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Timothy R. Deer
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Treatment of Chronic Pain by Interventional Approaches

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Textbook on Patient Management

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To my wonderful wife, Missy, and the blessings I have been given in my children Morgan, Taylor, Reed, and Bailie.
I also want to thank my team for their awesome, continued support: Chris Kim, Rick Bowman, Doug Stewart, Matt Ranson, Jeff Peterson, Michelle Miller, Wil Tolentino, and Brian Yee.

Timothy R. Deer, M.D.

To all of my mentors, colleagues, and patients who have taught me about pain medicine. I would also like to acknowledge the patience and love of my family, particularly my children, Isabelle and Adam, as well as Brad, PFP, and little Mia. I have discovered more about myself during my short career than I thought possible and hope to help many more people cope with pain in the exciting future.

Michael S. Leong, M.D.

To my very supportive wife, Gowthy, and my wonderful kids: Dhanya and Arjun Asokumar.

Asokumar Buvanendran, M.D.

To my very supportive wife, Claire, and my wonderful kids: Alex, Keira, and Grant.

Philip S. Kim, M.D.

To my children, Neha, Anjali, and Naresh, for their patience, support, and understanding.

Sunil J. Panchal, M.D.

Foreword to *Comprehensive Treatment of Chronic Pain by Medical, Interventional, and Integrative Approaches*

A brand new textbook is a testament to many things—an editor's vision, many authors' individual and collective expertise, the publisher's commitment, and all told, thousands of hours of hard work. This book encapsulates all of this, and with its compendium of up-to-date information covering the full spectrum of the field of pain medicine, it stands as an authoritative and highly practical reference for specialists and primary care clinicians alike. These attributes would be ample, in and of themselves, yet this important addition to the growing pain medicine library represents a rather novel attribute. It is a tangible embodiment of a professional medical society's fidelity to its avowed mission. With its commission of this text, under the editorial stewardship of highly dedicated and seasoned pain medicine specialists, the American Academy of Pain Medicine has made an important incremental step forward to realizing its ambitious mission, "to optimize the health of patients in pain and eliminate the major public health problem of pain by advancing the practice and specialty of pain medicine."

This last year, the Institute of Medicine (IOM) of the National Academies undertook the first comprehensive evaluation of the state of pain care in the United States. This seminal work culminated in a report and recommendations entitled "Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research." Clearly, as a nation, we have much work to do in order to meet the extraordinary public health needs revealed by the IOM committee. This comprehensive textbook is both timely and relevant as a resource for clinicians, educators, and researchers to ensure that the converging goals of the American Academy of Pain Medicine and the Institute of Medicine are realized. This book has been written; it is now all of ours to read and implement. Godspeed!

Salt Lake City, UT, USA — Perry G. Fine, M.D.

Foreword to *Comprehensive Treatment of Chronic Pain by Medical, Interventional, and Integrative Approaches*

The maturation of a medical specialty rests on both its ability to project its values, science, and mission into the medical academy and the salience of its mission to the public health. The arrival of the American Academy of Pain Medicine (AAPM)'s *Comprehensive Treatment of Chronic Pain by Medical*, *Interventional*, *and Integrative Approaches*: *the American Academy of Pain Medicine Textbook on Patient Management* is another accomplishment that signals AAPM's emergence as the premier medical organization solely dedicated to the development of pain medicine as a specialty in the service of patients in pain and the public health.

Allow me the privilege of brief comment on our progress leading to this accomplishment. The problem of pain as both a neurophysiological event and as human suffering has been a core dialectic of the physician-healer experience over the millennia, driving scientific and religious inquiry in all cultures and civilizations. The sentinel concepts and historical developments in pain medicine science and practice are well outlined in this and other volumes. Our history, like all of medicine's, is replete with examples of sociopolitical forces fostering environments in which individuals with vision and character initiated major advances in medical care. Thus the challenge of managing chronic pain and suffering born of injuries to troops in WWII galvanized John Bonica and other pioneers, representing several specialties, into action. They refused to consider that their duty to these soldiers, and by extension their brethren in chronic pain of all causes, was finished once pain was controlled after an acute injury or during a surgical procedure. They and other clinicians joined scientists in forming the IASP (International Association for the Study of Pain) in 1974, and the APS (American Pain Society) was ratified as its American chapter in 1978. Shortly thereafter, APS physicians with a primary interest in the development of pain management as a distinct medical practice began discussing the need for an organizational home for physicians dedicated to pain treatment; in 1984, they formally chartered AAPM. We soon obtained a seat in the AMA (American Medical Association). Since then, we have provided over two decades of leadership to the "House of Medicine," culminating in leadership of the AMA's Pain and Palliative Medicine Specialty Section Council that sponsored and conducted the first Pain Medicine Summit in 2009. The summit, whose participants represented all specialties caring for pain, made specific recommendations to improve pain education for all medical students and pain medicine training of residents in all specialties and to lengthen and strengthen the training of pain medicine specialists who would assume responsibility for the standards of pain education and care and help guide research.

Other organizational accomplishments have also marked our maturation as a specialty. AAPM developed a code of ethics for practice, delineated training and certification requirements, and formed a certifying body (American Board of Pain Medicine, ABPM) whose examination was based on the science and practice of our several parent specialties coalesced into one. We applied for specialty recognition in ABMS (American Board of Medical Specialties), and we continue to pursue this goal in coordination with other specialty organizations to assure the public and our medical colleagues of adequate training for pain medicine specialists. We have become a recognized and effective voice in medical policy. The AAPM, APS, and AHA (American Hospital Association) established the Pain Care Coalition (PCC), recently joined by

the ASA (American Society of Anesthesiologists). Once again, by garnering sociopolitical support galvanized by concern for the care of our wounded warriors, the PCC was able to partner with the American Pain Foundation (APF) and other organizations to pass three new laws requiring the Veterans Administration and the military to report yearly on advances in pain management, training, and research and requiring the NIH (National Institute of Health) to examine its pain research portfolio and undertake the recently completed IOM report on pain.

AAPM has developed a robust scientific presence in medicine. We publish our own journal, *Pain Medicine*, which has grown from a small quarterly journal to a respected monthly publication that represents the full scope of pain medicine science and practice. Annually, we conduct the only medical conference that is dedicated to coverage of the full scope of pain medicine science and practice and present a robust and scientific poster session that represents our latest progress. Yet, year to year, we lament that the incredible clinical wisdom displayed at this conference, born out of years of specialty practice in our field, is lost between meetings. Now comes a remedy, our textbook—*Comprehensive Treatment of Chronic Pain by Medical, Interventional, and Integrative Approaches*.

Several years ago, Editor Tim Deer, who co-chaired an Annual Meeting Program Committee with Todd Sitzman, recognized the special nature of our annual conference and proposed that the AAPM engages the considerable expertise of our membership in producing a textbook specifically focused on the concepts and practice of our specialty. Under the visionary and vigorous leadership of Tim as Editor-in-Chief and his editorial group, *Comprehensive Treatment of Chronic Pain by Medical*, *Interventional*, *and Integrative Approaches* has arrived. Kudos to Tim, his Associate Editor-in-Chief Michael Leong, Associate Editors Asokumar Buvanendran, Vitaly Gordin, Philip Kim, Sunil Panchal, and Albert Ray for guiding our busy authors to the finish line. The expertise herein represents the best of our specialty and its practice. And finally, a specialty organization of physician volunteers needs a steady and resourceful professional staff to successfully complete its projects in the service of its mission. Ms. Susie Flynn, AAPM's Director of Education, worked behind-the-scenes with our capable Springer publishers and Tim and his editors to assure our book's timely publication. Truly, this many-faceted effort signals that the academy has achieved yet another developmental milestone as a medical organization inexorably destined to achieve specialty status in the American medical pantheon.

Philadelphia, PA, USA Rollin M. Gallagher, M.D., M.P.H.

Preface to *Treatment of Chronic Pain by Interventional Approaches*

We are grateful for the positive reception of ***Comprehensive Treatment of Chronic Pain by Medical, Interventional, and Integrative Approaches: The American Academy of Pain Medicine Textbook on Patient Management*** following its publication last year. The book was conceived as an all-encompassing clinical reference covering the entire spectrum of approaches to pain management: medical, interventional, and integrative. Discussions with pain medicine physicians and health professionals since then have persuaded us that the book could serve even more readers if sections on each of the major approaches were made available as individual volumes – while some readers want a comprehensive resource, others may need only a certain slice. We are pleased that these "spin-off" volumes are now available. I would like to take this opportunity to acknowledge once more the outstanding efforts and hard work of the Associate Editors responsible for the sections:

Treatment of Chronic Pain by Medical Approaches:
The American Academy of Pain Medicine *Textbook on Patient Management*
Associate Editor: Vitaly Gordin, MD

Treatment of Chronic Pain by Interventional Approaches:
The American Academy of Pain Medicine *Textbook on Patient Management*
Associate Editors: Asokumar Buvanendran, MD, Sunil J. Panchal, MD, Philip S. Kim, MD

Treatment of Chronic Pain by Integrative Approaches:
The American Academy of Pain Medicine *Textbook on Patient Management*
Associate Editor: Albert L. Ray, MD

We greatly appreciate the feedback of our readers and strive to continue to improve our educational materials as we educate each other. Please send me your input and thoughts to improve future volumes.

Our main goal is to improve patient safety and outcomes. We are hopeful that the content of these materials accomplishes this mission for you and for the patients to whom you offer care and compassion.

Charleston, WV, USA — Timothy R. Deer, M.D.

Preface to *Comprehensive Treatment of Chronic Pain by Medical, Interventional, and Integrative Approaches*

In recent years, I have found that the need for guidance in treating those suffering from chronic pain has increased, as the burden for those patients has become a very difficult issue in daily life. Our task has been overwhelming at times, when we consider the lack of knowledge that many of us found when considering issues that are not part of our personal repertoire and training. We must be mentors of others and elevate our practice, while at the same time maintain our patient-centric target. Not only do we need to train and nurture the medical student, but also those in postgraduate training and those in private and academic practice who are long separated from their training. We are burdened with complex issues such as the cost of chronic pain, loss of functional individuals to society, abuse, addiction, and diversion of controlled substances, complicated and high-risk spinal procedures, the increase in successful but expensive technology, and the humanistic morose that are part of the heavy load that we must strive to summit.

In this maze of difficulties, we find ourselves branded as "interventionalist" and "non-interventionalist." In shaping this book, it was my goal to overcome these labels and give a diverse overview of the specialty. Separated into five sections, the contents of this book give balance to the disciplines that make up our field. There is a very complete overview of interventions, medication management, and the important areas of rehabilitation, psychological support, and the personal side of suffering. We have tried to give a thorough overview while striving to make this book practical for the physician who needs insight into the daily care of pain patients. This book was created as one of the many tools from the American Academy of Pain Medicine to shape the proper practice of those who strive to do the right things for the chronic pain patient focusing on ethics and medical necessity issues in each section. You will find that the authors, Associate Editor-in-chief, Associate Editors, and I have given rise to a project that will be all encompassing in its goals.

With this text, the American Academy of Pain Medicine has set down the gauntlet for the mission of educating our members, friends, and concerned parties regarding the intricacies of our specialty. I wish you the best as you read this material and offer you my grandest hope that it will change the lives of your patients for the better.

We must remember that chronic pain treatment, like that of diabetes and hypertension, needs ongoing effort and ongoing innovation to defeat the limits of our current abilities. These thoughts are critical when you consider the long standing words of Emily Dickinson…

"Pain has an element of blank; it cannot recollect when it began, or if there were a day when it was not. It has no future but itself, its infinite realms contain its past, enlightened to perceive new periods of pain."

Best of luck as we fight our battles together.

Charleston, WV, USA — Timothy R. Deer, M.D.

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Part I

Anatomy and Physiology of Pain

Neuroanatomy and Neurophysiology of Pain

1

Adam R. Burkey

Key Points

- All chronic pain, to a greater or lesser extent, alters nervous system physiology and is therefore neuropathic.
- Electrical neuromodulation may be employed against the peripheral and intraspinal nervous system in a variety of ways to "gate" the flow of pain information to consciousness.
- Modern functional imaging of the forebrain has confirmed and extended our understanding of pain neuroanatomy and may be an outcome measure for studies of pain in the future.
- In the future, research may be able to better match particular clinical characteristics to underlying pain physiology, understand how to act on autonomic and visceral pathways, and control glial and inflammatory activity to reduce neuropathic pain.

Introduction

The neuroanatomy and neurophysiology of pain can be discussed with regard to every level of the nervous system, from peripheral nerve to cerebral cortex. Rudimentary *nociception* is the physiologic perception of a potentially tissue-damaging stimulus and is the commonplace conception that holds when one claims that "something hurts." However, as we review here, "something hurting" for an extended period of time will induce changes in the nervous system that may be irreversible. For this reason, many experts believe that all chronic pain is, to some extent, *neuropathic*. This makes it often impossible to merely remove the thorn from the lion's paw (treat a defined bodily source) and eliminate chronic pain, as much as patients wish we could. Pain as a subjective, even abstract, experience involving a complex array of emotions may occur independent of *any* discernable bodily tissue damage, such as the case of fibromyalgia. For this reason, most chronic pain treatments – whether with medications, cognitive therapies or interventional procedures – attempt to alter physiological pain processing in the peripheral nerve, spinal cord, or forebrain.

In the modern era, there have been three watershed moments in the scientific understanding of pain. The first was the "gate theory" of Melzack and Wall [1]. This theory held that circuitry existed in the spinal cord whereby an innocuous stimulus could block transmission of a noxious stimulus to the brain. This theory is still discussed and referenced by researchers who study pain processing in the spinal dorsal horn. The second was the delineation of a descending pathway from the brain stem to the spinal dorsal horn that could block ascending pain-related information, the so-called descending inhibitory system [2]. This opened the door for the study of mechanisms of analgesia, as it became clear that many analgesics, including morphine, utilized this endogenous circuitry to produce their effects. Thirdly, the advent of functional imaging in the early 1990s has yielded a wealth of information on how chronic pain is processed in the forebrain, defining potential sites of action for novel analgesics and providing more objective data than previously available on chronic pain outcomes and the mechanisms of action of therapeutic interventions.

Pain Neuroanatomy and Physiology

Peripheral and Spinal Neuroanatomy

Primary afferent (or sensory) neurons provide ongoing information about the external environment and the internal bodily milieu. Primary afferent nociceptors (PANs) detect chiefly temperature, trauma, and acidosis of tissues [3].

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Their cell bodies reside in the "dorsal root ganglion" (DRG) which sits just outside the spinal cord. Their axons bifurcate within the ganglion, sending one branch out to innervate various tissues and the other to innervate the dorsal horn of the spinal cord. Most PANs have smaller cell bodies and thin lightly myelinated (Aδ) or unmyelinated (C) axons, the latter terminating as free nerve endings in various organs – skin, muscle, and visceral organs. The conduction velocities of PAN are slower than the large, heavily myelinated axons that act as motoneurons or mechanoreceptors that detect vibration or position sense.

Lightly myelinated Aδ nociceptors enter the spinal cord often in or near Lissauer's tract with terminations primarily in laminae I and IIo of the superficial dorsal horn [4]; some terminations can be found in deeper laminae III–V and X as well. A subset of Aδ nociceptors ramify rostrally and caudally through several spinal segments of Lissauer's tract before terminating. These neurons respond to different stimulus modalities (mechanical or thermal) and are thought to convey fast pricking or sharp pain.

Unmyelinated C fibers respond to a diversity of noxious mechanical, thermal, or chemical modalities. They are classified into two broad types: peptidergic and non-peptidergic [5]. Peptidergic C fibers carry TrkA, the high-affinity receptor for nerve growth factor, and contain peptides such as calcitonin gene-related peptide, substance P and/or galanin. The second type appears to lack peptide neurotransmitters, responds to glial cell line-derived neurotrophic factor, and can be identified using binding sites for the lectin IB4. Studies indicate that these two types of C fiber segregate differently in the dorsal horn. Non-peptidergic IB4-labeled C fibers gather in the central part of inner lamina II, while peptidergic fibers branch out through lamina I and outer lamina II, but with scattered terminals deeper (laminae III–V) [5].

Nearly all visceral afferents are small unmyelinated C fibers which express similar markers to somatic nociceptors, such as vanilloid receptor TRPV1 and tetrodotoxin-resistant sodium channels [6]. Visceral afferents terminate in laminae I, V–VII, and X of the spinal cord. Laminae I and V contribute fibers to the spinothalamic tract in the contralateral lateral-ventral portion of the cord; thus, visceral travels with somatic nociceptive information from both somatic C fibers (lamina I) and Aδ fibers (lamina V) rostrally [7, 8]. In addition, a second pathway for visceral pain information from medial lamina VII and lamina X propagates along the dorsal columns [9]. Viscerally innervated lamina X neurons are particularly numerous in the sacral spinal cord and important for pelvic and perineal pain transmission.

Peripheral and Spinal Physiology

Injury to peripheral nerves is believed to cause paroxysmal, spontaneous pain through changes in voltage-sensitive sodium channel expression that lead to ectopic action potentials in sensory neurons [10]. These Na(v) channels accumulate in neuromas and demyelinated areas of peripheral nerve in animal and human models. Four such channels are of particular interest given their restricted distribution in nociceptors and their experimental association with neuropathic pain: tetrodotoxin-sensitive Na(v) 1.3 and 1.7 and tetrodotoxin-resistant Na(v) 1.8 and 1.9 [11]. Demyelination and the more even distribution of sodium channels along axons after peripheral nerve injury can lead to difficulty with obtaining a peripheral block in response to local anesthetic agents.

A phenotypic switch has been observed after axotomy, whereby large Aβ fibers begin to express neuromediators that transmit nociceptive information, including substance P [12, 13]. Some investigators insist that a subset of Aβ fibers maintains extensive projections throughout the superficial dorsal horn which, after the phenotypic switch, could excite spinothalamic neurons [14]. There is a larger body of work to suggest ingrowth of large-diameter sensory afferents into the superficial dorsal horn when there has been loss of small-fiber inputs due to cell death [15]. Because large-diameter afferents transmit innocuous sensory information such as light touch, it is believed that a pathological change allowing them to excite the superficial dorsal horn – either through a phenotypic switch that provides them with pain-related neurotransmitters or pathological ingrowth into deafferented portions of superficial dorsal horn – underlies the phenomenon of mechanical allodynia.

Nociceptive afferents provided excitatory glutamatergic, and sometimes peptidergic (substance P), inputs to their respective spinal laminae that increase activity in spinothalamic projection neurons. Glutamate acts primarily on AMPA or NMDA receptors and substance P on the neurokinin-1 (NK1) receptor. Glutamatergic activity leads to increased intracellular calcium and changes in gene expression of these neurons, or, in some cases, neuronal cell death [16].

Two primary mechanisms reduce excitation in the dorsal horn. The first is presynaptic inhibition of neurotransmitter release from primary afferent terminals in the dorsal horn. Serotonergic, adrenergic, opioidergic, and dopaminergic receptors are present on nociceptive afferents whose activity will block calcium entry and vesicular release of glutamate or substance P. Secondly, dopaminergic D2, serotoninergic 5-HT1A, and GABAergic receptors on spinothalamic neurons will inhibit neuronal cell firing when those receptors are activated. The monoamines, serotonin, norepinephrine, and dopamine acting on pre- and postsynaptic receptors in the dorsal horn are released from the terminals of descending fibers from brain stem nuclei. As a sidenote, spinal presynaptic serotonergic 5-HT3, postsynaptic 5-HT2 and dopaminergic D1 receptors are all generally pro-nociceptive, in that activation of these receptors will either increase excitatory transmitter release and/or directly increase spinothalamic neuronal activity [17–19].

Intrinsic local inhibitory neurons containing GABA will reduce activity in spinothalamic neurons. About 30 % of neurons in superficial laminae I–III are inhibitory, all GABAergic of which some also contain glycine [4]. Most islet cells in the substantia gelatinosa contain GABA and receive excitatory input from C fibers; they provide monosynaptic, bicuculline-sensitive input to excitatory "central" neurons which also receive direct excitatory input from other C fibers. The "central" neurons, responding to convergent inputs from islet cells and C fibers, gate output from lamina I through the spinothalamic tract [20]. A recent study [21] detected large numbers of GABA-inhibitory interneurons postsynaptic to large, heavily myelinated dorsal root ganglia neurons (presumably Aβ fibers) in spinal laminae III–V, consistent with the gate theory of large-fiber inhibition of nociceptive transmission [1]. It has been shown that partial nerve injury will lead to loss of GABAergic inhibition in the superficial dorsal horn secondary to neuronal cell death [22, 23]; loss of this endogenous suppression of central sensitization is a key factor in the difficulty with treating neuropathic pain.

Inflammatory and immune mediators also maintain neuropathic pain. With peripheral nerve injury, mast cells, neutrophils, and macrophages will release immune mediators such as prostaglandin E2, histamine, and tumor necrosis factor-alpha [24]. Supportive glia and Schwann cells can also release nerve growth factor, interleukins, cytokines, chemokines, and ATP which excite axons under pathological conditions [25]. Central glial cells can modulate neuronal activity in other ways, i.e., by acting as ion buffers, and their role has lead to the term "gliopathic" pain [26].

Preganglionic sympathetic neurons, which reside in the intermediolateral cell column of the thoracic spinal cord to the upper second or third lumbar segments, are controlled by both spinal and supraspinal inputs. Particularly, they appear to be subject to tonic GABAergic inhibition which is lifted to quickly increase sympathetic outflow ("disinhibition") [27, 28]. Preganglionic sympathetic fibers exit through the ventral root of the spinal nerve and then connect to the paravertebral sympathetic chain via the "white ramus communicantes" to travel to the appropriate sympathetic ganglion to synapse with its postsynaptic neuron. Visceral afferents travel with the sympathetic nerves to that organ, and therefore, the clinician should consider the possibility of thoracic radiculopathy when confronted with poorly localized unilateral flank and abdominal or pelvic pain, especially if a separate thoracic dermatomal pain can be determined on careful interview.

Sympathetic nerve terminals have been observed to form basket structures around dorsal root ganglion cells after peripheral nerve lesions and can thereby activate these neurons [29, 30]. Nociceptive axons as well may exhibit adrenergic sensitivity in peripheral nerve. These anatomical observations may have relevance to mechanisms of sympathetically maintained pain and their responsiveness to blockade of sympathetic ganglia and dorsal column neuromodulation (see below).

Supraspinal Pain Neuroanatomy

Functional imaging methods have been a powerful complement to traditional anatomical methods in ascertaining the supraspinal networks involved in pain processing. The spinothalamic tract terminates in six distinct regions of the thalamus, mostly intralaminar and ventrolateral complex nuclei. Along the way, terminations from spinobulbar neurons, which travel with spinothalamic tract neurons, are found in the brain stem reticular formation, periaqueductal gray (PAG), parabrachial nucleus, and regions of catecholamine cell groups. It is also likely that the hypothalamus receives spinothalamic tract input either through a mono- or multisynaptic pathway.

The PAG and rostral ventromedial (RVM) nuclei of the brain stem are involved with descending pain inhibitory modulation already mentioned above [31]. The PAG controls spinal nociceptive activity through relays in the RVM and the dorsolateral pontine tegmentum. The RVM contains both serotonergic and non-serotonergic projection neurons that can increase or decrease nociceptive activity in the spinal dorsal horn. The dorsolateral pontine tegmentum sends noradrenergic fibers to the dorsal horn to reduce activity through alpha-2 receptor activation.

Ascending spinothalamic input from lamina I of the dorsal horn is relayed by the thalamus to four principal regions of the cerebral cortex: area 24c of the anterior cingulate gyrus, area 3a of the primary somatosensory cortex (SI), secondary somatosensory cortex on the parietal operculum (SII), and dorsal insular cortex. Not coincidentally, these four regions have shown activation in a consistent way across functional imaging studies, including PET and fMRI, using many different experimental paradigms [32, 33]. Ascending spinothalamic input from wide dynamic range neurons in lamina V is ultimately received in the SI and SII cortices. Of all the cerebral cortical areas activated by pain, the anterior cingulate cortex appears to be the most specific for pain itself. The insular cortex serves a more general role for visceral integration and monitoring bodily homeostasis [34]. Finally, nociceptive input to the parabrachial area may be relayed to the central nucleus of the amygdala, where a major lamina I pathway exists in rats [35]. This input could account in part for some of the emotional, "suffering," aspects of pain experience.

Clinical Applications

Neuromodulation

Virtually every level of the nervous system discussed above can be subjected to electrical neuromodulation with some benefit for chronic pain, particularly neuropathic pain. Here, we briefly list these targets with appropriate references for further review by the interventionalist.

Forebrain

Typically, the forebrain is modulated through superficial motor cortex stimulation or deep brain stimulation. To date, regions targeted for deep brain stimulation include the medial septal nuclei, sensory thalamus, and PAG. More commonly, superficial motor cortex stimulation is chosen for dense neuropathic pain conditions [36, 37]. Typical indications include central neuropathic pain, trigeminal neuralgia, phantom limb pain, and postherpetic neuralgia. Anatomic mapping is performed by identifying the central sulcus with electrophysiologic stimulation and monitoring. EMG and somatosensory-evoked potentials are used to match the motor cortex area with the pain pattern. The mechanism of action of motor cortex stimulation is unknown; it may have to do with the relationship of the motor cortex to suppression of activity in SI and SII somatosensory cortices.

Intraspinal Neuromodulation

The commonest location for placement of electrodes for pain relief is within the spinal canal. Dorsal column neuromodulation via epidural electrodes is an implantable, surgical treatment modality commonly used for chronic pain and vascular disorders [37, 38]. Several features of the neural target influence the efficacy of stimulation: a longitudinal rather than transverse orientation of the fibers relative to the electrode, the distance from the electrode to the fiber, and the fiber diameter itself [39]. Currently available devices activate heavily myelinated Aβ fibers, not the unmyelinated C fibers or lightly myelinated Aδ fibers. Every attempt should be made to align the electrode along the axis of the fibers being stimulated. Furthermore, neuromodulation will be more effective at levels of the spinal cord with less intervening CSF volume, such as at the lumbar and cervical enlargements, when leads are placed in the epidural space.

The ability of dorsal column neuromodulation to block neuropathic pain depends on endogenous mechanisms to reduce excitability in the dorsal horn. A substantive body of work implicates GABAergic mechanisms of analgesia for dorsal column neuromodulation [40]. Conversely, treatment failures for dorsal column neuromodulation may be attributable to loss of large-fiber function, transformation in the phenotype or connectivity of large fibers, or loss of GABAergic inhibitory networks in the dorsal horn.

For traditional neuromodulation, a Tuohy needle is placed into the epidural space after aseptic preparation of the skin several segments caudal to the final desired position. Using fluoroscopic guidance, the electrode is advanced into the midline position overlying the spinal segments to be stimulated. Trial stimulation is carried out using an external programmable pulse generator. The patient describes the location and type of paresthesia in relation to their pain. Sometimes, more than one electrode is required to cover all of the painful areas. A variety of paddle and alternately spaced quadric and octopolar leads are available to cover the necessary area of the dorsal columns; sometimes, staggered leads are placed one above the other in a linear fashion to cover a greater rostrocaudal number of segments.

With satisfactory stimulation obtained, the lead(s) are sutured into place for a trial period of up to 2 weeks. The needle is withdrawn without disturbing the electrode placement and anchored into place on skin with bandaging of a tension loop to decrease the likelihood of dislodgement. The externalized leads can be reprogrammed throughout the trial period to optimize capture of the painful territory. At any sign of superficial infection, they are removed. If successful, permanent leads can be placed in the dorsal epidural space and tunneled to a rechargeable, programmable battery pack.

Other intraspinal neural targets have been successfully utilized to provide relief from neuropathic pain. Electrodes may be placed laterally over the entering dorsal root entry zone, which includes the dorsal roots, Lissauer's tract, and the spinal dorsal horn; this technique has been referred to as "intraspinal nerve root stimulation" (INRS; Fig. 1.1). INRS benefits from a closer apposition of the electrode to the target fibers than in the dorsal columns. The electrodes are placed along the rostrocaudal axis of the spine and therefore are oriented in parallel to ramifying fibers in Lissauer's trace. Placement of an electrode along laterally over the entering dorsal roots uses the same approach as for midline dorsal column placement. Lateral fluoroscopic views should be used to ascertain that the electrode is not ventrally located in the epidural space but rather along the posterior border of the neural foraminae.

Selective nerve root stimulation (SNRS) involves targeting the dorsal root of the spinal nerve at the neural foramen through an intra- or extraspinal approach where the electrode lies in a parallel with the entering fibers. We include sacral nerve stimulation in this category. SNRS accomplishes the goal of capturing paresthesia in some difficult-to-treat lumbosacral segments where traditional methods fail. A cephalocaudal (retrograde) lateral epidural approach at L2/3 below the conus was developed to facilitate placement of the electrode "in line" with lumbosacral roots. Using this technique, a quadripolar electrode enters at midline and is rotated toward but not into the L4 foramen. The distal contact is commonly programmed as an anode and the three proximal contacts as cathodes. Appropriately positioned, one may capture the L4, 5 and S1 roots with a single lead. Retrograde cervicothoracic electrode placements have not been performed due to the risk of cord injury.

S2–4 roots can be captured by directing the quadrupole toward but not through the S2 foramen. For sacral neuromodulation, trial leads are commonly placed through the caudal sacral hiatus and advanced over the lumbosacral nerve roots of interest; if successful, a surgically implanted paddle lead may be placed via laminotomy. Conditions treated with this approach include interstitial cystitis and perineal and rectal pain syndromes.

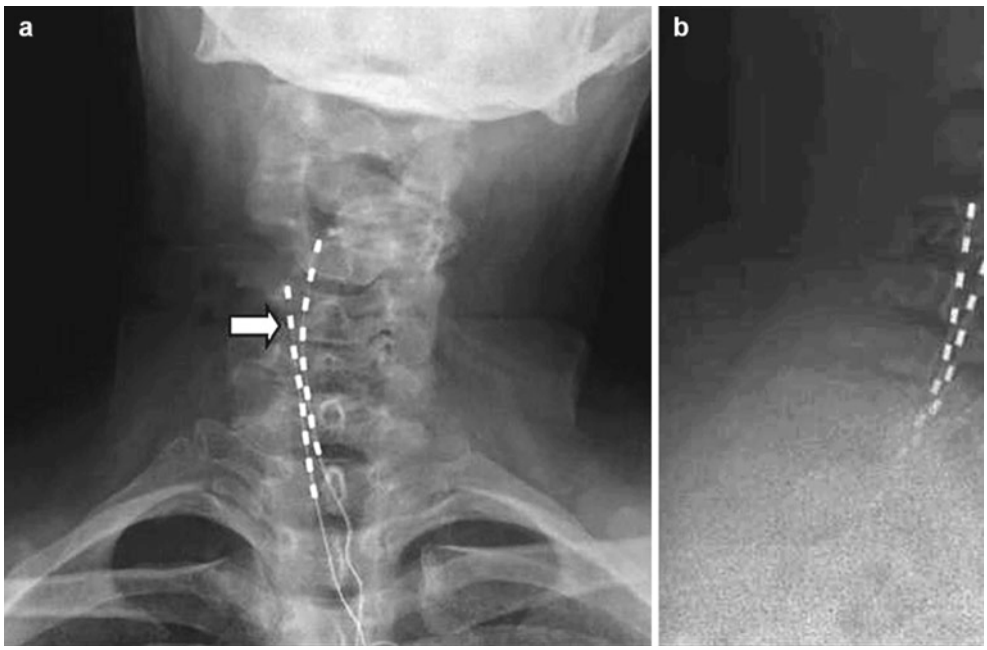

Fig. 1.1 Dual Octrode leads for INRS (a) The left, lateral lead (arrow) in this case overlies the entering fibers of C5, C6, and C7 for treatment of C6 dermatome central pain in an MS patient. The more medial lead guards the lateral lead to isolate stimulation over the dorsal root entry zone at C6. On the lateral view (**b**), the lateral lead is positioned immediately at the dorsal border of the neural foraminae. The more medial lead rises dorsally over the convexity of the spinal cord as it courses rostrally toward the dorsal columns [53]

The DRG is another potential target for neuromodulation (Fig. 1.2). The DRG is reliably located intraspinally between the pedicles of the neural foramen. This structure has been targeted with radiofrequency energy to treat radicular neuropathic pain. It may be that a reversible treatment like neuromodulation is preferable to a destructive technique like radiofrequency. In the lumbosacral region, a retrograde approach is generally used and the electrode into the neural foramen. The difference between this target and SNRS is that the electrode is advanced farther into the foramen with this procedure, isolating a single dermatome and acting on the sensory cell bodies of the DRG. Although it may be more effective for this dermatome, it has less breadth of coverage than SNRS which can capture several nerve roots.

Peripheral Nervous System

Peripheral nerves may be individually stimulated or an electrical field generated through an electrode array placed subcutaneously [41]. In peripheral nerve stimulation, an attempt should be made to direct the electrode along the trajectory of the target nerve. Common peripheral nerves treated with neuromodulation include ilioinguinal nerves for postherniorrhaphy pain, greater and lesser occipital nerves for occipital neuralgia, intercostal nerves for rib pain, and lower extremity nerves (saphenous, peroneal, tibial, sural) for foot pain. One may also use a combination of intraspinal and peripheral stimulation to treat, for instance, back and leg pain [42]. The lead is placed in proximity to the nerve rather than in contact to the nerve with most cases. In some cases, often because of lead migration or failure to capture with appropriate coverage, a paddle-type electrode is recommended for implantation.

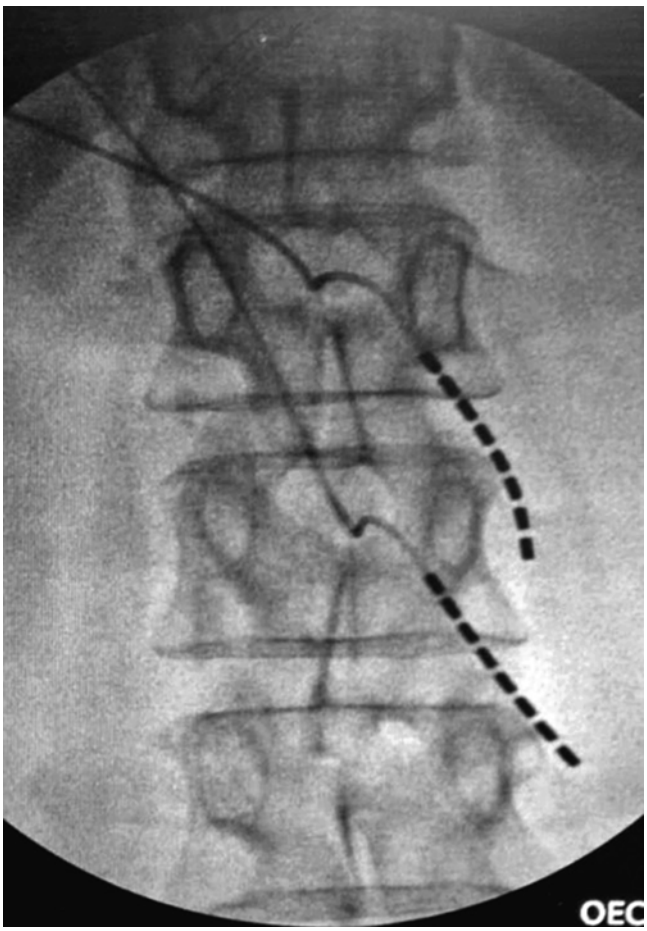

Fig. 1.2 DRG stimulation for postherpetic neuralgia. This patient had worsened symptoms with dorsal column neuromodulation. This arrangement of two leads stimulating the sensory neuronal perikarya at L1 and L2 provided 100 % relief with subthreshold stimulation (amplitude 0.5–0.8 mA with pulse width 120) (Photo courtesy of Dr. Christopher Vije, MD)

In some cases it is not possible to isolate a single nerve branch that is responsible for the pain problem. Implantation of dual electrodes with appropriate spacing will generate a peripheral field that captures the pain problem. There is evidence that the two leads can cross talk to complete an electrical circuit and are thus creating a true field and not functioning independently [43]. This has been performed for a variety of conditions including lower back pain and abdominal pain [44].

Intrathecal Drug Delivery

Carefully selected patients may benefit from the implantation of an intrathecal drug-delivery system, typically an opioid with or without an adjunctive medication. These patients have failed more conservative options and have poor benefit and/or unacceptable side effects from oral medications. It is considered a good option for some patients with cancer pain who require large doses of opioid and suffer from severe constipation or sedation.

Typically, the catheter enters the intrathecal space at the lumbar level and is tunneled to a programmable, refillable pump usually in the lower quadrant of the abdomen. The catheter tip should be advanced to the optimal spinal level for the worst pain. For instance, back pain should have the catheter delivering medication at T10 or to the upper cervical spine for head and neck pain. These pumps are not without risk; beyond the immediate surgical risks of hematoma, cord injury, and infection, granulomas may form over time and require surgical intervention.

Pumps are typically filled with morphine, but the interventionalist may use other opioids such as hydromorphone or fentanyl. Common adjuncts to the opioid are clonidine or a local anesthetic such as bupivacaine. Clonidine takes advantage of the endogenous alpha-2 receptor mechanisms of spinal analgesia but can be complicated by hypotension or sedation. Intrathecal bupivacaine can cause numbness, edema, incoordination, or urinary retention; in other cases, it is difficult to deliver a clinically significant amount of bupivacaine, given that bupivacaine cannot be concentrated beyond 0.75 % and the low volumes required for intrathecal infusion.

Intrathecal opioid pumps produce their analgesia through an action on the mu-opioid receptors which are equally distributed on presynaptic fibers and postsynaptic neuronal cell bodies in the dorsal horn. Over time, typically several years, significant tolerance can develop. The loss of GABAergic inhibitory interneurons in the dorsal horn secondary to direct morphine neurotoxicity is thought to be one mechanism of tolerance development [45]. This is one factor that has prompted the development of alternative agents, such as ziconotide [46]. Ziconotide acts as a N-type voltage-dependent calcium channel. It blocks the release of glutamate and pro-nociceptive peptides in the dorsal horn. It has a narrow therapeutic window, with significant side effects of sedation, hallucinations, and dizziness. It has the benefit of no apparent development of tolerance or dependence, however. It is currently used for severe neuropathic pain refractory to other therapies.

Future Directions

Functional Imaging of Pain

PET and fMRI have disclosed activations in certain brain areas with chronic pain, including the anterior cingulate and insular gyri and the somatosensory cortices and thalamus. In some studies, standard MRI has shown reductions in gray matter volumes as a consequence not cause of the chronic pain of such common conditions as irritable bowel syndrome and chronic back pain [47–49]. In the case of chronic low back pain, effective treatment in one study showed reversal of the gray matter changes [50]. Should reliable protocols for common conditions such as back pain be developed, imaging studies could become outcome measures for interventional therapies.

Neuropathic Pain

Technological improvements in neuromodulation will continue to enhance their efficacy and improve our ability to treat certain pain states. Chief among these improvements, already on the horizon, is the development of small, self-contained stimulator devices that may be placed directly next to the nerve root or peripheral nerve, obviating the need for tunneling electrode leads to a battery pack. This will improve accessibility of the DRG and peripheral nerve targets, in particular, to neurostimulation.

The field of neuromodulation, like most other in medicine, would benefit from cohort studies of these different approaches used in different neuropathic pain states. Although the utility of dorsal column neuromodulation for failed back surgery syndrome/lumbosacral nerve root injury syndrome is well-established [37, 51, 52], to date, only anecdotal reports exist for the utility of this and alternate neuromodulatory strategies for other chronic neuropathic conditions. For instance, one case of central pain from multiple sclerosis was successfully treated by INRS [53]. Positive results from SNRS have been reported for lumbosacral nerve injury syndrome, ilioinguinal neuralgia, vulvodynia, interstitial cystitis, neuropathic extremity pain, and pelvic and rectal pain [54–59]. Subcutaneous peripheral nerve or field stimulation has been tried for neuropathic head and neck pain, occipital neuralgia, inguinal neuralgia, and chronic pelvic or abdominal pain [60–65].

"Sensory profiles" for neuropathic pain could enhance the study of alternate strategies and indications for neuromodulation. The concept proposes that a particular pattern of sensory description corresponds to a specific physiological change, even among patients with the same disease process. Thus, allodynia may represent a greater GABAergic inhibitory deficit in the dorsal horn; numbness, a significantly greater degree of deafferentation; spontaneous pain, a greater degree of Aδ fiber activity; and so on. Physiology in turn determines the efficacy of neuromodulation. These "sensory profiles" could then be used to stratify patients within a population to address the issue of nonresponders.

A case in point is postherpetic neuralgia, where dorsal column neuromodulation and peripheral field stimulation have both been reported effective in several patients [66, 67], yet is a condition where neurostimulation is not generally regarded as a useful modality [68, 69]. A descriptive study of 2,100 patients with either PHN or DPN demonstrated differences in hyperalgesia and allodynia between the two populations [70]; five patterns of sensory symptom description were detected within these two populations although differing in frequency within each. Distinct neuropathic signs and symptoms in PHN (i.e., paroxysmal vs. continuous pain) are generated by different patterns of abnormality among primary afferent neurons (Aβ- vs. Aδ- and C fibers). This type of research where clinical description is matched to underlying physiology may point the way forward, in identifying subtypes of neuropathic pain responsive (or not responsive) to different approaches to neuromodulation. This could greatly reduce the number of unnecessary trials and failed implants (see Fig. 1.2).

Visceral and Autonomic Systems

There exists a great deal of information on the utility of dorsal column neuromodulation for chronic stable angina and nonreconstructable lower extremity ischemia (Fig. 1.3) [38, 71, 72]. These indications are more widely used in Europe; practitioners in the USA have not managed to partner with vascular surgery, cardiology, and primary care in such a way as to be able to provide this treatment modality to the appropriate patients effectively. There is also burgeoning interest in the use of cervical spinal cord stimulation to increase cerebral perfusion in low-flow states, including enhancing chemotherapy delivery to brain tumors and improving cerebral oxygenation in patients poststroke [73, 74].

For chronic visceral pain such as pancreatitis, a guarded tripolar lead array is frequently used to drive stimulation deeper into the dorsal columns. Presumably, this allows activation of fibers in the midline visceral pain pathway which engages inhibitory mechanisms in deeper laminae VII and X where visceroceptive neurons reside. This existence of this pathway has led some to promote the efficacy of T10 midline punctuate myelotomy for intractable cancer-related pelvic pain [75], which may be considered by the surgical interventionalist in their palliative care population.

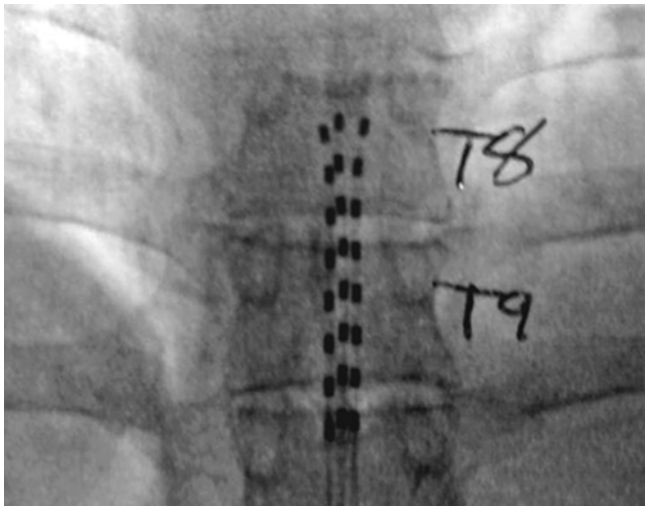

Fig. 1.3 Dorsal column tripole configuration. Using an Octrode lead on either side of a third Octrode allows one to "guard" the midline lead with positive charge. This drives the stimulation deeper into the dorsal columns and can prevent limb and thoracic dermatomal paresthesias. This arrangement has been used for chronic pancreatitis and axial low back pain

Intrathecal Drug Delivery

Currently available technology would benefit greatly from novel analgesics to deliver intraspinally. Gabapentin, a well-established drug for the treatment of neuropathic pain, is one such candidate for intrathecal administration [76, 77]. Alternatively, it may be that adjuncts to morphine, such as baclofen, enhance its efficacy and reduce tolerance development [78]. An intriguing possibility in this regard would be medications to inhibit proinflammatory mediators in the spinal cord. Cytokine and chemokine activation appears not only to drive neuropathic pain itself, but to specifically reduce analgesia and promote tolerance development associated with opioids [79, 80].

Summary

Pain is a neurological condition that affects every level of the nervous system. The most reasonable target for therapy remains the peripheral nerve and spinal dorsal horn, as first proposed by the gate theory; at more rostral levels, pain-related activity is distributed among a "pain matrix" whose complexity makes it difficult to act upon. Imaging of this pain matrix, however, may become an objective surrogate marker for studies of pain and its treatment. Studies of neuromodulation

for a variety of neuropathic pain states will benefit from correlation with clinical characteristics and physiology to reduce the number of failed implants. New medications, either alone or adjunctive to intrathecal opioids, will make infusion pumps a more attractive modality for pain control.

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Spinal Targets for Interventional Pain Management

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Key Points

- Interventional techniques that target specific nociceptive transmission sites can reduce pain without having the systemic impact that oral medication have on other organ systems.
- Convergence of nociceptive afferent signals in the spinal cord may explain the clinical observation that injury of different organs may produce the same pain sensations.
- Destruction of specific spinal neural targets with either neurolytic solutions or thermal probes provides long-term relief for a limited number of pain conditions.
- The primary pharmacological receptors that are targeted for intrathecal medication management of pain include opioid receptors, alpha-2 adrenergic receptors, sodium channel receptors, and calcium channel receptors.
- Electrical stimulation can provide effective analgesia by targeting various spinal targets including the spinal cord, nerve roots, and dorsal root ganglia.
- New minimally invasive percutaneous techniques have recently been developed to address some of the structural pathologies including spinal stenosis caused by ligamentum flavum hypertrophy.

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Introduction

As noted in the previous chapter, the transmission of pain signals from the peripheral nervous system to the brain involves a variety of specialized neuronal and nonneuronal cells each with a host of specific receptors involved in the processing of these signals. The goal of this chapter is to briefly review the various image-guided interventional pain management techniques that target spinal structures aimed at reducing pain and improving patients' quality of life. Comprehensive medical management aims to accomplish these goals by utilizing systemic medications that target specific receptors throughout the peripheral and central nervous system. In many cases, this approach is successful with few untoward complications. However, in more severe pain conditions or higher doses of medications, patients may experience medication side effects and toxicities that limit the utility of a systemic approach. In contrast, interventional pain management techniques employ a variety of technologies to influence specific targets involved in nociceptive transmission while aiming to minimize the effects on systems not involved in the nociceptive process. For the purposes of this chapter, the interventional pain management techniques to be discussed will be limited to fluoroscopic procedures that target the structural and neural components in four distinctive spinal regions: the paraspinal region located immediately adjacent to the spine, the structural components of the spine including the bone and connective tissues, the intraforaminal region located within the spinal foramen, and the intraspinal region located within the spinal canal. Where appropriate, a distinction will be made between the epidural targets and intrathecal targets located within the intraspinal region. Knowledge of the spinal structures subject to interventional procedures is critical for all pain physicians, not just those who perform the interventions. For example, by understanding the spinal components involved in nociception and how they can be targeted, the clinician

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