postradiation) iatrogenic impairment of the neural structures. Criteria for selection should be very restrictive: long life expectancy, general conditions compatible with open surgery, and topographically limited pain caused by well-localized lesions. The thoracic apex syndrome is typically a good indication for MDT,[39] currently from C7–T2. For more extended cervicothoracic cancers, stereotactic spinothalamic tractomy, open high cervical anterolateral cordotomy, or percutaneous CT (computed tomography)-guided cordotomy[40] is preferable. Further potential indications for MDT are painful conditions caused by circumscribed malignancies in the thorax, the abdomen wall, or the perineal floor, and also pain due to limited neoplastic involvement of

Table 56.3 DREZ lesioning for peripheral nerve pathologies, postamputation, Hz: Literature reports

Reference	Technique	Number of patients	Follow-up, in years: range (mean)	Percentage of patients having > 75% relief
Peripheral nerve pathologies/complex regional pain syndrome (CRPS)				
Taira (p.c.)	Microsurgery	7 (CRPS)	> 1	57
Sindou	Microsurgery	42	1–15	Paroxysmal/allodynic: good outcome Continuous/deep: poor outcome
Postamputation pain				
Weigand and Winkelmüller[73]	RF-Th	7	1	14
Saris et al[79]	RF-Th	9	0.5–5	67
Kanpolat et al[72]	RF-Th	4	?	?
Taira (p.c.)	Microsurgery	2	> 1	50
Sindou	Microsurgery	4	1–3 (2)	66
Postherpetic pain				
Friedman and Bullitt[37]	RF-Th	32	0.5–6	25
Young[48]	RF-Th	11	1–5 (4)	54
Kanpolat et al[72]	RF-Th	2	?	100
Taira (p.c.)	Microsurgery	2	> 1	0
Sindou	Microsurgery	12	1–15	Paroxysmal/allodynic: good outcome Continuous/deep: poor outcome

the lumbosacral roots/plexuses. For perineal pain, midline myelotomy can be an alternative. Intrathecal morphine is the technique of choice for advanced widespread pelvic cancers. Because extensive DREZ operations at the lumbar/sacral segments would inevitably result in leg hypotonia and sphincter disturbances, for pain below the waist the procedure is indicated only if it will be limited. The relevant literature has been recently analyzed by Gadgil and Viswanathan[41]; data are summarized in **Table 56.4.**

■ Hyperspastic States with Pain

Because muscular tone was found very much diminished in the operated areas after MDT was performed for treatment of pain,[42] the procedure was applied as early as 1973 for disabling harmful spasticity.[43,44] The hypotonic effect is explained by the fact that MDT interrupts the afferents of the myotatic (monosynaptic) and of the nociceptive (polysynaptic) arch reflexes, and so deprives the somatosensory relays of the ventral horn of most of their excitatory inputs (**Fig. 56.1**).

Briefly, two groups of patients may benefit from DREZ surgery. The first group includes hemiplegic patients with severe hyperspasticity in the upper limb; MDT is performed from C5–T1 segments through a C3–C7 hemilaminectomy. The second group corresponds to paraplegic patients with disabling spasticity who are bedridden, when intrathecal baclofen is not indicated or has failed. MDT is performed bilaterally through a T11–L1 laminectomy from L2 down to S2, and additionally down to S5 when there is a hyperactive bladder with urine leakage around the catheter. For MDT in the spastic patient, intraoperative neurophysiological mapping helps in identifying root and cord levels, as well as quantifying the extent of MDT.[45–47] Results have been reported in detail in the cited publications.

■ Complications

Appraisal of complications through the literature was made difficult by the lack of precise figures in a number of publications. However, it appears that complications related to the surgical approach—such as hematomas, CSF leak, infection, and meningitis—were rare and most often without sequelae. Deaths were scarce and essentially linked to precarity of the patient's general conditions.

Neurological complications occurred as a consequence of long tract damage due to misplacement or overextension of the therapeutic lesion. There is a general agreement that the adjacent dorsal column and corticospinal tract are particularly at risk in the thoracic spinal cord due to thinness and depth of the dorsal horn at that level. At any level mistargeting may result when the dorsolateral sulcus is hard to identify because of root

Table 56.4 DREZ lesioning for pain in malignancies: Literature reports

Reference	Technique	Number of patients	Follow-up, in months: range (mean)	Percentage of patients having > 75% relief
Nashold et al[6,80,81]	RF-Th	2 (cauda equina K)	8-4	100
Sindou and Lapras[39]	Microsurgery	13 (thoracic apex K)	1–30	90
Samii and Moringlane[82]	RF-Th	2 (breast K)	?	50
Powers et al[83]	Laser	3 (K)	?	100
Esposito et al[84]	Microsurgery	8 (K)	?	100
Kumagai et al[66]	RF-Th	1 (pelvic K)	2	0
Zeidman et al[85]	RF-Th	2 postradiation	29–48	100
Sindou	Microsurgery	46 (K): cervical MDT 35 (K): lumbar/sacral MDT	1–48	87 78
Rath et al[68]	RF-Th	2 postradiation	6–8	50
Teixeira et al[86]	RF-Th	7 postradiation	2–36	85
Ruiz-Juretschke et al[87]	RF-Th	3 (cervical K)	?	33
Kanpolat et al[72]	RF-Th	7 (K)	?	60
Taira (p.c.)	Microsurgery	3	> 1	?

avulsion, myelomalacia, or severe arachnoiditis. Also, coagulation of vessels, notably at the conus medullaris, known to harbor important arteries along the dorsolateral sulcus, may be the cause of uncontrolled extension of the lesional volume. Complications compiled from the literature are summarized in **Table 56.5**.

Complications According to Level and Etiology

DREZ surgery in the cervical spinal cord, for pain after brachial plexus avulsion, for instance, entails the risk of motor weakness, ataxia, paresthesias, and other complications in the ipsilateral lower limb. In patients who retain use of the affected upper limb, excessive lesioning might compromise the residual function through additional sensory loss. DREZ surgery in the conus medullaris, after spinal cord injury, for instance, theoretically poses no major danger in patients who are already totally paraplegic. However, excessive lesioning could raise the height of deficits; create hypotonia, making transfers difficult; and suppress useful genito-sphincterian automatisms when these are present.

DREZ surgery may generate new pain at the borders of the operated territory. When reported, such pain was most often considered bearable compared with the original pain that led to surgical indication. Mechanisms remain putative: unmasking of previous pain, damage to the DH cells at the origin of the spinoreticular/thalamic tract, along with other possible factors.

Complications According to Lesion Maker

Although all are directed at DREZ, the various modalities for lesioning do not have the same anatomical target and the tissular lesions vary in shape and extent. Consequently, they are not all associated with the same effects and level of danger. The RF thermocoagulation procedure is performed with an electrode implanted through the pia mater; the lesion has an ovoid shape and involves the whole dorsal horn with no clear-cut limits. Lesions made by lasers, usually the carbon dioxide laser, are more superficial and have a v shape; they are often accompanied by small infarcts because of the coagulation of vessels located at the DREZ.[48–50] The ultrasonic probe has been almost exclusively used in BPA; it has the particularity to evacuate the spongy and gliotic tissue situated in the DH apex.[10] All of these methods destroy the entire DREZ and DH structures.

The MDT procedure aims at targeting predominantly the ventrolateral portion of the DREZ. It is performed under direct vision of the dorsal horn and the adjacent white matter tracts, after opening the dorsolateral sulcus—which is the key to the operation because this allows direct control of the location and extent of the lesioning process. This likely is the reason for its lower rate of side effects.

Conclusion

Surgery in the DREZ has its place in the armamentarium for treating pain when medications have proven insufficient and conservative neurostimulation methods have failed or are not indicated. Because DREZ lesioning is a delicate procedure and entails the risk of undesirable side effects, the criteria for indication should be very strict and based on solid comprehension of the mechanism(s) of pain in the individual patient. Provided the prerequisites are met, DREZ lesioning can be very useful for those patients who have no alternative avenue for pain relief.

Pain after root avulsion, especially at the cervical or, less commonly, the lumbar–sacral region, and segmental pain after spinal cord/cauda equina injury

Table 56.5 Complications reported in literature: Incidence (%) according to etiology and lesion maker

	BP avulsion 19 publ. totaling 672 pts.		SC/CE injury 7 publ. totaling 347 pts.		PN, postamputation (Hz) 3 publ. totaling 92 pts.	
RF-Rh	396 pts.	M: 2–50% S: 9–72% g-sph: 0–1.3% New pain: 0–28.5%	336 pts.	M: 3–14% S: 2–70% g-sph: ? New pain: 10%	50 pts.	M: 8–19% S: 24–50% g-sph: 1.3–8% New pain: ?
Microsurgery	148 pts.	M: 1.8–4.7% S: 1.6–14% g-sph: 0–3% New pain: 0–2.6%	112 pts.	M: 3–14% S: 2–70% g-sph: ? New pain: ?	42 pts.	M: 2.3% S: 4.7% g-sph: none New pain: ?
Ultrasound	124 pts.	M: 10% S: 15% g-sph: ? New pain: 10%	None		None	

Abbreviations: M, motor; S, sensory; g-sph, genito-sphincterian, deficits.

are prominent indications. For those conditions SCS cannot be effective because of the degeneration of the corresponding dorsal column fibers up to the brainstem,[34] and even more important, pain generators are located in the deafferented dorsal horn.[15,16,18]

Pain after peripheral nerve lesions is a rare indication for DREZ surgery because SCS is generally effective. However, when SCS has failed and the main components are paroxysmal and/or allodynic, DREZ lesioning may be considered.

Pain in malignancies when limited in extent, as in the thoracic apex syndrome, may benefit from DREZ surgery, especially in patients with long life expectancy.

Pain linked to an excess of spasticity in severely disabled patients may also benefit from DREZ lesioning performed for both spasticity and pain. DREZ surgery must be considered as a second option in patients who could not benefit from botulinium toxin injections or intrathecal baclofen therapy.

Whatever the indication might be, the key point for safety of procedures in the DREZ is to perform lesioning under direct vision of the DH and adjacent tracts after microsurgically opening the dorsolateral sulcus.

DREZ surgery must be considered within the frame of the multidisciplinary armamentarium available for pain surgery.[51]

Editor's Comments

Dorsal root entry zone (DREZ) lesioning has proven to be one of the most important advancements in pain surgery over the past half century. There are many aspects of this procedure that are surprising.

First, this procedure seems to defy the general dictum that further injury to the central (or peripheral) nervous system is unlikely to improve pain that develops after nervous system injury. We are all well advised to not expect relief from deafferentation pain, after a destructive procedure. The outcome from DREZ lesions for nerve root avulsion pain does not seem to follow this rule. Perhaps the only other exception to this guideline is trigeminal rhizolysis (radiofrequency, radiosurgical, glycerol, or surgical) for trigeminal neuralgia. In fact, the latter example may not be a violation of the rule, since the efficacy of these denervating procedures may depend simply on diminishing, or eliminating, triggering stimuli rather than changing the generator of the pain. Thus, DREZ lesions may represent a unique category of surgical procedures for deafferentation pain.

Second, the generator of pain from nerve root avulsion must, to a large extent, exist within the spinal cord dorsal horn. This seems contrary to the general notion that once a nervous system injury occurs, whether peripheral or central, the sensory system central to the injury is physiologically altered, to some extent irreversibly, and that there is no unique "focus" of pain generation. This is probably true for spinal cord injury pain that is perceived below the injured spinal segment, as Dr. Sindou points out in this chapter. Something about plexus avulsion pain is different from spinal cord injury pain, in that despite complete deafferentation distal to the injury, pain relief can be achieved by DREZ lesions in the former, but not the latter.

Finally, the success rates for DREZ lesions in the problem of plexus avulsion pain, the most common indication for the procedure, are surprising. Complete cure (no pain, no medication) of these pains, which are otherwise almost completely refractory to pharmacological or surgical intervention, in three fourths of the patients is, to say the least, quite remarkable.

I do not have the experience of Professor Sindou, in the treatment of pain of malignant origin, or spasticity, using DREZ lesions. What experience I do have in treating brachial plexus and lumbosacral plexus avulsion pain, and spinal cord injury pain, is completely congruent with Dr. Sindou's narrative. He invented this procedure, has provided consistently forthright assessments of its outcomes, and continues to teach us how it might be best employed. The world of pain surgery is deeply in his debt.

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Section V

New Directions for Pain Surgery

57 Functional Imaging of Pain: Insights and Implications

Robert C. Coghill

Pain is a highly complex experience engaging tightly integrated sensory, emotional, motor, and attentional processes within the central nervous system (CNS). These components are heavily influenced by cognitive appraisal of the potential impact of the stimulus or disease evoking the painful sensation. Until the early 1990s, much of our current understanding of CNS processing of pain was derived from classical methodologies such as single-neuron electrophysiologic recordings in animals, focal electric stimulation of patients undergoing neurosurgical procedures, and studies of patients with localized CNS damage. These methodologies have provided a significant amount of information about the neural infrastructure supporting pain. The view of CNS pain processing mechanisms that these classical methodologies have provided, however, was inherently limited by the inability to assess the responses of multiple CNS regions simultaneously.

Functional imaging studies have revealed that pain is processed in a highly distributed fashion and this distribution of processing produces a system that is highly resilient to disruption (see below).[1] Destruction of just one of the multiple brain areas engaged in processing is generally not sufficient to abolish the experience of pain. Conversely, focal stimulation of one cerebral cortical region does not produce sufficient activation across the network of brain regions that subserve pain to recreate the experience of pain. In contrast to conventional methodologies, functional imaging provides an important tool for investigating such distributed processing mechanisms by providing the capability to examine the responses of multiple CNS regions simultaneously.

■ Indices of Neural Activity

To fully appreciate the contributions that functional imaging studies have made to pain, one must first be acquainted with the methodology and limitations of these paradigms. Functional imaging techniques do not directly assess neuronal activation, but instead measure changes in cerebral blood flow (CBF) or glucose metabolism. CBF has long been known to be closely correlated with brain activation. In a classic study examining cerebrovascular regulation in dogs, Roy and Sherrington (1890)[2] concluded that "the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity." The mechanisms supporting the coupling between neural activity and regional changes in CBF remain unclear, but may involve a multiplicity of mechanisms, including the involvement of astrocytes.[3]

Measurement of glucose utilization provides a somewhat more direct assessment of neuronal activation. As a neuron fires, the Na/K-ATPase is activated to repolarize the cell. This process consumes ATP. The increased demand for ATP during activation in turn increases glucose metabolism.[4] Thus, glucose uptake serves as a reasonable index of neuronal activity. However, glucose itself is rapidly metabolized, and thus is not an ideal tracer. This problem was overcome in 1977 by Sokoloff and colleagues with the development of tracer techniques employing a metabolically stable analogue of glucose, 2-deoxyglucose.[5] This compound is taken up and phosphorylated by cells in a manner identical to that for glucose. However, it is not metabolized further and accumulates in cells in proportion to glucose utilization.

■ Functional Imaging Methods

Positron Emission Tomography: Blood Flow, Metabolism, and Beyond

In studies of humans, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are the two most frequently used methods of assessing brain activation. PET relies on radiotracers labeled with a positron-emitting isotope. The PET

technique is quite flexible in that any molecule that can be labeled with a positron-emitting isotope may serve as a potential tracer. Prior to the advent of fMRI techniques, oxygen-15-labeled water ($H_2{}^{15}O$) served as the most frequently used tracer for cerebral blood flow[6] and, hence, brain activity. Deoxyglucose labeled with fluorine-18 (^{18}F-DG) has long been used for tumor screening, but only rarely to image brain function, particularly during pain. Currently for studies of pain, PET is used largely for pharmacological investigations where the binding or displacement of a ligand is used to gain insight into neuropharmacological mechanisms supporting various processes. For example, [^{11}C]carfentanil has been used to assess the release of endogenous opioids during experimentally induced pain.[7] Such techniques have shown that endogenous opioids are involved in placebo analgesia.[8] Other tracers, such as the dopamine D2 receptor antagonist radiotracer [^{11}C]raclopride, have been used to assess basal ganglia function during pain.[9]

Functional Magnetic Resonance Imaging of the BOLD Effect

Functional MRI, in contrast to PET, is generally limited to the examination of CBF changes. This technique typically relies on the blood oxygenation level dependent (BOLD) effect.[10] This effect is based on an apparently paradoxical feature of CBF. When a brain area is activated, its blood flow increases in excess of its needs for oxygen, and oxygenated blood travels further into the venous side of the capillary bed than during rest. Oxyhemoglobin and deoxyhemoglobin have different susceptibilities to magnetization, allowing local shifts in the concentration of deoxyhemoglobin to be detected by MRI.[11] Animal studies using direct optical imaging of CBF have determined that immediately after activation, very early (< 3 s) changes in CBF are accompanied by a decrease in oxygenated hemoglobin, consistent with increased oxygen consumption.[12] These changes are currently too small and too focal to be accurately imaged with conventional MRI scanners. However, later (> 3 s), more diffuse increases in CBF are characterized by an excess of oxygenated hemoglobin and serve as the basis for the BOLD effect.[11] BOLD MRI offers spatial and temporal resolution vastly superior to that of PET, and exposes the subjects to no radioactivity. Taken together with the widespread availability of MRI scanners, fMRI studies have now become the standard tool for assessing brain activity during pain.

Direct MRI Assessment of Cerebral Blood Flow

The BOLD technique, despite its substantial utility, is subject to a number of limitations. First and foremost, it is not a fully quantitative technique. Thus, it is very sensitive to signal drift during the course of an MRI series. Accordingly, task conditions need to be interleaved with control conditions because sensitivity drops off substantially if one condition is sustained for a period of longer than approximately 30 seconds. Moreover, although resting-state functional connectivity studies are being widely used to gain insight into brain mechanisms of pain, BOLD fMRI cannot easily be used to determine activation in a resting or a steady state.[13] Thus, BOLD activation studies of chronic pain, drug effect, or long-duration cognitive manipulations are largely limited to studies of responses to transient stimuli.

An alternative technique, arterial spin labeled (ASL) MRI,[14,15] was developed shortly after the BOLD technique and can image CBF directly. ASL MRI is analogous to PET studies in that it directly measures CBF. However instead of injecting a radioactive tracer to image CBF, blood is tagged magnetically during ASL. Due to largely hardware-associated constraints, this technique lagged substantially behind BOLD because signal-to-noise ratios were very low, and whole-brain acquisition was not possible. Recent advances in MRI scanner technology have led to this technique's becoming more readily available in a form that makes it extremely useful for studies of pain. The combination of new scanners and highly evolved sequences is now allowing whole-brain acquisition at a resolution nearly equaling standard BOLD fMRI.

Signal-to-noise ratios are still very low in the perfusion images obtained with ASL MRI. As a result, they are optimal for imaging relatively steady cognitive states during scans that take approximately 3 to 6 minutes. Such long-duration scans allow for substantial signal averaging in order to provide a clearer image of CBF. However, this time scale is far too long for BOLD imaging, so ASL MRI offers the ability to image phenomena that would normally be beyond the reach of BOLD. Moreover, ASL MRI is a fully quantitative technique and is capable of assessing global as well as regional changes in CBF. Global CBF can be either a major variable of interest or a potential confounder. For example, in studies of opioid analgesia slowed respiration may lead to increased arterial pCO_2 and increased global CBF; or in studies of meditation, changes in breathing could result in decreased pCO_2 and reduced global CBF. Both of these changes could have a significant impact on the interpretation of regional actviation-related changes. ASL MRI has been used to image pain-related brain activation and its modulation by meditation,[16] and low back pain.[17]

Imaging of Spinal Cord Nociceptive Processing

Early functional imaging studies of the spinal cord using the autoradiographic 2-deoxyglucose technique to map spinal nociceptive processing have confirmed much of what has been previously demonstrated with single-unit recordings.[18] Stimulation of the hindpaw of the rat with 49°C water, a temperature that is painfully hot for humans, produces increased glucose utilization in a number of dorsal and ventral horn regions previously known to be involved in pain processing. These include regions with spinothalamic and spinoreticular projections, and ventral horn areas important in the generation of reflex withdrawal responses. In the superficial dorsal horn, pain-induced activation occurs in a pattern appropriate for the known somatotopy. Activation occurs in the medial but not lateral portions of the superficial dorsal horn, consistent with the medial representation of the distal (stimulated) portion of the hindlimb.

The strength of functional imaging becomes apparent when activation is assessed across multiple spinal cord segments simultaneously. Painful stimulation of the hindpaw of the rat produces an extensive rostrocaudal spread of metabolic activity.[18,19] This activation is focused on the fourth lumbar segment, but encompasses five spinal cord segments (L1–L5). In contrast, an innocuous brushing stimulus produces tightly focused activation within the caudal aspect of L3.[19] Spatially distributed recruitment of neural activity also occurs in a manner dependent on pain intensity. Progressive increases in stimulus intensity recruit increasing numbers of spinal cord segments.[18] A weakly painful stimulus (immersion of the rat's paw in 45°C water) produces activation that is focused largely within L4, whereas a robustly painful stimulus (49°C) produces activation spreading through up to five spinal cord segments. This extensive spread and spatial recruitment of activity may provide a substrate for the radiation of intense pain.

In chronic neuropathic pain states such as reflex sympathetic dystrophy, pain has long been known to radiate to body regions far removed from the territory of the injured nerve.[20,21] Functional imaging studies of neuropathic pain models in rats indicate that there is an extensive ipsilateral rostrocaudal recruitment of activity similar to that evoked in studies of acute pain.[22] Such an extensive rostrocaudal distribution of activity during neuropathic pain provides the neural substrate for the unilateral radiation of clinical pain. Radiation of pain may frequently involve body regions contralateral to the initial site of injury.[23] Such bilateral spread of pain has been difficult to explain with conventional evidence because primary afferents project exclusively to ipsilateral regions of the dorsal horn. However, in rat models of neuropathic pain, both dorsal horns are activated by a unilateral nerve injury.[22] Thus, this bilateral recruitment of activation can clearly provide an explanation for bilateral radiation of clinical pain.

In humans, imaging of spinal cord nociceptive function is still in its infancy. The small size of the spinal gray matter as well as the movement of both the spinal cord and cerebral spinal fluid (CSF) make functional imaging highly challenging. However, fMRI studies have revealed that the spinal cord is activated during both placebo analgesia[24] and during attentional modulation of pain.[25]

Brain Systems of Pain

Since the publication of the first two PET studies of pain, by Talbot et al[26] and Jones et al[27] in 1991, functional imaging has now emerged as the tool of choice for exploration of supraspinal mechanisms contributing to the capacity to experience pain. After more than two decades of research since these first studies, meta-analyses reveal that a considerable number of brain regions are consistently activated during pain.[28]

Despite the power and popularity of functional imaging of pain, it is nevertheless important to consider these findings together with data derived from a variety of sources, including anatomical and neurophysiological investigations of animals, and neurological and psychophysical studies of humans. Furthermore, given the tremendous complexity and interconnectivity of brain areas that are engaged in the processing of pain, it is important to realize that there is rarely (if ever) a one-to-one relationship between activation of a particular brain region and a discrete component of the pain experience. Instead, a growing body of data indicates that discrete cerebral cortical areas are likely engaged in multiple, often overlapping, functions and network-based analyses are becoming a primary topic of research.

Thalamus and Bilateral Processing

The thalamus has long been known to serve as a site engaged in significant processing of somatosensory information arriving from both the spinal cord and the trigeminal system. Contralateral activation of the thalamus is frequently detected[28] and would be consistent with activation of the ventroposterior-lateral nucleus of the thalamus, whose nociceptive neurons are characterized by relatively small, contralateral receptive fields.[29,30] However, in many instances, ipsilateral activation of the thala-

mus is additionally detected.[28] This bilateral activation would be consistent with activation within the posterior complex, dorsal medial nucleus, and intralaminar nuclei during afferent processing of nociceptive information. These regions have nociceptive neurons with predominantly bilateral receptive fields.[31–34] The thalamus, however, is acting as more than a site of afferent nociceptive processing. Considerable regulation of cerebral cortical responses is obtained via modulation from corticothalamic loops. As such, much of the very widely distributed activation observed in the thalamus may also reflect the involvement of such loops, particularly with cortical regions exhibiting bilateral activity, such as the anterior cingulate cortex and anterior insular cortex.

Brain Mechanisms Supporting the Localization of Painful Stimuli

The primary somatosensory cortex is one of the major targets of the lateral thalamic nuclei and has long been thought to be critically involved in processes contributing to the sensory-discriminative aspect of pain. In particular, the primary somatosensory cortex is thought to play a critical role in painful stimulus localization, in part because of the well-documented somatotopic organization of this area.[35] Just as with innocuous stimuli, painful stimuli produce somatotopically appropriate activation of the contralateral primary somatosensory cortex. When pain-related somatotopy has been directly explored in a within-subjects fashion, painful stimulation of the foot produces activation within the dorsomedial aspect of primary somatosensory cortex, consistent with the known representation of the foot; stimulation of the hand produces activation of the ventrolateral aspect of primary somatosensory cortex.[36] Both the insular cortex and the secondary somatosensory cortex have also exhibited somatotopically organized activation during pain,[37,38] although this organization is considerably less clear.

Although the somatotopic organization of primary somatosensory cortex underscores its potential role in stimulus localization, conscious awareness of a stimulus's location on the body likely involves the interaction of many other brain regions with the primary somatosensory cortex (**Fig. 57.1**). These include regions such as Broadmann area 40 of the inferior parietal lobule, gray matter regions surrounding the intraparietal sulcus, and portions of the dorsolateral prefrontal cortex. These areas are frequently activated during painful stimulation. The posterior parietal cortex receives input from the primary somatosensory cortex,[39–41] and the dorsolateral prefrontal cortex receives significant input from posterior parietal areas.[42] The posterior parietal cortex has been demonstrated to be important in the process-

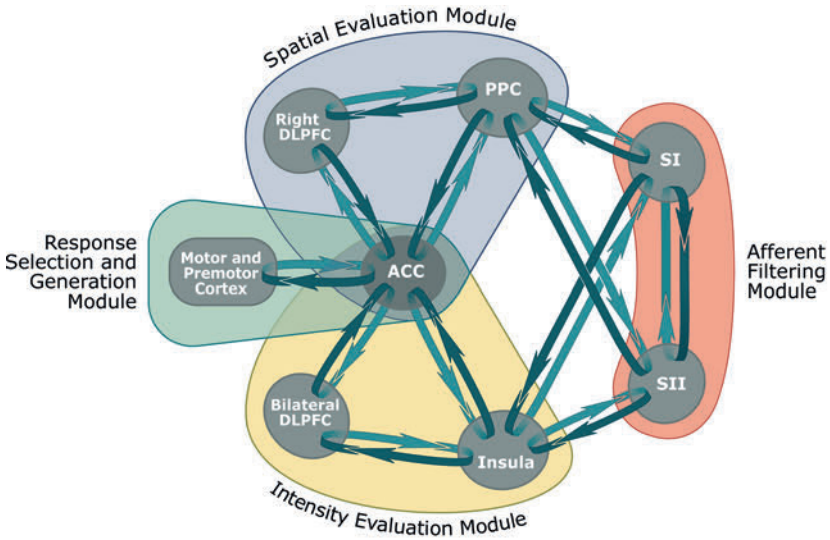

Fig. 57.1 Brain mechanisms supporting evaluation of sensory features of pain. The primary and secondary somatosensory cortices act as an afferent filtering module, in which neural responses are adjusted by top-down information to optimally process afferent nociceptive information. Spatial information is preferentially processed by a dorsally directed mechanism involving the posterior parietal cortex (PPC) and dorsolateral prefrontal cortex (DLPFC), predominantly in the right hemisphere (in right-handed subjects). In contrast, intensity-related information is processed by a more bilateral, ventrally directed stream involving the insula and prefrontal cortex. It is important to note that both of these pathways involve the bidirectional flow of information, such that bottom-up information can be integrated with top-down information. The anterior cingulate cortex (ACC) is active during both spatial and intensity discrimination and is well positioned to evaluate comparisons of this information and to select a response.[49]

ing of spatial aspects of visual and auditory information, and when lesioned can produce multisensory neglect syndromes.[43–46] Similarly, the dorsolateral prefrontal cortex has been closely linked with spatial attention and spatial memory.[47] Consistent with this evidence, studies of brain mechanisms associated with the discrimination of pain location reveal right-lateralized activation of the IPS and dorsolateral prefrontal cortex, as well as the anterior cingulate cortex.[48] Accordingly, a dorsally directed processing stream engaging the primary somatosensory cortex, the posterior parietal cortex, and the dorsolateral prefrontal cortex, among other brain regions, may constitute a brain network important for conscious appreciation of spatial aspects of pain.[48,49]

Brain Mechanisms Engaged in the Processing of Pain Intensity

The single most salient feature of a painful stimulus is its intensity. Pain intensity is at the core of nearly all aspects of pain. Affective, motor, attentional, and autonomic responses are all driven by intensity of pain. This critical ability to be consciously aware of the intensity of a painful stimulus is preserved in the face of a wide variety of brain lesions. For example, surgical removal of the primary somatosensory cortex produces no effects on pain threshold[50]; lesions of the secondary somatosensory cortex raise pain thresholds to some extent, but do not abolish the ability to consciously perceive pain.[51] Vascular lesions of the insular cortex produce minimal effects on the appreciation of pain intensity.[52] Similarly, surgical lesions of anterior cingulate cortex and the prefrontal cortex actually lower pain thresholds and produce exacerbated responses to acute pain.[53–57] Finally, lesions as extensive as complete removal of one cerebral hemisphere have little effect on the appreciation of pain intensity.[58]

The failure of this wide variety of brain lesions to abolish the ability to appreciate the intensity of pain does not indicate that the cerebral cortex plays a minimal role in the processing of pain. Instead, functional imaging studies indicate that the vast majority of brain areas implicated in the processing of pain receive detailed information about the intensity of a painful stimulus. Coghill et al have demonstrated that the cerebellum, bilateral portions of the thalamus and putamen, primary somatosensory cortex, secondary somatosensory cortex, supplementary motor cortex, insula, and anterior cingulate cortex all exhibit responses that are significantly related to subjects' perceptions of pain intensity.[59] Of these cerebral cortical areas, all have been demonstrated to receive direct input from the thalamus that would be sufficient for parallel transmission of nociceptive information. Accordingly, this widespread processing of pain intensity results in a system that is extremely resilient to injury and can explain how a degree of pain intensity appreciation is preserved despite widespread injury to brain regions involved in the processing of pain.

When pain intensity discrimination has been examined in a prospective fashion, a subset of these brain regions appears to be critically involved in the cognitive evaluation of intensity of a noxious stimulus (**Fig. 57.1**). When subjects perform a delayed match to sample task of identifying differences between intensities of sequential noxious stimuli, a ventrally directed processing stream is engaged. This set of regions includes the anterior insula, the prefrontal cortex, and the anterior cingulate.[49] These findings are further supported by the differential activation of the anterior insular cortex during the rating of pain intensity.[60]

Affect and Meaning

Pain is clearly a sensory experience that is defined by a negative emotional valence. The anterior cingulate cortex and the prefrontal cortices have long been thought to be crucial for pain-related affect, largely on the basis of apparent disruption of chronic pain-related affect following cingulotomies or prefrontal lobotomies.[54,61] Both the anterior cingulate cortex and the prefrontal cortex are frequently activated during functional imaging studies of pain, and this activation is generally interpreted as affective processing. Although considerable inferences can be drawn from the combination of lesion, anatomical, and observational functional imaging studies, direct experimental manipulation of affective responses to pain is critical for the identification of brain regions engaged in the processing of pain-related affect. One such experiment has been accomplished by Rainville et al by tailoring hypnotic suggestions to either minimize or maximize pain affect while subjects experienced painful heat stimuli during PET scans.[62] A rostral portion of the anterior cingulate cortex exhibited responses that were significantly correlated with subjects' affective ratings of pain, while responses of the somatosensory cortex remained uninfluenced. This finding clearly suggests that the anterior cingulate cortex is engaged in a process that is intimately related to emotional aspects of the pain experience, and that somatosensory components and affective components of pain can be experimentally separated.

The prefrontal cortex may be particularly important for later, more cognitively driven stages of pain affect that are intrinsically linked with their meaning. In some of the earliest observations of the

effects of prefrontal lobotomies on pain, Freeman and Watts[54] remarked "that the frontal lobes are important structures, not so much for the experiencing of pain as for the evaluating of the sensation, the estimation of its significance in terms of the self and of the future." In contrast to classic notions, during acute pain patients with cingulotomies or prefrontal lobotomies frequently exhibit decreased thresholds, exaggerated behavioral responses, and increased ratings in reaction to suprathreshold stimuli.[53–57] The fact that cingulotomies and prefrontal lobotomies reduce chronic pain–related affect, but exacerbate responses to acute painful stimuli, points to a complex role in their involvement in the application of contextually relevant meaning to the incoming nociceptive information.

Another brain area that may be crucially involved in providing meaning and context-related information to the nociceptive processing system is the anterior insular cortex. Affective and meaning-related processing of acute painful stimuli have been reported to be disrupted in subjects who have lesions of the insular cortex.[63] These subjects retain the capacity to recognize a stimulus as painful, but they report that it fails to bother them and they fail to recognize that these stimuli may potentially damage their bodies. Conversely, in an experiment when subjects with insular lesions are provided with instructions that the experimental stimuli will not cause tissue damage, they exhibit markedly and significantly higher ratings of pain intensity than age-matched control subjects.[52] Consistent with their elevated ratings of pain intensity, they also exhibit markedly elevated activation of the primary somatosensory cortex contralateral to stimulation, but ipsilateral to the insular lesion.[52] This pattern of activity suggests that prior knowledge about the stimulus is no longer able to modulate afferent processing, leading to increased pain sensitivity (**Fig. 57.1**).

Anatomically, the insular cortex is well positioned to be engaged in the integration of meaning with nociceptive processing. It receives "top-down" input from the amygdala, parahippocampal gyrus, and prefrontal cortex. The insular cortex can then transmit this information to more caudally located somatosensory areas around the lateral sulcus. These areas, in turn, project to the primary somatosensory cortex. Accordingly, the insula has been proposed to be one part of a corticolimbic pathway for somatosensory information[40,64,65] and, as such, can provide a route for cognitive modulation of pain (**Fig. 57.1**). Consistent with this role, the insular cortex is activated during many cognitively driven phenomena that elicit reduction of pain. It is robustly activated during placebo analgesia,[66] and its activity is positively related to the magnitude of pain reduction during medication.[16]

Functional Imaging and Chronic Pain

Chronic pain can be produced by any of a tremendous number of diseases and injuries. In some syndromes, pain can sometimes spread far beyond the initial site of disease or injury, and beyond our current capacity to explain such changes. Otherwise mentally healthy patients often develop psychiatric problems as a result of their pain, and conversely, patients with psychiatric problems may develop chronic pain. In all of these cases, better methods of diagnosing chronic pain could lead to earlier and/or more efficient treatment. Although the use of functional imaging to characterize brain activity related to chronic pain is still in the early stages of development, ongoing refinements in both data acquisition and data processing offer the possibilities of new diagnostic tools for assessing chronic pain.

Functional Connectivity and Default Mode Activity

As noted above, imaging a steady state of chronic pain with BOLD fMRI is largely not feasible. However, activity within the brain is constantly fluctuating, even when the subject is not actively performing a task. Such activity has been termed default mode activity and generally encompasses several sets of brain regions in healthy subjects.[67] These resting-state fluctuations can be used to identify functional connections within discrete brain networks, and such patterns of connectivity hold the potential to provide insight into chronic pain. During rest, the default mode network exhibits greater connectivity with the anterior cingulate cortex, insular cortex, and inferior parietal cortex in patients with low back pain versus healthy controls.[68] Functional connectivity of the nucleus accumbens with the prefrontal cortex has been used to predict the chronicity of low back pain over the course of a 1-year period.[69] Subjects with subacute back pain who exhibited higher connectivity between these two regions at their initial scan were more likely to have chronic pain at a 1-year follow-up.

Multivariate Pattern Analysis for Classification of Imaging Data

A single brain volume from a functional scan can contain easily more than 20,000 statistically independent voxels, and structural data can contain far more. Traditional univariate statistical analyses are directed at the identification of differences within

individual areas and, unfortunately, cannot use the aggregate activity of all voxels to distinguish between different brain states. A variety of multivariate techniques using machine learning are currently being refined and applied to the analysis of data from both acute and chronic pain states. Such techniques can automatically determine if an individual is experiencing a noxious heat stimulus or a warm stimulus.[70] Application of these techniques to brain structure can distinguish patients with chronic low back pain from healthy controls.[71]

Diagnostic Utility versus Individual Variability

Although there is considerable promise for imaging techniques in providing useful diagnostic and prognostic information, these studies are still in their very early stages. Very little is known about the variability of nociceptive processing at the single-subject level. However, individual differences in pain sensitivity are tremendous. Healthy subjects experiencing a 49°C stimulus on the back of the leg report pain intensity ratings that range from 1/10 to almost 9/10. This variability in the perceptual experience is consistent with pain-related brain activation. Highly sensitive subjects activate the primary somatosensory cortex, anterior cingulate cortex, and prefrontal cortex more frequently and at a greater magnitude than insensitive subjects[72] (**Fig. 57.2**).

Virtually nothing is known about how even the simplest variables like race and gender may influence the observed patterns of activity or connectivity. Moreover, the sensations associated with a given chronic pain syndrome are highly variable across individuals, so it remains unknown how much brain activation will vary in response to differences in chronic pain, and if such variations will turn out to be noise or will contribute to diagnostic/prognostic utility. However, the continuing accrual of experience, in combination with dramatic improvements in computing power, are driving rapid advances in both image acquisition hardware and data processing software. Functional imaging technologies will

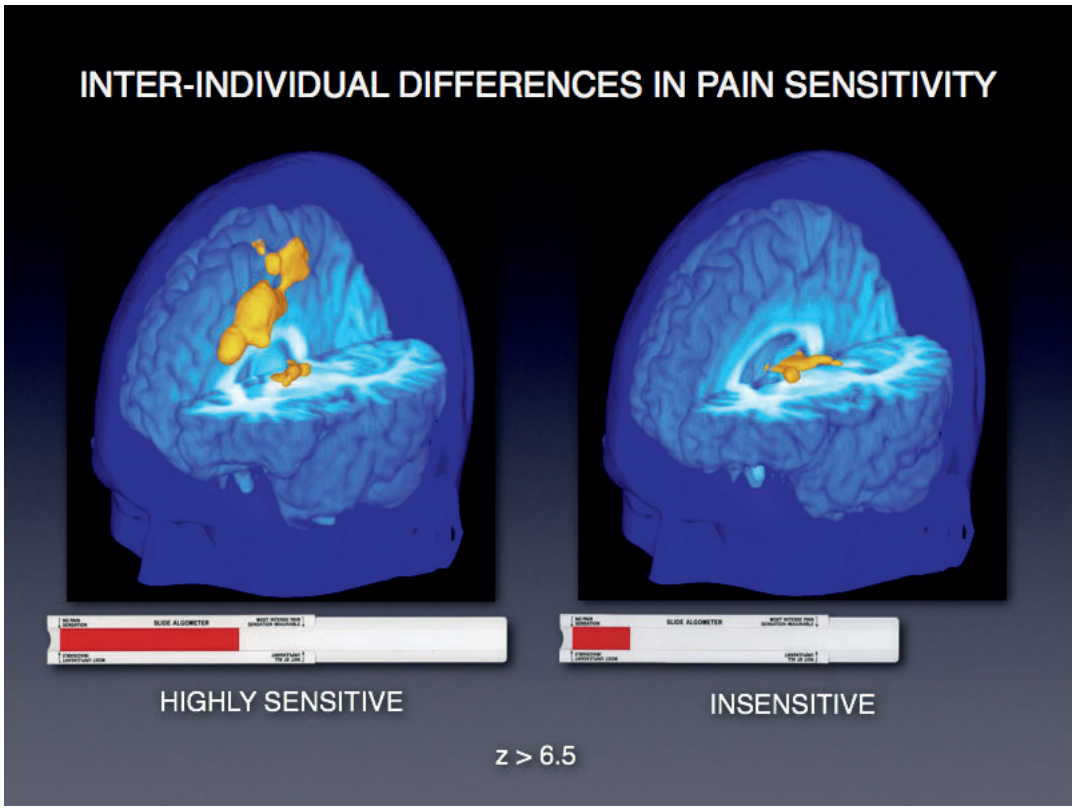

Fig. 57.2 Individual differences in pain sensitivity and pain-related brain activation. These three-dimensional volume renderings of fMRI data depict pain-induced activation of the primary somatosensory cortex, anterior cingulate cortex, and thalamus in highly sensitive individuals, and activation of only the thalamus in insensitive individuals.

become increasingly powerful, with finer spatial and temporal resolution, and with lower noise. These advances hold the potential to make single-subject functional imaging studies highly reliable. Pain, however, is a variable experience, and the individual variability in patterns of pain-induced brain activation remains totally unknown. Accordingly, characterization of this physiological variability is critical for the future development of functional imaging as a diagnostic tool for chronic pain.

Conclusion

Functional imaging techniques are providing a powerful mechanism to better characterize the complex spinal and supraspinal substrates of pain. As research tools, they are already providing new insights into aspects of pain that have remained unexplained by conventional methodologies. These new insights will provide a more accurate base of knowledge for the diagnosis and treatment of clinical pain.

Editor's Comments

Professor Coghill has reprised his chapter from the first edition of this book, and it is fascinating to see the advancements in the field of functional imaging of pain in the past decade. For example, techniques such as arterial spin labeled (ASL) magnetic resonance imaging (MRI) were not mentioned in that earlier chapter, and now hold considerable promise for the steady-state imaging of pain.

As the story of imaging of pain unfolds, the concept of single centers that can be ablated or stimulated almost seems to have been completely abolished. There is no doubt that pain perception at the cerebral level involves multiple brain areas and systems. Although imaging now seems to be one of the principal tools with which we can enhance our knowledge of the complex process of pain processing and perception, the possibility that this will lead to a breakthrough surgical therapy for pain seems more remote than ever. The pursuit of these studies is likely to improve our understanding of conditions such as reflex sympathetic dystrophy, or how nonsurgical methods of pain treatment, such as cognitive-behavioral therapy, are effective.

Given advancements in informatics and machine learning, there seems to be a very real possibility that scans will someday be able to diagnose certain broad types of pain conditions, to determine if nociception plays a major or minor role in the individual's pain experience, and to even help us better understand the placebo effect. I suspect the expansion of the field of functional imaging of pain will be even more dramatic in the next decade.

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58 Evidence, the Practice of Pain Surgery, and the Institute of Medicine Report

Robert J. Coffey

Why data, evidence, and clinical studies? What is, and what is not evidence? Not all words and pictures are data; valid data are not necessarily information; not all information is evidence; disagreements about facts are not matters of opinion; and facts are not established by majority rule. By using existing data and evidence, one can analyze the current state of pain diagnosis along with the reported efficacy of surgical procedures to treat chronic noncancer pain.[1–6] Principles of cognitive science further inform plausible explanations for the enduring vitality of certain beliefs and practices. This analysis finds that some diagnoses are so contentious as to raise questions of whether medical evidence—or something else—explains the reported effects of certain interventions. Herein we examine contradictions in the theory and practice of pain medicine and surgery. The goal is to prod neurosurgeons to think analytically about pain, about the diagnoses that make sense, and about the operations that have a high likelihood of success. The task is difficult because, in the words of American author and journalist Mignon McLaughlin, "No one really listens to anyone else, and if you try it for a while you'll see why."

A Few Noncancer Chronic Pain Conditions Are Amenable to Treatment

The Canadian Medical Association (CMA) articulated a schema to rate medical evidence, and Weintraub published a guide on how to evaluate reports of clinical trials.[7,8] Using those criteria, we examined the nature of evidence that supports the use of electrical stimulation of the brain, spinal cord, and peripheral or cranial nerves to treat chronic noncancer pain. (**Table 58.1**).[4–6] We found a mismatch between the results of a prospectively designed and systematic analysis and hundreds of uncritical publications in which data were interpreted in favor of arguably ineffective therapies. Others have performed structured reviews of destructive neurosurgical operations to treat noncancer pain.[1] With respect to intrathecal opioid and other drug infusions to treat cancer pain, Level I evidence of efficacy is straightforward.[9] Comparable evidence for noncancer pain remains elusive.

Destructive Procedures Are Effective for a Few Noncancer Indications

Destructive procedures, with a few exceptions, do not have sufficient safety or long-term efficacy to justify routine use. Reviews often cite classic works on pain surgery as evidence of efficacy when the original publications report results that would dissuade most neurosurgeons from repeating the experience of a bygone era.[10–13] Newer quasi-destructive procedures[14–17] and operations on the sympathetic nervous system to treat noncancer pain also lack evidence of lasting efficacy.[18,19] The operations that are effective for classic, treatable, pain syndromes due to cancer or other causes are performed routinely in general neurosurgical practice, and are not the sole province of specialists in pain or functional neurosurgery.[20–28] With respect to adverse consequences apart from operative complications, the desire to avoid painful numbness leads surgeons to reserve destructive operations for well-established indications. Publications and presentations now indicate a renewed interest in destructive procedures that had fallen out of practice.[29–31] The sources of structural bias outlined in **Table 58.1** and addressed in greater detail in **Table 58.2** bedevil these recent claims by the surgeons who selected the patients, developed operative nuances, performed the operations, evaluated the results, and wrote the articles.

Stimulation-Produced Analgesia Remains to Be Proven

Structured analyses of publications that support the analgesic efficacy of neurostimulation therapies reveal scant high-level evidence of efficacy attributable to

Table 58.1 Factors used to evaluate reports of surgical procedures for chronic pain

Levels of evidence[9]	Criteria adapted and modified from Weintraub[8]
I: Evidence obtained from at least one properly randomized controlled trial	*Nature of the reports* Objectives and regulatory phase, if applicable Type of report: case series or prospective study Level of peer review
II-1: Evidence obtained from well-designed controlled trials without randomization	Patient population Number of eligible cases evaluated and excluded Screening tests and reasons for patient exclusions Demographics, diagnoses, and previous therapy
II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group	Study design Uniformity of protocols and experience for all patients necessitates sham surgery and/or device implantation adjusted to "no therapy" in the control group during the blinded phase. Drug and other ancillary therapy reported Control groups and method of group assignment
II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin in the 1940s) could also be regarded as this type of evidence.	*Data collection and bias control* Individuals who assessed patients Blinding of evaluators and/or patients Criteria for continuation of therapy Nature of outcome categories Timing and reproducibility of outcome criteria
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	*Reporting and analysis of data* Outcome measures addressed Patient and investigator compliance Accounting of missing data or patient dropouts Follow-up cohort compared with original population Cases tracked in serial publications Predictors of success Denominators used in calculations Clinical relevance of results Other logical or methodological features

the therapies themselves. Positive reports and reviews contain the biases that are listed in **Table 58.2**, and that we address in the following sections. Patient selection, pain category, externalized trials, paresthesia coverage, and device programming are among the foundational principles that are reported to correlate with efficacy—but do not.[4–6]

One important point is that blinding is not impossible in neurostimulation trials; studies that employ deception to compare like to like in terms of patient perceptions have been done.[32–34] A publicly discussed but unpublished trial of motor cortex stimulation (MCS) for pain, which involved a randomized crossover design, employed successful blinding of patients in the stimulation-on versus stimulation-off conditions (Fifteenth Meeting of the World Society for Stereotactic and Functional Neurosurgery, Toronto, Canada, 2009). The study was closed prematurely, but revealed no preference for the blinded "on" condition regardless of whether it was the initial or the final (crossed over) condition in subjects with pain states that reportedly were the most amenable to MCS therapy: trigeminal deafferentation pain and central poststroke pain. Blinding, mild deception, and experimental equipoise also were successful in a recently published trial of spinal cord stimulation (SCS) for refractory angina pectoris, which employed an active-sham control group. The trial design was exemplary, and serves as a standard against which to compare other studies.[34] It also ended prematurely owing to futility and slow enrollment. The results did not validate expectations of the investigators and the sponsor in that SCS was no more effective against angina than the 1-minute-per-day, low-stimulation control condition. The unpromising results of adequately controlled clinical studies, and similar results when more permissive studies are analyzed to control for bias, suggest that better-quality data are less likely to support efficacy claims. Yet, despite regulatory and payer skepticism,[35–37] imperfect studies and compilations of flawed data continue to be cited—and new ones undertaken.[38–44]

Table 58.2 Optimal clinical trial design features to investigate the efficacy of procedures to treat chronic pain

Optimal design features	Rationale, details, and execution
Investigator equipoise	Agree that hypotheses under study remain to be verified or refuted
Team of at least three individuals	Blinded implanter and evaluator, blinded or neutral programmer
Multiarm or multiphase project	Three-arm study example: active vs. sham vs. deliberately ineffective All patients are implanted; patients and evaluators cannot tell who is on therapy from who is on sham or no therapy.
Study arms appear the same to subjects and evaluators.	Comparisons of active treatment to "best medical therapy" are inherently and fatally biased.
Well-defined diagnostic criteria for eligibility	Unequivocal diagnosis supported by imaging and electrophysiological data
Inclusive selection, limited exclusions	Candidates with the correct diagnosis and no exclusions are eligible
Personality tests, and psychological or pharmacological screening may be performed and the results recorded	Investigators, evaluators, and patients are blinded to results, which do not affect subject eligibility.
Prospectively defined efficacy denominator	Either intention-to-treat, or last value carried forward for implanted-internalized subjects
Optimization period is brief and blinded.	Optimization/trial period is shorter than the blinded study period, and subject and evaluator are unaware of stimulation parameters.
Days to weeks interval between trial and randomization	Permits washout of stimulation effects; helps to maintain blinding
Long-duration, blinded-randomized study period	As long as feasible, consistent with subject retention for chronic therapy
Drug and ancillary therapy tracked and reported	Significant decrease in opioid and other drug intake verified by testing
Prospective data collection, analysis, and success criteria	50% PPR or other standard vs. control group (not difference from baseline) at 1–2-year endpoint

With respect to safety, publications,[45] regulatory actions (St. Jude Medical, Neuromodulation Division, Dear Doctor Letter Re: Spinal Cord Stimulation Leads, June 14, 2012), and informed searches of public FDA databases suggest that the risk of neurological injury associated with SCS lead implantation is higher than previously recognized. Neurosurgeons are a minority of pain device implanters, but likely comprise the majority of implanters of surgical or paddle-style stimulation leads.[45] In light of the procedure's questionable efficacy and historically underappreciated safety risks, neurosurgeons may reconsider their participation as implanters in patients managed by pain medicine specialists.

Intrathecal Drugs: Evidence Is Elusive

Level I evidence supports the use of intrathecal opioids and drug combinations to treat cancer pain with fewer systemic side effects compared with other routes of opioid administration.[9] Comparable evidence does not exist for noncancer pain, the most common indication. Reviews of intrathecal drug therapy for this indication predominantly are compilations of anecdotal reports and low-level evidentiary sources—often in support of unapproved drug usage, and based upon consensus conferences underwritten by industry.[46–51] In light of the ease with which intrathecal drug therapy achieved statistical and clinical importance in a seminal clinical trial,[9] the lack of comparable evidence to support intrathecal polypharmacy for noncancer pain bears close attention.[52] One explanation—which also applies to other interventional and surgical pain procedures—involves the error of irrational escalation. This is the phenomenon whereby individuals justify increased investment in a series of decisions based on cumulative prior investments, despite evidence that the initial decision was wrong. If modest dosages of morphine do not relieve pain sufficiently after the physician and patient have invested time, trouble, expense, and risk, then in all likelihood higher dosages, higher drug concentrations, and more potent opioids or drug admixtures will not work either—and will entail escalating risks to the patient. The same applies to conversion of an unsuccessful percutaneous stimulation system to a surgical one. We

previously quantified the mortality risks associated with implantation, and the greater risks during long-term intrathecal therapy maintenance in noncancer pain patients.[53,54] Despite published evidence, we have observed no indication that physicians have altered the practice habits of outpatient surgery, therapy escalation, or other controllable risks associated with mortality.

Before prescription opioid mortality risks gained media attention, a few practitioners developed intrathecal microdose programs that claimed to achieve efficacy with minimal risks while proscribing all systemic opioid intake whatsoever. Patient contracts stipulated periodic drug tests for program entry and refills, whereas positive drug tests led to removal of morphine from the device and temporary suspension of therapy. The rationale for this practice—for which we could locate no indexed publications—is to have the patient's cerebral (as opposed to spinal) opioid receptors remain in the naïve state. Patient-physician contracts in light of (to-date) unsubstantiated practices provide a segue into an examination of how social and cognitive phenomena influence patients and physicians so strongly.

Pain Medicine and Pain Surgery: Powerful Stories

If operations and therapies do not work as well as claimed, why do physicians persist and patients go along? The longevity of questionable practices is not extraordinary in light of irrational escalation and other phenomena. Everyone is susceptible to the same fallacies and biases that we ridicule in doctrinaire politicians and inarticulate celebrities. And no medical or neurosurgical exceptions exist to the phenomena of bias blind spots (illusory immunity to bias), ostrich effects (disconfirming information is ignored), and reactive devaluation (arguments against adversarial statements).

The contractual scenario described in the previous section appears to work because patients who enroll are a self-selected and suggestible population willing to surrender autonomy and discretion to an authority in exchange for benefits. In turn, the physician authorities and their staffs provide tangible and intangible rewards to compliant contractees; deviations are punished by withholding rewards. In the example above, if one assumes that intrathecal morphine really helps the patient, weeks without it (and without systemic opioids) means days of withdrawal followed by weeks of pain. Device refill occurs only after a negative drug test scheduled by the physician's office personnel. When stripped of jargon, this scenario entails forced compliance (contract), temptation and sin (positive drug test), punishment and penance (withdrawal and pain), and redemption with forgiveness (resumption of intrathecal morphine)—social control mechanisms characteristic of cults.[55–57]

Contemporary pain medicine involves the same transactional model as the opioid contract, only not so explicitly. The patient dilemma is best understood in light of more than 30 years of social and governmental policies. These have kept unemployment rates artificially low by medicalizing unemployment in the United States (and other Western democracies) under the rubric of disability, Supplemental Security Income, and early access to Medicare.[58] Individuals with persistent pain complaints enter a system that provides benefits on a "no (serious) questions asked" basis. Physician approval yields direct payments, medical insurance coverage, absence from or modification of work duties, narcotic prescriptions, physical therapy, and other ancillary benefits. An intangible benefit is social validation of the patient's illness status. Loss of physician approval—for example, owing to patient dissatisfaction with ineffective therapy—risks economic loss from cancellation of disability payments, medical insurance reimbursement, narcotic prescriptions, and other benefits. In the pain literature patients who report little efficacy from interventions, but who request the continuation of benefits and prescription drugs, are dismissed as being manipulative or nonorganic. Many patients learn, or are coached, to respond to physicians and their office staffs in ways that ensure their benefits will continue. The cycle of expectations, responses, and rewards—wherein caregivers and patients reinforce each other's beliefs—is conscious behavior that does not involve placebo effects.[55] The phenomenon also accounts for the finding that patients uniformly express subjective global satisfaction with a treatment program even when their pain scores do not change during clinical trials or outcome surveys. Patients want to do well, physicians want to do good, and they need to receive fees for their services. In the current system, fees for physician services also must underwrite substantial disability and benefits-related paperwork.

Things That Are Not Evidence

Tradition and Authority

Medical researchers recognized the operation of ordinary biases when they introduced control groups to research in the 1750s and blinding in the 1940s.[59,60] "We have always done it that way" and "because the professor says so" are examples of bias and habits enabled by appeals to authority. Authoritative publications enable physicians to continue practice habits that are not based upon best evidence. Habits are one form of illusion of truth and of repetition effects wherein people identify as true statements that they

have heard before. Habit and authority were in play when William Osler instructed physicians on the proper timing and patient selection for venesection during the 1918 to 1920 influenza pandemic.[61] Marshall and Warren's *Helicobacter pylori* theory of peptic ulcers could not be true because experts knew that bacteria could not survive an environmental pH comparable to that in an automobile battery—except that *H. pylori* could. As a fungal meningitis outbreak linked to epidural corticosteroid injections unfolds, popular media focus attention on the failures of the New England Compounding Center and its regulators. A more fundamental matter is the practice habit of epidural corticosteroid injections, a pain medicine practice habit-based procedure with no efficacy, but with substantial previously identified risks.[62–64]

Quantity versus Quality and Stories That Deserve to Be True

Related examples of nonevidentiary reasoning involve large *N* values (illusion of statistical power), long time intervals (experience), and large numbers of publications (illusions of truth). We previously showed[4–6] that aggregation of flawed data presented in the color of evidence-based medicine creates an illusion of statistical power and clinical meaning.[39–51] Data aggregation does not repair flaws in the underlying data sets, and does not settle questions of analgesic efficacy. The cycle of logical errors is complete when the contributors to such publications consult with industry sponsors who, in turn, rely upon biased advice to inform clinical trial designs and topics for future research.

According to American author, editor, satirist, and critic H.L. Menken, "For every complex problem there is an answer that is clear, simple, and wrong." Despite the 1965 gate theory of pain having been falsified by the early 1970s, tradition, habit, authority, simplicity, and a belief that the originators of the hypothesis deserve to be correct have contributed to the theory's vitality for so many decades.[65]

Social and Cognitive Phenomena

Anchoring Bias

Anchoring or focalism is the tendency to rely on the first information that one perceives when making a series of decisions. It creates a bias that skews the interpretation of newer information toward validation of the initial anchor. Expectancy effects and groupthink may follow anchoring when a patient's physicians accept material in referral records without critical thought or further investigation.[66,67] Anchoring compromises clinical trial data when mistaken or nonexistent diagnoses are accepted at face value in the absence of critical review, an expert neurological examination, or confirmatory tests. Anchoring bias also may lead to treatments that fail to address a patient's real illness—or in extreme cases, that are administered when the patient has no organic pathology. Anchoring bias further allows advocates for particular practices to focus upon early positive reports or phase 1 studies while neglecting controlled studies or long-term data that falsify their hypotheses.[68–70]

Illusion of Explanatory Depth

Neuroanatomy and physiology are difficult subjects to master. Missed or mistaken neurological diagnoses contribute to physician errors in emergency departments and office practice.[71,72] Pain physicians and neurosurgeons who may not have reference sources at hand while reading journal articles, attending medical meetings, or consulting with patients are susceptible to the illusion of explanatory depth—a phenomenon whereby individuals think they understand particular things in far more detail than is actually the case—especially when exposed to new information (the proinnovation bias).[73] **Fig. 58.1** shows examples of complex mechanical and neurophysiological realities in the left-hand column, and examples of the limited knowledge that most individuals have about those mechanisms or physiological principles in the right-hand column. Physician statements and publications sometimes reveal that their knowledge of neural circuitry and pharmacology pertaining to somesthetic sensation often approximates the rudimentary drawings in the right-hand column, not the complex realities (themselves summarized) on the left. Knowledge lacunae are not to blame, but disregard of knowledge deficits can lead to ineffective therapy and patient harm.

Alluring Explanations

Investigators have reported experiments in which three groups—naïve adults, neuroscience students, and neuroscience experts—read descriptions of psychological phenomena followed by one of four types of explanation, according to a 2 × 2 design: good or bad explanation; with or without neuroscience information.[74] The neuroscience information, when provided, was irrelevant (**Fig. 58.2**). Subjects in all three groups judged good explanations as better than bad ones. But subjects in both nonexpert groups (naïve adults and students) responded that explanations that contained irrelevant neuroscience information were better than explanations without the irrelevant material. The neuroscience information had the largest effect on nonexpert preferences for bad explanations, obscuring obvious deficiencies.

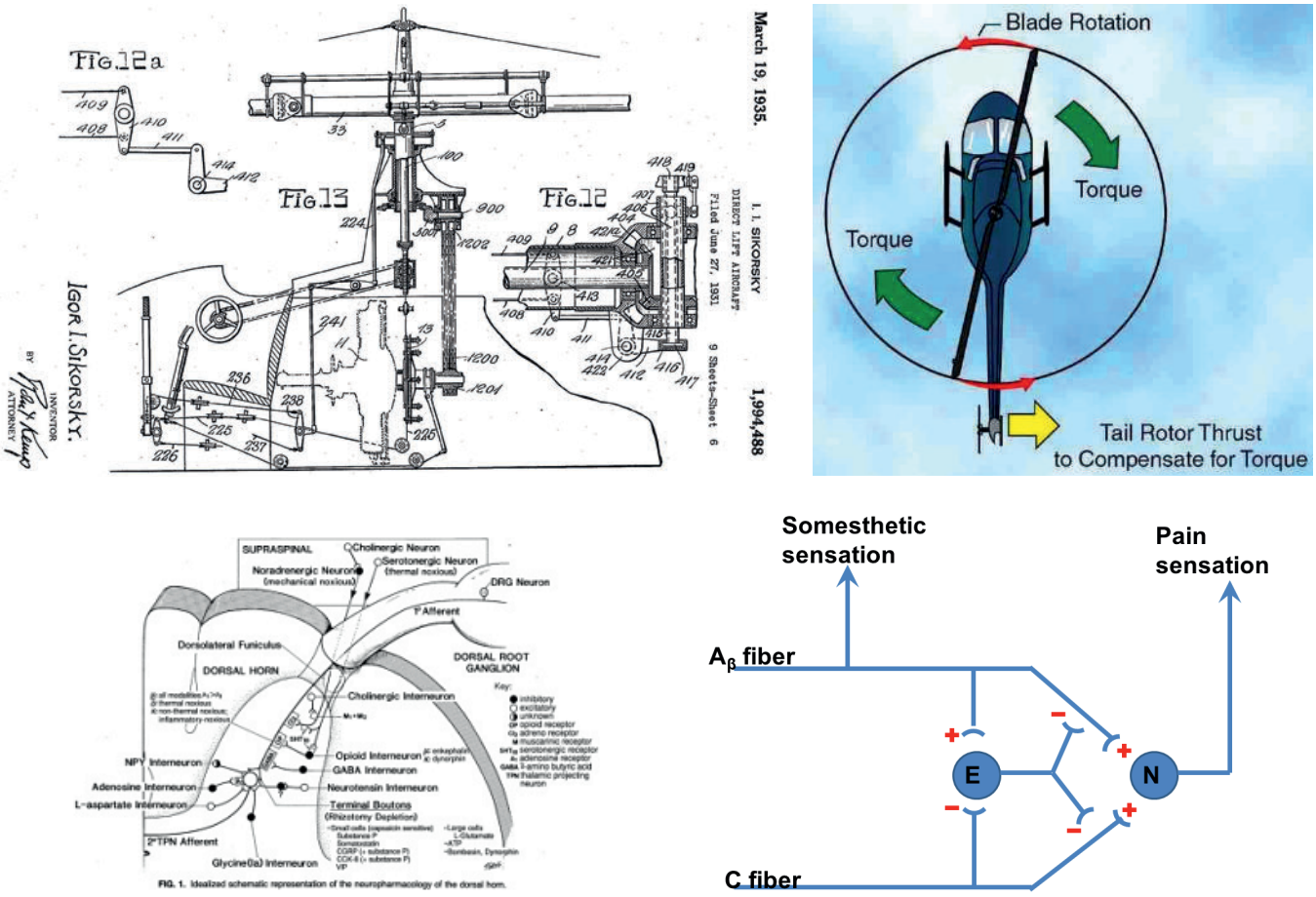

Fig. 58.1 The left-hand column shows examples of complex realities. (*Top*) Igor Sikorsky's patent drawing of a mechanism that eventually became the helicopter, and (*bottom*) a simplified schematic representation of neurotransmitter functions in the dorsal horn of the spinal cord. According to the illusion of explanatory depth,[75] many individuals who express confidence in their understanding of complex realities are, upon questioning, able to convey only limited knowledge, as illustrated in the right-hand column. (*Top left:* Patent Number US 1,994,488 issued March 19, 1935, p. 6. *Top right:* FAA Rotorcraft Flying Handbook, Figure 3-2. Bottom left image reprinted with permission from Raven Press: The general aspects of neuropharmacology of dorsal horn function by Bennett Blumenkopf—in Volume 19, *Advances in Pain Research and Therapy*, edited by BS Nashold Jr and Janice Ovelmen-Levitt. Raven Press, New York, 1991.)

In experiments by other investigators, subjects gave higher ratings of scientific reasoning to mock-scientific articles accompanied by brain images compared with the same articles accompanied by other graphics or no illustrations—possibly representing a subset of pictorial superiority effects **(Fig. 58.3).**[75] The authors surmised that "part of the fascination, and the credibility, of brain imaging research lies in the persuasive power of the actual brain images themselves." Brain images provide "a physical basis . . . appealing to people's affinity for reductionist explanations" — a neuroscientific echo of Menken's observation about the power of "clear, simple, and wrong" solutions to complex problems. A striking feature of the imaging work was the absurdity of the mock research article, entitled "Watching TV Is Related to Math Ability." Purportedly similar levels of activation were found in individuals' temporal lobes when watching television as when solving arithmetic problems.

Superficially persuasive neuroimaging explanations for analgesic efficacy appear frequently in publications. **Fig. 58.3** (bottom) explains the analgesic effects of occipital nerve stimulation in a chronic headache disorder for which subsequent controlled trials, designed in consultation with the article's author, failed to reveal superiority versus the control groups. Incongruence often emerges between initial reports of high (but illusory) explanatory power for functional imaging in other pain-related, neurological, and psychiatric disorders when viewed in retrospect after formal clinical trials reveal no meaningful efficacy.[76–82]

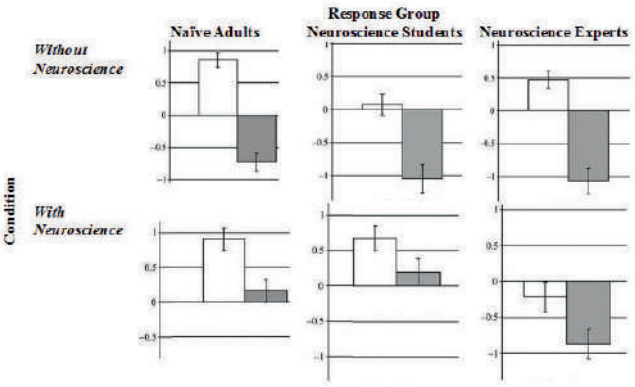

Fig. 58.2 White boxes indicate each group's preferences for the *good* explanation, and gray boxes indicate each group's preferences for the *bad* explanation about the so-called curse of knowledge, a phenomenon in which subjects who know particular facts (e.g., state capitals) find it difficult to adopt the point of view of individuals who do not know those facts.[74] The same irrelevant and untrue neuroscience information was provided to each group for the *good* and *bad* explanations ("Brain scans indicate that this 'curse' happens because of the frontal lobe brain circuitry known to be involved in self-knowledge"). Subjects judged *good* explanations as better than *bad* ones. But naïve adults and students judged explanations that contained irrelevant neuroscience information as better than explanations without the irrelevant material. The neuroscience information had the largest effect on nonexpert preferences for *bad* explanations (bottom left-hand cell).

False Equivalence

False equivalence is a logical error where there is a superficially apparent equivalence, when in fact there is none.[83] The fallacy is expressed in computational terms as "If *A* is the set of *c* and *d*, and *B* is the set of *d* and *e*, then since they both contain *d*, *A* and *B* are equal." The classically absurd example is "They are both soft and cuddly, so there's no difference between cats and dogs." False equivalence need not rely upon specific variables (i.e., soft and cuddly) to exist in sets *A* and *B*, but instead may rely "only [on] a passing similarity."[83] False equivalence underlies statements that a shared trait—for example, holding a doctoral degree—equates with expertise to validate one statement at the expense of another. Framing discussion in this manner allows the dismissal of disruptive facts as matters of opinion.

A salient example was a clinical trial for persistent pain after low back surgery where false equivalence was integral to the trial design.[84] The study was prospective and involved randomization of pain patients to either spinal cord stimulation or repeat open surgery. Data tables and study flow diagrams were straightforward. On formal grounds, the results were Level 1 evidence. However, even Level 1 trials may contain features that warrant closer examination. In this case, subjects were randomized to treatments

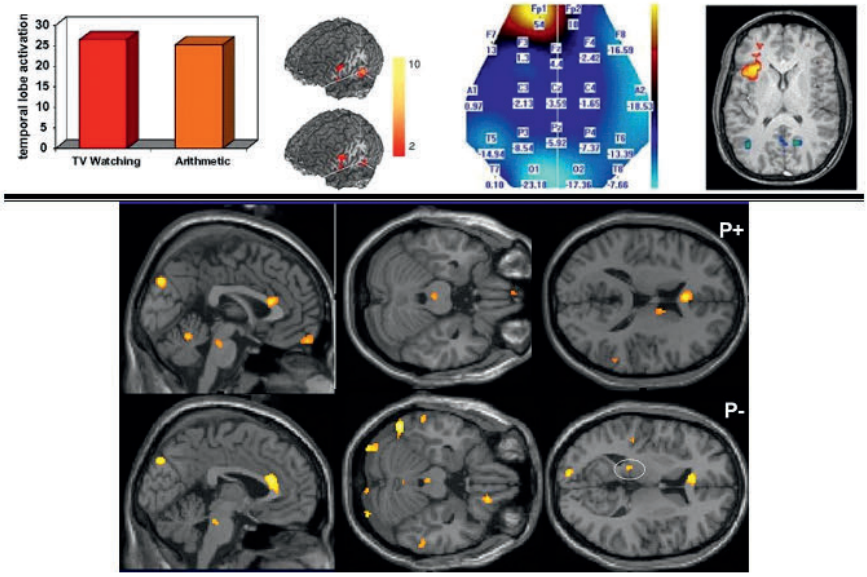

Fig. 58.3 *Top:* Positron emission tomography (PET) brain images versus bar graphs (*top left*), and PET brain image versus a topographical map of brain activation (*top right*).[75] Subjects consistently preferred versions of a mock research article when it was accompanied by bogus PET images. The article was titled "Watching TV Is Related to Math Ability," and it provided fake descriptions of similar activation in the temporal lobes when watching television as when solving math problems. *Bottom:* Montage of PET brain images reporting loci of ipsilateral pontine and thalamic activation due to occipital nerve stimulation in patients with chronic migraine headache. (Top row adapted with permission from McCabe and Castel.[75] Bottom row courtesy of Dr. Peter J. Goadsby.)

that were markedly dissimilar in magnitude, complexity, morbidity, recovery rate, and expectations. After that, five other kinds of major open operations were performed in patients assigned or crossed over to open surgery. Along with falsely equivalent randomization and subsequent treatments, the compound primary endpoint that determined the success of each study arm was based on self-reported pain relief and patient satisfaction. The satisfaction question was "Considering the overall pain relief you have received from this procedure and considering the operation[s], hospitalization[s], discomfort, and expense involved, would you go through it all again for the result you have obtained?"

Elements of the trial design and analysis—false-equivalent randomization, compound endpoint, patient satisfaction question, and unbalanced denominators (survivorship bias, no intention to treat)—created biases in favor of the lesser-magnitude spinal cord stimulation procedure. Uncritical acceptance of such errors invokes the phenomena of illusory immunity to bias; confirmation biases; observer, experimenter, and expectation biases; and backfire effects (disconfirming evidence strengthens original beliefs). These phenomena help to explain experts' perseveration on false comparisons—for example, between SCS and conventional medical care,[85] tendentious econometric analyses,[86] and expert resistance to unbiased analyses and disconfirming evidence.[87]

Misplaced Rationality

The error of misplaced rationalism (or rationality) is the pursuit of rational explanations for a reported phenomenon when there is no good evidence that the phenomenon exists. A classic example is the question "How many angels can dance on the head of a pin?" Misplaced rationality applies to discussions of the original gate theory, and to illusory neuroimaging or mechanism-of-action research when no convincing evidence for analgesic benefits exists. Misplaced rationality also may arise from neglect of the fact that the efficacy of all categories of pain surgery, including highly effective ones, decays over time.[88,89] In the case of neurostimulation, percutaneous lead migration is a commonly cited reason for revision, replacement, or conversion of a surgical lead. Predicate reasoning behind this error conflates diminished analgesia with changes in paresthesias as proof that lead migration has occurred. Years ago we developed devices, evoked-potential-based electrophysiological methods, and experiments to distinguish reliable versus unreliable self-reported loss of paresthesias for this very reason.[90] Lacking objective proof, assumptions about lead migration involve misplaced rationality because enduring analgesic efficacy remains unproven. Moreover, no evidence supports the notion that paresthesias predict analgesia; and apart from occasional cases of obvious dislodgement, migration per se rarely is demonstrated in before-and-after radiographs in cases where the phenomenon is invoked.

Misattribution and Post Hoc Ergo Propter Hoc

The first is the error of attributing a result to a particular cause when other causes are more likely. The second is the error of believing that temporal succession implies a causal relation (after this, therefore because of this). Both are elements of superstition, such as when athletes believe that a pregame ritual or an article of clothing is lucky or unlucky, or can cause a game to be won or lost. Chiropractic, complementary-alternative medicine, folk remedies, and certain pain medicine practices base efficacy claims upon misattribution, post hoc ergo propter hoc, and other logical errors. Given that most minor musculoskeletal aches and pains are self-limited in duration and severity, chiropractors, alternative or folk medicine practitioners, and their adherents misattribute perceived benefits to the treatment when the patients would have gotten well after the passage of time with no treatment. Claims or beliefs that a particular medical or surgical intervention cured a painful condition also are subject to inquiry regarding misattribution or post hoc ergo propter hoc reasoning. The natural history of some painful peripheral or central nervous system disorders (e.g., postherpetic neuralgia, postthoracotomy syndrome) and other injuries is for the pain to fade over a period of months to years.[91–95] Physicians may misattribute eventual patient improvement to the therapy when the same degree of improvement would have occurred after the passage of time. Misattribution also may account for a substantial portion of the perceived efficacy of low-back or articular injections of corticosteroid drugs. Another plausible explanation might invoke systemic effects owing to drug absorption, making the real effects of the injection—apart from the physician's and patient's perception of actively having done something—little different from a course of oral corticosteroid medication.

Illusory Superiority, Dunning–Kruger, and Lake Wobegon Effects

All individuals have difficulty evaluating their own knowledge and performance. Participants in a set of cognitive experiments were given specific tasks (e.g., logic problems, grammar) and were asked to evaluate their own performance relative to the rest of the group.[96] This enabled a direct comparison of actual versus self-perceived performance. Results were

divided into quartiles based upon actual performance. All four groups evaluated their performances as above average (the Lake Wobegon effect), meaning that the lowest-scoring group in the bottom quartile exhibited the largest-magnitude illusory superiority bias. Individuals who performed worst were also the worst at recognizing their poor performances. The two highest-performing quartiles exhibited the least superiority bias because their actual performances were above average. After all four groups received task-specific training and retesting, the lowest quartile performed minimally better, but escalated their self-assessment disproportionately higher. Dunning and Kruger's paper on this phenomenon won an Ig Nobel Prize in 2000.

Illusory superiority also appears in academia (68% of university faculty rated themselves in the top 25% for teaching ability; 87% of students rated their academic performances as above the median), finance (large stock trading volumes reflect the illusion that each trader thinks he or she is more likely to succeed), and law (many lawsuits go to trial because attorneys have an inflated belief that they will win).[97–100]

Conflicts of Interest Are Not Exclusively Financial

In activities related to medicine and health, quid pro quo delivery of something of value in exchange for favors is a betrayal of public trust. Industry standards prohibit the overt exchange of money, lavish gifts, spousal travel, extravagant meals, and other favors for physician participation in industry-sponsored activities, seminars, or promotional events. Most companies adhere to stricter, more explicit standards. The U.S. Food and Drug Administration (FDA) has adopted a waive-and-disclose approach to manage the material conflicts of experts on advisory committees. Only two conditions absolutely exclude a panelist: patent or trademark royalties are payable, or he or she has testified as an expert witness on the matter under consideration. In contrast to the FDA, the National Institutes of Health (NIH) recognizes that conflicts of interest may involve personal or professional relationships and long-standing scientific or personal differences that may distort scientific judgment in the absence of material gain.[101]

However, beliefs and attitudes can go undetected easily when no obvious trails exist to document them. Detection, then, depends upon insider knowledge regarding unfavorable decisions relating to publications or grant proposals that challenge a conflicted reviewer's beliefs or previous work. Another potentially adverse consequence of interest conflicts is the development of therapies in which expert proponents may have intellectual property or academic credibility at stake. Confluent monetary and intangible conflicts, and common errors in reasoning may explain the apparent inability of experts to accept research findings that challenge their beliefs.[102]

The Contemporary Model as Omnishambles

Omnishambles, defined as "a situation that has been comprehensively mismanaged, characterized by a string of blunders and miscalculations," was the Oxford University Press (UK) 2012 word of the year.[103] Omnishambles may aptly describe the current state of affairs with respect to chronic pain diagnosis, and in a broader sense to the contemporary model of pain medicine articulated in a 2011 Institute of Medicine (IOM) report, Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research.[104]

Diagnosis

Surgically Treatable, Nontreatable, and Questionable Noncancer Pain Diagnoses

Neurosurgically Treatable Pain Syndromes
- Trigeminal and glossopharyngeal neuralgia
- Cluster headache
- Plexus avulsion
- Peripheral nerve entrapment
- Failed back surgery syndrome with persistent anatomical findings (e.g., wrong level surgery, inadequate decompression)

Surgically Nontreatable Pain Syndromes
- Facial, limb, or trunk deafferentation pain, except plexus avulsion
- Occipital neuralgia with documented nerve injury
- Postherpetic neuralgia
- Central poststroke pain
- Spinal cord injury pain
- Major causalgia after peripheral nerve injury
- Failed back surgery syndrome without anatomical findings

Pain Syndromes of Questionable Veracity
- Occipital neuralgia without documented nerve injury
- Chronic migraine or variants
- Complex regional pain syndrome (CRPS)-I (reflex sympathetic dystrophy)
- Failed back surgery syndrome without anatomical, imaging, or electrophysiological investigations
- Fibromyalgia
- Interstitial cystitis and other chronic pelvic pain

The lower portion of the accompanying box contains a list of pain diagnoses that vary from having questionable utility to being of improbable veracity. Recent trends in pain nosology have veered toward pathologization of the normal. As we recently observed in a commentary:

> The diagnosis of CRPS-I—and perhaps its existence as a genuine disorder—remains unsettled despite the existence of diagnostic codes. Splitting CRPS-I (reflex sympathetic dystrophy, RSD) from CRPS-II (causalgia) has, in actual practice, provided a diagnostic code for a cohort of patients in industrialized Western countries who are predominantly middle-aged Caucasians (in some series, mostly women) who complain of regional pain that affects one or more body parts in the setting of a trivial soft tissue injury (or no injury), and without a neuroanatomical basis or pattern. In actual practice, as opposed to theory, it is nearly impossible to rule out CRPS-I in the presence of otherwise inexplicable pain complaints. These are not the patients that Mitchell, Morehouse & Keen described nearly 150 years ago.[105] Although trivial soft-tissue injuries have troubled our ancestors since pre-historic times, the emergence of CRPS-I as a nosologic entity has coincided with the growth of interventional pain medicine. Genuinely organic cases of persistent pain after paper cuts, hang-nails, or similar injuries may exist, but the demographics of CRPS-I and the permissive way the diagnosis is applied arguably suggests a predominantly socio-cognitive-behavioral (psychiatric) disorder. This raises the matter of what, besides unexplained or at least questionably physiological pain, physicians are treating.[106]

Arguably, the same goes for nonfalsifiable disorders such as chronic migraine, general neuropathic condition, fibromyalgia, interstitial cystitis, and others. A skeptic might observe that fictitious therapies work best for these fictitious illnesses. French writer Anatole France's remarks upon visiting the shrine at Lourdes likely are apocryphal. He is said to have exclaimed, "What, what, *no wooden legs*?" or "All those canes, braces and crutches, and not a single glass eye, wooden leg, or toupee!" The accurate passage goes "Happening to be at Lourdes, in August, I paid a visit to the grotto where innumerable crutches were hung up in token of cure. My companion pointed to these trophies of the sick-room and hospital ward, and whispered in my ear: 'One wooden leg would be more to the point.' It was the word of a man of sense."[107]

Diagnostic Dichotomies Deconstructed

Cancer versus noncancer pain, acute versus chronic pain, somatic versus visceral pain, peripheral versus central pain, and presently, nociceptive versus neuropathic or deafferentation pain are diagnostic dichotomies without nosologic utility for patient selection or predictive value for the results of pain surgery. We have shown that expert investigators consistently apply the nociceptive versus neuropathic distinction in an arbitrary manner in clinical trials and case series, between patients with the same underlying diagnoses at different centers, and among different patients with the same diagnosis at the same center.[4–6] The present author previously subscribed to these errors before considering the work of P.W. Nathan (recommended by R.R. Tasker, personal communication, 1987) and others. Studies of differential neural blockade, induced pain, and single-unit recordings[108,109] suggest that another pain categorization schema—namely, transmitted versus nontransmitted pain—may have greater utility. Regardless of amenability to surgical treatment, one can map any of the well-established diagnoses listed in the two upper sections of the text box on the previous page to peripheral or central territories of innervation. The principle applies to so-called central pain after a brain or spinal cord injury in that such pains respect anatomical and physiological principles (e.g., laterality or spinal sensory levels). Diagnoses of uncertain or improbable veracity often fail to respect such boundaries, or fluctuate across nonanatomical boundaries without explanation. Whether or not one is disposed to discard other pain categorization schemata, the notion of transmitted versus nontransmitted pain has diagnostic utility and some therapeutic predictive value, and should be less susceptible to arbitrary application than other categorization methods.

The Contemporary Model

Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research (2011 Institute of Medicine Report)

IOM authors and reviewers represented broad interests: business, divinity, journalism, neuroscience, naturopathy and acupuncture, and patient advocacy. Contributors included medical specialists in anesthesiology, bioethics, chronic diseases, dentistry, epidemiology and biostatistics, health systems, microbiology and immunology, neurology, neurosurgery, nursing, oncology research, oral and maxillofacial surgery, pain medicine, palliative care, pediatrics, pharmacology, psychiatry, and psychology. Summary excerpts of principles, findings, and recommendations from the IOM report are reproduced and discussed below.[8] The inclu-

siveness of committee work is a virtue within the contemporary social zeitgeist; but virtue is not immunity against examination for errors, biases, and faulty logic.

> *Common chronic pain conditions affect at least 116 million U.S. adults at a cost of $560–635 billion annually in direct medical treatment costs and lost productivity.*

The United States does not contain 116 million chronic pain patients unless one down-defines chronic pain considerably. As of the 2010 census, the 308,746,000 U.S. residents included 225,479,000 adults age 20 and above. One hundred sixteen million pain patients would comprise greater than 51% of adults residing in the United States.[110] The statistic arises from counting ailments that people self-treat with over-the-counter analgesics, and that neurosurgeons would not encounter in patients. Many would not seek medical care, much less require multidisciplinary management. Moreover, adding direct medical costs (an empirical number) and lost productivity costs (an assumption-dependent number) yields inaccurate social cost estimates. The range of $560 to $635 billion annually yields a per-patient range of $4,827 to $5,474. That is an overestimate because those who use over-the-counter or prescription nonnarcotic analgesics do not incur such sums per year in pain-related costs and lost wages. The IOM cost range also is an underestimate because the numerator of 116 million is inflated. A smaller number of individuals who receive medical, prescription narcotic drug, surgical, interventional, and other pain management treatments each spend (and cost society) considerably more than the IOM average per year. In fact, overall U.S. health care spending currently exceeds $8,000 per capita, per annum. A neurosurgical operation or a medical device implant can cost three times that amount. More accurate calculations would find many fewer patients in the pain care system, but at greater per-capita expense. The deployment of unsupportable statistics is a long-standing practice among social policy agencies and advocates.[111]

> *Chronic pain can be a disease in itself [and] has a distinct pathology, causing changes throughout the nervous system that often worsen over time. It has significant psychological and cognitive correlates and can constitute a serious, separate disease entity.*
>
> *Pain results from a combination of biological, psychological, and social factors and often requires comprehensive approaches to prevention and management.*
>
> *Given chronic pain's diverse effects, inter-disciplinary assessment and treatment may produce the best results for people with the most severe and persistent pain problems.*
>
> *The effectiveness of pain treatments depends greatly on the strength of the clinician–patient relationship; pain treatment is never about the clinician's intervention alone, but about the clinician and patient (and family) working together.*

These interrelated propositions contain several contradictions. One struggles to grasp how observable pathology throughout the nervous system (this statement, incidentally, is false) and psychosocial and cognitive correlates can cohabit consecutive sentences. If pain were a disease rather than a behavioral expression, quintessential subjectivity would not be such a steep stumbling block to collective understanding. Painful pathological processes, including cancerous tissue destruction, respond to specific treatments, not to interdisciplinary conferences in the absence of specific treatments. The most at-risk patients under the current system are those with genuine neural injury–related pain that does not respond well to surgical or device-based therapies. They are disabled, subjected to escalating levels of ineffective and/or risky procedures, and endure demeaning psychobehavioral programs to preserve official legitimacy and receive needed benefits. Patients without underlying organic pathology comply with the psychobehavioral model when tangible rewards and validation are forthcoming. But medicalization of nonorganic patients still puts them at risk from unnecessary somatic therapies. Such individuals used to be labeled as crocks. Despite its pejorative sound, the absence of discernible, treatable pathology implicit in that label protected patients from receiving prescriptions for opioid drugs, invasive interventions and operations, and possibly iatrogenic harm. Expressions of pain that require medical attention should more closely resemble the top portion of the text box on page 613 than the bottom. The IOM may have made more progress by reconsidering the utility of current diagnoses rather than advocating so strenuously for physicians to accept patient self-reports at face value, and prescribe accordingly. Cautious neurosurgeons should demand anatomical and physiological concordance between complaints, diagnostic signs, and characteristic symptoms before performing surgery for all painful conditions—the same as they do for trigeminal neuralgia, plexus avulsion injuries, or peripheral nerve entrapment.

> *Chronic pain has such severe impacts . . . that every effort should be made to achieve both primary prevention (e.g., in surgery for a broken hip) and secondary prevention (of the transi-*

tion from the acute to the chronic state) through early intervention.

While there is much more to be learned . . . existing knowledge is not always used effectively, and thus substantial numbers of people suffer unnecessarily.

[E]ducation can help counter the myths, misunderstandings, stereotypes, and stigma that hinder better care.

Nobody can prevent pain by repairing a broken hip or by any other means. And the notion of secondary prevention is a canard against the medical profession, implying that chronicity emerges predominantly because of lack of proper or timely medical attention. Neurosurgeons bear daily witness to congenital deformities, traumatic injuries, or strokes wherein the chronicity and intractability of painful syndromes arise de novo regardless of the adequacy of care or interventions that are undertaken early on. The IOM committee's implication that experts possess specific knowledge and abilities to prevent acute pain from becoming chronic is a case of mistaken rationality: acute pain does not necessarily become chronic, and chronic intractable neural injury–related pains arise de novo. Adoption of the multidisciplinary model advocated by the IOM—or adoption of any particular belief system—does not prevent chronic pain.

[W]hen opioids are used as prescribed and appropriately monitored, they can be safe and effective, especially for acute, postoperative, and procedural pain, as well as for patients near the end of life who desire more pain relief.

If the statement were posed as a question, the correct answer would be "false." If opioids were prescribed as needed and in the quantities required, the surplus of prescription opioids currently available for nonmedical consumption would not exist. That surplus did not exist before experts in pain management and ethics legitimized the long-term usage of prescription oral opioid drugs in outpatients with chronic pain. The medical basis for this policy shift was the mistaken belief that pain patients were a different neurophysiological species from drug addicts. Physician acceptance of self-reported pain symptoms meant that pain patients would not become addicts who crave drugs, but merely manageably habituated. But no evidence exists that a medical record diagnosis influences opioid receptors, the development of tachyphylaxis, μ-receptor up-regulation or down-regulation, dosage escalation, or withdrawal phenomena.[112,113] It is not physiology that distinguishes the patient from the addict, merely the milieu within which the drugs are distributed: pharmacy versus street. Patients with legitimate diagnoses or questionable diagnoses will visit physician offices regularly to ensure a continued supply of opioids to which they have become habituated. The policies advocated and taught by experts, ethicists, and advocates have created the present epidemic of prescription narcotic overdose deaths. Broadening the same policies is unlikely to reverse the trend.

Effective pain management is a moral imperative, a professional responsibility, and the duty of people in the healing professions.

Many features of the problem of pain lend themselves to public health approaches—concern about the large number of people affected, [and] disparities in occurrence and treatment.

The first statement is true, but not necessarily in the context of policies and practices advocated in the IOM report. Neurosurgeons may find that skepticism about uncertain diagnoses and therapy expectations better fulfills their medical duties and yields more satisfying operative results than the open-ended approach to pain medicine practice advocated by the IOM committee. The second statement, especially the "disparities" clause, refers to the established fact that medically underserved populations exist in the United States based on class, race, and ethnicity. In general medical and public health terms, such differences warrant correction. Ironically, in the case of pain management, otherwise disturbing disparities may be saving pain patients in those underserved populations from the frustrating experience, expense, and potential harms associated with prescription drug overuse and ineffective or risky interventions and operations.

Multidisciplinary Bottom Line

We are aware of no unbiased analyses that contradict the findings from a long-term study of 300 injured workers that was published approximately 10 years ago. "At 4.6 years follow up, there was no evidence that pain center treatment affects either disability status or clinical status of injured workers."[37]

Conclusion

According to Irish playwright George Bernard Shaw, "That a believer is happier than a skeptic is no more to the point than the fact that a drunken man is happier than a sober one." Evidence does not appear to influence medical practice habits any more than in other social domains where the phenomenon has been examined: education, finance, and law. Tradition, authority, pow-

erful stories, common biases, and reasoning errors endow pain medicine with many attributes of a cult.[59] Similar attributes pertain to subspecialties in stereotactic and functional neurosurgery, and to medicine in general. Consequently, generational shifts among students and trainees, accompanied by a new skepticism borne of economic and social retrenchment during recessionary times, are more likely to transform pain medicine practices than any journal article, textbook chapter, or institute report.

Pain Surgery Is a Part of, Not Apart from, General Neurosurgery

Neurosurgeons have the capacity to reassert primacy as the best-qualified physicians to identify and treat patients with painful conditions that respond to effective operations. Department chairs have the authority to ensure that trainees and students are well schooled in diagnostic reasoning, and that residents and fellows learn how to perform operations that produce predictable and successful results. Such departmental norms may entail a polite separation from pain medicine clinics. Separation may be the best way to insulate surgeons from pressure to participate in potentially risky and irrational therapy escalation practices.

Neurosurgical Primacy Can Diminish the Supply Side of Chronic Pain

The next generation of neurosurgeons to pursue subspecialty expertise in stereotactic, functional, and pain surgery may—like emeritus officers of the specialty societies—decide to maintain a general practice in spinal and cranial surgery. They may then have an opportunity to interdict chronic pain by the judicious practice of spine surgery, in contrast to the performance and coding of operations to maximize reimbursement.[114,115]

Skepticism and Logic Beyond Pain

Principles of evidence and of error avoidance may apply broadly to the recent enthusiasm for surgical therapies and implanted devices to treat psychological and behavioral disorders. Neurosurgical history in this domain has not reflected well on the specialty, revisionist histories notwithstanding.[116–125] As in the theory and practice of pain medicine, current nosology in psychiatric and behavioral medicine is unstable, subject to core disputes over pathologization of the normal, and subject to bootstrapping from hypothetical treatments for one disorder to another.[126] Contrary publications in clinical neurosurgical journals, even in experimental animals, are unusual.[127] Disinterested faculty within academic departments and neurosurgical societies already have a platform from which to advocate rational inquiry and thereby minimize harm to patients from the interplay of errors, illusions, and fallacies that dominate current discussions in pain medicine and functional neurosurgery.

Disclaimer

The author is solely responsible for the content of this chapter, which does not necessarily represent the ideas of any other person or entity. All of the information contained herein has been published previously, presented in public, and/or is available on the Internet/World Wide Web.

Editor's Comments

My advice is to stop right now, and read this chapter again. Dr. Coffey presents a dense array of ideas, which makes this perhaps the most important chapter in this book. Whether you agree with every argument in this chapter, working through each section can pave the way for a renaissance in critical thinking in our specialty.

Pain medicine and pain surgery are at a nexus. Over the past 40 years the treatment of pain has become a substantial part of medical practice, and a large industry. As Dr. Coffey points out, much of that development has been driven by economic influences, which has advanced aspects of interventional pain management, including surgery, well beyond what the evidence would reasonably support. Coupled with that, the liberalization of opiate usage and the medicalization of a host of conditions of dubious substance have created an environment that is in dire need of revision.

Change in pain medicine will not be easy. An entire generation of specialists have grown up during this era, and their combined vested interests, personal and industrial, will slow the pace of progress. To some extent, as Dr. Coffey suggests, a generational change will be required. This is why setting a high bar for the next generation of pain clinicians will represent the most potent change agent.

I am grateful to Dr. Coffey for his sustained commitment to changing the dialogue in pain medicine. Although it is probably true that "generational shifts among students and trainees . . . are more likely to transform pain medicine practices than any journal article, textbook chapter, or institute report," I am hopeful that this chapter will make a difference.

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59 Bridging the Gap: Translational Research and Pain Surgery

Kim J. Burchiel and Mary M. Heinricher

A century after the ablation of sensory pathways was first used to alleviate pain in humans, it does not seem likely that new breakthroughs will occur in destructive procedures for chronic pain control. Certainly, percutaneous anterolateral cordotomy remains an underutilized procedure for regional pain control in cases of cancer-related pain, and its use should be expanded. There may also still be a role for procedures such as cingulotomy for cancer pain, but this would have to be reserved for very select cases. The absence of a "labeled line" for pain in the suprasegmental central nervous system (CNS) forces us to be much more discreet, and creative, in the analysis of the potential future methods of surgical pain management.

Given the general practice trend away from destructive procedures, our conclusion is that pain surgery will continue to be dominated by *neuromodulation*. However, the forefront of our field may well reside in *neuroreconstruction*. The inception of serious studies in the *genomics* of pain disorders may illuminate mechanisms by which chronic pain, particularly neuropathic pain, develops and is perpetuated. This chapter discusses examples of all three of these areas, including ongoing research and suggestions for investigation.

Neuromodulation

The theory that certain extant elements of the nervous system could inhibit pain perception was conceived by Noordenbos.[1] In 1953 he observed that a signal carried from the area of injury along large-diameter "touch, pressure, or vibration" fibers might inhibit the signal carried by the thinner "pain" fibers, with the ratio of large-fiber signal to thin-fiber signal determining pain intensity. This was taken as a demonstration that the profile of fibers stimulated (large or small) could influence the perception of pain intensity.

Later Melzack and Wall introduced their "gate control" theory of pain in the 1965 *Science* article "Pain Mechanisms: A New Theory."[2] The authors proposed that large- (touch, pressure, vibration) as well as small-diameter (pain) axons carry information from the site of injury to both transmission cells that carry the pain signal up to the brain, and inhibitory interneurons that tend to block pain transmission. Their concept was that although activity in both small- and large-diameter fibers *excites* transmission cells, small-fiber activity *blocks* the inhibitory cells (allowing the transmission cell to fire). By contrast, large-diameter fiber activity *excites* the inhibitory cells (inhibiting transmission cell activity).

Melzack and Wall also hypothesized that input generated by an injury could be conveyed to the brain, where it could trigger a signal back down the spinal cord to modulate inhibitory cell activity. This was the first fully conceived model of the neuromodulation of pain.

Within a few years of the gate theory proposition, Shealy[3] described the analgesic effects of stimulating the dorsal columns, an ascending pathway comprising large fibers conducting touch, vibratory, and position sense. Based on the gate theory, he postulated that pain could be inhibited by invoking pure large-fiber input to the dorsal horn and suprasegmental systems. This technique became known as "dorsal column stimulation," and later as simply spinal cord stimulation. Today this is the most widely practiced technique of neuromodulation. Shortly after the introduction of spinal cord stimulation, *peripheral nerve* stimulation was established for pain control, and is still used for a variety of conditions.

Electrical stimulation of other parts of the nervous system has been somewhat less successful. Chapters 36 and 37 detail the history of motor cortex stimulation (MCS) and deep brain stimulation (DBS) for pain. Although both of these techniques enjoyed early enthusiasm and produced seemingly gratifying results, predictable and durable pain relief has not been a reliable characteristic of either. There is no U.S. Food and Drug Administration (FDA)-approved device

for delivery of either MCS or DBS, and almost no insurance plan in the United States, including Medicare, will fund these approaches.

Another mode of neuromodulation involves intrathecal administration of pharmacological agents. As discussed in Chapter 38, many agents, including μ-agonist opioids, have been used with success. To date, no agent has been found that both successfully targets neuropathic pain with high efficacy and has an acceptable side effect profile. The search for a specific agent that can be used intrathecally goes on.

In retrospect, why have some neuromodulation procedures endured and others disappeared? Although the data to support the use of spinal cord and peripheral nerve stimulation are limited and not up to contemporary standards, these procedures were established historically more than four decades ago, and persist to some extent due to the momentum of past practice. Despite the lack of high-quality evidence to support these techniques, overall patient and surgeon satisfaction with both procedures has sustained these practices. That, combined with their relative simplicity and safety, keeps them in the mainstream of surgical pain management. In general, the patient experience with both DBS and MCS has largely been disappointing. That, combined with their relative technical difficulty and potential morbidity, has contributed to their waning application.

How, then, can neuromodulation be improved? The answer may lie in physiology or imaging.

Physiology

Our knowledge of descending control systems and their role in pain modulation has grown substantially over the past several decades. The critical output node is in the rostral ventromedial medulla (RVM, see Chapter 2). Are there surgical approaches to this region that are practical, and can we take advantage of our understanding of "on" and "off" cells? Given the location, small size, and dispersion of the RVM, it is unlikely that we can stimulate these cells selectively by any existing methodology. Since the pain-facilitating "on" cells and pain-inhibiting "off" cells have distinct pharmacology, selective activation of cells by microinfusion may be a possibility, but this goal also defies current technology. The major hope for selective manipulation of descending influences from the RVM might be cellular transplantation (see below), control of genetic expression through viral or other vectors, or selective activation of inhibitory RVM cells by pharmacological means.

Are there areas in the brain that are safer and more accessible to neurostimulation that can indirectly influence the RVM? This question harkens back to periaqueductal gray (PAG) stimulation, the history of which was neither positive nor encouraging. However, stimulation could be effective if local activation of a more rostral pathway could activate RVM indirectly, thereby overcoming the impracticality of stimulating such a small center within the medulla.

As noted in Chapter 2, the parafascicular nucleus (Pf) in the medial thalamus receives ascending projections from the PAG. In animal studies, neurons in Pf respond to noxious cutaneous or visceral stimulation over large receptive fields, and electrical stimulation or morphine microinjection in this area produces antinociception, preferentially suppressing the "emotional" component of pain. Would stimulation of Pf by electrical or chemical means be a safer means of producing analgesia? If neuromodulation for pain is to be resurrected, careful hypothesis-based clinical studies will be required. Candidate targets like Pf could be systematically reexplored to determine if pain perception can be alleviated by electrical or chemical stimulation.

Imaging

Functional magnetic resonance imaging (fMRI) scans may provide some insight into the roles of various brain regions in the perception of acute and chronic pain. As Coghill notes in Chapter 57, based on imaging, both the prefrontal and insular cortex may be involved in the processing of pain sensation.

The prefrontal cortex may be involved in the affective processing of pain, and incidental collateral stimulation of this region during precentral stimulation may well be the mechanism by which MCS is (inconsistently) effective. A reappraisal of MCS based on this hypothesis might be worthwhile.

The anterior insula is another candidate area that may be involved in the integration of "meaning" during nociceptive processing. It receives input from the amygdala, parahippocampal gyrus, and prefrontal cortex and has been proposed to be one part of a corticolimbic pathway for somatosensory information. The insular cortex may also provide a route for cognitive modulation of pain, and may be the substrate for pain modulation by placebo or by meditation. It is known to project directly to the RVM, raising the possibility that it could serve as a gateway to descending control. The anterior insular cortex may therefore represent another region that could be activated by electrical stimulation.

■ Neuroreconstruction

Neuropathic pain is at least in part due to durable changes in the CNS that are likely both segmental and suprasegmental. There is a long-held concept that inhibition in the ascending "system" may be deficient, or that sensitization develops that biases sensory neurons to levels or patterns of response that are perceived as painful. For example, the excitabil-

ity of nociceptive dorsal horn neurons is known to be abnormally enhanced in animal models of nerve injury.[4,5] These pathologic response patterns may be the underlying basis of chronic neuropathic pain. Restitution of more normal response patterns, either by reversal of neuronal hyperactivity or by increased inhibition, has been the Holy Grail of pain research over the past few decades.

Basbaum and colleagues[6] have recently shown that transplantation of immature telencephalic GABA-ergic interneurons from the mouse medial ganglionic eminence (MGE) into the adult mouse spinal cord dorsal horn completely reverses the mechanical hypersensitivity produced by peripheral nerve injury. Underlying this improvement is a remarkable integration of the MGE transplants into the host spinal cord circuitry, in which the transplanted cells make functional connections with both primary afferent and spinal cord neurons. By contrast, the MGE transplants are not effective against inflammatory pain. These findings suggest that MGE-derived GABA-ergic interneurons overcome the spinal cord hyperexcitability that is a hallmark of nerve injury–induced neuropathic pain.

The potential for the dorsal horn to be "rebuilt" by cellular transplantation is extremely exciting, and is perhaps the only example of cell transplantation that not only produces both viable and integrated cells, but also reverses a neurological problem—in this case pain. The implications of this work for the field of spinal cord reconstruction, for the treatment of neuropathic pain, and for neurological surgery are substantial.

Genomics

In 1990 Devor and his associates[7] at the Hebrew University in Jerusalem showed that a behavior thought to be a consequence of hyperalgesia from a deafferenting nerve injury in rats, autotomy, appeared to be an inherited trait. Male and female rats underwent transection and ligation of the sciatic and saphenous nerves, and the development of autonomy was monitored. The deafferented animals were then interbred, with the strict selection of males and females that expressed relatively high (HA) and, alternatively, relatively low (LA) levels of autotomy. Offspring were similarly operated on and interbred. By the sixth generation of selective breeding, lines were achieved in which autotomy was consistently high or consistently low. There was no indication of gender linkage. Signs of thermal or mechanical hyperalgesia were linked to the autotomy behavior. F1 hybrids, formed by crossing homozygous HA and LA animals, showed low levels of autotomy, similar to LA stock.

These results indicate that there was a *recessive* inheritance of the autotomy trait. Furthermore, back-crossing F1 hybrids onto the LA line yielded a low autotomy phenotype in almost all cases, whereas back-crossing F1 hybrids onto HA stock yielded about 50% high autotomy and 50% low autotomy. These ratios are consistent with *simple Mendelian inheritance of a single gene*. Taken together, the data suggest that autotomy is inherited as a *single-gene autosomal recessive trait.*

This was perhaps the initial and most definitive evidence that certain neuropathic pain states may have a genetic component. The implications were clear: the variability in the phenotype of patients with neuropathic pain disorders that is commonly seen in the clinical setting may ultimately have a strong genetic basis. This theory has been bolstered by evidence that a variety of genetic polymorphisms may be responsible for the conversion of acute nerve injury into a chronic neuropathic pain state.

For example, the susceptibility to chronic pain following a nerve injury has been shown to be affected by a protein (CACNG2) that is intimately involved in the trafficking of glutamatergic AMPA receptors.[8] Further, a mutation (P451L) of the gene that encodes for an ionotropic ATP-gated receptor (P2X7R) also regulates variability in chronic pain sensitivity.[9] Finally, multiple chronic pain states are associated with a common amino acid–changing allele in a potassium channel subunit (KCNS1).[10] It also appears that the transition from acute postoperative pain to chronic pain may have predictable genetic markers, the analysis of which may indicate more aggressive pre-emptive analgesic treatment in individuals who are determined to be at risk for the development of chronic postsurgical pain.[11] As the field of pain genetics rapidly expands, it is likely that the genetic and molecular bases of particular pain states will be uncovered.

One of the best-characterized pain syndromes is type 1 trigeminal neuralgia (TN1). As discussed in Chapter 41, it appears that neurovascular compression (NVC) of the trigeminal nerve cannot be the sole mechanism behind this disorder, as almost one third of patients with TN1 do not exhibit NVC, and 99.96% of individuals with trigeminal NVC do not have TN1. TN1 also seems to recur at a steady rate after microvascular decompression (MVD), and at the time of a second MVD renewed NVC is almost never found. Thus, if TN1, either in its primary presentation or at the time of recurrence after MVD, is not clearly related to NVC, there must be some other common origin. There is no clear amilial inheritance pattern for TN1, so a single gene is unlikely to be the cause. A polygeneticor epigenetic pattern may be discovered that predisposes individuals to TN1. In that case, NVC may associated, but not required to produce TN1, and NVC may simply be one factor acting in concert with that genetic substrate to produce the syndrome. If we accept the genetic model, then it is possible that other factors, such as demyelination from multiple

sclerosis or nerve compression from a tumor, may also combine to produce TN1.

Currently an international effort is under way to discover the genes that predispose individuals to the development of TN1. The results of this study may well point the way for genomic analysis of other pain disorders.

Conclusion

Innovation in surgical pain management has plateaued over the past several decades because we have not made a completely successful transition from destructive to nondestructive procedures. We have not fully exploited our knowledge of the anatomy and physiology of pain perception. Recent insights into the mechanisms of CNS pain modulation combined with advances in imaging may well direct future surgical pain therapies. Genomic studies will almost certainly enhance our understanding of the development of neuropathic pain, and this work will allow us to both target and individualize therapies going forward. The possibility that we may also be able to *correct* pathologic networks in the dorsal horn, and higher centers, thereby palliating or eliminating neuropathic pain, is obviously very exciting. The treatment of chronic pain is likely to take many new directions in the coming years, and surgeons will be participants in these developments only if they continue to be actively involved in the discovery process.

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