Pain Management for Clinicians

A Guide to Assessment and Treatment

Carl Edward Noe
Editor

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Editor
Carl Edward Noe
Professor in the Department of Pain Management and Anesthesiology
UT Southwestern Medical Center
Eugene McDermott Center for Pain Management
Dallas, TX
USA

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Introduction

Divinum est opus sedare dolorem
(Divine is the work to subdue pain).
–Hippocrates

Pain is an essential part of human life. Through unpleasant experiences, we learn to avoid sharp objects and fear the flames of fire. It is the great teacher that tutors us to avoid emotional harm and physical injury. "We cannot learn without pain," Aristotle once wrote. When pain leads to suffering, it ceases to be a teacher and becomes the oldest medical malady. The early twentieth century saw pain evolve from being an inevitable consequence of aging or a religious cleansing of the soul to the subject of scientific study in medicine, supported by academic research, education, and interventions. The struggle to establish pain as an independent specialty came from the challenge of recognizing pain as more than a symptom and the difficulty in defining pain itself. In 1986, the International Association for the Study of Pain (IASP) defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." At the same time, the IASP also defined chronic pain as "pain that lasts beyond the normal healing time for a given injury, operationalized as pain lasting >3 months." These definitions helped to unify a newly formed field of medicine built upon the early work of Dr. John Bonica, widely regarded as the father of pain management, and his dream of creating multidisciplinary pain management programs for patients. Along with Dr. Bonica in Seattle, the Department of Anesthesia at the University of Texas Southwestern was one of the early institutions to incorporate pain management into the scope of anesthesia and provide a foundation for pain research and treatment. This led to the fundamental work of Dr. Prithvi Raj and Dr. Carl Noe, pioneers in acute regional anesthesia and chronic pain, respectively. Both would go on to be founding members of the Texas Pain Society.

In the late twentieth century, pain was identified as the fifth vital sign after an initiative by the American Pain Society to raise awareness of pain assessment and management. This was followed by mandates from regulatory bodies such as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) requiring the assessment and treatment of pain in all patients. With a distinct body of

knowledge, dedicated and focused research, and influential institutional practices and guidelines, pain management has established itself alongside other medical specialties.

Today, over 100 million Americans suffer from chronic pain, with the economic cost related to both healthcare and lost productivity ranging from $560 to 635 billion dollars annually in the United States. Pain remains the most feared symptom for patients, having significant medical, social, psychological, and financial consequences. Even among clinicians, the treatment of pain can be a complex and arduous duty that leaves practitioners feeling helpless and hopeless. For pain practitioners, the fear of addiction dangles like the sword of Damocles, but has not prevented a tendency toward overreliance on opioids. Currently, the United States consumes 80% of the world's opioids with prescription numbers quadrupling in the past decade. This practice has fueled both a prescription culture and a crisis. Renewed scrutiny over such practices has led to greater research into non-opioid pharmacotherapy and education on safer opioid prescribing practices. It is our hope that the current emphasis on opioid alternatives will portend the start of the "post-opioid" years for pain management.

Looking forward, tremendous advances in the prevention, detection, and treatment of pain in patients are on the horizon. Scientific advances continue to unravel the mysteries of pain through advanced neuroimaging, molecular cell biology, and discoveries in the genetics of pain. Such advances will offer innovative and improved interventions for the early diagnosis and treatment of pain. This, coupled with the growth of multidisciplinary treatment teams, patient-centered care, and exciting translational research, will yield the greatest reduction in the burden of chronic pain on patients in the decades to come. It is our hope that this work will, in some way, assist in shaping a new era in pain management.

Asif Khan
Charles Whitten

Department of Anesthesiology
and Pain Management
UT Southwestern Medical Center,

Dallas, TX, USA

Contents

Contributors

Robert S. Ackerman Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA

Salah G. Aoun Department of Neurological Surgery, UT Southwestern Medical Center, Dallas, TX, USA

Alexis Barina, MD Department of Internal Medicine, Section of Palliative Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

Danielle M. Brecht Department of Psychology, The University of Texas at Arlington, Arlington, TX, USA

William G. Brose Department of Anesthesia, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, CA, USA

Trenton D. Bryson Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA

Stephanie I. Byerly Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA

Jonathan Chang Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA

Avinash S. Chavda Physical Medicine and Rehabilitation, University of Texas Southwestern Medical Center, Dallas, TX, USA

Jonathan Cheng Department of Plastic Surgery, University of Texas Southwestern Medical Center, Dallas, TX, USA

Jeanette Chong Clinical Psychology, Graduate School of Biomedical Sciences and Department of Psychiatry, UT Southwestern Medical Center, Dallas, TX, USA

Daksh Datta Opos Solutions, Opos Inc, San Mateo, CA, USA

Tom Mario Davis Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA

Adriane dela Cruz Department of Psychiatry, UT Southwestern Medical Center, Dallas, TX, USA

Shaina Drummond Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Parkland Ambulatory Surgery Center, Dallas, TX, USA

Ahmad Elsharydah Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, TX, USA

Ahmed Embabi Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, TX, USA

Rachel Feinberg Feinberg Medical Group, Palo Alto, CA, USA

Steven D. Feinberg Department of Anesthesia, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, CA, USA

Deborah I. Friedman Department of Neurology and Neurotherapeutics, Department of Ophthalmology, UT Southwestern Medical Center, Dallas, TX, USA

Shannon Garitty Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, TX, USA

Robert J. Gatchel Department of Psychology, Center of Excellence for the Study of Health and Chronic Illnesses, The University of Texas at Arlington, Arlington, TX, USA

Mehari Gebreyohanns, MD, FAHA, FAAN Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas, TX, USA

Oren Guttman Jefferson Health System, Sidney Kimmel Medical College, Philadelphia, PA, USA

Steve Hong Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA

Thomas J. Hong, DO Department of Interventional Pain Management, Regency Pain and Therapy Institute, Mansfield, TX, USA

Syed S. Jaffery Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA

Ivanshu N. Jain Department of Psychiatry, UT Southwestern Medical Center, Dallas, TX, USA

Zachary D. Johnson Department of Neurological Surgery, UT Southwestern Medical Center, Dallas, TX, USA

Stephanie C. Jones Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA

Enas Kandil University of Texas Southwestern, Dallas, TX, USA

Dennis Kao Department of Plastic Surgery, University of Texas Southwestern, Dallas, TX, USA

Department of Surgery, University of Washington, Seattle, Washington, USA

Stephen T. Krazit, MD Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA

Justin Kromelow Opos Solutions, Opos Inc, San Mateo, CA, USA

Vernon L. Krueger Krueger Law Group, LLP, Dallas, TX, USA

Frederick Li Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA

Shelby R. Lies Department of Plastic Surgery, University of Texas Southwestern Medical Center, Dallas, TX, USA

Yuan-Chi Lin Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Boston, USA

Department of Anaesthesia, Harvard Medical School, Boston, MA, USA

Nathaniel Loo Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA

Anthony T. Machi Anesthesiology and Pain Management, University of Texas Southwestern, Dallas, TX, USA

Una E. Makris Division of Rheumatology, UT Southwestern Medical Center, Dallas, TX, USA

Shamin Masrour Department of Neurology and Neurotherapeutics, UT Southwestern Medical Center, Dallas, TX, USA

Andrew M. Mendelson Department of Anesthesiology, Thomas Jefferson University Hospital, Philadelphia, PA, USA

Archana Murali Department of Anesthesiology, Thomas Jefferson University Hospital, Philadelphia, PA, USA

Dawood Nasir Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA

Jennifer L. Nelson, Pharm D, BCPP Parkland Health & Hospital System, Dallas, TX, USA

Kelley Newcomer, MD Department of Internal Medicine, Section of Palliative Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

Candler Paige School of Behavioral and Brain Sciences and Center for Advanced Pain Studies, University of Texas at Dallas, Richardson, TX, USA

Biral Patel Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, TX, USA

Peter B. Polatin International Rescue Committee, Dallas, TX, USA

Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA

Harvard Program in Refugee Trauma, Cambridge, MA, USA

Global Mental Health, Department of Psychiatry, George Washington University, Washington, DC, USA

Heather Poupore-King Department of Anesthesiology, Perioperative and Pain Medicine, Division of Pain Medicine, Stanford University School of Medicine, Stanford, CA, USA

Theodore J. Price School of Behavioral and Brain Sciences and Center for Advanced Pain Studies, University of Texas at Dallas, Richardson, TX, USA

Gabor Bela Racz Department of Anesthesiology, Texas Tech University Health Science Center, Lubbock, TX, USA

Gabor J. Racz Epimed International, Dallas, TX, USA

Tibor A. Racz Optimal Pain Doctors, Addison, TX, USA

Padmaja Reddy, MD Department of Internal Medicine, Section of Palliative Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

Richard C. Robinson Clinical Psychology, Graduate School of Biomedical Sciences and Department of Psychiatry, UT Southwestern Medical Center, Dallas, TX, USA

Susan Sager Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Boston, USA

Department of Anaesthesia, Harvard Medical School, Boston, MA, USA

Hisham Salahuddin Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas, TX, USA

Kelly M. Scott Physical Medicine and Rehabilitation, University of Texas Southwestern Medical Center, Dallas, TX, USA

Stephanie Shiers School of Behavioral and Brain Sciences and Center for Advanced Pain Studies, University of Texas at Dallas, Richardson, TX, USA

Max Shilling Department of Anesthesiology, Thomas Jefferson University Hospital, Philadelphia, PA, USA

Caitlin Siropaides, DO Department of Internal Medicine, Section of Palliative Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

Alwin Somasundaram UT Southwestern Medical Center, Dallas, TX, USA

Steven Stanos Swedish Health System Pain Medicine and Services, Swedish Pain Services, Seattle, WA, USA

Jessica Stephens Department of Psychology, The University of Texas at Arlington, Arlington, TX, USA

Megan Still UT Southwestern Medical Center, Dallas, TX, USA

Nilofar Syed Division of Rheumatology, UT Southwestern Medical Center, Dallas, TX, USA

Mazin Al Tamimi Department of Neurological Surgery, UT Southwestern Medical Center, Dallas, TX, USA

Stephanie Terauchi, MD Department of Internal Medicine, Section of Palliative Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

Kate Tindall, MD Austin Palliative Care, Austin, TX, USA

Lisa To, MD Department of Anesthesiology, UT Southwestern Medical Center, Dallas Veterans Hospital, Dallas, TX, USA

Coby Tran Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA

Kavita Trivedi Department of Physical Medicine and Rehabilitation, UT Southwestern Medical Center, Dallas, TX, USA

Michael Van Hal Department of Orthopedic Surgery, UT Southwestern Medical Center, Dallas, TX, USA

Aaron Van Wright III, MD Department of Psychiatry, UT Southwestern Medical Center, Dallas, TX, USA

Sidarth Wakhlu Department of Psychiatry, UT Southwestern Medical Center, Dallas, TX, USA

Winnie Wang, MD Department of Internal Medicine, Section of Palliative Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

Jason Zafereo Department of Physical Therapy, UT Southwestern Medical Center, Dallas, TX, USA

Part I
Acute Pain

Chapter 1
Pain Assessment and Treatment for the Trauma and Burn Patient

Shaina Drummond, Robert S. Ackerman, and Alwin Somasundaram

Pain Management of the Trauma Patient

Introduction

Management of the acute and chronic pain manifestations of a patient with trauma can be a challenge to all clinicians. Traumatic injuries can include the brain, spinal cord, chest wall, bones, and visceral organs, each with diagnostic and therapeutic distinctions. The mainstay of pharmacotherapy with opioids has been well studied but more recently presents with more limitations and cautions. Non-opioid medications, interventional pain procedures, and other non-pharmacologic therapies play a role in the multimodal and multidisciplinary approach to managing pain in this population. This chapter reviews many common traumatic pain pathologies, describes the current evidence for pharmacological interventions, and relates the indications and utility of various procedures and strategies. A detailed discussion of assessment and management of the patient with burn injury follows this section.

S. Drummond (✉)
Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Parkland Ambulatory Surgery Center, Dallas, TX, USA
e-mail: shaina.drummond@utsouthwestern.edu

R. S. Ackerman
Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: robert.ackerman@utsouthwestern.edu

A. Somasundaram
UT Southwestern Medical Center, Dallas, TX, USA
e-mail: alwin.somasundaram@utsouthwestern.edu

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Traumatic Pain Pathologies

Chest trauma Chest wall trauma is common and contributes to several hundred thousand emergency room visits. The most common causes are from blunt injuries – motor vehicle crashes, falls, and crush. The morbidity and mortality of chest trauma varies widely, largely related to injury of intrathoracic structures, organ contusion, number of rib fractures, and age [1]. Acute pain control is paramount as it can afford the greatest ability to ambulate, cough, breathe deeply, and perform pulmonary exercises needed to recover from the injury fully. Long-term complications of chest wall trauma can include chronic pain, disability, and occupational challenges, including unemployment [1]. As further discussed later, local anesthetics and regional anesthetics may offer better analgesia than opioids for this type of injury while limiting the patient's risk for opioid dependence.

Bone pain Traumatic bone pain arises primarily from fractures of long bones, hips, and joints. Skeletal pain can be attributed to a simple bone fracture but is often reviewed in relation to each patient's comorbidities; non-traumatic causes of skeletal pain include hyperparathyroidism, sickle cell disease, metastatic cancer, and arthritis [2]. In the elderly, hip fractures are one of the most common injuries and present a clinical challenge to the primary practitioner and the rest of the treatment team [3]. Post-injury recovery strongly emphasizes full participation in physical therapy and early mobilization, both of which can be impaired by post-fracture skeletal pain. A multimodal analgesic strategy may be best employed in this patient group as the potential for oversedation with opioid medications may prolong recovery and increase the likelihood for a skilled nursing facility disposition postoperatively [3]. Patients with trauma to the extremities often require hospital-based trauma partly due to severe levels of post-injury pain. The transition from acute to chronic pain in this group has been well documented and could be detrimental to post-injury quality of life such as the ability to perform activities of daily living [4]. Functional magnetic resonance studies showing changes in the brain's response to nociception 6 months post-injury further emphasize the necessity of adequate pain control in both the acute and chronic phases of post-trauma care [4].

Vertebral compression fractures Vertebral compression fractures involve a decrease in height of part of the spinal vertebrae compared to baseline. Clinical management is often challenging as they do not often come to attention at the time of injury and are diagnosed late. Furthermore, co-existing osteoporosis can increase the risk of a future fracture [5]. A patient-centered approach to treatment of a vertebral compression fracture is important given the variety of fracture morphologies and characteristics of back pain [6].

Spinal cord injury Patients with spinal cord injuries often develop neuropathic and nociceptive pain. Nociceptive pain is often treated with opioids and non-steroidal anti-inflammatory drugs (NSAIDs) [7]. A meta-analysis of pharmacologic therapies for neuropathic pain demonstrated the best evidence and strongest recommendation for the use of tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and gabapentinoids. Evidence for the use of lidocaine and capsaicin patches as

well as the opioid tramadol was weaker, with the weakest evidence related to the use of strong opioids [8]. In addition to medications, other therapeutic strategies for the treatment of neuropathic pain include patient education, treatment of comorbidities (such as depression), continued follow-up, and referral to subspecialists and psychologists when appropriate [8]. Treatment of spinal cord injury refractory pain may involve intrathecal medications using an implanted pump [7]. Non-pharmacological treatments such as acupuncture and hypnosis have been less studied in this population [9]. In addition to pain, patients with spinal cord injuries often exhibit increased stress and decreased well-being, coping abilities, self-efficacy, and illness acceptance, all of which hinder the emotional recovery from such a traumatic injury [4].

Traumatic brain injury Pain after a traumatic brain injury (TBI) is often complicated by the concurrent headaches, psychological stress, and anxiety after the injury. It is not always clear whether the pain is a consequence of the brain injury or related to comorbidities such as post-traumatic stress disorder [10]. Chronic pain is reported in over half of TBIs with headaches and neck, shoulder, and back pain being the common manifestations. Further confounding pain management of this demographic are post-injury disabilities and legal concerns [10].

Assessment of Pain in the Trauma Patient

An accurate and holistic assessment of pain in the patient with trauma can be quite challenging. In addition to the traumatic injury itself, concurrent emotional distress, anxiety, and fear can confound an accurate description. A patient could be unconscious, delirious, or acutely intoxicated and fail to report any descriptors of the pain such as severity, location, quality, and other key features [11]. The size of the wound and estimated blood loss do not always correlate with the true injury severity. For most cooperative, alert, and oriented adults, the numerical rating scale, visual analog scale, and verbal rating scale can provide a sufficient self-report from the patient [11]. Further qualifying with other pain characteristics enhances the pain assessment. In patients mechanically ventilated, other parameters such as painful gestures, hemodynamic changes, and overall autonomic function can best guide a pain assessment and assist with medication dosing and selection. Patients in acute delirium often require a more detailed diagnostic evaluation as to the underlying cause and potential treatments of such [12].

In addition to assessing characteristics of pain and other related factors, the initial interview and encounter should complete other significant communication goals. Establishing a positive relationship and discussing realistic expectations of pain management can augment treatment benefits, alleviate anxiety, and increase satisfaction [13]. Often, relating functional recovery goals can be more beneficial than targeting a certain pain score. Additionally, screening for opioid abuse and addiction can not only help guide medication selection but also reinforce a non-judgmental relationship between the patient and his or her care team [13].

Opioid Medications

For procedural sedation in a patient with acute trauma pain, one study found a combination of propofol and fentanyl to have both improved analgesia and improved sedation compared to propofol and ketamine [14]. While some studies describe a benefit to the combination of morphine and ketamine compared to morphine alone for out-of-hospital trauma pain management, a meta-analysis showed no superior medication in terms of pain relief – fentanyl compared to morphine, ketamine compared to morphine, ketamine and morphine compared to morphine alone, etc. [15, 16]. In a randomized trial of patients with long bone fractures, both morphine and ketamine decreased pain severity, but neither medication was superior to the other [17]. When high-dose morphine was compared to low-dose morphine for patients with acute trauma pain in the emergency department, there was a significant reduction in pain 1 hour after medication administration in the high-dose group, but no notable difference 30 minutes after administration [18].

While opioids have a clear role in the acute management of pain from trauma, the long-term effects of opioids can introduce cautions with its appropriate patient population and indications. The concern of opioid-induced respiratory depression exists, especially when patients also present acutely intoxicated. In one study, patients who received opioids had higher Injury Severity Scores and initial pain scores than those who did not receive opioids; however, they were less likely to be intubated within 4 hours of admission and had lower blood alcohol levels [19]. In addition, opioid administration versus no opioid administration was not associated with an increased risk of respiratory depression, though higher cumulative fentanyl dose was found to be a risk factor [19].

When patients have been on opioids for more than 3 months, over half of them continue to use them years later, this transition from acute to chronic pain being a major risk in use of this medication class for patients with trauma-related pain [20]. It is believed that opioids for chronic pain carry an increased risk for overdose, abuse, and major cardiac events [21]. Additionally, it has been recently shown that opioid use can contribute to adrenal insufficiency and hypogonadism, both endocrine consequences that limit quality of life [22, 23]. One study of opioid prescribing habits related a higher likelihood of opioid prescription as discharge in patients with a higher Injury Severity Score with male sex and anxiety being negative predictors of prescription. This correlates with an appropriate prescribing practice, not one solely based on regulations alone [24].

Non-opioid Medications

Given the aforementioned cautions with opioid therapy and the potential issues from the transformation of acute, traumatic pain to chronic, debilitating pain, there is a strong emphasis on multimodal analgesic techniques to minimize opioid use

while treating pain effectively. The addition of concurrent muscle relaxants, gabapentinoids, and clonidine can reduce the total opioids prescribed without compromising pain relief [25]. Several non-opioid medications have been both studied and hypothesized to have a clinical benefit in patients with trauma pain.

Gabapentin and pregabalin Gabapentinoids, which act via blockade of the alpha-2-delta voltage-gated calcium channels, include the medications gabapentin and pregabalin. They are believed to mechanistically decrease excitatory neurotransmitter release, activate noradrenergic pain inhibitory pathways, and influence the levels of pro-inflammatory cytokines [26]. This class of medication has best shown to provide relief for neuropathic pain, most pronounced for peripheral neuropathy secondary to diabetes mellitus and post-herpetic neuralgia and less so for spinal cord injury [27]. Its role in the patient with trauma is not well studied, though it is believed that gabapentinoids can potentially reduce the severity of acute and chronic pain post-thoracotomy [28].

Acetaminophen Acetaminophen is in a class of medications unique to itself, with multiple mechanisms of action, most notably cyclooxygenase inhibition and decreased prostaglandin synthesis. This class of drugs provides analgesic and antipyretic effects with minimal gastrointestinal and renal toxicity due to its low affinity for plasma proteins and acid-base neutrality [12]. One study of patients with limb trauma found no difference between morphine and acetaminophen in overall analgesic effects or need for rescue analgesia [29]. A study of hip fracture patients also demonstrated the analgesic benefits while also reporting decreased length of stay and incidence of opioid-related complications [30]. However, it is believed that acetaminophen alone cannot treat trauma pain sufficiently, but plays an important role as an adjunct to other analgesic modalities.

Non-steroidal anti-inflammatory drugs (NSAIDs) This class of medications, which includes ibuprofen, ketorolac, and naproxen, also inhibits the cyclooxygenase enzyme and decreases downstream prostaglandin synthesis, both in the central and peripheral nervous systems [12]. These medications provide most benefit for inflammation-based pain with indications such as musculoskeletal sprains, synovitis, and soft tissue injuries [31]. The low analgesic ceiling and dose-dependent side effects of the digestive, renal, and cardiovascular systems provide the greatest risk. Gastrointestinal side effects alone include dyspepsia, gastric ulcers, and abdominal pain [12, 31]. There has yet to be sufficient evidence demonstrating superior benefits in the patient with trauma pain.

Muscle relaxants The anti-spasmodic medication class that includes cyclobenzaprine and methocarbamol is believed to be beneficial in acute musculoskeletal pain, its primary mechanism related to sedation. An extension of its intended physiology, side effects include drowsiness and headaches [31]. Research into its use for trauma pain is limited.

Ketamine Ketamine, an antagonist of the N-methyl-D-aspartate (NMDA) receptor, has shown significant analgesic benefits in several patient populations and

demonstrates concurrent amnesia and dissociation. The principal benefits of this medication in patient with trauma are the ventilatory maintenance and cardiovascular stimulation, though agitation, hallucinations, and airway secretions limit its use [12]. As mentioned before, a comparison of ketamine, fentanyl, and morphine showed no medication superiority in trauma pain relief [15]. Both ketamine and morphine reduced pain severity significantly, but not compared to each other [17]. Pre-hospital administration of ketamine yielded better physiologic parameters in patients with higher Injury Severity Scores compared to opioid analgesics, while a similar study of pre-hospital analgesics did not show an analgesic benefit, but reported increased agitation in the ketamine group [32, 33]. When formulated as a patient-controlled analgesic (PCA) for patients with trauma in the intensive care unit, ketamine was shown to decrease total opioid consumption and supplemental oxygen use compared to hydromorphone, though it yielded more frequent hallucinations [34]. Two similar studies comparing ketamine as an infusion to placebo found no analgesic benefit nor a reduction in total opioids administered. However, when stratified for higher Injury Severity Scores, one study found a reduction in total opioids administered [35, 36]. A long-term study comparing persistent pain 6–12 months after trauma found no perceived superiority in either the ketamine or morphine groups [37]. While ketamine has clear physiologic benefits compared to other analgesics, evidence is mixed, and its benefits are less pronounced in the trauma pain literature.

Botulinum toxin (Botox) Commonly referred to as "botox," botulinum toxin interferes with the transmission of acetylcholine across the synaptic cleft. It has been shown to improve pain, mood, and activity levels in patients with post-traumatic neuralgia, though further benefits have been less pronounced in the literature [38].

Serotonin-norepinephrine reuptake inhibitors (SNRIs) Antidepressants including the amine reuptake inhibitor duloxetine are believed to yield most clinical benefit in neuropathic pain relief via action of the noradrenergic descending pathways. Its anti-pro-inflammatory cytokine effects and neuroplasticity have also recently been described [26]. Some studies have found decreased opioid consumption and longer times to rescue analgesics with SNRIs, though this has not been shown in the trauma literature [39].

Tricyclic antidepressants (TCAs) Similar in effect to SNRIs, tricyclic antidepressants such as amitriptyline are believed to have mechanistic action via increasing norepinephrine in the spinal cord with downstream effects on the locus coeruleus and descending inhibitory pain pathways [40]. Shown to improve pain, sleep, and depression in patients with trauma injuries and neuropathic pain, the extent of the evidence relating these benefits is limited [12].

Benzodiazepines The benzodiazepine class of medications, which acts at the GABA receptor, includes midazolam, diazepam, and lorazepam. The analgesic

component is believed to be related to anxiety exacerbating pain and the medication's anterograde amnesia improving a patient's perception of pain [12]. While it ideally would best help patients with high anxiety and severe pain, it was not found to augment or provide synergy with morphine for pre-hospital treatment of trauma pain [41]. It can be administered intranasally or rectally in patients with difficult intravenous access [42].

Clonidine Clonidine, an alpha-2 adrenoreceptor agonist, has been known to be synergistic with opioids and local anesthetics [43]. Its role for the management of trauma pain is largely unstudied, but its prolongation of local anesthetics and reduction of perioperative analgesics make it a viable agent to consider its use. However, a hemodynamically unstable trauma patient may have exacerbated hypotension with administration of clonidine [12].

Steroids Corticosteroids inhibit the phospholipase A2 enzyme, inhibiting downstream prostaglandin and other inflammatory mediator synthesis [31]. It is suspected to have the most benefit in extremity radicular pain, peripheral nerve injuries, spinal cord injury, and soft tissue damage [12]. Side effects include psychological changes, insomnia, and hyperglycemia [31]. Weak evidence exists for perineural steroids in short-term analgesia for peripheral neuropathy related to a traumatic or compression injury [44].

Topical creams Topical analgesics exist from several medication classes including local anesthetics, NSAIDs, TCAs, and gabapentinoids. Topical NSAIDs can alleviate a focal area of pain while minimizing systemic toxic effects [31]. Lidocaine patches are indicated for acute herpetic neuralgias [45]. The use of topical creams for trauma-related pain has not been well studied.

Medical marijuana Cannabinoids, such as THC and CBD, act as agonists at the cannabinoid receptor and are believed to have strong analgesic effects if the psychotropic reactions are minimized. The evidence supporting its use is often anecdotal with some relation to the medication's physiologic mechanisms. Examples of diseases and conditions with supposed benefits include fibromyalgia, multiple sclerosis, phantom limb pain, and autoimmune disease [46, 47]. Benefits specific to trauma pain have not been shown.

Infusions Medication infusions, such as ketamine and lidocaine, have been proposed for the treatment of both acute and chronic pain [48]. While the trauma pain demographic has very limited evidence, the fibromyalgia, complex regional pain syndrome (CRPS), and diabetic neuropathy populations have more related research.

Vitamin supplementation Vitamin supplementation as an analgesic modality has not been proven or applied in clinical practice, but a study of several week supplementation of vitamin C showed a decreased incidence of CRPS type 1 1 year after a wrist fracture [49].

Interventional Pain Procedures

Peripheral nerve blocks It is believed that regional anesthesia techniques can potentially reduce the severity of acute and chronic pain post-thoracotomy [28, 50]. The intercostal block has been shown to improve pain scores while minimizing total hospital days and mechanical ventilator days for patients with chest wall trauma [1]. Other studies have shown improved peak expiratory flow rates and oxygen saturation after administering the block in patients with rib fractures [51]. Beyond the improvement in mean pain scores, sustained maximal inspiratory lung volumes, length of stay, and mechanical ventilation rates were found to be improved in patients who received continuous intercostal nerve block with catheter placement [52]. The evidence for paravertebral and intrapleural anesthesia is more limited with no strong guidelines or clinical recommendations for their use over other therapeutic modalities [51]. One meta-analysis reports improvement in acute pain scores (postoperative day 0) and hospital stay, but no improvement in pain scores at 24 hours [46]. Of more interest is the potential use of a paravertebral block in patients receiving anticoagulant or antiplatelet therapy, known contraindications for neuraxial anesthesia per the American Society of Regional Anesthesia and Pain Medicine. While the paravertebral block is not officially endorsed or recommended for patients who present with this contraindication to neuraxial anesthesia, the primary concern is the potential for blood loss and less so for neural deficits [53]. The most recently utilized erector spinae plane block has been shown to target the ventral and dorsal rami of spinal nerves with coverage of the anterior, lateral, and posterior thorax, providing fair coverage to the sites of interest in post-thoracotomy pain syndrome. While far less studied than other regional modalities, the erector spinae plane and other technically easier myofascial plane blocks can benefit patients with acute and chronic pain syndromes after surgery [54, 55]. Fractures and crush injuries of the upper and lower extremities are often managed with regional anesthetic techniques. The interscalene, supraclavicular, infraclavicular, and axillary nerve blocks can be advantageous for shoulder, forearm, arm, and hand analgesia. The lumbar plexus, femoral, and sciatic nerve blocks can be used for lower extremity analgesia [12]. For example, femoral nerve blocks for patients with hip fractures can both decrease pain intensity and the need for rescue analgesics [56, 57].

Neuraxial anesthesia Epidural anesthesia is strongly recommended with a fair amount of evidence for its use in patients with rib fractures and chest trauma [51]. Retrospective reviews have shown decreased mortality in patients with blunt chest trauma who received thoracic epidural anesthesia compared to traditional intravenous opioids; patients in the epidural group also were older, fractured more ribs, and had more frequent comorbidities such as pneumothoraces, lung contusions, and flail segments [58]. The most important perceived benefits include subjective pain perception and pulmonary function testing postoperatively [8]. The side effects of opioids are further limited. Local anesthetics and opioids are most often administered via the epidural catheters providing both sodium channel blockade and opioid receptor agonism, respectively. A major

disadvantage is the segmental spread of anesthesia and potential hypotension from preceding sympathectomy [12].

Kyphoplasty and vertebroplasty Both the kyphoplasty and vertebroplasty procedures have shown small benefits in back pain after acute vertebral compression fracture compared to non-operative management [59]. They can decrease morbidity and increase survival. No one procedure is superior to the other, though kyphoplasty is often more expensive and takes longer to perform [6].

Non-pharmacological Interventions

Hypnosis While not well studied in the trauma pain population, the practice of hypnosis is believed to improve subjective pain intensity for both acute (periprocedural) and chronic conditions. A careful understanding of the patient's pain can better guide the hypnotist in drafting suggestions for dissociations from unpleasant and painful conditions [12, 60].

Biofeedback Biofeedback therapies are described as relating information to patients that would be unknown otherwise; these can relate to the cardiovascular, respiratory, or neuromuscular systems [61]. In a study of biofeedback in chronic back pain, coping strategies were improved, while depression, disability, and muscle tension all decreased [62]. The benefits of biofeedback in trauma pain are not known.

Transcutaneous electrical nerve stimulation (TENS) The use of TENS as an adjunct in treatment of trauma pain has been mildly described. In addition to its analgesic benefits, it was also shown to improve respiratory dynamics in patients with rib fractures [12]. Further uses in trauma have been hypothesized, but not well studied.

Acupuncture The pain mechanisms of acupuncture involve the ascending inhibitory and descending analgesic pathways, as well as cortical, subcortical, and brainstem processing. It is believed to be most beneficial in inflammatory, neuropathic, and cancer pain via its many actions in the central and peripheral nervous systems [63, 64]. The overall evidence quality is low to moderate and limited as it relates to trauma pain.

Special Populations

Crucial to the discussion of trauma pain is an examination of special populations that could confound some of the aforementioned therapies and strategies, such as the patient acutely intoxicated, the patient with opioid tolerance, and the patient with prior substance abuse and addiction.

Alcoholic patients The patient with acute or chronic alcohol exposure presents a unique challenge to pain management during trauma. This is a high-risk population with intoxicated trauma victims known to have more severe injuries and higher mortalities. Additionally, chronic alcoholism is associated with coagulopathies, liver disease, and poor physiologic status [65]. Askay described several concerns with trauma pain management and alcoholism. The patient acutely intoxicated can yield questions about the interaction between opioids and alcohol, the belief that ethanol can affect the binding of opioids to its receptors. The effects of opioids and alcohol together are believed to be additive. The chronic alcoholic introduces tolerance and pain thresholds as therapeutic roadblocks [66]. This may require increasing dosage of analgesics with caution that those with liver disease may show a decreased hepatic metabolism and increased sensitivity and duration of action to opioids [12]. In the patient with an addiction to alcohol but in a recovery state, there is a mixed opinion and, at times, confusion as to the best course of action to prevent a relapse [66]. Ultimately, pain should be treated with the chronic alcoholism in mind with realistic expectations at the initial encounter.

Opioid-tolerant patients The benefits of opioid agonist therapy, such as methadone and buprenorphine, in the patient with opioid tolerance are far-reaching and include decreased drug abuse, improved functioning, decreased criminal activity, and decreased infectious disease transmission. There are several misconceptions contributing to the treatment of the opioid-tolerant patient in pain including the use of opioids in analgesia will result in relapse, they will cause severe respiratory or nervous system depression if doses are increased, and the provider is being manipulated by drug-seeking tendencies [67]. The best treatment strategy starts with partnering with the patient and discussing the pain management plan and realistic expectations. In addition to opioids, multimodal analgesic medications that include acetaminophen, NSAIDs, TCAs, and SNRIs should be used [68]. To treat the injury, use conventional opioids, often times higher doses at shorter intervals given the increased pain sensitivity. Patients receiving methadone should be continued on their maintenance dose with addition of short-acting opioids [67]. Patients taking buprenorphine can either be continued at maintenance dose with addition of short-acting narcotics, continued at divided doses, discontinued and started on short-acting opioids with re-start upon discharge, or discontinued and started on methadone and short-acting opioids with re-starting buprenorphine on discharge [67].

Substance abuse and addicted patients Patients with a history of other substance abuse and addictions during a traumatic episode require careful assessment of the injury and associated pain physiology. Sympathomimetics such as methamphetamine can cause tachycardia just as the compensatory mechanism of hemorrhagic shock does [65]. It is important to assess for historical and physical signs and symptoms of substance abuse to best ascertain the severity of the injury and which analgesics may interfere with the drug of abuse. Furthermore, patients with a history of trauma-related pain, such as a TBI, may have long-term cognitive impairments and psychosocial difficulties, contributing to the potential for substance abuse [69].

Summary of Treatments for Trauma Pain (Tables 1.1, 1.2, 1.3, and 1.4)

Table 1.1 Evidence-based treatments for trauma pain

Intervention	Pain phase	Studies	Study features
Propofol-fentanyl	Acute	Aminiahidashti et al.	RCT (n = 136)
Fentanyl	Acute	Haske et al.	SR/MA (n = 69 K)
Ketamine (bolus, PCA)	Acute	Haske et al. Majidinejad et al. Takieddine et al. Losvik et al. Tran et al.	SR/MA (n = 69 K) RCT (n = 126) RCT (n = 20) Cohort (n = 1876) RCT (n = 298)
Morphine-ketamine	Acute	Jennings et al. (2011)	RCT (n = 135)
Morphine	Acute	Haske et al. Majidinejad et al. Farsi et al.	SR/MA (n = 69 K) RCT (n = 126) RCT (n = 200)
Epidural	Acute	Galvagno et al. Jensen et al. Simon et al.	Guidelines RCR (n = 1347) Guidelines
Acetaminophen	Acute	Craig et al.	RCT (n = 55)
Perineural steroids	Chronic	Bhatia et al.	SR/MA (n = 353)

Table 1.2 Emerging or promising treatments for trauma pain

Intervention	Pain phase	Studies	Study features
Vitamin C (prophylaxis of CRPS-1 after wrist fracture)	Chronic	Aim et al.	SR/MA (n = 875)
Paravertebral	Acute	Galvagno et al.	Guidelines

Table 1.3 Accepted but unproven treatments for trauma pain

Intervention	Pain phase	Studies	Study features
Morphine-ketamine	Chronic	Jennings et al. (2013)	Cohort (n = 135)
Ketamine (low-dose infusion)	Acute	Carver et al. Wiel et al.	RCT (n = 91) RCT (n = 44)
Intrapleural analgesia	Acute	Galvagno et al.	Guidelines
Intercostal analgesia	Acute	Simon et al.	Guidelines

Table 1.4 Disproven treatments for trauma pain

Intervention	Pain phase	Studies	Study features
Midazolam	Acute	Auffret et al.	RCT (n = 91)
Opioids (high dose)	Acute	Shenk et al.	Cohort (n = 268)

Pain Management for the Burn Patient

Introduction

Despite the historical prevalence of burn injury, medical literature is limited with regard to the proper management of adult victims' pain and secondary psychiatric comorbidities. Much of the evidence available as of now is through smaller randomized controlled trials or extrapolation through other populations. This chapter defines burn injury, its pathophysiology with regard to pain evolution, and available evidence for pharmacological and non-pharmacological treatments for the varied types of burn pain.

Burn Insult Classification

In order to effectively manage burn pain, one must first identify the severity and degree of burns involved. Although the same injury has a markedly variable pain response depending on patient characteristics, attention must be given to the type of burn as management will vary [70]. Additionally, the heterogeneity of sensory innervation between epidermal and dermal layers leads to important implications in both the acute and chronic process evolutions of pain after a noxious insult [71].

The traditional classification of burns as "first-, second- or third-degree" was formulated by Peter Lowe in 1597 and modified by Guilielmi Hildani Fabricii in 1610 [72]. Clinical classification of burns currently based on the International Society for Burn Injuries (ISBI) originates from Douglas Jackson in 1953 [73]. This classification system of burn insult includes superficial, moderate, and deep partial thickness as well as full thickness. An alternative classification, from superficial to deep, is epidermal, superficial epidermal, mid-dermal, deep dermal, and full thickness [71]. Traditionally, pain is more severe in more superficial burns due to searing of afferent nerve endings with deeper insults. However, this has not proven to be the case in all patients [74]. This is because pain from burns incorporates a complex interplay between psychological and somatic factors, thus requiring individualized, patient-centered management and monitoring (Fig. 1.1).

Mechanism of Burn Pain

Thermal insult (above 42 °C) to the skin results in an amalgam of downstream nociceptive pathway activation. Thermosensitive channels on afferent sensory C- and A-delta fibers promote calcitonin gene-related peptide (CGRP) and transitively significant transmission of nociception to the dorsal horn of the spine [75]. Tissue necrosis also stimulates sensory fibers via P2X and toll-like receptors (TLRs) on

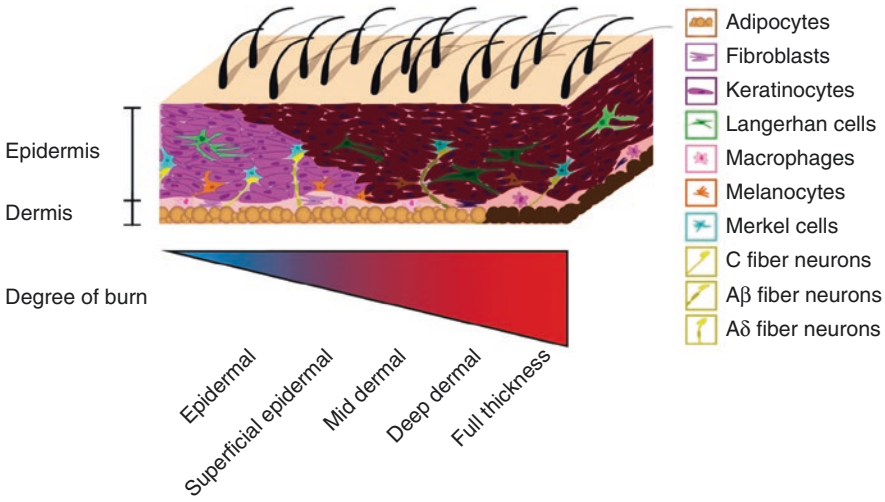

Fig. 1.1 The severity of a burn injury is determined by the depth of tissue injury. The skin is intensely innervated with many morphologically and functionally distinct sensory nerve endings that respond to a multitude of non-noxious and noxious stimuli. Noxious heat stimuli are generally conducted to the dorsal horn of the spinal cord via nociceptive Aδ and C- fiber neurons. Only the epidermis is affected in epidermal or superficial epidermal burns, while increasing damage to the dermis occurs in mid-dermal, deep -dermal, and full-thickness burns (Morgan et al. [71])

recruited leukocytes, with downstream effects of significant cytokine, bradykinin, and prostaglandin release [71]. PGE2 stimulates mast cells to release histamine, responsible for the significant pruritis associated with burn injury [71].

Understanding neuropathic mechanisms that evolve in burn pain facilitate management of postburn distress, sedation, and long-term morbidity [73]. Primary (pain in affected tissue) and secondary (pain in unaffected tissue) hyperalgesia and allodynia (pain without noxious insult) are common in burn injury and facilitated through multiple mechanisms. Immediately after insult, primary hyperalgesia and thermal allodynia are mediated via activation of voltage-gated sodium channels on sensory afferents [76]. Soon after injury, inflammatory cytokines IL-1B, IL-8, and TNF-α as well as platelet-activating factor are released from neutrophils, all contributing as well to primary hyperalgesia. Nerve growth factor (NGF), released into regenerating skin, contributes to systemic hyperalgesia and allodynia via downregulation of lumbar spinal μ-opioid receptors and upregulation of NMDA receptors in the same location [71].

Central neuronal adaptations in the burn patient have been found to involve the phenomenon described as windup and central sensitization. The windup phenomenon is an etiology for the evolution of background, breakthrough, procedural, and chronic pain in the setting of continuous, low-frequency activation of C-fibers. These depolarizations appreciate exponentially in the dorsal horn of the spinal cord, leading to hypersensitivity to pain (primary and secondary hyperalgesia) mediated by the NMDA receptors [77].

Central sensitization, often confused for windup, is a downstream effect of windup occurring at a cellular level. Central sensitization involves increased intracellular calcium in dorsal horn neurons. This increased intracellular calcium decreases threshold for depolarization, causing secondary hyperalgesia and allodynia via myelinated Aβ mechanoreceptors [77, 78].

Acute Management of Burn Pain

The mechanisms described above manifest in burn patients in the form of four variable types of pain: background, breakthrough, procedural/postoperative, and chronic pain [79]. Background pain serves as a low-grade, continuous stimulus stemming directly from thermal insult. It contributes significantly to windup and central desensitization. Breakthrough pain in the burn patient is defined as pain at rest piercing the efficacy of the analog-sedative regimen. Wound debridement, dressing changes, and therapy all cause bouts of brief, severe pain known as procedural pain. Chronic burn pain, primarily neuropathic, is pain beyond 6 months of injury [71]. Management of each type of pain is summarized in Tables 1.5, 1.6, 1.7, and 1.8.

Direction of analgesic therapy should be governed by pain institutionally approved scoring systems, preferably with a focus on patient self-reporting [73]. The numerical rating scale (NRS) has been found to be an accurate standard for assessment of pain in the non-sedated patient, although confounded by pain interference [80]. There does not appear to be a significant difference in validated pain scales for sedated patients, and all have similar efficacy [81].

The ideal approach to managing burn pain invokes a multimodal and systematic regimen [73]. Interestingly, management of acute psychological comorbidity has been shown to decrease acute pain, and management of acute pain, specifically through early opiate administration, has been shown to decrease the incidence of chronic psychiatric comorbidity [70, 82]. This interplay is significant in the burn patient, as the rehabilitative aspect of burn medicine is what necessitates multimodal therapy.

Opioids

Opiates are the foundation of burn pain management due to their accessibility and studied pharmacokinetics in the setting of the two phases of burn physiology – burn shock and hypermetabolism [74, 83, 84]. They should be employed in the treatment of background, breakthrough, procedural, and even chronic pain. For the most extreme acute cases, continuous intravenous infusion of morphine or fentanyl for those in the intensive care unit is appropriate, thanks to the regular monitoring

capacity for opioid-induced respiratory depression [76]. In less critical inpatient settings, patient-controlled analgesia (PCA), when feasible, of morphine or fentanyl is considered ideal and carries minimal risk of respiratory depression when administered without background infusions of opioids or benzodiazepines [79, 85]. Given that fentanyl has a shorter duration of action and longer elimination half-life than morphine, it is preferable for procedural burn pain [86]. A 30 mcg PCA bolus dose of fentanyl is optimal in burn patients [87]. Additional benefit to fentanyl over morphine is its stronger association with significant histamine release than other opioids, theoretically exacerbating pruritis and hypotension in the susceptible burn population [86]. Intravenous boluses of fentanyl, hydromorphone, or morphine administered by nurses are an alternative to PCA but are more labor intensive, and the patient may have to wait on pain control depending on staffing.

Breakthrough pain can be managed with a mix of opioid and non-opioid analgesia [71, 74, 75]. An appropriate opioid option for breakthrough pain consists of short-acting (not ultra-short-acting) opiates such as hydromorphone and fentanyl [78]. Non-opioid analgesics that have proven to synergize well with opioids for breakthrough pain include clonidine and ketamine [75, 78, 88]. These options carry over into management of procedural pain as well [87]. Chronic pain, to be discussed later, should involve management of neuropathic and psychiatric comorbidities to minimize opiate requirement due to the known long-term repercussions of chronic opiate therapy.

Opioid-induced hyperalgesia (OIH) has become an increasing concern in burn patients, as patients' hypermetabolic state and variable level of pain requirements invoke significant opioid burden. OIH manifests as paradoxical primary and even secondary hyperalgesia most commonly observed in the setting of high-volume, short-acting parenteral opioids such as remifentanil [89, 90]. Studies are limited, but OIH is thought to be mediated by peripheral (nociceptive receptor) and central sensitization [76]. Clinical manifestations of OIH can be confused with opioid tolerance, as both involve increased analgesic consumption and pain scoring [90]. The most robustly studied treatment for OIH is the potent NMDA receptor antagonist ketamine, with other options including non-steroidal anti-inflammatory drugs (NSAIDs), opioid switching, α2 agonists, buprenorphine, and methadone [74, 76, 89, 90].

While some side effects of opiates are well documented, such as pruritus, nausea/vomiting, opioid-induced bowel dysfunction, and respiratory depression, there are emerging studies demonstrating novel short-term and long-term complications of this drug class. Opioid-induced hypogonadism and adrenal insufficiency have been confirmed to have significant and lasting impacts on psychiatric well-being in patients on acute and chronic opioid therapy [22, 23]. Monitoring for these endocrine aberrancies should be implemented in the correct setting in any and all patients on chronic opiate therapy. Finally, burn patients often fall into the at-risk categories for overdose and addiction as many are Caucasian, middle-aged males with histories of mental illness and cardiopulmonary comorbidities [91].

Non-opioid Analgesics

While an appropriate opiate base is necessary for burn pain management, non-opioid analgesia is necessary for mitigating opioid-induced sequelae, providing potentiation of analgesia, and controlling psychiatric comorbidity.

Acetaminophen

Acetaminophen is an antipyretic and analgesic without anti-inflammatory properties and provides minor background pain relief for low-to-moderate pain as a combination agent [76]. Although the mechanism of action remains elusive, it is believed to inhibit cyclooxygenase-3 after crossing the blood-brain barrier, thus decreasing central PGE3 [79]. It has demonstrated efficacy in preventing central sensitization and is opiate-sparing [70, 76]. Given the commonality of liver dysfunction in the burn population, full-dose acetaminophen should be avoided for more than 4 days [78].

Non-steroidal Anti-inflammatory Drugs

NSAIDs inhibit prostaglandin synthesis with downstream effects involving inhibition of central sensitization and opiate-sparing by up to 30–50% (without opiate side effect profile) while providing synergistic analgesia with acetaminophen and opiates [33, 76, 78, 89, 92]. As such, they have been implemented early in management of background and postoperative pain to alleviate central adaptations contributing to hyperalgesia and allodynia [33, 73]. Studies have demonstrated maximum efficacy of preventing central sensitization with administration about 30 minutes prior to opiate administration [89]. Risk of renal dysfunction, gastric ulceration, and bleeding should be assessed on an individual level, with attention in elderly patients. Gastrointestinal prophylaxis with H-2 blockers and proton pump inhibitors is recommended in burn patients receiving NSAID therapy.

Antidepressants

While antidepressants do not have robust evidence in the acute management of burn patients, many sources have extrapolated their efficacy in management of chronic pain due to significant neuropathic and pruritic sequelae from burn injury. Neuropathic analgesia provided by tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have demonstrated modest outcomes [8]. Analgesia from these drugs takes less time than mood modification, but limited titratability makes them inappropriate for acute management of burn pain [76, 93]. However, given the importance of managing potential for PTSD, neuropathic pain development, and significant pruritus, TCAs and SNRIs have efficacy in subacute and chronic burn

pain management [74, 76, 93]. The US Food and Drug Administration (FDA) has approved duloxetine (SNRI) and amitriptyline, nortriptyline, desipramine (TCAs) for the treatment of neuropathic pain [94]. Duloxetine has the most robust evidence for this patient population and should be considered a first line. Caution should be used with TCAs, specifically in the older population, due to increased risk of cardiac arrhythmia, anticholinergic, and antihistaminergic effects [8].

Antiepileptics

The most robust evidence for antiepileptics in burn pain as of now involves gabapentin and pregabalin. Gabapentin and pregabalin, although structurally like the GABA neurotransmitter, have primary action at the α2-δ subunit of voltage-activated calcium channels. This class of medications is thought to decrease substance P and glutamate while increasing norepinephrine release in certain areas of the nervous system [8]. Gabapentin has been found to have little opioid-sparing effect in the immediate postburn period; however, both gabapentin and pregabalin remain efficacious in neuropathic pain management postburn [71, 76, 95].

Local Anesthetics

Topical bupivacaine and lidocaine, specifically in the postoperative period, have demonstrated modest efficacy for procedural pain [78]. While concern for systemic toxicity has limited the use of lidocaine in burn patients, lidocaine-prilocaine cream (5 g to 25 cm^2 for a 30-minute interval) has been identified as an appropriate option for debridement of partial-thickness burns [76, 96]. Use of IV lidocaine for background or procedural burn has not been adequately assessed as of now, but its use is becoming more prevalent with the current movement to utilize opioid-sparing techniques for acute pain management [97].

α2-Adrenoreceptor Agonists

Clonidine and dexmedetomidine have favorable analog-sedative effects with peripheral and central mechanisms that mitigate a myriad of mechanisms in the evolution of burn pain. They are sympatholytic via inhibition of the hypothalamic-pituitary-adrenal axis [78]. Clonidine provides central analgesia in dorsal horn neurons, promotes release of peripheral enkephalins, blocks C-fiber activation at high concentrations, and inhibits OIH when co-administered with opiates [89]. Dexmedetomidine, studied less extensively in this population, has a similar mechanism of action. Favorability in management with dexmedetomidine comes from opioid-sparing effects, lack of tolerance, and amelioration of respiratory depression and need for propofol- and benzodiazepine-induced sedation [74, 76, 78]. Dexmedetomidine is only available in the intravenous form, whereas clonidine is available in both intravenous and oral forms.

Both clonidine and dexmedetomidine are viable options for management of background, breakthrough, procedural, and chronic pain, particularly in combination with ketamine and opiates [76, 89]. Side effects include hypotension, bradycardia, and rebound hypertension with abrupt discontinuation.

Benzodiazepines

Benzodiazepines are $GABA_A$ agonists that provide anxiolytic, sedative, hypnotic, and amnestic effects. They are the mainstay of sedation in burn patients for breakthrough and procedural pain. They can be co-administered with ketamine to reduce dysphoria and potentiate analgesia from opiates [71]. Per the ISBI, they should be minimized to prevent delirium, oversedation, and respiratory depression, all of which prolong ICU stay and increase mortality.

Ketamine

Ketamine is a phencyclidine derivative that antagonizes the NMDA receptor and serves as a potent analgesic and dissociative anesthetic [75]. It prevents windup (when administered with morphine), central sensitization, and OIH while also providing opioid-sparing analgosedation with relative preservation of cardiopulmonary function [70, 74–76, 78]. As a result, it is the most common deep sedative employed for procedural and, occasionally, background pain via infusion [71, 75, 98]. Ketamine used intravenously has been shown to reduce secondary hyperalgesia when compared with placebo [75]. The option of oral ketamine (5 mg/kg) has been explored in the adult population with better procedural analgosedation compared to dexmedetomidine (4 mg/kg) [99]. In fact, 20 mg ketamine/0.5 mg midazolam PCA has demonstrated efficacy in controlling procedural pain with the only side effect being hallucination [75]. Controversy with ketamine use in burn injury involves its dose-dependent dysphoric, hallucinatory, and delirium-induced effects, often minimized by concomitant dexmedetomidine or benzodiazepine administration [70, 74–76, 78, 99]. There have been no long-term studies on the effects of regular ketamine use in the adult burn population.

Periprocedural and Intraoperative Management of Burn Pain

Burn injury patients require frequent dressing changes, skin grafting, and other medical interventions that are accompanied by a significant amount of anxiety and pain. Appropriate pharmacological intervention is integral to managing procedural pain. Multimodal pain regimens are key to management of procedural pain in order to prevent severe anxiety and the stress response that can accompany dressing changes.

Conscious procedural pain should be managed with a foundation of opioids (PCA or continuous infusion) alongside short-acting opioids such as dilaudid or fentanyl [70, 71, 76, 87]. Agents utilized solely for sedation include benzodiazepines (midazolam or lorazepam) and first-generation antipsychotics, specifically haloperidol [71, 74, 76, 78]. Per ISBI recommendations, non-benzodiazepine sedatives should be employed before benzodiazepines. As mentioned previously, analgosedation has been proven in dexmedetomidine, propofol, and ketamine boluses or infusions, with the added benefit of prevention of OIH and central sensitization [71, 75–77, 89, 90]. Although ketamine has an unfavorable profile with regard to emergence delirium, dysphoria, increased respiratory secretions, hypertension, and tachycardia, these are seen at anesthetic doses [75, 76]. Utilization of ketamine for conscious sedation at rate of 0.15–0.3 mg/kg/h provides synergistic analgesia with opioids, maintains airway patency, and prevents chronic pain [70, 75, 76, 78, 89]. Additionally, dexmedetomidine has a favorable hemodynamic profile and does not exhibit tachyphylaxis, making it ideal for burn patient management when available. Subanesthetic nitrous oxide-oxygen mixture has also proven efficacious in analgosedation with a manageable side effect profile [16, 71, 93]. Propofol is commonly utilized for dressing changes due to its amnestic effects. It is commonly given with an opioid or ketamine secondary to the fact that it does not possess any analgesic properties. Propofol has been found to have increased clearance and volume of distribution in the burn population, requiring doses that may be overly sedating upon emergence [74, 78]. With regard to pain, propofol may increase sensitivity to thermal stimuli [78]. Co-administration with ketamine for prevention of these effects has had mixed evidence [70, 78].

When possible, regional anesthesia consisting of single-shot nerve blocks and peripheral nerve catheters (PNCs) should be incorporated in order to avoid risks of general anesthesia [76]. PNCs allow for continuous infusion of local anesthetics, leading to decreased systemic opioid requirements and improved patient satisfaction [70, 71, 74, 76]. Neuraxial anesthesia has generally been avoided due to risk of sepsis and coagulopathy in burn patients.

Non-pharmacologic Management of Burn Pain

Non-pharmacological treatments have increasing efficacy in the adult burn patient [73]. The goal is to incorporate these treatments early on during hospitalizations in order to reduce agitation, anxiety, and sedation – all of which have proven to increase ICU stay and mortality [73, 100].

Hypnosis (via Barber's *Rapid Induction Analgesia* method [101]) for procedural analgosedation has been moderately researched in the burn population. The method employs a set of suggestions for facilitating rapid comfort, relaxation, and dissociation [101]. A meta-analysis of six studies demonstrated improved pain intensity and anxiety without change in medication usage [102]. Hypnosis and distraction

techniques such as virtual reality and sensory focusing interventions appear to efficacious in pain relief secondary to utilization of the gate control theory of pain, whereby attention dictates conscious interpretation of pain severity [103].

Music therapy has been studied in burn patients as well, demonstrating pain alleviation, anxiety reduction, and heart rate reduction [46]. Other promising non-pharmacologic management of burn patients include deep breathing, virtual reality, guided imagery, mindfulness meditations, cognitive behavioral therapy, extracorporeal shockwave therapy (ECSWT) for scar pain, and transcutaneous electrical nerve stimulation (TENS) [4, 103, 104].

Outpatient Management of Chronic Burn Pain

Chronic postburn pain is primarily neuropathic in nature and can be challenging to treat, requiring the use of a multitude of analgesic agents concurrently. Multimodal analgesia allows for better analgesic outcomes while concurrently permitting opioid sparing and limiting medication-related side effects. Optimal chronic pain therapy for burn pain should include not only opioids but other adjuvant and neuropathic medications. Some of the most commonly used neuropathic pharmacologic agents include antiepileptic medications (gabapentin, pregabalin, topiramate), TCAs (amitriptyline, desipramine, nortriptyline), SNRIs (venlafaxine, duloxetine), as well as other adjuvant medications such as acetaminophen and non-steroidal anti-inflammatory drugs. Some opioid medications such as methadone, tramadol, and tapentadol possess both opioid and non-opioid qualities, making them particularly useful in the treatment of neuropathic pain [24].

Opioids

Opioids are considered the cornerstone of therapy for moderate-to-severe acute pain or pain of similar intensity due to life-threatening illnesses, but their long-term use in non-cancer pain is controversial. Opioids provide analgesia by binding to opioid receptors of the mu and kappa class and blocking the release of neurotransmitters such as substance P. Opioid receptors are expressed both centrally and peripherally (during the inflammatory response in injured tissue) [105]. Based on their mechanism of action, it has been postulated that methadone, tramadol, and tapentadol have been thought to treat neuropathic pain.

Methadone is metabolized in the liver via the cytochrome P-450 system and is excreted via the kidneys and intestines. Dosage adjustment is not required in renal or hepatic insufficiency or in hemodialysis. Additionally, methadone does not appear to produce active, potentially toxic metabolites. Methadone has a long, biphasic elimination half-life. It may take up to 10 days to reach steady-state serum levels. It is inherently long acting and is significantly less expensive than opioids

that are pharmaceutically manipulated into controlled-release formulations. Its slow onset and offset is also thought to confer methadone a lower risk of addiction in comparison with other opioids. Methadone is also a N-methyl-D-aspartate (NMDA) receptor antagonism. Activation of the NMDA receptor by excitatory amino acids, such as glutamate, has been implicated in the development of neuropathic pain and appears to have a role in the development of opioid tolerance and opioid-induced hyperalgesia. In 2017, a Cochrane review was done to assess whether there is evidence for using methadone to treat neuropathic pain in adults. According to the review, there was very low-quality evidence regarding the efficacy and safety of methadone for chronic neuropathic pain, and there were too few data for pooled analysis of efficacy or harm or to have confidence in the results of the individual studies. No conclusions can be made regarding differences in efficacy or safety between methadone and placebo, other opioids, or other treatments [105].

Tramadol and tapentadol are short-acting, mixed opiates found to have mechanisms like methadone but with varied degree of affinity for the serotonin (5-HT3) and NMDA receptors. They have minimal efficacy in the treatment of chronic neuropathic pain based on limited existing literature [106].

More than half of trauma and burn patients are discharged from the hospital with an opioid prescription. The question remains as to whether long-term use of opioids leads to a transformation of acute to chronic pain. With increased scrutiny from the Drug Enforcement Agency and growing concerns regarding opioid use, dependence, and abuse, there has been a push in the healthcare field toward greater regulation for the chronic prescribing of opioid pain medications. The current paradigm for chronic opioid therapy is to limit opioid dosing to the lowest necessary amount to control pain symptoms in combination with non-opioid analgesic supplementation and multidisciplinary pain management [26].

Summary of Treatments for Burn Pain

Table 1.5 Evidence-based treatments for burn pain

Intervention	Pain phase	Studies	Study quality
Opioids	Procedural Breakthrough Background Chronic	Faucher (2006) [86] ISBI Yang (2018) Prakash (2004)	Guidelines Guidelines SR/MA ($n = 9$) RCT ($n = 60$)
Ketamine	Procedural Background	Kundra (2013) [99] McGuinness (2011)	RCT ($n = 60$) SR ($n = 4$)
Non-steroidal anti-inflammatory drugs	Procedural Background	Marret (2005)	MA ($n = 22$)
Benzodiazepines	Procedural Background Breakthrough	Zor (2010) [107] Patterson (1997) [108]	RCT ($n = 24$) RCT ($n = 79$)

Table 1.6 Emerging or promising treatments

Intervention	Pain phase	Studies	Study quality
Peripheral nerve blockade	Procedural Procedural Procedural	Cuignet (2004) [109] Cuignet (2005) [110] Shtyenburg (2013) [111]	RCT (n = 20) RCT (n = 81) RCT (n = 16)
α2-Agonists	Procedural Breakthrough Background	Asmussen (2013) [16] Kundra (2013) Kariya (1998) [88]	MA (n = 4) RCT (n = 60) RCT (n = 100)
Antidepressants	Chronic	Finnerup (2015)	SR/MA (n = 229)
Antiepileptics	Procedural Chronic	Gray (2011) [112] (pregabalin) Finnerup (2015)	RCT (n = 90) SR/MA (n = 229)
Virtual reality	Procedural Background	Scheffler (2018) Sharar (2007) [113]	MA (n = 21) RCT (n = 88)
Hypnosis	Procedural Background	Scheffler (2018) Provencal (2018)	MA (n = 7) MA (n = 18)
Music therapy	Background	Li (2017) Scheffler (2018)	MA (n = 17) MA (n = 5)
Nitrous oxide	Procedural	Li (2017) do Vale (2014)	RCT (n = 240) RCT (n = 15)
EMLA cream	Procedural Procedural	Lillieborg (2017) Jellish (1999) [114]	RCT (n = 8) RCT (n = 60)

Table 1.7 Accepted but unproven treatments

Intervention	Pain phase	Studies	Study quality
Acetaminophen	Procedural Breakthrough Background Chronic	Koppert (2004) [115] Koppert (2004) [115]	RCT (n = 14) SR/MA

Table 1.8 Disproven treatments

Intervention	Pain phase	Studies	Study quality
Gabapentin	Background (non-neuropathic)	Wibbenmeyer (2014)	RCT (n = 53)

Conclusion

Pain is among the most common causes of distress during the first year after recovery from trauma and burns. Early pain treatment is assumed to effectively reduce pain in patients and improve long-term outcomes. Despite advances in the various areas of trauma and burn care, control of pain is often inadequately managed during the acute and chronic rehabilitation phases of treatment. In the past, opioids have been the first-line treatment for acute pain following trauma; however, increased regulation and a lack of data for long-term opioid use for the management of chronic non-malignant pain in trauma and burn patient have created a need for creation of multimodal pain management treatment algorithms designed to minimize opioids and their side effects. Current evidence has shown that the most advantageous

methods for treatment of pain associated with trauma and burns incorporate both pharmacologic (opioid and non-opioid analgesics) and non-pharmacologic therapies targeting the specific clinical pain settings unique to the patient and hospital system/institutional capabilities.

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Chapter 2
Perioperative Pain Management

Anthony T. Machi

Perioperative Pain Management

Perioperative pain management is a narrow slice of the medical experience that can have an outsized impact on individuals. The experience is exceedingly common with 10.3 million inpatient surgical procedures performed at hospitals in the United States in 2014 and 48.3 million surgical and nonsurgical procedures performed at ambulatory surgery centers [1, 2]. Inadequately treated perioperative pain may lead to undesired psychological and physiological effects. This pain may cause misery and suffering that lead to increased morbidity and mortality and that delay recovery and prolong rehabilitation. These, in turn, lead to increased costs of care, increased length of hospital stay, and patient dissatisfaction. The role of the perioperative healthcare provider is to facilitate healing, combat the untoward physiological and psychological effects of the surgery, and alleviate pain.

The importance of adequate perioperative pain management was recognized by the American Society of Anesthesiologists when they convened their first Task Force on Pain Management, Acute Pain Section in 1994, and published guidelines for the treatment of perioperative pain in 1995 [3]. These were followed by guideline updates in 2004 and 2012 [4, 5]. In the meantime, medicine broadly recognized the importance and unique role of pain management within the patient experience when the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) instituted standards for assessment, monitoring, and treatment of pain and made adequate pain management a patient's right in 2000 [6]. Other societies recognized its importance and published collaborative guidelines on the treatment of perioperative pain including a recent multilateral

A. T. Machi (✉)
Anesthesiology and Pain Management, University of Texas Southwestern, Dallas, TX, USA
e-mail: anthony.machi@utsouthwestern.edu

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guideline [7]. Although awareness helped address a real scourge of healthcare, the JCAHO requirements are cited for unwittingly opening the door to fuel the opioid crisis of the twenty-first century in the United States [8].

Opioids have had a prominent role in treating moderate to severe pain including perioperative pain for millennia as opium and later laudanum [9]. Their use accelerated in the nineteenth century when morphine was first industrially produced. The nineteenth century saw episodes of opioid proliferation and the first modern era opioid crisis with opioid-related addiction, abuse, and deaths until the Harrison Narcotic Control Act of 1914 limited availability of opioids. Subsequent perioperative opioid use remained relatively limited, primarily to morphine and meperidine, until the advent of synthetic opioids in the 1960s and the publication of the high-dose opioid technique for cardiac anesthesia in 1969 [10, 11]. Further proliferation of opioids occurred in 1981 when fentanyl went off patent, and even further growth occurred in the United States, Europe, and other developed countries in the 1990s and 2000s, with a plethora of different synthetic opioids [12]. While opioids are potent analgesics for the treatment of nociceptive pain, they are associated with numerous severe dose-related side effects. Their use in medicine, including perioperative medicine, over the past three decades has contributed to a national opioid crisis in the United States of opioid addiction, opioid abuse, and opioid-related deaths [13–16]. Opioids were involved in 47,600 overdose deaths in 2017 alone—a 5.9-fold annual increase as compared to 1999 in which 8050 people died from an opioid overdose [17–19]. Approximately 5.9–6.5% or 1.8 million surgical patients proceed to have new persistent opioid use following major and minor surgery each year [20, 21]. While judicious use of opioids for perioperative pain management remains important, other medications and treatments have supplanted opioid mono-analgesic therapy for optimal efficacious perioperative pain management. Opioid-sparing and possibly even opioid-free approaches to pain management can have a tremendous effect not only for the individual patient but our society as a whole.

Throughout the era of opioid predomination, multiple competing perioperative analgesic theories developed, notably preemptive analgesia and, later, preventive analgesia and multimodal analgesia. These developments were marked by the 2004 ASA Pain Task Force clinical practice guidelines [4]. For decades, laboratory data supported the theory that initiation of analgesia prior to a traumatic insult led to the best pain relief—a concept known as preemptive analgesia; however, clinical data was conflicting or equivocal for different modalities with regard to the timing of analgesic initiation with the possible exception of central or peripheral neural blockade [22–24]. This led to the development of the theory of preventive analgesia whereby pain is decreased by the attenuation of central sensitization and mitigation of inflammation for a duration that exceeds the expected activity of the analgesic medication. Preventive analgesia theory relied on multimodal analgesia to affect different pain pathways and aimed to have a duration of effect that exceeded the clinical duration of the analgesic by more than 5 half-lives [25, 26]. Here, too, clinical data trailed behind laboratory data. Meanwhile, multimodal

analgesia was developed as an approach whereby two or more drugs that act by different mechanisms provide superior analgesia with fewer side effects because they target different parts of the physiologic pathways of pain with ideally additive or synergistic effects [27, 28]. Because perioperative pain results from a variety of mechanisms, nociception, inflammation, and nerve injury with subsequent neurohumoral physiologic consequences, peripheral and central sensitization, transcriptional and post-transcriptional dysregulation, augmented facilitation, structural organization, and disinhibition, multimodal analgesia provides an approach capable of addressing the distinct analgesic requirements of the perioperative patient [28, 29].

The treatment of perioperative pain is still in part an art. Even treatments with good evidence base can be suboptimal depending on the patient circumstance and surgery type. Consequently, the newest wave of perioperative pain theory applies multimodal analgesia within Enhanced Recovery After Surgery (ERAS) pathways to tailor components of the approach to surgery type and patient experience. However, because pain encompasses emotional experience related to actual or potential tissue damage or described in terms of such damage, even the best treatments and ERAS protocols addressing nociceptive, inflammatory, and neuropathic insults may fall short if biopsychosocial factors are not adequately addressed [30, 31]. For example, proper preoperative discussion of expectations for postoperative pain and how pain will be managed are crucial to improving postoperative outcomes [7]. Often postoperative pain may not entirely be prevented or even be desired to be entirely prevented as the risk of the side effects of medications that could drive away pain entirely outweighs the benefits of having done so. Rather, a balanced perioperative pain management approach seeks to achieve the best analgesia possible with the least amount of side effects or physiologic disturbance and the fastest functional recovery. This chapter will address evidence-based multimodal analgesic strategies. Their application within different ERAS pathways aims to optimally decrease—if not prevent—postoperative pain, accelerate recovery, and improve the postoperative patient experience. It includes a shift away from opioid therapy to the extent possible and provides a roadmap on how to achieve opioid-free analgesia and opioid-reduced analgesia and how to layer analgesic approaches for the ERAS pathways. The cornerstones of this approach are the rational selection of pain mechanism-specific medications and the strategic use of peripheral and central neural blockade. Important questions to consider when selecting a strategy include the following:

1. How much pain is anticipated from the surgery, for how long, and where is the pain?
2. What are the specific postoperative functional goals to facilitate?
3. Will the patient be ambulatory or hospitalized following surgery?
4. Can regional anesthesia be utilized?
5. Does the patient have specific baseline pain modifying considerations, such as advanced age, chronic pain, or opioid tolerance?
6. Are there any contraindications to any of the treatments or techniques?

Acetaminophen

Acetaminophen can be used to prophylactically reduce and treat postoperative pain. It is singularly useful, cheap, widely available, effective, and generally well-tolerated. A single preoperative dose of intravenous acetaminophen 1000 mg is associated with an approximate decrease of 10 mg IV morphine equivalents and is associated with a reduction in postoperative nausea and vomiting with a number needed to treat (NNT) of 3.3 [32]. Intraoperative and postoperative administration of acetaminophen similarly decrease postoperative pain at 4–6 h after surgery with an NNT of 3.6 to achieve a 50% pain reduction and elimination of treatment of breakthrough pain [33–35]. Although quicker and greater penetration of acetaminophen occurs in CSF following IV administration via higher serum levels due to the absence of first-pass hepatic metabolism [36], numerous studies show similar clinical efficacy with oral as compared to intravenous acetaminophen for a variety of different types of surgical related pain [37–40]. This is notable given the substantial cost difference between intravenous and oral acetaminophen in the United States.

While a tight dose-response relationship has not been clearly shown for acetaminophen, improved analgesia seems to occur up to a dose of 1000 mg or 15 mg/kg and not beyond it [32, 33]. Doses as low as 5 mg/kg may be utilized if given intravenously [41]. Acetaminophen (paracetamol; N-acetyl-p-aminophenol) is well absorbed from oral administration from the first part of the small bowel with oral bioavailability estimated between 63% and 89% in adults [42]. Given the high bioavailability of oral acetaminophen and the high cost of intravenous acetaminophen, intravenous acetaminophen is recommended primarily for patients who cannot take oral medication. A recommended perioperative dosing regimen is to schedule acetaminophen 15 mg/kg up to 1000 mg every 8 h given orally beginning before surgery and continuing until resolution of moderate to severe or acute pain. Additionally, because acetaminophen is effective, safe, cheap, and lacking in side effects, it is recommended for analgesia for most types of surgery.

Though acetaminophen has been used clinically for over 50 years, its mechanism of action is unknown. It may exert its clinical effect at a number of different receptors in different pain pathways, and numerous potential receptor targets have been identified. Acetaminophen causes weak inhibition of COX-1 and COX-2, but it is not thought to have anti-inflammatory properties. It appears to reinforce descending serotonergic inhibitory pain pathways, affects a pathway activating vanilloid receptor TRPV1, and may have an indirect effect on cannabinoid CB_1 receptors [42].

Adverse events following administration of acetaminophen are rare and occur at a rate similar to placebo [33]. Hypersensitivity reactions are also rare [43]. Though acetaminophen is very well-tolerated, the potential for hepatic toxicity from excess acetaminophen plasma concentration is well documented. The minimum plasma concentration needed to cause hepatotoxicity is thought to be 150 mcg/ml, which is approximately 10 times the concentration thought to be effective for analgesia (10–20 mcg/ml). Metabolism occurs largely by glucuronidation and sulfation to form non-toxic metabolites which are excreted in the urine. A small amount is

oxidized by cytochrome P450 enzymes to N-acetyl-p-benzo-quinoneimine (NAPQI) which reacts with and depletes hepatic glutathione. If large amounts of NAPQI accumulate and hepatic glutathione is depleted, hepatic necrosis and hepatic failure can occur.

NSAIDs

Nonsteroidal anti-inflammatory agents (NSAIDs) are a large and chemically heterogeneous group of analgesics that act by inhibiting prostaglandin synthesis at the first enzyme in its synthetic pathway—prostaglandin G/H synthase, also known as cyclooxygenase (COX). In so doing, they exert anti-inflammatory, analgesic, and antipyretic effects, and they can reduce perioperative opioid consumption and opioid-related side effects [44–50].

Analgesia from NSAIDs is dose dependent, and the lowest effective dose is recommended for initiation of use. While there are many different NSAIDs to choose from, commonly available medications for oral and IV administration in the perioperative period with NNT between 1.6 and 3 for at least 50% acute pain relief over 4–6 h include ibuprofen 400– 600 mg PO every 6–8 h, celecoxib 200–400 mg PO every 12 h, diclofenac 50–100 mg PO every 8–12 h, meloxicam 7.5–15 mg PO daily, and ketorolac 15–30 mg IV every 6 h [45, 51, 52]. Such low NNTs indicate that NSAIDs are some of the most effective treatments for acute perioperative pain. Strong evidence of analgesic efficacy for one selective or nonselective NSAID over another is lacking. Rather, medication selection may be driven by the selectivity of inhibition of COX-1 versus COX-2 and the resultant side effect profile and the desired route of administration. For example, it is recommended to limit the duration of ketorolac IV to 5 days due primarily to its potential for COX-1-related GI adverse effects and COX-2-mediated renal and CV effects and to initiate its use at the end of surgery due to its potential effects on hemostasis. The benefit of a duration and dosing regimen for each NSAID administration must be considered against the risk of the unique side effect profile for each NSAID. Finally, whichever NSAID is chosen should be scheduled around the clock to optimize efficacy [5].

NSAIDs exert their clinical effect by impacting prostanoid synthesis [53]. This begins with the release of arachidonic acid from the phospholipid membrane of cells in response to inflammatory mediators and active acyl hydrolases. Arachidonic acid is a polyunsaturated fatty acid present in cell membranes throughout the body. Following its release, arachidonic acid is converted to prostaglandin G2 and then prostaglandin H2 by the sequential cyclooxygenase and hydroperoxidase actions of the two isoforms of the cyclooxygenase enzymes, COX-1 and COX-2. PGH2 then takes different pathways leading to the production of thromboxane A2 and other prostaglandins, such as PGE2, PGI2, and PGD2. The prostanoids are then released outside the cell after intracellular biosynthesis and act locally in an autocrine or paracrine fashion. These prostaglandins then sensitize local pain receptors to mechanical and chemical stimulation by lowering the threshold of polymodal

nociceptors of C fibers. While COX-1 has roles in regulating normal cell processes, COX-2 is normally expressed at low levels unless triggered by inflammatory mediators. NSAIDs exert their effect on COX enzymes by competitively inhibiting the active sites of the enzymes which ultimately leads to their analgesic effects.

Although NSAIDs are a fundamental component of postoperative analgesia, their administration may be limited by a number of clinically relevant adverse effects that depend on the degree of alteration of various aspects of the COX pathway: inhibition of platelet aggregation, impairment of renal function, effects on bone healing, gastric mucosa injury, gastrointestinal anastomotic wound healing, and cardiovascular events.

Reversible platelet dysfunction by non-aspirin NSAIDs occurs by inhibition of COX-1 which is responsible for the first step synthesis of thromboxane A2 from arachidonic acid, which mediates platelet activation and aggregation [54]. Although clinically relevant bleeding has been shown in the setting of impaired hemostasis of "raw" surfaces, such as tonsillectomy and adenoidectomy [55], the clinical impact on other sites has been shown to be minimal or equivocal [56, 57].

Cyclooxygenase-2 mediates a number of effects in the kidneys via PGE2 and prostacyclin [58]. Its inhibition can lead to a decrease in renal perfusion and mild increases in peripheral edema and blood pressure in susceptible patients. Because these are COX-2-mediated effects, they occur similarly across COX-2 selective and nonselective NSAIDs. Thus caution for the use of any of these medications is advised in patients at risk for renal problems: advanced age, renal or hepatic disease, congestive heart failure, or concomitant therapy with diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. However, the effects have been found to be mild, transient, and clinically unimportant in patients with normal preoperative renal function [59, 60].

Laboratory evidence suggests that nonspecific NSAIDs and even COX-2-specific medications affect bone healing in a number of ways via inhibition of prostaglandin E2, osteoblast function, and angiogenesis [61]. Though this may be of particular concern for the healing of fractures, joint implants, and spinal fusion, many studies show that COX-2 inhibition is not injurious to healing in these clinical settings. This may be because interference of bone healing is thought to be smaller with COX-2-specific medications. More studies are necessary to determine clinical implications.

Gastrointestinal adverse effects arise with NSAIDs in the perioperative setting in a couple of different ways. First, gastric mucosa injury and gastropathy may occur via inhibition of COX-1 mucosal prostaglandin production from nonselective NSAIDs [54]. This effect combined with platelet inhibition can increase the risk of gastrointestinal bleeding with chronic use, but the risk is limited in the perioperative setting when used for 5 days or less. Because prostaglandins are involved with epithelial migration in the gastrointestinal tract, myofibroblast function, collagen deposition, and leukocyte adhesion, concern has arisen that NSAIDs may alter the wound healing of gastrointestinal anastomoses and lead to an increased risk of anastomotic failure. A number of studies have been conducted with conflicting results [62–66]. While caution may be warranted in the setting of colorectal anastomoses, evidence

for an increased risk of anastomotic leak is limited, and the evidence does not support an increased risk for small bowel anastomoses.

The final adverse effect of NSAIDs is the potential higher incidence of cardiovascular events such as myocardial infarction, stroke, and congestive heart failure exacerbation when they are used. Numerous theories exist as to the mechanism of vascular-related adverse effects and appear to be most strongly related to the overall degree of COX-2 inhibition [67]. Because COX-2 inhibition decreases PGI2, thromboxane A2 action on platelets is left unopposed, leading to platelet aggregation, vasoconstriction, smooth muscle proliferation, and ultimately coronary and cerebral thrombosis [68]. Increased salt and water retention via COX-mediated renal effects and increased arterial blood pressure via COX-mediated vascular effects can increase the risk of congestive heart failure exacerbation in patients with impaired renal and cardiac function [69]. Most studies investigating these risks address chronic use in the non-perioperative setting. Perioperative studies are lacking but do not support an increased risk when NSAIDs are administered in the short-term acute setting [70, 71]. Thus NSAIDs and COX-2 inhibitors have great efficacy for perioperative analgesia for a wide range of surgeries, but their use for analgesia for any specific surgical patient must be weighed against the potential adverse effects.

Steroids

The neuroendocrine stress response and inflammation created by the tissue injury of surgery involves many agents and affects many pathways of organ systems throughout the body. Broad attenuation of this response leads to improved perioperative analgesia. Steroids are the category of analgesic medication that can impact more mediators than any other, and many clinical studies support their role in perioperative analgesia. Perioperative steroid administration leads to lower pain at rest, lower pain with movement, reduced opioid consumption, decreased incidence of postoperative nausea and vomiting, improved oral intake after tonsillectomy, reduced incidence of atrial fibrillation after cardiac surgery, shorter PACU stays, and shorter hospital length of stay [72–76].

There are many steroids which could be given in the perioperative setting via oral or intravenous routes. The most common steroid and route of administration for perioperative use is dexamethasone given intravenously as a one-time dose. Dexamethasone has a high level of glucocorticoid and hence anti-inflammatory activity without mineralocorticoid activity, in contrast to other steroids. Additionally, it is nonparticulate, cheap, and widely available. The optimal intravenous single dose for perioperative analgesia is unknown, but studies indicate that it is likely at least 0.1 mg/kg but less than 0.2 mg/kg [72, 73]. Dexamethasone may also be administered as an adjuvant to local anesthetic to prolong duration of perineural blockade [77]. Although the administration of additional perioperative doses may seem intuitive and beneficial, this practice isn't supported by evidence and may increase the risk of glucocorticoid-related adverse effects.

Glucocorticoids work at multiple levels of pain pathways to decrease perioperative pain. They primarily exact their effect by inhibition of the synthesis of cytokines and inflammatory mediators at the site of tissue injury [78]. These inflammatory agents activate peripheral nociceptive receptors on peripheral primary afferent sensory nerves. Reducing their production decreases the signals transmitted to the neurons of the dorsal column of the spinal cord. Thus decreased signals are projected along central ascending pathways to many other sensory processing areas including the thalamus, hypothalamus, and somatosensory cortex. At higher central nervous system locations, such as the hypothalamus and pituitary, glucocorticoids again inhibit nociception via reduced levels of cytokines and inflammatory mediators [79]. In addition to their analgesic effect, they more generally attenuate early organ dysfunction mediated by the neuroendocrine, inflammatory, and immunological surgical stress response that manifests in a multitude of adverse effects including postoperative nausea and vomiting, swelling, fatigue, delirium, and weakness [76]. Consequently, they play an important role in many ERAS protocols.

Dexamethasone is a synthetic corticosteroid that is not highly bound to plasma proteins. It has a terminal phase half-life of approximately 3 h following intravenous injection but a longer duration of action because it exerts much of its effect by modulation of downstream events [53, 80]. Metabolism occurs primarily by the liver to inactive glucuronide and sulfate metabolites that are then excreted in the urine.

While there are many adverse effects of excess corticosteroid when administered over long periods of time, there appear to be few adverse short-term effects when given in the perioperative setting. Because of their effect on inflammation and the immune system, concerns have risen for the potential for poor wound healing and infection. At lower doses, steroids do not increase the risk of delayed wound healing or postoperative infections [81, 82]. However, it is possible that these adverse effects could be dose related, and it is unclear if there may be increased risk at high perioperative doses [76]. Steroids transiently cause hyperglycemia in patients with and without diabetes when given perioperatively—by 13 and 32 mg/dl, respectively—but they do not increase glucose so much that they adversely affect clinical outcomes [81]. It appears that perioperative steroids may be given safely to patients with diabetes in conjunction with postoperative monitoring of blood glucose and treatment if necessary [83]. Additional steroid side effects that can be problematic with chronic administration but that do not appear to be problematic in the perioperative short- term setting include Cushing's syndrome, osteoporosis, myopathy, cataract formation, glaucoma, gastrointestinal effects such as stomach ulcer formation, cardiovascular effects such as hypertension, leukocytosis, psychologic effects such as psychosis, and skin changes [84].

Local Anesthetics

Local anesthetics are a highly versatile, cheap, and useful category of medication with many applications in the perioperative setting including wound infiltration, peripheral nerve blockade, neuraxial blockade, intravenous administration, and

even as a combination of approaches. Because of their utility and favorable side effect profile, local anesthetics, particularly in a local or regional administration, should be used whenever possible and in combination when appropriate, such as intravenous administration and incisional wound infiltration for major abdominal surgery unfavorable for an epidural.

Infiltration of local anesthetic at the site of surgery is one of the simplest techniques to administer local anesthetics for perioperative pain [85]. The biggest limitation to this approach is that common long-acting local anesthetics administered as infiltration are limited to 6–8 h of analgesia. Continuous wound infiltration is an approach to achieve longer-lasting wound infiltration via continuous catheters that has found to be beneficial for certain types of surgery, such as abdominal surgery associated with moderate to severe pain [86]. Their use is limited by concerns of technical failure, wound infection, and catheter dislodgement. They should additionally not be used for intra-articular infusion due to the increased risk of chondrolysis [87]. Liposomal bupivacaine offers another possibility to increase duration of analgesia from surgical site infiltration. It is an extended release formulation in which bupivacaine is bound within liposomes and released slowly offering the potential to extend analgesia [88]. While some studies comparing liposomal bupivacaine to placebo for surgical site infiltration have shown small benefits, significant analgesic benefit has not been shown against infiltration with plain bupivacaine nor has prolonged benefit been shown in many randomized controlled trials [89–94]. Liposomal bupivacaine also costs significantly more than plain bupivacaine [95].

When it is possible, a regional approach to administering local anesthetic can provide excellent and cheap analgesia with few side effects. There is robust evidence for superior analgesia provided by peripheral nerve blockade for surgeries of the extremities and trunk when local anesthesia is used for a single perineural injection or via continuous blockade with a perineural catheter [96–99]. Common evidence-based neural and anatomic targets for perioperative analgesia of the extremities include the brachial plexus, median nerve, ulnar nerve, radial nerve, suprascapular nerve, axillary nerve, lumbar plexus, femoral nerve, saphenous nerve, adductor canal, and sciatic nerve [100, 101]. While the duration of a single-injection peripheral nerve block is typically limited to 8–18 h, the addition of a perineural catheter allows for analgesia to continue for 3–5 days and possibly beyond. In addition, multiple studies have found a decrease in persistent postsurgical pain following peripheral nerve blockade [102–104]. There is additional efficacy for truncal blockade with local anesthetics in the form of paravertebral blocks, transversus abdominal plane blocks, ilioinguinal-iliohypogastric blocks, and rectus sheath blocks [105–108]. There is emerging evidence for the efficacy of new truncal blocks: Pecs 1 block, Pecs 2 block, serratus anterior plane block, erector spinae plane block, and quadratus lumborum plane block [108–110]. Because the blockade is limited to a specific area of the body, there is typically little systemic effect of sympathectomy, and the analgesia is associated with hemodynamic stability. Limitations of peripheral nerve blockade are most often related to undesirable blockade effects related to motor blockade, such as falls with femoral nerve block, or to blockade of other nerves near those that are intended to be blocked, such as

phrenic nerve block and subsequent hemidiaphragmatic paresis with interscalene brachial plexus blockade. Complications such as infection, nerve injury, serious catheter-related issues, and local anesthetic systemic toxicity are rare [96].

Strong evidence also exists for the use of epidurally administered local anesthesia for perioperative analgesia, particularly for major open thoracic, abdominal, and pelvic surgery [7, 111–117]. There is even evidence for preemptive analgesia with epidural administered local anesthetics [23]. In addition, epidurals are associated with a decreased risk of venous thromboembolism, myocardial infarction, pneumonia, respiratory depression, and ileus, though many of these secondary benefits were found in the context of open surgical techniques and outdated perioperative analgesic techniques [118, 119]. In contrast to the studies questioning the benefit of epidural analgesia on secondary outcomes, a recent analysis of 9044 patients found a 25% relative reduction in 30-day post-surgery mortality and improved outcomes for each of the mentioned effects with epidural analgesia [120]. Epidurally administered local anesthetics block autonomic nerves in addition to somatic nerves. While this can be beneficial for analgesia and in reducing the surgical stress response, it can also lead to sympathectomy-related hypotension and bradycardia and motor blockade, which limit its utility in various clinical settings. Additional cumulative epidural procedure-related complications occur at a rate of 3.1% and include 1.1% unsuccessful placement, 0.7% dural puncture, 0.2% postoperative radicular pain, and 0.2% peripheral neuropathy [121]. Rare complications include epidural hematoma and epidural abscess [122].

Intravenous administration of local anesthesia can also improve analgesia and functional outcomes in a variety of perioperative settings. While many local anesthetics are used in clinical practice, only lidocaine is recommended for intravenous administration due to its long history of evidence of safety when used as an antiarrhythmic [99]. Although an optimal dosing regimen is unknown, most studies showing the lowest risk to most benefit profile initiated intravenous lidocaine treatment with a bolus of 1.5 mg/kg followed by an infusion of lidocaine 1–3 mg/kg/h [7, 99]. The best evidence for lidocaine's impact on perioperative analgesia is with laparoscopic and open abdominal surgery, genitourinary surgery, major spine surgery, and thoracic surgery [123, 124]. It has been shown to act as a preventive analgesic in these settings, and in gastrointestinal surgery, it hastens the time to first flatus and time to first bowel movement and reduces the risk of paralytic ileus. It also has positive secondary effects: reduced hospital length of stay, reduced risk of postoperative nausea and vomiting, and reduced perioperative opioid consumption. When compared to epidural administration of local anesthetics, intravenous administration resulted in inferior analgesia but had superior secondary outcomes such as less episodes of hypotension and urinary retention and earlier urinary catheter removal [125]. Other studies have shown intravenous lidocaine to be equivocal to epidural local anesthetic for analgesia and secondary outcomes for open and laparoscopic colorectal surgery [126, 127]. Intravenous lidocaine has not shown benefit for certain other types of surgery: ambulatory surgery, breast surgery, gynecologic surgery, and orthopedic surgery other than spine surgery [124, 128]. Given the shorter duration but prolonged analgesic benefit of an intravenous infusion, an intravenous infu-

sion is a good alternative when a neuraxial or peripheral nerve approach is not possible or in select patient and surgery groups.

A full analysis of the different perioperative uses of local anesthetics is beyond the scope of this chapter; however, there are books to consult for further information [100, 101].

Local anesthetics' principal mechanism of action is to reversibly bind a specific receptor site within the pore of the voltage-gated sodium channel in nerves and block ion movement, thereby blocking nerve conduction [53]. A secondary but important mechanism of action for perioperative pain is that local anesthetics appear to have anti-inflammatory properties by modulating the response of some inflammatory cells, such as polymorphonuclear granulocytes and macrophages [129]. A wide variety of compounds can have local anesthetic properties; however, the typical local anesthetics in clinical use have hydrophilic and hydrophobic groups separated by an ester or amide linkage. This linkage determines some of their properties. For example, those with ester links are metabolized by plasma esterases and hepatic enzymes, while those with amide links are typically processed only by hepatic CYP enzymes. A high percentage of amide local anesthetics are bound to plasma proteins which affects their availability for activity and their metabolism [130]. Factors that increase or decrease plasma proteins and in particular α1-acid glycoprotein will alter the amount of local anesthetic delivered to the liver and influence plasma levels and systemic toxicity.

While there are few side effects of local anesthetics when used within the appropriate clinical dose range, systemic toxicity can occur. The desired effects of local anesthetics occur principally from their blocking action on local peripheral or neuraxial nerves, and their adverse effects occur at higher systemic levels by the same mechanism of conduction blockade which happens to all organs in which conduction or transmission of impulses occurs [53]. In addition, local anesthetics can inhibit transduction of calcium and potassium through the voltage-gated channels. This is of particular concern for the central nervous system and cardiovascular system. The phenomenon of excess local anesthetic is well characterized as local anesthetic systemic toxicity (LAST). Depending on the free plasma level of local anesthetic and patient factors, LAST follows a sequential pattern from CNS stimulation to CNS depression, seizure, cardiovascular problems, cardiovascular collapse, and cardiac arrest. Exact presentation and observed mix of CNS versus CV features depend on a variety of factors and may initially present as severe cardiac symptoms in almost 25% of cases [131]. The pattern arises from local anesthetics relatively complex and widespread impact on channel blockade, metabolic signaling, and intracellular energy production that lead to effects on CNS inhibitory neurons, followed by more global CNS effect, followed by the impact on cardiac muscle of electrical excitability, conduction rate, and force of contraction and on systemic vascular resistance. The incidence of LAST in peripheral regional anesthesia is 3/10,000 [132]. If signs or symptoms of LAST occur, critical treatment includes rapid administration of lipid emulsion therapy and if necessary airway management, treatment of seizures, cardiovascular support, and, if necessary, cardiopulmonary bypass for situations refractory to lipid emulsion and vasopressor therapy [131].

Gabapentinoids

The anticonvulsants gabapentin and pregabalin are analogues of the gamma-aminobutyric acid (GABA) molecule. Though originally marketed for their antiseizure activity, numerous studies have shown efficacy in relief from chronic and neuropathic pain and anxiety. Their impact on perioperative analgesia appears to be modest, and the literature is conflicting. A systematic review found that a single 250 mg perioperative dose of gabapentin achieved a 50% reduction in postop pain for over 6 h in 15% of patients compared with 5% of patients who had taken a placebo, giving an NNT of 11 [133]. The NNT to prevent use of a rescue medication for breakthrough pain in that same review was better at 5.8, and numerous studies have shown a reduction in postoperative opioid requirement and opioid-related side effects [134, 135]. Though reduction of postsurgical opioid consumption by gabapentinoids has been called into question by a recent meta-analysis which showed only 3.1 mg morphine reduction on average in the first 24 h after surgery [136], modest evidence exists for improved pain relief at rest and pain relief with movement, while more robust evidence supports decreased postoperative nausea or vomiting [137]. Limited evidence also suggests that the gabapentinoids may reduce the incidence of chronic postsurgical pain [138].

Perioperative dosing of gabapentin may range from 300 to 600 mg PO TID and of pregabalin may range from 75 to 150 mg PO either BID or TID. Common preoperative single-dose regimens are gabapentin 300–600 mg PO and pregabalin 75–150 mg PO with dose reduction recommended in the elderly and those at risk for side effects. Higher single-dose perioperative regimens have been utilized—gabapentin 1200 mg and pregabalin 300 mg—but are also associated with a higher incidence of side effects [139]. Typical multi-dose regimens trend toward the low end of the dosing ranges due to the significant incidence of serious adverse effects. There is insufficient evidence to recommend either gabapentin over pregabalin or vice versa in the perioperative setting.

Despite the molecular similarity to the inhibitory neurotransmitter GABA, the gabapentinoids do not mimic GABA and do not bind to GABA receptors, affect GABA uptake or degradation, or modulate GABA. Rather, both gabapentin and pregabalin bind to the $\alpha_2\delta$ subunit of the voltage-gated calcium channel found in the central nervous system. This binding may inhibit or modulate the neurotransmitters that result from the influx of calcium after a pain-evoked action potential and the subsequent fusion of synaptic vesicles with the neuronal membrane [139]. They may also activate descending inhibitory noradrenergic pathways in the dorsal horn of the spinal cord.

Both gabapentin and pregabalin are largely excreted unchanged in the urine. They do not undergo hepatic metabolism and are not bound to plasma proteins. Common side effects include sedation, dizziness, ataxia, fluid retention, peripheral edema, and fatigue and are dose dependent [53]. These may be accentuated by the concomitant use of other analgesics, such as opioids. The sedating effects are particularly concerning in the perioperative setting, and gabapentinoids have been

associated with prolonged PACU stays [140]. In addition, the incidence of dizziness has been shown to be as high as 70% when pregabalin is administered for perioperative analgesia with a total daily dose of 600 mg [141]. Elderly patients appear particularly vulnerable to these side effects. Respiratory depression also has been reported to be accentuated in patients with concomitant opioid use [142, 143]. Caution is advised, and dose reductions are recommended in the elderly and when administering gabapentinoids in the setting of opioid treatment. Less common potential side effects include dry mouth, blurred vision, and inability to concentrate [144]. In summary, while gabapentinoids are helpful analgesics for moderate to severe pain, there is insufficient evidence to recommend broad usage in light of associated adverse effects. Their profile for perioperative pain management may be most favorable for hospitalized surgical patient populations with potential severe postoperative pain, those at most risk for chronic persistent postsurgical pain, and non-elderly adult patient populations.

Ketamine

Ketamine, 2-(o-chlorophenyl)-2-(methylamino)cyclohexanone, is a chemical derivative of phencyclidine that acts as an NMDA receptor antagonist [145]. At higher doses, it produces a dissociative hypnotic state and can induce anesthesia. At lower doses, it provides antinociceptive analgesia and has effects on central sensitization, descending inhibition, neural modulation, and inflammation [146, 147].

Ketamine can cause an absolute reduction in perioperative VAS pain score of about 1 point on a scale of 1 to 10, 20% approximate relative reduction in opioid requirement, and mild reduction in opioid-related adverse effects and double the time to first postoperative analgesic request [148–150]. Patients who benefit most are those undergoing surgery associated with severe pain and those who have chronic pain, are opioid tolerant, and have hyperalgesia [147]. Ketamine has not been shown to be beneficial for mild postsurgical pain [149]. It may be particularly efficacious for patients with chronic pain, neuropathic pain, opioid tolerance, hyperalgesia, and refractory pain [151, 152]. Although it is unclear if ketamine results in better long-term recovery or improved functional outcomes, it has been shown to improve mobilization following total knee arthroplasty [153].

Ketamine can be administered via different routes: intravenous, intranasal, oral, intramuscular, and rectal. Plasma concentrations for analgesia are 100–200 ng/ml—much lower than for general anesthesia: 9000–25,000 ng/ml [147]. Consensus guidelines from multiple pain societies recommend IV bolus initiation of 0.35 mg/kg with or without an infusion of 0.06–0.2 mg/kg/h up to a max dose of 1 mg/kg/h [147]. Analgesic dosing in studies ranges from a bolus of 0.014–1.0 mg/kg and infusions of 0.06–1.2 mg/kg/h, while dosing regimens at higher levels may not be considered subanesthetic [154, 155]. There is the suggestion from the use of ketamine for the treatment of chronic complex regional pain syndrome that a total episode dose may need to be greater than 200 mg to provide lasting analgesia; however, this

has not been examined for perioperative analgesia [156]. Although higher doses of ketamine are associated with more adverse effects, higher doses have not clearly shown greater analgesia, and evidence does not support an exact threshold for a higher rate of adverse effects [155]. Some individuals may still have adverse effects even at low analgesic dosing [157]. Importantly, some of the psychologic and neurologic adverse effects may be attenuated by the co-administration of benzodiazepines and potentially other medications such as α_2-adrenoceptor agonists [151, 158]. Ketamine has also been investigated for intrathecal and epidural use; however, side effects, an unknown safety profile, and possible neurotoxicity limit its clinical neuraxial use [159, 160]. In addition, ketamine may be given via other routes, such as intranasal, oral, and rectal. The utility of these routes in a perioperative setting remains unclear.

Ketamine is principally known as an NMDA receptor antagonist, and this mechanism most likely explains its antinociceptive effect and role in perioperative analgesia [148, 161]. However, ketamine also acts on a variety of other receptors that may explain additional analgesic effects: decreasing central sensitization, enhancing descending inhibition, neural modulation, and anti-inflammation. These receptors include nicotinic receptors, sodium channels, mu kappa and delta-opioid receptors, monoaminergic and voltage-gated calcium channels, serotonergic receptors, cholinergic receptors, and cannabinoid receptors [146, 155].

Ketamine undergoes hepatic metabolism by the cytochromes CYP3A4, CYP2B6, and CYP2C9 to the weakly active metabolite norketamine via *N*-demethylation [151]. Norketamine undergoes further hepatic metabolization by glucuronidation and is excreted in urine and bile. The half-life of intravenous ketamine is about 7 minutes.

Ketamine has multiple psychologic, neurologic, cardiovascular, and respiratory effects. At a high enough dose, it provides an anesthetic state characterized by hypnosis, amnesia, unresponsiveness to painful stimuli, and dissociation [162]. It is an indirect sympathomimetic. This activity can manifest as pupil dilation, salivation, lacrimation, and increased muscle tone. Ketamine increases cerebral blood flow, intracranial pressure, and possibly intraocular pressure. Emergence delirium can occur with anesthetic doses, and even subanesthetic doses may cause dysphoria, agitation, hallucinations, and nightmares. Because the subanesthetic dosing limit is not well-defined, caution is advised for CNS-related side effects and the need for additional monitoring and precautions, such as nil per os [147]. Though anesthetic doses can cause increases in blood pressure, heart rate, and cardiac output, analgesic doses typically have minimal cardiovascular effects. Caution is advised for the use in patients with severe cardiovascular disease or poorly controlled hypertension. At anesthetic doses, ketamine is a potent bronchodilator and causes only minimal decreases in minute ventilation. Caution is also warranted for the potential abuse of ketamine due to its psychedelic effects. Although physical dependence is not observed after long-term use, psychological dependence and tolerance may occur [163]. Ketamine is known to be abused as a recreational drug and is placed in Schedule III of the US Controlled Substances Act. These are not known to be problems in the setting of perioperative administration.

Alpha-2-agonists

Dexmedetomidine and clonidine are highly selective α_2-adrenoceptor agonists that act on central and peripheral nerves. Dexmedetomidine is more selective than clonidine for the α_2-adrenoceptor as compared to the α_1-adrenoceptor with a ratio α_2:α_1 of 1620:1, whereas clonidine has a ratio of 200:1 leading to somewhat different effect profiles [164, 165]. Both provide modest analgesia with an approximate 1.5-point reduction on a 10-point scale at 12 h and an approximate 0.7-point reduction on a 10-point VAS scale at 24 h in a meta-analysis across a wide variety of surgeries, while another meta-analysis focusing on abdominal surgery found no significant impact on analgesia [166, 167]. In an experimental pain model, the analgesia during a cold pressor test was a modest 14% less than baseline with a less than 1 mcg/kg dexmedetomidine intravenous bolus but increased with higher doses [168]. The reduction in perioperative opioid consumption is more pronounced with dexmedetomidine reducing morphine consumption by 6 mg at 12 h and 15 mg at 24 h and with clonidine reducing morphine consumption by 9 mg at 12 h and 4 mg at 24 h [166]. In addition, both dexmedetomidine and clonidine decrease the incidence of PONV within the first 8 h after surgery with an NNT of 9 [166]. Studies also confirm greater utility in patients experiencing moderate to severe pain as compared to mild pain, as well as utility for anxiolysis in patients experiencing moderate to severe pain [169, 170]. Because α_2-agonists cause sedation and anxiolysis, they are useful for ICU sedation, procedural sedation, and reducing emergence agitation and delirium in pediatric populations [171, 172]. The α_2-agonists are also useful in modulating the surgical stress response [173]. Given the associated sedation, anxiolysis, and hemodynamic effects, α_2-agonists have most appeal as analgesics for hospitalized and pediatric patients undergoing major surgery associated with severe pain and scenarios in which same-day mobilization is not an important goal.

Various routes of administration and doses are used for α_2-agonists depending on the indication: for clonidine, oral, transdermal, intravenous, neuraxial, and perineural and, for dexmedetomidine, intravenous, oral, sublingual, intranasal, intramuscular, and perineural [174]. It is unclear from the literature whether dexmedetomidine or clonidine is superior for analgesia across different routes of administration. Neither is routinely administered for analgesia due to their side effect profile, and neither is specifically approved by the FDA for perioperative pain management [175, 176]. However, clonidine is approved by the FDA for the treatment of severe cancer pain. Selection of either clonidine or dexmedetomidine may be guided by the desired route of administration and acceptability of each relative side effect profile.

An optimal dosing regimen for clonidine or dexmedetomidine to produce perioperative analgesia is unknown. Perioperative clonidine is most commonly administered via oral, intravenous, transdermal, or perineural routes in doses for adults ranging from 150 to 300 mcg as an oral preoperative dose to 2–5 mcg/kg IV as a one-time intraoperative dose to a transdermal 0.2 mg/24 h application to 100–150 mcg added to local anesthetic for perineural blockade [166, 177].

Perioperative dexmedetomidine administration is typically intravenous, intranasal, or perineural. An infusion as low as 0.2 mcg/kg/h has been shown to produce analgesia [178]. The max approved dose for sedation is 0.7 mcg/kg/h, and initiation is recommended with a 1 mcg/kg bolus over 10 minutes. Studies investigating dexmedetomidine for perioperative analgesia all used less than 0.7 mcg/kg/h [179]. Unless the patient is monitored in the ICU, dexmedetomidine is not commonly administered in the postoperative phase due to sedation and hemodynamic effects. When given intranasal, dexmedetomidine produces reliable sedation at 45 minutes with a peak effect of 90–150 minutes, but the resulting analgesia is uncertain [180]. Dexmedetomidine 30–100 mcg or 0.75–1.0 mcg/kg when added to local anesthetic for peripheral neural blockade prolongs sensory and motor blockade [181]. The full safety profile of perineural administration is unknown.

Clonidine and dexmedetomidine both act on central and peripheral α_2-adrenoceptors. Their relative effect on different central presynaptic α_2-subtype receptor sites, particularly α-2A and α-2C, predominates [182]. Activation of these receptors inhibits adenylyl cyclase. This decreases cyclic adenosine monophosphate (cAMP), which, in turn, leads to hyperpolarization of noradrenergic neurons in the locus coeruleus leading to suppression of neuronal firing and activity [183, 184]. While evidence indicates this is the mechanism of α_2-adrenoceptor-mediated sedation, the mechanism of analgesia is less clear. Several potential sites of mechanism of action exist for analgesia: supraspinal, ganglionic, spinal, peripheral, or possibly a combination of sites [168]. It is thought that systemic analgesia is mediated primarily by α_2-adrenoceptor activation in the dorsal horn of the spinal column [185]. This activation inhibits nociceptive neurons and decreases the release of glutamate and substance P.

Clonidine has an elimination half-life of 9–12 h [164]. Approximately half is metabolized by the liver to inactive metabolites, while the remainder is excreted unchanged by the kidneys. Dexmedetomidine has an elimination half-life of 2 h and is highly bound to plasma proteins [174], while the context-sensitive half-life ranges from 4 minutes after a 10-minute infusion to 250 minutes after an 8-h infusion [186]. It is metabolized by the liver via glucuronidation and cytochrome P450 2A6 oxidation and excreted primarily by the kidneys.

Alpha-2-agonists have well-characterized effects on the central nervous system and the cardiovascular system that are relevant as potential adverse effects in the context of perioperative pain management. Although α_2-agonists' hypnotic effects may be desirable for procedural and ICU sedation, these effects may be undesirable in the context of perioperative analgesia, inhibiting progression of early functional recovery due to continued sedation. Also, while the central decrease in sympathetic activity and relative increase in parasympathetic activity is useful in blunting the surgical stress response, it can also lead to undesirable intraoperative and postoperative bradycardia and hypotension [166]. An important additional adverse effect correlating with dexmedetomidine-related sedation is airway obstruction, and caution is advised [174]. Additional adverse effects associated with clonidine when used for chronic treatment but rare in the perioperative setting are rebound hypertension, dry mouth, and orthostatic hypotension.

Opioids

Opioids are a large family of compounds related to opium, which is derived from the poppy, *Papaver somniferum*. Opiates are an even larger group of compounds comprising opioids as well as semisynthetic and synthetic compounds that act as ligands at opioid receptors [53]. Opioids are commonly used for the treatment of moderate to severe surgical pain and are a standard medication for perioperative analgesia due to their profound analgesic effects [187–189]. They range in analgesic potency from relatively weak to very potent. While opioids do not have a ceiling effect for analgesia, they are associated with numerous severe and non-severe side effects that limit their clinical efficacy and utility including respiratory depression and sedation. Moreover, they are associated with the relatively rapid development of tolerance and hyperalgesia [190, 191]. In addition, they cause euphoria and tranquility which may lead to reward-seeking behavior in some individuals and has led to a crisis in the United States of opioid addiction, opioid misuse, opioid abuse, and opioid-related overdose deaths [192, 193]. Given the multitude of serious adverse effects, opioids should be reserved for the scenario in which non-opioids are inadequate rather than as the default analgesic [193]. In addition, consideration should be given to administer the smallest amount of opioid required to achieve adequate analgesia rather than the complete absence of postoperative pain to minimize the risk of side effects.

Opioids may be administered by many routes: oral, sublingual, intravenous, intramuscular, subcutaneous, neuraxial, and transdermal [194]. Perioperative administration tends to be oral, intravenous, and neuraxial owing to favorable bioavailability and pharmacodynamic relationships. The intravenous route may also be used in the postoperative period for patient-controlled analgesia (PCA) which permits rapid administration, compensates for interpatient variability in analgesic needs, and relies on a negative feedback loop to provide safety from respiratory depression and sedation [195]. PCAs are particularly useful when hospitalized patients are unable to take analgesics by other routes, though the negative feedback loop may be violated and appropriate monitoring is required [7]. Morphine, hydromorphone, and fentanyl are the most common intravenous opioids for intraoperative analgesia and in the post-anesthesia care unit, while sufentanil, alfentanil, and remifentanil are three rapid, short-acting opioids that can be useful for intraoperative analgesia. In the postoperative period, a transition is often made to oral opioids with a longer duration of action including tramadol, hydrocodone, and oxycodone. Common intraoperative doses are morphine 0.025–0.15 mg/kg, hydromorphone 0.01–0.02 mg/kg, and fentanyl 1–2 mcg/kg IV [196]. Patient factors, such as age and comorbidities, should influence empiric dosing decreases [197]. Additionally, the common practice of titrating intraoperative opioids to a respiratory rate of 12–14 is lacking in evidence and should be avoided given the risk of acute opioid-related adverse effects. Originally suggested for opioid-dependent patients, the approach is misapplied when used for opioid-naïve patients and lacking in evidence for all patients [198, 199]. Common PCA doses are hydromorphone 0.2 mg IV demand

dose with an 8–10-minute lockout interval with or without a loading dose and without a basal infusion and morphine 1–2 mg IV demand dose with an 8–10-minute lockout interval with or without a loading dose and without a basal infusion. 1-h and 4-h limits may be used to provide additional safety [200]. Finally, common postoperative oral opioid dose regimens include tramadol 50 mg every 6 h as needed, hydrocodone 5 mg every 4–6 h as needed, and oxycodone 5 mg every 4–6 h as needed [53, 196].

Opioid medications exert analgesia primarily by binding to opioid receptors that are part of the superfamily of G-protein-coupled receptors [201]. Three opioid receptors are clinically relevant: mu (μ), kappa (κ), and delta (λ). All opioids in clinical use activate the μ-opioid receptor to some extent, while some also activate the κ-opioid receptor and λ-opioid receptor. Other opioid receptors have been identified including the nociceptin receptor. Though it has been shown to mediate analgesia, it does not bind naloxone and is therefore considered to be in a non-opioid branch of the opioid receptor family [202]. Opioid receptor agonist binding leads to analgesia by reduction of neurotransmission in the following manner. The agonist binds to a G-protein-coupled opioid receptor on the transmembrane portion. This causes the α-subunit of the G-protein to exchange its guanosine diphosphate (GDP) molecule with intracellular guanosine triphosphate (GTP), which then dissociates from the βγ complex resulting in the inhibition of adenylyl cyclase, which in turn reduces levels of cyclic adenosine monophosphate (cAMP). This leads to increased potassium conductance (hyperpolarization), calcium channel inactivation, and reduced neurotransmitter release. Opioid receptors are located throughout the central nervous system including the periaqueductal gray, locus coeruleus, rostral ventral medulla, and substantia gelatinosa of the dorsal horn. They are additionally located on peripheral afferent nociceptive nerves and non-nervous system tissue such as the heart, liver, lung, gut, lymphocytes, and mononuclear phagocytes [203–205]. All three opioid receptors are implicated in supraspinal and spinal level analgesia, while each has varying roles in other opioid-mediated effects, such as respiratory depression:μ, and decreased gastrointestinal motility:μ and κ [206, 207].

The pharmacokinetics of opioids vary among compounds; however most opioids are metabolized by the liver and excreted by the kidneys [189]. A notable exception is remifentanil which has an ester structure that undergoes rapid metabolism via hydrolysis by blood and tissue-specific esterases.

Because the μ-opioid receptor mediates both analgesia and respiratory depression, opioid analgesic treatment is intrinsically handicapped by the potential for respiratory depression. Although there are opiate medications, such as buprenorphine, in which there is a ceiling for the respiratory depressant effect but not analgesia [208], the majority of opiates share pharmacodynamic characteristics for analgesia and respiratory depression [209]. Thus it is possible that a patient may exhibit moderate to severe respiratory depression while still lacking adequate pain relief.

Opioid-induced hyperalgesia (OIH) is another vexing, serious problem due to opioid therapy wherein a paradoxical increase in pain occurs from opioid administration [210]. OIH is related to the total dose of opioid, and thus severe pain that is treated with opioids begets greater sensitivity to painful stimuli which perpetuates a cycle of pain—opioid treatment—increased pain [211]. It can occur within the intra-

operative period and last hours to days with duration correlating to opioid dose [190, 191]. There is even evidence from animal studies that OIH may occur at low doses of opioids, although the data in human trials is conflicting. OIH is also complicated by the development of tolerance to opiate compounds wherein the dose of opioid must be increased over time to maintain analgesic benefit such that patients exhibit a more painful response to stimuli; yet opioid treatment is less effective at that same level. Even more problematic is that opioids exhibit differential tolerance where tolerance develops at different rates for different effects—fastest for analgesia, slower for respiratory depression, and even slower for peripheral effects such as decreased gastrointestinal motility [190]. This can potentially position patients with severe pain to need ever-increasing doses of opiates with less analgesic effect but greater risk for respiratory depression and GI disturbance. The respiratory depression is compounded by the sedative effect of opioids which increases the risk for airway obstruction and respiratory arrest. While sedation may be desirable during the intraoperative period, it has a decidedly negative impact in the postoperative period. Despite causing sedation, opiates inhibit restorative sleep by inhibiting REM sleep [212, 213]. This exacerbates the fatigue induced by the surgical stress response.

Another important adverse effect of opioids in the perioperative period is decreased gastrointestinal motility potentially leading to nausea, vomiting, ileus, decreased biliary motility, and constipation. Opioids stimulate the chemoreceptor trigger zone in the area postrema of the medulla directly leading to nausea and vomiting, and their effect on postoperative nausea and vomiting is well documented [214]. Antiemetics such as ondansetron, dexamethasone, and droperidol have been shown to mitigate opioid-induced nausea, while methylnaltrexone and alvimopan are two medications that alleviate GI motility symptoms by acting as peripheral μ-opioid receptor antagonists at the gut that do not cross the blood-brain barrier and affect analgesia. Other opioid-related adverse effects include urinary retention, pruritus, delirium, immunosuppression, and aberrations of the hypothalamic-pituitary-adrenal axis [205, 215]. There is also substantial laboratory and some clinical evidence that opioids play a role in cancer progression and directly adversely affect cancer survival [216].

Beta-Blockers

Beta-blockade blunts the autonomic nervous system's adrenergic response to intense perioperative stimuli such as endotracheal intubation, surgical incision, organ manipulation, and emergence from anesthesia [217]. While the hemodynamic effects are well understood, less clear is how beta-blockade leads to analgesia. Nonetheless, there is strong clinical evidence for beta-blockers to have an intraoperative and postoperative opiate-sparing effect with associated decrease in opiate side effects, such as PONV [218, 219]. The beta-blocker esmolol is also associated with a decreased induction dose requirement of propofol and a reduction in end-tidal volatile anesthetic requirement [218]. In addition, esmolol can hasten time to discharge from PACU [220].

While most medications that block β-adrenergic receptors have some activity at β_1- and β_2-adrenoceptors and sometimes other types of receptors, esmolol is highly selective for the β_1-adrenoceptor where it has a 34-fold higher affinity than at the β_2-adrenoceptor [221]. The β1 receptor is found almost exclusively in the heart, while the β2 receptor is found on organs throughout the body [222]. Thus esmolol has rapid onset and resolution and highly selective cardiac activity, making it the preferred beta-blocker for perioperative use where these effects are most desirable. While these effects are well characterized, it is unclear if and how esmolol has an analgesic effect. It is also unclear how long the analgesic effect persists, and studies have questioned whether it is truly analgesia or, if by treating hemodynamic response to stimulation with esmolol instead of an opioid, the observed analgesia is actually a reflection of decreased opioid consumption and subsequent decrease in acute opioid-induced hyperalgesia and acute opioid tolerance [219, 223, 224]. This theory is supported by the study by Collard and colleagues where three groups of patients were examined for analgesia for laparoscopic cholecystectomy following treatment with remifentanil, fentanyl, or esmolol during the intraoperative period. The investigators then examined fentanyl usage in the PACU [220]. Patients in the esmolol group, who did not receive any intraoperative opioids, required 46% less fentanyl than the intraoperative fentanyl group and 62% less fentanyl than the intraoperative remifentanil group. Pain scores were similar among the three groups.

Esmolol has an ultra-short duration of action because it is metabolized by esterases in erythrocytes and highly perfused organs, such as the liver and kidneys [225]. The peak hemodynamic effect occurs within 6–10 minutes of a loading dose, and blockade resolves within 20 minutes of cessation of infusion [53, 226, 227].

An optimal dose for perioperative hemodynamic stability and analgesia is unknown; however, most studies investigating these perioperative effects start with a slow 0.5 mg/kg intravenous bolus at induction of anesthesia and then continue with an infusion of 5–15 mcg/kg/min with a max infusion dose of 50 mcg/kg/min [218, 219].

The side effects and potential toxicity of all beta-blockers are beyond the scope of this discussion. Beta-blockade is generally well-tolerated in the perioperative setting, and more specifically, esmolol is not known to have effects beyond the impact of β_1-adrenoceptor antagonism in specific patient contexts [218, 219, 228]. However, there are potential risks to this type of physiologic manipulation. In a meta-analysis of 67 controlled clinical trials with 3766 patients undergoing noncardiac surgery, investigators found that esmolol was associated with an increased incidence of unplanned hypotension when it was administered as a bolus [229]. This incidence was neutralized if only an infusion was utilized and mitigated if the bolus dose was <0.5 mg/kg. Beta-blockade in general has a somewhat less neutral impact on perioperative adverse effects. One of the largest trials to examine perioperative beta-blockade was the POISE trial [230]. The aim of this study was to examine the impact of perioperative beta-blockade on the risk of cardiovascular events and death

and not analgesia in 8534 patients undergoing noncardiac surgery. Beta-blockade was empiric and not adjusted to fit hemodynamic goals. Consequently, there was a 30% increase in all-cause mortality in the metoprolol group. This was due in part to a twofold increase in the incidence of stroke. Both mortality and stroke were associated with increased incidence of hypotension, bradycardia, and significant bleeding. The risk of myocardial infarction was reduced, reflecting the improved balance of myocardial oxygen demand and supply. The subsequent DECREASE-IV trial allowed for titration of beta-blockade and resulted in a reassuring safety profile for bisoprolol, but analgesia was not examined [231]. These and other trials examined longer-acting beta-blockers that were not modified to achieve individual hemodynamic goals, such as can be done with intraoperative administration of esmolol [232–234]. In summary, esmolol can be considered as an adjunct to an analgesic plan if appropriate hemodynamic parameters are maintained. Caution is advised against administration of esmolol in such a way that it leads to hypotension and bradycardia, which could increase the risk of stroke or death [235]. Evidence does not support the use of other beta-blockers specifically for perioperative analgesia purposes.

Potentially Helpful Agents with Less Evidence

In addition to the medications reviewed, there are a variety of other medications which may be helpful but where the evidence is less robust or where the evidence supports only more limited usage. One such medication is magnesium which acts as an NMDA antagonist [236]. Outcomes on analgesia from systemic magnesium in the past were conflicting [237]. Two recent meta-analysis of 20 and 25 RCTs and 1257 and 1461 patients, respectively, had similarly positive results: nearly 10 mg morphine sparing with very small improvements of analgesia and no improvement of opioid-related side effects [238, 239]. It is unclear which patient populations would benefit most from magnesium administration or if they would benefit if another NMDA antagonist, such as ketamine, were given. Another category of medication for which there is weak and conflicting evidence is the heterogeneous category of muscle relaxants. While there is at least the suggestion of benefit in some patient populations prone to muscle spasm such as breast augmentation and spine surgery, they have not shown benefit in other populations [240–242]. Evidence is lacking to recommend broader usage. Another category of medications that has been investigated for perioperative analgesic use are antidepressants. Various antidepressants have effects on serotonin and norepinephrine reuptake, sodium channel inhibition, and NMDA receptors—all of which are known to play roles in pain processing and have shown benefit in the treatment of chronic pain [243, 244]. Nonetheless, investigations of antidepressants for perioperative analgesia have found insufficient evidence of benefit, even when initiated in advance of surgery for patients deemed most likely to benefit [244, 245].

Nonpharmacologic Treatments that May Be Useful

In addition to multimodal pharmacologic analgesics, there are physical nonpharmacologic treatments which may be useful as analgesic adjuncts, though evidence is generally weak. Transcutaneous electrical nerve stimulation (TENS) is a modality that delivers low-voltage electrical currents across the skin to activate superficial nerves via a small device [7]. Based on the gate control theory, TENS is thought to modulate pain transmission via C fibers by stimulating large myelinated afferent fibers; however, the mechanism may be more complex. They have been shown to have analgesic benefit with up to a 25% reduction in pharmacologic analgesics with few side effects [246]. There is less clear benefit for some other types of physical nonpharmacologic treatments due to insufficient evidence. These include acupuncture, massage, and cold therapy [7].

There are also nonpharmacologic nonphysical interventions which may provide postoperative analgesic benefit. Many studies support a positive effect of preoperative education and pain management counseling [7]. Discussion and instruction can allay anxiety, improve coping, and set appropriate expectations. Cognitive-behavioral modalities have also shown benefit for reduction in postoperative analgesic use, reduction of perioperative anxiety, and improvement of coping ability [7]. Approaches include various guided imagery, meditation and relaxation techniques, hypnosis, and intraoperative suggestion. There is no clear superiority of one approach to others, and overall the evidence is weak. Some techniques require patient engagement, and many can be conducted by a variety of providers including psychologists, nurses, physicians, social workers, and others. Another intervention which may provide benefit is music therapy. Music therapy may be beneficial in reducing the stress response to surgery and improving analgesia in a nonpharmacologic nonphysical way [247, 248]. Given the low risk involved in employing such modalities, they may be considered across a wide variety of perioperative situations to improve analgesia and enhance recovery despite weak evidence.

Future Perioperative Pain Management Modalities

Many pharmacologic and nonpharmacologic therapies are under investigation and in some instances in limited clinical use for perioperative pain management. The following are some of the more promising emerging modalities. Virtual reality is a technology beginning to have widespread adoption throughout healthcare. It capitalizes on immersive distraction from unpleasant physical sensation toward positive emotional and cognitive processing to help users change their thoughts and perception of pain and cope better [249, 250]. Initial clinical investigations into virtual reality for analgesia addressed burn dressing change pain, dental procedure pain, and hospitalized inpatients with acute pain [251–253]. More investigations specific to perioperative pain management are ongoing, and virtual reality seems potentially

promising as a perioperative analgesic adjunct. Another category of technology-driven pain management intervention is smart phone delivered applications (apps). Though many were initially oriented toward improving well-being in the context of chronic pain management, research is beginning into their use for perioperative pain [254]. Finally, artificial intelligence and machine learning are beginning to be investigated for applications relevant to perioperative pain management including the evaluation of pain, prediction of perioperative pain management need, and forecasting postoperative pain outcomes [255–257].

Two promising procedural interventions under investigation for perioperative pain management are neuromodulation via percutaneous peripheral nerve stimulators and cryoanalgesia via ultrasound-guided percutaneous cryoneurolysis. Neuromodulation has widespread applications in the treatment of chronic pain syndromes through delivery of electrical current to specific nerves [258]. Until recently devices required surgery for implantation and removal and were costly. In 2018 the FDA approved a percutaneous peripheral nerve stimulator for the treatment of postoperative pain. Initial investigations for shoulder, knee, and foot surgeries revealed marked reduction in pain scores at rest and with movement without sensory or motor blockade [259–261]. Moreover, at least one device is approved for therapy of up to 60 days, offering the potential for extended pain relief. Another device for extended duration of perioperative analgesia is a cryoprobe for cryoneurolysis. A handheld cryoprobe has been approved by the FDA for the treatment of osteoarthritis pain of the knee [262], and perioperative use is being investigated. Cryoneurolysis involves the direct application of cold temperatures to nerves resulting in reversible injury to the nerve. Consequently, its use may be limited to peripheral sensory nerves or if motor blockade is acceptable, such as post amputation [263]. Investigational perioperative use has shown promise for analgesia for total knee arthroplasty, rotator cuff repair, lower limb amputation, iliac crest bone harvest, and burn-related pain [264].

Finally, many medications are under clinical investigation for perioperative pain management. Two notable ones include oliceridine (TRV 130) and neosaxitoxin. Oliceridine is a novel μ-receptor agonist similar to opioids that specifically differentially activates intracellular signaling. Unlike all clinically available opioids, oliceridine is selective for G-protein pathway activity which mediates analgesia via the μ-receptor. It has low activity for the β-arrestin pathway that mediates opioid-related adverse effects including respiratory depression, sedation, and delayed gastrointestinal function [265]. Perioperative analgesia has been shown to be similar to conventional opioids but with a lower incidence of adverse effects [266, 267]. In contrast to systemic analgesia offered by oliceridine, neosaxitoxin is in development for prolonged neural blockade. Neosaxitoxin is a site 1 sodium channel toxin that provides selective prolonged peripheral nerve blockade. It has low affinity for cardiac sodium channels (Nav 1.5) and relatively higher affinity for the sodium channel isoforms of peripheral nerves (Nav 1.7, Nav 1.8) [268]. In addition, it does not cross the blood-brain barrier, so it does not cause cardiovascular and central nervous system toxicity like traditional local anesthetics. Initial clinical trials have shown efficacy for perioperative analgesia and an excellent safety profile in a phase I clinical trial [269, 270]. Clinical trials continue for the development of neosaxitoxin.

Opioid-Free Analgesia?

As discussed in this chapter, a variety of pharmacologic and nonpharmacologic treatments are available for the treatment of perioperative pain and offer the possibility to provide excellent analgesia, accelerate recovery, and improve the patient experience. Some have taken these treatments and used the current opioid crisis as a platform to advocate opioid-free analgesia [271, 272]. Given the concerns that arise for opioid-related adverse effects, opioid-induced hyperalgesia, opioid tolerance, and opioid abuse, this effort seems appealing to an extent. Some surgeries, particularly those associated with mild-moderate pain, may well benefit from opioid-free analgesia [273]. However, outcome evidence is lacking to recommend this approach broadly over an opioid-sparing analgesic approach [10]. The selective use of opioids for severe and breakthrough perioperative pain remains crucial to perioperative analgesia [274]. The central tenet to provide optimal perioperative analgesia is selecting pain mechanism-specific medications and techniques that alleviate pain without causing side effects. It is the challenge of the perioperative provider to assemble the complement of medications, interventions, and modalities to personalize effective perioperative pain management regimens with or without opioids.

Charts

Evidence-Based Treatment

Strong Evidence

- Acetaminophen
- NSAIDs
- Steroids
- Local anesthetics: wound infiltration, peripheral and truncal nerve blockade, thoracic epidural analgesia
- Gabapentinoids
- Ketamine
- Alpha-2-agonists
- Opioids
- Esmolol

Weak or Insufficient Evidence

- Magnesium
- Muscle relaxants
- Antidepressants
- Transcutaneous electrical nerve stimulation

- Cognitive-behavioral modalities
- Acupuncture
- Music therapy
- Hypnosis
- Patient counseling and education

Emerging or Promising Treatments

- Novel truncal blocks with local anesthesia
- Virtual reality
- Neuromodulation
- Cryoneurolysis
- Oliceridine
- Neosaxitoxin

Timing Basic Options

Throughout

- Acetaminophen scheduled
- NSAID vs COX-2 scheduled

Preop

- Local anesthesia: regional analgesia—peripheral or neuraxial depending on type of surgery
- Gabapentinoid
- Patient counseling

Intraop

- Local anesthesia: wound infiltration ± IV lidocaine infusion
- Ketamine for surgery associated with severe pain, opioid tolerant, chronic pain (etc.; see section)
- Alpha-2-agonist
- Steroid
- Esmolol
- Minimal opioid

Postop

- Gabapentinoid
- Local anesthesia: regional analgesia vs IV lidocaine infusion
- Ketamine
- Opioid for breakthrough pain

Enhanced Recovery After Surgery Example Pain Management Protocols

Inguinal Hernia Repair (Ambulatory: Mild to Moderate Pain Anticipated)

Preop

- Acetaminophen 15 m/kg up to 1000 mg PO
- Ibuprofen 400 mg PO
- Patient counseling
- ± Local anesthetic: ilioinguinal nerve block, field block, infiltration

Intraop

- Dexamethasone 0.1 mg/kg IV at induction of anesthesia.
- Local anesthesia: infiltration.
- Consider esmolol.
- Minimal opioid; consider fentanyl 1–2 mcg/kg IV; consider opioid-free.

Postop

- Acetaminophen 15 m/kg up to 1000 mg PO.
- Ibuprofen 400 mg PO.
- Minimal opioid; consider tramadol 50 mg Q6h prn for breakthrough pain; consider opioid-free.

Laparoscopic Cholecystectomy (Ambulatory: Moderate Pain Anticipated)

Preop

- Acetaminophen 15 m/kg up to 1000 mg PO
- Ibuprofen 400 mg PO
- ± Gabapentin 600 mg PO
- Patient counseling

Intraop

- Dexamethasone 0.1 mg/kg IV at induction of anesthesia.
- Pre-incisional wound infiltration with long-acting local anesthetic.
- Consider esmolol.
- Minimal opioid; consider fentanyl 1–2 mcg/kg IV; consider opioid-free.

Example Modifiers

- If patient is opioid tolerant or has a history of chronic pain, consider:

- Ketamine 0.35 mg/kg IV bolus + 0.1–0.2 mg/kg/h IV infusion
- Lidocaine IV 1.5 mg/kg bolus + 2 mg/kg/h infusion

Postop

- Acetaminophen 15 m/kg up to 1000 mg PO
- Ibuprofen 400 mg PO TID
- Tramadol 50 mg Q6 h prn or oxycodone 5 mg PO Q6 h prn for breakthrough pain

Open Reduction Internal Fixation Calcaneus (Ambulatory: Severe Pain Anticipated)

Preop

- Acetaminophen scheduled 15 m/kg up to 1000 mg PO
- Celebrex 400 mg PO
- Gabapentin 600 mg PO
- Local anesthetic: popliteal sciatic continuous nerve block ± adductor canal continuous nerve block
- Patient counseling

Intraop

- Dexamethasone 0.15 mg/kg IV at induction of anesthesia.
- Minimal opioid; consider fentanyl 1–2 mcg/kg IV; consider opioid-free.

Example Modifiers

- If patient is opioid tolerant or has a history of chronic pain, consider:
- Ketamine 0.35 mg/kg IV bolus + 0.1–0.2 mg/kg/h IV infusion

Postop

- Acetaminophen scheduled 15 m/kg up to 1000 mg PO TID
- Celebrex 200 mg PO BID
- Continue popliteal sciatic and adductor canal nerve blocks for 3–4 days
- Tramadol 50 mg Q6h prn or oxycodone 5 mg PO Q6h prn for breakthrough pain

Multilevel Spine Fusion (Hospitalized: Severe pain, Opioid tolerance, and Comorbid Conditions Anticipated)

Preop

- Acetaminophen scheduled 15 m/kg up to 1000 mg PO
- Celebrex 400 mg PO

- Gabapentin 600 mg PO
- Patient counseling

Intraop

- Dexamethasone 0.15 mg/kg IV at induction of anesthesia
- Pre-incisional wound infiltration with long-acting local anesthetic
- IV lidocaine 1.5 mg/kg bolus + 2 mg/kg/h infusion
- Ketamine 0.35 mg/kg IV bolus + 0.1–0.2 mg/kg/h IV infusion
- Dexmedetomidine 1 mcg/kg IV bolus, 0.5 mcg/kg/h infusion
- Minimal opioid necessary. Caution as patient may be opioid tolerant and have higher baseline requirements

Postop

- Acetaminophen scheduled 15 m/kg up to 1000 mg PO TID
- Celebrex 200 mg PO BID
- Gabapentin 300–600 mg PO TID
- Ketamine 0.1–0.2 mg/kg/h IV infusion
- ± Lidocaine IV infusion 2 mg/kg/h
- Oxycodone 5 mg PO Q6h PRN and hydromorphone 0.5 mg IV Q3h PRN for breakthrough pain

Open Thoracotomy (Hospitalized: Severe Pain and Comorbid Conditions Anticipated)

Preop

- Acetaminophen scheduled 15 m/kg up to 1000 mg PO
- Celebrex 400 mg PO
- Gabapentin 600 mg PO
- Local anesthetic: epidural catheter vs paravertebral catheter
- Patient counseling

Intraop

- Dexamethasone 0.15 mg/kg IV at induction of anesthesia.
- Epidural infusion bupivacaine 0.0625% ± fentanyl 2 mcg/ml 6–10 ml/h, 2–4 ml bolus, 15–30-minute lockout.
- Pre-incisional wound infiltration with long-acting local anesthetic if an epidural is not utilized.
- Minimal opioid necessary; consider fentanyl 1–2 mcg/kg IV.
- Ketamine 0.35 mg/kg IV bolus + 0.1–0.2 mg/kg/h IV infusion, if opioid tolerant or history of chronic pain

Postop

- Acetaminophen scheduled 15 m/kg up to 1000 mg PO TID
- Celebrex 200 mg PO BID
- Gabapentin 300–600 mg PO TID
- Epidural infusion bupivacaine 0.0625% ± fentanyl 2 mcg/ml 6–10 ml/h, 2–4 ml bolus, 15–30-minute lockout
- Oxycodone 5 mg PO Q6h PRN and hydromorphone 0.5 mg IV Q3h PRN for breakthrough pain

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Chapter 3
Inpatient Pain Management

Biral Patel, Ahmed Embabi, and Shannon Garitty

Acute Pain Service with Regional and Neuraxial Blocks

The inpatient pain service is often consulted on patients with either uncontrolled postsurgical pain or pain after a traumatic incident. These patients often have chronic pain at baseline, so their pain is considered acute-on-chronic pain, and the inpatient pain service may be consulted to aid in the management of this more difficult patient population [1].

Besides medication treatment, regional or neuraxial blocks or catheters can help mitigate this pain while sparing the patient from a high opioid medication regimen. While these procedures are not commonly done in the chronic pain clinical setting and are often thought of as regional anesthesia for perioperative pain, they can be successfully used in these settings to aid in patient recovery. There is a wide variety of blocks that can be helpful depending on the patient situation and the site of the pain. These blocks are usually not as effective for cancer pain, phantom limb pain, or CRPS, but the sympathetic ganglion blocks and even spinal cord stimulation can be considered for these situations. It is important to consider not only medication management but also possible interventional procedures when indicated for these patients. Often the interventions can wait until the patient is in an outpatient setting, but an important part of inpatient pain management is to provide a bridge toward long-term chronic pain treatment.

B. Patel (✉) · A. Embabi · S. Garitty
Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, TX, USA
e-mail: Biral.Patel@UTSouthwestern.edu

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Upper Extremity Pain

These blocks are effective in treating a variety of upper extremity pain including surgery or trauma involving finger, hand, forearm, arm, or shoulder injuries. The choice in blocks depends on the exact site of the injury and patient-specific risk factors. The choice of a single shot block vs catheter depends on multiple factors including patient cooperation, expected length of hospitalization, level of pain, type of injury, anticoagulation status, and discussions with the primary team.

Thoracic Pain

For patients with thoracic pain either from surgery or trauma, there are also regional options for pain control. If the pain extends across midline and is equal bilaterally, a thoracic epidural may be an effective treatment option depending again on patient cooperation, coagulation status, length of hospitalization, and discussions with the primary team. Thoracic epidurals that are correctly dosed should not cause lower extremity weakness; therefore, they will not limit early ambulation but can simultaneously be very effective in thoracic and upper abdominal pain. Broken ribs that are affecting ventilation are effectively treated with a thoracic epidural, often aiding in extubation of patients that are difficult to wean off the ventilator due to painful respirations, as well as improving the respiratory dynamics and dyspnea for the spontaneously breathing patients.

If the pain is unilateral, there are multiple regional blocks that will decrease the pain, depending on dermatomal distribution. Unilateral pain in the thoracic region can be treated with a paravertebral, erector spinae, or serratus plane block. Again the decision will have to be made of whether a single shot or catheter is more appropriate for each patient.

Abdominal Pain

Abdominal pain is often very difficult to treat and manage from both a medication and interventional status. Low thoracic epidurals can be helpful if the incision is limited to the upper abdomen, but it is rare that the thoracic epidural will provide full coverage for abdominal pain. Lumbar epidurals are often contraindicated due to the lower extremity weakness that will likely result which will cause both increased fall risk and decreased early ambulation. Abdominal pain can be treated with transverse abdominis plane (TAP) block, rectus sheath block, or ilioinguinal/iliohypogastric nerve blocks, and these are used commonly perioperatively. Local wound

infiltration by the surgeons has also been found to decrease postoperative pain. For pain caused by trauma or chronic abdominal pain, these interventions are less likely to be beneficial.

Lower Extremity

Lower extremity injuries and surgical pain can once again be treated with regional anesthesia. Neuraxial anesthesia is rarely appropriate long term in this setting due to resulting lower extremity weakness limiting ambulation and increasing risk for falls. Depending on the dermatomal distribution of the pain, a fascia iliaca, femoral, sciatic, or adductor canal block can be done. Some of these blocks, including femoral and sciatic blocks, result in motor weakness. A single shot will only last for a short period, often aiding in acute recovery, and a catheter with a low infusion rate can block sensory fibers while largely sparing motor weakness.

The goal of all of these procedures would be to limit patient pain while sparing high doses of narcotics and other pain medications that could have harmful short- and long-term side effects [2]. Patients are able to ambulate earlier, participate in physical therapy, and therefore be discharged with shorter hospital stays.

Summary of Treatment Principles and Methods

Chronic pain patients that are being admitted to the hospital with new or worsening medical conditions should be treated differently than chronic pain patients being admitted for surgical procedures. Both groups of patients should have their pain medication and diagnosis history carefully researched and documented with the goal being to keep the patient near their home pain medication regimen. However this goal has different feasibilities in these different clinical settings, with medical settings often requiring a short-term decrease in medication dosages, while a surgical setting might require a transient escalation in dose, but only for the acute period.

For medical patients, coordination and communication between the primary team and the pain team is critical. These patients have changes to their day-by-day conditions that could affect both their pain level and their ability to tolerate a pain regimen. Medications such as methadone, neuropathic medications, or renally metabolized medications can be significantly affected by the additions of new medications or organ dysfunction in the acute medical setting. Medication reactions are a common cause of overdose, oversedation, or unwanted side effects in the hospital setting due to patients needing acute changes in their medications as their condition varies, especially in the more critical settings. Opioids

and benzodiazepines have to be carefully managed in this setting to balance comfort and avoid withdrawal while ensuring patient safety and avoiding risk factors such as respiratory depression, oversedation, and delirium. Naloxone and flumazenil should be kept available and on the medication list for patients with risk factors for overdose and still on these medications, while knowing that giving these antidotes for opioid and benzodiazepines, respectively, can also precipitate withdrawal.

For surgical patients, the difficulty in treatment becomes the acute-on-chronic pain they are dealing with due to the recent procedure. In this patient population, even relatively simple procedures can result in significant postoperative pain for multiple reasons. Due to the patients' common tolerance for opioids, they are often relatively under-dosed intraoperatively. They also are missing doses of their home medication in the perioperative period, and PACU staff is often hesitant to give equivalent IV opioid doses. For these patients, ideally a multimodal or regional intraoperative pain management technique is employed to aid with immediate postoperative pain. In the acute postoperative setting, the patients' baseline morphine equivalency should be calculated and taken into account when prescribing postoperative opioids. A patient-controlled analgesic (PCA) pump can be effectively used with this patient population until they are tolerating PO medications, and attempts should quickly be made to return them to their home pain medication regimen. A short-acting opioid can be added in the acute setting with the goal of weaning it quickly as the acute pain from the surgery decreases. A postoperative multimodal approach with use of anti-inflammatories, acetaminophen, neuropathics, NMDA antagonists, and muscle relaxants when appropriate for each specific patient should also be a mainstay of treatment.

Formulation of Individualized Treatment and Rehabilitation Plan

Many chronic pain patients are patients that have been frequently hospitalized for some reason or another (trauma, chronic illness, congenital disease) and often have a treatment plan that they feel "works best for them." Having a thorough knowledge of these patients' medical history and treatment history is key in forming a doctor-patient relationship. The team approach should be taken when treating these patients, which can often involve contacting the patients outside pain management doctor for further information. Finding a balance of treating the patient in their best interest medically while caring for their mental well-being and comfort is a difficult but crucial part of taking care of inpatient chronic pain patients.

While the inpatient hospital setting is not the ideal time for medication weaning or for significant changes to chronic pain medication regimen in patients, it is a good opportunity to ensure the patient is in the ideal situation for long-term success. That includes helping the patient search for a proper support system, attempting to establish a multimodal pain management plan, and ensuring adequate follow-up for

outpatient rehabilitation upon discharge from the hospital. For many patients, this can include an inpatient psychiatric or addiction specialist consult to aid with further medication management and follow-up care.

Evaluation of Medications for Effectiveness, Side Effects, Dependency, and Interactions

Medications

Upon admission, the need for medication will be assessed, and all medications that a patient is taking will be reviewed. Medications can produce side effects and can interact with other medications; thus there is the need to thoroughly review all medications that were being prescribed prior to admission to the hospital before initiating any new medication therapy. Ineffective medications should be discontinued; this may require tapering off of the medication over a period of time to avoid any withdrawal symptoms (e.g., opioids, benzodiazepines, muscle relaxants, and psychotropics). Education can be provided on pharmacological treatments for pain and related conditions that may not include medications like opiates and benzodiazepines that are commonly prescribed for pain, but may not be the best option. Most chronic pain conditions, especially neuropathic pain, can be treated with non-opioid medications, and many options are available.

Classes of Medications

It is now a consensus that a multimodal pain management regimen is essential to not only limit opioid dose escalation but also more importantly to effectively manage all aspects of a patient's pain. Phenomena such as opioid tolerance and opioid-induced hyperalgesia continue to point toward multimodal management being key.

Antiepileptics

Gabapentinoids such as gabapentin and pregabalin should be first-line therapy for neuropathic pain secondary to a variety of issues such as nerve compression, nerve injury, or peripheral neuropathy. While they do not act directly on the GABA receptor, they do decrease pain signal transmission. These medications can help in the acute-on-chronic pain setting as an adjunct or can be a mainstay of treatment for patients with largely specific nerve, such as pure lumbar radiculopathy. Side effects of these medications do include sedation, GI intolerance, and psychiatric symptoms. Table 3.1 summarizes anticonvulsant drugs used in pain management.

Table 3.1 Anticonvulsant medications for pain management

Carbamazepine	Starting dose: 100 mg twice a day; doses titrated to 400–800 mg/day usually are adequate. Maximum of 1200 mg/day	Anticholinergic effects, blood dyscrasias, hyponatremia, increase in LFTs, ECG changes. CYP450 inducer, many DDIs
Gabapentin	Starting dose: 100–300 mg at bedtime or 100–300 mg 3 times a day, slow titration, maximum of 3600 mg/day	Dizziness, sedation, weight gain, peripheral edema. Adjust dose in renal insufficiency
Lamotrigine	200–400 mg/day	Sedation, headache, dizziness, ataxia, GI upset, blurred vision. Risk of life-threatening rash
Oxcarbazepine	Starting dose: 300 mg/day and then titrated as tolerated to a maximum of 1800 mg/day	Adverse drug reactions similar to carbamazepine, less anticholinergic effects, more hyponatremia. Fewer DDIs than carbamazepine
Pregabalin	Starting dose: 50 mg 3 times a day or 75 mg twice a day, may increase every 3–7 days as tolerated, maximum of 600 mg/day	Same adverse drug reactions as gabapentin, less sedation. Adjust dose in renal insufficiency. More costly than gabapentin
Topiramate	Starting dose: 12.5–25 mg once or twice a day for 4 weeks; then double the dose every 4 weeks to reach a maximum dose of 100–200 mg/day in divided doses	Weight loss, anorexia, nephrolithiasis, cognitive impairment

Psychotropic Drugs This class of drugs will be discussed in more detail in a separate section of this chapter, but these medications target the brain and nervous system and can help mood as well as treat pain.

Anti-inflammatories This class of medications does come with a higher side effect profile and in the postoperative setting may be contraindicated but when appropriate can be effective at limiting inflammatory and bone-type pain. While the renal, gastric, and hematological side effects may limit use, with careful dosing and patient risk factors taken into account, NSAIDs and acetaminophen should be the first level and often mainstay of treatment for most patients. COX-1 inhibitor-type NSAIDs will have more systemic side effects, while COX-2 inhibitor-type NSAIDs have less gastric and renal side effects.

N-Methyl-D-aspartate (NMDA) receptor antagonists This class of medication includes drugs from multiple other classes of medications including ketamine, lidocaine, dexmetomidate, methadone, and even magnesium infusions. These medications are rarely first-line management for chronic pain except methadone but can be used effectively as opioid-sparing adjuncts. Most can be used effectively as infusions that can be titrated as opioid doses are weaned. Unfortunately most of these medications, except methadone, have low bioavailability and are less effective in the oral form for patients to be discharged with and are therefore often limited to the inpatient setting. Opioid-induced hyperalgesia is often encountered in the inpatient setting and can be treated or limited by adding NMDA antagonists. The side effect profile for each medication varies greatly and must be considered for each specific patient.

Muscle relaxants This class of medication includes methocarbamol, cyclobenzaprine, baclofen, tizanidine, and multiple others. First-line therapy is often provider preference. Significant side effects are rare, but all medication in this class can cause significant sedation and should be used carefully especially in patients on other classes of sedating medications such as opioids or benzodiazepines.

Infusions In the inpatient setting, these can be highly successful both in the post-operative/trauma setting and for patients with opioid-induced hyperalgesia or as opioid-sparing techniques. Ketamine, lidocaine, and dexmetomidate infusions can be highly useful as an adjunct to opioid therapy and can even be used concurrently under the correct circumstances. Patient-specific contraindications must be reviewed such as arrhythmias, electrolyte abnormalities, or medication interactions.

Topicals Topical options in an inpatient setting should be taken advantage of due to their limited systemic effects and therefore limited side effects. These medications work locally and can be effective in treating well localized pain especially in patients with contraindications to other classes of medications due to comorbidities. Topical local anesthetics, topical NSAIDs, capsaicin, heat/cold packs, and even a TENS unit could be considered in these settings.

Opioids

Analgesics: In the inpatient setting, every effort should be made to keep the patient as close to their home analgesic medication regimen as possible while considering any acute changes in patient condition. If there is concern for acute-on-chronic pain with a largely somatic component, then an analgesic medication such as an NSAID or opiate might be needed. The WHO analgesic ladder can be followed in the inpatient setting for pain that is clinically deemed largely somatic especially in the post-surgical or post-trauma patient [3]. Figure 3.1 summarizes a comprehensive approach to pain including non-drug treatments.

The STEPS method has been proposed for pharmacologic pain treatment in elderly patients and includes the use of acetaminophen, aspirin, non-selective non-steroidal anti-inflammatory drugs, cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs, and opioids [4]. The drug selection is based on the pain severity, the individual patient's risk factors, and the drug's cost and efficacy.

Treatment of the Psychological Distress that Often Accompanies Intractable Pain

While a patient is admitted to the hospital, it may be beneficial to consult a psychiatrist/psychologist who specializes in pain management. This in no way means that the pain is not real or that it is only in the patients' head. Psychiatric problems such

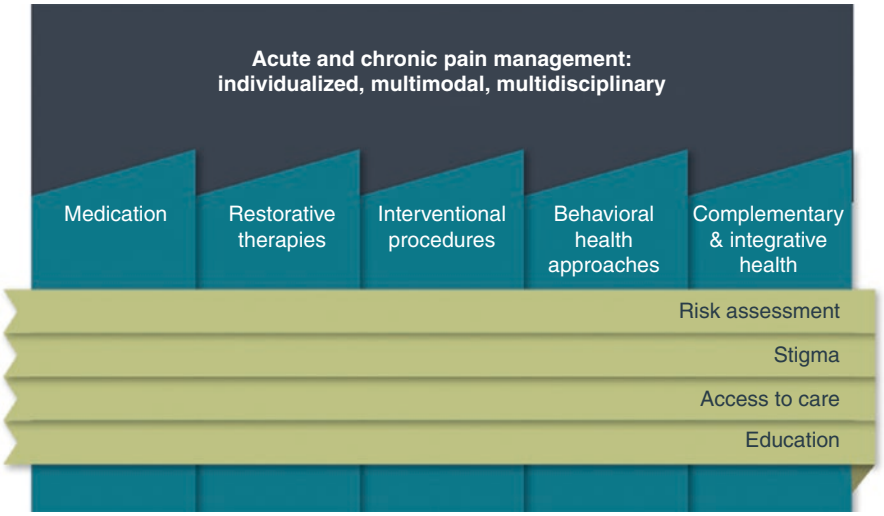

Fig. 3.1 Comprehensive approach to pain management. (U.S. Department of Health and Human Services (2019, May). Pain Management Best Practices Inter-Agency Task Force Report: Updates, Gaps, Inconsistencies, and Recommendations. Retrieved from U. S. Department of Health and Human Services website: https://www.hhs.gov/ash/advisory-committees/pain/reports/index.html)

as depression and anxiety often accompany chronic pain and can exacerbate the problem. It is important that both conditions be addressed and assessed and specific causes treated. Psychiatrists/psychologists can help teach patients about communication, interpersonal, and coping skills that are essential in treating chronic pain. There are also techniques for creating a daily routine that helps to optimize management of symptoms and functionality in everyday activities. Utilization of these skills may help in eliminating medications that may be ineffective in treating pain and detrimental to the patient's overall health. Patients will undergo a full psychiatric evaluation of any past psychiatric conditions, current psychiatric symptoms, and any current medications being used for the treatment of psychiatric disorders as these may be causing side effects that mimic psychiatric disorders or may interact with other medications.

Relaxation Training

This technique can help to decrease muscle tension and possibly increase blood flow that can help reduce certain types of pain. Relaxation can also help direct attention away from the pain experience through active, focused exercises involving muscle relaxation, imagery, and breathing techniques. This activity can help to decrease anxiety and help the patient feel a sense of taking control over the problem at hand.

Biofeedback

Biofeedback is a process in which a patient can try to gain greater awareness of certain physiological systems using instruments/monitors that provide information on the activity of those same systems. The overall goal is to be able to manipulate those systems at will and eventually be able to maintain to do this without the use of extra equipment. It has been shown to be helpful in pain perception. Using biofeedback equipment can give a sense of mastery over physical and mental function. It can be used to help improve health, performance, and physiological changes that can occur with changes in thoughts, emotions, and behavior. The experience of patients as well as pain research has taught us that catastrophizing over one's symptoms can be a particularly distressing aspect of chronic pain.

Group Therapy

Daily group therapy sessions with patients can provide a forum to explore the challenges of coping with chronic pain and its toll on relationships, work, and emotional life. These meetings provide the opportunity to learn from other patients and decrease the loneliness and isolation that emerge with chronic pain syndromes. Cognitive-behavioral principles provide the foundation for discussing how patients can objectively analyze their circumstances and sustain their function despite the challenges of illness.

Family Involvement

Social workers and other staff can help a patient examine the impact of pain and illness on a patient's family. Family members will likely be asked to participate in patient care to help increase support and emphasize the benefits of close personal relationships. Additional meetings and education sessions may be recommended as part of your treatment.

Medications

The psychiatrist/psychologist may also recommend some medications that can be more effective in treating anxiety and depression. Psychotropic drugs that target the brain and nervous system can help mood as well as treat pain. These drugs can be antidepressants, anti-anxiety medications, or medications that help with sleep. Some antidepressants can also target anxiety and sleep disturbance, so using a

single medication to target multiple diseases (depression, anxiety, pain) is possible. Some of these medications that were developed for conditions other than pain (e.g., depression) are more effective and commonly used for pain. Antidepressants have become a staple in the treatment of chronic pain even if a patient does not have depressive symptoms. The mechanism by which some antidepressants treat pain has not been determined. They may work by increasing certain neurotransmitters, but often take a period of time to reach full effect. Typically antidepressant medications will be used with other medications from other drug classes to maximize response.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

This class of drugs includes drugs like venlafaxine and duloxetine. These drugs are effective for depression and anxiety at the same dosages useful for treating pain.

Side effects of these two medications can include drowsiness, insomnia, nausea, dry mouth, dizziness, and constipation. Milnacipran is used to relieve fibromyalgia pain and can cause side effects such as nausea and drowsiness. Its effects are limited in other types of pain.

For patients who do not tolerate neuropathic medications, such as gabapentin or pregabalin, duloxetine should be considered. It has the added effect of being an SNRI with the potential to improve mood and energy level along with its effect on pain. Pregabalin and duloxetine are currently FDA approved as first- and second-line therapy for fibromyalgia as well. Duloxetine has also been recently studied for its positive effects on pain resulting from osteoarthritis from both knees and low back. Depending on the patient, duloxetine can be used as an adjunct to a gabapentinoid or as a single agent. As with all neuropathic medications, dosage should be up-titrated slowly over weeks to months but can be started in the inpatient setting if the patient has proper follow-up. Patients on concurrent psychiatric medications should have their psychiatrist consulted before starting duloxetine due to possible medication reactions. Table 3.2 summarizes the serotonin-norepinephrine reuptake inhibitors used in pain management.

Tricyclic Antidepressants (TCAs)

This class of drug is antidepressants that help to alter imbalance in certain neurotransmitters. Tricyclic antidepressants increase norepinephrine and serotonin and block acetylcholine. While typically used for depression, off-label uses include

Table 3.2 Serotonin-norepinephrine reuptake inhibitors used in pain management

Duloxetine	60–120 mg/day	FDA maximum recommended dose is 60 mg/day
Milnacipran	25–200 mg/day	Approved for treating depression outside the United States
Venlafaxine	75–225 mg/day	Monitor blood pressure, LFTs, and kidney function

Table 3.3 Tricyclic antidepressants used in pain management

Amitriptyline	10–100 mg/day	High sedation, high anticholinergic side effects
Amoxapine	50–100 mg/day	Low sedation, moderate anticholinergic side effects
Clomipramine	25–100 mg/day	Low sedation, low anticholinergic side effects
Desipramine	25–100 mg/day	Low sedation, low anticholinergic side effects
Imipramine	25–100 mg/day	Moderate sedation, moderate anticholinergic side effects
Nortriptyline	10–75 mg/day	Moderate sedation, low anticholinergic side effects

chronic pain such as post-herpetic neuralgia, phantom limb pain, and diabetic neuropathy, among others. Typically, they have more side effects than other antidepressants. Table 3.3 summarizes tricyclic antidepressants used in pain management.

Selective Serotonin Reuptake Inhibitors (SSRIs)

These include the drugs paroxetine and fluoxetine. These drugs may help with pain, but there is lack of evidence that they can help with nerve pain. SSRIs generally don't work as well as tricyclic antidepressants for pain, but they often produce fewer side effects. Side effects include insomnia and dizziness.

Physical Function/Behavior Modification

Chronic pain often leads to a loss of physical activity and general deconditioning which can contribute to a patient's disability. Programs or therapy that works to normalize body mechanics and increase level of activity and endurance can help in reducing pain levels. Suggestions may also be made on ways to change behaviors to help take the focus off of the specific pain experience and become more productive. Other options include the use of targeted myofascial treatments in appropriate patients. Depending on the type of pain being evaluated/treated, a TENS (transcutaneous electrical nerve stimulation) unit may be used to see if transcutaneous electrical stimulation is of benefit for the pain. These units work to disrupt or block transmission of pain signals to the brain.

Usually a baseline physical assessment will be performed before any exercise or therapy begins. The idea is that a regular activity program will increase overall level of physical functioning, and in conjunction with other therapies improve pain and overall quality of life. The activity programs that may be initiated in the hospital are meant to be continued on a long-term basis for ongoing improvement of physical conditioning and level of function. Often it can be expected that through improvement of physical function, there will be a reasonable amount of pain relief. Some may even obtain complete relief from their pain, but most will at least receive significant benefit in physical function and quality of life.

Palliative Care for Pain

The palliative care team is made up of medical professionals such as physicians, social workers, chaplains, pharmacists, and other specialists that can work with your primary hospital team and are trained in the care of patients with very serious illness. Efforts are focused on managing not only medical conditions but also physical, emotional, and practical matters as well. They may help patients get relief from the symptoms, stress, and pain of these serious illnesses, but not work on treatment or cure of disease. Some of the symptoms that may be addressed are pain, depression, anxiety, appetite issues, nausea, vomiting, and constipation. Goals of the palliative care team include improvement of quality of life for both the patient and their family. They can help with decision-making, answer questions about a disease process or treatment, and work as an in-between for the patient and the primary team. This can be of great benefit since the whole process of being admitted to the hospital can be quite overwhelming and stressful for the patient and their family.

Palliative care physicians are well trained in the management of pain, resulting from diseases such as cancer, which can be very difficult to control. They are experts in treating pain with high doses of opioids, doses that other physicians may not feel comfortable using [5]. They may also have knowledge of and access to medications (pain medications and others) that other physicians may not be able to use or be comfortable in using. Palliative care can be involved in any stage of a disease process, not just at the end of life.

Treatment Approach

Patient-Centered

Treatment goal is to increase function including the reduction of chronic pain, accompanying emotional and medical complications, and physical deterioration. This can only be accomplished when a patient forms collaborative relationships with a staff of experts [6].

Length of Time in the Hospital

The length of time in the hospital for each patient depends on many individual factors. The principles and practices that begin in the hospital are meant to be continued once a patient returns home. Every attempt will be made to communicate with any outpatient care to ensure a coordinated approach for continuing rehabilitation after discharge. If additional outpatient services are needed, the primary team will make these referrals with specific recommendations for your overall treatment plan.

Searching for the Sources of Pain

While finding a cure for the cause of pain would be ideal, the search can lead to even more problems. Repeated consults, diagnostic tests, and therapeutic interventions carry the risk of making pain worse and even causing new types of pain. They cost time, money, and other resources that delay rehabilitation. Every patient's case will be reviewed individually. Patients must be open to hearing the primary teams' formulation and avoiding the trap of having just one more consult, test, or surgery.

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Chapter 4
Pain Management for Obstetrical Patients

Stephanie I. Byerly and Trenton D. Bryson

Introduction

The process of labor is the onset of regular contractions leading to progressive dilation and effacement of the cervix and descent of the fetus from the uterus to the birth canal. Labor is also referred to as parturition and is defined by three stages: first, second, and third.

The International Society for the Study of Pain describes pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1]. During the perinatal and labor and delivery process, each woman will experience pain in a unique way. Pain is not only a sensory experience but also has emotional consequences. A sense of personal control over decision-making processes in labor has consistently been shown to correlate with overall maternal satisfaction with childbirth [2, 3]. As an example, a study of 100 women undergoing vaginal delivery reported that satisfaction with pain relief was associated with a feeling of being in control and having input in the decision-making process [3].

Bajaj et al. studied women who underwent experimental cervical dilation and compared them to women who were in labor, who were undergoing spontaneous abortion, or who had dysmenorrhea as to the sensory and affective qualities to their pain [4]. There was a vast array of descriptors for each category, but the women experiencing dysmenorrhea reported descriptors that indicated suffering versus the women in labor who did not describe similar severity. To some women, the effects are almost a rite of passage and expected, but to others it can be psychologically damaging including but not limited to depression, post-traumatic stress disorder,

S. I. Byerly (✉) · T. D. Bryson
Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: Stephanie.Byerly@UTSouthwestern.edu; Trenton.Bryson@UTSouthwestern.edu

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and negative thoughts about their sexual relationships if the pain is not treated appropriately.

Pain control options for labor and delivery can be classified into nonpharmacologic and pharmacologic modalities. Nonpharmacological options are offered to increase the patient's comfort and to allow the parturient to confront the pain without suffering. Pharmacological options are offered to prevent or greatly decrease the pain of the labor and delivery process.

Over 40 years ago, Melzack and Wall described the gate control theory for pain which has revolutionized the understanding of the mechanisms responsible for pain and analgesia [5]. The gate control theory has been updated to a concept of a neuromatrix which a dynamic system which has the capability to undergo rapid change [6]. The gate theory and neuromatrix have led to greater understanding of the mechanisms and treatment for chronic pain, but studies are lacking outlining the neurophysiologic mechanisms for the pain of labor and delivery.

This chapter will describe the stages of labor and delivery and explore nonpharmacological as well as pharmacological options for pain control.

Knowledge about the stages of labor and delivery and its effects on the mother is important when deciding on the appropriate pain control modality that would be the most beneficial for patients.

Stages of Labor Pain

During the labor and delivery process, the pain experienced by parturients is dynamic and changes as multiple different neurologic sites become effected. Figure 4.1 shows the location of thoracic innervation associated with labor.

First Stage of Labor Labor pain during the first stage is a visceral or cramp-like and is primarily due to distention of uterine and cervical distention mechanoreceptors and by ischemia of uterine and cervical [7]. The first stage concludes when cervical dilation is complete at 10 cm. The period of time during which the cervix dilates from 7 to 10 cm is referred to as transition and may cause increased pain secondary to vaginal distension and somatic pain. Primary nerves involved in the first stage include T10, T11, T12, and L1 (Fig. 4.1). Labor pain can cause referred pain to the abdominal wall, lumbosacral region, iliac crests, as well as gluteal and thigh areas.

Second Stage of Labor The pain associated with this stage is a combination of somatic pain from the vagina, perineum, and pelvic floor and stretching of the pelvic ligaments and visceral pain from uterine contractions and cervical stretching. Pain is transmitted to the spinal cord through nerves, S2, S3, and S4. The second stage begins when the cervix is completely dilated and is complete when the fetus is delivered. The parturient will additionally experience rectal pressure as the fetus descends into the pelvic outlet [7].

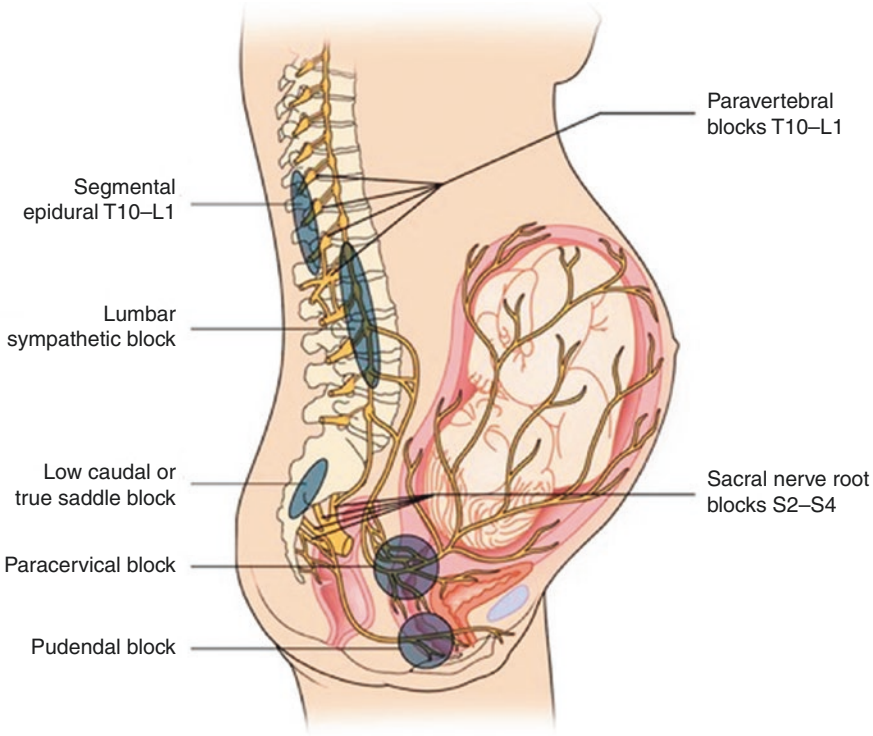

Fig. 4.1 Location of thoracic innervation associated with labor

Third Stage of Labor The third stage of labor begins when the infant is delivered and continues through delivery of the placental tissue [7].

Maternal Effects of Labor Pain

The stress and pain associated with labor and delivery can cause many physiologic changes within the mother and potentially affect the fetus. Studies in primates reveal that pain and stress can lead to decreased fetal oxygenation, acidosis, and a slow fetal heart rate [8].

Hyperventilation/increased oxygen consumption The intermittent pain of uterine contraction causes hyperventilation with resultant hypocarbia and respiratory alkalosis. Profound hypocarbia may inhibit the patient's respiratory drive between contractions which may lead to maternal and fetal hypoxemia, lightheadedness, and rarely loss of consciousness [9]. Respiratory alkalosis may impair maternal to fetal oxygen transfer. Additionally, alkalosis causes shifting of the oxygen hemoglobin dissociation curve to the left which results in increased affinity of oxygen for

maternal hemoglobin and may also cause uteroplacental vasoconstriction leading to decreased uterine blood flow [9]. The respiratory effects of labor are generally well tolerated by healthy parturients [10].

Increased peripheral vascular resistance and cardiac output Labor causes increases in circulating catecholamines which result in an increase in maternal peripheral vascular resistance and cardiac output. With severe labor pain, plasma epinephrine levels can reach equivalent levels of an epinephrine bolus of 15. Increased norepinephrine and epinephrine levels have been associated with decreased uterine blood flow [11]. Increased levels of catecholamines can lead to uterine artery vasoconstriction with resultant decreased placental blood flow to the fetus. The cardiovascular effects of labor are generally well tolerated by healthy parturients.

Gastric inhibition/delay gastric emptying The combination of the pain associated with labor along with the anxiety and emotional distress results in an increase in gastrin release and inhibits the segmental and suprasegmental reflexes of gastrointestinal and urinary motility [12]. There is also an increase in gastric acidity. These may lead to an increased risk for aspiration if emergent airway manipulation occurs as in induction of general anesthesia for emergent cesarean section.

Methods for Managing Labor Pain

The pain, stress, and emotional factors associated with the process of labor and delivery bring unique challenges with each patient. The ultimate goal for these patients is as pleasant of an experience as possible for what some women is the most memorable joyous occasion of their lives. Each patient will present with a different set of expectations for this experience which include a variety of methods for pain control and methods for relieving the suffering. Suffering may be defined by several psychological elements including a perceived threat to the body and/or psyche, helplessness and loss of control, distress, insufficient strategies for coping with the distressing situation, or fear of death of the mother or baby [10].

Many parturients are choosing birth plans to reduce conflicts and misunderstandings between women and the healthcare providers surrounding the birth. Plans discussed prior to the birth should also include normal, complicated, and emergency scenarios and the possible options for pain control in each scenario. The plan may change as the process progresses, but this agreement serves as documentation of agreement between the patient and provider emphasizing issues most important to them.

The majority of women use some form of nonpharmacologic control and may in addition use pharmacologic forms of pain control. If a patient opts for nonpharmacologic forms of pain control, these methods do not take away the pain but rather

help women cope with the intense pain of labor and maintain a sense of personal control over the birth process, thus reducing suffering [2]. During the prenatal process, women need to be presented with the risks and benefits of both methods of pain control in order to make informed decisions when it comes to their care in the labor and delivery process. There should be discussions with their partner, support team, and healthcare provider to understand the issues important to the mother, so she feels safely supported and confident in labor [13].

Some scientific thought leaders still consider labor pain to be minor. Melzack developed a questionnaire to study the intensity and emotional impact of pain and reported that nulliparous women with no prepared childbirth training rated labor pain to be as painful as a digit amputation without anesthesia [14]. Nulliparous women report labor pain as more severe than multiparous women although the difference is not significant. Women who experience unrelieved pain during childbirth may be more likely to develop postpartum depression [13] and a study of 1288 patients who either had cesarean section or vaginal delivery, developed postpartum depression not based on delivery method but on the severity of postpartum pain [15]. Post-traumatic stress disorder has also noted to occur in women who are postpartum with a reported range from 1.7% to 6.9% [16].

Nonpharmacological Methods of Pain Control

Lamaze proposed psychoprophylaxis as a method to prepare for birth, and his philosophy has shaped natural childbirth methods. Individuals have stated that labor pain is minor and there is no need for medication alternatives [17]. Table 4.1 illustrates several nonpharmacological methods of pain control with natural childbirth and comfort measures.

Table 4.1 Nonpharmacological methods

Natural childbirth pain control methods
Simple relaxation
Breathing techniques with relaxation
Position changes-walking, rocking, birth ball
Mind/body interventions
Biofeedback
Psychoprophylactic methods
Massage/touch therapy
Hydrotherapy-water baths/shower
Aromatherapy
Music/meditation/hypnosis/yoga/accupressure/ acupuncture/transcutaneous electrical nerve stimulation/sophrology/herbal medicine
Use of hot/cold

Pharmacological Methods of Pain Control

Analgesic medications decrease the sensation of pain without complete loss of sensation or loss of consciousness. In contrast, anesthetic medications block partial or complete sensation of pain with or without loss of consciousness. Pharmacologic approaches to pain control for labor include systemic, local, and regional methods.

Systemic Analgesics

Systemic analgesics provide relief to the entire body rather than a localized area as regional analgesia provides. Some parturients prefer to have less invasive methods of pain control and opt for systemic analgesics which are known to be less effective than regional anesthesia and can produce side effects that are discussed below.

There are several reasons parturients either choose not to or are unable to receive neuraxial analgesia. There still remain hospitals worldwide that do not have the resources including specialized staff and equipment to provide safe neuraxial analgesia to patients. Additionally, some women may have contraindications to neuraxial analgesia such as coagulopathy, complicated anatomy, and previous complicated back surgery. In 2011 the United Kingdom reported less than one third of parturients received a neuraxial analgesic technique during labor and vaginal delivery [18].

Systemic parenteral opioids are very commonly used due to the fact that they are easy to administer, have lower costs, and are readily available. They also negate the need for specialized equipment and specialized care providers. Systemic opioids are frequently administered during early labor but should be discontinued as the patient advances toward delivery due to potential effects of respiratory depression and level of consciousness in the infant and potential sedative effects on the mother that could prevent her from actively and effectively participating in the delivery process.

Parenteral opioids have many side effects including but not limited to respiratory depression, sedation, dizziness, nausea/vomiting, delayed gastric emptying, constipation, pruritus, urinary retention, and dysphoria.

Opioids can be administered via intravenous (IV) bolus, intramuscular (IM), subcutaneous (SQ), and patient-controlled analgesia (PCA) routes.

Following SQ or IM administration of opioids, the onset, quality, and duration are variable and dependent on absorption at the injection site and local and regional blood flow. Subcutaneous and IM administration can also be painful depending on the drug administered in contrast to intravenous administration which is generally not painful, is easy to administer, and has predictable effects. Patient-controlled administration of opioids is also an effective method of pain control during labor and delivery and provides rapid onset of analgesia and better control in contrast to side effects than parenteral opioid injection and also provides the patient with a sense of control [19].

A review by Smith [20] et al. demonstrated that parenteral opioid administration by either IM, IV, or PCA routes provided some pain relief and moderate satisfaction with analgesia, although up to two thirds of patients who received opioids reported moderate or severe pain and/or poor or moderate pain relief 1–2 hours after administration, and maternal side effects included maternal nausea, vomiting, and drowsiness. The sedation and somnolence may contribute to the relief without great strides in pain scores.

Opioids are highly lipophilic with a low molecular weight which leads to rapid crossing of the placenta. The consequences of these properties add risk of respiratory depression and neurobehavioral changes in the neonate. The effects are dose dependent and associated with the timing of last administration prior to birth. Opioids have been shown to decrease fetal heart rate variability, although this change usually does not reflect a worsening of fetal oxygenation or acid-base balance [21]. In utero, the fetus can be affected as well. Metabolism and elimination of these drugs is prolonged as well as a less developed blood-brain barrier which may lead to greater effects centrally.

Halpern et al. [22] reported in a multicenter randomized study comparing patient-controlled epidural anesthesia with local anesthetic and opioid vs systemic parenteral opioids and found there was an increased requirement for active neonatal resuscitation in the parenteral opioid group (52% vs 31%).

Labor analgesia reduces circulating catecholamines and therefore reduces the beta-adrenergic effects on the myometrium. It has been noted that once analgesia, including epidural, paravertebral, or systemic meperidine, is administered, labor patterns may go from dysfunctional to normal [23]. The rapid onset of decreased catecholamine levels with intrathecal opioids has led to a transient period of uterine hyperstimulation with decreased beta-adrenergic tocolysis which may lead to fetal stress and heart rate abnormalities [24, 25].

Opioid Analgesics

There are a number of opioid analgesics used to relieve pain during labor.

Meperidine

In 1947, meperidine (pethidine) became the first synthetic opioid used for intrapartum analgesia [26] and still remains the most commonly administered opioid for labor analgesia worldwide. Meperidine can be administered via an IV or IM route with intermittent bolus dosing. Dosages range from 25 to 50 mg IV and can be repeated every 4 hours, with onset within 5 minutes and duration of action of 2–3 hours. Meperidine can be given IM in doses between 50 and 100 mgs with a time to peak effect of 45 minutes. Meperidine is metabolized in the liver to normeperidine which is an active metabolite. Unfortunately, the effects of normeperidine

cannot be reversed by naloxone [27]. Both compounds rapidly cross the placenta, and neonatal effects are related to accumulation of normeperidine especially if the parturient received multiple doses. Normeperidine has a long half-life ranging from 14 to 21 hours and may affect newborn neuroadaptive scores and breastfeeding behaviors [28].

Meperidine should be administered within 1 hour or more than 4 hours of delivery as maximum fetal concentration occurs 2–3 hours after the drug is administered [29, 30].

Maternal side effects include nausea, vomiting, and sedation [31]. Other potential side effects include serotonergic crises, seizures, and normeperidine neurotoxicity and possible drug interactions with MAOIs [32]. Meperidine has also been associated with temporary decreased fetal heart rate variability [33, 34].

The analgesic effect of meperidine is variable with some reports stating less than 20% of laboring women receiving satisfactory pain control. Elbohoty et al. [35] compared meperidine 50 mg IV with acetaminophen 1000 mgs IV and found the analgesic effects comparable and the meperidine group having 64% incidence of side effects compared with none for the acetaminophen group.

Morphine

Morphine has been administered since the late 1800s for analgesia and was used in the past in combination with scopolamine for "twilight sleep." Morphine has fallen out of common use due to excessive maternal sedation and neonatal respiratory depression [36]. Morphine 2–5 mgs IV is the standard dose administered and can be given every 4 hours with a peak onset in 3–5 minutes and duration of action of 3–4 hours. Morphine can also be administered IM with dosing of 0.1–0.2 mg/kg [36]. The peak effect occurs in 10–30 minutes with duration of action of 3–4 hours.

Morphine is primarily metabolized in the liver with up to 70% being transformed into the largely inactive metabolite morphine-3-glucuronide and the other 30% to an active metabolite morphine-6-glucuronide which is 13 times more potent than morphine [36]. Morphine crosses the placenta and has been detected in the fetal circulation within 5 minutes of administration.

Maternal side effects include sedation, respiratory depression, nausea and vomiting, dysphoria, and histamine release with possible rash. Respiratory depression is the biggest concern for the neonate. Olofsson et al. [37] compared IV morphine (up to 1.5 mg/kg) with meperidine (up to 1.5 mg/kg) and found both groups to have high pain scores and high levels of maternal sedation.

Fentanyl

Fentanyl is a highly lipophilic and protein-bound short-acting synthetic opioid which crosses the placenta and is commonly used for labor analgesia. Fentanyl is a potent opioid that is 100 times more potent than morphine and 800 times more

potent than meperidine [36]. Fentanyl has properties that make this drug attractive for use during labor including peak onset after administration of 2–4 minutes with a duration of action of 3–60 minutes and no active metabolites [36]. After maternal administration in sheep, fetal levels can be detected within 1 minute of administration with peak levels at 5 minutes post-maternal administration [38]. Standard dosing for fentanyl is 50–100 mcg loading dose and PCA dosing of 10–25 mcg every 5–10 minutes [39]. Fentanyl can also be given in intermittent IV boluses. Fentanyl is metabolized in the liver by CYP34A to inactive metabolites hydroxyfentanyl, norfentanyl, and despropionyl fentanyl [40].

Side effects of fentanyl include respiratory depression, sedation, nausea, and vomiting. Fentanyls can cause neonatal depression as reported by Morley-Forster et al. who found a 44% incidence of 1-minute APGAR <6 in 32 parturients who received fentanyl during labor [41].

Remifentanil

Remifentanil is an ultra-short-acting synthetic potent opioid that is a mu-receptor agonist which is 2 times more potent than fentanyl and 100–200 times more potent than morphine and is used for sedation or general anesthesia during procedures requiring anesthesia and analgesia. Some key features of remifentanil that make it an excellent choice for analgesia during labor include its quick onset and offset due to its short half-life. Unlike other opioids that are hepatically metabolized, remifentanil undergoes metabolism by nonspecific plasma esterases. Remifentanil is administered by PCA and may have a basal infusion along with the PCA function. The recommended dosing is PCA bolus of 15–50 mcg IV. An infusion of remifentanil will have an onset of action in 1 minute and rapidly achieves steady-state levels in the plasma. Remifentanil's effects resolve within 3–10 minutes after discontinuation. The context-sensitive half-time for remifentanil is 3–4 minutes and is not dependent on the length of the infusion [42–44]. There must be careful attention paid to the time interval between dosing. Lockout intervals of 1–5 minutes has been suggested [45]. An interval of 3 minutes will avoid additional doses before the peak analgesic effect has occurred as well as enough time for the side effects has occurred [46]. The primary metabolite is remifentanil acid which has minimal pharmacologic activity. Remifentanil has been shown to rapidly cross the placenta with rapid fetal metabolism and/or redistribution [47]. The initial analgesic affect decreases as labor progresses. Abrupt discontinuation of a long-term infusion of remifentanil can cause withdrawal-like symptoms.

Remifentanil is a Category C drug for use in pregnancy. It is unknown if Category C agents cause fetal harm when administered to parturients. The manufacturer states "the safety of remifentanil during labor has not been demonstrated" and "the drug should be given to a pregnant woman only if clearly needed and the benefit justifies the potential risk to the fetus" [48].

Remifentanil is an effective analgesic and has fewer opioid-related side effects on the neonate compared with other opioids for labor but is inferior to neuraxial

analgesia. Comparison studies have been performed with remifentanil and nitrous oxide with results revealing remifentanil provides more effective analgesia than nitrous oxide when evaluating pain scores and patient preference for nitrous oxide vs remifentanil [49].

In order for remifentanil to be effective in labor, the patient would have to predict the onset of a contraction in order to administer the bolus in time to be effective with the peak of the contraction. This would be ideal for patients that have begun a regular contraction pattern and could anticipate when to administer the medication. The standard contraction time is between 60 and 80 seconds.

Remifentanil is known to be a potent respiratory depressant and has been associated with four case reports of respiratory and/or cardiac arrest [46]. Patients may experience hypoventilation, desaturation, and apnea. Van de Velde and Carvalho performed a literature search which included 36 original studies and concluded that remifentanil patient-controlled intravenous anesthesia should not be routinely administered during labor due to the safety concerns [50]. These patients require one-to-one nursing and require continuous monitoring of respiratory rate and oxygenation [50–52].

Additional side effects of remifentanil include bradycardia, hypotension, nausea, and skeletal muscle rigidity. Skeletal muscle rigidity occurs more frequently when remifentanil is administered in bolus form.

The rapid elimination of remifentanil also reduces the risk of neonatal respiratory depression compared with other long-acting opioids [53]. Hill et al. stated maternal administration of remifentanil PCA during labor appears to have minimal effect on fetal heart rate abnormalities, umbilical cord blood gas measurements, and APGAR scores [45].

Nalbuphine

Nalbuphine is a synthetic mixed opioid agonist-antagonist with agonist binding at kappa, mu, and delta receptors. It is primarily a kappa-agonist providing analgesia and a partial agonist of the mu receptor. A partial agonist at the mu receptor correlates to less respiratory depression than a full agonist drug profile. Nalbuphine has a ceiling effect on respiratory depression due to its mixed receptor activity in doses up to 0.5 mg/kg [54]. Additionally, nalbuphine can cause maternal sedation but is associated with less maternal nausea and vomiting, drowsiness, and dizziness [55]. Fetal heart rate variability may be decreased, and pseudosinusoidal fetal heart rate patterns have been reported [55, 56]. If respiratory depression does occur, the effects can be reversed with naloxone [56].

Nalbuphine has equal analgesic potency to morphine in equivalent doses. Nalbuphine can be administered via the IV, IM, or SQ route with dosing of 10–20 mg every 4–6 hours. The onset is 2–3 minutes through IV administration and usually within 15 minutes of IM or SQ administration. Metabolism occurs in the liver and produces inactive elements.

Butorphanol

Butorphanol is a synthetic opioid agonist-antagonist with agonist activity at the kappa opioid receptor and an antagonist at the mu opioid receptor [57]. The standard dosing is 1–2 mg IV or IM with a peak onset of 2–3 minutes with IV administration and 10–20 minutes with IM administration and a duration of action of 4–6 hours with both routes of administration [58]. This drug is metabolized in the liver to hydroxybutorphanol, an inactive metabolite [59]. Butorphanol is five times as potent as morphine and 40 times more potent than meperidine [60].

Butorphanol has a ceiling effect on both respiratory depression and analgesic effect; therefore, increased doses do not provide additional analgesic effect or increase respiratory depression but will increase the side effects of the medications.

Non-opioid Analgesics

Non-opioid analgesics are not as effective as IV opioids but do provide some relief in labor.

Acetaminophen is an alternative analgesic for labor as it has minimal side effects on the mother and neonate. It's analgesic activity is exerted by inhibiting the synthesis of prostaglandins in the central nervous system and has peripheral effects by blocking pain control generation [61, 62]. Acetaminophen also has a serotonergic mechanism and cannabinoid agonist mechanism in providing pain relief [63]. Acetaminophen is also a powerful antipyretic.

Zutshi et al. studied IV acetaminophen 1000 mgs vs normal saline infusion and noted VAS scores at 15 minutes, 1 hour, 2 hours, 3 hours, and 4 hours after drug administration. The reduction VAS scores were significantly higher in the acetaminophen group at all time points excluding the initial 15-minute score. There were no adverse neonatal or maternal effects [64].

Elbohoty et al. performed a randomized prospective study analyzing IV paracetamol (acetaminophen) vs IV pethidine (meperidine) as an analgesic in the first stage of labor. The VAS scores were lower at 15 min, 1 hour, and 2 hours after treatment in both groups and no reduction after 3 hours. The reduction in pain was significantly greater in the pethidine group only at the 15-minute score [65]. Acetaminophen had fewer adverse maternal effects.

Other non-opioid analgesics include promethazine (phenothiazine) and hydroxyzine (antihistamine). The medications do provide some relief during labor when used alone but are most commonly administered in combination with an opioid. Promethazine may be administered IV or IM, while hydroxyzine is usually administered IM, and both help prevent nausea and vomiting associated with opioids [66].

Table 4.2 Non-opioid analgesics

Class	Dosage/route	Onset of action	Duration of action
Promethazine	25–75 mg IV/IM	10–20 minutes	3–4 hours
Hydroxyzine	25–50 mg IM	30 minutes	4 hours
Ketamine	10–20 mg IV	1 minute IV	5–10 minutes IV
		2–8 minutes IM	10–20 minutes IM
Midazolam	1–5 mg IV	3–5 minutes	1–2 hours
Diazepam	2–5 mg IV	5 minutes	1–2 hours

Ketamine was commonly used when it was first released for labor analgesia but feel out of favor due to its side effects. Ketamine is a phencyclidine derivative medication that is a noncompetitive antagonist at the NMDA receptor and at high doses is a mu receptor agonist [54]. It's a dissociative anesthetic providing pain relief, sedation, and memory loss and can be administered by IM or IV routes. Ketamine has a rapid onset of action of less than 1 minute of administration and has a duration of action of 5–10 minutes when given IV and when given IM has an onset of 2–8 minutes with a duration of 10–20 minutes [54]. Ketamine is known to maintain airway reflexes and respiratory effort but also increases oral secretions. Ketamine's sympathomimetic effects may cause an increase in heart rate, systolic blood pressure, and cardiac output and should be used cautiously in parturients with preeclampsia or hypertension. Ketamine is frequently administered after benzodiazepine dosing to prevent its psychological effects which may include agitation, confusion, or hallucinations. Providers must consider the potential of the mother not remembering the birth due to its amnestic effects. Jagatia et al. utilized a low-dose ketamine infusion for labor in 100 parturients and found low-dose ketamine infusion is safe without significant maternal or fetal effects, reduces maternal pain and exhaustion, and does not prolong duration of labor or have increased rate of instrumented delivery or cesarean section [67].

Benzodiazepines including midazolam and diazepam are anxiolytics and have been used for sedation during labor. Benzodiazepines are potent amnesics and may decrease the mother's memory of the birth. Additionally, they blunt airway reflexes and may place the parturient at risk for aspiration. Diazepam crosses the placenta and accumulates in the fetus and has an elimination half-life of 28–48 hours. The active metabolites may be present for up to 120 hours. Diazepam may cause maternal respiratory depression and neonatal respiratory depression/hypotonicity.

Midazolam has an elimination half-life of 1–4 hours [54] and readily crosses the placenta. Table 4.2 summarizes medications used as co-analgesics.

Nitrous Oxide

Nitrous oxide (NO) has been used in Great Britain, Scandinavia, Australia, New Zealand, Canada, and other countries for several decades, while nitrous oxide is becoming more commonly used in the United States [68]. The Food and Drug Administration has approved delivery room administration equipment. The equipment is required to have a scavenging system to decrease the exposure of healthcare personnel and other individuals in the labor room.

Nitrous oxide delivery systems are self-administered by the parturient using a handheld mask that covers the nose and mouth or a mouthpiece with a mixture of 50% oxygen and 50% nitrous oxide. The patient must be sufficiently awake to take a forceful enough breath to open the demand valve which closes with exhalation. This should prevent the patient from inhaling too much as the drowsiness effect will prevent the patient from inhaling. Patients receiving NO should have continuous pulse oximetry, and consideration should be given to patients with baseline oxygen saturations <95% or in patients with respiratory issues. Special risk should be taken in patients who are also receiving opioids also to decrease the risk of respiratory depression. Nitrous oxide is eliminated through the lungs via exhalation and has no effect on uterine contractions and has not been found to accumulate in the mother/fetus/neonate or cause newborn depression [69]. It is common for NO administration to be delivered by obstetric nurses and certified registered nurse-midwives. Special training and maintenance training need to be in place with protocols for nitrous administration. Bobb et al. reported in 2016 that the rate of neuraxial placement for labor has not changed since nitrous oxide has become more common [70].

The effects of NO on the neonatal brain are not known nor are the effects of low-dose environmental exposure in hospital personnel [71]. Animal studies reveal prolonged exposure to NO inhibits methionine synthetase activity and that exposure to anesthetics and sedatives causes neurodegenerative changes in developing animals [72].

The key to effective use of nitrous oxide depends upon pre-contraction inhalation in preparation for the contraction as the analgesic takes approximately 50 seconds to take effect; therefore if the patient waits to inhale with the contraction, the effect may occur after the contraction which in general last 1 minute. In order to obtain the maximum effect of nitrous oxide, inhalation should begin 30 seconds before the contraction begins and continue until the contraction begins to recede.

Side effects of NO include nausea (5–40%) and vomiting (15%) [73].

Currently there is a paucity of quality studies to report the efficacy of NO [71, 74–76]. A systematic review by Likis et al. reported that NO relieves labor pain to a significant degree in most patients but does not provide complete analgesia with some patients having no response at all [73]. Richardson et al. evaluated in 6242 parturients the relationship between analgesic effectiveness and patient satisfaction with analgesia in women who delivered vaginally using NO, neuraxial analgesia with either epidural or combines spinal – epidural, or neuraxial analgesia after a trial of NO [77]. They concluded that patients who received NO alone were as likely to report satisfaction with anesthesia care as those who received neuraxial analgesia, even though they were less likely to report excellent analgesia.

Other Modalities for Pain Control

Two alternative methods of pain control for labor and delivery include local anesthesia blocks including pudendal and paracervical nerve block. These nerve blocks are administered in obstetrics for pain control in patients who request minimal pain control during delivery, patients who decline regional anesthesia, patients with a

contraindication to regional anesthesia, or patients with regional anesthesia that is not providing adequate pain relief for labor and delivery. These blocks are most commonly performed by OB/GYNs and were commonly used prior to the initiation of epidural anesthesia for labor and delivery. Both types of blocks can additionally be used for gynecologic procedures and can be performed by single-shot injection or multiple injection methods with local anesthesia.

Pudendal Block

The pudendal nerve includes somatic nerve fibers from the anterior primary divisions of the second, third, and fourth sacral nerves. These nerves represent sensation innervation of the lower vagina, vulva, and perineum as well as motor innervation to the perineal muscles and urethral and external anal sphincter [78]. The nerves blocked by a pudendal do not provide pain relief during uterine contractions or cervical dilation. Indications for pudendal block include pain from introital distension during the second stage of labor, operative vaginal delivery (forceps/vacuum), or perineal repair for complex laceration repairs [79]. This block is ineffective for pain relief associated with manual exploration of the uterine cavity (manual extraction of the placenta) or mid-forceps-assisted births and upper vaginal repairs and may be incomplete for cervical repair and forceps rotation [80].

Pudendal blocks may inhibit the bearing-down reflex; therefore this nerve block is most commonly placed immediately prior to the birth of the infant to avoid increasing the second stage of labor [80]. If the duration of the block is inadequate, the block can be repeated keeping in mind the total safe dose of local anesthetic that the patient can receive.

Pudendal blocks can also be used for gynecologic procedures that require cervical dilation and manipulation, pregnancy termination, hysteroscopy, and cervical ablation or excision [81]. McCulloch et al. reported on successful McDonald cerclage placement under pudendal nerve block [82].

The success of the block is largely associated with the experience, skills, and knowledge of the proper site of placement of the individual performing the block. Block inadequacy or failure may be due to decreased opportunities for education of the correct procedure for pudendal block secondary to the increased use of regional anesthesia for delivery. Case studies reveal a block ineffectiveness rate of 10–50% on one or both sides [83]. Pudendal nerve block can be given via a transperineal approach but most commonly is delivered via a transvaginal approach especially in the United States [84]. Scudamore et al. reported bilateral success rates of 50% with transvaginal approach vs 25% after transperineal approach.

The pudendal nerve crosses posterior to the sacrospinous ligament in proximity to where the ligament attaches to the ischial spine [85]. Figure 4.2 shows the transvaginal technique.

The block is most commonly administered bilaterally but can be placed unilaterally if only one-sided coverage is needed. Pudendal nerve kits are available which

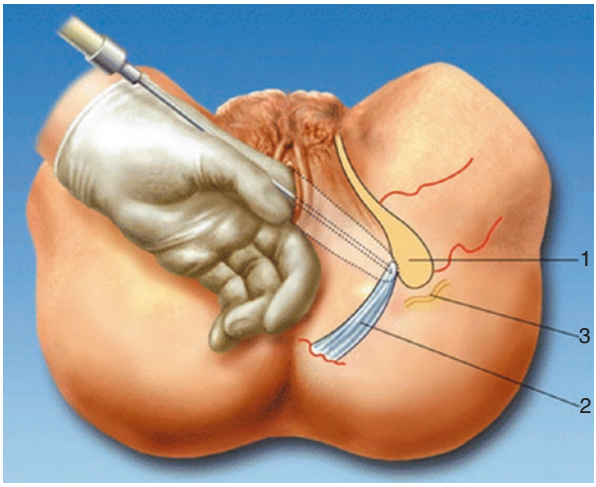

Fig. 4.2 Local infiltration of the pudendal nerve. 1 Ischial spine, 2 sacrospinous ligament, 3 pudendal nerve

include a disposable plastic needle guide and needle. If kits are not available, a 20-gauge 15 cm spinal needle with a non-disposable Iowa trumpet (to prevent damage to the vaginal and fetus) can be used. Total local anesthetic doses on each side range from 7 to 10 mL. The local anesthetic most commonly utilized is lidocaine 1% with a maximum recommended dose of 300 mgs. Mepivacaine 1%, bupivacaine 0.25%, and 2-chloroprocaine 2% can also be used. Chloroprocaine can be used for faster onset but has a short duration of action and may be repeated if the second stage of labor is prolonged (15–30 minutes) [84]. With uncomplicated block placement, relief occurs within 5 minutes and with maximum time set up between 10 and 20 minutes [86].

A pudendal block with lidocaine has an average duration of action of 30–60 minutes [87].

Merkow et al. [88] studied the use of 30 mL of 0.5% bupivacaine, 1% mepivacaine, or 3% 2-chloroprocaine for pudendal block and perineal infiltration and had no significant effects on newborn neurobehavioral indices at 4 and 24 hours with the exception of a better response to pinprick at 4 hours with the mepivacaine. Studies have been performed to evaluate the advantages and disadvantages of adding epinephrine to the local anesthetic solution for pudendal blocks. Langhoff et al. [89] performed a double-blind randomized study of 865 who received pudendal block with either 16 mL of 1% mepivacaine, 1% mepivacaine with epinephrine, or 0.25% bupivacaine. The patients who received mepivacaine with epinephrine had adequate analgesia more often and additionally had a greater "loss of the urge to bear down" than the other anesthetics. There was no significant difference in duration of the second stage of labor and incidence of instrumented vaginal delivery.

Aissaoui et al. [90] looked into using a nerve stimulator during pudendal nerve block and reported that administering a unilateral pudendal nerve block following episiotomy repair significantly decreased the need for additional analgesic agents during the first 48 hours postpartum [91].

Potential Complications of Pudendal Nerve Block

Pudendal nerve blocks are safe with a quick onset of pain relief but also pose risks for complications which include laceration of the vaginal mucosa; vaginal, ischiorectal, or retroperitoneal hematomas; retro-psoas space or subgluteal abscess; nerve damage; local anesthetic toxicity; intravascular injection with systemic toxicity; temporary paresthesia in the ischial region; and sacral neuropathy. Abscesses of the retro-psoas or gluteal region can cause significant morbidity and mortality. Hematomas usually resolve on their own unless the patient is on blood thinning medications or has coagulopathy or other bleeding issues. Although there are known complications as above, the risk associated with this procedure is low.

Neonatal and fetal complications are rare but may occur. There can be direct fetal trauma with inadvertent puncture of the infant's scalp or other body regions [92]. A case report by Pages et al. described three inadvertent scalp injections which resulted in lidocaine toxicity with complete recovery. Bozynski et al. published a case report of lidocaine toxicity; after them other received a pudendal block with symptoms of postnatal apnea, bradycardia, and a prolong QT interval in a term infant [93].

Contraindications to pudendal block include allergy to local anesthetic, known coagulopathy, and vaginal infection.

Paracervical Nerve Block

Pain associated with the first stage of labor is due to cervical dilation and lower uterine segment distention and distention of the upper vagina. Pain impulses are transmitted from the upper vagina, cervix, and lower uterine segment by viscera afferent nerve fibers that join the sympathetic chain (define) at L2 to L3 and enter the spinal cord at T10 to L1 [94] and sacral nerve roots (s1–4). This technique blocks transmission through the uterovaginal plexus (Frankenhauser's plexus) [95].

Paracervical block does not block the pain caused by the late first stage or second stage of labor. Per Chestnut, contemporary experience suggests that paracervical block results in satisfactory analgesia during the first stage of labor in 50–70% of parturients. Paracervical block (PCB) is not commonly performed in the United States due to fetal complications and neuraxial anesthesia but remains popular in other countries. This block has the advantage of not affecting the time course of labor.

Paracervical nerve block can be administered for gynecologic procedures that involve uterine intervention and cervical dilation. Two percent lidocaine, 1.5% mepivacaine, and 0.2–0.5% ropivacaine are most commonly used for local anesthesia. It is common to add either vasopressin or epinephrine to reduce intra- and postoperative blood loss [95, 96]. Additionally, other benefits of adding a vasoconstrictor include inhibition of drug redistribution/elimination from the injection site,

increased block potency and longer duration of action, and reduced systemic toxicity [95]. The effects were more pronounced when vasoconstrictors lidocaine and mepivacaine were used. Epinephrine can lead to cardio-stimulatory effects as well as tachyarrhythmias which may be detrimental to certain groups of patients.

Paracervical blocks for obstetrical analgesia commonly utilize buffered local anesthesia with sodium bicarbonate and don't contain epinephrine. Commonly used local anesthetics are 2% 2- chloroprocaine and 1% lidocaine. Bupivacaine is not commonly utilized secondary to the cardiac toxicity effects in adult patients [97]. A double-blind study performed by Weiss et al. [98] compared paracervical block in 60 patients that were randomly assigned to 20 mL of 2% 2-chloroprocaine or 20 mL of 1% lidocaine. In the 2% 2-chloroprocaine group, 1 fetus out of 29 fetuses experienced fetal bradycardia compared with 5 of 31 fetuses in the 1% lidocaine group. The results were not statistically significant with a P value of 0.14.

Paracervical blocks are usually administered during active labor in the first stage during cervical dilation between 4 and 8 cm and can be repeated at regular intervals. Once the parturient reaches 8 cm, the procedure is less desirable as the procedure becomes more technically difficulty, is less effective, and has a higher risk of causing fetal bradycardia [99].

Paracervical blocks may be performed with a PCB block kit which includes a needle guide (i.e., Iowa trumpet) to prevent injury in the vagina, a plastic needle spacer, and a needle for injection. If kits are unavailable, a 22-gauge 15 cm spinal needle with a metal Iowa trumpet as a needle guide may be used.

Vidaeff et al. [100] recommend injection of local anesthetic at the 4 and 8 o'clock position as they are less vascular than the recommended 3, 5, 7, and 9 o'clock positions. Figure 4.3 shows the locations for injections. Vidaeff recommends the

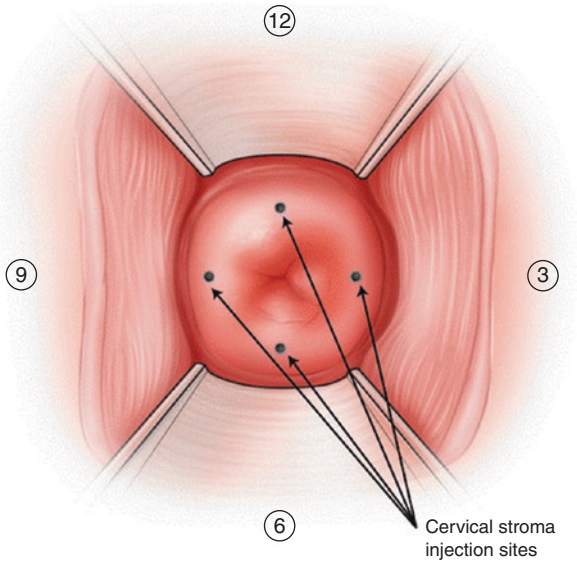

Fig. 4.3 Paracervical nerve block infiltration locations

two point approach to decrease the number of painful injections with similar analgesia to the patient. It is recommended that the needle insertion depth is no more than 3 mm to avoid risks especially fetal bradycardia [101]. A total of 20 ml of local anesthetic is administered for the nerve block. After completion of the injections, the local anesthetic spreads rapidly to the broad ligament. The onset of pain relief is rapid within 2–5 minutes. The duration of analgesia is based upon the pharmacokinetics of the local anesthetic chosen. The block can be repeated, but it is not recommended to repeat more than once an hour.

Cochrane reported on a study of 109 parturients who received opioids vs paracervical block. The paracervical block group was found to have more effective pain relief with additional studies reporting no increased rate of instrumented deliveries or cesarean section rate [102].

Fetal bradycardia usually occurs within 2–10 minutes of block placement with bradycardia usually resolving within 5–10 minutes but can persist up to 30 minutes [103]. The mechanism of fetal bradycardia is unclear. Palomki et al. in a prospective study reported 3.2% of 440 parturients who received a paracervical block developed fetal bradycardia lasting from 2 to 8 minutes [104] with similar rates from labor epidurals [105].

The mechanism of fetal bradycardia is unknown but there are several theories. The local anesthetic injected for PCB rapidly crosses the placenta and is in close proximity to the uterine circulation which may lead to myocardial depression, fetal central nervous system depression, or umbilical vasoconstriction [106]. The local anesthetic has been shown to cause uterine artery vasoconstriction and decreased uteroplacental blood flow [107]. Rogers et al. proposed manipulation of the fetal head, uterus, and uterine blood vessels may cause a reflex fetal bradycardia [108].

The effects have been attributed to the direct toxic effects of the local anesthetic on the fetal heart [109, 110]. Chestnut reports most investigators believe the fetal bradycardia from PCB is due to reduced uteroplacental and/or fetoplacental perfusion. A reduction in uteroplacental blood flow may occur due to increased uterine activity and/or direct vasoconstrictive effects of local anesthesia, while decreased umbilical cord flow may lead to increased uterine activity and/or umbilical cord vasoconstriction.

Levy et al. reported no association between PCB and low umbilical arterial blood pH at delivery [111].

Maternal complications are not common and include vasovagal syncope (cervical shock); laceration of the vaginal mucosa; systemic local anesthetic activity; hematoma; paracervical, retropsoal, or subgluteal abscess; and postpartum neuropathy.

Regional/neuraxial analgesia methods include spinal, epidural, and combined spinal-epidural and are the recommended form of treatment for intrapartum analgesia in the United States and Canada, largely replacing systemic drug administration [112, 113].

Neuraxial Anesthetics

Neuraxial anesthetics are a group of techniques used to create analgesia or anesthesia by targeting the central nervous system directly. These techniques include spinal, epidural, and combined spinal-epidural (CSE) interventions. Because anesthetic is deposited directly at or very near to the central site of action, total dose of local anesthetic and adjuncts are minimized while creating anesthesia in a wide area of the body. Often a primary concern of patients and physicians alike is avoiding treatment that involves sedating medications which can impair maternal participation in the birth process as well as cross the placenta and have postpartum effects on the newborn. The transition from visceral pain during the first stage of labor to somatic pain during the second stage of labor can be difficult to endure as a patient and to manage as a physician. Neuraxial techniques again are ideal for this type of transition because they provide analgesia effective against both types of pain. The labor process can endure for many hours, and epidural catheters can be used reliably for the entire duration of this process to provide continuous, non-sedating analgesia. Pumps are available that can be programmed to allow safe and secure patient-controlled epidural analgesia (PCEA), which give the patient autonomy in the treatment as well as unburdening healthcare providers.

An enduring concern of parturients is the fear that the risk of a cesarean section is increased when an epidural is used for labor pain control. Patients should be reassured that modern randomized controlled trials show that epidurals do not increase the risk of cesarean section. In studies after 2005, the rate of instrumented delivery is no different with epidural analgesia either [114, 115]. Some studies did, and some studies did not find increased rates of use of oxytocin, and the second stage of labor is increased by 15–30 minutes with epidural analgesia versus none [116]. Studies have also shown that timing of placement of the epidural does not impact rate of cesarean section [117].

A major advantage of epidural placement is the ability to transition quickly from labor analgesia to surgical anesthesia should the need for urgent or emergent cesarean section arise. Especially in situations where this transition is more likely, such as during a trial of labor after cesarean, early placement of epidural is highly beneficial in avoiding the risks of general anesthesia for cesarean. Parturients with high-risk comorbidities such as cardiovascular or pulmonary compromise also may benefit from early placement and careful titration of epidural analgesia.

Neuraxial techniques are not risk-free though. Short-term local discomfort is common, but there is no association with neuraxial anesthetics and long-term back pain [115]. Hypotension from sympathetic blockade is common and frequently requires treatment with low doses of vasopressors [117]. Accidental dural puncture can happen, which in some patients leads to the development of a postural headache, called post-dural puncture headache (PDPH), with varied migraine-like symptoms and a variable presentation. The more frightening complications of neurologic injury, epidural abscess, and epidural hematoma are exceedingly rare. The most

common of these three is neurologic injury, occurring at a rate of 1 in 6700 (0.015%). Epidural abscess is even rarer at a rate of 1 in 145,000 (0.0007%). Epidural hematoma is the rarest at a rate of 1 in 240,000 (0.0004%) [117]. Airway management supplies should be readily available to manage unintentional intrathecal injection of local anesthetic intended for epidural dosing. Also, unintentional intravenous injection of local anesthetic can lead to total cardiovascular collapse. Lipid emulsion rescue therapy and functioning ACLS resuscitation equipment and medications should be available on site in any location where epidural anesthetics are administered [117].

Few true contraindications to neuraxial anesthesia exist. They include, but are not limited to, patient refusal, clinically significant coagulopathy, use of thrombolytics, hypovolemia, elevated ICP that could result in herniation with dural puncture, and localized infection to intended site of needle entry [117]. The decision to acquire a platelet count prior to placement should be an individualized decision based on patient history and exam but should not be required prior to epidural placement in healthy parturients [118]. The safety of placement with a platelet count greater than 100,000 per microliter is well established. Recent large retrospective reviews suggest that in the absence of abnormal bleeding or bruising or other signs of a hypocoagulable state, it is likely safe to proceed with epidural or spinal placement with platelet counts as low as 70,000 per microliter [119].

Over the past 30 years, hospitals are increasingly offering 24-hour availability of anesthesia services as well as increasingly utilize combined spinal-epidural technique and patient-controlled epidural analgesia [120]. US birth certificate surveillance has shown that from 2009 to 2015, at least 61% of all mothers utilized some form of neuraxial analgesia or anesthesia for their delivery [121]. In stratum 2 and 3 hospitals where in-house anesthesia services may not be continuously available, ACOG recommends that labor and delivery nursing staff should be trained to manage infusions in already established epidural catheters [122].

Epidural

The epidural space is the space immediately surrounding the spinal dura, the tissue that encases the spinal cord, spinal roots, and cerebrospinal fluid. The epidural space contains blood vessels and fat and is progressively wider moving from cephalad to caudad. The posterior aspect of the epidural space is bounded by the ligamentum flavum. Entering the epidural space can be achieved by passing a needle between vertebral spinous processes through the interspinous ligament and then through the ligamentum flavum. As the clinician advances the needle, injection of either air or saline is tested periodically as the needle is advanced. When the needle tip is located within ligamentous structures, injection is very difficult. Upon entry of the needle tip into the epidural space, a sudden loss of resistance against the injection is found, and the air or saline is easily injected into the epidural space. Once loss is achieved, a catheter is passed through the needle into the epidural space, and the needle is

withdrawn over the catheter, and the catheter is then secured in place with an occlusive dressing. An epidural must also be tested for inadvertent vascular or intrathecal entry. Once the catheter is believed to be in the epidural space, it must first be tested. This is done by two methods: aspiration and medication testing. If blood or clear fluid is freely aspirated from the catheter, concern for vascular or intrathecal entry should be raised, and catheter removal should be considered. If aspiration is negative, then a test dose of a volume of 3 mL of 1.5–2% lidocaine with 5 μg of epinephrine per mL is injected. If the catheter is intrathecal, the 3 mL of lidocaine will rapidly induce spinal anesthesia creating sensory and motor block of the lower extremities and abdomen. If the catheter has entered a vessel, the 15 μg of epinephrine will rapidly cause an increased heart rate, an increased blood pressure, and typically a sense of anxiety. If either intravascular or intrathecal placement is confirmed by the test dose, the catheter should be withdrawn, and replacement can be attempted. One option with intrathecal placement is to leave the catheter in place and to alter the planned epidural infusion rate and disallow patient-controlled features of the infusion [123].

Two modalities of administering local anesthetic are typically used, continuous infusion and programmed intermittent bolus (PIB) that can be run either with or without the addition of patient-controlled demand doses. PIB has been shown to provide equivalent analgesia while consuming a lower total volume of local anesthetic. It is theorized that greater spread through the epidural space is achieved with PIB administration because the bolus injection is delivered at a higher pressure resulting in a higher ejection velocity of the medication and thus spreading further in the epidural space [124].

Spinal

Spinal anesthesia, also known as a subarachnoid block, is a viable option that provides both a deep sensory and motor blockade. It is performed by first passing a short introducer needle into the posterior midline space usually between the L2–3, L3–4, and L4–5 interspace. A pencil-point spinal needle is then passed through the introducer and advanced periodically removing the introducer to check for the presence of clear fluid. Once the needle passes through the dura and enters the subarachnoid space, CSF will begin to drain from the needle when the introducer is removed. At this point, the syringe containing the local anesthetic should be attached to the spinal needle after careful removal of all air from the syringe. Aspiration is first performed which serves to verify that after syringe attachment, the needle tip remained within the subarachnoid space. Aspiration is usually easy to note within the syringe as a “swirl” appearance of CSF mixing with local anesthetic. The local is then injected, and the needle and introducer are removed. Patients often experience a fleeting paresthesia when the needle first passes through the dura. However, should that paresthesia persist, the needle should be retracted and injection not performed.

Choice of local depends on desired duration of effect and desired positioning of the patient during the procedure. Hyperbaric 0.75% bupivacaine is the most commonly used medication for cesarean sections. Hyperbaric solutions are denser than CSF and will sink within the CSF when injected. Full coverage of all lumbar, sacral, and lower thoracic levels is desired for cesarean section. Total dose ranges from 7 to 15 mg depending on the addition of opiates and desired longevity of block. Injection should be performed slowly to prevent rapid upward spread within the CSF.

Combined Spinal-Epidural

To perform a combined spinal-epidural, the entire process of placing an epidural is performed up to the point of the loss of resistance to injection. At this point, instead of threading the epidural catheter through the needle, first a pencil-point spinal needle is passed through epidural needle and into the subarachnoid space and opiates; local anesthetic or a combination thereof is injected. The spinal needle is withdrawn and the epidural catheter is placed and secured. Typically the test dose is delayed until just prior to the anticipated use of the epidural catheter, if it will not immediately be connected to an infusion.

Surgical Delivery

For surgical deliveries, it has long been the standard of care to provide surgical anesthesia via either an epidural or spinal anesthetic while maintaining the patient awake. While this enables the mother to be awake and involved during the delivery, it also avoids complications associated with general anesthesia. For this reason, the American Society of Anesthesiologists (ASA), the Society for Obstetric Anesthesia and Perinatology (SOAP) [118], and the American College of Obstetricians and Gynecologists (ACOG) [125] recommend routine use of neuraxial regional techniques for cesarean sections. Workforce survey studies should that regional techniques are used in over 95% of all surgical deliveries in the United States and nearly all elective deliveries unless a contraindication exists [126, 127].

Anesthetic Technique

There are numerous benefits to using a neuraxial technique routinely for cesarean deliveries including avoiding maternal airway management risks, improved neonatal well-being [128], maternal recall of and participation in the birth, and the ability for involvement of family members. In addition to these benefits, the use of spinal, epidural, or combined spinal-epidural procedures also allows for neuraxial administration of opiates. There have been numerous studies comparing spinal anesthesia

versus epidural anesthesia. A systematic review [129] of these was performed which included ten such studies and measured outcomes which included adequacy of anesthesia, additional analgesic intervention, patient satisfaction, time from block to starting surgery, hypotension treatment, neonate outcomes, and treatment of side effects. The only advantage spinal offered over epidural was speed, showing an almost 8-minute benefit. However, there was also significantly more hypotension requiring treatment with spinal anesthetics. The ASA practice guidelines for obstetric anesthesia largely agree with these findings, although they cite that epidural vs spinal techniques have equivocal outcomes in all findings including umbilical pH, APGAR scores, and total operating room [118].

A combined spinal-epidural technique has become more commonplace over the last 20 years [127] and offers several benefits to either procedure performed in isolation. Procedurally this can be done by either a needle-through-needle technique or performing the spinal anesthetic and then separately performing the epidural anesthetic. There are fewer studies available comparing CSE to epidural or spinal anesthetics for cesarean section, but those that are available show block failure rates with CSE as low as 0.6% compared to 2–4% failure with spinal or epidural techniques alone [130]. Paradoxically, it was shown that compared to epidural anesthetics, the CSE anesthetics required more frequent additional local via the epidural. This "top-off" rate could be due to a bias toward smaller spinal local anesthetic doses or even due to the fact that the epidural is available, so it is used instead of alternative means such as IV analgesics that could cross the placenta and affect the newborn.

Neonatal outcomes appear to be equivocal when comparing CSE to spinal and epidural techniques as well [131]. The ASA practice guidelines agree with these findings that CSE was equivocal to epidural or spinal anesthetics alone [118]. The most robust comparison and assessment available of the three techniques is the 2009 Audit Project of the Royal College of Anesthetists [132] which surveyed over 700,000 neuraxial blocks. There were no obstetric-specific outcomes such as fetal acid-base status or APGAR scores assessed although it did stratify the assessment based on obstetric versus perioperative use. In obstetric patients, the incidence of permanent harm with CSE was 0–3.9 per 100,000 compared to 0–1.5 per 100,000 with spinal anesthetics and 0.6 per 100,000 with epidural anesthetics.

Neuraxial Opiates

Regardless of neuraxial technique, one of the largest benefits of neuraxial access to pain management of the obstetric patient is the ability to add opiate to the anesthetic. In light of the rising overuse and abuse of opiates among the American population, the ASA, SOAP, and ACOG [118, 125, 133] all have issued practice advisories which recommend inclusion of long-acting neuraxial opiates for women having cesarean sections. This is because after neuraxial administration of opiates, especially hydrophilic ones such as morphine, there is prolonged high-quality analgesia with minimal increased plasma concentrations or euphoric

Table 4.3 Neuraxial morphine dosing ranges for cesarean section

Neuraxial morphine dosing ranges for cesarean section		
	Spinal	Epidural
Ultra-low dose	≤50 μg	≤1 mg
Low dose	>50 and ≤150 μg	>1 and ≤3 mg
High dose	>150 μg	>3 mg

effects. Preservative-free morphine is the most commonly used and studied medication used for this purpose. Several systematic reviews [134, 135] comparing doses have been compiled and show a dose-dependent relationship between the dose of intrathecal morphine and the duration of analgesia it provides. Dosage can be divided into three main categories: ultra-low dose, low dose, and high dose. Ultra-low dose is classified as either ≤50 mcg intrathecal or ≤ 1 mg epidural. Low dose is defined as doses >50 and ≤ 150 mcg intrathecal or > 1 and ≤ 3 mg via epidural. High dose is defined as any dose greater than 150 mcg intrathecal or 3 mg epidural.

Table 4.3 summarizes intrathecal and epidural does ranges for morphine used for caesarian section.

The primary advantage of high-dose morphine is the duration of effect, as defined by duration until first request for postoperative analgesic, which was shown to last from 14 to 39 hours (median 27 hours) across various studies included in systematic reviews. Low-dose morphine on average lasted 4.5 hours less than high dose in these reviews. With either dosing strategy, the prolonged effect is due to morphine's highly hydrophilic nature. Instead of rapidly crossing into neural tissue or undergoing vascular resorption, it largely remains within the cerebrospinal fluid (CSF) for the duration of its effect [136]. Onset of action is largely dependent on diffusion into the dorsal horn of the spinal cord, where it can act on G-protein-linked opiate receptors. Because this process is reliant on diffusion through neural tissue, the hydrophilic nature of morphine leads to a prolonged time to onset of action up to 2 hours compared to only a few minutes for lipophilic drugs such as fentanyl and sufentanil [137].

A secondary advantage of intrathecal opiates is an improved quality of the anesthesia attained from the local anesthetic. Although the analgesic onset of intrathecal morphine may take up to 2 hours, systematic review shows that the rate of no supplemental intraoperative analgesic increases from 76% without morphine to 96% with both high- and low-dose intrathecal morphine [138]. Statistically this translates to a direct benefit in one out of every five surgical cases (NNT 4.9) which comparatively makes it a highly effective anesthetic adjunct.

However, choice of dose must also be balanced against frequency and severity of side effects. The most feared complications of neuraxial opiates are sedation and respiratory depression. The American Society for Regional Anesthesia (ASRA) with the ASA laid forth updated recommendations in 2016 for routine monitoring for patients who receive neuraxial opiates [139]. These recommendations are not targeted at the obstetrical population, but rather at a broader general surgical population. As their first recommendation, ASRA strongly recommends performing a

focused history and physical exam specifically looking for signs or symptoms of sleep apnea and high-risk co-existing disease such as diabetes or obesity and an assessment of current medication regimen for potential additive or synergistic combinations. Other high-risk patient factors also include chronic opiate use or abuse, concomitant use of other sedative or hypnotic medications, other respiratory or cardiac comorbidity, intraoperative respiratory events, or magnesium infusion for the treatment of preeclampsia.

Special attention should be paid to signs and symptoms of sleep apnea. As the American population becomes increasingly more obese, the prevalence of sleep apnea has risen too. In 2010, the prevalence of obstructive sleep apnea (OSA) was estimated to be 8.7% in American women between the ages of 30 and 49, of which 2.7% had severe OSA [140]. However, pregnancy independently increases the risk of OSA. Among all women, the rate of OSA rises to 8.4% during the first trimester and up to 19.7% in the third trimester [141]. In the general population, the STOPBANG screening tool has been validated to identify both patients who are at risk to have any degree of sleep apnea (score of ≥3) and at risk to have severe sleep apnea (score of ≥5) [142]. The STOPBANG questionnaire consists of eight questions which each contribute 1 point to the total score. The criteria are age >50, either treated or untreated hypertension, BMI of 35 or greater, neck circumference of 16 or greater in women or 17 or greater in men, male gender, loud snoring, daytime fatigue, and a third party having observed possible apnea episodes. However, it has been shown that the sensitivity and specificity of the STOPBANG tool is significantly reduced within the pregnant population. Within the pregnant population, the risk factors found to be most highly associated include pre-pregnancy BMI >30, 3rd trimester BMI >35, history of treated or untreated hypertension, and a history of falling asleep while talking to someone [141, 143]. If a patient is identified as at risk for sleep apnea, a sleep study should be performed and treatment initiated.

ASRA continues to further recommend that all patients who receive neuraxial opiate should be monitored for signs of respiratory depression [139]. With regard to hydrophilic opiates such as morphine, they state "(1) monitoring should be performed for a minimum of 24 h after administration and (2) monitoring should be performed at least once per hour for the first 12 h after administration, followed by monitoring at least once every 2 h for the next 12 h (i.e., from 12 to 24 h). The ASA members agree and the consultants strongly agree that after 24 h, the frequency of monitoring should be dictated by the patient's overall clinical condition and concurrent medications." For lipophilic medications such as fentanyl, these recommendations are reduced from a total of 24–2 hours of monitoring. With either type of drug, ASRA does recommend maintaining IV access for the duration of monitoring and having ready access to reversal agents and oxygen for immediate treatment should oversedation or respiratory depression develop.

In 2018 Sharawi et al. compiled an extensive systematic review looking for clinically significant respiratory depression after administration of morphine [144]. This review covered 75 studies including over 18,000 women who received neuraxial morphine or diamorphine for either scheduled or urgent cesarean section. Clinically significant respiratory depression (CSRD) was defined as any episode that required

oxygen therapy for bradypnea ≤8 breaths per minute or a pulse oximetry oxygen saturation ≤90%, pharmacologic therapy with respiratory stimulants or opioid antagonists, sedation requiring anything beyond verbal stimulation to rouse the patient, or airway intervention including basic maneuvers, adjuncts, or any invasive or noninvasive ventilation. Among the 18,452 study patients, there were only 11 cases of definite morphine-related CSRD and 5 cases of probable morphine-related CSRD. All events happened within the first 16 hours after administration. Only 3 of these 16 cases occurred using low-dose morphine as defined earlier in this chapter as ≤150 μg intrathecal or ≤3 mg epidural. Thus, at all dose ranges, the rate of CSRD was 0.0867% which was further reduced to 0.0163% in the setting of low-dose morphine. The same study also examined ASA Closed Claims Project data looking for any claims involving respiratory events in obstetrical patients following neuraxially administered morphine and found no claims filed.

Given the paucity of respiratory events in the obstetrical population who receive low-dose intrathecal or epidural morphine, there is some debate as to whether obstetrical patients without high-risk features warrant prolonged and close monitoring for a vanishingly rare complication [144]. However, without further clarification or guidance from professional societies, it is difficult to recommend deviating from the guidelines established by ASRA and the ASA.

A standing concern that should be held among any population receiving neuraxial hydrophilic opiates is that order writing for further doses of opiate within the first 24 hours should be limited to a single team with an understanding of the pharmacokinetics and dynamics of both the neuraxial opiate and the additional drug. Systems and workflows should be established so that a nurse always knows to whom to direct requests for additional pain medication. In addition, an evaluation of the patient's clinical status, including level of pain, opiate side effects, and expected continued effects of the medications already given must be completed prior to administration of additional opiate.

Fentanyl may also be via an epidural or intrathecal route. While morphine doses are approximately tenfold stronger from IV to epidural and again from epidural to intrathecal routes, fentanyl has a much less steep conversion ratio appearing to only increase in potency threefold from IV to epidural and from epidural to intrathecal. This is largely due to fentanyl's lipophilic nature, which helps it cross membranes and be much more rapidly absorbed and metabolized. It has been shown to significantly reduce the required dose of bupivacaine to achieve an adequate anesthetic for cesarean section [145] from 12 mg bupivacaine without additive to as little as 8 mg bupivacaine when mixed with 10 μg of fentanyl. Reducing the total bupivacaine dose is associated with less motor block, less hypotension, less vasopressor usage, and less intraoperative nausea and vomiting [146].

Addition of fentanyl to bupivacaine also speeds onset of block [147]. A major drawback to fentanyl compared to morphine is its much shorter duration of action. Time to first administration of analgesic after bupivacaine alone is about 2 hours. With additional of fentanyl, median time to first analgesic increases to 4 hours compared to 27 hours with morphine [138].

When considering the faster onset of block with fentanyl, prolonged analgesic action of morphine, and ability of both to improve the quality of anesthesia during

surgery, some physicians advocate for adding both opiates to the local anesthetic. Relatively few studies exist comparing the combination of local with morphine and fentanyl to local with a single opiate. The data that does exist is conflicting between studies, and the true risk/benefit ratio is not as clearly defined as it is for either drug in isolation compared to the mixture. Weigl et al. compared 60 patients in a double-blind randomized control trial comparing 100 μg of morphine to a mixture of 100 μg and 25 μg fentanyl. Fewer patients who received the mixture required additional intraoperative analgesia, had non-inferior 24-hour opioid consumption, but did have higher opiate consumption in the first 12 hours and saw more nausea and vomiting than morphine alone [148] In contrast, Thorton et al. found that the addition of 10 μg of fentanyl to 100 μg of morphine resulted in a trend toward faster onset of block with morphine alone achieving T6 block at 6.3 minutes compared to 5.05 minutes when combined with fentanyl. They found no significant contribution of the mixture over morphine without fentanyl but did find a statistically significant higher incidence of pruritus [149]. Finally, Carvalho et al. looked further at postoperative pain scores and opiate consumption and concluded that within the first 24 hours, postop pain scores were higher in women who received the combination than morphine alone. They postulated that fentanyl may "induce a subtle acute opioid tolerance of uncertain significance" [150]. Comparing the various data available, it appears mixing fentanyl with morphine results in an improved intraoperative block at the expense of slightly higher postoperative pain scores for the first 12 hours as well as higher rates of nuisance side effects, although more studies need to be done so meta-analysis can be performed on the topic.

In order to extend the benefits of high-quality analgesia from neuraxial morphine, liposomal morphine (extended-release epidural morphine, DepoDur) has been developed and studied for use in cesarean sections and abdominal surgery [151–153]. When delivered into the epidural space, the clinical effects can be appreciated upward of 48 hours. After initial FDA approval in 2004, the package insert has been twice revised. These revisions strengthened the warning on individualized dosing, clarified use only via the epidural route, and cautioned with timing the epidural administration to more than 30 minutes apart from any dose of epidural bupivacaine. When used for treatment of post-cesarean pain, the FDA approval is for administration only after the umbilical cord is clamped. Care should be taken to never confuse preservative-free morphine which is commonly used for intrathecal administration with this liposomal formulation. Case reporting of accidental intrathecal administration does exist and describes successful postoperative management using a low-dose titrated naloxone infusion which was discontinued when the patient first began reporting pain as well as scopolamine and ondansetron for side effect management [154]. In the ASA Task Force guidelines, the only guidance given is that monitoring should be extended to 48 hours instead of only 24 hours as with preservative-free morphine. Monitoring after 24 hours can be reduced from every 2 hours to every 4 hours [139].

In the patient who cannot receive morphine, an option for postoperative pain control is to provide a patient-controlled epidural analgesic with fentanyl. Doing so first requires the presence of an epidural. If the patient is scheduled for an elective

cesarean section, this would then dictate that the surgical anesthetic be achieved either via epidural or combined spinal-epidural technique [155, 156]. Various dosing strategies exist although typically the maximum dose per hour is kept at or below 120 μg to be equivalent to a single dose of 3 mg of epidural morphine. This can be balanced between continuous infusion and patient demand doses. The duration of action of epidural fentanyl is short enough that using an all demand dosing strategy has the limitation of requiring the patient to not sleep for several consecutive hours. One distinct disadvantage of this technique is it does require the patient to keep the epidural in place postoperatively. Most women after an uneventful cesarean delivery are encouraged to mobilize early, which is impeded by the presence of an extra pump to mobilize with the patient and an epidural site to be maintained covered with occlusive dressing and kept clean and dry. Patient satisfaction may be impaired by the inability to shower following delivery until removal of the epidural. Should this technique be employed, the ASA again recommends monitoring for the entire duration of the infusion. This monitoring should, at a minimum, be continuous for the first 20 minutes, then at least hourly for the first 12 hours, every 2 hours until 24 has passed, and then every 4 hours until the infusion is stopped [139].

Neuraxial Opiate Side Effect

Aside from the previously discussed risk of sedation and respiratory depression, intrathecal opiates may induce a handful of other side effects. Most common are pruritus, nausea and vomiting, and urinary retention. Rare side effects of neuraxial opiates may include bradycardia, sweating, delayed gastric emptying, constipation, headache, hiccups, hypothermia, or nystagmus [137].

Nausea

Nausea and vomiting during cesarean section are common, happening in as high as 42% of operations. Causation is multifactorial including spinal-/epidural-induced hypotension, manipulation of abdominal and pelvic viscera, administration of opiates, administration of uterotonic medications, and increased vagal activity [157].

Postoperative nausea is much less common and happens much more frequently after intrathecal morphine compared to intrathecal fentanyl. Nearly 1 in every 6 of those who receive intrathecal morphine experience postoperative nausea and/or vomiting compared to only 1 in 22 who receive IT fentanyl [138]. Morphine is thought to directly stimulate the chemotactic zone after rising in the cerebrospinal fluid. Intrathecal morphine may also sensitize the vestibular system, delay gastric emptying, and reduce overall gastrointestinal motility [138, 158].

Because the causative factors are varied, one's approach to treatment should focus on diagnosis of cause. Hypotension, either spinal anesthetic induced or from acute blood loss hypovolemia, should be ruled out first. Vagal overactivity often will also present with bradycardia and should also be immediately evaluated and treated with a chronotropic agent and/or vasopressor such as ephedrine. Phenylephrine should be avoided with bradycardia due to the reflexive tachycardia it reliable induces. For other causes, a combination therapy or prophylaxis regimen has been found to be most effective. Drugs often used may be a combination of any of ondansetron, dexamethasone, or metoclopramide [159].

Pruritus

Pruritus is the single most common side effect of intrathecal opiates and can be extremely uncomfortable for the patient to the point in rare cases of being unable to tolerate even clothing or linens resting on their skin. One of every 2.6 patients who receive intrathecal morphine for cesarean section will experience pruritus of some degree. Similarly, 1 in every 2.2 who receive intrathecal fentanyl will also develop itching [138]. For morphine, this effect is dose dependent and continues to rise in a linear manner with increasing dosage up to reported rates as high as 100% [160, 161]. Compared to other patients, parturients have higher rates of pruritus than other populations possible due to estrogens interacting with the opioid receptor [162]. The exact mechanism of action leading to this pruritus is not entirely clear, however. Postulated theories include opiate interaction with a cephalad central "itch center" within the spinal trigeminal nucleus, activation of 5-hydroxytryptamine 3 (5HT3) serotonin receptors, prostaglandin activation, interaction with the medullary dorsal horn, or neurotransmitter inhibition [160].

Treatment and prophylaxis against pruritus include several varied options. Nalbuphine, a mixed opiate agonist-antagonist, has been shown to be effective in reversing pruritus without reversing analgesic effect by antagonizing the mu opioid receptor and activating the kappa opioid receptor [163]. Nalbuphine has been shown to be effective at reducing the incidence of opiate-induced pruritus for both fentanyl and morphine delivered by either intrathecal or epidural routes in doses as low as 2–3 mg intravenously.

Ondansetron, a 5HT3 receptor antagonist widely used for treatment and prophylaxis against nausea, has also been shown to effectively reduce the incidence of intrathecal morphine-induced itching. However, it does not appear to have the same potency in reducing fentanyl-induced itching. Mirtazapine inhibits 5HT2 and 5HT3 receptors upstream as a a2-antagonist and can reduce intrathecal morphine-induced pruritus via a similar mechanism [164]. Gabapentin, which is a structural GABA analogue, has also been shown to have some efficacy at mitigating intrathecal morphine-induced pruritus similar to the efficacy of ondansetron and mirtazapine. The mechanism by which it achieves this is not clear [164].

Histamine release is a common causative factor of itching from intravenous morphine. Intrathecal and epidural administered morphine however do not cause the same histamine release thus limiting the efficacy of diphenhydramine in treating morphine induced pruritis when given via a neuraxial route [165, 166].

Urinary Retention

Urinary retention can present in as many as 20–40% of patients within the first 2 hours after intrathecal morphine and up to 10% of patients 24 hours after [167]. Urine output should be followed closely after receiving intrathecal morphine. Low or no output should prompt evaluation for incomplete bladder emptying or complete retention. Untreated retention can lead to the development of neurogenic bladder, so it is important to not allow bladder to become overdistended for prolonged period [137].

Regional Techniques

Wound Infiltration

The wound infiltration technique is performed by the surgeon just below the fascial layer while closing the wound. This can be done either with injection of local anesthetic alone or injection followed by placement of a multi-orifice catheter used to provide a continuous infusion of local anesthetic to the wound postoperatively. Catheter can be placed above the fascia but results in significantly inferior pain control [168]. Choice of local is typically ropivacaine or bupivacaine. Typical dosing of either ropivacaine or bupivacaine infusions is 2–3 mg/mL at a rate of 5 mL/hour. This technique has been shown repeatedly to result in lower postoperative opiate consumption [169].

Transversus Abdominis Plane (TAP) Block

The innervation that provides sensation to the skin and soft tissues that comprise that abdominal wall can be found coursing in the fascial plane superficial to the transversus abdominis muscle and deep to the internal oblique muscle. Depositing local anesthetic within this plane in the lateral abdominal wall immediately superior to the iliac crest results in a field block that anesthetizes many of the sensory nerves that supply the tissues involved in a Pfannenstiel incision when performed bilaterally. This block is often described as done using ultrasound guidance which allows in-plane guidance and identification of the three circumferential muscular layers and viscera. Ropivacaine or bupivacaine is often used dosing to 1.5 mg/kg per side,

for a total dose of 3 mg/kg up to a maximum of 300 mg. Use of a blunt tip needle allows for the clinician to appreciate a tactile "pop" as the needle passes through each fascial layer. It is recommended to maintain visualization of the needle tip and inject in a manner that hydro-dissects laterally the fascial plane just superior to the transversus abdominis [170]. TAP blocks have been shown to significantly reduce total postoperative opiate consumption and pain scores for the first 36 hours after surgery [170, 171]. This analgesic effect, however, has not been shown to outperform or even augment the pain relief achieved from intrathecal morphine [172]. TAP block and wound infiltration had no significant difference in outcome, pain relief, or side effects [173].

Post-cesarean Pain Management

Meta-analysis comparing opiates, non-opiates, and combination of opiate/non-opiates shows there is no ideal postoperative pain regimen after cesarean section. All strategies were similar in terms of need for further pain relief and presence of side effects, although opiates had the greatest amount of side effects [174]. Early oral intake should be encouraged which among its many benefits allows for use of oral medication as the mainstay of pain treatment and reserving intravenous options for breakthrough only. Postoperative pain should not be undertreated, however, as poor pain control delays ambulation, functional recovery, and maternal bonding [175]. In addition to synergistic effects with opiates, acetaminophen also has additive effects with NSAIDs. In patients who received intrathecal morphine, postoperative scheduled acetaminophen with a scheduled NSAID and PRN-only opiates provides an excellent and well-tolerated analgesic recovery for most women with minimal impact on breastfeeding [176]. ACOG has issued a committee opinion that directly addresses postpartum pain control, and they recommend neuraxial opiates at the time of cesarean birth followed by multimodal use of acetaminophen and NSAIDs with parenteral opiates reserved for severe breakthrough. In addition, ACOG does not endorse routine administration of gabapentin, which should only be considered for uncontrolled pain or patients with a history of chronic pain [177].

When the parturient intends on breastfeeding her infant, concerns are often raised regarding drug transfer into breastmilk. Ketorolac should be reserved for use only in the immediate first few days after delivery before the onset of copious milk production. After this point, the preferred NSAID of use is ibuprofen as it is well studied and shown to have minimal transference into breastmilk [133]. Opiates can be given to breastfeeding women, but should be done so with caution, specifically drugs containing codeine or tramadol. In 2017 the FDA issued a warning and modified labeling of all drugs containing codeine and tramadol with enhanced warnings against use with breastfeeding mothers. This is because some patients will rapidly metabolize those drugs to their active opiate

metabolites and thus will have much higher than typical serum levels and breastmilk levels of these active metabolites. ACOG recommends then that all postpartum mothers who are prescribed an opiate should be counseled regarding the risks and signs of maternal and newborn toxicity. In addition, mothers should also be counseled regarding limiting the use of opiates to as short a time as possible [133]. SOAP has issued a statement as well that encourages multimodal analgesia with minimal opiates which are reserved for breakthrough pain only and use of oral oxycodone or hydrocodone as the preferential first-line rescue agents [178].

Conclusion

Every woman has a unique experience during labor and delivery with most describing the pain as moderate to severe. There are unique analgesic challenges during labor, delivery, and recovery because concern must always be taken for maternal and neonatal well-being. A patient's satisfaction with their pain control has short- and long-term ramifications, and every effort should be made to educate parturients regarding effective and safe pain control methods. This allows the parturient control in the decision-making process.

Fortunately, there are many methods to provide safe and effective analgesia for labor and delivery. The process of labor and delivery is dynamic which may cause changes in pain control choices as the process progresses. Some parturients choose unmedicated childbirth methods, while others choose systemic or neuraxial techniques.

Neuraxial analgesia is the most effective form of analgesia for labor and delivery but may be contraindicated or not desired by patients. For those patients, other methods of pain control including opioids by IM, IV, and PCA routes, adjuvants such as hydroxyzine and promethazine, sedatives such as midazolam and ketamine, and inhaled nitrous oxide are commonly used. Pudendal and paracervical nerve blocks are also effective choices for these patients.

When cesarean section must be performed, there are many options including neuraxial opiates, wound infiltration, and regional nerve blocks that can provide high-quality analgesia during the initial stages of surgical recovery.

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Part II
Common Pain Conditions

Chapter 5
Migraine

Deborah I. Friedman and Shamin Masrour

Diagnosis

The official diagnostic criteria for all headache disorders are codified in the International Classification of Headache Disorders, 3rd edition (ICHD-3) [link here]. The most common type of migraine, previously termed "common" migraine, is migraine without aura which affects about 70–75% of individuals with migraine. It is a recurring headache of moderate to severe intensity that may be hemicranial or global, is often described as throbbing, and worsens with movement or routine physical activity. There is either associated photophobia and phonophobia or nausea and vomiting. Attacks last between 4 and 72 hours in adults, typically less than a day. The neurological exam, including ophthalmoscopy, is normal between episodes.

The migraine attack is divided into five phases which are not present in all individuals: prodrome, aura, headache, postdrome, and interictal period. The prodrome occurs up to 48 hours before the headache starts and is often not recognized. It is likely mediated by the hypothalamus, causing uncontrollable yawning, food cravings (which may be incorrectly ascribed to a trigger), mood changes (euphoria, depression, irritability), confusion, excessive thirst or urination, neck pain or stiffness, or fatigue. Some people begin to experience migraine-associated symptoms during the prodrome, such as heightened sensitivity to light, noise, cutaneous stimulation, or odors, as well as nausea or trouble concentrating.

D. I. Friedman
Department of Neurology and Neurotherapeutics, Department of Ophthalmology, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: Deborah.Friedman@UTSouthwestern.edu

S. Masrour (✉)
Department of Neurology and Neurotherapeutics, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: Shamin.masrour@UTSouthwestern.edu

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The aura is comprised of fully reversible neurologic symptoms and may precede, accompany, or, rarely, follow a migraine headache. Cortical spreading depression, beginning in the occipital cortex and spreading anteriorly and inferiorly, is the likely physiologic basis of aura. The most common aura manifestations are binocular visual disturbances, followed by somatosensory and language dysfunction (aphasia). Infrequently, motor weakness, brainstem symptoms, or monocular visual disturbances occur. Migraine with aura (previously termed "classic" migraine") is virtually pathognomonic of migraine. Each aura symptom lasts between 5 and 60 minutes. With the exception of homonymous hemianopia, symptoms develop gradually over several minutes or longer and occur in succession.

The headache typically builds in severity over minutes to hours, but rare individuals describe an abrupt onset at full intensity. It arises from the trigeminal nerve and its projections to central trigeminal structures, as well as the meningeal blood vessels which are innervated by V1 and the first three cervical roots. The character of the pain is classically throbbing, pulsating, or pounding, but there may be a component of stabbing, aching, pressure, or tightness. It may be unilateral or bilateral. It is associated with photophobia, phonophobia, osmophobia, difficulty concentrating, nausea (or anorexia), or vomiting. Worsening of the headache with movement or physical activity is a distinguishing feature of migraine among the primary headache disorders; most people prefer to lie down or remain still in a dark, quiet room during an attack. In some cases, nausea and vomiting are more distressing than the pain, and vomiting may hasten relief, especially in children.

Migraine in adolescence is similar to migraine in adults, but there are some notable differences in younger children [4]. Prior to puberty, boys and girls are equally affected. The pain of childhood migraine is often bilateral and may be of shorter duration than in adults, lasting only 2 hours in some cases. The associated symptoms are inferred by behavior when children are too young to verbalize their symptoms. For example, ceasing activities to lie down implies worsening with activity, avoiding screen time of television indicates sensitivity to light or noise, and refusing to eat suggests nausea. Asking children to draw their headache is useful in assessing their symptoms. Childhood variants of migraine include infantile colic, torticollis, attacks of unexplained vertigo, cyclic vomiting syndrome, and abdominal migraine (recurrent attacks of abdominal pain) [5, 6]. A history of childhood motion sickness is common among individuals with migraine [7].

Migraine is also categorized by the frequency of attacks. People with at least 15 days of headache of any intensity per month for at least 3 months, of which the headache on at least 8 days meets criteria for migraine, have chronic migraine. Episodic migraine, while not an official ICHD-3 diagnosis, refers to those with fewer than 15 days of headache per month.

Migraine tends to fluctuate with hormonal variations in females. It often starts around the time of menarche and improves after menopause. Many females experience migraines during ovulation or with menses, and menstrual migraines may be more severe than attacks at other times of the month [8, 9]. Migraine without aura generally improves during pregnancy beginning in the second trimester, but migraine with aura may worsen or occur only during pregnancy [10]. Migraines tend to increase in frequency in the perimenopausal period.

Certain medical conditions tend to occur more frequently in individuals with migraine than in the general population and awareness of these conditions often helps guide treatment. Anxiety and depression are considered "bidirectional" comorbidities, as patients with these conditions have a high prevalence of migraine than the general population [11]. Other co-existing psychiatric conditions with migraine include bipolar disorder, post-traumatic stress disorder, and obsessive-compulsive disorder [12]. Associated neurologic conditions are epilepsy, restless legs syndrome, essential tremor, and benign positional vertigo [13–15]. Common medical comorbidities include hypertension, Raynaud phenomenon, irritable bowel disease, fibromyalgia, and asthma [13]. Population studies indicate that migraine with aura increases the risk of ischemic heart disease, cervical arterial dissection, and stroke [13].

Lastly, people with migraine often experience more than one type of migraine or have other primary headache disorders, including tension-type headache, cluster headache, and primary stabbing headache.

The headache history is often complex. It is helpful to have an intake form to obtain the details. BonTriage is a web-based program that queries patients about various symptoms and formulates a narrative report to be used during their office visit [www.bontriage.com]. It is also important to inquire about the effect of migraine on one's life, even when not experiencing a migraine.

Pathophysiology

The numerous manifestations of migraine imply a complex pathophysiology involving the central and peripheral nervous system. There is likely a genetic predisposition to migraine and specific genetic mutations occur in hemiplegic migraine. Genomic analysis does not implicate any particular genetic locus for other forms of migraine which may have a polygenetic inheritance [16]. The migraine brain has a lower threshold for activation of the migraine process, often referred to as neuronal hyperexcitability. The posterior and lateral hypothalamus are the structural bases for the initiation of a migraine attack, implicated in the symptoms of the prodrome via their connections to the limbic system [17]. The locus coeruleus and dorsal raphe nucleus, involved in the noradrenergic and serotonergic systems respectively, modulate the intensity of sensory stimuli, cerebral blood flow, and nociception. Activation of these nuclei explains photophobia, phonophobia, osmophobia, and alterations in cerebral blood flow occurring during the prodrome [17, 18].

An early component of the migraine attack is cortical spreading depression, which appears to be the physiologic basis of aura but also occurs in individuals without aura. Cortical spreading depression CSD) is a wave of neuronal and glial cell depolarization with hyperperfusion followed by relative hypoperfusion. CSD originates in the occipital cortex and propagates anteriorly at a rate of 3 mm per minute. It is accompanied by increased extracellular potassium, glutamate release, and intracellular calcium influx. Although initially discovered in experimental animals, functional neuroimaging confirms its presence in humans with migraine [19]. The process of cortical spreading depression activates other regions in the trigeminovascular system.

The headache phase is mediated by peripheral trigeminal sensory afferents, primarily the ophthalmic nerve (V1), C2 and C3, and their central connections in the brainstem. The peripheral neurons converge on second-order neurons in the trigeminocervical complex [20] which, in turn, project to the brainstem, thalamus, hypothalamus, basal ganglia, and nociceptive centers in the cerebral cortex. Peripheral trigeminal sensory afferents innervate the dura, eye and periocular region, forehead, periosteum, and cervical regions.

The release of various neurotransmitters propagates signals to the central nervous system, including substance P, calcitonin gene-related peptide (GCRP), pituitary adenylate cyclase-activating peptide-38 (PACAP-38), glutamate, and nitric oxide, resulting in mast cell degranulation and cranial vessel dilation [21]. It is postulated that activated meningeal nociceptors become sensitized as a result of neurotransmitter release, leading to a lower threshold for a response and a heightened magnitude of the response. This phenomenon, known as peripheral sensitization, creates allodynia during a migraine attack, resulting in throbbing pain and worsening with Valsalva maneuvers. Central sensitization develops secondarily after about an hour of pain onset, affecting the second- and third-order trigeminal neurons and producing scalp tenderness, skin sensitivity, photophobia, and myalgias [17].

Patients with very frequent migraine may have persistent central sensitization in the interictal period manifested as continuous allodynia and a reduced threshold for additional attacks. This phenomenon may perpetuate the cycle of chronic migraine.

Examination

The diagnosis of migraine is based on the history and exclusion of a secondary cause of headache; the response to a "migraine-specific" therapy is not a diagnostic test. Thus, in addition to a general neurologic exam to look for focal neurologic deficits, ophthalmoscopy is particularly important. Palpation over the sinuses and pericranial nerves, examination for neck tenderness and range of motion, and assessment of jaw movement are also included.

Diagnostic Testing

There is no need for brain neuroimaging in patients with a typical history and normal neurological exam. Baseline thyroid function tests and vitamin D levels may be useful in some patients. Other evaluations, such as magnetic resonance imaging, lumbar puncture, or testing for giant cell arteritis, may be needed if there are "red flags." Table 5.1 lists red flags for secondary headaches. Non-contrast computed tomography (CT) is useful to exclude stroke or intracranial hemorrhage in patients with an acute, severe headache in the emergency setting but is of very low yield for the evaluation of recurrent headache in the outpatient setting.

Table 5.1 Red flags for secondary headache

Thunderclap headache
New-onset headache >50 years of age
Systemic symptoms (fever, weight loss)
Papilledema
Worsened with Valsalva maneuvers
Change in existing headache pattern
Abnormal neurological exam
Postural aggravation
New headache in pregnancy

Treatment

The treatment of migraine begins with informing the patient of their diagnosis. Treatment incorporates a combination of education, a headache calendar, lifestyle modifications, and acute and preventive therapies.

Lifestyle: Migraine loves change and tends to occur with variations in the daily routine. Sleeping too much or too little, missing meals, dehydration, and major stressful events can all precipitate migraine. Thus, keeping a regular sleep schedule every day and eating regular meals may be of considerable benefit. While it is impossible to avoid stress, techniques such as regular exercise, mindfulness meditation, yoga, stress management, and cognitive-behavioral therapy help to moderate the response to stress and are often helpful in migraine management.

Triggers: Worldwide, people with migraine ascribe their attacks to various environmental and dietary triggers, many of which are unsubstantiated in carefully done studies. Dietary triggers are perhaps the most controversial, but if a patient can identify a pattern, avoiding the trigger may be helpful. Dietary triggers include alcohol (particularly beer and wine), aged cheeses, aged and processed meats, overripe fruits, smoked and cured foods, monosodium glutamate, soy, caffeine, artificial flavorings, and sweeteners, among others. Chocolate, often implicated as a trigger, may be a manifestation of the prodromal food craving in some individuals. A diet and symptom log helps identify potential food triggers. Some patients benefit from avoiding dairy products. A ketogenic diet may be helpful but should be done under medical supervision [22]. Removing gluten from the diet is of questionable benefit in the absence of celiac disease. Overall, a healthy Mediterranean diet is recommended.

Odors, such as cigarette smoke, perfumes, other scented products (e.g., cleaning products, lotions, soaps, dryer sheets, laundry detergent), and volatile substances (e.g., gasoline, fumes), are frequent culprits, particularly in the workplace setting. Other environmental triggers include bright light, fluorescent lighting, and loud noise. Weather patterns are implicated, such as impending storms, changes in barometric pressure, heat, and high winds; of these, heat and high winds are the best substantiated [23, 24].

Symptomatic (acute) treatment is used during a migraine attack. Inadequate acute therapy is a risk factor for progression from episodic to chronic migraine [25]. Non-pharmacologic therapies include rest, sleep, ice, heat, and massage (unless the patient is allodynic) and aromatherapy (if odors are not a trigger) [26]. Symptomatic

medications include migraine-specific therapies, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), combination analgesics, and other analgesics and antiemetics. These medications are summarized in Table 5.2 [27]. Devices, such as supraorbital nerve stimulation, transcranial magnetic stimulation, and noninvasive vagus nerve stimulation, have shown efficacy in randomized studies [28, 29]. Clinical trials of lasmiditan, a 5-HT1F receptor agonist, showed efficacy for acute migraine treatment compared to placebo without vasoconstrictive actions [30].

Table 5.2 Medications for acute migraine treatment (Marmura)

Medication	American Headache Society evidence level for efficacy[a]
Acetaminophen 1000 mg	A
Nonsteroidal anti-inflammatory drugs	
Acetylsalicylic acid 500 mg	A
Diclofenac 50 mg, 100 mg	A
Ibuprofen 200 mg, 400 mg	A
Naproxen 500 mg, 550 mg	A
Triptans	
Almotriptan 12.5 mg	A
Eletriptan 20 mg, 40 mg	A
Frovatriptan 2.5 mg	A
Naratriptan 1 mg, 2.5 mg	A
Rizatriptan 5 mg, 10 mg	A
Sumatriptan oral 25 mg, 50 mg, 100 mg	A
Sumatriptan nasal 10 mg, 20 mg	A
Sumatriptan subcutaneous 4 mg, 6 mg	A
Zolmitriptan oral 2.5 mg, 5 mg	A
Zolmitriptan subcutaneous 2.5, 5 mg	A
Ergots	
Dihydroergotamine nasal 2 mg	A
Dihydroergotamine subcutaneous 1 mg	B
Dihydroergotamine IV, IM 1 mg	B
Combinations	
Sumatriptan/naproxen 85 mg/500 mg	A
Acetaminophen/acetylsalicylic acid/caffeine 500 mg/500 mg/130 mg	A
Butalbital/acetaminophen/caffeine 50 mg/325 mg/40 mg	C
Opioids	
Butorphanol nasal 1 mg	A
Ergots	
Ergotamine 1–2 mg	C

IM intramuscular, *IV* intravenous

[a]Level A = medications are established as effective for acute migraine treatment based on available evidence; level B = medications are probably effective based on available evidence; level C = medications are possibly effective based on available evidence

The selection of acute therapy incorporates a number of factors such as other medical conditions, pregnancy status, concomitant medications, and the characteristics of the migraine episode. Gastric stasis during a migraine attack may impede the absorption of oral medications, decreasing their benefit [31]. Additionally, peripheral and central sensitization influence the effectiveness of treatment; administration early in the migraine process is associated with improved benefit for most acute medications [32]. A non-oral route of administration is preferred for patients who experience nocturnal awakening from migraine, migraines that are already present upon awakening, migraine pain that escalates rapidly to peak intensity, and migraines associated with pronounced nausea or vomiting [32]. The nausea and vomiting associated with migraine is sometimes the most disabling part of the attack and should be addressed. Additionally, selection of a particular treatment considers its times to onset and the duration of action. A medication with a long half-life may lessen the likelihood of recurrence after initial relief.

Another important consideration is the frequency of acute medication usage. Preventive treatment is recommended for individuals requiring symptomatic therapy more than 2 or 3 days weekly to reduce their migraine burden and the development of medication overuse ("rebound") headache (MOH) [33, 34]. Acetaminophen, triptans, opioids, caffeine, butalbital, and possibly short-acting NSAIDs are implicated in producing MOH [35]. Overuse of such medications may increase the frequency of migraine attacks, hasten the development of chronic migraine, and render the condition more refractory to treatment [35]. The physiologic basis of MOH may result from latent and persistent trigeminal sensitization that promotes enhanced susceptibility to subthreshold triggers mediated through descending pain-modulatory circuits [36].

Preventive treatment is considered when individuals have at least 4 migraine days monthly of moderate to severe intensity; when migraines of any frequency are severe enough to impact their ability to function, such as migraine with brainstem aura or hemiplegic migraine; and if a patient prefers it. Preventive treatment options range from "natural" products to agents targeted to affect the migraine pathobiology and are elaborated upon in Table 5.3. Natural treatments with the highest levels of evidence include vitamin B2 (riboflavin), magnesium oxide, and coenzyme Q10. Non-specific preventive treatment incorporates antidepressants (i.e., tricyclics, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors), anticonvulsants (e.g., topiramate, sodium valproate), anti-hypertensive agents (non-selective beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers for specific migraine types), and therapies targeting calcitonin-gene-related peptide [37, 38]. Long-acting triptans, such as frovatriptan and naratriptan, are utilized for the short-term prevention of menstrual migraine, and onabotulinumtoxinA has a high level of evidence for the prevention of chronic migraine [39–41]. Daily long-acting NSAID use is effective in some patients but carries risks of medication overuse headache, GI and renal complications, and cardiovascular disease [42]. Opioids and butalbital are not generally recommended as they have limited efficacy data, can be addictive, and are a well-recognized cause of MOH.

Table 5.3 Medications and nutraceuticals for migraine prevention (Holland, Silberstein, Simpson)

Medication	American Academy of Neurology evidence level for efficacy[a]
Metoprolol 100–200 mg	A
Propranolol 80–240 mg	A
Topiramate 50–200 mg	A
Timolol 20–60 mg	A
Nadolol 20–160 mg	B
Atenolol 50–200 mg	B
Amitriptyline 10–200 mg	B
Divalproex sodium/sodium valproate 500–2000 mg	A
Venlafaxine 75–225 mg	B
Gabapentin 600–3600 mg	U
Candesartan 16–32 mg	C
Lisinopril 10–40 mg	C
Verapamil 120–480 mg	U
OnabotulinumtoxinA 155 units every 12 weeks	A
Erenumab 70 or 140 mg each month	N/A
Fremanezumab 225 mg each month or 675 mg every 3 months	N/A
Galcanezumab 240 mg once and 120 mg each month	N/A
Nutraceuticals	*American Academy of Neurology evidence level for efficacy*
Coenzyme Q10 300 mg	C
Magnesium citrate 400–600 mg	B
Riboflavin 400 mg	B
Feverfew 50–300 mg	B

N/A not applicable

[a]Level A = medications are established as effective for preventive migraine treatment based on available evidence; level B = medications are probably effective based on available evidence; level C = medications are possibly effective based on available evidence; U = inadequate or conflicting data to support or refute medication efficacy

Similarly to acute treatment, the selection of a preventive agent takes into account many factors, including other medical conditions, potential drug interactions, the type of migraine (migraine with brainstem aura, retinal migraine, and hemiplegic migraine may improve with agents that have relatively low levels of medical evidence for the treatment of migraine with typical aura), affordability, and both desired and undesired side effects of a given medication. Polytherapy using medications from different classes may be helpful although there is a paucity of clinical trials assessing combination treatment. Many patients benefit from these medications although the side effects of treatments may be substantial, requiring discontinuation. There are no specific guidelines regarding the cessation of effective preventive therapy; if the patient desires to reduce their medication burden, it is considered after at least 6 months of excellent migraine control with gradually decreasing dosages.

Procedures and Devices Greater occipital nerve blockade using local anesthesia showed benefit for treatment of migraine in the emergency department setting [43, 44]. Despite anecdotal experience to the contrary, there is a paucity of double-blind, placebo-controlled evidence to support the use of greater occipital nerve blocks for migraine prevention [45] which has resulted in lack of coverage by many third-party payers. Other peripheral nerve blocks (supraorbital, supratrochlear, auriculotemporal, lesser occipital, zygomaticotemporal) have utility in the outpatient setting, but their use is also limited by cost and coverage. Transnasal sphenopalatine ganglion blockade has been shown to be effective for acute migraine treatment but lacks robust evidence of efficacy for use as a migraine preventive [46, 47].

Neurostimulation devices are beneficial for both the acute and preventive treatment of migraine. Supraorbital nerve stimulation and transcranial magnetic stimulation are FDA-cleared for acute and preventive migraine treatment. Noninvasive vagus nerve stimulation is FDA-cleared for acute migraine treatment, and trials for migraine prevention are underway in the United States.

Any evidence for cervical procedures? Although there have been a few reports indicating benefit of paraspinal cervical nerve blocks for acute treatment of headache [48, 49], there are no double-blind, placebo-controlled studies to support its use for migraine treatment.

Any evidence for implanted neurostimulators? A few published studies have shown efficacy of implantable occipital nerve stimulation for preventive treatment, and it may have a role in medically intractable chronic migraine [50–52].

Address Co-Existing Conditions Evaluation and treatment for co-existing psychiatric conditions, sleep disorders, and other medical conditions are important aspects of migraine management. Validated questionnaires for anxiety, depression, posttraumatic stress disorder, and sleep apnea can be easily incorporated into clinical practice to identify patients at high risk, with appropriate referrals for an integrated approach to care.

Summary: Migraine is a common and disabling condition that is highly rewarding to treat. Targeted treatments and devices have expanded the therapeutic options for previously refractory patients. A treatment plan incorporating lifestyle management with effective acute treatments is often adequate to manage patients with relatively infrequent migraine. Patients with frequent or chronic migraine will also require preventive therapy and a multi-disciplinary approach to address co-existing conditions that may be contributing to their overall well-being.

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Chapter 6
Painful Medical Diseases

Robert S. Ackerman, Frederick Li, Tom Mario Davis, and Nathaniel Loo

Introduction

Many diseases and syndromes are associated with pain that is only partially responsive to the best available treatment. Thirty percent reduction in pain severity is the extent of analgesia achieved for many of these conditions, and there is limited data to guide therapy beyond standard analgesics. Almost any medical disease has the potential to cause pain, so the extent of this chapter will be to focus on studies of treatment modalities that may also be applied to other diseases not covered in this book.

Opioids are frequently necessary for breakthrough pain and rescue doses. However, the laws, rules, and guidelines surrounding opioid prescribing are rapidly becoming more restrictive. Prescribers must stay current and comply with the documentation requirements for opioid prescribing within their jurisdiction of practice, even for acute pain.

2018 Arizona opioid prescribing guidelines address the evaluation of new patients who are seeking to transfer their care and who are taking opioids prescribed by a different provider. The guidelines recommend that medical providers do not prescribe opioids on the first visit, but always perform drug testing and review electronic prescription records [1]. Also, opioid tapering and managing patients with substance use disorder is addressed with specific information.

The Department of Health and Human Services is developing a new report on pain management and best practices [2]. This chapter will focus on treatment options for painful conditions that often are poorly responsive to initial treatment.

R. S. Ackerman · F. Li · T. M. Davis · N. Loo (✉)
Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: Nathaniel.Loo@UTSouthwestern.edu

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Blood Disorders

Sickle Cell Disease (SCD)

Recurrent, highly variable, and severe pain requiring hospitalization are the hallmarks of vaso-occlusive crisis. Although the basic mechanism is simple, the precise details of the vaso-occlusion are poorly understood, involving complex interactions between red cells, endothelium, white cells, and platelets. Acute pain frequently occurs spontaneously, but may be precipitated by infections, decreased body temperature, dehydration, or stress. Acute pain in SCD is described as throbbing, sharp, or gnawing, and patients can usually recognize whether or not it is typical of their SCD. When the pain is not typical, it is important to distinguish other causes of the pain. Distinguishing between acute and chronic pain is critical to pain control in this patient population. Ideally the choice of drug should be influenced by an individual's analgesic history. Often patients will be seen for the first time in a particular hospital and an empirical approach is necessary.

The World Health Organization analgesic ladder is used for pain management in patients with sickle cell disease. The ladder, in its simplicity, states that acetaminophen and NSAIDs, with or without adjuvant non-opioid analgesics, are used initially for mild pain. Opioids are added for moderate pain, and higher doses of opioids are used for severe pain.

Acetaminophen and NSAIDs

Multimodal therapy is important in treating patients with difficult-to-control acute and chronic pain. Intravenous acetaminophen was shown to be effective in treating vaso-occlusive crisis pain in pediatrics in a retrospective study. Patients were divided into two groups, one with opioids and another with combination of opioids and acetaminophen. With a total of 46 patients, acetaminophen decreased pain on the visual analog scale by 2.3 out of 10 points. There was also a reduction in morphine equivalent dosing by −0.5 mg/kg and adverse effects from opioids [3].

In the case of NSAIDs, studies have been mixed in terms of results of pain relief and opioid reduction during vaso-occlusive crises, with some studies showing benefit and others showing no benefit. In one study with 21 patients admitted for vaso-occlusive crisis, a continuous infusion of ketorolac reduced total meperidine requirements and shortened hospital stay compared to placebo [4].

Another randomized study with piroxicam and aspirin in 58 patients showed pain relief within 24 hours in patients on piroxicam, without side effects or changes in liver function tests [5]. However, another study with 29 pediatric patients showed no difference between ketorolac and placebo [6, 7]. Ketoprofen, a nonselective cyclooxygenase inhibitor, was not helpful in one double-blind, randomized, placebo-controlled trial with doses of 300 mg/day for 5 days. The authors note that although there were no side effects, there was no significant difference in morphine consumption and pain reduction in 66 patients with vaso-occlusive crises [8].

Overall, for moderate and severe pain, NSAIDs could be considered as an adjunct for pain control, especially if patients are requiring large doses of opioids and hospitalization. On the other hand, NSAIDs should be avoided in patients with contraindications such as peptic ulcer disease, chronic kidney disease, NSAID allergy, asthma, or gastrointestinal bleeding [9].

Other Treatment Modalities

In addition to the WHO analgesic ladder, other options for pain control have been explored. A newer study in a multicenter, randomized, placebo-controlled, double-blind phase III trial is focusing on reducing oxidative stress contributing to sickle cell pain. The amino acid, L-glutamine, has been reported to be effective in reducing the number of pain crises and number of hospitalizations in both children and adults by increasing the amount of reduced nicotinamide adenine dinucleotides [10].

Complementary pain therapies such as relaxation training, cognitive behavioral therapy (CBT), yoga, and music therapy are also helpful non-pharmacologic treatments. A randomized controlled pilot study concluded that CBT appears to be immediately effective for the management of SCD pain in terms of reducing psychological distress pain as well as improving coping. The researchers suggest that CBT should be offered on a 6-month basis for maximum effectiveness [11].

CBT is able to incorporate treatment of multiple components besides the physical aspect of pain, including psychological, social, and behavioral aspects of daily life. CBT reduces stress and improves confidence, which leads to a more effective treatment of chronic pain. In addition, yoga was compared to an attention control in 73 pediatric patients with vaso-occlusive crisis, and it was found that children randomized to yoga showed a significant reduction in pain but no difference in anxiety, length of hospitalization, or opioid use [12–14].

Since SCD may also have a neuropathic element, it would be helpful to further study whether neuropathic adjuvants may be helpful in treatment of SCD pain. One trial randomized 22 patients with pregabalin versus placebo over 3 months. It looked at average scores of pain and composite pain index. There were no significant initial differences between the groups, but there was a decrease in pain as well as an increase in mean quality of life scores over time in the pregabalin group. The study was limited by small sample size and encouraged further studies for pregabalin in SCD [15].

Opioids

With severe pain management, opioids have been one of the main treatment modalities. In one trial, continuous intravenous morphine was more effective than intermittent morphine for pain relief. Average opioid dose was similar in both groups, but duration of severe pain was shortened in the continuous infusion group by approximately 1 day [16].

Unfortunately, continuous opioid infusions and long-acting opioids are also associated with more respiratory depression, so caution and vigilance would be essential in these cases. Some centers have established specialized emergency room areas to manage patients with hydration and analgesics to improve pain control and reduce hospitalizations.

Finally, after treatment of acute crises, it is important for long-term management, including follow-up treatment with hydroxyurea and L-glutamine as well as education about avoiding dehydration and other triggers of vaso-occlusive crisis.

Summary: The WHO analgesic ladder is the suggested approach to managing pain in vaso-occlusive crisis. In addition, other therapies including L-glutamine and complementary therapies may be helpful as well. It is important, however, to discern the cause of the vaso-occlusive crisis in order to treat the inciting event and to establish follow-up for long-term management.

Hemophilia

Joint injury from intra-articular hemorrhage in the patient with hemophilia results in acute pain that is typically treated with mild analgesics, rest, ice, compression, and elevation. For more severe pain, opioids may be necessary to provide adequate relief to aid restoration of function. After years of repeated injury of a joint and exposure to the inflammatory and oxidant effects of hemoglobin, a complex hemophilic arthropathy may ensue resulting in further chronic pain and specialist care. A discussion of factor replacement is beyond the scope of this chapter, but the patient's hematologist should be involved early in the course of an episode to coordinate care and minimize bleeding.

Guidelines for replacement therapy emphasize early recognition of factor replacement indications [17]:

1. Suspected bleeding into a joint or muscle
2. Any significant injury to the head, neck, mouth, or eyes or evidence of bleeding in these areas
3. Any new or unusual headache, particularly one following trauma
4. Severe pain or swelling at any site
5. All open wounds requiring surgical closure, wound adhesive, or Steri-Strips
6. History of an accident or trauma that might result in internal bleeding
7. Any invasive procedure or surgery
8. Heavy or persistent bleeding from any site
9. Gastrointestinal bleeding
10. Acute fractures, dislocations, and sprains

Pain, disability, and reduced quality of life are the long-term effects burdening the patient with hemophilic arthropathy. Patients with hemophilia and hemophilic arthropathy experience substantially more disability and morbidity than the general population. A survey in the United Kingdom of 68 patients (mean age, 41 years)

with severe hemophilia A or B found that more frequent pain correlated with negative thoughts about pain (e.g., anger, fear, isolation-seeking behavior, and anticipating catastrophes) and increased concern about using pain medication. Pain and the associated psychological aspects are an important part of the lives of individuals with hemophilia; thus, treating both is crucial to the complete treatment for this disease state [18].

Complementary or alternative medicine continues to be a mainstay for treatment in patients with hemophilia. RICE, acronym for rest, ice, compression, and elevation, is arguably the most well-known and deployed method of pain management. RICE is performed as follows [19]:

1. Rest
   Rest affected area.
   Avoid weight-bearing activities.
   Use splints and crutches, if necessary.
2. Ice
   It produces superficial vasoconstriction leading to pain reduction and reduced metabolic rate. With this physiologic response, it creates a local anesthesia secondary to a reduction in rate of conduction of sensory nerves.
   Change in local circulation.
   Apply ice for no longer than 20 min at a time, four to eight times per day.
   Use crushed ice, a cold pack, or frozen bags of peas or corn.
3. Compression
   It prevents or reduces swelling.
   Use elastic wrap or compression bandage (not wrapped too tightly).
   Wrapped area should not hurt or throb from the bandage.
4. Elevation
   Elevate the extremity as often as possible. Elevate the injury above the level of the heart with pillows, etc. This action reduces swelling in the effected joint.

A step approach to pharmacological treatment has been used to manage acute pain from bleeding [20, 21].

1. Acetaminophen or NSAID
   Acetaminophen: up to 650 mg/dose and 3250 mg/day
2. COX-2 inhibitor celecoxib: 100–200 mg once or twice daily
3. Acetaminophen +codeine or acetaminophen +tramadol 10–20 mg up to six times daily or 50–100 mg three to four times daily
4. Morphine or equivalent slow-release formulation: 20 mg twice daily allow rescue dose of rapid release 10 mg, four times daily. Increase slow-release dose if rapid release is used >4 times daily.

Aspirin is contraindicated for patients with hemophilia secondary to the antiplatelet effect of aspirin. Nonselective NSAIDs are used for chronic pain but not during an acute bleeding episode for risk of worsening the bleed. Selective COX inhibitors such as rofecoxib and celecoxib have been used to treat young patients with synovitis and joint pain with hemophilia. A retrospective study looked at 12

hemophilia A and B patients treated with celecoxib for chronic synovitis and joint pain, and results suggested that it was safe and effective for joint pain [22]. Overall, however, topical NSAIDs may be safer given the decreased potential for systemic absorption and side effects.

Summary: Acetaminophen, opioid, and non-pharmacologic treatments are used for acute bleeding episodes. Celecoxib has been used outside of acute bleeding episodes, but topical NSAIDs may also be preferable for chronic joint pain.

Multiple Sclerosis

Multiple sclerosis (MS) is a progressive inflammatory disease of the central nervous system (CNS) caused by axonal demyelination. Thought to be autoimmune in origin, MS results in dysfunction of the CNS, causing a range of symptoms including spasticity, spasms, fatigue, bladder dysfunction, and pain. Central neuropathic pain is a common symptom in MS. This type of pain has been difficult to control with current modalities of gabapentinoids, antidepressants, and carbamazepine.

With the growing legalization of marijuana and commercial spread of cannabinoids, this is a growing area of research for central neuropathic pain. A preparation of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) is approved in Canada and several European countries for spasticity in patients with MS. Cannabinoids have been shown to have therapeutic effects in animal models via interactions with specific cannabinoid receptors. These studies suggest there is potential in cannabinoid agonists at various receptors for inflammatory and neuropathic pain [23].

However, findings with humans have been mixed. In one study, a meta-analysis of THC/CBD spray, dronabinol (synthetic THC), and CBD in neuropathic and MS-related pain revealed statistically significant neuropathic pain relief in six articles and one randomized controlled trial compared to placebo [24]. However, another study with a phase III placebo control with 339 patients showed that a large portion of patients did respond with reduction in pain after THC/CBD spray as well as the placebo group. Therefore results were inconclusive and thus show the need for further studies to elucidate future treatment possibilities with THC/CBD [25].

In another study, nabilone is an oral synthetic cannabinoid that is usually used to help with cachexia and treat nausea and vomiting. This study involved evaluating pain scores of 15 relapsing-remitting MS patients already on high doses of gabapentin (>1800 mg/day) after the addition of nabilone versus placebo. Evaluation of visual analog scale, pain intensity, and daily activities showed that nabilone may be an effective adjunct to gabapentin for extremely difficult-to-control neuropathic pain [26].

Overall, THC and cannabinoids are promising modalities to the neuropathic pain treatment for MS. However, with mixed studies, more research is needed. While evidence shows that cannabinoids are effective for MS pain, federal law in the United States only authorized cannabidiol for Lennox-Gastaut syndrome and Dravet

syndrome, two rare pediatric seizure disorders. The drug was reclassified by DEA from schedule I to schedule V for this indication only.

Other medications with neuropathic components have been effective, including duloxetine, levetiracetam, TENS units, and nortriptyline. In one study with 239 patients, duloxetine 60 mg daily versus placebo had greater mean improvement in analgesia 6 weeks after initiation of therapy, but did have increased side effects such as decreased appetite. Another smaller study looked at levetiracetam versus placebo in 20 patients over 3 months and found a significant difference in pain reduction as well as quality of life. It suggests that larger studies are needed to confirm the role of levetiracetam in MS neuropathic pain [27–29].

Summary: While cannabinoids are efficacious, duloxetine and levetiracetam may be effective first-line agents for MS pain. Trigeminal pain has been traditionally been treated with carbamazepine. Baclofen has been used for muscle spasms. Gabapentin has been used for lancinating pain.

Osteoporotic Compression Fractures

Osteoporosis is the most common metabolic disease of the elderly population. Vertebral collapse commonly occurs with this population given the increased likelihood of falls and trauma in combination with decreased bone density. Pain resulting from the compression fractures often requires multiple treatment approaches. Bed rest, as well as medications, helps to control pain initially, and eventually steps to improve mobilization can be taken. However, in the elderly population, medications and conservative treatments that do not interfere with balance or sedation are paramount to deliver effective treatment.

A recent review and meta-analysis of 13 trials found that calcitonin, beginning 1 week after initial treatment, reduces severity of acute back pain associated with recent osteoporotic vertebral compression fractures [30]. Calcitonin exhibits analgesic properties in acute fractures without the unpleasant side effects associated with narcotics. However, the evidence to support its use in chronic fractures is lacking.

Conservative approach of bracing and physical therapy are effective treatments. These measures can reduce pain and increase mobility, which results in improved quality of life and daily activities. More interventional measures to treat vertebral compression fractures such as vertebroplasty (VP) and kyphoplasty (KP) are currently widespread and provide quick pain relief. However, their role for pain management versus conservative medical management is still controversial. A systematic review of VP/KP studies found that VP has superior pain control within the first 2 weeks after intervention compared to medical management [31]. Larger randomized trials are still needed to confirm this.

Current literature shows that for good outcomes, vertebral body augmentation should be performed within 3 months of fracture, within a few days of traumatic fracture to promote good restoration of vertebral height, and with a 1-month minimum wait time after fractures due to natural history [32].

Summary: A consultation with a vertebroplasty expert should be obtained early after a fracture in case a vertebroplasty is needed after less than 6 weeks of conservative management. Calcitonin may also be considered for acute fractures in patients that may not tolerate other medications.

Shingles/Herpes Zoster

Vaccine

Shingrix reduces the incidence of shingles dramatically. A phase III randomized trial of greater than 15,000 participants who were assigned to the HZ/su vaccine subgroup or placebo demonstrated significant reduction in the risk of herpes zoster acquisition. The overall vaccine efficacy was 97.2%, with an incidence rate of 0.3 per 1000 person-years compared to 9.1 in the placebo group. Vaccine efficacy was found to be similar among all age groups [33].

Post-herpetic neuralgia is reduced by similar orders of magnitude.

Antivirals

Oral famciclovir 500 mg three times daily or oral acyclovir 800 mg five times daily for 7 days is similarly effective at shortening the duration of shingles and reducing symptoms of ophthalmic zoster. Both medications were well tolerated [34].

Steroids

Oral and local injections of steroids have been used. For oral steroid, the treatment is prednisone 60 mg/d for the first 7 days, 30 mg/d for days 8–14, and 15 mg/d for days 15–21. Combined with acyclovir, steroids shorten the duration of herpes zoster. In a randomized study, 208 immunocompetent patients with newly diagnosed localized herpes zoster were randomized to four groups, with acyclovir and with prednisone, with one and not the other, or without both medications. Patients in the acyclovir plus prednisone group had accelerated time to crusting and healing, time to cessation of neuritis, sleep and activity improvements, as well as sooner discontinuation of analgesics [35].

Intralesional injections of local anesthetic and steroid are effective. Ninety-three patients with thoracic herpes zoster pain were randomized to receive standard treatment with antiviral therapy and oral analgesics or standard treatment plus intracutaneous injection of local anesthetics and steroid. 15 ml 0.25% ropivacaine with 40 mg methylprednisolone is used [36]. The treatment group had significantly lower visual analog pain scores and decreased zoster-associated pain at 1, 3, and 6 months

post-therapy initiation. Quality of life was also found to be improved in the treatment group. The dense intracutaneous injections may have increased intraneural blood flow and led to vasodilatation of the affected dermatomes, accelerating the skin healing process [36].

Interlaminar epidural steroid injections relieve pain from shingles but do not reduce post-herpetic neuralgia. A study of 558 patients randomly assigned to receive standard therapy or antivirals and analgesics or standard therapy plus an epidural injection of 80 mg methylprednisolone and 10 mg bupivacaine demonstrated improved pain symptoms in the epidural group at 1 month after treatment initiation, but no significant benefits at 3- and 6-month follow-up [37]. The benefits of the epidural injection were found to be modest. These are attributed to the steroid inhibition of inflammation and the related neural ischemia in addition to sympathetic blockade and altered sensitization from the local anesthetics [37].

A comparison of interlaminar and transforaminal steroid injections showed no difference. A randomized trial of 40 patients with shingles who were assigned to receive epidural steroid injections via transforaminal or interlaminar approaches showed overall improvement in visual analog scores at 1- and 3-month follow-up, but no major difference between the groups. In addition, the occurrence of post-herpetic neuralgia was roughly equivalent. The transforaminal group was hypothesized to be more effective as it would enable injection of steroids closer to the dorsal root ganglion, but this was not observed in the study [38].

Amitriptyline

During shingles, 25 mg of amitriptyline daily reduces the prevalence of post-herpetic neuralgia by greater than 50% at 6 months. Administering this analgesic pre-emptively with an antiviral agent may have the best effects [39].

Post-herpetic Neuralgia

Gabapentin, pregabalin, topical lidocaine, and capsaicin patches are indicated for post-herpetic neuralgia. However, topical capsaicin is tolerated poorly due to burning pain upon application.

Tricyclic Antidepressants

Tricyclic antidepressants are also first-line treatments. In a randomized trial, 49 patients with post-herpetic neuralgia were assigned to receive both amitriptyline and fluphenazine, one medication only, or placebos. Pain evaluations from the visual analog scale and McGill Pain Questionnaire both demonstrated statistically

significant decreases in pain with amitriptyline without improvement from the addition of fluphenazine. The belief that the combined analgesic effects of amitriptyline and antalgic effects of phenothiazines would yield some therapeutic synergy was not demonstrated in the study [40].

A meta-analysis of 229 studies of neuropathic pain yielded several recommendations of treatment options based on moderate- to high-quality evidence. Serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and gabapentinoids are deemed first-line agents with fair effect size, tolerability, and cost. Second-line agents include tramadol, capsaicin patches, and lidocaine patches, while third-line agents include strong opioids and botulinum toxin A [41]. These recommendations were made to apply to all forms of neuropathic pain and did not apply caveats or adjustments for specific disorders. Desipramine may be better tolerated compared to amitriptyline.

Opioids

Opioids are effective for post-herpetic neuralgia but should be used as third-line treatments or for rescue doses.

Summary: New vaccines are very effective and acute zoster should be treated with an antiviral drug. Post-herpetic neuralgia may be treated with gabapentinoids, tricyclic antidepressants, and topical lidocaine.

Chronic Pain After Cancer Treatment

With treatment advances, many patients with life-threatening neoplasms are surviving indefinitely. Many of these patients transition from being cancer pain patients to being chronic pain patients.

They are treated with opioids for pain according to current cancer-related pain treatment practices, and they are experiencing the same problems related to long-term opioid treatment that are seen in patients with chronic non-cancer pain.

New guidelines from the American Society of Clinical Oncology address this with recommendations for risk evaluation, non-opioid treatments, and opioid discontinuance. Pain should be screened for at each encounter and an initial comprehensive pain assessment performed when appropriate, including monitoring for recurrent disease or malignancy in patients with new-onset pain. Non-pharmacologic interventions should be pursued whenever possible and referrals made to the appropriate professionals [42]. Non-steroidal anti-inflammatory drugs, acetaminophen, and adjuvants such as SNRIs and gabapentinoids should be prescribed to relieve chronic pain conditions. Opioids can be considered in cancer survivors with chronic pain who do not respond to initial, conservative therapy and continue to have functional limitations and distress. Risk assessments

for medication side effects, potential for abuse or addiction, legal regulations, etc. should be performed frequently [42].

The World Health Organization analgesic ladder has been questioned in a review showing that NSAIDs are effective for cancer pain and should be maximized before adding or switching to opioids [43]. A meta-analysis of over 3000 patients and 42 trials found that NSAIDs were more effective compared to placebo. No NSAID was found superior to the others. In addition, combination therapy of NSAID and opioids found a slight, statistically significant advantage compared to either agent alone in 9 of 14 relevant papers [43]. Long-term studies with longer follow-up intervals will better elucidate the potential benefits of NSAID use in cancer pain treatment.

Post-amputation Pain

Good pain control after amputation reduces phantom limb pain. In patients with limb amputations, half to three-quarters experience difficult-to-manage phantom limb pain, having a detrimental impact on quality of life and functional status. In a study of 65 patients randomized to receive perioperative epidural analgesia and anesthesia, intravenous patient-controlled analgesia (PCA), and general maintenance anesthesia, favorable visual analog scale (VAS) scores and McGill Pain Questionnaire scores were associated with patients who had more rigorous perioperative analgesia, noting similar benefits between pre-, intra-, and post-operative epidural anesthesia and intravenous PCA for phantom pain symptoms at 6 months [44]. A strong limitation of this study type includes the contraindication for neuraxial catheter placement in patients taking chronic anticoagulants or antiplatelet agents, deemed more common in patients who undergo an amputation procedure. The greatest benefits were observed in patients receiving epidural analgesia or PCA 48 hours before and 48 hours after amputation [44].

Also, epidural calcitonin during epidural anesthesia for amputation may reduce the severity of phantom pain. Calcitonin has been hypothesized to be of benefit for patients with chronic pain as it affects endorphin release, opioid receptor modulation, and catecholamine and serotonin balance. In a study of 60 diabetic patients undergoing lower limb amputation, those who received epidural fentanyl in addition to bupivacaine and fentanyl did not have significant improvements in VAS scores, but had a lower grade of post-operative phantom pain and fewer allodynia and hyperalgesia symptoms 1 year after surgery [45].

Additionally, transcranial magnetic stimulation (TMS) has a positive effect. Maladaptive plasticity, entailing reorganization of the sensory and motor cortices and peripheral nociceptive inputs, has been implicated in the mechanism of phantom limb pain. Improvements in post-stroke pain and spinal cord injury-related pain after repetitive TMS stimulation of the primary motor cortex sparked a study in the phantom limb pain demographic. Patients randomized to daily TMS sessions for 10 days demonstrated clinically significant pain reduction and intensity at 15 days

post-procedure, expressed as VAS scores, compared to sham therapy. There was no significant benefit observed 30 days post-procedure [46].

Progressive muscle relaxation, mental imagery, and phantom exercises are also beneficial. These therapies and strategies are believed to help modify and reverse cortical reorganization, each with unique focal activity within the brain. The combination of these training exercises was shown in 20 subjects to have a significant decrease in intensity of phantom limb pain and rate of phantom limb sensations 1 month after treatment [47].

Several medications have been studied for phantom pain. Dextromethorphan, amitriptyline, tramadol, and gabapentin are effective. Phantom limb pain is believed to be partly due to the excitability of dorsal horn neurons by amino acids at the N-methyl-D-aspartate (NMDA) receptor, with pharmacologic antagonist therapy potentially blocking this excitability and sequelae [48]. Dextromethorphan, an NMDA receptor antagonist, was studied for relief of incapacitating phantom pain in amputees. Self-rated subjective evaluations of pain, sedation, and overall well-being favored those who received between 120 and 270 milligrams per day of dextromethorphan; this potentially explains one feature in the pathophysiology of this condition [48].

Tramadol and amitriptyline, drugs shown to be effective for neuropathic pain, were tested against placebo in treatment-naïve patients with limp amputations and phantom pain. Mean doses of 448 mg of tramadol and 55 mg of amitriptyline were found to be effective in decreasing pain intensity after 1 month of pharmacotherapy [49]. Most notably, electrical sensation thresholds on the stump were increased with tramadol after 1 month, and pain tolerance thresholds were increased on both legs for both the tramadol and amitriptyline treatment arms. Further analyses of limb dominance demonstrated possible asymmetry in nervous system reorganization responses to amputation [49].

Gabapentin, also deemed an effective treatment option for neuropathic pain, was hypothesized to have benefit in post-amputation phantom pain patients. A crossover study of 19 patients showed improvement in pain intensity difference compared to placebo, but failed to show improvements in rescue analgesics, sleep patterns, activities of daily living, or mood symptoms. The most frequently reported side effect was somnolence [50].

Morphine has been shown to be more effective than mexiletine. Morphine was found to have lower pain scores compared to mexiletine and placebo with decreased numbers needed to treat for 33% and 50% pain intensity decreases [51]. However, no improvements in daily activities or functional status were noted in the morphine group, with a higher rate of side effects, most notably constipation. Later studies on the use of mexiletine for neuropathic pain have described no differences in allodynia, quality of life, and pain scores compared to placebo, thus reducing its supposed benefit in neuropathic pain relief and similar modulation [51].

Ketamine is believed to be more effective than calcitonin. A crossover study of 20 patients with phantom limb pain treated with ketamine, calcitonin, combination (ketamine and calcitonin), and placebo infusions further examined the potential benefits of NMDA antagonist therapy on pain modulation in this subpopulation.

Both the ketamine and combination infusions reduced pain intensity, rated using visual analog scales, but the combination infusion was not found to be superior to ketamine alone [52]. No difference in basal pain thresholds was noted comparing the amputation and contralateral limbs, suggesting peripheral sensitization may not play a large role in phantom limb pain. Ketamine, as a centrally acting NMDA antagonist, has more of a profound impact on central sensitization and likely phantom limb pain as well. Overall, calcitonin administration was found not to affect pain thresholds or intensity [52].

Mirror therapy is an effective intervention. Mirror therapy employs an open top box with a mirror on one side. The patient positions their remaining limb inside the box such that the reflection of the remaining limb appears in the mirror as the missing limb. The remaining limb is moved and the patient sees what appears to be the missing limb move without pain. This has a positive effect on pain in the missing limb. Upper extremity pain seems to respond better than lower extremity pain.

A randomized trial comparing mirror therapy to imagery therapy in 22 patients with phantom limb pain demonstrated decreased pain intensity as well as number and duration of pain episodes. The covered-mirror and mental-visualization treatment groups did not show a pain decrease. An association between activation of mirror neurons in the contralateral hemisphere to the amputated limb and phantom pain relief is hypothesized [53].

The activation of mirror neurons may block protopathic pain in the phantom limb. Null input from the amputated limb can yield a tactile sensation, whereas a person with an intact limb can only "empathize" to the amputation since the null inputs from his/her intact limb are functional [54].

Risk factors for phantom limb pain include female sex, upper extremity amputation, pre-amputation pain, residual pain in the remaining limb, and time after amputation. Hypothesized mechanisms to explain phantom limb pain include stump and neuroma hyperactivity, cortical reorganization, spinal cord sensitization, and some psychogenic mechanisms [54].

Summary: Phantom pain is treated with gabapentin and tricyclic antidepressants as well as mirror therapy and relaxation techniques.

Post-mastectomy Syndrome

Post-mastectomy syndrome may be declining in incidence and severity due to the introduction of sentinel node biopsy techniques and fewer axillary lymph node dissections. The intercostobrachial nerve may be resected or injured during axillary dissection in many cases of post-mastectomy neuralgia.

A nationwide questionnaire of nearly 4000 women who underwent surgery and adjuvant therapy for primary cancer demonstrated several factors associated with chronic pain: young age (18–39 years), adjuvant radiotherapy, and axillary lymph node dissection compared to sentinel lymph node dissection [55]. In addition, pain complaints from other parts of the body were associated with an increased risk of

pain in the surgical region. This study suggested that this persistent pain be best characterized as a neuropathic pain and potentially related to intraoperative intercostobrachial nerve injury [55].

Paravertebral blocks and intravenous lidocaine infusions may reduce the incidence of post-mastectomy pain. In a meta-analysis of 18 studies describing the incidence of persistent pain 3–12 months after breast cancer surgery, regional anesthesia was shown to prevent persistent pain in 1 out of every 7 women, compared to conventional pain therapies with opioids and NSAIDs [56]. When isolated for the paravertebral block, the number needed to treat for benefits was 11. Adverse effects of paravertebral blocks for breast surgery were found to be low in frequency and not systematically reported [56].

Venlafaxine treatment at the time of surgery may help reduce post-mastectomy syndrome. In a study of 150 patients who underwent partial or radical mastectomy with axillary dissection, patients reported roughly equivalent immediate pain reduction in the groups receiving venlafaxine and gabapentin, compared to placebo. In addition, analgesic requirements from opioids were decreased in both groups. However, at 6-month follow-up, the venlafaxine group had a decreased incidence of chronic pain and intensity as well as decreased need for co-analgesics [57].

Amitriptyline is effective for post-mastectomy pain. A randomized crossover study of 15 patients with neuropathic pain after breast cancer treatment who received escalating doses of amitriptyline showed benefit, described as a greater than 50% decrease in pain intensity, in roughly half the patients [26]. The poor responders, in addition to decreased analgesic benefits, had significantly more adverse effects and toxicity, most notably "incapacitating tiredness," dry mouth, and constipation. In addition to the analgesic benefits reported in the good responders, improvements in daily activities and quality of life were also more prominent in this group [56].

Post-thoracotomy Pain

Post-thoracotomy pain can be prevented by thoracic epidural analgesia. In a meta-analysis of seven studies examining persistent pain 3–18 months after a thoracotomy, five studies showed the strongest benefits to thoracic epidural analgesia, as compared to conventional analgesics such as opioids and NSAIDs [56]. The incidence of persistent pain after thoracotomy was found to be between 25% and 65%. Regional anesthesia, in general, was found to prevent persistent post-thoracotomy pain in one of seven people treated, whereas thoracic epidural anesthesia may prevent this pain in one out of every five people. The results were not able to be extrapolated to video-assisted thoracotomy procedures or paravertebral blocks [56].

Post-thoracotomy pain syndrome responds to pregabalin. In one study 50 patients who underwent thoracotomy were randomized to pregabalin and diclofenac treatment groups. While no difference was appreciated at the 0-, 1-, and 7-day time points, visual analog scores were found to be improved at time points of 3, 6, 12, and 24 weeks, without significant adverse effects reported. The belief is that inter-

costal nerve involvement in chronic post-thoracotomy pain can explain why gabapentinoids and other neuropathic pain modulators would show a benefit in this syndrome [58].

Chemotherapy-Induced Neuropathic Pain

Duloxetine is effective. In one study 231 patients diagnosed with chemotherapy-induced pain after paclitaxel, oxaliplatin, or other taxane treatments were randomized to receive the serotonin-norepinephrine reuptake inhibitor duloxetine or placebo. Fifty-nine percent of those patients who initially received duloxetine reported some decreased pain compared to 38% in the placebo group [59]. A mean decrease of 1.06, as measured by the Brief Pain Inventory-Short Form, was found in the duloxetine group compared to the placebo group. The patients who received platinum-based chemotherapy regimens experienced more benefit from duloxetine than those who received taxane-based regimens. The duloxetine groups were also found to have decreased pain interference with daily functioning and increased quality of life symptoms [59].

Gabapentin is not effective. A crossover study of 115 patients randomized to receive gabapentin or placebo after diagnosed chemotherapy-induced peripheral neuropathy did not show any benefit of the anticonvulsant [60]. Average and worst pain scores, non-opioid analgesics used, and WHO neuropathy scores were not significantly different between the groups. In terms of pathophysiology, the belief that upregulation of the α2–δ1 subunit of voltage-gated calcium channels in dorsal root ganglia does not occur in chemotherapy-related nerve injury suggests why gabapentin's nociceptive benefits might not be seen in this population [60].

Studies are inconclusive for other drugs including tricyclic antidepressants and topical gel containing baclofen, amitriptyline, and ketamine. Clinical practice guidelines from the American Society of Clinical Oncology regarding the prevention and management of chemotherapy-induced peripheral neuropathy yielded several treatment recommendations [61]. As the only formal recommendation, duloxetine may be offered to patients. Benefits to the use of acetyl-L-carnitine (ALC) have not yet been published in a peer-reviewed journal. Tricyclic antidepressants are reasonable options with the caveat that limited data supports the use in context of harms, costs, etc. Gabapentin and pregabalin are also suggested options as known beneficial treatment options are limited. Lastly, one trial showed some benefit to a baclofen, amitriptyline, and ketamine topical gel, though this has also not been further studied or proven beneficial [61].

Neurofeedback has been used successfully for chemotherapy-induced peripheral neuropathy. A randomized trial of patients with chemotherapy-induced peripheral neuropathy assigned to receive 20 sessions of focused neurofeedback sessions compared to wait-list controls demonstrated improvements on the Brief Pain Inventory worst pain scores, as well as several features from the pain quality assessment scale. These benefits can be further amplified as the harms of neurofeedback are quite few compared to those of pharmacotherapeutic modalities [62].

Radiation Therapy Neuropathic Pain

Radiation is effective for pain from bone metastases; however, patients may develop neuropathic pain after radiation treatment for neoplasms.

A report of two cases of radiation-induced (RI) lumbosacral polyradiculopathy used pentoxifylline, tocopherol, and clodronate (Pentoclo) with some success [63]. The RI neuropathy is not well described in the literature; it either stabilizes or worsens with time while spontaneous improvement is not likely. Proximal demyelination with an ensuing conduction block could be related to extrinsic nerve compression by RI fibrosis or radiotherapy-induced Schwann cell injury. Other pathophysiologic mechanisms of RI neuropathy include vascular hypoxia and atrophy [63].

Gabapentin did not help pain from mucositis after radiation for head and neck cancer. Pain related to radiation-induced mucositis is believed to be from tissue damage and resulting inflammation. The suggestion that patients with head and neck cancer who had pain at the time of diagnosis had mixed nociceptive and neuropathic pain led to the belief that gabapentin may be of benefit to this subpopulation as it has already been shown to be beneficial in patients with other neuropathic pain syndromes [64]. However, when 22 patients were assigned to receive standard pain control of acetaminophen and opioids or standard pain control plus gabapentin, the combined group had higher maximum visual analog scale scores, higher opioid doses at maximum pain score, higher total opioid usage, and a worsened score on quality of life analysis [64].

A case report described return of vision after treatment with bevacizumab in a patient with radiation optic neuropathy. It has previously been shown to be effective in the treatment of radiation necrosis of the central nervous system. This suggests that modulation in the production of vascular endothelial growth factor (VEGF) can play a role in radiation damage control [65].

Neuropathic Pain from Other Diseases and Conditions

Acute Sciatica

Indomethacin has been shown to be superior to placebo for radicular pain. A 1968 randomized study of 25 patient pairs comparing indomethacin to placebo demonstrated improvement in lumbar spine flexion and straight-leg raising in addition to subjective pain severity and movement restrictions without a considerable side effect limitation. This suggests a strong inflammatory component to this pain subtype [66].

Oral corticosteroid is more effective than gabapentinoids. In a randomized study, 54 patients with radiating lumbar pain assigned to oral corticosteroid and gabapentinoid (gabapentin or pregabalin) therapy were evaluated over a several-week interval in terms of potential subjective and objective benefits [36]. The corticosteroid

group showed significantly improved pain scores at 2-, 6-, and 12-week time points in addition to fewer disabling symptoms and greater overall physical health scores. The superiority of corticosteroids is suspected to be related to reduced stretching pain for an acutely inflamed spinal nerve because of its decreased nerve root swelling effects [67].

However, other trials have not shown significant analgesic effects with steroids. Goldberg's large randomized study of 269 patients with acute sciatica from a herniated disk assigned patients to a 2-week course of oral prednisone or placebo [68]. A very modest improvement in functional status was noticed in the steroid group, as measured by the Oswestry Disability Index, at the 3-week and 52-week time intervals. However, no improvement in pain symptoms was demonstrated. The belief that oral steroids can decrease the need for surgical interventions was also not shown as there were no differences in surgery rates at 1-year follow-up [68]. An interview by Goldberg about this study further emphasized that steroids should not be completely disregarded as a treatment option, but a thorough discussion between doctors and patients is crucial [69].

Chronic Sciatica

In a trial comparing morphine, nortriptyline, and the combination of the two drugs, nortriptyline alone was more effective than placebo, morphine alone, or the combination. In 28 patients, there were no statistically significant improvements in average leg pain scores. Nortriptyline alone had a 14% pain reduction compared to placebo while morphine alone and the combination therapy each had a 7% pain reduction compared to placebo [70]. Several patients also exhibited adverse effects including constipation and dry mouth. This study is limited most by its >50% drop-out rate. Overall, it can be inferred that opioids and/or tricyclic antidepressants may be ineffective in the treatment of lumbar radicular pain, whereas more of a profound benefit for these medications can be seen in diabetic neuropathy and post-herpetic neuralgia syndromes. The controversy of "opioid resistance" in neuropathic pain is further debated here [70].

The combination of gabapentin and naproxen in this population was found in a study of 56 patients to cause improvement in walking abilities and activity status overall, but it is not statistically significant compared to the NSAID-only group [71].

While tricyclic antidepressants (TCAs) have significant side effects, the number needed to treat (NNT) for this drug class is lower compared to other drug classes including opioids and serotonin-norepinephrine reuptake inhibitors (SNRIs) for diabetic neuropathy and post-herpetic neuralgia [72]. Graphical representation of NNT and number needed to harm (NNH) demonstrates favorability toward TCAs and lidocaine patches and opioids. Painful polyneuropathy also showed favorable NNT values for TCAs and opioids compared to SNRIs, anticonvulsants, and topical capsaicin, among other pharmacotherapeutics [72].

Diabetic Neuropathy

Guidelines recommend tricyclic antidepressants as first-line drugs along with gabapentinoids for post-herpetic neuralgia and SNRIs for diabetic neuropathy. For diabetic neuropathy, first-line therapies include duloxetine, gabapentin, pregabalin, and venlafaxine, in addition to TCAs. Second-line therapies include tramadol with strong opioids as third-line therapy [73]. Further studies at tailoring neuropathic pain options to etiology or symptomatology are mixed. Some recommend focusing on classification based on pathophysiology, suggesting painful diabetic neuropathy should be viewed much differently than post-herpetic neuralgia. However, other studies have shown more generalizability when focusing on specific neurologic symptoms or "pain dimensions." The aging, increasingly more obese population, in addition to the increased survival of cancer patients, may increase the prevalence of neuropathic pain in the future [73].

Trigeminal Neuralgia

The electrical "shocking" pain of trigeminal neuralgia often elicits extreme pain from light stimulation. Classically, carbamazepine has been thought to be the most effective treatment as it can suppress ectopic neuronal discharge [74]. Carbamazepine has an NNT of 1.7 and is considered to be the most effective non-surgical treatment. Baclofen has an NNT of 1.4 from one study and is a good add-on therapy. Lamotrigine has an NNT of 2.1. Other potentially beneficial medications include phenytoin, gabapentin, lidocaine, and sodium valproate, though not yet as clearly demonstrated. Combination therapy is a treatment strategy, but not evidence-based [74].

Atypical facial pain may be treated with amitriptyline. A study of 28 patients with musculoskeletal and neurogenic chronic facial pain randomized to amitriptyline and placebo groups demonstrated effectiveness of this tricyclic antidepressant for this unique pain subtype. No significant effects were realized after 1 week of treatment but observed after 4 weeks [75]. Additionally, upon stratification for depressive symptoms, amitriptyline was found to improve pain symptoms in both depressed and non-depressed individuals in addition to improved depressive symptoms in the depressed group. The demonstration of analgesic benefits to non-depressed individuals further nullifies the older notion that subjective improvements are due to mood symptoms alone [75].

Inflammatory Pain

Gout

Evidence-based guidelines from the European League Against Rheumatism established several recommendations and treatment principles for the management of gout [76]. For gout attacks, colchicine, non-steroidal anti-inflammatory drugs

(NSAIDs), and oral or intra-articular steroids are recommended. Colchicine, NSAIDs, corticosteroids, and an interleukin-1 blocker are options for patients with frequent flare-ups. Allopurinol is used to lower serum urate. Febuxostat, a uricosuric, and a xanthine oxidase inhibitor are secondary treatments. Pegloticase is used for chronic refractory and tophaceous gout [76]. Knowledge of contraindications to each treatment modality is crucial, such as severe renal failure for colchicine and NSAIDs. In addition, tailoring treatment strategies to the severity, number of joints affected, and attack duration can improve outcomes. Combination therapy, such as colchicine and an NSAID concurrently, is also a treatment strategy. Further research in the treatment of gout should include the optimal combined therapy for an acute gout attack, the best strategies for tophaceous gout, and the optimal duration of prophylactic therapy for acute attacks [76].

NSAIDs and corticosteroids are both effective options. A meta-analysis of 817 patients showed no difference in response to NSAIDs or corticosteroids at less than or greater to 1-week duration of treatment. In addition, no significant differences were appreciated [77]. In addition, there was no significant difference in terms of time to disease resolution or supplementary analgesic use. Corticosteroids were slightly better tolerated in terms of side effects, most notably nausea and indigestion; however, the review demonstrates that both medication classes are equally effective choices [77].

Vascular and Ischemic Pain

Scleroderma, vasculitis, and embolic disease are important causes of vascular ischemic pain. Several medication classes have been described as treatment options for digital ischemic pain, all trying to protect vessels from damage or disease progression as well as prevent thrombosis [78]. Vasodilators include alpha adrenergic blockers, calcium channel blockers, nitrates, phosphodiesterase inhibitors, prostacyclins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. Vasoprotective medications include antiplatelet agents, endothelial receptor antagonists, statins, and thrombolytics [78].

Non-medical therapies for ischemic digital pain include lifestyle adjustments such as avoiding extreme cold or temperature fluctuations. Biofeedback, relaxation techniques, and conditioning have shown mixed results. Protective clothing and gloves are also effective and helpful in protecting the skin from trauma and cold temperatures [78].

Sildenafil, nifedipine, and topical nitroglycerin have been used to treat ischemic pain. A case report of a man with progressive fingertip pain and ischemia refractive to medical and surgical therapies was given a trial of oral sildenafil and noticed significant symptomatic improvement. An improvement in digital blood flow is described as the primary mechanism. Small studies have shown improved digital circulation, decreased pain, warmer extremities with improved coloration, and progressive healing of toe ulcers. In addition, animal studies of sildenafil relate a potential benefit in skip flap survival [79].

Nifedipine was shown to have improvements in patients with coronary artery disease with recurrent ischemic pain at rest despite maximum treatment with beta blockers and/or nitrates, as hemodynamic status allowed [80]. Of the 11 patients, all but one had resolution of the ischemic pain symptoms with addition of nifedipine and remained symptom-free for 5-plus months after treatment initiation. The patients with severe coronary artery disease requiring bypass grafting found the least benefit to nifedipine [80].

Topical nitroglycerin ointment was found to be beneficial to three elderly men with severe peripheral vascular disease and lower extremity ulcers with difficult-to-achieve wound pain. The major benefits of nitroglycerin in wound repair involve its roles in cellular remodeling and proliferation, angiogenesis, inflammation, and extracellular matrix deposition [81].

Intravenous lidocaine has been used to treat ischemic pain. The proposed mechanism entails reduction in sensory pathway transmission, cortical spreading depression, and inhibition of ectopic discharges from injured nerves, among others [82]. A meta-analysis of patients treated in the emergency department with several different pain types compared intravenous lidocaine treatment to intravenous morphine. In the subgroup with critical limb ischemia, the intravenous lidocaine group had comparable to superior pain reductions compared to the morphine group without serious adverse effects [82].

Lidocaine was more effective than morphine in one randomized trial. Sixty-three patients randomized to lidocaine infusion or intravenous morphine for critical limb ischemia showed a decreased visual analog score at time points of 15 and 30 minutes after treatment initiation with faster onset to pain relief. Pain scores were not assessed beyond the 30-minute time point as the need for immediate surgery terminated further evaluation [83]. Warmth and garments are used to prevent cold-induced vasoconstriction.

Acute Pain Medications

Acute pain conditions may lead to chronic pain and effective acute pain treatment may reduce the incidence and severity of chronic pain. The efficacy of different analgesics may be compared using their number needed to treat (NNT). The NNT is the number of patients who need to be treated in order for one patient to respond. The lower the NNT, the more effective a drug is. An NNT of 4 or less is considered to be a good treatment.

The number needed to treat (NNT) is calculated using the reciprocal of the number of responders in an active treatment group divided by the number of patients in the active treatment group minus the number of placebo responders divided by the number of patients in the placebo group.

NNT = 1/[number of treatment responders/number in treatment group]–[number of placebo responders/number in placebo group]

For example, the NNT for the combination of 500 mg of acetaminophen together with 200 mg ibuprofen is 1.6. This is as low as almost any other analgesic from studies for single-dose acute pain. Doubling the doses to 1000 mg of acetaminophen and 400 mg of ibuprofen has an NNT of 1.5. The NNT for oxycodone 10 mg with 650 mg of acetaminophen is 1.8 so the case can be made for avoiding opioid as first-line therapy for acute pain. Acetaminophen with codeine is not a very effective analgesic and it is not clear if it is any safer than other opioids.

NSAIDs inhibit cyclooxygenase-dependent prostanoid formation, which plays an important role in inflammatory and nociceptive processes. Acetaminophen lacks significant anti-inflammatory activity, implying a mode of action distinct from that of NSAIDs. Regardless, both NSAIDs and acetaminophen may be important for driving early and overall good pain relief. Simple drug combinations and fast-acting formulations can deliver good analgesia in many people with acute pain at relatively low doses.

Topical NSAIDs are effective alternatives to oral NSAIDs. Use of topical NSAIDs to treat acute musculoskeletal conditions has become widely accepted because they can provide pain relief without associated systemic adverse events. The NNT for diclofenac gel was 1.8. The NNT for ketoprofen gel was 2.5. The NNT for ibuprofen gel was 3.9 [84].

The Oxford pain group has constructed the Oxford League Table for analgesics in acute pain by giving each analgesic a number to grade its efficacy, expressed as NNT for one to achieve at least 50% relief of pain compared with placebo over a 4- to 6-hour treatment period [85].

The NNT for other common analgesics are listed.

From Table 6.1, it is clear that NSAIDs and COX-2 inhibitors do extremely well. Weak opioids perform poorly on their own. However, combining them with simple analgesics improves analgesic efficacy.

Older clinical data suggested that acetaminophen is as effective as NSAIDs in many pain conditions. However, it can be seen from the Oxford League Table that, overall, NSAIDs are clearly more efficacious than acetaminophen. It should be noted, however, that acetaminophen has a safer profile than NSAIDs. The adverse effects of NSAIDs include alterations in renal function, hepatic injury, platelet inhibition, and gastrointestinal and cardiovascular toxicity [86].

More information on NNT for other drugs can be found by referring to the 2007 Oxford League Table of analgesic efficacy.

Chronic Pain Medications

Chronic pain is not self-limited and has been defined as pain persisting for 6 months or persisting longer than anticipated. The Government of Western Australia has developed a number needed to treat table for analgesics and the chronic pain conditions they are used to treat [87]. This information is summarized in Table 6.2. Government of Western Australia, Department of Health

Table 6.1 Oxford League Table for analgesics in acute pain

Drug (oral route unless otherwise noted)	NNT
Naproxen 200 mg	3.4
Naproxen 400/440 mg	2.7
Naproxen 500 mg/550 mg	2.7
Celecoxib 200 mg	4.2
Celecoxib 400 mg	2.6
Diclofenac 25 mg	2.4
Diclofenac 50 mg	2.1
Diclofenac 100 mg	1.9
Etodolac 100 mg	4.8
Etodolac 200 mg	3.3
Etodolac 400 mg	2.9
Ibuprofen 100 mg	4.3
Ibuprofen 200 mg	2.9
Ibuprofen 400 mg	2.5
Ibuprofen 600 mg	2.7
Ketorolac 10 mg	2.6
Ketorolac 20 mg	1.8
Ketorolac 30 mg (intramuscular)	3.4
Ketorolac 60 mg (intramuscular)	1.8
Acetaminophen 500 mg	3.5
Acetaminophen 1000 mg	3.6
Acetaminophen/codeine 600/60 mg	3.9
Acetaminophen/codeine 1000/60 mg	2.2
Acetaminophen/oxycodone 650/10 mg	2.6
Acetaminophen/oxycodone 1000/10 mg	2.7
Oxycodone 15 mg	4.6 (2.3 Oxford)
Gabapentin 250 mg	11
Tramadol 50 mg	9.1 (8.3 Oxford)
Tramadol 100 mg	4.8
Tramadol 150 mg	2.4 (2.9 Oxford)
Paracetamol 600 mg/650 mg + codeine 60 mg	4.2
Oxycodone IR 5 mg + paracetamol 500 mg	2.2

Table showing effectiveness of NSAIDs and acetaminophen based on lower NNT

Antidepressants

Antidepressants are attractive analgesics for chronic pain since depression is also common among patients with chronic pain. Using one drug for two problems is potentially more effective and safer than drugs with abuse potential or toxicity.

Serotonin-norepinephrine reuptake inhibitors (SNRIs) are used to treat chronic pain conditions such as neuropathy and fibromyalgia and mood disorders such as depression and anxiety. They generally have a more favorable side-effect profile than tricyclic antidepressants (TCAs). Common adverse effects of SNRIs include nausea, dry mouth, somnolence, fatigue, constipation, decreased appetite, and hyperhidrosis. Nausea usually resolves with continued use. SNRIs are contraindi-

Table 6.2 Chronic pain medications and NNT by the Government of Western Australia, Department of Health

Drug	Condition	NNT 50% relief	NNH
Opioids	Neuropathic pain	2.5–4.3	4.2–8.3
Tramadol	Neuropathic pain Post-surgical	3.4–4.7 2.4–4.8	8.3
TCAs: Amitriptyline Nortriptyline	Neuropathic pain	3.6	6 (minor)–28 (major)
Gabapentinoids Gabapentin Pregabalin	Neuropathic pain Central neuropathic pain Diabetic neuropathy Post-herpetic neuralgia Fibromyalgia	7.2–7.7 5 2.9–5 3.9 13–22	3.7 (minor)
SNRIs: Venlafaxine Duloxetine	Neuropathic pain	3.1 6–8	16.2 (major) 9.6 (minor)
Paracetamol	Chronic arthritis	4–5	12 (GI SEs)
Lidocaine patch Capsaicin patch	Peripheral neuropathic pain	4.4 10.6	Minimal

Table showing antidepressants (tricyclic antidepressants and gabapentin) with lower NNT and higher NNH values, supporting their use prior to initiating opioids
https://painhealth.csse.uwa.edu.au/wp-content/uploads/2016/04/painHEALTH-NNT-and-NNH-for-pain-medications.pdf

cated for patients taking monoamine oxidase inhibitors (MAOIs) and uncontrolled narrow-angle glaucoma.

Duloxetine is an SNRI indicated for diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain. Duloxetine has an NNT of 7 for osteoarthritic pain. The recommended starting dose for duloxetine is 30 mg once daily, with a target and maximum dose of 60 mg/d. Doses >60 mg/d have similar efficacy to lower doses but greater side effects. Duloxetine should not be used in patients with hepatic insufficiency nor in patients with severe renal impairment [88].

Venlafaxine is an alternative serotonin-norepinephrine reuptake inhibitor. However, duloxetine is more effective than venlafaxine for peripheral neuropathies. Venlafaxine should be used with caution in patients with a history of cardiac disease.

Tricyclic antidepressants are used in low doses to treat chronic pain conditions, particularly neuropathic pain conditions such as painful polyneuropathy and post-herpetic neuralgia. TCAs are used in high doses to treat mood disorders such as depression. TCAs may have more side effects compared with SNRIs. Use caution with high doses and when combined with other serotonergic agents such as SSRIs, SNRIs, MAOIs, lithium, and triptans.

TCAs may be efficacious in central pain. Amitriptyline has been found to be helpful in central post-stroke pain [89]. Imipramine has been studied in atypical chest pain and may be helpful in visceral pain syndromes [90]. Amitriptyline is effective for peripheral nerve injury pain [72].

Anticonvulsants

Anticonvulsants are used to treat neuropathic pain and fibromyalgia. Carbamazepine is first-line treatment for trigeminal neuralgia and can also be effective in painful polyneuropathy. Oxcarbazepine can also be considered for trigeminal neuralgia and painful polyneuropathy. Pregabalin has been shown to be effective for various peripheral and central neuropathic conditions including post-herpetic neuralgia, diabetic neuropathy, fibromyalgia, and spinal cord injury pain. Gabapentin is used to treat similar conditions as pregabalin. There is no overall evidence for superior efficacy of either of these two drugs in neuropathic pain, although the lower cost may favor the use of gabapentin. Long-acting formulations of gabapentin can be a reliable alternative if daytime somnolence or TID dosing affects compliance.

Muscle Relaxers

Muscle relaxants are recommended only for short-term therapy when treating musculoskeletal conditions. Baclofen and tizanidine are recommended for acute back pain. They are approved on the Beers drug list for older adults. Baclofen should be used with caution in patients with renal insufficiency. Baclofen withdrawal can happen if abruptly discontinued. Baclofen-induced encephalopathies have been reported. Tizanidine should be used with caution in patients with hepatic insufficiency. Cyclobenzaprine has TCA-like qualities and therefore should be avoided with concomitant use of MAOIs and used with caution with TCAs and other serotonergic drugs and CNS depressants.

Miscellaneous

Lidocaine patch has been shown to be effective for patients with post-herpetic neuralgia or focal neuropathy with allodynia. Topical capsaicin has also been shown to be effective for post-herpetic neuralgia, and its high-concentration (8%) patch formulation has a long-term effect of 12 weeks and may also be effective for HIV neuropathy pain. Cannabinoids have a modest effect on central pain in multiple sclerosis.

Chronic Pain and Long-Term Opioid Treatment

Chronic pain was described as a disease requiring opioids in the 1990s. Assumptions were made about the efficacy and safety of long-term opioid treatment including low addiction rates, no ceiling dose, tolerance to respiratory depressant effects, and functional improvement.

Now, chronic opioid therapy is recognized as a risk factor for overdose, opioid diversion, substance use disorder, motor vehicle accidents, fractures, poor surgical outcomes, prolonged hospitalization, and increased healthcare costs. Chronic opioid therapy has become a disease as a treatment for the disease it was intended to treat.

In the first long–term randomized trial of opioids compared with non-opioids, treatment with opioids was inferior to treatment with non-opioid medications for improving pain–related function over 12 months for moderate to severe chronic back pain or hip or knee osteoarthritis pain. Non-opioid treatment was associated with better pain intensity while opioids caused significantly more medication-related adverse symptoms [91].

The most common chronic pains are back pain, headache, and arthritis. So for back pain and osteoarthritis of the hip and knee, opioids are less effective than non-opioids. Of course, the combination of opioid and non-opioid might be effective, but this is unproven. For migraines, there is no data to support opioid treatment.

In a study of chronic opioid users, most patients on chronic opioid therapy began opioids after surgery or trauma. Sixty-one percent of these patients had complications and 58% required corrective surgery. A large percentage of these patients had concurrent depression and anxiety. Many of these patients continued opioids without a clear treatment plan or opioid agreement. One-fourth of the patients continued opioids for a different pain than the original pain [92].

Long-term opioid use among family members is a risk factor for prolonged opioid use in young people after dental and surgical procedures [93]. Unfortunately, long-term opioid treatment for chronic pain has become associated with several problems including unauthorized dose escalation. Patients may deplete their supply of medication prematurely. Their prescribing doctor may not refill the prescription early, and the patients will likely have pain or withdrawal and seek medical attention.

The Association of Depression, Pain, and Opioid

Physical symptoms are common in depression, and, in fact, vague aches and pain are often the presenting symptoms of depression. Some patients with depression only report physical symptoms. Dysregulation of serotonin and norepinephrine influences both pain and mood [94].

Comorbidity between depression and pain is common. They also appear to facilitate development of each other, and chronic pain is a strong predictor of subsequent onset of major depressive disorder (and vice versa) [95].

Low back pain is the number one cause of disability worldwide. Depression is the second most common cause of disability. Neck pain is fourth most common, and migraines are sixth most common. Therefore, it is likely that a lot of overlap of pain and depression exists in the disabled population [96]. Fifty-one percent of

opioid prescriptions are prescribed to patients with depression and other mental health conditions [97]. In some studies, the effectiveness of antidepressants in treating neuropathic pain was greatest in those who had many depressive symptoms at baseline. Thus the analgesic effect was associated with the antidepressant effect [98].

There is significant interplay of opioids with mood and pain. Long-term opioid use has "drug-opposite" response. The euphoria associated with acute opioid effects is eventually replaced with a negative mood response. This is similar to the "drug-opposite" effect with opioid-induced hyperalgesia. Thus, for mood and pain, the chronic opioid user under the influence of the drug does not simply experience an opioid effect diminished by tolerance but a state opposite to the effect of the drug. This effect may only be reversed by long-term abstinence from the opioids [99].

There is an abundance of literature examining the effects of opioids on mood and vice versa. Depression is a risk factor for prolonged opioid treatment for postoperative pain. In one study utilizing the Beck Depression Inventory-II (BDI-II), the self-loathing aspects of depression (past failure, guilty feelings, self-dislike, self-criticalness, suicidal thoughts, worthlessness) were most predictive of continuing opioids [100].

In a trial of oral morphine for chronic musculoskeletal pain, no psychological or function improvement was found on the Symptom Checklist-90 (SCL-90), Profile of Mood States (POMS), Sickness Impact Profile, and Pain Disability Index [101]. Depression, anxiety, and neuroticism have been found to be associated with diminished opioid analgesia in patients with discogenic low back pain [100]. Interestingly, in a 16-week trial of opioids for chronic back pain, higher doses of opioids were associated with improved anxiety, depression, irritability, and pain [102].

Anxiety has also been found to be improved in patients treated with opioids for chronic musculoskeletal pain. The Patient Health Questionnaire (PHQ-8) depression measure and the Generalized Anxiety Disorder Measure (GAD-7) were used [91]. However, another study suggested that opioids can interfere with treatment for anxiety [103].

Opioids may contribute to depression in patients with chronic pain. Opioids have a dose-dependent association with depression, and the duration of opioid exposure is correlated with depression. Furthermore, opioids are associated with antidepressant failure, and opioid dose reduction is associated with mood improvement [104]. In another study, opioid treatment for 30 days was found to be associated with new-onset depression. This was not dose dependent [105].

Patients with depression are twice as likely to continue opioids. Depressed patients take opioids for less severe pain and less severe physical impairment. Opioids are associated with new episodes of depression, recurrent depression, and treatment-resistant depression [106]. This problem is compounded by the fact that patients who are at the highest risk of adverse outcomes from opioids (those with substance use disorders and other psychiatric conditions) are more likely to be prescribed long-term opioids [107]. A longer duration of initial opioid therapy prescribed is associated with an increased risk of long-term opioid use [108].

Suicides and Opioids

Suicide is a significant contributor to the death rate associated with the opioid-overdose epidemic [109]. While the use of potentially lethal drugs such as opioids has a direct relationship to the risk of unintentional overdose, opioids are also linked to suicide (intentional overdose) risk. Opioid involvement in suicides has doubled [110]. Overdose and suicide have shared risk factors, such as male sex, 41–64 years of age, identifying as white or Native American, and having mental health conditions [111].

In one study, suicidal ideation is reported in 36.5% of patients with chronic pain who were treated with opioids. 16.4% and 2.5% had made a suicide attempt in their lifetime and within the past 12 months, respectively. A low self-efficacy score on the Pain Self-Efficacy Questionnaire was an independent risk factor [112].

There is a dose-dependent risk of suicide whether suicide is by opioid overdose or by other means. The risk doubles in patients with doses above 100 MME as compared to those with doses below 20 MME. Thus, high opioid doses can be viewed as a marker of elevated risk for suicide [113].

Substance Use Disorder and Opioids

In 2017, 18 million Americans (5.5%) took opioids daily for pain. 4.2% of the US population aged 12 or older misused opioids (including heroin). Ninety-two percent of the people who misused were taking prescription opioids, whether acquired legally or illegally [114, 115].

Many patients have both chronic pain and substance use disorder. These patients may exaggerate their pain complaint in order to increase their opioid dose. This has implications since opioid use disorder risk is dose dependent. The duration of opioid therapy is also very important in opioid use disorder risk [116].

The opioid epidemic has had three waves. The first wave began with increased prescribing of opioids in the 1990s. The second wave began in 2010 with heroin. The current third wave began in 2013 with illicit fentanyl. On average, 130 Americans die every day from an opioid overdose [117].

Heroin used to predominantly be the first opioid used, but now, 75% of heroin users start opioid use with prescription opioids, involving now primarily white men and women in their late 20s living outside of large urban areas [118].

With the shift in the demographic face of heroin users, physicians need to be more vigilant in identifying and optimizing patients at risk for chronic pain and drug abuse.

Overdoses and Opioids

An alarming study in 2013 reported that more than half of overdoses occur within just 90 days of starting opioids and one-third of overdoses occur on doses below 50 mg of morphine equivalents per day. These opioid overdose events occurred in

patients without high-dose or long-term opioid therapy. Thus, simply implementing more conservative dosing and duration guidelines is insufficient in preventing morbidity and overdoses [119].

A history of substance abuse is a strong predictor for subsequent overdose. In a study among four groups of patients, the overdose death risk is highest among patients with substance use disorder compared to the groups of patients with cancer pain, chronic pain, and acute pain [120].

Another study found that a history of substance abuse was the strongest predictor for inpatient overdose post-operatively [121]. Opioid discontinuation after nonfatal overdose is associated with lower risk for repeated overdose. Shockingly, one study showed that 91% of patients were prescribed opioids again after a non-fatal overdose [122].

Interdisciplinary Pain Management as a Treatment for Opioid Reduction

Patients with chronic pain often benefit from an interdisciplinary pain management program that includes care from a pain management physician, pain management psychologist, and pain management physical therapist as a core team. Other disciplines, such as nursing, case management, occupational therapy, nutrition, vocational rehabilitation, and other medical specialties, are equally important [123]. Interdisciplinary pain programs may help provide effective alternatives to opioids for patients with chronic pain.

Recommendation

Painful medical conditions may require treatment with opioids, but clinicians should increase their skills at treating pain with non-pharmacologic and non-opioid analgesics. In addition, physicians must increase their skill with opioid prescribing, namely, by evaluating and acting upon risk factors for initiating, continuing, and discontinuing opioids. Using evidence-based treatments as first-line therapies will reduce opioid prescribing and, in many cases, avoid it.

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Chapter 7
Osteoarthritis

Nilofar Syed and Una E. Makris

Introduction

Osteoarthritis (OA) is the most common type of arthritis worldwide and one of the most common reasons for chronic pain. It affects an estimated 250 million adults globally and is a major cause of disability. OA is the main reason for patients undergoing total knee or hip replacement.

Risk factors for OA include advanced age, gender, obesity, genetic predisposition, prior trauma, and occupation [7]. Osteoarthritis is strongly correlated with advancing age; prevalence is greater in patients over age 60, and greater than 80% of patients over 75 years of age can have osteoarthritic changes in their joints [8]. Some risk factors are more frequently associated with certain joints compared to others. For example, OA is more common in women. Patients with obesity more commonly report knee OA versus OA in other joints.

Abnormal mechanics is also a risk factor for OA [5]. Patients with meniscal tears are associated with increased risk of developing OA. In young athletes, tears typically occur as a result of traumatic injury, but even incidental tears have been found in as many as 30–60% of people over age 50. Another mechanical factor is malalignment. Varus deformity is associated with increased likelihood of developing cartilage loss compared to knees without deformity [15]. Mechanical causes such as congenital dysplasia and femoroacetabular impingement increase the risk of hip OA.

Osteoarthritis is most often primary, due to an unknown cause, or secondary, due to an underlying cause. Etiologies of secondary OA include underlying inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis), calcium pyrophosphate deposition disease, prior trauma or joint injury, and hemochromatosis. Osteoarthritis

N. Syed (✉) · U. E. Makris
Division of Rheumatology, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: Nilofar.Syed@utsouthwestern.edu

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commonly affects weight-bearing joints such as the hips and knees. It can also affect the hand (mainly DIP, PIP, and thumb) joints or the spine. Often, more than one site is affected, which can be referred to as generalized OA.

Pathogenesis

Traditionally, OA has been referred to as a degenerative, non-inflammatory condition. Recent evidence suggests there is a complex interplay of inflammatory, mechanical, and age-related changes that result in OA findings and symptomatology. Normal cartilage contains chondrocytes and extracellular matrix composed of collagen and proteoglycans. In OA there is degradation of cartilage and chondrocyte activity that leads to an increase in degradative enzymes such as matrix metalloproteinases (MMPs) that break down collagen and proteoglycans. Cytokines such as IL-1 are also produced by chondrocytes which stimulate production of proteinases leading to further matrix degeneration. The resulting cartilage loss then leads to alterations in the subchondral bone resulting in subchondral sclerosis and osteophyte formation.

Clinical Symptoms

In symptomatic OA, patients typically report aching and stiffness in their joints. The joint pain is described as worse with activity and improved with rest. The pain can worsen throughout the day depending on activity level. Patients can report gelling phenomenon after prolonged periods of immobility. They report stiffness upon moving after sitting for a long time, usually lasting only a few minutes in duration.

On physical exam there may be tenderness to palpation around the joint line, crepitus with movement of the joint, and decreased range of motion. There may be evidence of mild inflammation and/or joint swelling, bony enlargement, and deformity in advanced arthritis. Heberden's and Bouchard's nodes which affect the DIP and PIP joints, respectively, are easily palpated on exam (see Fig. 7.1).

Imaging/Lab Findings

While changes of OA can be seen on X-rays, in patients with classic clinical presentation, there is often no need for imaging for diagnostic purposes. There is typically poor and inconsistent correlation between radiographic findings and clinical symptoms. If X-rays are obtained, findings include joint space narrowing, subchondral sclerosis, and presence of osteophytes (see Fig. 7.2). Synovial fluid, if aspirated from a joint with OA, will be non-inflammatory, usually with less than 2000 white blood cells/mm^3. Serum inflammation markers are often normal.

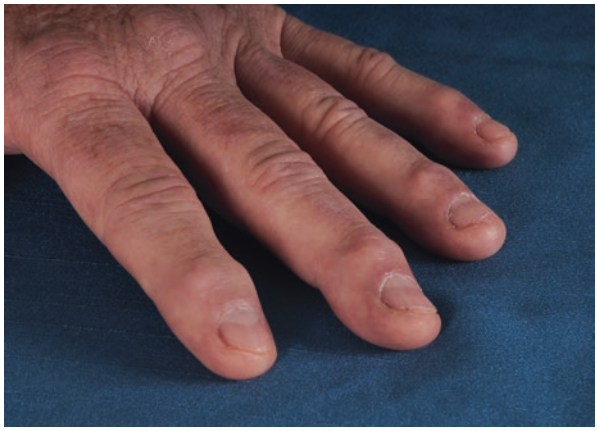

Fig. 7.1 Osteoarthritis of DIP joints

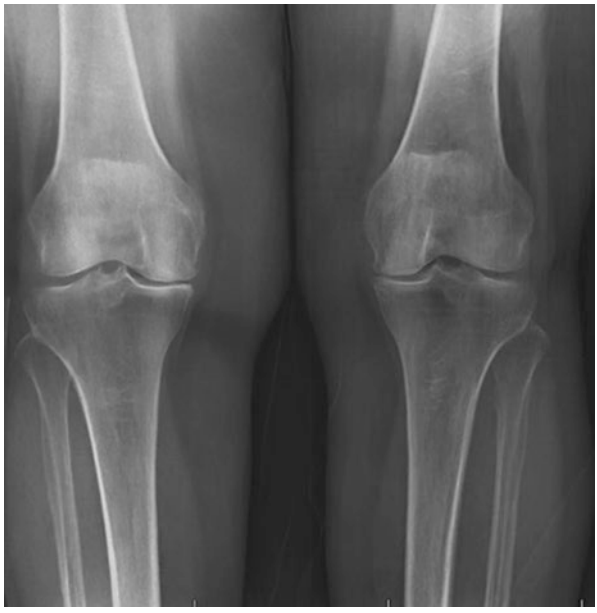

Fig. 7.2 Medial joint space narrowing in osteoarthritis

Treatment

Treatment of OA is aimed at relieving pain and improving physical function, often requiring a combination of non-pharmacologic therapy and pharmacotherapy. Working with patients to assess goals and expectations for management of their OA symptoms is critical to achieving success. Access to multi-modal, interdisciplinary management for OA, which includes rehabilitation techniques, self-management, medications, and often behavioral or psychological therapies, as appropriate, is most effective.

Table 7.1 Pharmacologic treatment recommendations

Topical NSAIDs
Oral NSAIDs
Acetaminophen
IA corticosteroid injections
Duloxetine

Non-pharmacologic therapy recommendations from the American College of Rheumatology 2019 guidelines include exercise, weight loss, self-management programs, and use of assistive devices for the management of OA [6]. It is strongly recommended that all patients with knee OA participate in an exercise program tailored to their specific abilities. This can include aquatic therapy and/or land-based program with aerobic or strengthening exercises. Tai chi is a low-impact exercise that, when compared with physical therapy for knee OA, showed similar reduction in pain levels and improvement in physical functioning [16]. There are also several non-pharmacologic modalities, such as acupuncture, cognitive behavioral therapy (CBT) and yoga, with varying levels of evidence that can be considered, based on patient preference and access. Assistive devices such as canes and knee braces are helpful for knee OA when it affects ambulation and stability and hand orthoses can be used in 1st CMC joint OA.

Patients who are overweight should be counseled on weight loss. Studies have shown that weight loss can decrease radiographic progression and also improve symptoms of pain. The combination of weight loss plus moderate exercise led to overall improvements in self-reported function and pain as well as performance measures of mobility in patients who were overweight or obese with knee OA [2, 12].

Pharmacologic treatment recommendations are summarized in Table 7.1.

Topical and oral NSAIDs are recommended as initial therapy if no contraindications exist. Patients, especially >65 years of age, must be advised regarding the risks associated with chronic oral NSAID use such as gastrointestinal toxicity (peptic ulcers and GI bleeding) and adverse effects on the kidneys. For hand OA, in patients >75 years of age, topical NSAID is preferred over oral NSAIDs.

Acetaminophen was traditionally considered as a first-line treatment for patients with OA. However, a recent review confirmed that acetaminophen provided only slight improvement in pain and function in hip or knee osteoarthritis and the effects on pain and function did not differ according to the dose of acetaminophen [9]. The effectiveness of acetaminophen is limited but it may be an option in patients with contraindications to NSAIDs.

Tramadol has also been recommended conditionally as a treatment option for knee and hip OA [6]. However, this medication has concerning safety/adverse event profile while showing only mild efficacy in these conditions [18]. Several guidelines (CDC) suggest that opioids are not recommended as first-line therapy for OA pain but may be considered if other therapies are ineffective [4]. Duloxetine is an approved adjunctive treatment of chronic musculoskeletal pain, including OA. Studies have shown that duloxetine when compared with placebo results in greater reduction in pain and improved function in knee OA [1, 17].

Intra-articular injections are often used as short-term treatment for improving pain related to knee OA [3, 13]. Corticosteroid injections have been shown to sig-

nificantly improve pain and physical function up to 6 weeks although less improvement was seen in patients with obesity and/or advanced arthritis [10]. A recent study compared intra-articular triamcinolone with intra-articular saline every 3 months in patients with symptomatic knee osteoarthritis, and they were followed with annual knee magnetic resonance imaging. In these patients intra-articular triamcinolone, compared with intra-articular saline, resulted in potentially greater cartilage volume loss and no significant difference in pain at 2 years [11]. Therefore, we do not routinely provide intra-articular knee steroid injections more than 2–3 times per year.

Hyaluronic acid injections may also be considered; however, study results are mixed. A meta-analysis showed no clinically significant benefit but a trend for increased risk for flare-ups and adverse events [14]. Given the limited benefit, ACR guidelines conditionally recommend against use of intra-articular hyaluronic acid injections in knee OA [6].

Patients who continue to be symptomatic despite adequate trials of non-pharmacologic and pharmacologic treatment should be referred for total joint arthroplasty. Joint replacement for knee or hip OA is successful in many patients in relieving pain and improving function. However, for patients who are not candidates for surgery, then the mainstay of treatment can involve revisiting trials of previously attempted non-pharmacologic and pharmacologic management in different combinations and, if needed, use of opioid medications as well as adjunctive medications such as duloxetine.

As with all chronic pain conditions, symptomatic OA requires follow-up with patients to determine effectiveness and safety of therapies. Ideally, patients will provide assessments of both pain intensity and functional status/limitations that will help guide future management approaches. An interdisciplinary approach that involves primary care providers, rheumatologists, physical and occupational therapists, physical medicine and rehabilitation specialists, surgeons, pharmacists, and clinical psychologists (if appropriate) is ideal to effectively manage these patients over time.

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Part III
Regional Pain Problems

Chapter 8
Orofacial Pain

Ahmad Elsharydah

Introduction

Orofacial pain is acute or chronic pain generated from different structures of the head, face, and neck. The innervation of these components is complex and therefore may generate pain with different types of mechanisms. The most common chronic orofacial pain disorders are usually linked to recurrent acute and persistent dental and temporomandibular conditions [1]. Temporomandibular disorders in general generate three main types of orofacial pain including myofascial pain, arthritic pain, and more common pain caused by the temporomandibular joint dysfunction (such as clicks, crepitus, and locking) [2]. Another type of chronic orofacial pain is related to the interaction between the trigeminal nerve (the cranial V nerve) and cervical nerves roots close by (the so-called trigeminal-autonomic reflex). This may explain the spectrum of symptoms associated with the trigeminal neuralgia (TN) and the trigeminal autonomic cephalalgias (TACs) [3]. Many patients with orofacial pain also complain of headache such as tension headache or migraine. Some of the trigeminal autonomic cephalalgias are occasionally misdiagnosed for toothache, TN, or migraine headache. Another type of orofacial pain includes pain related to dysfunction of the nerve (neuropathy). Facial neuropathic pain may be caused by nerve compression, neoplasia or other lesions, bone compression such as acromegaly, or vitamin deficiencies (vitamins B12 and D). Other causes of orofacial neuropathic pain include hormone-related neuropathy (diabetes, hypothyroidism), stroke, demyelination (such as multiple sclerosis), and Parkinson's disease. Different types of infections, autoimmune diseases (lupus erythematosus, rheumatoid arthritis), and sarcoidosis also can lead to orofacial neuropathic pain. Complex regional pain syndrome (CRPS) is also described after orofacial surgery or trauma [4].

A. Elsharydah (✉)
Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, TX, USA
e-mail: ahmad.elsharydah@utsouthwestern.edu

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This chapter is a concise summary for the assessment and management of patients with orofacial pain based on the available scientific evidence.

Epidemiology of Orofacial Pain

Orofacial pain is a very common pain problem. Some demographic studies have shown that greater than 39 million people, 22% of United States population, report pain in the orofacial region [5]. One study reported that more than 81% of the population have some type of significant jaw pain in their lifetime [6]. Orofacial pain is rarely an isolated complaint; it is commonly part of other conditions such as teeth-related conditions and fibromyalgia. The overall prevalence of orofacial pain is 26% [7]. It is higher in women and young adults (18–25) [7]. However, another more comprehensive study by the same author reported a significantly lower prevalence of 1.9% in 2012 [8].

Neurophysiology and Neuroanatomy for Orofacial Pain

It is important for the clinician managing patients with acute or chronic orofacial pain to understand the basic neuroanatomy and neurophysiology of this type of pain. Most of the orofacial pain pathways communicate through the trigeminal nerve [9]. They are mostly transmitted by sensory, motor, and autonomic nerve networks. The trigeminal nerve is the largest and most complex cranial nerve. To better understand chronic orofacial pain, it is essential to understand the peripheral and the central connection of the trigeminal nerve system. It is out of the scope of this clinician guide to describe these connections. In general, nociceptors in the facial and oral regions are responsible for the recognition of proprioception, mechanical stimuli, thermal stimuli, and pain perception [10]. Trigeminal nerve (via afferent fibers A, B, and C fibers) is the dominant nerve that relays sensory impulses from the orofacial area to the central nervous system. The facial nerve, the glossopharyngeal nerve, the vagus nerve, and the upper cervical nerves (C2 and C3) also transmit sensory information from the face and surrounding area. The upper cervical nerves provide innervation to the back of the head, lower face, and neck. More importantly, they converge in the brainstem at the trigeminal nucleus. Most nociceptive orofacial pain impulses are transmitted by the somatic nerves, a significant portion is transmitted by autonomic nerves, and a small portion may be transmitted by motor nerves.

Heterotopic and referred pain are common in the orofacial pain conditions. Orofacial heterotopic pain occurs when the source of pain is not located in the region of pain perception, while referred pain is described as pain felt at a location served by one nerve but the source of nociception arrives at the subnucleus caudalis of the trigeminal nerve by a different nerve. The heterotopic and referred phenomena

Table 8.1 Differential diagnosis of orofacial pain (American Academy of Orofacial Pain classification)

Intracranial pain disorders	Neoplasm, aneurysm, abscess, hemorrhage, hematoma, edema
Primary headache disorders (neurovascular disorders)	Migraine, migraine variants, cluster headache, paroxysmal hemicrania, cranial arteritis Carotidynia, tension-type headache
Neurogenic pain disorders	Paroxysmal neuralgias (trigeminal, glossopharyngeal, nervus intermedius, superior laryngeal) Continuous pain disorders (deafferentation, neuritis, postherpetic neuralgia, posttraumatic and postsurgical neuralgia) Sympathetically maintained pain
Intraoral pain disorders	Dental pulp, periodontium, mucogingival tissues, tongue
Temporomandibular disorders	Masticatory muscle, temporomandibular joint, associated structures
Associated structures	Ears, eyes, nose, paranasal sinuses, throat, lymph nodes, salivary glands, neck

explained by the complexity of the trigeminal network and the convergence of multiple sensory nerves carrying input to the trigeminal spinal nuclei from cutaneous and deep tissues located throughout the head and neck set the stage for referred pain. Table 8.1 reveals the American Academy of Orofacial Pain classification-differential diagnosis of orofacial pain [11].

Based on the pathophysiological and patho-anatomical mechanism of orofacial pain, the following discussion is divided into orofacial neuropathic pain and orofacial neurovascular pain. Other pain conditions manifested with some orofacial pain were discussed in other chapters of this book.

Orofacial Neuropathic Pain

Orofacial neuropathic pain is defined as a pain caused by a lesion or injury of the somatosensory nerves innervating the orofacial region. For clinical purposes, it may manifest as continuous or episodic based upon its temporal presentation. Continuous neuropathic pain is constant, ongoing, and unremitting pain. Patients usually experience varying and fluctuating intensities of pain, often without total remission. Examples of continuous orofacial neuropathic pain include peripheral neuritis, peripheral trigeminal neuritis, herpes zoster/postherpetic neuralgia, atypical odontalgia/nonodontogenic toothache, and burning mouth syndrome. On the other hand, episodic neuropathic pain (neuralgia) is a sudden severe, shooting electric-like pain lasting only a few seconds to several minutes. Often, there exists a perioral or intraoral trigger zone whereby non-traumatic stimuli such as light touch elicit a severe paroxysmal pain [12]. Common examples of orofacial episodic neuropathic pain include trigeminal neuralgia, glossopharyngeal neuralgia, and occipital neuralgia.

For the purpose of this chapter as a clinician guide, I will summarize the most common orofacial neuropathic pain disorders/syndromes.

Trigeminal Neuralgia

Trigeminal neuralgia (TN), also called *tic douloureux*, is defined as a sudden, severe, brief, stabbing, shock-like, usually unilateral and recurrent orofacial pain within one or more branches of the trigeminal nerve. Most common triggers are mastication, touch, eating, talking, cold air on the face, and tooth brushing. Pain is most commonly distributed along the V2 and V3 branches of the trigeminal nerve. Figure 8.1 shows the distribution of the sensory areas of the trigeminal nerve [13].

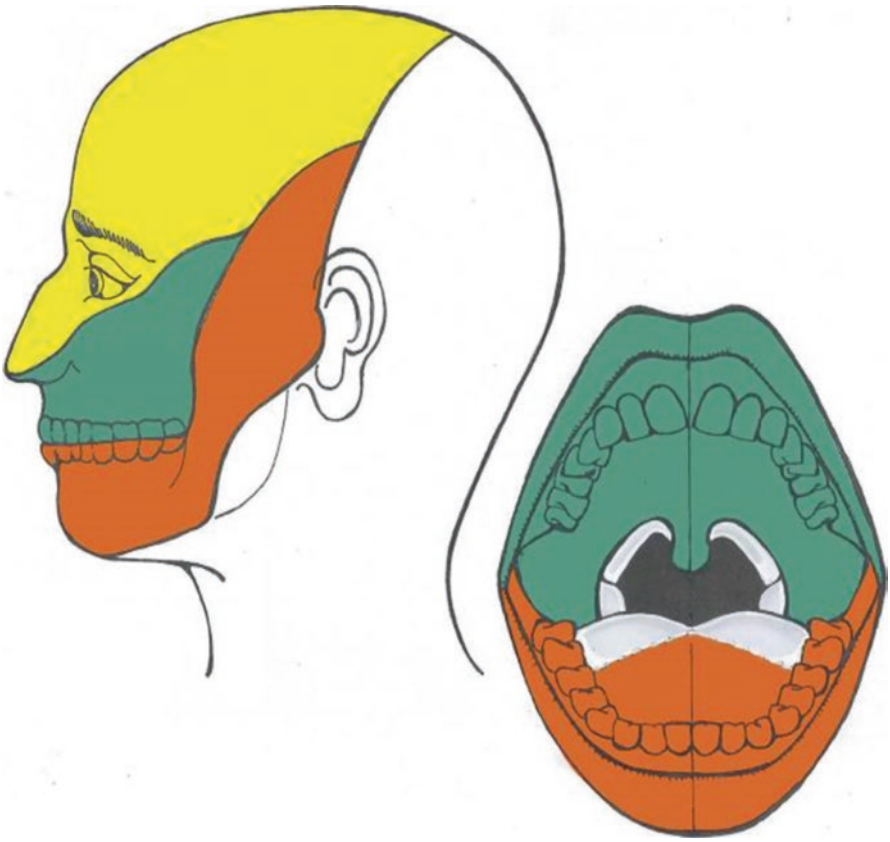

Fig. 8.1 Innervation territories of the trigeminal nerve. Facial and intraoral territories of innervation of the three trigeminal branches (ophthalmic, maxillary, and mandibular). The white areas are innervated by cervical nerves. The light gray areas in the back of the tongue and throat are innervated by the glossopharyngeal nerve. (From Cruccu et al.)

TN is a rare pain disorder (12/100,000 by the National Institute of Neurological Disorders and Stroke estimate) [14]. It is more common in females than in males. It occurs mostly after the age of 50. The International Classification of Headache Disorders (ICHD-3) diagnostic criteria for TN include pain lasting from a fraction of a second to 2 minutes which is severe in intensity and with a quality of shock-like, shooting, stabbing, or sharp. This pain has to be precipitated by innocuous stimuli within the affected trigeminal distribution. The last criterion is this pain is not better accounted by another ICHD-3 diagnosis.

TN etiology and pathophysiology is not very clear; however, the vascular compression theory of the trigeminal nerve appears to be the leading theory at this time [15]. TN pain is consistent of two types of pain: type 1 as intermittent and type 2 as constant pain represent distinct clinical, pathological, and prognostic entities [16]. Although multiple mechanisms involving peripheral pathologies at root (compression or traction) and dysfunctions of brain stem, basal ganglion, and cortical pain modulatory mechanisms could have a role, neurovascular conflict is the most accepted theory.

Imaging studies such as MRI (magnetic resonance imaging) and MRA (magnetic resonance angiography) may help to confirm the diagnosis, detect pathological changes in affected root and neurovascular compression (NVC), and rule out secondary causes and other similar orofacial pain disorders. Pain medical therapies are needed in most patients. The goals of the treatment are to decrease the intensity of pain and the frequency and the duration of the pain episodes. Furthermore, the medical treatment may help to relieve associated symptoms such as headache and depression. The drug of choice to treat TN is carbamazepine (CBZ). It is the only Food and Drug Administration (FDA)-approved drug to treat TN. It is an anticonvulsant that inhibits the sodium channel activity and also modulates calcium channels. The starting dose is usually 100 mg BID, which may increase gradually to 200 mg twice a day or higher dose as tolerated by the patient to reach pain relief, not to exceed 1200 mg/day. Some of its common side effects are dizziness, drowsiness, and nausea. Severe adverse reactions are uncommon including aplastic anemia, hyponatremia, and abnormal liver function tests; therefore, it is recommended to routinely monitor liver function tests, sodium level, and blood counts in these patients. Other drugs used to treat TN include oxcarbazepine (analog of CBZ); however, it has better risk profile and similar efficacy for CBZ. Pregabalin, gabapentin, topiramate, valproic acid, baclofen, lamotrigine, and phenytoin are also useful. Multidrug regimens and multidisciplinary approaches are useful in selected patients. Local anesthesia, steroids, phenol, glycerol, alcohol, and botulinum toxin type A have been used to treat and diagnose TN. Patients who do not respond or tolerate medical therapy and injections may consider other interventional therapies including percutaneous trigeminal ganglion balloon compression rhizotomy, percutaneous radiofrequency gangliolysis, microvascular decompression, or Gamma Knife or CyberKnife radiosurgery. Table 8.2 summarizes topical and other drugs commonly utilized to treat TN and other orofacial pain conditions.

Burning Mouth Syndrome

Burning mouth syndrome (BMS) presents as burning sensations within the oral cavity involving mucosa, tongue, gingiva, and lips. This sensation is continuous and it increases throughout the day. This disorder is more common in females (6:1) during their premenopausal and postmenopausal years. It incidence is 1–3% of general population. It is worse and more frequent in the anterior part of the oral cavity including the first one-third of the tongue, palate, and gingiva. Its diagnosis is a diagnosis of exclusion. Associated symptoms include dry mouth and dysgeusia. It is critical to exclude other systemic disorders such as gastroesophageal reflux disease (GERD), diabetes, and vitamin deficiencies (such as vitamin B12 and folic acid) before starting the symptomatic treatment for BMS. Table 8.2 lists some of the pharmacological agents used to treat BMS [17].

Neurovascular Orofacial Pain

Referred pain to the orofacial area from other neurovascular craniofacial pain-producing disorders is common. This pain is usually located around the eyes and the frontal regions of the face. The most common pain disorders in this group are

Table 8.2 Pharmacologic agents used to treat selected conditions of chronic neuropathic and neurovascular orofacial pain

Orofacial pain disorder		Pharmacologic agents (daily dosage varies)
Trigeminal neuralgia Glossopharyngeal neuralgia Occipital neuralgia	First line	Carbamazepine, oxcarbazepine
	Second line (+first line)	Lamotrigine, baclofen
	Third line	Phenytoin, gabapentin, pregabalin, valproate, tizanidine, tocainide, local anesthetics
Peripheral neuritis		NSAIDs, corticosteroids
Postherpetic neuralgia		Antivirals, acetaminophen, NSAIDs, opioids, TCAs, gabapentin, pregabalin
Burning mouth syndrome		Benzodiazepines (clonazepam, chlordiazepoxide), gabapentin, pregabalin, TCAs (amitriptyline, nortriptyline), selective serotonin reuptake inhibitors (paroxetine, sertraline, trazodone), selective norepinephrine reuptake inhibitors (milnacipran, duloxetine), antioxidants (alpha-lipoic acid), topiramate
Atypical odontalgia		TCAs, gabapentin, pregabalin, benzocaine mixed with carbamazepine and/or ketamine
Hemicrania continua		Indomethacin, ibuprofen, celecoxib, gabapentin, topiramate
Cluster headache	Preventive therapy	Verapamil, lithium, topiramate, melatonin
	Abortive therapy	Triptans (sumatriptan is the most effective), oxygen, intranasal lidocaine

Modified from Halpern et al.
NSAIDs nonsteroidal anti-inflammatory drugs, *TCAs* tricyclic antidepressants

migraine and trigeminal autonomic cephalalgias (TACs). Migraine is discussed in other parts of this book. Distinct neurovascular orofacial pain does also exist; however, it is significantly less common that the above-described referred pain. Clinician has to be aware of these different types of pain and be able to differentiate them from pain produced by dental pathology or referred pain from migraine or TACs. Facial migraine was reported in the medical literature as lower facial pain associated with nausea, vomiting, phonophobia, photophobia, or other autonomic symptoms usually associated with migraine [18]. Treatment is similar to common migraine including preventive medications, abortive medical therapies, and behavioral changes including good sleep hygiene.

Trigeminal Autonomic Cephalalgias (TACs)

TACs are a group of facial pain and headache disorders associated with autonomic symptoms. This group as classified by ICHD-3 includes hemicrania continua (the most common with 900/100,000 of general population) [19] and the less common cluster headache, paroxysmal hemicranias, and short-lasting unilateral neuralgiform headache attacks.

Hemicrania Continua (HC)

It is a primary headache (almost 1.7% of total headache patients) characterized by strictly unilateral orofacial pain in the trigeminal distribution (mainly V1) with cranial autonomic features (such as conjunctival injection and tearing) in the pain area and also associated with agitation and restlessness during attacks. It is usually a continuous headache with superimposed severe attacks. Being a continuous headache makes this type of headache different from other TACs. The average age is around 40 and it is more common in females. Stress is the most common trigger for exacerbations. This type of headache is usually being misdiagnosed as a migraine. Furthermore, many patients may experience HC and migraine at the same time. One of its specific features is a good response to indomethacin. Many other drugs are used to treat HC if indomethacin is not effective or not safe as a long-term treatment. These drugs include topiramate, celecoxib, ibuprofen, gabapentin, and other medications usually used for treatment of other types of headaches and orofacial pain. Interventional therapies such as nerve blocks and surgery also have been used to treat this pain [20].

Cluster Headache

Cluster headache is a rare trigeminal autonomic cephalalgia characterized by severe one-sided headache attacks associated with autonomic symptoms on the same side or agitation and restlessness or both. Episodes usually are frequent and may last

from minutes up to 3 hours. It is three times more common in females than in males. Its prevalence declines significantly with age. Cluster headache is prevalent in cigarette smokers, and alcohol intake is considered as a trigger for it; therefore, it is recommended to avoid alcohol [21]. This headache, especially in cases with long attacks, has usually devastating and disabling effects on the patient life. Its mechanism is not completely clear and believed to involve a synchronized abnormal activity in the hypothalamus, the trigeminovascular system, and the autonomic nervous system. Treatment consists of abortive (during the attack) and preventive (to decrease the frequency) therapies. Triptans are the most effective drugs to abort cluster headache attack. Sumatriptan, usually used in 6 mg single dose subcutaneously, is the most effective triptan. The onset of action is generally within 15 minutes. Sumatriptan is also used as a nasal spray (2 mg single dose); however, it may take longer time to act (around 30 minutes after administration). Inhalation of 100% oxygen administered through a high-flow mask with a rate of 12–15 liters/minute is a proven effective therapy unique for this type of headache and is effective in more than 65% of the cases. The effect for the oxygen therapy usually begins in 15–20 minutes, and in most of the cases, no other abortive treatments are needed. Furthermore, intranasal lidocaine (4–10%) spray in the ipsilateral nostril may provide relief within 10 minutes. Lidocaine is usually used if oxygen and triptans are not effective or not available during the attacks [21]. Verapamil is the most widely drug used for preventive treatment (generally dosage ranges from 360 to 560 mg/day). EKG should be done initially and every time the dose changes because of its cardiac side effects. Other drugs used to decrease the frequency of cluster headache attacks include lithium, topiramate, and melatonin. Nerve blocks such as the greater occipital nerve block with local anesthetic and steroids are also used to treat cluster headache. Botulinum toxin type A is used with good results in some cases. Several neuromodulatory strategies have proven to be effective in the preventive or even acute treatment of cluster headache including deep brain, sphenopalatine ganglion, and greater occipital nerve stimulation. Other promising treatments in development include the uses of two monoclonal antibodies against calcitonin gene-related peptide (CGRP) for the prevention of episodic cluster headache and chronic cluster headache.

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Chapter 9
Chest Pain

Thomas J. Hong and Jonathan Chang

Visceral Chest Pain

Incidence of cardiogenic chest pain from myocardial infarction (MI), angina, pulmonary embolism (PE), and heart failure is estimated to be 50% of patients presenting to the emergency department [1]. Comparatively chest pain seen in the outpatient setting is commonly caused by stable coronary artery disease (CAD), musculoskeletal conditions, gastrointestinal disease, pulmonary disease, or psychiatric disorders. In the outpatient setting, the incidence of pain secondary to pulmonary disease is 5%, gastrointestinal disease is 19%, musculoskeletal conditions is 36%, and psychiatric disorders is 8%. Differential for cardiovascular causes of chest pain is extensive consisting of coronary artery disease (CAD), MI, angina, aortic dissection, pericarditis, cardiac tamponade, PE, heart failure, or cardiomyopathies. Pulmonary causes of chest pain include but are not limited to pneumonia, pneumothorax, COPD, or lung cancer. Gastroesophageal reflux disease (GERD) is the most common cause of gastrointestinal disease but may include other peptic ulcer disease, esophagitis, esophageal rupture, esophageal spasms, pancreatitis, splenomegaly, biliary colic, or cholecystitis [2]. Musculoskeletal pain can be caused by common conditions such as costochondritis, traumatic injuries, myofascial pain, or more rare conditions such as Tietze syndrome. Psychiatric causes include generalized anxiety disorder, panic disorder, major depressive disorder, illness anxiety disorder, post-traumatic stress disorder (PTSD), or substance use disorders (cocaine, methamphetamines, or alcohol) [3]. Seventy percent of panic disorders have chest pain as a symptom. Up to 15% of chest pain is determined to be nonspecific without a definitive diagnosis [4].

T. J. Hong (✉)
Department of Interventional Pain Management, Regency Pain and Therapy Institute, Mansfield, TX, USA

J. Chang
Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: Jonathan.chang@va.gov

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Diagnosis

A thorough history and physical examination coupled with an electrocardiogram and/or chest radiograph can help reveal serious conditions such as acute coronary syndrome, acute chest syndrome, pneumonia, and pulmonary embolism [1]. Further workup such as troponin levels, cardiac stress testing, and angiography can be performed if the patient has exertional chest pain, electrocardiogram changes, or significant cardiac risk factors. D-Dimer assay with subsequent helical CT pulmonary angiography or nuclear ventilation-perfusion (V/Q) imaging may be obtained if suspicion is high for pulmonary embolism [5]. Pain exacerbated with exertion and relieved upon rest is considered typical chest pain and may be associated with radiation to the arms, diaphoresis, and characterized as "chest pressure." While dyspnea is a common symptom in cardiopulmonary diseases, dyspnea with fever can be indicative of pneumonia which can be confirmed with a chest radiograph. Gastrointestinal disease may manifest as epigastric chest pain or discomfort sometimes described as a burning-type pain. Burning pain from gastrointestinal disease can be difficult to differentiate from chest-pressure pain associated with cardiogenic pain. Pain reproducible with palpation or with the initiation of movement as well as recent traumatic injury in the medical history can be suggestive of musculoskeletal etiology [2, 3]. Chest pain associated with psychiatric disorders may exhibit as hyperventilation once psychological triggers are activated which can lead to chest tightness and shortness of breath similar to musculoskeletal-type pain. Figure 9.1 shows the differential diagnosis for chest pain.

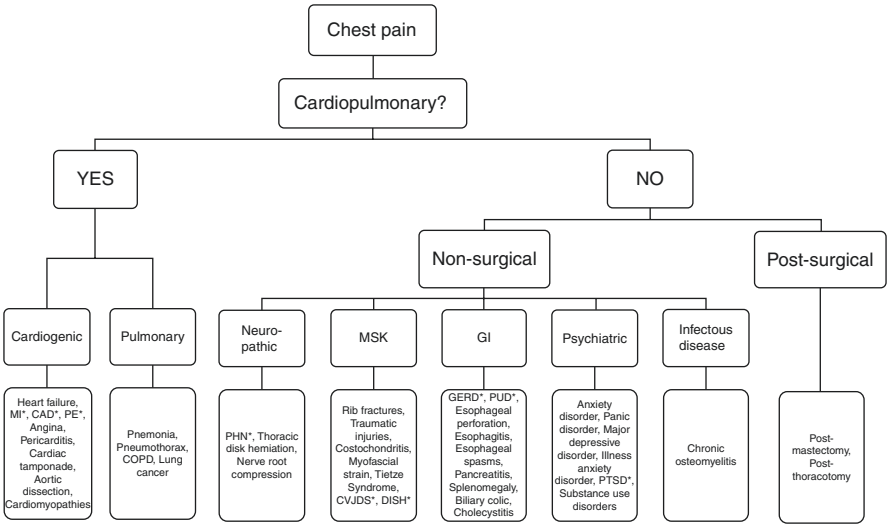

Fig. 9.1 Differential diagnosis for chest pain. MI* myocardial infarction, CAD* coronary artery disease, COPD* chronic obstructive pulmonary disease, PE* pulmonary embolism, PHN* postherpetic neuralgia, DISH* diffuse idiopathic skeletal hyperostosis, CVJDS* costovertebral joint dysfunction syndrome, GERD* gastroesophageal reflux disease, PUD* peptic ulcer disease, PTSD* post-traumatic stress disorder

Up to 3% of patients whose chest pain was originally diagnosed as non-cardiac chest pain experience a myocardial event within 30 days of initial presentation so it is important to consider cardiac risk factors such as older age, male gender, diabetes, hypertension, prior CAD, hyperlipidemia, or heart failure to help guide clinical judgment [6]. If a comprehensive assessment reveals cardiovascular or neoplastic conditions, it is imperative to appropriately transition care to a specialist or the emergency department depending on the acuity of the condition. The patient should be encouraged to establish care with the appropriate specialist for longitudinal care.

The epidemiology of chest pain differs between primary care and an emergency department setting [4, 5]. Musculoskeletal and gastrointestinal conditions are most common in primary care settings while serious cardiovascular disease is most common in an emergency department setting.

Persistent or Chronic Postsurgical Pain Syndrome

Perhaps the most prevalent cause of chest wall pain seen in clinical practice in a pain management clinic is chronic postsurgical pain (CPSP). The first attempt at establishing a definition for CPSP was by Macrae and Davies in 1999 which was proposed as pain that develops after an operation and is at least 2 months in duration with other causes of pain evaluated and excluded [7]. Persistent or chronic postsurgical pain involving the chest wall is most frequently seen in patients who have undergone mastectomy, thoracotomy, and video-assisted thoracotomy surgeries. The prevalence of CPSP described in studies varies between different surgeries: 11–57% in mastectomy and 22–67% in thoracotomy. The high variance in incidence percentages is due to the lack of uniformity when defining CPSP among studies [8]. Risk factors for CPSP can be categorized into patient factors and perioperative factors. Patient factors include female gender, young age, genetic predisposition, and psychosocial factors. Perioperative factors include but are not limited to duration of surgery, type of surgery, surgical technique, severity and duration of acute perioperative pain, and extent of nerve damage intraoperatively. Perhaps the most consistent element associated with the occurrence of CPSP is the severity and duration of acute postoperative pain. Up to 90% of thoracotomy patients experience postoperative pain requiring daily pain medication 1 week after discharge from the hospital [9]. Poorly controlled postoperative pain can lead to central sensitization and the development of "neuroplasticity" thus reducing the mechanical threshold for pain with an exaggerated response to noxious stimuli [10].

- *Post-mastectomy pain syndrome (PMPS)* is a complex neuropathic pain syndrome seen in patients after breast cancer procedures [11]. Although a common condition, there is no current standardized definition of PMPS. The etiology is likely due to damage to the intercostobrachial nerve (primarily during axillary node dissection), medial and lateral pectoral, long thoracic, or thoracodorsal nerves (notably during operations involving removal of tissue from the outer quadrant of the breast or axilla which is especially vulnerable). Risk factors for developing

PMPS are long duration of surgery, surgical technique, axillary node dissection, inadequate perioperative pain control, and patient factors. Although the etiology of PMPS has been well studied, consistently effective treatment options have yet to be discovered [12]. Pain may be severe and debilitating involving the ipsilateral arm and shoulder which may consequently lead to the patient developing adhesive capsulitis or complex regional pain syndrome (CRPS) [13]. PMPS is characterized by pain involving the anterior chest wall of the affected side, upper arm, and axilla more than 3 months after the initial surgery and cannot be attributed to other causes [14]. Patients may exhibit sensory features similar to other neuropathic pain syndromes such as burning, tingling, stinging, shooting, stabbing, or hyperesthesia [15]. Also, local radiation therapy and neurotoxic systemic chemotherapy which are often critical elements in breast cancer treatment may worsen PMPS pain [16, 17]. Further, a painful neuroma may develop at the end of a transected nerve which can be aggravated by palpation in the region of the scar sending painful nerve impulses along the distribution of the involved nerve [18].

- *Persistent thoracotomy pain syndrome (PTPS)* is a common occurrence after thoracic surgery. Persistent thoracotomy pain syndrome (PTPS) was first described in 1944 by United States Army surgeons as "chronic intercostal pain" in patients who had undergone thoracic surgeries or sustained chest trauma during World War II. These patients had significant persistent pain which interfered with rehabilitation and recovery [19]. The International Association for the Study of Pain (IASP) defines PTPS as "pain that recurs or persists along a thoracotomy incision at least 2 months following the surgical procedure." Although there are a variety of surgical techniques (posterolateral, muscle sparing, sternotomy, transverse sternothoracotomy, video-assisted thoracoscopic surgery [VATS]), PTPS can be attributed to intercostal nerve damage, pleural and muscle irritation, and costovertebral joint dislocation during surgery. Intercostal nerve damage from surgical trauma is the most common presentation of chest wall pain after thoracotomy which manifests as intense dysesthesia pain patients describe as shooting, sharp, or burning in quality sometimes accompanied by sensory loss and allodynia [20]. Symptoms may be appreciated with palpation along the interspace between ribs resulting in sharp pain. Patients may also complain of pain during active inhalation and exhalation which can lead to "intercepting" breathing [21]. The pain may also be band-like or belt-like along the distribution of the affected dermatome. It may also be associated with involuntary contractions or twitching in the muscle groups along the distribution of the neuralgia. Half of the PTPS is believed to be neuropathic in character. Pain caused by rotation, lateral flexion, flexion, or extension could be indicative of a musculoskeletal etiology. This type of pain is often non-dermatomal, with painful symptoms in the upper thoracic region which may limit shoulder function. Localized pain and tenderness may present in the sternal, sternocostal, and costovertebral junctions (i.e., costochondritis, Tietze syndrome). The intensity of acute postoperative pain directly correlates with the risk of developing a persistent pain state [22, 23].

Although the mechanisms for the development of chronic postsurgical pain syndromes are complex and not fully understood, most of the mechanisms pro-

posed involve neuroplasticity (spinal sensitization). More specifically, ephaptic conduction (cross-excitation) with alterations in Na+ and Ca2+ channel expression, collateral sprouting of nerve fibers into de-innervated areas, and direct coupling of sympathetic nerve and sensory nerve systems in the dorsal root ganglion have been proposed and studied in lab models as peripheral nerve changes leading to chronic pain. Additionally, mechanisms in the central nervous system have been proposed: primarily spinal cord reorganization and central sensitization. Ultimately, neuroplasticity may develop if there is inadequate perioperative pain control leading to the conversion of acute pain to chronic pain [23, 24]. Surgical technique changes including intercostal muscle flap and intercostal sutures placed through drilled holes in the lower rib decreased the incidence of postoperative pain but with questionable differences in pain at the 3- and 6-month mark. There was also a trend toward lower opioid consumption.

Modern perioperative anesthetic techniques focus on a multimodal approach combining traditional intravenous anesthetics with regional anesthesia techniques such as wound infiltration, epidural anesthesia, and nerve blocks (paravertebral, intercostal, erector spinae) to provide appropriate analgesia [25, 26].

Thoracic epidurals effectively decreased acute postoperative pain. However, studies have mixed results on the incidence of chronic post-thoracotomy pain. There appears to be a trend toward decreased incidence of chronic post-thoracotomy pain with early/preoperative epidural placement. Epidural opioids were also shown to offer improved analgesia compared to systemic opioids. However, epidurals were not shown to be consistently superior to thoracic paravertebral blocks or other regional techniques. There was however a noted increase in the risk of hypotension with epidurals in comparison to systemic analgesia, paravertebral blocks, and intercostal nerve blocks [27].

- *Incidence and prevalence*: A meta-analysis by Bayman et al. showed the incidence of persistent chronic pain after thoracotomy or video-assisted thoracoscopic surgery (VATS) to be 57% at 3 months after thoracotomy and between 23% and 81% at 6 months after thoracotomy with overall incidence at 6 months at 47%. A study by Perttunen et al. showed the incidence of PTPS was 80% at 3 months, 75% at 6 months, and 61% at 1 year after surgery with severe pain in 3–5% of patients. More than half of the study patients reported interference with daily life due to PTPS. Higher consumption of analgesic medication during the first postoperative week was directly correlated to the risk of developing PTPS [28].
- *Symptoms*: Patients describe a variety of pain symptoms with approximately 23–50% of the symptoms being characterized as neuropathic and the remaining as myofascial in nature. Commonly related neuropathic symptoms include dysesthesia, allodynia, burning numbness, and pins and needles. Common myofascial symptoms include aching, tenderness, and point tenderness. The pain is not influenced by respiration and there is often an associated shoulder pain (75%) [29, 30].
- *Risk factors*: Leading risk factors associated with increased incidence of PTPS include severity of postoperative pain intensity especially in the first 24 hours

which leads to suprasensitization, age < 60, loss of superficial abdominal reflex, female gender, benign esophageal disease, posttraumatic intercostal neuroma, healing rib fracture, frozen shoulder, local infection, costochondritis or costochondral dislocation, and local tumor recurrence. Psychological factors such as anxiety, depression, malignant disease, social network, and social status can also have an impact on the occurrence of PTPS. Other risk factors include intraoperative radiotherapy or cryoprobe neurolysis of intercostal nerves, preoperative pain and analgesic consumption (especially pain at another site), and genetic factors such as COMT (catechol-O-methyltransferase), voltage-gated Na channels, and GTP cyclohydrolase and tetrahydrobiopterin-related genes [31–33].

Postherpetic Neuralgia

Postherpetic neuralgia (PHN) is a pain syndrome regularly seen in the elderly population and is often difficult to treat. The underlying etiology is acute herpes zoster (HZ) from the reactivation of varicella-zoster virus (VZV). The virus remains dormant in the dorsal root ganglia of cranial or spinal nerves after the patient recovers from the primary infection. As cellular immunity weakens with age or is immunocompromised, the virus migrates along the peripheral nerves resulting in an acute neuritis. This acute neuritis often manifests with a rash and/or pain in the distribution of the infected nerves [34, 35]. At the cellular level, herpes zoster is distinguished by hemorrhagic inflammation of the dorsal root, the dorsal root ganglion, and the peripheral nerve with subsequent fibrosis upon completion of the acute phase [36, 37]. There are three common times pain occurs with herpes zoster. Historically, the three times were prodromal, acute herpetic neuralgia, and PHN. Prodromal HZ-associated pain often presents 3–5 days prior to the rash but in some instances may occur several weeks prior to the rash. Acute herpetic neuralgia occurs with the onset or right after the rash appears. PHZ occurs once the rash has resolved. These phases/times were revised, and currently the three phases of herpes zoster pain are as follows:

- Acute herpetic neuralgia: Associated pain prior to or concurrent to the eruption of rash, persisting up to 30 days from the initial presentation
- Subacute herpetic neuralgia: Persistent pain after the resolution of rash but dissipates within 4 months of initial presentation
- Postherpetic neuralgia: Persistent pain beyond 4 months from initial presentation of rash [38–40].

HZ is estimated to affect approximately 0.4% of the population annually, age-adjusted to the 2000 US population, or approximately 1 million individuals annually in the United States [41]. The incidence of HZ appears to increase with age from 0.4% to 1% at age 80 and up to 50% at age 90. Additionally, 6% of the population will have the second episode of HZ [42]. Incidence and prevalence of

PHN is estimated to be between 5% and 21%. This number is variable depending upon the definition used but also seems to increase with age. Oxman et al. and data from the United Kingdom General Practice Research Database both show the incidence of PHN increasing with age. Specifically, the incidence of PHN was found to increase from 6.9% in patients 60–69 years of age to 18.5% in patients 70 years or older who developed HZ [43]. Data from the United Kingdom General Practice Research Database showed the incidence of PHN (defined as pain at 3 months) increased from 8% at 50–54 years of age to 21% at 80–84 years of age. Interestingly, PHN occurs in 35% of patients not receiving antiviral therapy for HZ at 6 months and 15% of patients being treated for HZ with antiviral drugs [43, 44].

- Major risk factors for developing PHN include greater age (>60), female sex, presence of a prodromal pain, greater severity of the rash, and greater acute intense pain [45]. Other risk factors for HZ and therefore PHN include causes of impaired cellular immunity: disease (HIV), tumor, or medications (chemotherapy, immunosuppressive agents). VZV in peripheral blood, adverse psychosocial factors, white race, physical trauma, genetic susceptibility, diabetes, and female sex increase the likelihood of developing PHN [44, 46].
- *Pathophysiology*: There does not appear to be a definitive mechanism for the development of PHN. Histologic examination shows inflammation of the dorsal root, the dorsal root ganglion, and the peripheral nerve with subsequent fibrosis upon completion of the acute phase. Johnson found research showing that animal models of PHN, where VZV virus is injected in a rat footpad, showed upregulation of Nav 1.8 and Nav 1.3. Additionally, injection of VZV virus has also been shown to be capable of causing hyperalgesia. This combination of data suggests that the accumulation of extra channels may be responsible for lowering of action potential thresholds and thereby causing hyperalgesia. Neurophysiologic testing suggests that the loss of innervation and demyelination are important aspects of the pathophysiology of PHN [47]. Truini et al. used neurophysiologic testing to study patients with ophthalmic PHN found impairment of all sensory fibers. Specifically, Truini et al. found that the paroxysmal pain component correlated with A beta-fiber demyelination and the constant pain component correlated with marked loss of nociceptive afferents, both A delta and C fibers. However, allodynia did not correlate with neurophysiologic data [48]. Thus, current research suggests multiple mechanisms are involved in the development of PHN and further research is necessary.
- *Clinical manifestations*: Initial primary clinical symptoms associated with herpetic neuralgia are rash and/or acute neuritis pain with a small percentage of patients developing significant systemic symptoms, such as headache, fever, malaise, or fatigue [49]. Patients describe acute neuritis pain as a deep "burning," "throbbing," or "stabbing" sensation [50, 51]. Ninety days after resolution of cutaneous rash, the patient may continue to complain of significant pain along the similar distribution of the rash associated with the

original infection. Patients describe this pain as numbness, dysesthesia, pruritus, and allodynia (70% of patients) in the affected dermatome. Rarely patients will complain of weakness. Commonly affected nerves include thoracic (particularly T4-T6), cervical, and trigeminal nerves [52]. Approximately 50–70% of HZ infections occur in a thoracic dermatome, 10–20% present in a cranial or lumbar dermatome, and 2–8% occur in a sacral dermatome [53].

- *Diagnosis*: In most cases, the diagnosis of PHN is straightforward and is made when pain persists beyond 4 months in the same distribution as a preceding documented episode of acute herpes zoster. Thus, the diagnosis of PHN is based solely upon the clinical presentation. Additional factors supporting the diagnosis are as follows [54]:

  – Advanced age
  – Severe prodromal pain with acute herpes zoster
  – Severe preceding rash
  – Distribution in trigeminal or brachial plexus dermatomes
  – The presence of allodynia

  However, the diagnosis of PHN can be missed if the rash has resolved and the patient no longer remembers it or does not ascribe the pain to it [54]. Uncommonly, the nerve pain in acute herpes zoster may emerge in the absence of any skin eruption, as occurs in a condition called "zoster sine herpete" or in intercostal neuralgia. The presence of pain in trigeminal or radicular distribution combined with the detection of varicella-zoster virus (VZV) by polymerase chain reaction (PCR) in the cerebrospinal fluid supports the diagnosis of zoster sine herpete [55]. On examination, the areas affected by PHN may be remarkable for scarring related to the vesicular eruption of the preceding acute herpes zoster infection, or by areas of excoriation caused by scratching. The affected skin may display decreased sensation to mechanical and thermal stimuli, hyperalgesia (increased sensitivity to painful stimuli), or allodynia (pain produced by normally non-noxious stimulation).

  No diagnostic laboratory or imaging tests are usually required to make the diagnosis. Laboratory data that may be used to help confirm the diagnosis include CSF analysis, viral PCR, immunofluorescent staining, antibody titers, and MRI. CSF analysis was found to be abnormal in 61% of patients. Pleocytosis was seen in 46% of patients, elevated protein in 26% of patients, and VZV virus in 22% of patients [56]. Viral cultures, PCR, immunofluorescent staining, and significant increases in HZ antibody titers (4× increase) may be used to help differentiate and diagnose difficult cases of HZ from herpes simplex and confirm the diagnosis of "zoster sine herpete" [57]. Finally, a study by Haanpaa et al. found that out of 16 patients diagnosed with HZ, 56% of patients had visible lesions on MRI that could be attributed to herpes zoster. In 56% of those, patients with lesions on MRI developed PHN. Interestingly, none of the patients without lesions on MRI developed PHN [56].

Treatment

The treatment of chronic pain is difficult at its core, with patients often presenting to chronic pain clinics after failing conservative measures from a single or multiple providers. The challenges in the management of chronic pain translate to CPSP which is magnified due to lack of ample effective treatment options despite being well researched. Although the pain generator in CPSP may be mixed with both nociceptive and neuropathic elements, it is widely accepted that the primary mechanism in CPSP is neuropathic in nature with most treatment options focused on the neuropathic aspect of the pain [58]. As a result, there is a considerable overlap of treatment options between CPSP and other neuropathic pain syndromes (i.e., PHN, diabetic neuropathy). There are limited studies on the specific treatment of PTPS/PMPS, rather the majority of data has been extrapolated from general studies on neuropathic pain. Generally, the first step in treatment is focused on gabapentinoids (gabapentin, pregabalin) and antidepressants (tricyclic antidepressants, SNRIs) which have the strongest evidence supporting their use in neuropathic pain. Second-line agents include topical agent capsaicin and lidocaine with tramadol and strong opioids forming third-line options [59]. Although most treatment protocols are focused on the more common neuropathic component of CPSP, myofascial pain remains as a treatable element of pain that should be considered when formulating a treatment strategy [60]. Treatment is largely focused around medication management with procedural and surgical options lacking strong evidence showing favorable outcomes.

- *First-line agents*:
  - Gabapentin, pregabalin, and tricyclic antidepressants (TCAs) have all been shown to be more effective than placebo in systemic reviews [59, 61–63].

    Gabapentin, an anti-convulsant, is the most commonly used medication in the treatment of neuropathic pain conditions. Although the use of gabapentin in chronic neuropathic pain is well documented, studies also support its use as a pre-emptive analgesic. In a prospective study by Solak et al. on 40 patients with PTPS, gabapentin was titrated up as tolerated to 2400 mg/day for 60 days and was compared to naproxen 1000 mg/day. Eighty-five percent of gabapentin group versus 15% of naproxen group had VAS <5 by day 60 [64]. A study by Sihoe et al. on 60 patients with refractory pain persisting for 4 weeks or greater after thoracic surgery or trauma found that 73% and 75% experienced a reduction in pain and paresthesia, respectively [65]. Dosing range was 300–900 mg/day and mean duration of gabapentin use was 21.9 weeks.

    Pregabalin, similar to gabapentin, is an amino acid derivative of gamma-aminobutyric acid (GABA) and is classically used to treat neuropathic pain. Compared to gabapentin, pregabalin can achieve equivalent analgesia at lower doses due to its superior bioavailability, rapid absorption, and linear increases in plasma concentration with increasing doses [66]. Studies examining the use of pregabalin for PTPS specifically are small with variable results. The largest available study is a prospective randomized, double-blind, placebo-controlled

study in 99 patients which showed an increase in the likelihood to develop PTPS when using pregabalin compared to placebo [67]. However, the pregabalin group required less analgesics, reported less severe pain, and presented with less neuropathic characteristics than placebo at 3 months post-surgery. In another randomized prospective study, early use of pregabalin in the immediate postoperative period was found to lead to lower VAS scores at up to 24 weeks post-surgery when compared to oral diclofenac [66].

A meta-analysis by Finnerup et al. revealed 14 RCTs of gabapentin (nine positive), 6 RCTs of gabapentin extended release (ER) (4 positive), and 25 RCTs of pregabalin (18 positive) [59]. Pooled analysis revealed combined NNT was 6.3 (5.0–8.3) for gabapentin, 8.3 (6.2–13) for gabapentin ER, and 7.71 (6.5–9.4) for pregabalin. Dosing regimens used in gabapentin RCTs were between 900-3600 mg/day, while those of gabapentin ER were between 1200–3600 mg/day. Eighteen of the 25 RCTs with pregabalin were considered high-quality evidence and showed increased responders with 600 mg/day vs 300 mg/day. A 2017 Cochrane systematic review by Wiffen et al. identified eight placebo-controlled randomized trials comparing various formulations of gabapentin in over 2200 patients with moderate to severe pain due to PHN [68]. In this meta-analysis, daily doses of gabapentin at between 1200 and 3600 mg were associated with higher rates of benefit (at least 50% reduction in pain intensity) than placebo (32% versus 17%, risk ratio 1.8, 95% CI 1.5–2.1, number needed to treat 6.7). A pooled analysis of side effects across 37 trials for multiple types of neuropathic pain gabapentin compared to placebo revealed most common adverse effects were somnolence or drowsiness (14% versus 5%), dizziness (19% versus 7%), peripheral edema (7% versus 2%), and ataxia or gait disturbance (14% versus 3%). Two randomized controlled studies with over 400 patients found pregabalin improved sleep and pain at daily doses of 150–600 mg [69, 70]. Pooled analysis showed most common side effects were dizziness, somnolence, dry mouth, peripheral edema, and weight gain. Another important consideration for prescribing purposes is the designation of pregabalin as a schedule V controlled substance in the United States for abuse potential due to the medication's ability to cause euphoria. Gabapentin and pregabalin are not recommended in patients with renal insufficiency.

Antidepressants such as tricyclic antidepressants (TCAs) and SNRIs have been shown to be effective for painful neuropathic syndromes such as diabetic neuropathy and postherpetic neuralgia. Analgesic effects have been shown to be independent of its antidepressant properties [71]. TCA inhibits the reuptake of serotonin and norepinephrine in the descending inhibitory fibers of the pain pathway, thus resulting in an increased inhibition of nociceptive signals from the periphery [72, 73]. The use of SNRIs duloxetine and venlafaxine has been shown to be effective for neuropathic pain. SNRIs work by inhibiting monoamine reuptake [59]. TCAs are appropriate for moderate to severe pain in patients who cannot tolerate gabapentinoids but should be avoided in patients with heart disease, epilepsy, or glaucoma due to their anticholinergic effects. The efficacy of TCAs in patients with PHN was first described by Watson et al.

in 1982 [74]. A double-blinded, randomized, crossover study in 58 patients with PHN compared amitriptyline with lorazepam and placebo. Doses were titrated to the maximum tolerated dose and patients were instructed to record pain scores in a diary using verbal descriptions. Mean amitriptyline dose was 65 mg/day, and maximum dose was 150 mg/day. Forty-seven percent of patients reported moderate or greater relief with amitriptyline, 16% with placebo, and 15% with lorazepam. Greater pain relief was reported with higher amitriptyline doses [75]. The authors concluded that serum levels of amitriptyline and active metabolites must be maintained at concentrations of 100 ng/mL for at least 3 weeks before a patient is considered to have failed TCA therapy. In a small crossover study, 68% of 33 patients with PHN were found to be responders to either amitriptyline, nortriptyline, or both. Amitriptyline and nortriptyline were found to have similar analgesic effects; however, nortriptyline was associated with fewer side effects [76]. Anticholinergic side effects can be significant, leading to patient noncompliance and abrupt cessation of medication usage. Desipramine has the fewest side effects out of the first-generation TCAs and in a randomized, double-blinded, crossover study in 26 patients desipramine was found to be superior in relieving painful PHN symptoms when compared to placebo. Another consideration to note when prescribing TCAs is the lag time of 3 weeks before the patient begins to experience the beneficial effects of the medication.

- *Second-line agents*:
  - Topical agents such as lidocaine and capsaicin have been shown to be beneficial in patients who want to avoid systemic therapy.

    Capsaicin is a topical analgesic derived from capsicum chili peppers. Method of action was previously believed to be secondary to reduction of substance P content in the skin, but subsequent studies have shown that it is more likely that the altered expression of the capsaicin receptor TRPV1 in peripheral nociceptive nerve fibers results in attenuation of cutaneous hypersensitivity and decreased pain. Early capsaicin preparations of creams, lotions, and patches, generally in the range of 0.025–0.1% by weight, were dosed at 3–5 topical applications for 2–5 weeks with statistically significant modest beneficial effects for various pain syndromes (PHN, diabetic neuropathy, chronic musculoskeletal pain) [61, 77]. A significant percentage of patients have difficulty tolerating capsaicin-based products due to cutaneous reactions, contamination of patient environment (clothing, bedding, contact lens) due to frequent removal, and application of topical patches and creams in as high as one-third of patients leading to noncompliance. A 2013 Cochrane systematic review by Derry et al., which was later updated in 2017, identified four randomized controlled trials that evaluated 1272 subjects with PHN treated with one application of either high-concentration capsaicin patch or standard-concentration capsaicin. A $\geq$30% pain intensity reduction at 8 weeks, compared with baseline, was significantly greater for high-concentration capsaicin patch (43% versus 34%, relative benefit 1.3, 95% CI 1.1–1.5) than standard-concentration

capsaicin [78]. In clinical practice, 60-minute application of high-dose capsaicin (8% Qutenza patch) may be a superior option to multiple self-applications of standard-concentration capsaicin creams. High-concentration capsaicin must be administered by a healthcare professional and patients monitored for 2 hours post-treatment. To mitigate the local pain from capsaicin application, the skin can be pretreated by local anesthetic with post-treatment oral analgesics [79].

- *Third-line agents*:
  - *Opioids*: The use of opioids in the treatment of neuropathic pain syndromes is controversial. Opioids should be initiated at low doses before slow titration up to pain relief and weaned down once more definitive treatments take effect. Although opioids have been found to be effective for pain relief in patients with neuropathic pain, there is a significant risk of abuse potential, physical dependence, overdose, tolerance, and addiction. Due to these risks, many experts recommend opioids to be used with caution as a second- or third-line agent in treatment [50, 59, 80]. Some experts argue for the use of low-dose opioids in the treatment of PHN particularly in the elderly population citing lower risk of psychiatric comorbidities and lower risk of addiction and opioid abuse. Unfortunately, available RCT studies supporting the use of opioids focus on the efficacy in pain reduction and do not definitively discuss the concern for abuse, tolerance, overdose, and dependence. Studies favoring the use of the opioids have described pain relief in patients with PHN. A randomized placebo-controlled trial by Raja et al. compared morphine 91 mg or methadone 15 mg and nortriptyline 89 mg or desipramine 63 mg in 76 patients [81]. Opioids and TCA reduced pain (1.9 and 1.4) more than placebo (0.2; $p < 0.001$), with no discernible effects on any cognitive measures. Pain relief was 38% when treated with opioids, 32% with TCA, and 11% with placebo ($p < 0.001$). In patients who completed all three treatments, 54% preferred opioids and 30% preferred TCA ($p = 0.02$). A multicenter, randomized double-blind, placebo-controlled trial by Boureau et al. compared the safety and efficacy of extended-release tramadol to placebo in the treatment of PHN over a period of 6 weeks in 127 patients. The tramadol group had significantly lower pain intensity requiring less rescue medication than the placebo group. Average tramadol dose was 275.5 mg/day after 1-week dose adaptation with no difference between the two groups in percentage of patients with treatment-associated adverse effects (TAAEs), 29.7% in the tramadol group, and 31.8% in the placebo group [82].
- *Interventional therapies*:
  - *Pulsed radiofrequency*: Pulsed radiofrequency (RF) is a technique in which the target neural structure is exposed to high frequency (300–500 kHz) and relatively low voltage (40–60 V) in RF pulses in contrast to the traditional coagulation achieved by continuous high-temperature RF current during rhizotomies. Although its mechanism is not well understood, the technique is appealing to

clinicians largely due to the technique's superior safety profile to achieve pain relief without the destruction of neural tissue [83]. A randomized trial by Cohen et al. comparing 49 patients with chronic postsurgical pain (thoracotomy, sternotomy, mastectomy) demonstrated that pulsed RF of the dorsal root ganglion (DRG) reduced pain by 60% compared to 21% and 27% pain reduction with pulsed RF of the intercostal nerve and standard medical management respectively after 6 weeks [79]. Pulsed RF is a technique that may be utilized in the setting of PTPS after failing conventional medication management prior to neuromodulation options [84, 85].

- *Peripheral field nerve stimulation*: Peripheral field nerve stimulation (PFNS)) is the nonspecific stimulation of peripheral nerves with subcutaneous placement of an electrode. This technique is differing from peripheral nerve stimulation which is placed directly adjacent to the target nerve. PFNS was first described with occipital nerve stimulation in the treatment of chronic migraines [86]. A study by Hamza et al. in 50 patients with diabetic peripheral neuropathy found improved VAS in PNFS (6.2–2.5) when compared to sham treatments (6.4–6.3). Patients also reduced their daily oral non-opioid analgesic requirements by 49 and 14% after PNFS and sham treatments respectively [87]. PNFS is a less-invasive technique than spinal cord stimulation (SCS) and may be utilized as a bridge therapy between injections and spinal cord stimulation [88, 89].
- *Spinal cord stimulation*: Spinal cord stimulation (SCS) or dorsal column stimulation is an interventional technique utilizing high-frequency, low-stimulation currents delivered via electrodes placed into the epidural space of the spine to stimulate the dorsal column. Although Melzack and Wall provided the earliest explanation for the analgesic effects of SCS with the gate control theory of pain [90], the general belief is that there are multiple mechanisms responsible for the ischemic, sympathetic, and neuropathic pain relief offered by SCS [91]. For chest pain associated with PTPS and PMPS, two leads are placed with one midline and the second lead is placed more laterally in the paramedian position between T1 and T4 [91].
- *Cryotherapy*: Cryotherapy is the use of small controlled spray of liquid nitrogen to freeze peripheral nerves. There is a paucity of clinical studies studying the use of cryotherapy for PHN. The results of a retrospective review of 70 patients with chronic intercostal PHN treated with cryotherapy were poor, and the authors did not recommend the use of cryotherapy in the treatment of intercostal PHN [92].

  The use of cryoablation in post-thoracotomy pain has been conflicting, but overall data does not support its use for PTPS with some studies even discovering increased incidence of pain [93].
- *Surgery*: Surgical options include electrical stimulation of the thalamus, anterolateral cordotomy, and electrocoagulation of the dorsal root. These invasive techniques are associated with considerable risk of permanent neurological damage without clear and consistent benefit in patients with PHN. Dorsal column stimulation and dorsal root ganglion stimulation are still

considered experimental. In a literature review performed by Kurklinsky et al. in 255 patients with PHN-treated permanent implantation of a dorsal column stimulator, 120 experienced long-term relief [94]. There are currently no studies describing the use of dorsal root ganglion stimulation in the treatment of PHN.

Surgical options in PMPS are limited to patients who have painful neuromas which may develop at the end of transected nerves causing radiating pain along the distribution of the affected nerve [18]. Neuromas can be localized with careful palpation along the axilla which may trigger painful radiating impulses. Once identified, a diagnostic test can be performed by injection at the localized site with 1% lidocaine. If pain relief is achieved after local infiltration, the patient has a positive diagnostic test and is a suitable candidate for surgical excision of the neuroma for permanent pain relief. Another surgical option is axillary scar release in the setting of painful postsurgical scar in the axilla which is meant to improve contour, release scar contracture, relieve skin tension, and mobilize tissue for reconstructive surgery (Z-plasty) [11].

- *Inconclusive therapies*:
  - *NSAIDs*: Studies looking at the use of NSAIDs in the management of CPSP are limited. One small randomized controlled trial showed improved VAS at 6 months post-surgery with pre-emptive dexketoprofen and epidural when compared to pre-emptive epidural-only and control groups [95].
  - *Carbamazepine, oxcarbazepine, lamotrigine*, and *valproic acid* have showed some benefit in small trials for PHN and in other neuropathic conditions (diabetic peripheral neuropathy and trigeminal neuralgia). This group of medications may have serious undesirable side effects; however, it may be an option as an alternative second-line regimen when patients have failed first-line agents or choose to avoid injections and opioids while continuing to have intractable pain.
  - *Intrathecal glucocorticoid injections* are an option for patients with intractable pain despite medication management and more conservative measures. Patients with PHN not involving the trigeminal nerve may have pain relief with intrathecal administration of glucocorticoids. In a large study involving 277 patients with intractable PHN, patients were randomized into three groups (60 mg methylprednisolone and 3 ml of 3% lidocaine combination, 3 ml of 3% lidocaine only, no treatment). Intrathecal injection of the prepared solution was administered once per week for up to 4 weeks. There is reduction of pain intensity and area of pain >70% at 4 weeks in the methylprednisolone-lidocaine group. Minimal improvement was found in the lidocaine-only and the control group. Interleukin-8 levels in the cerebrospinal fluid (CSF) were also measured (inverse relationship between concentrations of interleukin-8 in the CSF and the duration of neuralgia) and found to be decreased by 50% in the methylprednisolone-lidocaine group while there was no significant change in the lidocaine-only and the control group. Interleukin-8 has been associated with chronic inflammatory conditions and found to be elevated in the CSF of patients with intractable PHN [96]. Another trial comparing the

effects of intrathecal vs epidural methylprednisolone in 25 patients found that intrathecal methylprednisolone provided superior pain relief at all time points with increased reduction in interleukin-8 levels in the CSF [97].

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Chapter 10
Pain Management for Chronic Abdominal Pain

Enas Kandil

Introduction

Chronic abdominal pain is a complex medical problem and is the leading symptom for referral to a gastroenterologist [1]. Causes of chronic abdominal pain are diverse and can require an extensive workup and repeated imaging sometimes with no clear etiology [2, 3]. Abdominal pain may be due to somatic reasons transmitted through A-delta nociceptors as in chronic abdominal wall pain (CAWP) or visceral reasons transmitted through C-type nociceptors as in chronic pancreatitis and ulcerative colitis. A detailed history and physical examination are key in addressing abdominal pain. Attention to the patient's pain symptomatology details may reveal the etiology and assist in decision for the best management approach.

Somatic Reasons for Abdominal Pain

Chronic abdominal wall pain: CAWP should be suspected if pain is localized, is unrelated to food, and worsens with movement. CAWP is seen in 10–30% of patients presenting in gastroenterology clinics complaining of chronic abdominal pain and is usually overlooked [4]. CAWP is due to entrapment of the anterior cutaneous sensory branch of the neurovascular bundle of T7–T12 spinal nerves. Other causes of CAWP are spigelian hernia, myofascial pain, slipped rib syndrome, and diabetic radiculopathy. CAWP is four times more common in women with incidence in abdominal pain studies reported at varying percentages. One large study with more than 2000 patients reported incidence close to 5% while in another study

E. Kandil (✉)
University of Texas Southwestern, Dallas, TX, USA
e-mail: Enas.Kandil@UTSouthwestern.edu

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incidence was close to 4%. The prevalence of CAWP in the general population has not been studied and should be suspected when pain is sharp localized with a positive Carnett's sign on physical examination [5]. Carnett's sign is described as increased pain at the point of maximal tenderness on contraction of abdominal wall muscles. This is in contrast to visceral pain where contraction of anterior abdominal muscles causes pain relief. A positive sign is accurate in 97% of cases and indicates that pain is of somatic origin [6]. Treatment of CAWP is usually supported with physical therapy with strengthening of abdominal wall muscles, activity modification, patient reassurance, over-the-counter analgesics, and trigger point injections in moderate to severe pain and where other interventions have failed. Treatments with anticonvulsants, lidocaine patches, and muscle relaxants have also been used [7].

Visceral Reasons for Abdominal Pain

Visceral pain occurs due to receptor response to mechanical and chemical stimuli. Mechanical stimuli are in the form of stretch, distention, contraction, traction, and compression relayed through visceral receptors located on the serosal surfaces, within the mesentery and the walls of the viscera, which can also relay chemical stimuli. Input from the abdominal viscera travels along the afferent visceral fibers and then through the main thoracic splanchnic nerves and ends in the dorsal horn of the spinal cord. This signal is further transmitted to the brain through the spinothalamic, spinoreticular, and the spinomesencephalic tracts. The spinothalamic tract terminates in the thalamus where the thalamocortical fibers transmit the signal to the somatosensory cortex while the spinoreticular and the spinomesencephalic fibers terminate in the medial thalamus where thalamocortical fibers further ascend to the anterior cingulate cortex and insula. In addition to these ascending pathways, several descending inhibitory pathways modulate the perception of visceral pain. Visceral pain is usually described as dull and poorly localized and sometimes associated with other symptoms such as nausea, vomiting, and radiation to other structures [8]. Treatment of visceral pain depends on the etiology and diagnosis. A detailed history and physical examination are essential to determine if visceral pain should be treated symptomatically or is an indication of a systemic disease requiring further workup which most likely will be conducted by the patient's primary care provider or gastroenterologist. The vast majority of patients with somatic and visceral pain seen by a pain management specialist will have undergone an initial workup by a primary care provider where treatable systemic diseases have been ruled out or proper treatment has been initiated and deemed ineffective in controlling of pain symptoms. Pain management has a unique perspective on treatment of chronic abdominal pain where multimodal techniques are usually applied combining interventional, non-interventional, and interdisciplinary approach guaranteeing a favorable environment for improvement of pain symptoms. Most common functional causes of visceral pain are functional dyspepsia (FD), irritable bowel syndrome (IBS), and centrally mediated abdominal pain syndrome (CAPS). FD is

associated with early satiety, sense of fullness, and epigastric burning. IBS is a chronic inflammatory condition associated with abdominal pain and change in stool frequency and consistency, with a remitting and relapsing disease course. Both FD and IBS are believed to be due to increased visceral sensitivity with decreased descending inhibitory modulation and central sensitization. CAPS is characterized by severe, frequent, prolonged abdominal colicky pain which is sometimes described as burning and is more widespread [9]. CAPS is believed to be due to central sensitization [10]. Other functional causes included irritable bowel diseases such as Crohn's and ulcerative colitis. The most common non-functional cause of chronic abdominal pain resulting in referral to a pain management specialist is chronic pancreatitis.

Non-interventional Treatment of Visceral Pain

Non-steroidal Anti-inflammatory Drugs

Once other causes of visceral pain exacerbation have been ruled out and underlying disease medications have been escalated with no improvement in pain symptoms, patients should be started on over-the-counter analgesics. Acetaminophen was preferred over non-steroidal anti-inflammatory medications (NSAIDs) despite being less effective due to its lower side effects. NSAIDs have been initially reported to precipitate pain in conditions such as IBD; however, later case reports and small studies have shown no association between NSAIDs and IBD flares [11]. Large randomized studies of NSAIDs and IBD are still lacking. NSAIDs act as anti-inflammatory through inhibiting prostaglandin production by inhibiting cyclooxygenase enzyme (COX) [12]. Nonselective NSAIDs inhibit COX1 enzyme which is responsible for intestinal mucosal integrity. Selective COX2 inhibitors inhibit inflammation without affecting the mucosal integrity; thus, their use is preferred in IBD due to their fewer gastrointestinal effects; however, their cardiovascular risk should also be considered [13]. Several controlled studies have shown no increase in IBD flares with selective COX2 when compared to placebo [14–16]; however, long-term controlled trials are still needed.

Opioids

Opioids have been used in visceral pain; however, their use has not been without complications. Opioids are known to be effective for treatment of acute pain; however, their long-term effectiveness for chronic non-cancer pain (CNCP) is questionable [17]. Opioid use for visceral pain has been complicated with side effects such as tolerance, dependence, and the potential for misuse and abuse in addition to other common opioid side effects such as respiratory depression, constipation, and sedation [18]. More specific side effects are opioid bowel syndrome characterized by

increased pain intensity which worsens with increase of the dose of opioids. Another concerning side effect for opioids in visceral pain management is toxic megacolon which may be precipitated or worsened by constipation [19]. In an analysis of the TREAT registry patients, which is a prospective long-term registry of patients with Crohn's disease, opioids were shown to be associated with increased mortality (OR, 1.84; $p = 0.004$). On further analysis this was not significant; however, opioids were found to be associated with increased infection (OR, 2.38; $P < 0.001$) which was consistent even after adjustment for disease severity and immunosuppressant drugs. This was believed to be explained by the effect of opioids on gastrointestinal motility and bacterial invasion of damaged mucosa [20]. This is consistent with other studies showing opioids having a direct immunosuppressant effect and predisposing patients to serious infections [21]. If opioids are to be considered in visceral pain, patients should be assessed for opioid misuse using opioid risk assessment tools (ORT); patients should be frequently monitored with urine toxicology screens and using the state prescription database to monitor all scheduled medication use [22, 23].

Antidepressants

The most studied antidepressant in IBD is tricyclic antidepressants (TCA). Several meta-analyses have shown benefit with TCA. TCA should be considered in IBS treatment [24]. Selective serotonin reuptake inhibitors (SSRIs) have not been as effective in treatment of IBS where several studies did not show any improvement in pain symptoms [25]. One meta-analysis showed an overall risk reduction as compared to placebo (OR, 0.66; 95% CI, 0.57–0.78) [26]. As for other antidepressants, several studies have shown paroxetine to improve quality of life [27] while other studies showed benefit with bupropion [28, 29]. Antidepressants are found to be effective as it is not unusual to have coexisting depression in chronic abdominal pain patients [30].

Anticonvulsants

Several small studies have shown the effectiveness of gabapentin [31] and pregabalin [32] for treatment of visceral pain. It is believed that they target visceral hypersensitivity similar to their effects on neuropathic pain [33]. Larger more randomized controlled studies are needed to test this hypothesis further [34].

Psychotherapy

Most interdisciplinary pain practices have access to a psychologist. Chronic pain patients including chronic abdominal pain patients benefit from psychotherapy [35]. Psychotherapy has been effective in treating anxiety, depression, and pain flare-ups which is further translated in less utilization of healthcare services [36]. The most

utilized psychotherapy in IBD has been cognitive behavioral therapy (CBT). CBT improves coping skills while decreasing anxiety and depression despite no change in disease progression [37]. Several studies [38, 39] and two meta-analyses have demonstrated overall improvement in quality of life in patients with IBD [40].

Interventional Treatment of Visceral Pain

Interventional procedures for visceral pain are best incorporated in conjunction with medical and psychological interventions as part of multidisciplinary or interdisciplinary programs for guaranteed best results. Sympathetic blocks for pain relief have been used for decades [41] and are most effective for visceral and neuropathic pain. Some of the most commonly targeted sympathetic ganglia are celiac plexus (CP) and splanchnic, superior hypogastric (SHG), and ganglion impar (GI).

Celiac and Splanchnic Plexus Block

The celiac plexus is anterior and anterolateral to the aorta just below the celiac artery at the level of the first lumbar vertebra. The plexus is a result of the union of the greater (T5 through T10), lesser (T10 and T11), and least (T11 and T12) splanchnic nerves with the celiac branch of the right vagus. It has both sympathetic and parasympathetic fibers. The celiac plexus innervates the distal esophagus, stomach, duodenum, small intestine, ascending and proximal transverse colon, adrenal glands, pancreas, spleen, liver, and biliary system [42]. Celiac plexus block is most effective for visceral pain originating from pancreatic malignancy or visceral abdominal pain from chronic pancreatitis. In a meta-analysis evidence supported the use of CPB which provided improved analgesia and/or decrease in opioid consumption, and thus a decrease of opioid-induced adverse effects, in comparison with a conventional treatment [43]. This has been demonstrated in several other randomized controlled clinical trials, mainly in pancreatic cancer pain [44–47]. CPB is performed using fluoroscopy with the patient in the prone position. The needle entry point is just below the tip of the 12th rib, and using X-ray screening in two planes, the needle is advanced until it hits the side of the L1 vertebra. The needle is withdrawn slightly and then redirected forward until it is in the area of the celiac plexus, avoiding the aorta and inferior vena cava. Radio-opaque dye is injected to confirm the proper placement of the needle, and then the appropriate mixture is injected, 10 ml of local anesthetic of choice on each side. For neurolytic block, 5 ml 6% aqueous phenol +5 ml of local anesthetic is injected on each side which is usually reserved for visceral pain due to malignancy. Diarrhea is the most common side effect, occurring in up to 44% of cases, and is usually self-limiting. Diarrhea occurs due to interruption of the sympathetic outflow allowing the unopposed parasympathetic one. Other reported potential complications include hypotension in dehydrated patients, arterial injury, pneumothorax, hematoma, pleuritis,

pericarditis, intervertebral disk injury, and retroperitoneal abscess. Anterior spinal cord infarction due to injection or injury to spinal arteries has also been reported [48, 49].

Superior Hypogastric Plexus Block (SHPB)

The superior hypogastric plexus is located at the lower third of the fifth lumbar vertebral body and upper third of the first sacral vertebral body. SHPB is responsible for sympathetic innervation to all the pelvic viscera except the ovaries and fallopian tubes. It continues distally as the hypogastric nerves, which form the inferior hypogastric plexus. SHPB is effective for visceral pelvic pain secondary to malignancy and non-malignant conditions such as endometriosis, pelvic inflammatory disease, testicular pain, proctalgia, and ilioinguinal neuralgia. SHPB has been shown in a randomized controlled study by Mishra et al. to decrease pain intensity and morphine consumption [50]. In that study 50 patients with visceral pain due to pelvic cancer were randomized to either ultrasound-guided SHPB and oral morphine or oral morphine only. Patients who received SHPB had a decrease in pain intensity and a less morphine consumption with no differences in adverse effects. The block is performed using fluoroscopy with the patient in the prone position. The fluoroscopy tube is tilted in a cranio-caudal direction to square off the L5–S1 disk space. The fluoroscopy tube is then rotated obliquely toward the side of needle entry until the tip of the respective transverse process is superimposed on the anterolateral border of the L5 vertebral body or iliac crest appears to be coming into the path of the needle. A 22-gauge, 5-inch spinal needle is advanced through anesthetized skin in a coaxial view at the anterior margin of the L5–S1 disk until needle tip reaches the anterolateral border of the vertebral body. The needle is then advanced under AP and lateral projection until needle tip is seen at the lateral one-fifth of the vertebral body on AP projection and at the anterior one-fifth of the vertebral body on lateral projection. Radio-opaque dye is injected to confirm the correct placement of the needle, followed by 10 ml of local anesthetic of choice on each side. For neurolytic block, 5 ml 6% aqueous phenol +5 ml of local anesthetic is injected on each side [51]. Potential side effects include backache; care should be given to more serious potential complications such as retroperitoneal hematoma; bowel, bladder, or ureteral injury; and somatic nerve damage.

Ganglion Impar Block

The ganglion impar or “Walther’s ganglion” is the terminal ganglion of the sympathetic chain. It is a single ganglion located at the sacrococcygeal junction. Ganglion impar innervates the perineum, distal rectum, distal vagina, distal urethra, and anus [52]. The most common indications are visceral pain associated with pain from malignancy of primary or metastatic lesion of the vulva, rectum, anus, or perineum. The use of GI block and neurolytic block for visceral pain in cancer is supported by

case reports and case series showing pain improvement and no significant adverse events [53]. Ganglion impar block should be avoided in patients with open wounds involving the rectal area, patients who are anticoagulated, or those suffering from coagulopathies as they are poor candidates.

The procedure is done with fluoroscopy with the patient in the prone position. In the transsacrococcygeal technique, a 22-gauge, 1.5-inch spinal needle is advanced through the sacrococcygeal disk and positioned carefully anterior to the sacrococcygeal junction. After injection of contrast where a classical comma sign is seen, an injection of 3–5 ml of bupivacaine 0.25% or phenol 6–10% is usually effective. Ganglion impar block is a low-risk procedure; however, injury to visceral structures such as the rectum and infection have been reported.

Conclusion

Chronic abdominal pain can be complicated, difficult to treat and manage. Careful attention should be given to history and physical examination which may reveal key clues and direct proper management while avoiding costly and unnecessary tests and interventions [54]. Chronic abdominal pain is best addressed using a multidisciplinary approach where care is also given to psychological aspects of chronic pain; building coping skills and medication management complemented with interventional techniques when deemed appropriate are usually successful in controlling pain symptoms and improving quality of life [55].

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Chapter 11
Pelvic Pain

Avinash S. Chavda and Kelly M. Scott

Introduction

Chronic pelvic pain is an increasingly important, multifactorial condition requiring a multidisciplinary approach to diagnosis and treatment. Terminology often varies across specialty, and practice guidance for the majority of etiologies of pelvic pain remains nebulous. Randomized controlled trials are emerging. A summary of treatments that are evidence-based, emerging, accepted, and disproven by etiology is provided in tabular form at the end of the chapter.

Epidemiology

Pelvic pain is a multifactorial condition that arises from disorders of the viscera, bony structures, soft tissues, nerves, and muscles of the pelvis, bounded anteriorly by the anterior abdominal wall, posteriorly by the buttocks, superiorly by the umbilicus, and inferiorly by the pelvic floor musculature.

The causes of pelvic pain—acute and chronic—span roughly 70 diagnoses and are listed in Tables 11.1 and 11.2. Patients frequently consult a series of providers across specialties and may be given multiple diagnoses resulting in multiple, sometimes conflicting treatment plans. Specialties commonly seen for pelvic pain include primary care, OB/GYN, gastroenterology, neurology, urology, psychology, physical therapy, and physical medicine and rehabilitation. The breadth of providers involved in treatment and the rarity of interdisciplinary centers may help explain a lack of uniform terminology addressing the many manifestations of pain in the pelvis.

A. S. Chavda · K. M. Scott (✉)
Physical Medicine and Rehabilitation, University of Texas Southwestern Medical Center, Dallas, TX, USA
e-mail: avinash.chavda@phhs.org; kelly.scott@utsouthwestern.edu

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Table 11.1 Common acute pelvic pain causes

Gastrointestinal	Urologic	Gynecologic	Musculoskeletal
Acute appendicitis	Acute prostatitis	Ectopic pregnancy	Acute fracture
Bowel obstruction	Nephrolithiasis	Ovarian cyst rupture	Acute hip or gluteal tendinopathies
Hernia	Urinary tract infection	Ovarian torsion	Osteitis pubis
	Sexually transmitted infection	Endometriosis	
		Sexually transmitted infection	
		Pelvic inflammatory disease	
		Vaginal yeast and bacterial infection	

Acute pelvic pain is frequently dealt with in an emergent or urgent setting, as many causes of acute pelvic pain, including acute appendicitis, ectopic pregnancy, ovarian torsion, and ovarian cyst ruptures, can be life threatening. Other common causes of acute pelvic pain, particularly those managed by primary care providers and gynecologists, include urinary tract infections and endometriosis. The percentage of acute pelvic pain that cannot be given a diagnosis ranges between 8% and 37% across multiple studies [63]. Cases of acute pelvic pain that remain undiagnosed are unlikely to receive timely treatment and may become chronic.

Pelvic pain lasting greater than 6 months is considered chronic (CPP) and is likely of greater interest to the pain specialist. CPP is thought to arise from a variety of visceral, myofascial, and neuropathic etiologies. CPP is associated with significantly decreased quality of life and disproportionately affects women with a prevalence of up to 33% of women worldwide with an average symptom duration of 2.5 years. Approximately 2–16% of men under 50 are also affected worldwide [62].

CPP is often multifactorial and is accompanied by comorbidities that commonly attend chronic pain disorders including depression, sleep disturbance, and impaired social and sexual functioning. Physical, sexual, and emotional abuse may be one of many causes of CPP and may perversely discourage patients from seeking or accepting care.

Tables 11.1 and 11.2 list common causes of acute and chronic pelvic pain, respectively. They are not exhaustive.

Anatomy

Pelvic anatomy is complex and comprises a richly layered tapestry of the pelvic viscera, muscles, and nerves within a bony girdle. The pelvic girdle is composed of the two innominate bones that join anteriorly at the pubic symphysis joint and articulate posteriorly with the sacrum at the sacroiliac joints. The pelvic girdle's

Table 11.2 Common chronic pelvic pain causes

Gastrointestinal	Urologic	Gynecologic	Neurologic	Musculoskeletal	Psychological
IBS	Interstitial cystitis	Fibroids	Pudendal neuralgia	Overactive pelvic floor dysfunction (PFD) with myofascial pelvic pain (MFPP)	Anxiety
IBD	Chronic prostatitis	Ovarian cysts	Inferior clunealgia	Pubic symphysis pain, osteitis pubis	Depression
Hemorrhoids	Nephrolithiasis	Endometriosis	Border nerve syndrome (ilioinguinal, iliohypogastric, genitofemoral neuralgia)	Sacroiliac joint pain	Stress
Chronic appendicitis	Penile pain syndrome	Adhesions	Plexopathy	Hip disorders (labral tear, OA, FAI)	Sleep disturbance
Proctalgia fugax	Chronic epididymitis	Adenomyosis	Cauda equina syndrome	Piriformis syndrome	Physical abuse
Anal fissures	Orchialgia	Lichen planus/lichen sclerosus	Radiculopathy, including sacral radiculopathy associated with Tarlov cysts	Hip flexor tendinopathy	Sexual abuse
Meckel diverticulum		Vaginal mesh	Adhesive arachnoiditis	Greater trochanteric pain syndrome	Substance abuse
Diverticular disease		Vulvodynia		Ischiofemoral impingement syndrome	
Hernia		Pelvic congestion syndrome		Coccydynia	

stability derives from a combination of form closure (the shape, structure, and form of the joint that provides stability) and force closure (compressive and frictional forces at the pelvic joints provided by the associated ligaments and muscles of the gluteal region, hip girdle, and pelvic floor) [30]. The pelvic floor muscles form the inferior boundary of the pelvis and include the puborectalis, pubococcygeus, iliococcygeus, ischiococcygeus (often referred to as simply coccygeus), piriformis, and obturator internus. Above this lower boundary, the pelvis contains all reproductive organs, the lower urinary system, and the distal gastrointestinal tract. A list of pelvic nerves and the structures they innervate is provided in Table 11.3. Disturbances to any of the extensive pelvic structures can shift a precarious balance, leading to pain, paresthesias, weakness, bowel or bladder incontinence, and sexual dysfunction.

Table 11.3 Pelvic nerves and the structures they innervate

Nerve involvement and spatial distribution of symptoms		
Nerve	Location and distribution of sensory symptoms	Associated signs
Lumbosacral nerve roots	Gluteal area, lower extremities along distribution of affected nerve roots	Leg weakness, pain, paresthesias
Femoral	Groin and anterior thigh	Leg weakness, knee buckling
Sciatic	Posterior gluteal area, posterior thigh, posterior-lateral calf and top of foot	Leg weakness, gluteal cramping
Superior gluteal	Deep and superior gluteal area	Abductor muscle weakness
Inferior gluteal	Deep and inferior gluteal area	Hip extension weakness
Posterior femoral cutaneous	Inferior gluteal area and posterior thigh	May have ischial or labial/perineal pain due to involvement of inferior cluneal branches
Iliohypogastric	Anterior and lateral lower abdominal wall, lateral gluteal region	
Ilioinguinal	Groin and medial thigh	
Pudendal	Deep pelvis, anterior pelvis, genital area	Urinary and defecatory pain and dysfunction, dyspareunia
Pudendal branches	Anorectal region (inferior hemorrhoidal nerve), perineum (perineal branches), genitalia (dorsal nerve of clitoris or penis)	Urinary and defecatory pain and dysfunction, dyspareunia
Genitofemoral	Groin, scrotum and labia, and superior anterior thigh	Testicular pain
Lateral femoral cutaneous	Anterolateral thigh	
Superior cluneal nerves (dorsal rami of L1–L3)	Posterior superior iliac spine and iliac crest, mid-gluteal region	
Middle cluneal nerves (dorsal rami of S1–S3)	Lateral gluteal crease, posterior perineum, ischial region	
Inferior cluneal nerves (branches of the PFCN)	Coccyx and rectal area, perineum	
Ganglion impar	Medial gluteal region	

Diagnosis

The diagnosis of pelvic pain requires a thorough history, physical exam, and, when necessary, electrodiagnostic (EDx) testing, laparoscopy, and imaging modalities that may include ultrasound (US), magnetic resonance imaging (MRI), and computed tomography (CT).

A patient history should be collected in a manner that invites self-disclosure, as abuse in various forms—physical, sexual, and emotional—is strongly associated with pelvic pain [15]. An extensive review of systems questionnaire can help narrow an otherwise broad differential prior to exam, and it is especially important to ask about associated urinary, defecatory, and sexual dysfunction.

A full review of physical exam techniques and imaging indications for evaluating pelvic pain is beyond the scope of this chapter. A thorough yet targeted physical examination may involve abdominal, neurological, musculoskeletal, lumbosacral, pelvic girdle, external pelvic floor, and internal pelvic floor (per vaginam in females, per rectum in both genders) evaluations, as suggested by the patient's chief complaint and history [11]. Where the physical exam is non-diagnostic, additional studies may be more illustrative.

US and MRI may be effectively used for evaluation of varied diseases of the pelvic organs, including endometriosis, adenomyosis, fibroids, pelvic congestion syndrome, cysts, and foreign bodies [59]. US for CPP evaluation is typically performed through the transabdominal or through the more sensitive transvaginal approach. The main advantages of US over MRI include decreased cost and compatibility with pacemakers and other implanted metals. Chronic pelvic infections such as pelvic inflammatory disease (PID), tubo-ovarian abscess (TOA), peritonitis, oophoritis, and endometritis, however, are more readily distinguished on MRI. Suspected neuropathy can potentially be evaluated by MR neurography (MRN) as an asymmetric hyperintensity on T2-weighted fat-saturated images and diffusion tensor imaging (DTI). CT may be used to evaluate the pelvis for fractures, arthritis, heterotopic ossification, and other space-occupying lesions. CT, with or without contrast, is also commonly used to evaluate the various gastrointestinal and pelvic organ causes of CPP.

Electrodiagnostic studies (EDx) consist of nerve conduction studies and electromyography and may be employed to diagnose disorders of the lumbosacral nerve roots and of the nerves arising from the lumbosacral plexus to further elucidate the cause of neuropathic pelvic pain. EDx may be helpful in identifying lumbosacral radiculopathy, lumbosacral plexopathy, and peripheral neuropathies of the pelvis and lower extremities. Of the peripheral nerves implicated in chronic pelvic pain, only the pudendal motor nerve is routinely tested on nerve conduction studies (typically via an intrarectal St. Mark's electrode), and axonal neuropathy can be evaluated with EMG testing of the external anal sphincter (EAS). Pudendal nerve conduction studies and EMG have not been shown to be sensitive or specific, however, and are therefore considered unreliable indicators of pudendal neuropathy [60, 64, 67].

Laparoscopy may be used for direct visualization of the peritoneum and the pelvic organ surfaces. The most common findings on laparoscopy performed on women with pelvic pain are adhesions and endometriosis. CPP is the indication for between

15% and 40% of all laparoscopies performed in the United States [53]. And while up to 40% of patients undergoing laparoscopy for evaluation of symptoms have negative results, laparoscopy has multiple distinct advantages over MRI, specifically biopsy capability and pain mapping [51].

Pain Etiologies

CPP includes a broad category of symptoms and pain etiologies, most commonly myofascial/musculoskeletal pelvic pain, neurogenic pelvic pain, chronic prostatitis, interstitial cystitis, endometriosis, and vulvodynia. It may prove difficult to discretely identify primary and secondary pain generators in CPP. Differentiating these etiologies on history is complicated by overlap in visceral innervation across the rectum, sigmoid colon, lower ileum, bladder, uterus, cervix, and adnexa. A thorough but non-exhaustive list of treatments is summarized in the following tables.

Musculoskeletal (MSK) pelvic pain is a widely encompassing category of diagnoses that commonly follow joint and musculotendinous stress from overuse, trauma, or hormonal changes. Myofascial pelvic pain (MFPP) is pain arising from the pelvic floor muscles (PFMs) and pelvic fascia and commonly arises from a background of pre-existing pelvic girdle derangements, visceral organ pathology, or prior pelvic surgeries or trauma (including childbirth). MFPP is typically a sequela of overactive pelvic floor dysfunction (PFD), which has associations with the aforementioned MFPP etiologies but also has been linked to chronic anxiety and may also be a manifestation of central sensitization. MFPP is diagnosed on vaginal/rectal examination as tender, taut bands of muscle or as trigger points with reproducible radiation patterns. Mainstay treatments include pelvic floor physical therapy, supportive therapy, analgesics, muscle relaxants per os and per vaginam, trigger point anesthetic injections, dry needling, chemodenervation, and neuromodulation therapy. Additional studies hope to provide further guidance on evidence-based treatment for MFPP.

Other common forms of MSK pelvic pain include sacroiliac joint (SIJ) pain, pubic symphysis pain, pelvic insufficiency fractures and bone stress injuries, hip disorders, piriformis syndrome, greater trochanteric pain syndrome, hip flexor tendinopathy, ischiofemoral impingement syndrome, coccydynia, and pelvic floor dysfunction. Treatment mainstays of these complaints may include activity modification, rehabilitation, medical management, injections, and surgery when indicated.

Neurogenic pelvic pain or pelvic neuralgias may present as neatly or poorly demarcated sensory changes, lower limb weakness, sexual dysfunction, and bowel or bladder dysfunction/incontinence. The most common clinical finding, however, is pain in the absence of any sensory disturbance due to the overlap in the cutaneous distributions of these nerves. Common diagnoses under this category include lumbosacral radiculopathy, lumbosacral plexopathy, cauda equina syndrome, the frequently overlooked sacral Tarlov cysts (which can cause sacral radiculopathies), and disorders of cutaneous nerves, including the iliohypogastric, ilioinguinal, geni-

tofemoral, pudendal, posterior femoral cutaneous, and cluneal nerves. A variety of neuropathic pain medications and interventions tabulated below are accepted treatment mainstays; evidence is strongest for pudendal nerve interventions, specifically nerve block and radiofrequency treatment [35, 60, 89, 91].

Urologic- and gynecologic-origin pelvic pain commonly arise from infectious, inflammatory, or malignant causes. Pain generators may be vulvar, vaginal, cervical, uterine, ovarian, adnexal, urethral, ureteral, prostatic, vesicular, or renal. Urologic and gynecologic pain may have severe implications for future reproductive success, and delay in diagnosis and treatment may result in infertility. Additionally, as urologic and gynecologic malignancies are commonly advanced by time of presentation, prompt evaluation, diagnosis, and treatment decision-making are vital. In this chapter, focus is placed on treatment of vulvodynia, endometriosis, chronic prostatitis/chronic pelvic pain syndrome, and interstitial cystitis.

Vulvodynia manifests as burning, itching pain that primarily affects the labia and vestibule on application of pressure or with vaginal penetration. Vulvodynia affects up to 20% of women across their lifetimes, most commonly young women, and the associated dyspareunia and sexual dysfunction commonly lead to psychological distress and depressive symptoms [34, 47]. Conservative treatment is inconsistently supported by the literature, but there is growing consensus for the use of pelvic physical therapy to relieve associated overactive PFD which may be contributing significantly to the symptom profile. While surgery has shown greater effectiveness than non-PT conservative care in the reduction of pain across longitudinal follow-ups (regardless of surgical technique used), vestibulectomy generally remains a last resort following unsuccessful conservative management [12, 13, 57, 61, 110, 111].

Endometriosis is the manifestation of endometrial tissue outside of the uterus and affects approximately 10% of all women and a significantly higher proportion of women with fertility issues [33]. Endometriosis may present acutely but commonly persists beyond the acute phase in an inflammatory and estrogen-dependent cyclic pattern of dysmenorrhea, dyspareunia, and dyschezia. Non-steroidal anti-inflammatory drugs (NSAIDs) constitute first-line therapy, though the use of combined oral contraceptive pills (COCPs) has risen with increasing evidence of their effectiveness [18, 45, 102, 108]. Laparoscopic surgery to remove endometrial implants and lyse adhesions can be effective in symptom alleviation [19]. Hysterectomy is considered a last resort, and symptoms of endometriosis can frustratingly persist following surgery, perhaps because of associated overactive PFD and MFPP that developed over the course of the disease process [7].

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) affects approximately 5% of men during their lifetime and is responsible for nearly 25% of all urology visits [10, 66]. CP/CPPS may be divided into three categories: chronic bacterial prostatitis (distinguished by confirmed infection), chronic non-bacterial prostatitis (characterized by inflammation without infection), and prostadynia (absence of both infection and inflammation), with the third type being by far the most common. The etiology of CP/CPPS is unknown though some studies suggest an underlying autoimmune process, and there is growing recognition that the prostate may not be responsible for the pain in a majority of men with this condition; CP/CPPS symptoms are often associated with PFD/MFPP and pelvic PT is often an

effective treatment option [37]. Therefore, current recommendations suggest that the term "chronic prostatitis" (CP) not be used at all, in favor of the broader but more accurate "chronic pelvic pain syndrome" (CPPS). CP is associated with reduced sunlight exposure, stress, BPH, and UTIs. Approaches to treatment should begin with treating any potentially underlying infection; alpha-blockers are the most evidence-based treatment available as a next step.

Interstitial cystitis (IC)—also known as bladder pain syndrome (BPS)—is a nebulous disease and is commonly a diagnosis of exclusion that may in fact be several illnesses not yet differentiated. IC results in inflammation of the bladder wall for unknown reasons and affects women more commonly than men in a 9:1 ratio. The symptoms of IC considerably overlap those of a UTI and include urinary urgency, urinary frequency, dysuria, and suprapubic pain associated with bladder filling. Terminology for subcategories of IC continues to evolve, and some providers consider Hunner lesion IC and non-Hunner lesion IC as distinct diseases. Similar to CP/CPPS, there is increasingly consensus and evidence that non-Hunner lesion IC is a manifestation of PFD/MFPP, and pelvic floor PT has been shown to be effective in randomized controlled trials [38]. Pentosan polysulfate and adalimumab constitute evidence-based medications, and a variety of urological interventions including bladder distention and instillations of various medications have proven effective [16, 21, 22, 28, 31, 49, 79–82]. Fulguration of Hunner lesions is an accepted form of treatment but lacks randomized controlled trials [31, 48, 100]. Treatments and their level of evidence are provided in the treatment tables at the end of this chapter.

Iatrogenic pelvic pain is most commonly caused by synthetic material surgically implanted in the pelvis including mesh and slings or may arise directly as a result of surgical manipulation. More than 10% of women by age 80 will undergo surgical management for stress incontinence or pelvic organ prolapse, and those requiring surgical revision for implanted mesh range from 7% to 18% [72, 86]. Complications of surgical mesh include erosion or exposure, contracture, infection, nerve entrapment, obstruction, and fistula formation. Changes to mesh may arise as a result of chronic inflammation, and some studies have shown that synthetic mesh causes greater inflammatory reactions than does organic mesh [119]. Retrieval of surgical mesh, however, introduces additional complications, including risk of anatomical defects, residual pain, and prolapse or hernia recurrence [65].

Treatment

Just as the causes of pelvic pain are often multifactorial, so are the recommended treatments multifaceted in approach. Given the breadth of providers seen by the average pelvic pain patient, patients frequently attempt multiple treatment modalities seeking relief. These treatments include medications, ultrasound, biofeedback, chiropractic, acupuncture, dry needling, physical therapy, psychological therapy, injections, interventional procedures, and surgery. While providers may vary in their approach to treating pelvic pain, most will agree that more research is needed

Table 11.4 Evidence-based treatments

	Medications	Surgery	Interventions/injections	Physical therapy	Supportive
Chronic prostatitis/ chronic pelvic pain syndrome (CP/CPPS)	Levofloxacin [114], terazosin [23, 24], tamsulosin [84], alfuzosin [76]				Aerobic exercise [43]
Endometriosis	Hormonal therapy [20, 45, 102, 108]	Laparoscopic endometrectomy, lysis of adhesions, hysterectomy [7]	Superior hypogastric plexus block [31]		
Interstitial cystitis	Pentosan polysulfate (PPS) [79, 80, 82], adalimumab [16]		Bladder distention [31], intravesical instillation of hyaluronic acid/ chondroitin, of DMSO, and of lidocaine [21, 22, 81]	Pelvic floor physical therapy [14, 55]	
Neurogenic			Pudendal nerve block [35, 60, 89, 91]		
Pelvic floor dysfunction/ myofascial pelvic pain (PFD/MFPP)_				Pelvic floor physical therapy [14, 55]	
Vulvodynia					

Table 11.5 Emerging treatments

	Medications	Surgery	Interventions/injections	Physical therapy	Supportive
Chronic prostatitis/ chronic pelvic pain syndrome (CP/CPPS)	Pentosan polysulfate (PPS) [79, 80]		Extracorporeal shockwave therapy [46], transrectal thermotherapy [106]	Pelvic floor physical therapy [112]	Traditional Chinese medicine (TCM) [116], curcumin/calendula suppository [77]
Endometriosis					
Interstitial cystitis			Intravesical botox [54, 113], intravesical instillation of heparin [42, 52, 71, 87]		Mindfulness-based stress reduction [56]
Neurogenic			Caudal ESIs [3], ganglion impar block, radiofrequency ablation (continuous vs pulsed) [35], sacral neuromodulation [73, 74, 92, 99], genitofemoral nerve block, ilioinguinal nerve block, iliohypogastric nerve block [4]		
Pelvic floor dysfunction/ myofascial pelvic pain (PFD/MFPP)_			Trigger point injections [6], botulinum toxin injections [1, 2, 78, 94, 97]	Pelvic biofeedback [88, 95, 103]	
Vulvodynia				Pelvic floor physical therapy [44], pelvic biofeedback [27, 93, 82, 29, 75]	Psychological therapy [44], acupuncture [104]

Table 11.6 Accepted treatments

	Medications	Surgery	Interventions/ injections	Physical therapy	Supportive
Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)	Rofecoxib [85], finasteride [83]	Prostatectomy [105]			Acupuncture [25, 40, 66, 101]
Endometriosis	NSAIDs [18]	Hysterectomy, lysis of adhesions [96]		Pelvic floor physical therapy [14, 55]	Exercise [115], acupuncture [117], psychological therapy [118]
Interstitial cystitis		Bladder diversion, bladder augmentation [87], fulguration of ulcers or trigonitis [26, 48, 100]			TENS [41, 109]
Neurogenic	Gabapentinoids [5, 70], TCAs [32], capsaicin [69]	Neurectomy (for ilioinguinal/ genitofemoral nerves) [58]		Pelvic floor physical therapy [14, 55]	Exercise [14, 55], acupuncture [32]
Pelvic floor dysfunction/ myofascial pelvic pain (PFD/MFPP)_	Amitriptyline, gabapentin [36]				Exercise [14, 55], acupuncture [40]
Vulvodynia	Gabapentin [8, 17], TCAs [107], topical lidocaine [34, 39]	Vestibulectomy [12, 13, 57, 61, 110, 111]			

Table 11.7 Disproven treatments

	Medications	Surgery	Intervention/ injections	Physical therapy	Supportive
Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)	Steroids [9]		Transurethral needle ablation [68]		
Endometriosis					
Interstitial cystitis	Tiaprofenic acid				
Neurogenic					
Pelvic floor dysfunction/ myofascial pelvic pain (PFD/MFPP)	Vaginal valium [50]				
Vulvodynia			Botulinum toxin injections [90]		

to scientifically support treatments for their various indications. Summarized in Tables 11.4, 11.5, 11.6 and 11.7 below are existing treatments by categories of evidence-based treatments, emerging treatments, accepted but as-yet unproven treatments, and disproven treatments. Evidence-based treatments are those supported by at least one large randomized controlled trial (RCT) or multiple smaller RCTs. Emerging treatments are supported by a single small RCT or evidence of lower level. Accepted treatments are mainstays of current practice without evidence or with evidence of passable quality. Disproven treatments are treatments with evidence of harm or of ineffectiveness.

Conclusion

Pelvic pain is a disabling condition that is very common and multifactorial in etiology. Continued research is necessary to find treatments which are truly effective for pelvic pain, but emerging treatments such as pelvic physical therapy and procedural interventions hold great promise.

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Chapter 12
Diagnosing and Treating Complex Regional Pain Syndrome

Steven D. Feinberg, Rachel Feinberg, Steven Stanos, Heather Poupore-King, and William G. Brose

Introduction

Complex regional pain syndrome (CRPS) is defined as a disorder of regions of the body characterized by pain that is disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is not restricted to a specific nerve territory or dermatome and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time.

S. D. Feinberg (✉) · W. G. Brose
Department of Anesthesia, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, CA, USA
e-mail: wbrose@brosemd.com

R. Feinberg
Feinberg Medical Group, Palo Alto, CA, USA

S. Stanos
Swedish Health System Pain Medicine and Services, Swedish Pain Services, Seattle, WA, USA

H. Poupore-King
Department of Anesthesiology, Perioperative and Pain Medicine, Division of Pain Medicine, Stanford University School of Medicine, Stanford, CA, USA

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CRPS Definition

Complex regional pain syndrome (CRPS) is a chronic pain condition characterized by spontaneous and evoked regional pain, usually beginning in a distal extremity that is disproportionate in magnitude or duration to the typical course of pain after similar tissue trauma. CRPS is distinguished from other chronic pain conditions by the presence of signs indicating prominent autonomic and inflammatory changes in the region of pain.

History of the Name CRPS

CRPS is often a disputed diagnosis. When considering sources of reliable opinion on the issue of chronic pain, the recognized scientific body is the International Association for the Study of Pain (IASP). IASP published their first definition of standardized diagnostic criteria for CRPS in 1994 [1]. At that time a history of precipitating injury, the presence of burning pain in a regional distribution involving the primary injury site, and the presence of signs including vasomotor (temperature, color, edema), sudomotor (sweating), pilomotor (hair growth), and/or trophic skin changes present during exam confirmed the diagnosis. These criteria were loosened subsequently by the IASP to incorporate patients with variability in signs by allowing a history of the signs if they were not present at the time of exam. The resulting increase in sensitivity, while desirable, was outweighed by a loss of specificity, and yet further revision by multiple authors has been proposed. Continued research and information gains since that time have led to continued developments in diagnostic criteria for CRPS.

Returning to the authority of the IASP, a multiauthor publication dedicated to CRPS has been released. The peer review literature regarding diagnostic criteria for CRPS includes an article [1] which describes "the new IASP criteria." This new criteria was approved and codified by the IASP committee on taxonomy and is based on the Budapest criteria. The article describes the empirical/statistical methods for validating diagnostic criteria for CRPS, discusses the results of validation studies to date, and encapsulates the latest international consensus group's action in Budapest, Hungary, which approved and codified empirically derived criteria as a revision of the Orlando consensus group criteria. Table 12.1 details the revised complex regional pain syndrome by the Budapest consensus group (accepted and codified by the Committee for Classification of Chronic Pain of the International Association for the Study of Pain).

General Features of the Syndrome

CRPS symptoms and findings are summarized in Table 12.2 below.

There are two versions of the proposed diagnostic criteria: a clinical version meant to maximize diagnostic sensitivity with adequate specificity and a research

Table 12.1 Complex regional pain syndrome Budapest criteria

General features of the syndrome
CRPS is a syndrome characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time.
There are two versions of the proposed diagnostic criteria: a clinical version meant to maximize diagnostic sensitivity with adequate specificity and a research version meant to more equally balance optimal sensitivity and specificity. These proposed criteria are described in [the tables below].

Reproduced [1]

Table 12.2 *Clinical* diagnostic criteria for complex regional pain syndrome

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in *three* of the *four* following categories:
Sensory: Reports of hyperalgesia and/or allodynia
Vasomotor: Reports of temperature asymmetry and/or skin color asymmetry
Sudomotor/edema: Reports of edema and/or sweating changes and/or sweating asymmetry *Motor/trophic*: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least *one* sign[a] at time of evaluation in *two* or *more* of the following categories:
Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
Vasomotor: Evidence of temperature asymmetry and/or skin color changes and/or asymmetry
Sudomotor/edema: Evidence of edema and/or seating changes and/or sweating asymmetry
Motor/trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms

Reproduced [1]

[a]A sign is counted only if it is observed at time of diagnosis

version meant to more equally balance optimal sensitivity and specificity. These proposed clinical criteria are described in Table 12.2.

Subtypes of complex regional pain syndrome (CRPS) are summarized in Table 12.3.

A test of these proposed criteria regarding ability to determine CRPS conditions from non-CRPS neuropathic pain groups indicates that the modifications from the previous IASP 1994 diagnostic criteria may increase diagnostic accuracy. Results indicate that applying a decision rule requiring *"two of four sign* categories and *three of symptom* categories to be positive…resulted in a sensitivity of 0.85 and a specificity of 0.69" for clinical diagnosis [1].

The Committee for Classification of Chronic Pain of the IASP has accepted and codified the "Budapest" criteria. In response to the consensus group's concern with

Table 12.3 Subtypes of complex regional pain syndrome (CRPS)

CRPS I (old name, reflex sympathetic dystrophy)
CRPS II (old name, causalgia): defined earlier with electrodiagnostic or other definitive evidence of a major nerve lesion
CRPS-NOS[a] (not otherwise specified): partially meets CRPS criteria; not better explained by any other condition

Reproduced [1]

[a]This subtype was added to capture any patients previously diagnosed with CRPS who now did not meet the criteria

the approximately 15% of patients previously diagnosed with CRPS, a third diagnostic subtype called CRPS-not otherwise specified was created that would capture those patients who did not meet the new clinical criteria but whose signs and symptoms could not be better elucidated by any other diagnosis. This subtype was a practical compromise and may not be necessary in the long term, as research provides specific information about mechanism(s) and thus diagnostic techniques.

In discussion of laboratory tests for CRPS [2], it is recommended that to establish a diagnosis "a detailed case history and examination are mandatory and should be documented carefully." Tests to verify the clinical findings, including dynamic temperature evaluation and standardized functional tests, should be applied to enhance the accuracy of clinical diagnosis.

The problem of distinguishing CRPS type I vs type II is complicated clinically by the fact that the definitive tests of nerve damage, such as EMG, are considered unnecessarily painful (even cruel) to CRPS patients. Small nerve "dropout" has been demonstrated in the skin of the affected part in most subjects studied, but there is no guidance as to whether this constitutes "major" or "minor nerve damage" [3]. Moreover, these diagnostic distinctions may not have clinical significance or affect the specific therapeutic method used. Despite these limitations, the distinction between these two existing CRPS subtypes was preserved by the Budapest group, and the eventual reevaluation of this matter was postponed until more data pertaining to its clinical importance becomes available.

Recognizing that the current understanding of the pathophysiology of the syndrome is incomplete, the statistical method described remains one of the few existing objective techniques for validating the IASP/CRPS criteria and indicating the direction of the modifications necessary to optimize their clinical and research value; we would promote that reliance on the newest and most evolved IASP criteria would be most appropriate.

Causation of CRPS

In looking to the specific causation of the regional pain, the determination of a causative triggering event is often relatively simple. While there are reports of very delayed onset and much more cryptogenic causation, most cases present within

days to weeks of an inciting trauma with the hallmark pain and hypersensitivity. However, the causation for the subsequent CRPS is far more complicated than a simple coincident trigger.

Reviewing the literature on the prevalence of CRPS in the general population, there is published literature that describes an incidence rate of 5.46/100,000 and a prevalence rate of 20.57 for a population base of >100,000 in a single county in Minnesota [3] and 26.2/100,000 for larger population-based incidence estimate from 600,000 patients reviewed in the Netherlands [4].

The presentation with an evolution of pain and other symptoms outside of an originally injured body part is reported in absence of subsequent trauma and when reinjury of the same or alternative body part occurs. In CRPS that has been reported with patients who have concurrent and recurrent disease, there is published research which has been reviewed in the more distant literature [5] where reflex sympathetic dystrophy was found to recur in the same and/or another limb in a minority of 1183 patients, 34 of whom developed a recurrence of previous complex regional pain syndrome in the same limb and 76% who presented with recurrence in a different limb. These observations have fueled the investigation into disease rather than injury-related contributions of causation to CRPS.

In a retrospective study of 185 CRPS patients, Eighty-nine patients exhibited CRPS in multiple limbs 72 patients spread from a first to a second limb occurred showing a contralateral pattern in 49%, ipsilateral pattern in 30%, and diagonal pattern in 14%. A trauma preceded the onset in the second limb in 37, 44, and 91%, respectively [6]. These authors argue that the compelling relationship between spreading and recurrence argues a supraspinal mechanism, which would be clearly established as a preexisting disease-related factor in the patient with expression dependent upon as yet incompletely understood factors.

Looking to the influence of heritability and genetics as well as prior disease-related contributions, it is difficult to argue that a patient did not have disease-related risk. Spontaneous presentation of CRPS is clearly documented in the literature [7]. Many authors describe this as unusual suggesting that traumatic triggering of such CRPS is required. But the data to support this empiric observation does not reach the level of strong medical evidence.

Satteson E et al. set out to establish the epidemiologic basis for this question in their 2017 study [51]. Ninety-three patients had a diagnosis of primary CRPS. Nineteen (20.4%) developed CRPS in one or more additional extremity compared to the incidence of 23.4 per 100,000 (0.0234%) in the literature (odds ratio 1069.6, $p < 0.0001$, 95% CI 562.0–2035.7). Twenty patients had a documented secondary injury or surgery in a second extremity. Fifteen (75%) developed secondary CRPS compared to a CRPS incidence rate of 6.4% following distal radius fracture, as determined by literature review (odds ratio 11.7, $p < 0.001$, 95% CI 5.9–23.2). Analysis of this data argues that "an odds ratio of over 1000 when comparing the reported population incidence of CRPS to the rate of secondary CRPS documented in this study strongly suggests that patients with a history of CRPS may be at considerable risk of developing secondary CRPS. This finding is further supported by more than 11-fold increased rate of secondary CRPS following a second-

ary inciting event seen in this study when compared to the reported rates of CRPS following distal radius fracture." While these data are retrospective and the issue warrants further study, it clearly supports a general predisposition for the development of secondary CRPS in those with a history with or without subsequent trauma. From this data the question as to whether CRPS is behaving more like a disease than like a response to injury is developed.

Adding to the evolution of CRPS as a disease rather than a consequence to injury, a recent analysis of risk factors for posttreatment CRPS in a Danish population [8]. Dr. Petersen and colleagues describe "Female gender, surgical treatment, and treatment to the upper limb were risk factors. Elective surgery accounted for a large number of post-treatment CRPS patients. In CTS patients developing CRPS, normal neurophysiological examination findings were common, and it could be suspected that these patients were suffering from a pre-clinical stage of CRPS, not CTS."

This misdiagnosis of preclinical CRPS rather than CTS in the presence of normal neurophysiologic examination would add further credence to the disease-specific rather than injury-specific causation of CRPS in patients presenting with spreading or recurring disease. These authors go on to describe the correlation between other autoimmune disease states and CRPS as an explanation for the evolution of symptoms. "A preclinical stage of disease has been described in autoimmune diseases such as rheumatoid arthritis, type 1 diabetes, and systemic lupus erythematosus, among others, and typically there is the presence of autoantibodies related to the diseases years prior to the diagnosis. These autoimmune conditions exhibit three distinct phases during their development. In the initial phase, patients have a genetic risk for development of disease but show no active autoimmunity or inflammation. Phase 2 is the preclinical stage, with presence of disease-specific autoantibodies and other immunologic factors but no apparent disease. Phase 3, clinically apparent disease, is characterized by development of clinical symptoms due to genetic, environmental, and/or endogenous factors. In the same manner, an autoimmune pathogenesis has been suggested in the development of CRPS. If a preclinical phase of CRPS and possible autoantibodies could be identified, it might lead to a better understanding of the disease."

Early efforts to identify specific antibodies for CRPS have been mixed [9]. In performing screening for antinuclear antibodies (ANA) to identify systemic autoimmune disease a high prevalnce is seen. Antineuronal antibodies directed against antigens in the central and/or peripheral nervous system have been tested. In their work 27 (33%) of the 82 CRPS patients for whom serum was available showed a positive ANA test. This prevalence is significantly higher than in the general population. But only six patients (7.3%) showed a positive result for typical antineuronal antibodies. This proportion, however, does not deviate from that in the general population. This clearly indicates that the usual antineuronal antibodies do not appear to mediate the CRPS. As this research continues further, elucidation of the autoim-

mune role in CRPS will be revealed, but the data present today does help to describe long-standing and disease-related risk factors that put the simplistic idea of injury-triggered mechanism of action into serious question. While at present there is a currently held belief that the temporal connection between injury and CRPS is a causal one, this belief is not established with clear pathophysiology. And furthermore, as more clues to the underlying pathophysiology are revealed, the more question there is about the injury as a primary etiology.

Of these, gender with a dramatic female predominance over men (3:1) [4] and HLA haplotypes are reported to confirm susceptibility for CRPS. These influences then the reporting of other authors who describe recurring CRPS manifestation in those with confirmed disease. These alone, however, do not satisfy the mechanism of the disease. Rather, it is perceived that there is more complex causation that has been incompletely elucidated.

The finding of recurrent and spreading CRPS in other sufferers has led to the speculation that brain stem activity rather than a triggering mechanism actually confers the risk of disease spread [10]. Drummond and colleagues have studied over 100 patients with CRPS describing "These findings suggest that heightened excitability of nociceptive pathways in CRPS spreads to hemisensory convergence points in the brain stem or higher brain centers, possibly in association with compromised pain controls. The similarity of symptom profiles in chronic CRPS I and II implies shared mechanisms despite different triggers."

Onset of Symptoms

From a specific insult, typical symptoms occur within the first few weeks of initiating event but certainly during 3–4 months after the initiating insult. Variable and evolving symptoms described above may occur later either due to natural evolution or though related to treatment for an original injury including surgery or additional insult secondary to compensatory trauma or misuse. Sometimes the diagnosis is made late because the symptoms were not recognized earlier by the treating physician(s).

CRPS Types

"Warm CRPS" is associated with a warm, red, and edematous extremity, whereas "cold CRPS" presents with a cold, dusky, sweaty extremity. Acute CRPS is more often associated with a warm CRPS presentation, whereas chronic CRPS is more often characterized by a cold CRPS presentation.

Prognosis

For acute CRPS, 74% of diagnosed CRPS cases resolved with relatively conservative care [3]. In chronic cases, about 3300 patients report resolution, 16% report progressive deterioration, and the remaining 54% report stable symptoms.

CRPS Prevention

While supplementation with vitamin C following fracture or surgery was reported to reduce the risk of developing CRPS, subsequent detailed review of multiauthor works over the last 5 years has failed to demonstrate a predictable effect [11].

Treatment

The selection of a treatment approach depends on the severity of symptoms and the degree of disability. Of paramount importance is that a successful treatment outcome for CRPS depends on a coordinated functional restoration interdisciplinary approach.

Building a therapeutic alliance between the patient and the treatment team is of critical importance.

Since pain and limb dysfunction are the major early complaints, pain control, education, physical rehabilitation, and emotional stabilization are the main treatment objectives. Coexisting problems such as depression, sleep disturbance, anxiety, fear of reinjury, and generalized physical deconditioning should be evaluated and treated.

Therapeutic approaches include physical rehabilitation (i.e., physical and occupational therapy), psychological care including cognitive behavioral therapy (CBT), relaxation training, medication management, and a variety of techniques that, directly or indirectly, are aimed at blocking or interrupting chronic changes to an overactive nervous system (i.e., sensitization process) and in some cases decreasing sympathetic hyperactivity. Patients are encouraged to use the affected limb. Treatment is more successful if started early rather than later in the disease process.

While physicians and therapists have many tools in their treatment armamentarium, the single most important treatment for these patients is education and learning how to manage their chronic pain condition. Patients who can learn about the cause and meaning of their pain are able to make better choices regarding the use of their extremity which may improve the natural history of the disease process. Virtually all patients who develop pain with CRPS begin their experience with an acute injury of some type that typically causes a nociceptive pain. The learned association between the pain and the injury is an important reinforcement of early belief systems that

whatever hurts is due to harmful injury. Recognizing that CRPS develops from these nociceptive roots and harmful meaning, patients almost uniformly attribute continuing pain after the usual time of tissue healing to a continued noxious source. Assisting patients to understand that while the injury was indeed harmful that the subsequent chronic pain state of CRPS that has emerged is not associated with ongoing actual or potential injury is critical to the recovery and rehabilitation process.

Most patients will not develop this understanding independently. They need to be taught and often need to borrow confidence from their teachers to proceed with a rehabilitative course against their intuition to regain control of the diseased region of the body.

The goals of medical treatment of CRPS will always be the facilitation of this learning and rehabilitation. Moreover, if the medical treatment is pursued without this teaching, the reinforcement of an even more refractory pain condition will ensue. Without being educated that their pain is due to abnormal function of the nervous system rather than ongoing tissue harm, patients with CRPS will simply develop a belief that the persistent pain is ongoing evidence of tissue damage that cannot be cured or relieved and that they themselves cannot influence. These patients become CRPS sufferers with increasing dependence on medications, interventions, and the providers who deliver those services. The search for a new and better pain reliever will be pursued to the detriment of their own health, relationships, and life.

Medication Management

Medications may include treatment with oral, transdermal, and topical agents, drug delivery patches, parenteral infusions, injections, and implanted devices. This may include steroids, anti-inflammatories, antidepressants, vasodilators, anti-spasm medications, and anticonvulsant-type medications. Membrane stabilizers or medications that suppress sensitization of the nervous system and/or sympathetic activity including alpha-1 adrenoceptor antagonists have been reported as effective in some CRPS patients without convincing benefits. Opioids and virtually every known or reported analgesic have been employed in the search of a predictable pain reliever but to no avail. No single oral medication or injection is specifically approved by the FDA (Food and Drug Administration) for CRPS. There is no curative therapy, and no single medication or combination of medications is proven to modify the disease [12]. Medications should be functionally oriented to facilitate recovery and manage the impact of the pain.

A group of less conventional analgesics are discussed here to provide information, but again these have no clearly established role. Bisphosphonates have been found effective for reducing pain in patients with early CRPS who have abnormal uptake on bone scan [13]. Published results of a trial enrolling 82 subjects with CRPS of the hand or foot who had a disease duration of 4 months or less and abnormal uptake in early and late phases of three-phase bone scintigraphy suggests a level

of specificity but not sensitivity. Serious adverse effects of bisphosphonates include esophageal ulceration with oral use and osteonecrosis of the jaw none of which were reported.

Calcitonin has been proposed due to a putative role in bone mineralization. The mechanism responsible for analgesia is uncertain. There is conflicting evidence regarding the benefit for CRPS. The optimal dose and duration are uncertain. A dose of 300 international units daily was used in one positive randomized trial [14]. If pain and/or function is improved with use, it can be continued, tapered, and discontinued as tolerated.

There has been considerable interest in N-methyl-D-aspartate (NMDA) blockers and particularly the anesthetic ketamine. The NMDA receptor complex may play an important role in the development of both peripheral and central nervous system hyperactivity. By blocking and/or desensitizing, the receptor may help to decrease pain. NMDA receptor antagonists include dextromethorphan, memantine, and ketamine. Ketamine infusion was compared with placebo in 60 patients with type I CRPS [15]. Patients assigned to 5-day ketamine infusions had a statistically significant decline in pain scores, but no sustained benefit was reported. Frequent side effects of ketamine in this trial included psychomimetic symptoms (e.g., hallucinations, delirium), nausea, and vomiting.

Interventional Procedures

Usual procedures employed in diagnosis and treatment can include stellate ganglion or thoracic sympathetic block, lumbar sympathetic block, intravenous regional sympathectomy, phentolamine infusion, and intravenous lidocaine infusion. Sympathetic blockade may provide a useful adjunct to aggressive medical therapy, but it should not be considered as a sensitive or specific test for the diagnosis.

Each of these procedures is designed to alter the function of the nervous system temporarily. During this temporary alteration, patients are evaluated to see if pain, function, and evidence of sympathetic dysfunction have been positively influenced. Frequently, patients will receive several of the above procedures as a trial to determine which, if any of them, should be integrated into the multidisciplinary management plan.

The goal of each of these techniques is to provide a temporary but effective pause in neuronal hyperactivity, a contributor to the pain, thereby allowing the rehabilitative care to restore more normal healing and function to the affected tissues. If, following a trial of the different procedures mentioned above, the treating physician feels that a significant benefit has been gained, then repeated administration of these procedures over a period of 6–12 weeks (and in some cases longer) is viewed as appropriate.

The desired outcome from each procedure should be as long a period of effective decreased pain and improved functional capacity as possible. The majority of practitioners recognizes a response profile of several days to a week as being optimal for the initial intensive treatment and would be willing to repeat these blocks on a

weekly or perhaps twice weekly basis in order to facilitate the rehabilitation process. One should recognize, however, that sympathetic blocks on their own infrequently, if ever, "cure" patients. These blocks should be viewed as any other medical treatment, an effective form of temporary palliation and a useful tool to help the patient with the remainder of the multidisciplinary management provided by physical rehabilitation and psychological services.

Patients may have a tendency to view the medical components of treatment as curative alone, and it is the job of the therapy team to reinforce the rehabilitative and psychological components as being critical, while the medical interventions are primarily palliative. This continued de-emphasis of the medical components of treatment will help to prevent patients from viewing the locus of control with regard to their ongoing improvement in this disease as being outside of themselves or within physician control. In other words, the patient should be responsible and in charge of their rehabilitation and pain management.

More aggressive medical strategies employed include the use of selective spinal analgesics and spinal cord or peripheral nerve stimulation.

Some physicians recommend selective intrathecal spinal analgesia via an implanted pump incorporates the delivery of extremely potent and selective analgesic medications to sites of action near the spinal cord and nerve roots, generally bypassing the brain and higher central nervous system. This selective delivery by intrathecal infusion pump potentially avoids many of the problems seen with systemic (oral or intravenous) administration of analgesics and may provide partial pain relief. My Experience with implanted intrathecal drug therapy for complex regional pain syndrome is anecdotal.

In addition to selective intrathecal spinal analgesics, there have been documented cases of clear beneficial effects from spinal cord stimulation (SCS) wherein small electrodes are placed in the epidural space outside the spinal cord to deliver microelectrical currents to the descending portions of the spinal cord. These currents induce activity in the patient's own intrinsic pain-modulating system. Similar case series promoting Dorsal Root Ganglion Stimulation (DRGS) merit further investigation rather than promotion.

Both selective spinal analgesics via intrathecal infusion pump and neuroaugmentation are potential treatments but, because of the associated risks and costs, should be considered only after conservative efforts at aggressive rehabilitative management mentioned above have failed. As noted, experience with intrathecal infusion pumps has not been positive, and while the use of spinal cord stimulation is potentially beneficial, its use is optimized in a multidisciplinary functional restoration type of treatment program.

With neuroaugmentation, a trial period is warranted. Permanent implantation should depend on objective evidence of benefit including improvement in functional capacity and in the overall rehabilitation program in order to justify the risk and expense associated with chronic implantation. Additionally, these modalities should be utilized only by physicians experienced with these techniques in a multidisciplinary setting. Patients who receive these therapies should be selected by careful medical and psychological screening.

All medical therapies whether conservative or sophisticated spinal cord stimulation or implanted drug delivery systems need to be presented to the patient and reinforced as approaches that are used to provide a "window of opportunity" for functional restoration therapy where they can be aggressively and intensively rehabilitated. Without this concept of medical faciliation of rehabilitation being emphasized, an avoidable risk of medical dependence and erosion of important self efficacy will occur.

Education

An education program is important for the patient, so they can understand what has happened to them and what they can do about it. Since treatment often involves a 24-hour-a-day, 7-days-a-week effort, the patient must be empowered to be able to provide self-treatment and gain confidence.

Education is one of the most important parts of any type of treatment of CRPS. The information on the internet can be beneficial but can also be frightening for patients as they read horror stories or see pictures of swollen limbs. Unfortunately, patients often have also either been told incorrect information from other sources or have misinterpreted information from a past provider. The patient may have been told to not use the limb if it was painful or that the symptoms are "all in their head."

Education on diagnosis, prognosis, and expectations of treatment must begin as soon as possible. Many patients do not truly understand the diagnosis of CRPS and more importantly how it relates to their personal experience. This education includes an easy to understand discussion of the changes in the nervous system and how that explains the typical symptoms of CRPS. As the patient is provided education about his or her symptoms, it is important that they receive confirmation that their symptoms are expected to be variable but are "normal" in the sense that they are part and parcel of how CRPS presents.

The patient should be made aware of the extent of effort and hard work that is involved in obtaining a good outcome and successful treatment. The patient must understand that treatment will be painful but that they will receive help with managing symptoms and that the outcome is significant improvement in functional use of the affected extremity. Many patients believe that the focus of treatment is to reduce their pain level. The impression is that if the pain level decreases, then the functional increases will soon follow. However, this is often not the case with CRPS. Unfortunately, pain levels typically increase throughout treatment as the patient pushes their current level of function. Therefore, education regarding goals based on function, not pain changes, is important to assist the individual in feeling successful and attaining their goals. The patient must also be an active participant who takes control of their treatment and participates in goal setting. If the patient is unable or unwilling to participate completely with treatment, results are minimal. Goal setting can be directed toward functional

activities that are important to the individual to assist them in becoming engaged in treatment.

Education must also include possible negative consequences of not using the affected extremity. These include spreading of CRPS proximally or to the contralateral or other limbs. Symptom spread may also be due to compensatory movement and overuse and development of secondary pain sites from guarding and abnormal movement with a worsening of symptoms.

Physical Rehabilitation

Although the diagnosis of CRPS is becoming increasingly recognized in the medical community, education on diagnosis, and especially treatment, is still limited in terms of physical and functional restoration for physical and occupational therapists.

The ultimate goal of therapy is to reduce pain and improve function of the patient's affected area. Physical rehabilitation can be detrimental if not applied appropriately.

Many therapists still limit treatment from concerns regarding causing further injury to the affected extremity due to the often-reported high levels of pain and color and swelling changes with use and movement.

Throughout the CRPS literature, there are recommendations for rehabilitation, and recent literature is bringing brain retraining techniques more into mainstream treatment. However, most research on CRPS treatment including physiotherapy treatments were varied between studies and were often provided in combination with medical management [16]. The available medical literature does not allow for an assessment of the effectiveness of specific treatments. Therefore, few of the therapy treatments have evidence-based research to support or refute their effectiveness.

Research suggests that working through the pain with an aggressive physiotherapy program often leads to far better results than a more cautious approach [17]. However, from a clinical perspective, it is important to determine the most appropriate approach for each individual patient and find the best individual balance of each of the rehabilitation treatments.

This section discusses a variety of treatment modalities used in physical and occupational therapy. Treatment modalities can be passive or active, but overall, the direction of treatment should be toward individual self-management.

The evaluation starts with an assessment of appearance along with active and passive range of motion and measurement of swelling. A related soft tissue assessment, including that for myofascial trigger points, should also be included. The therapist also evaluates strength, sensation and pain response, coordination, dexterity, temperature changes, and functional use ability.

Passive treatments include splinting, paraffin, massage, electrical stimulation, ultrasound, contrast baths, and edema control treatments.

Active treatments include various desensitization techniques, active exercise or functional use, stress loading (scrubbing and carrying), normalizing compensatory

movement patterns, and flare management techniques including pacing, cognitive behavioral therapy, and relaxation techniques.

Active treatments are essential in all cases and the benefits of passive treatments are person specific. A functional restoration program (FRP) combines these active treatments with psychological care and medical/medication management.

Treatment is directed toward pain relief, desensitization, edema reduction, normalization of tone and sensation, proper posturing and positioning, range of motion and stretching to maintain and improve flexibility, stress loading, and strengthening. In more severe cases, splinting and bracing may be utilized. Prolonged splinting or bracing should be avoided and may contribute to development of other compensatory problems.

Treatment is a team effort with adequate analgesia provided. Treatment in severe cases usually starts slowly with edema-relieving techniques, gentle desensitization, and the use of passive modalities followed by gentle flexibility and strengthening exercises.

Desensitization therapy can be a critical component to a successful rehabilitation plan. Desensitization techniques are aimed at normalizing sensation and consist of progressive stimulation with soft materials increasing to rougher textures as tolerated over time. It can include light touch progressing to deep pressure. Desensitization approaches may also include graded increases in carrying light objects for short periods of time, a number of times per day, or scrubbing or loading the affected limb on a daily basis. Vibration at different frequencies can also be used to assist in desensitizing the affected extremity. Contrast baths (switching back and forth from hot to cold water) are utilized and lead to increased hot and cold tolerance. A desensitization program is thought to reestablish normal sensory and motor integration and complex maladaptive connections between the brain and the affected body part.

Edema is managed by the use of specialized garments or wrapping techniques, and therapy is directed toward manual edema mobilization techniques and education, so the individual can practice edema reducing therapies at home and not in formal treatment.

Treatment may include stress loading (distraction and compression), elevation, and active range of motion exercises.

Postural training and positioning are important and can minimize protective guarding, promote balance, and facilitate improved functional use of the extremity.

As the patient improves, treatment consists of more aggressive range of motion exercises, stress loading, strengthening, and general aerobic conditioning.

While the importance of maximizing functional use of the affected limb cannot be overstated, it is just as important to realize that some individuals with residual symptoms of CRPS will need to learn proper pacing of activities and avoidance of pain-inciting events. The individual will need to learn skills to perform some functions in an alternate and less symptom-provoking manner. Additional skills such as diaphragmatic breathing, relaxation techniques, imagery, and special mind-body exercises such as tai chi or Feldenkrais may be beneficial.

Normalization of use and functional rehabilitation comprise the final stages of therapy. This stage may include work hardening, vocational rehabilitation or

retraining, and workplace modification. Patients may need weeks to several months to progress through this stage.

Patients need to understand their disease, which allows them to become active, educated participants in their treatment. The "locus of control" is patient centered. Rehabilitation is a full-time effort. Those in the early stages of the condition typically respond better to vigorous therapy than those with more advanced cases.

Specific physical and occupational therapy approaches include stretching, mobilization, active and passive exercises, aquatic therapy, strengthening, transcutaneous nerve stimulation (TENS), electrical stimulation, edema control (including massage, gradient pumps, and compressive stockings or gloves), splinting, modalities (deep heat, such as ultrasound), thermotherapy (heat or ice packs), and a program of tactile desensitization (whirlpool, contrast baths, massage, gentle tapping, and other sources of stimulation). Patients are encouraged to exercise and use the affected extremity. A home treatment program is essential, since even several hours a day with trained therapists may not be sufficient.

Fear and Avoidance

Fear of reinjury, fear of movement (kinesiophobia), and avoidance due to increased pain levels is a common barrier in returning to normal life, work, or recreational activities after an injury. Research suggests that an individual's pain-related fear and avoidance are important factors in determining activity level 6–12 months after an injury.

With CRPS, the patient and often the provider do not understand the heightened pain response, and the CRPS diagnosis may not be immediately recognized. The unrelenting pain of CRPS increases underlying fear and worry of a more malicious, yet undiagnosed, disease process. Driven by fear of further pain or the threat of further damage, many people with CRPS increasingly restrict activities and begin to exhibit a maladaptive avoidance response.

Fear, avoidance, and the effect that this has on recovery continue to be widely researched. There are a few measures that can provide the clinician with the knowledge that fear or avoidance may be a barrier to recovery. These measures include the Tampa Scale of Kinesiophobia (TSK), the Fear-Avoidance Beliefs Questionnaires (FABQ), the Pictorial Fear of Activities Scale-Cervical (PFActS-C), and the photograph series of daily activities for the upper or lower extremities (PHODA-UE/LE). However, there is limited evidence-based or clinical-based information that suggests how to treat this barrier from a physical therapy perspective.

When treating a person with CRPS, the different aspects of fear and avoidance must first be determined. In many of the questionnaires and in the research, fear of reinjury, fear of increased pain level, and avoidance due to other factors are grouped together, when in fact they are quite different. The clinician should spend the time to understand the concerns of the patient so that education can be directed toward addressing the aspect of fear that is limiting rehabilitation and recovery.

In an acute pain model, pain activates receptors at the site of injury which stimulate systems in the brain and spinal cord that signal us to avoid a painful activity and prevent additional damage as the body heals itself. This is an important and necessary process in an acute injury. However, in chronic diseases, this avoidance is not beneficial and can prevent recovery. A fear of reinjury implies the belief that pain equals damage and therefore should be avoided at all costs. When the diagnosis of CRPS is not quickly made, the patient can be left with many questions about why they are having so much pain. This lack of education can lead to an increased fear of reinjury. For patients that do have an underlying nerve disorder, it can be confusing as to how to differentiate pain that could be damaging and pain that is likely not damaging.

Unfortunately, this fear can be further propagated by healthcare providers as they instruct the patient to avoid painful movements. Treatment for overcoming fear of reinjury first involves the proper diagnosis and then determination of the patient's current beliefs on what processes are happening in their body. Education consists of what the diagnosis of CRPS is and why pain does not equal damage. Further education includes understanding the difference between pain and damage due to hypersensitivity and changes in the spinal cord and brain and the physiology behind why movement is not harmful. Much of this education can be done by a physical therapist, but due to beliefs in our society about the medical field, often a medical doctor must be the one to convince the patient that they are safe to move the affected limb.

A fear of increased pain levels with movement can be another barrier to recovery. In this case, the patient may understand that the pain is not damaging to them, but he or she does not want to suffer through high levels of pain and is fearful of being unable to control the increased pain level. One of the first steps is education on the detrimental effects of guarding and disuse and the importance of movement in treatment of CRPS. The patient must understand the short- and long-term goals and express a willingness to push through higher levels of pain. However, many patients will initially resist the idea of pushing through high levels of pain, and it is the clinician's responsibility to determine if this resistance can be changed. Often times, a strong resistance is based on a lack of education, the overwhelming nature of the fear, and the knowledge that tools currently being used, such as medication, will not be helpful. In these cases, further education can be the key in changing this resistance. Many times, once a patient is aware that using a limb will help them to treat the disease, then many are willing to push through higher levels of pain in order to meet their physical goals.

Further treatment includes education and instruction on flare management skills such as relaxation breathing, pacing, meditation skills, and appropriate activity progression. Initial sessions may be spent integrating these pain management tools into movements or exercises that the patient feels that they can already handle and slowly increasing the movement or demand level as these skills improve. Some patients will be ready to immediately tackle high levels of pain from the beginning. As the patient feels more comfortable using flare management skills and gaining control over higher levels of pain, the activity level is further progressed.

The fear-avoidance model (FAM) of musculoskeletal pain details potential maladaptive thinking styles that can lead to higher levels of disability. This model encourages a psychological approach, although the physical therapist must also be able to recognize the maladaptive thinking and address it from a physical perspective. There are many different maladaptive thinking styles, and once again, the clinician must ask questions to help determine which thoughts may be limiting each specific patient. Many people with CRPS deal with anxiety, a lack of feeling in control, catastrophizing, disappointment from only being able to perform at a low physical level, and many other emotions and thinking styles. Other examples include a patient with lower extremity CRPS who was resisting treatment and commented to his physical therapist, "A doctor told me that I was going to eventually have my leg cut off anyway, so what is the point of forcing myself to walk on it." More details on this can be found in the chapter addressing psychological treatment.

Daly and colleagues further examined specific methods of treatment for fear-related limitations [16]. There is a distinction in therapy between in vivo exposure and graded activity. Treatment with in vivo exposure has the patient perform specific tasks that they identify as "dangerous" or "threatening," starting with the least threatening [18]. In graded activity, healthy behaviors and activities are positively reinforced and systematically progressed [19]. Research suggested that while only trend differences were observed for pain-related disability, patients in the graded in vivo exposure condition demonstrated significantly greater improvements on measures of fear of pain/movement, fear-avoidance beliefs, pain-related anxiety, and pain self-efficacy when compared to those in the graded activity condition [18].

Overall, with any type of fear, treatment includes education, repeated exposure to activities that have been avoided, and taking an active role in recovery. The patient is provided with an extensive level of education and pain management tools to manage their expected increased pain level. The patient begins at a level of activity that is just above their comfort level and is encouraged to slowly, but consistently, push that level further.

Flare Management

To a patient dealing with the overwhelming symptoms of CRPS, the pain can appear uncontrollable with no way to manage it. The typical acute pain model tools are often minimally effective or can lead to further avoidance of use. In an acute pain model, healing and avoiding further pain are the main focus of treatment. Tools including medication, nerve blocks, passive modalities such as heat or ultrasound, rest, and guarding are the most commonly used. In treatment of CRPS, these passive modalities are not typically as effective.

Flare-ups (an increase from the normal baseline level of pain) can cause both physical and emotional reactions. Physical reactions include guarding the limb, avoiding activity, tightening of muscles, holding the breath, stomach and chest

tightening, and nausea. When these physical reactions occur, the pain level worsens and propagates the cycle of flare-ups.

Flare-up management consists of learning a new set of active tools that can assist people with CRPS to feel more in control of their symptoms and be able to push themselves harder to meet their physical goals. There are multiple physical and cognitive tools that can be effective for patient with CRPS. These tools overlap widely, and both physical and cognitive tools should be used in order to allow the best flare management success.

Flare management tools include but are not limited to relaxation breathing with focus on decreasing guarding, light movement, yoga, tai chi, mindfulness-based stress reduction, cognitive behavior therapy practice, distraction, guided imagery, positive self-talk, and pacing. Breathing and relaxation techniques are the foundations of active pain management skills and are taught early in treatment. Instruction on correct breathing and relaxation is imperative as the patient begins the painful rehabilitative process.

Pacing

Pacing is used as a flare management tool but also as a way of performing activities during the day. Many people believe that pacing means being less productive, but in reality, the overall goal is to best manage the symptoms of CRPS and to become as productive as possible. Learning how to pace can be very frustrating as there are many ways to pace tasks and there are multiple nonphysical barriers including old ways of doing things, thoughts of what someone should be able to do, and pushing to be able to meet others' expectations. Many people with CRPS become very frustrated due to a drastically different tolerance level and inability to perform even the simplest of activities due to high levels of pain.

Incorporating pacing into one's lifestyle does not mean giving up enjoyable or necessary activities. It is making modifications in intensity, duration, distance, and taking breaks. What most people find is that they are more productive and successful once they begin using the pacing techniques.

The purpose of pacing and goal setting is to regulate daily activities and to structure an increase in tolerance through gradually increasing activity. Pacing activity requires the person to break an activity up into active and rest periods. Rest periods are taken before significant increases in pain level occur. It provides structure to the overall activity level and guides the individual to build an optimum schedule to minimize pain and maximize productivity during the day. Pacing also brings about a structure to the day, giving the person a sense of control.

To begin pacing, a baseline is established for the specific activity. The baseline is the amount of that activity that can be performed before a significant flare-up occurs. Although increased pain is expected, especially with a new activity, the activity should be stopped before the pain becomes difficult to control. The baseline may include a specific amount of time, speed, distance, number of repetitions, or any other ways to measure tolerance. Baselines may also be required for sedentary posi-

tions including sitting, reading, and computer work. Rest breaks focus on time to rest, to stretch, to perform other flare management techniques, or to change to a less demanding activity. Activity level is gradually increased with focus on slow progression in one area at a time. Pacing techniques include planning in advance on performing the activity, breaking the activity down, avoiding repetitive movement, and taking rest breaks before the pain.

There are many activities that are not as compatible with taking structured and scheduled rest breaks. For these times, other tools such as relaxation breathing, change of position, cognitive behavioral techniques, and distraction can be helping in managing the pain level while completing the task.

Aerobic Conditioning, Strengthening, and Stretching

These approaches vary widely but are an important part of CRPS treatment. They are all geared initially to physical reactivation and use of the limb to the extent possible and within reason but provide considerable value to other non-affected body parts. Physical activity not only increases general health but appears to provide pain reduction benefits possibly through endorphin release but also serves to utilize time and keep the individual occupied, while having the potential for socialization in a group setting (i.e., walking, at a fitness center, etc.). An exercise program focused on the non-affected areas can provide both endorphin release and also a way to pace the exercise program and give the affected areas a break, while still staying active.

An aerobic conditioning program can vary widely depending on the severity of the CRPS and the areas affected. Sometimes walking can affect an upper extremity CRPS, and therefore other lower extremity aerobic programs are needed, or other ways to support the limb with walking are required. With CRPS in the lower extremity, an arm bike, stationary bike, or movement in the water may be the best way to perform an aerobic conditioning program. Often times, part of the overall program is increasing tolerance to an aerobic program even before the true benefits of aerobic conditioning can be gained.

A strengthening program can vary greatly depending on the limb affected, access to equipment, general endurance and strength of each individual, and irritability of symptoms. A strengthening program may initially include exercises with resistance of only gravity or weights of less than 1 lb. Strengthening exercises for the non-affected areas are performed as well, but there must be an awareness of how they contribute to increased symptoms in the affected area. Performing a few strengthening exercises on the affected area and then switching to the non-affected area can be part of a paced exercise program.

A stretching program in CRPS is often different than what is typically taught in the general community. Stretching should not consist of forcing through a movement as that leads to additional guarding and stress on the area. Instead, stretching focuses on teaching the body to relax through a movement as the muscle lengthens and relaxes. Many times, with CRPS, pain limits the person from reaching a position where they can even feel a stretch. Therefore, an initial stretching program

may have to focus on simply moving through a comfortable range of motion, while teaching the body to relax as the pain level increases further into the range.

These activities also should focus on correcting postural abnormalities, normalizing movement patterns, and overcoming avoidance. Depending on the patient's current level of disuse, each specific stretching or strengthening activity is modified to allow the patient to successfully complete the task. As the individual regains normalized movement patterns, increases their tolerance to use of the affected limb, and is able to participate with relaxed and smooth movement, the exercises are progressed for further flexibility and strength gains.

A trial of aquatic therapy may be beneficial for individuals who have comorbidities that preclude effective participation in a weight-bearing physical activity. Hydrostatic principles and buoyancy provide assistance in edema control and lessening stress on the affected joints. Aquatic therapy can be beneficial to begin to focus on movement and beginning weight-bearing techniques. Watsu is a gentle form of body therapy performed in warm water which combines elements of massage, joint mobilization, shiatsu, muscle stretching, and relaxation skills. However, land therapy should be started as soon as possible as the body must gain tolerance to the demands of gravity.

Functional Activities

Functional activity training consists of activities that increase the ability to use the affected extremity in daily, work, or recreational activities. These can include activities of daily living such as grooming or dressing, household activities such as cooking or cleaning, or activities such as driving or grocery shopping. These tasks may be avoided completely or may be completed by compensating in different ways or performed on a modified basis with difficulty. In CRPS of an upper extremity, functional activities with the affected extremity can become minimal to nonexistent, and often the non-affected extremity is overused. In CRPS of the lower extremity, any task that requires weight-bearing through that extremity is typically avoided, or a compensatory movement is performed.

Functional activities may focus on general tasks such as lifting, carrying, gripping, pushing, or pulling as well as specific activities such as brushing the teeth or writing. Treatment begins by determining the current level of function in a variety of different activities. For some people this may be lifting 1 lb.; for others it may be holding a toothbrush. Instruction consists of how to correct abnormal movement patterns, appropriate activity progression, modifications as needed, and any education required to assist in overcoming barriers to goal success. This may include education on fear of reinjury, negative self-talk, or expected symptom reaction with each activity. Each task is practiced with appropriate pacing of activity, use of flare management tools, and slow progression.

Work-specific tasks may also be part of the treatment. Depending on the severity of the disease, time since onset, and expected prognosis, permanent work modifica-

tions may need to be discussed. This can include voice-activated software, an ergonomic setup, permanent restriction of work tasks, and/or retraining to perform a new type of employment.

Recreational activities serve many purposes including exercise, socialization, time utilization, and general enjoyment. Typically, these activities will require extensive education on ways to modify them and how to pace to be able to participate in them on some level. Therapy can include ways to gain tolerance to these activities, much like gaining tolerance to daily activities or exercise. Often times, people with CRPS may have to give up some recreational activities and replace them with new ones that are more reasonable.

Desensitization

CRPS is known for its central and peripheral sensitization changes. Symptoms of CRPS commonly include increased sensitivity to both noxious and non-noxious stimuli. Desensitization is simply finding ways to decrease or desensitize the overexcited somatic pain response. Desensitization techniques are aimed at normalizing this overactive response with a variety of different sensations. Many people with CRPS report difficulty tolerating long pants, socks and shoes, bra straps, and jewelry on the affected limb. They may either avoid wearing these items or will wrap the affected area as a way to maintain a constant stimulus instead of a varying one such as the clothes and jewelry that shift and move.

A desensitization program is aimed at normalizing sensation by providing consistent stimulus to the affected area for short periods of time, frequently throughout the day. The brain responds to this sensory input by acclimating to the sensation, thereby gradually decreasing the body's pain response to the particular stimuli.

Desensitization can consist of progressive stimulation with soft materials increasing to rougher textures as tolerated over time. It can include light touch progressing to deep or sharper pressure. This can include a bowl of uncooked rice or beans, rubbing a piece of cotton on the affected skin, or using sticks covered with different textures such as velvet and burlap. Vibration tools and contrast baths are often used as another form of desensitization. Many people with CRPS begin by starting to decrease the use of the brace or wrap that they have been using to protect and guard their extremity. Just exposing the limb to the open air and ambient temperature changes can be very painful. Other people begin by starting to wear socks and shoes or long pants for short periods of time. In all cases, part of the patient's treatment is to expose the affected extremity to variable textures and conditions.

An important part of desensitization treatment is utilizing the flare management techniques. Focusing on relaxation breathing, different imagery techniques, and pacing are important tools during desensitization. Increased stress levels, guarding, and holding the breath can lead to increased symptoms, even greater than that caused by the actual treatment of desensitization.

Contrast Baths

Contrast baths are the immersion of a body part alternately in cold and hot water. This causes alternate contraction and dilation of blood vessels, which increase blood flow, white blood cell activity, and the oxidation process to speed up healing. However, the vasomotor changes in advanced cases of CRPS do not always allow for the desired response, and many clinicians believe that the immersion in the cold water may exacerbate CRPS symptoms.

There are different suggested amounts of time of immersion in each bath, whether to start in cold or hot, the duration of treatment, and the actual water temperature used. The most commonly suggested ratio of time in hot water to cold water is from 4:1 to 3:1 ratio. Many people start with 3 minutes of warm water and 1 minute of cool water.

Contrast baths can be used for different purposes in treatment of CRPS. Many people find relief from contrast baths and use them as a flare management tool. In these cases, the temperatures are kept at comfortable ranges. Others use contrast baths for desensitization as the temperature changes can be quite painful for the affected extremity. In this case, the water should be at a temperature that is just outside of the comfortable range. Even when used for desensitization, very cold water is not usually recommended if the limb is typically cold.

Paraffin

Paraffin can be used as a warm wax bath in which the body part is dipped into multiple times and then covered with a plastic bag and towel or covering like an oven mitt. While some people with CRPS cannot tolerate the feel of the wax on their skin or the warm temperature, many others find great relief in the warming properties. In the latter case, it is recommended to use paraffin before exercising the limb to allow for easier movement. Many people use paraffin as a way to control joint swelling or to help decrease contractures.

Electrical Stimulation

Electrical stimulation is a common tool, although clinical experience suggests that patients either find good benefit from the tool from a flare management perspective or are highly flared due to hypersensitivity, even at a proximal site. There are many different types of electrical stimulation units used in therapy today. A few of these include TENS, NMES, and H-Wave. There are other electrical stimulation forms, including microcurrent electrotherapy (MET), but these have limited support from the research literature.

Transcutaneous electrical nerve stimulation, or TENS, is one form of electrical stimulation. The mechanism of the analgesia produced by TENS is explained by the gate control theory proposed by Melzack and Wall in 1965 [20]. When painful stimuli occur, the gates are open, allowing pain transmission to the brain. With TENS, the electrical simulation competes with the pain transmission and causes inhibition of the pain transmissions.

Neuromuscular electrical stimulation (NMES) focuses on muscle activation and is used for muscle strengthening, to increase ROM, and for muscle reeducation/facilitation. NMES Some units function both for NMES and TENS. NMES can be beneficial in treatment of CRPS by encouraging muscle activation which can promote blood flow and the health of the muscle.

While TENS and NMES are more general terms for a type of electrical stimulation, the H-Wave® instrument states that the machine utilizes a completely distinct technology developed by Electronic Waveform Lab and that the treatment system is not available from any other brand name or company. Although there is no specific evidence-based research on H-Wave and CRPS, research on the use of H-Wave for other diagnoses show significant change in regard to increased blood flow, angiogenesis, and soft tissue rehabilitation [21]. Initial changes on CRPS in the affected area are similar to symptoms normally observed in an inflammatory response including swelling, redness, warmth, and pain. Most patients with CRPS experience changes in blood flow, sensation, and temperature in the affected area due to different pathophysiologic responses. Anecdotal experience in patients with CRPS suggests positive results of repeated treatment using the low-frequency settings which causes improved tissue fluid shifts versus the higher frequency which creates pain control.

With all electrical stimulation units, placing the pads directly on the affected area often causes high levels of increased pain due to the increased sensitivity in this area. Typically, pads are placed proximal to the affected site.

Splinting

Splinting is often discussed as a treatment option in CRPS, although this tool is limited in its actual clinical use. Splinting can be used for protection or guarding or to prevent or reduce contractures. Using this treatment for protection or guarding should only be done in the early stages and on a limited basis, as movement should be encouraged, not restricted. Ideally rigid splinting should be avoided but there may be certain circumstances where splinting may be necessary. Splinting may be necessary in severe cases of CRPS to maintain joint integrity and promote adequate circulation and nutrition to the tissues. For example, if a rapidly advancing flexion contracture is developing, a splint may be required. Splinting to prevent or reduce contractures is typically used later on when the patient is better able to control their pain level as this treatment can be very painful. Many patients will never be able to tolerate the use of splinting. Loss of movement may involve both flexion and exten-

sion. The treating therapist needs to be aware of finding the balance between increasing one range and not compromising the other. There is a wide variety of dynamic splints that help to restore function and prevent contracture. Flexion gloves can be useful but should only be used for short periods of time. These gloves are modular splints whereby the patient slips the hand into the glove and the fingers are held down by Velcro. Again, if splinting can be avoided, this is preferable. The fabrication of splints and the difficulty applying them to hands with CRPS limit their use.

Edema Management

Edema is a common sign of CRPS and can vary greatly between people diagnosed with this disease. Looking on the internet can be frightening for a patient newly diagnosed with CRPS due to the pictures of very discolored and swollen hands and feet.

Edema in the early stages of CRPS should be addressed with edema management garments (such as Isotoner gloves, Jobst garments, or Coban wrap) and active range of motion. Self-retrograde massage can be used if tolerated but should not be performed by the therapist unless there is a strong trust that the practitioner will stop treatment if the patient can no longer tolerate it.

In the later stages of CRPS, changing levels of edema are common with physical activity and especially during times of flare-ups. This edema often recedes to its normal level after the activity or when the flare-up calms down. If this is the case, the edema should not be a limiting factor when performing physical activity.

Stress Loading: Scrubbing and Carrying

The stress loading protocol is a widely used rehabilitation tool in treatment and management of CRPS [22]. The protocol involves stressful use of the affected extremity with minimal joint range of motion. Stress loading is comprised of two components: scrubbing and carrying. Each activity engages the affected extremity in consistent weight-bearing activities within a small range of movement for gradually increasing periods of time. The loading of the limb provides inhibitory proprioceptive input to the nervous system, through the use of deep pressure. The key to stress loading is providing as much force or weight-bearing as can be consistently tolerated during scrubbing and carrying, gradually increasing the frequency and duration of these activities throughout the day. Loading the affected area to tolerance and gradually increasing the frequency and duration of weight-bearing activities enable the nervous system to acclimate to these stimuli. This acclimation progressively desensitizes the heightened pain response and allows the nervous system to "remodel" itself; the nervous system shifts from recognizing the stimulus presented as threatening to accepting it as a normal sensation once again.

Scrubbing consists of applying a constant force through the affected area while the limb is moved back and forth as if scrubbing the floor. The protocol by Carlson and Watson calls for 3-minute scrubbing sessions, three times per day, gradually increasing in frequency and duration over a period of days or weeks, up until 7–10 minutes [22].

Carrying involves carrying a weighted object for increasing periods of time with the affected extremity or on the affected side, in order to provide "loading" to the area. Carrying any type of weighted object is effective for the upper extremity. Weight-bearing activities are effective loading for the lower extremity.

Unfortunately, although scrubbing and carrying are recommended in CRPS treatment in multiple articles and websites, there is no specific, evidence-based research on the effectiveness of these treatments.

Guarding/Postural Retraining

Due to the high levels of pain in CRPS, guarding and weight-bearing avoidance are common and are a typical initial reaction to the onset of symptoms. For an upper extremity, the limb is often held close to the body in an internally rotated and adducted position with the elbow and fingers flexed and the shoulder girdle elevated. For a lower extremity, weight-bearing is avoided as much as possible, even in the sitting position. Keeping the limb in a guarded position can be calming and allows the limb to feel protected. It can also keep the limb from being accidentally bumped or jostled. Unfortunately, this guarded positioning not only leads to avoidance of use of the limb but can also cause other musculoskeletal secondary issues such as muscle length changes and joint or soft tissue contractures.

Postural training and positioning can minimize protective guarding, promote balance, and facilitate improved functional use of the extremity. Postural instruction and exercise assist in placing the affected extremity in a correct position to facilitate normal movement patterns and proper muscle retraining.

One of the most difficult parts to changing a habitual position or movement pattern is that while beneficial to the treatment of CRPS or other musculoskeletal issues, the change is typically very painful. Frequent verbal cueing is often necessary, as these abnormal postures are now performed subconsciously. The transition to a more normal posture must often be done slowly but frequently and with a graded progression.

Gait training is another important part of postural retraining for an affected lower extremity. Whether weight-bearing through the limb is entirely avoided or the weight is placed on only one part of the foot, gait, or the walking mechanics becomes highly irregular. A normal gait pattern is typically painful and therefore avoided with multiple compensations. This can lead to patterns of weakness in the low back, hip, knee, and ankle musculature. Gait training begins by determining not only what areas of the foot are being avoided but also the tolerance to weight-bearing through these areas. Subtle changes in the weight-bearing through the foot are encouraged and complemented with weight-bearing exer-

cises. Depending on the tolerance, weight-bearing exercises may first need to be performed in a more controlled setting, such as standing, before the gait pattern can be altered.

Brain Retraining Techniques

Although the pathophysiology of CRPS is not well understood, peripheral and central changes have been observed, and altered central representation of perceptual, motor, and autonomic systems have been implicated [23].

Basic knowledge of cortical changes includes that prolonged non-painful stimulation during physical strain leads to an increase of cortical representation. However, many researchers have observed that the CRPS-affected cortical hand representation in the primary somatosensory cortex (S1) is dramatically decreased. Research has also shown that the magnitude of the reorganization was positively correlated with the extent of increased pain to painful stimuli and pain intensity of CRPS [24, 25]. Other research showed that there is an enhanced activation level of neurons that respond to painful inputs. In follow-up studies, Pleger and colleagues demonstrated that recovery from CRPS was paralleled by a reversal of these maladaptive cortical changes [24]. CRPS patients also show a significant reorganization of central motor circuits, with an increased activation of areas in the brain required for movement during finger tapping. Possible reasoning includes the requirement of more focus when having to complete motor tasks.

A brain-focused motor and sensory exercise program can help redevelop healthy nerve connections and brain organization. Certain pathways in the brain are activated when the brain needs to recognize a body part (sensory) and before and during a movement of that body part (motor). The goal of these treatments is to reorganize the brain and its pathways to diminish pain and sensitivity.

Graded motor imagery is a set of rehabilitation processes used to treat pain and movement problems related to an altered nervous system. The graded motor imagery program for patients with CRPS consists of limb laterality training, imagined hand movements, and then mirror box therapy, in that order. Limb laterality recognition training consists of viewing photographs of a right and left hand in a variety of postures. Patients are asked to quickly and accurately respond whether they recognized the pictured hand to be a left hand or a right hand. Recognizing a pictured hand to be a left or a right hand activates brain areas involved in higher-order aspects of motor output, the so-called premotor cortices [26]. Imagined hand movement training consists of patients deliberately imagining moving their own hand to adopt the posture shown in a given picture. Explicitly imagined movements activate the primary motor cortex [27]. A motor imagery program first activates cortical networks including premotor cortex in a manner that does not initially involve movement of the affected limb. This program retrains the brain before adding the demands of actual movement. One strategy that aims to activate cortical networks and has been successful for acute CRPS is mirror therapy [28]. Mirror therapy

involves movement of the limb inside a mirror box such that visual feedback of the affected hand is replaced with that of the (reflected) unaffected hand. Mirror therapy is thought to reconcile motor output and sensory feedback and activate premotor cortices, which have intimate connections with visual processing areas. Although McCabe and colleagues reported reduced pain in acute CRPS patients during mirror therapy, there was no benefit for patients with chronic CRPS [28–31].

In CRPS, the ability of the brain to recognize the affected body part and its sensations is affected. Sensory reeducation helps to adapt the brain's response to injured areas to normalize object shape, size, texture, and location. The brain is retrained for constant touch compared to moving touch, where on the skin the touch is actually occurring and what direction the touch is moving in. Treatment may incorporate unaffected areas using the same procedure so that the sensation on the two sides may be compared.

Conclusions Regarding Physical Restorative Therapies

Information about physical rehabilitation techniques for people with CRPS continues to grow and develop, although further research studies are needed to determine efficacy in both early and late CRPS. A trained therapist can be helpful in directing the rehabilitation efforts and determining the plan for using the abovementioned treatment tools. Overall, an active and patient-directed approach is important along with setting realistic short- and long-term goals.

Psychological Treatment

Patients with chronic pain problems benefit from psychological services offered in conjunction with physical rehabilitation and medical management techniques. Regardless of the individual's prior psychosocial history, it is common to struggle emotionally when dealing with chronic illness and pain.

Psychological services may include counseling for the patient and significant others, as well as a variety of techniques for pain control and reduction. This can include cognitive behavioral and acceptance and mindfulness-based interventions, biofeedback, stress reduction, meditation, relaxation training, and hypnosis. Services should be time limited, goal oriented, and coordinated as part of a multidisciplinary or interdisciplinary treatment approach.

"Multidisciplinary" approaches include treatment directed by one clinician with multiple disciplines included such as physical and occupational therapy, pain psychology, relaxation therapy, medical management, vocational rehabilitation, and nursing education. Multidisciplinary treatment plans commonly use disciplines at different sites. In contrast, an "interdisciplinary" approach may utilize the same disciplines as mentioned above but is more collaborative and structured.

Care is delivered in one facility, where therapists can better communicate and adjust care. These programs are usually structured, outpatient, day programs, multiple hours per week, for weeks at a time, and include both individual and group therapies [32].

Role of Psychology

Complex regional pain syndrome (CRPS) can have a devastating impact on the injured person and the family. It has effects on the person's ability to function physically and emotionally. Patients suffering with chronic pain report higher rates of pain intensity, disability, depression, anxiety, limitations in functional activities, and decreased quality of life [33].

Patients with CRPS are in need of considerable support while they learn how to effectively manage their pain symptoms while improving functioning. All current evidence-based medicine guidelines recommend a multidisciplinary approach for the management of chronic pain conditions. Given the complex nature of CRPS, a multidisciplinary approach focusing on improved function and treating psychosocial and behavioral issues is recommended [34]. A functional restoration approach has been widely studied in the treatment of chronic pain [35].

Patients may have some misconceptions as to why they were sent to be treated by a psychologist. It should be empathized when making a referral to a psychologist that the doctor does not think "they are crazy or that they are faking." Patients often need to be reassured that no one thinks that their pain is all in their head but that the referring doctor understands the impact living with CRPS has on their life, emotional state, and family interactions. They must be assured that their pain is real and that like many chronic illnesses, treatment with a psychologist can be helpful to better manage pain symptoms and the psychological sequelae of living with persistent pain. The person should be educated on the importance of a multidisciplinary approach to pain treatment which may include appropriate medications, physical therapy, and psychological care.

Psychologists assist in teaching cognitive coping skills, relaxation, and behavioral strategies for better pain control, improved mood, and enhanced quality of life. In the medical setting, they serve as an advocate for the patient and provide education regarding various medical conditions, cognitive and behavioral treatment options, and strategies to reduce barriers to recovery. Psychologists also assist patients with acceptance of their chronic physical condition. They will be taught and learn ways to manage pain, while improving function, but they also need to grieve losses and accept that their condition is chronic. Without acceptance they are less likely to be adherent with the self-care skills training and physical reconditioning. Acceptance helps to shift their focus from using passive tools (resting or avoiding activity) to active tools (cognitive and behavioral coping strategies and reconditioning exercises). Common psychological topics of treatment include cognitive behavioral therapy, stress management, communication, family support, time-based pacing,

goal setting, relaxation or self-regulation skills training, and neuroscience education regarding CRPS.

Because of the complexity of CRPS, a multidisciplinary team including a physician, psychologist, and physical or occupational therapist is recommended for a successful treatment outcome [36]. Treatment should address the influence that physiologic, biologic, cognitive, emotional, behavioral, and social/cultural factors have on the individual patient's reaction and perception of pain [37]. This approach is referred to as the biopsychosocial approach used in the assessment of chronic pain conditions [38]. It focuses on the whole person not just the physical pathology. It takes into account all facets of the individual and tailors the treatment to meet the patient's specific needs versus a "one size fits all" treatment approach. Psychosocial and behavioral factors have been found to play an important role in maintenance of chronic pain and disability [39].

The first step to psychological treatment includes a biopsychosocial clinical intake which may include standardized and validated psychological testing. A thorough clinical assessment for chronic pain should address the following domains: pain experience, pain-related behavior, mood/affect, cognitive coping skills, social functioning, healthcare utilization, and biological and physical fitness factors.

Clinical intake: It is standard practice in the health psychology field that chronic pain conditions are conceptualized and treated from a biopsychosocial perspective [40]. Assessment of a patient with CRPS should address psychiatric comorbidity; cognitive, behavioral, and emotional responses to CRPS; current psychosocial stressors; internal coping skills; and the family/support system. Untreated disorders, such as depression, can erode a person's adaptive energy, thus decreasing their ability to participate in functional reconditioning. In patients with chronic pain, depression has been associated with disability and reduced quality of life [41]. Psychosocial stressors such as chronic stress, depression, anxiety, fear, or anger may be associated with the arousal component associated with CRPS. These negative mood states maintain the "fight or flight" stress-pain cycle adding to increased pain and emotional suffering. Another important component of the clinical assessment is suicidal ideation and history. The level of uncontrolled pain, depression, hopelessness, age, gender, relationship status, social support network, decreased self-efficacy, psychological disorders, past suicide attempts, and family history are associated with increased risk for suicide [42].

Cognitive areas of assessment include the patient's knowledge and beliefs about CRPS, their role in treatment, their stage of change, and thinking patterns. By the time a person is sent for a psychological evaluation, they have most likely been treated by numerous physicians, physical therapists, and other medical providers. Many patients have not been adequately educated on CRPS, their role in recovery, and treatment options. In the worst-case scenario, their reports of pain may not have been believed by some of their providers or even their friends and family (support system). Understanding what a patient thinks about their condition is very important for treatment. Assessing maladaptive thinking styles and beliefs provides valuable insight into the person's internal thought processes. Negative thinking, such as catastrophizing (rumination, magnification, and helplessness around pain), has been

associated with higher levels of pain in CRPS patients compared to other chronic pain patients. A thorough assessment of a person's thoughts helps guide cognitive behavioral therapy (CBT) treatment (this is discussed in more detail later in this chapter). If a patient truly believes that increased pain is an indicator of further tissue damage, then they are less likely to be compliant with physical reconditioning exercises. Their understanding of CRPS should be thoroughly assessed. Another important assessment is determining which stage of change the person is in [43]. The stages of change model, developed by Drs. James Prochaska, John Norcross, and Carlo DiClemente, explores sequential psychological and behavioral stages that patients move through during the process of change [44]. The theory postulates that patients move through specific stages as they move from maladaptive behaviors to adaptive ones. These stages include precontemplation, contemplation, preparation, actions, maintenance, and relapse. Therapy approaches should match the stage the person is in for optimal results. For example, a patient in the beginning stages of change, precontemplation or contemplation will need a different treatment focus to help move them into the more active stages of change (action, maintenance). It is also common for patients to have a relapse in their use of active coping. Relapse prevention is an important component of any behavioral change program. The treatment focus will change depending on which stage of change the person is in. For more information on the stages of change model, see Prochaska, DiClemente, and Norcross and their book *Changing for Good* [44, 45].

Behavioral factors include health habits (exercise, smoking, and caffeine intake), substance abuse history, compliance with prescribed medication, sleep, compliance with medical and physical therapy treatments, activities of daily living (ADLs), self-care, healthcare utilization, and pain behaviors. Patients with CRPS have a high rate of disuse of the affected limb due to high levels of pain. Avoiding movement, in the short term, allows them to escape increased levels of pain, thus reinforcing this behavior. Although this strategy may seem like a good idea to the person with pain, it leads to reduced mobility and sensitization of the affected limb, increasing pain and disability. This cycle is summarized by Bruehl and colleagues who discussed the theoretical pathophysiological interaction in CRPS associated with learned disuse, pain-related behavior, and the autonomic nervous system [52]. This vicious cycle of pain avoidance behaviors serves as barriers to regaining function and should be thoroughly assessed at intake.

The neuromatrix of pain: One way to introduce the role of a psychologist in the treatment of CRPS is to explain the gate control theory [20]. The gate control theory describes the complex interplay between the perception of pain and one's thoughts, feelings, and behaviors. The theory postulates that there are hypothetical "gates" that can open (increasing pain) or close (decreasing pain) which are located in the brain and spinal cord. These gates are influenced by one's thoughts, mood state, and behaviors. This theory helps the patient with CRPS understand how negative thoughts, feelings, and behaviors can actually increase their perception of physical pain by increasing the pain signal received by the brain. Negative thinking, focusing on the pain, stress, anger, fear, depression, poor nutrition, smoking, alcohol, overuse of medications, inactivity, and poor nutrition contribute to opening the gates (increased pain).

Learning healthy coping skills such as relaxation, stress management, and cognitive restructuring can increase one's ability to control these gates and in turn reduce pain levels. The neuromatrix model of pain expanded the gate control theory of pain [21, 37, 40]. The neuromatrix model of pain describes the negative impact stress has on homeostatic balance, thus maintaining the stress-pain process. Increased stress leads to increased pain and increased pain is stressful leading to the stress-pain cycle. A helpful tool to explain this process is provided by www.PainEdu.org under Tools – the pathophysiology of pain. This teaching tool describes the transduction, transition, modulation, and perception of pain using the gate control theory. Adequately explaining this theory helps patients understand the role thoughts, feeling, and behaviors have on their experience of pain. This sets the foundation for teaching active coping skills, increasing self-efficacy, and allowing them to have an active role in recovery.

Cognitive behavioral therapy (CBT): Living with CRPS affects a person's emotional well-being, self-concept, mood, sleep, social and recreational involvement, ability to work, interpersonal relationships, familial role, and overall quality of life. As mentioned earlier psychosocial factors play an important role in the experience and maintenance of chronic pain conditions. The perception or experience of pain is both physical and emotional. The emotional impact on a person's life and secondary losses are referred to as suffering. The losses or suffering components are often more difficult to manage than the physical pain itself. The initial injury can have a rippling effect across many aspects of a person's life. If these losses are not addressed and treated, they can serve as barriers to recovery. This is especially important when developing a treatment plan for patients with CRPS, given the devastating impact the illness has. In 2006 Gatchel noted that research demonstrates that patients with chronic pain have higher rates of depression than the non-pain population and goes on to discuss the negative impact of anger and anxiety [37]. Mood symptoms can erode a patient's adaptive energy required to participate with their recovery. Cognitive behavioral therapy (CBT) has been found to be an empirically validated treatment for chronic pain and other mood disorders. CBT focuses on identifying, challenging, and changing negative automatic thoughts [37, 40, 46]. The theory postulates that negative thoughts lead to and influence dysphoric feeling and unhealthy behaviors and vice versa. Turk discussed the use of cognitive behavior theory (a person's thoughts, feelings, behaviors, and social environment) in the treatment of chronic pain [41]. He eloquently states "According to the Cognitive Behavioral model then, it is the pain sufferer's perspective, based on his or her idiosyncratic beliefs, appraisal and unique schemas, that filter and interact reciprocally with emotional factors, social influences, and behavioral responses, as well as sensory phenomena. Moreover, patient's behaviors elicit responses from significant others (including health care professional) that can reinforce both adaptive and maladaptive modes of thinking, feeling, and behaving" (page 140). CBT teaches persons with CRPS how their individual beliefs, memories, and reactions to their pain symptoms can be challenged and changed to help them effectively cope. By adaptively coping with the pain, they decrease emotional distress and pain intensity (the gate control theory can be used to illustrate this point). Common maladaptive think-

ing styles include catastrophizing, filtering, all or nothing thinking, should statements, and mind reading. Common maladaptive thoughts include "I will never be able to handle this pain" or "This is going to ruin my life" and "what if this continues to get worse." Exploring these maladaptive thinking patterns and teaching the patient how to challenge and change these thoughts can lead to increased self-efficacy and perceived control. There are several CBT techniques that are useful in addressing these thoughts: the use of thought logs or journaling is a helpful tool to identify, challenge, and change unhelpful thought patterns. The goal is to bring these automatic thoughts into conscious awareness, thus allowing the person to challenge and replace them with reality-based coping thoughts.

Fear-avoidance behaviors: Fear associated with increased pain and/or damage of tissue is common in patients with CRPS. This fear can be effectively addressed from a behavioral and cognitive approach. We are taught from young ages that if it hurts don't do it and that pain is the body's way of telling us something harmful is happening. Although this line of thinking may seem logical, it does not hold true for all types of pain. With an acute injury (less than 3 months from injury), allowing the body to heal by resting an injured body part would be appropriate – although even with most acute injuries we now stress careful use rather than rest. With chronic pain (more than 6 months), the majority of the healing has already taken place, and movement is essential to reconditioning the body.

Fear-avoidant behavior is a cycle of behavior that is often seen in patients with CRPS. Because movement can be excruciatingly painful, people fear that if they exercise or use the affected limb, they will cause further damage. This cycle of behavior is problematic in CRPS since non-use of the affected extremity leads to atrophy, hypersensitivity increased pain, and prolonged disability. By the time patients receive the proper diagnosis, they have received mixed messages about increased pain and movement. If previous doctors or physical therapists have told them not to lift more than 10 pounds or to discontinue all activity if it leads to pain, they may not have confidence in the new message that in order to regain function they must begin to use the painful extremity.

Education is the first step to managing this problem. The symptoms of CRPS can appear frightening and bizarre, so educating the patient that these symptoms are "normal" is important. Teaching the person with CRPS how to assertively communicate with their providers about their questions is essential. They may need to have the doctor go over all test results to help them confidently believe that movement will not cause further damage and that their symptoms are expected with CRPS. If they do not believe that it is safe for them to move the affected limb, then they will never do it. It is critical that these messages are consistent from all healthcare providers. It is essential that all healthcare providers communicate and work closely together when treating these complicated disorders.

In addition to fear of reinjury, the patient can also have intense fear of increased pain levels [40]. This fear-avoidance behavior is reinforced, by not moving the affected limb so they can avoid increased pain. Avoidance due to fear increases their pain and fear and this cycle of avoidance becomes a barrier to recovery. Addressing the underlying fear is essential to conquering the behavior pattern. The fear itself is

often worse than the actual experience of pain; however, this is not to underestimate the amount of pain involved with CRPS. Often, a combination of CBT, relaxation, and physical activity exposure can be very effective in addressing this issue. Addressing the thoughts that limit the person's willingness to participate in graded exposure exercises is essential to recovery. Challenging the automatic thoughts that drive this fear-avoidant behavior is the key to any successful rehabilitation effort.

Behavioral/pacing: Behavioral change is not about willpower; it is about setting realistic, measurable, achievable, and timely goals. These goals serve as a guide to help the person with CRPS improve the quality of his or her life by progressively resuming normal activities and participating fully in life. Exercise, relaxation, and cognitive and behavioral coping tools are essential skills that aid in returning to a productive and meaningful life. Planning how to incorporate these skills into the patient's daily routine is part of goal setting. Setting daily and weekly goals helps keep patients with CRPS on track. It also helps to hold oneself accountable. Setting realistic and achievable goals assists with prioritization of tasks reducing overwhelming feelings and procrastination. The use of pacing can help guide the person on goal attainment without causing significant pain flares. With CRPS, pain should not be the person's only guide to activity, since initially they will have pain even with minimal movement. Pacing is a skill that helps the person resume normal activities slowly without causing a huge pain flare. The goal with pacing is to engage in an activity based on time not pain, then take a break, over and over until the task is complete. During these rest breaks, it is important to use some of the self-soothing skills mentioned below such as breathing, stretching, meditation, etc. Breaks are intended for the person to use coping skills to help calm the nervous system (CRPS leads to changes in the nervous system and brain). The overall goal is to gradually increase tolerance for activities (time engaging in that activity) while decreasing the time of the rest break and to eliminate the "crash and burn" cycle of chronic pain. The CBT skills are helpful when teaching a person about pacing. Automatic negative thought like "If I take a break everyone will think I am lazy" or "I have so much to do, how can I take a break now?" if left unchallenged will interfere with the use of pacing.

Secondary loss: Another aspect of quality of life is engaging in social and recreational activities. Helping the person with CRPS fully participate in events that make them feel happy and connected should be part of their recovery. Living with pain is bad enough, but often times it is not the only problem the person faces. Being unable to work, socialize, recreate, and engage in activities that one enjoys can lead to increased depression and disability in patients with chronic pain [47]. Depression reduces one's pain threshold and can lead to a vicious cycle of disability. Engaging in quality life experiences helps reduce emotional suffering and is an important component of treatment.

Communication: Effective communication is an important skill to help us connect with the people in our lives and to get our individual needs met. Living with CRPS can cause a great deal of stress, disrupting the family system or social balance. The

person with CRPS is tired of talking about the pain, and significant others get tired of hearing about it which usually leads to a breakdown in communication. Learning to effectively communicate can help reduce the level of stress, while improving the overall quality of relationships. One goal of this training is to address underlying beliefs that interfere with assertive communication. Addressing these unhelpful beliefs can open the door to new ways of communicating. Another helpful tool is to use "I" statements. This allows one to express how they feel without blaming or attacking someone else. With assertive communication the person's words match his or her body language. They respect their own needs and feeling and the other person's point, even if there is a conflict of beliefs. Active listening without interrupting is also an important component of effective communication. Living with CRPS can lead to shutting down the lines of communication. Self-care is such an important component of recovery, and being able to communicate how things may have to change and why is important. The person with CRPS often feels isolated and misunderstood, while family members and friends feel helpless because they don't know how to help. Healthy communication can help reduce the negative impact living with CRPS has on the family system, thus reducing everyone's stress levels.

Family: An important component of treating CRPS is involving the person's support system. Social support helps us feel connected to others providing a deep sense of belonging and strength. Most family members and friends of the person with CRPS are very confused about what is happening to their loved one. The support system usually expects a "cure" so the injured individual can get back to normal. Education involves reinforcing that pain does not equal further damage, the course of treatment, the importance of movement in recovery, active coping skills, realistic expectations, and that the goal is to manage CRPS not cure it. Following the education, they are encouraged to discuss the information as a family.

Some family members have solicitous behaviors. Solicitous responses usually come from a place of caring, but unfortunately the consequence of the responses is passivity of the patient. Common responses include "Don't do that!" or "You might hurt yourself" or "I can do that for you" or "Maybe you should call your doctor, something is wrong." Family members can reinforce maladaptive pain behaviors so educating the family about CRPS is vital. Another common misconception is that family and friends often think of CRPS as an acute pain condition that can be "cured." It should be empathized that CRPS is a chronic pain condition that can be managed but not cured. They should be involved with treatment, so they can support healthy behavioral choices and have realistic expectations regarding the person's function. Attending support groups is a great place to receive support and ideas of how to manage living with CRPS.

Stress management: Stress has been shown to reduce the pain threshold, reduce immune functioning, slow healing times, and cause emotional distress. In patients with CRPS, unmanaged stress leads to muscular bracing and guarding and reduce blood flow to the affected limb resulting in increased pain. Living with high levels of chronic pain can lead to nonstop stress. Effective stress management skills are

essential in learning how to live a quality life even with pain. To describe the stress-pain cycle, it is helpful to explain the interaction between pain and stress on the autonomic nervous system. The National Geographic movie Stress: Portrait of a Killer is an excellent way to introduce the psychological and physiological relationship of the stress response. Having a basic understanding of the autonomic nervous system and stress sets the foundation for cognitive stress management skills and relaxation training.

Most patients believe that watching TV or sitting on the couch is "relaxation." This is an important concept to explore. Although one may believe this type of activity is relaxing, it is not "the relaxation response" used as a stress or pain management technique. Herbert Benson coined the term "the relaxation response" in the 1970s. He proposed that if a person makes an effort to engage in regular relaxation, then physiological changes occur. These changes include reduced blood pressure, heart rate, breathing, and muscle tension. In addition, vasodilatation increases blood flow to extremities and a reduction in stress hormones. Engaging in regular relaxation reduces pain levels and emotional distress. This also increases the person's level of perceived control and provides active coping tools to manage the pain.

Relaxation: Relaxation training teaches self-soothing skills to engage the parasympathetic nervous system (restorative system) and emotional balance. Self-soothing skills, such as formal relaxation, help a person with CRPS calm their nervous system. Since CRPS is often sympathetically driven, anything that engages the sympathetic nervous system has the potential to increase pain and stress hormones. Engaging the parasympathetic nervous system revitalizes a "restorative state" leading to increased blood flow and reduces muscular bracing and guarding, stress hormones, and emotional stress. There are a variety of relaxation techniques used in the treatment of CRPS which include biofeedback, autogenic training, guided imagery, affirmations, progressive muscle relaxation, diaphragmatic breathing, and mindfulness-based stress reduction (MBSR).

Biofeedback: Biofeedback is a type of training that teaches people how to improve their health by using bodily signals. The dictionary definition of biofeedback is "the technique of making unconscious or involuntary bodily processes (as heartbeats or breathing) perceptible to the senses (as by the use of an oscilloscope) in order to manipulate them by conscious mental control." The goal of biofeedback is to teach body awareness, in real time, to help with increased self-control through relaxation. Biofeedback therapy uses electronic sensors (EMG, skin conductivity, skin temperature, etc.) to help patients with CRPS learn how to change physiological bodily processes. Biofeedback combined with counseling has been found to be efficacious in patient with CRPS who failed previous treatment [48]. These results included long-term (up to 1 year) reduction in pain levels and increased return to work rates. "Bio" refers to body and "feedback" refers to visual or audio feedback provided by the machine. During times of stress, our body secretes stress hormones that lead to increased heart rate, blood pressure, vasoconstriction, and changes in breathing. Vasoconstriction causes blood to be diverted to the large muscle groups leading to less

blood flow to the periphery causing cold and clammy hands/feet. CRPS is often associated with decreased blood flow to the affected extremity leaving it cold or blue. Thermal biofeedback has been shown to be effective in managing CRPS [49]. Thermal biofeedback measures peripheral temperature using a thermistor (temperature gauge) attached to the affected body part (usually best to begin with the unaffected limb). Deep relaxation increases vasodilatation, diverting less blood to the large muscle groups, and so increases temperature to the periphery. Using thermal biofeedback can be a powerful tool to teach patients in "real time" how the skill they are using affects the temperature of their extremities. Other modalities include breathing, skin conductance, and muscle sensors. Muscle biofeedback helps patients make connections between muscle bracing and guarding, while practicing relaxation of that muscle group. EMG biofeedback is used in conjunction with progressive muscle relaxation and diaphragmatic breathing to induce a state of relaxation. This helps patients that have poor body awareness. For more information in biofeedback, please visit the Biofeedback Certification Institute of America (BCIA) – http://www.bcia.org.

Relaxation exercises: Diaphragmatic breathing, autogenics, guided imagery, progressive muscle relaxation, and mindfulness meditation are psychophysiologic techniques that are taught to patients with CRPS to help decrease pain and increase levels of perceived control. Breath training is a foundation skill to many types of relaxation training. Although breathing is an essential function of life, many people with chronic pain breathe in a way that leads to poorly oxygenated blood or a hyperventilation pattern of breathing. They take shallow rapid breaths mostly using their chest and other upper body muscles such as the upper trapezius and employ minimal use of the diaphragm muscle. This "chest" breathing pattern is associated with the stress response. Repetitive contraction of these muscle groups can also lead to pain in the upper trapezius and headaches. Psychologically this pattern of breathing is associated with anxiety and stress both of which is detrimental to chronic pain. During proper diaphragmatic breathing, engaging the diaphragm allows the lungs to fill fully. This is the way our body was intended to breathe. You can detect which patterns of breathing you have by placing one hand on the chest and one on the belly. Inhale and notice which hand moves more. The hand on the belly should rise with inhalation and fall with exhalation. The hand on the chest should remain mostly still and the shoulders should not rise. The goal is to breathe using your diaphragm taking slow relaxed breaths.

Autogenic training was developed by Johannes Schultz, a German psychiatrist, in the 1930s. Autogenics involves repeating phrases of relaxation that target the different systems associated with the autonomic nervous system. It is recommended that the phrases are practiced daily. Common phrases include "my arms are warm and heavy, and my breathing is calm and regular." These phrases target the systems associated with the PNS (restorative state). These phrases can be memorized and repeated in silence. In the beginning of learning relaxation, self-guidance can be challenging. There are a variety of relaxation CDs that can help with the facilitation of relaxation.

Progressive muscle relaxation (PMR) focuses on tensing then relaxing various muscle groups. This can help increase body awareness; it helps patients with CRPS recognize if they are bracing and guarding their muscles, increasing pain levels. Practice of PMR fosters healthy body awareness. Patients with CRPS are not conscious that they are bracing or guarding various muscle groups; this behavioral pattern has become an unhealthy habit that must be unlearned. PMR can help with changing this behavioral pattern.

Guided imagery is a form of mediation that incorporates the use of imagination. One imagines being in a place that is relaxing which could be a real or make believe place. It allows the mind to go on a mental vacation aiding in the experience of a relaxed state.

Mindfulness meditation has been found to improve overall quality of life and even changes in the brain [50]. Mindfulness was introduced to the field of western medicine by Jon Kabat-Zinn at the University of Massachusetts Medical Center. He developed mindfulness-based stress reduction (MBSR) which is offered in medical centers across the United States to treat a variety of disorders including chronic pain. Mindfulness focuses on paying attention, on purpose, without judgment. The concept underlying mindfulness helps patients living with CRPS to "notice" the pain without trying to change it and without judgment. Instead of fighting against the pain, one learns how to coexist with it. This also helps with acceptance and reduces the impact of negative emotional reactions.

With all forms of relaxation, the key to success is daily practice and passive concentration. These skills should become part of the patient's daily routine. If a person with CRPS waits to use breathing or the other relaxation skills until they have a huge pain flare, it is less likely to help. It should be emphasized that these skills should be used as a preventative strategy not just a reactive tool. It is like putting money in the bank every paycheck, so when you need to withdraw a large sum, you have enough funds to cover it. Patients are encouraged to schedule relaxation time into their daily routines just like they would any other appointment.

Summary of Psychological Approaches

The treatment of CRPS is complex. CRPS is a devastating disease that significantly affects all aspects of the person's life. A multidisciplinary treatment approach that focuses on the biopsychosocial model of chronic pain is recommended for a successful outcome. Psychological treatment has been empirically validated for the treatment of chronic pain conditions. The goals of treatment should be specific to the patient's idiosyncratic needs. This chapter is a brief overview of the psychological treatment of CRPS. Common psychological aspects of treatment include a biopsychosocial clinical intake, general education regarding CRPS, the gate control theory, cognitive behavioral therapy, fear-avoidance behaviors, stress management, communication, family support, pacing, goal setting, relaxation skills training, and relaxation skills training.

Functional Restoration and Multi- and Interdisciplinary Pain Management

The most effective approach for many CRPS patients involves a functional restoration multidisciplinary or interdisciplinary chronic pain program [36]. These programs are cost-effective and involve an individualized, but highly structured, medication optimization, behavioral/psychological rehabilitation, and physical conditioning program in a group setting.

Individuals engage in stretching, strengthening, aerobic conditioning, and desensitization techniques, while learning behavioral and psychological approaches to better manage pain along with educational activities and work simulation.

Dependency on the doctor and therapist is discouraged, and the program is geared toward healthy behaviors and return to leisure and work activities. The group setting provides friendship among patients and encourages mutual support.

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Chapter 13
Management of Peripheral Nerve Pain

Stephanie C. Jones

Specific Peripheral Nerve Pain Disorders

Painful Diabetic Neuropathy

Painful diabetic neuropathy is a frequent complication related to long-term diabetes. Painful diabetic neuropathy (PDN) is described as "asleep numbness, prickling, stabbing, burning, or aching" pain, which predominantly affects the toes, feet, or legs, in a symmetric and distal distribution [1]. Up to 25% of patients with diabetes develop neuropathic pain [2].

Diabetic neuropathy is classified into "typical" or "atypical" forms, based on occurrence, with the "typical" form being a chronic, distal, symmetric polyneuropathy that accounts for 75% of diabetic neuropathies. Other variations suggest an "atypical" form [3].

The mechanism of distal symmetric polyneuropathies in diabetes is not fully understood. The pathogenesis of diabetic neuropathy is thought to be multifactorial, involving interactions among glycemic control, duration of disease, intrinsic neuronal factors, as well as other factors such as blood pressure, lipids, and patient weight [4]. Hyperglycemia leads to alterations in several biomechanical pathways that affect cellular metabolism and ultimately leads to neuronal injury including segmental demyelination and even Wallerian degeneration. Human observational studies show that hyperglycemia is critical for the development of diabetic distal polyneuropathy. Therefore, it is not surprising that one of the most important treatments for managing pain in this condition is tight glycemic control. While tight glycemic control early in type I diabetes has been shown to reduce the development

S. C. Jones (✉)
Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: Stephanie.Jones@UTSouthwestern.edu

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of diabetic neuropathy [4], such findings have been less convincing in type II DM. Such findings reinforce the accepted belief that the pathophysiology of neuronal damage in diabetics is complex and multifactorial and not strictly associated with hyperglycemia.

Pain Relief Through Disease-Modifying Treatments

Outside of strict glucose control, patients often inquire about available treatments that may actually slow the progression of diabetic neuropathy. While some treatments are available that target the pathogenesis of diabetic neuropathy, these treatments have mostly shown promise in animal studies, while being less convincing in human randomized trials.

Alpha-Lipoic Acid (ALA)

Of potential disease-modifying treatments, alpha-lipoic acid has shown some efficacy in the treatment of painful diabetic neuropathy. Alpha-lipoic acid is an antioxidant proposed to slow progression and reduce pain in diabetic neuropathy by reducing oxidative stress related to hyperglycemia. Several trials have shown clinically meaningful symptomatic improvement compared to placebo [5]. A 2012 systematic review showed that 600 mg of ALA administered daily intravenously for 3 weeks led to clinically significant reductions in neuropathic pain in patients with diabetic neuropathy [6]. ALA is still considered an unproven treatment for diabetic neuropathy, and thus no specific dosage can be considered "safe." However, there is limited evidence to show intolerability or dangerous adverse effects when taken orally or intravenously at 600 mg daily. For these reasons, in those patients interested in supplemental therapies for diabetic nerve pain, 600 mg of alpha-lipoic acid may be a reasonable option.

Symptom Management

One of the most debilitating symptoms of diabetic neuropathy is the associated pain. Even if disease progression cannot be adequately reduced, one should focus on alleviating the symptoms of the disease (pain). The focus of this chapter will be on the available interventions (both pharmacologic and invasive) in the treatment of painful diabetic neuropathy.

Pharmacologic Management of Painful Diabetic Neuropathy

Available treatments in the treatment of pain in diabetic neuropathy fall into three major categories: antiepileptics, antidepressants, and other analgesics (including opioids). Of the many medications utilized in the treatment of neuropathic pain, the

only drugs approved by the Federal Drug Administration specifically for the treatment of pain associated with diabetic neuropathy include duloxetine, pregabalin, tapentadol, and fluoxetine [7].

Antiepileptic Medications

Pregabalin (Lyrica∗)

Pregabalin is an antiepileptic that has shown benefit in the treatment of painful diabetic neuropathy. It binds to the a2d subunit of the calcium channel. This in turn reduces calcium influx and reduces release of neurotransmitters involved in nociception.

Several randomized controlled studies have shown pregabalin to be effective in the treatment of painful diabetic neuropathy [8–15]. Results of these studies show that doses ranging from 150 to 600 mg daily are effective in reducing pain scores. There is a dose-related response, and 600 mg daily dosing results in lower pain scores than 300 and 150 mg daily. Treatment with pregabalin is also associated with improvements in patient-reported global health status, as measured by the Patient Global Impression of Change [16].

Common adverse effects of pregabalin include weight gain, dizziness, sedation, and peripheral edema. Adverse effects are also dose-dependent, with higher rates of edema and weight gain in the 600 mg/day dosing groups.

Pregabalin is renally cleared, and dosing should be adjusted in patients with renal insufficiency. Pregabalin can affect mood and has been associated with suicidal ideation in some patients. Patients should be warned of the potential for mood changes. It can also induce euphoria in some patients and can be a drug of abuse. It is a controlled substance in the USA and should be used cautiously in patients with a history of substance use disorder [17].

Gabapentin (Neurontin∗)

Gabapentin is an antiepileptic with the same mechanism as pregabalin. It binds to the a2d subunit of the calcium channel, inhibiting neurotransmitter release and modulating nociception.

In 2011, the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation published evidence-based guidelines for the treatment of painful diabetic neuropathy. These groups analyzed all available randomized controlled trials evaluating the treatment of painful diabetic neuropathy [18]. Only 1 RCT of gabapentin was considered high quality. In this study, gabapentin had a small effect of net pain reduction from baseline of 11% on the 11-point Likert scale compared to the change in placebo-treated patients [19]. Based on these findings, these guidelines recommend gabapentin as probably effective for painful diabetic neuropathy with level B evidence.

Pain reduction was significant at 1800 mg daily, and thus gabapentin should be titrated to a goal of at least 1800 mg daily to achieve pain relief. The maximal dose is 3600 mg daily in three times daily divided dosing. Adverse effects include dizziness, somnolence, and edema. Similar to pregabalin, gabapentin is also renally excreted, and dosing should be adjusted in those patients with renal insufficiency [17].

Antidepressants

Tricyclic antidepressants and serotonin norepinephrine reuptake inhibitors have shown analgesic efficacy in the treatment of multiple neuropathic pain conditions. For the treatment of pain in diabetic neuropathy, studies most support the use of amitriptyline, venlafaxine, and duloxetine.

SNRIs (Serotonin Norepinephrine Reuptake Inhibitors)

Duloxetine (Cymbalta∗)

Duloxetine is an antidepressant with both serotonin and norepinephrine reuptake inhibition. Three high-quality randomized controlled trials supported the use of duloxetine in the treatment of painful diabetic neuropathy [20–22]. In the Raskin trial, patients treated with duloxetine reported an 8% reduction in pain scores on the 11-point Likert scale. There was no difference in efficacy between the 60 mg daily dosing and the 60 mg twice daily dosing, though there were increased reports of adverse effects among those taking 120 mg daily. In the Goldstein study, 52% of patients treated with 120 mg duloxetine daily reported at least 50% reduction in their 24-hour average pain scores. Based on these results, duloxetine is recommended in the treatment of painful diabetic neuropathy per the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation guidelines for the treatment of painful diabetic neuropathy.

Venlafaxine (Effexor∗)

One class I study illustrated a moderate analgesic effect of venlafaxine in the treatment of painful diabetic neuropathy, with 23% greater pain relief in the treatment group vs placebo. At week 6 of treatment, patients treated with 75 mg venlafaxine daily reported 32% reduction in pain scores compared to 27% in the placebo group. However, those in the group receiving 150–225 mg daily of venlafaxine reported 50% reduction in pain scores [23]. Nausea and somnolence were the most common reported

adverse effects. Venlafaxine is associated with clinically significant ECG changes and should be used with caution in those patients with cardiac comorbidities.

Tricyclic Antidepressants

Amitriptyline (Elavil∗)

Three high-quality studies evaluated the efficacy of amitriptyline in the treatment of painful diabetic neuropathy [24–26]. In the study by Vrethem et al., 22 of 33 patients treated with amitriptyline at 75 mg daily reported statistically significant reductions in pain. In 2 other studies [25, 26], amitriptyline had a notable effect, reducing pain by 63% and 58% more than placebo on a verbal 13-item descriptor list converted to a numeric 5-point scale. Patients able to tolerate higher doses, up to maximum of 150 mg daily, reported greater improvement, implying a dose-related response. Amitriptyline is associated with multiple adverse effects, including orthostasis, sedation, dry mouth, and urinary retention. For these reasons, many patients do not tolerate it, and it should be used with caution in elderly patients who tend to be frail and at higher risk of falls.

Opioids

Opioids have been studied in the treatment of painful diabetic neuropathy. Specifically, morphine, extended-release oxycodone, and tramadol have shown some efficacy. Unfortunately, none of the studies evaluating opioids in the treatment of painful diabetic neuropathy extend beyond 3 months. Therefore, despite quality evidence to support the use of opioids in refractory cases of painful diabetic neuropathy, critics point out that these studies do not take into account the adverse effects of chronic opioid therapy, including tolerance, and the development of opioid-induced hyperalgesia, which may occur when opioids are utilized for extended periods (greater than 3 months). Due to the many potential adverse effects of chronic opioid therapy (including tolerance and iatrogenic opioid use disorder), opioids should be used only in refractory cases and with great caution.

One class II study showed that morphine reduced pain from baseline by 15%, and two class II studies showed that tramadol relieved pain by 16% and 20% more than placebo on a Likert scale [27–29]. One class II study evaluating opioids for painful diabetic neuropathy showed that oxycodone-controlled release caused a 27% reduction in the VAS compared to placebo [30]. Again, none of these studies evaluated patients for longer than 8 weeks, and thus there is actually no quality evidence available to support the use of *chronic* opioid therapy in the treatment of painful diabetic neuropathy. Without evidence to support chronic opioid therapy, opioids should be utilized with caution and only in refractory cases.

Other Pharmacologic Agents

Dextromethorphan

Dextromethorphan acts at the NMDA receptor and has been used in neuropathic pain conditions. One class I study showed that dextromethorphan relieved pain by 16% more than placebo on a 20-point scale in painful diabetic neuropathy [31]. Doses were titrated to the highest dose tolerated, the mean dose being 381 mg/day in painful diabetic neuropathy. High-dose dextromethorphan is associated with adverse effects, and 5 of 31 patients in this study dropped out due to sedation or ataxia.

Topical Capsaicin

Capsaicin is the active component of chili peppers (plants belonging to the genus *Capsicum*). It produces a sensation of burning in tissue with which it comes into contact. Research shows that capsaicin is an agonist at the transient receptor potential vanilloid 1 (TRPV1) receptor and can be effective in certain neuropathic pain conditions. The TRPV1 receptor is a ligand-gated ion channel receptor expressed on nociceptive skin neurons. Application of capsaicin to the skin initially causes an enhanced sensitivity and increased sensation of pain, followed by a decreased sensitivity attributed to a reduction in TRPV1 expression [32]. Studies indicate that capsaicin also has neurolytic properties, reducing epidermal nerve fibers in treated areas over time. Reinnervation does occur [33].

A class I study of topical 0.075% capsaicin showed a large effect (40% more reduction in pain on the VAS compared to placebo cream) [34]. A recent systematic review suggested that the high-dose 8% capsaicin patch may be as or more effective in painful diabetic neuropathy and have less systemic effects in comparison to other recommended systemic therapies such as tricyclic antidepressants and gabapentinoids [35]. A high-quality randomized controlled trial showed that a 30-minute application of the high-dose 8% capsaicin patch to the feet in painful diabetic neuropathy led to statistically significant reductions in pain scores at 12 weeks in comparison to the placebo group [36]. Though not strongly recommended in many guidelines for the treatment of painful diabetic neuropathy, topical capsaicin seems to be a reasonable choice with minimal systemic effects.

Topical Lidocaine (Lidoderm∗)

Lidoderm is a high-dose topical lidocaine patch (5% lidocaine). It has been utilized for focal areas of neuropathic pain. Topical lidocaine is theorized to improve pain in peripheral neuropathic pain due to its inhibition of upregulated sodium channels on nociceptors in pathologic pain states [37].

Two class III studies evaluating the efficacy of topical high-dose lidocaine patches (5%) for painful diabetic neuropathy showed moderate improvement in pain. Treatment with Lidoderm applied to the most painful sites provided a 20–30%

reduction in pain scores [38, 39]. Due to its very limited systemic effects and low side effect profile, Lidoderm is a reasonable adjuvant in the treatment of painful diabetic neuropathy.

Interventional Management of Painful Diabetic Neuropathy

Unfortunately, many patients with painful diabetic neuropathy continue to endure poorly controlled pain despite aggressive pharmacologic management. Interventional pain specialists have utilized various procedures in an attempt to reduce pain in this population. Due to lack of high-quality evidence, there are no guidelines for the treatment of painful diabetic neuropathy which recommend invasive management strategies. However, due to its very refractory nature in some patients, these invasive strategies may be considered when other pharmacologic management strategies have failed.

Peripheral Nerve Blockade

There are no studies evaluating the role of peripheral somatic nerve blockade in the treatment of painful diabetic neuropathy. In fact, due to the injured state of peripheral nerves in these patients, one might say it would be imperative to use caution when blocking peripheral nerves due to potential increased risk for nerve injury.

Sympathetic Nerve Blockade

The sympathetic nervous system has been implicated in many chronic pain states. For instance, blockade of the sympathetic innervation to the involved extremity in some complex regional pain syndrome cases can improve pain scores. There is very limited research available evaluating the role of sympathetic blockade in the treatment of painful diabetic neuropathy.

A 2012 case report illustrated sustained improvement in pain scores using a series of bilateral lumbar sympathetic blocks (9 over a course of 26 months) in a patient with refractory painful diabetic neuropathy in the lower extremities. Although this case is promising, it is difficult to recommend an invasive strategy with such limited evidence to support its use [40].

Spinal Cord Stimulation

The International Association for the Study of Pain, Neuropathic Pain Special Interest Group (IASP NeuPSIG) developed recommendations for the interventional management of neuropathic pain, published in 2013 [41]. At that time, three

prospective trials specifically evaluated the effects of spinal cord stimulation on painful diabetic neuropathy [42–44]. Though overall the trials revealed large benefits, there was a relatively large complication rate, as high as 33% in the de Vos trial. The trials were also very small, and thus the IASP guidelines describe spinal cord stimulation for painful diabetic neuropathy as still "inconclusive" and recommend more clinical trials prior to supporting this therapy.

Since these guidelines were published, Slangen et al. published another prospective trial evaluating spinal cord stimulation for painful diabetic neuropathy in 2014. This trial had very positive results (59% of the 22 patients randomized to spinal cord stimulation reported treatment success). Treatment success was defined as greater or equal to 50% pain relief during daytime or nighttime or "very much improved" for pain and sleep on the Patient Global Impression of Change (PGIC) scale at 6 months. Again, spinal cord stimulation is an invasive therapy not without risk, and one of the patients in the spinal cord stimulation group died due to a subdural hematoma (mortality rate of 4.5%) [45].

While spinal cord stimulation is quite promising in the treatment of painful diabetic neuropathy, there is still not a large body of research to support its treatment, and the morbidity and mortality are not insignificant. Despite inconclusive support, spinal cord stimulation may be an option for the treatment of refractory painful diabetic neuropathy.

Other Peripheral Neuropathies (Including HIV-Associated Neuropathy and Chemotherapy-Associated Neuropathy)

Most studies evaluating the pharmacologic management of painful neuropathies have focused on painful diabetic neuropathy. Therefore, in general, most guidelines on the treatment of painful neuropathies typically group all peripheral neuropathies together and may extrapolate data from the diabetic neuropathy studies to other peripheral neuropathic pain disorders. For these reasons, the management strategies of other peripheral neuropathies are typically very similar to painful diabetic neuropathy.

The International Association for the Study of Pain Neuropathic Pain Special Interest Group released updated guidelines for the pharmacologic management of neuropathic pain in 2015 [46]. These guidelines grouped many conditions together, and recommendations were focused more on the individual drugs and not on the etiology of pain. Pharmacologic management of peripheral neuropathies was similar across the board, with no specific recommendations for individual neuropathic pain states.

Based on their exhaustive review of the available literature, the following medications were recommended as first line: gabapentin, gabapentin ER/enacarbil, pregabalin, SNRIs duloxetine/venlafaxine, and tricyclic antidepressants (TCAs). These guidelines are similar to the specific guidelines for diabetic neuropathy. Table 13.1 summarizes the guidelines.

Table 13.1 First-line agents for the management of neuropathic pain, IASP NeuPSIG 2015 guidelines

Drug	Daily dosages (mg)	Recommendation
Gabapentin	1200–3600	First line
Gabapentin ER/ enacarbil	1200–3600	First line
Pregabalin SNRIs	300–600	First line
Duloxetine	60–120	First line
Venlafaxine ER	150–225	First line
Tricyclic antidepressants	25–150	First line

Finnerup [46]

HIV Sensory Neuropathy

Among those living with HIV, there is an estimated prevalence of HIV-SN (HIV sensory neuropathy) between 31% and 50% [47]. The underlying pathogenesis is incompletely understood but is believed to be a complex dysfunction affecting not only the peripheral nervous system but central neurological pathways as well. In the peripheral nervous system, there is an indirect inflammatory process affecting the nerves. HIV does not directly infect the peripheral nerves themselves, but affects the immune cells and leads to inflammatory damage to the peripheral nerves, and ultimately can contribute to the development of symptomatic painful sensory neuropathy [48].

HIV-SN is grouped into "neuropathic pain" in many treatment guidelines. However, medications which have shown significant benefit in other peripheral neuropathic pain disorders such as painful diabetic neuropathy have been less effective in this patient population. An exhaustive 2010 review of the literature showed that many medications typically recommended as first line in the treatment of neuropathic pain have failed to show efficacy in the treatment of painful HIV-SN, including amitriptyline, gabapentin, and pregabalin. This review of available randomized controlled trials showed that the only pharmacologic agents which have shown some improvement in HIV-SN-associated pain included smoked cannabis, human nerve growth factor, and topical 8% capsaicin (Qutenza∗). However, human nerve growth factor is not available clinically, and the long-term health risks of chronic cannabis use are unknown. Topical 8% capsaicin patches are only approved for postherpetic neuralgia in the USA. Some evidence supports the use of topical 8% capsaicin (Qutenza∗) over lower-dose capsaicin, but other evidence shows no difference between lower-dose capsaicin and the high-dose patches [49]. A comprehensive 2017 Cochrane review of topical 8% capsaicin in the treatment of neuropathic pain stated that only "very low-quality" evidence was available to support its use in the treatment of HIV-SN [50].

As with other peripheral neuropathies, there is limited evidence to support interventional techniques in the treatment of HIV-SN. A 2015 article showed significant pain relief using spinal cord stimulation for refractory neuropathic pain in two patients with HIV sensory neuropathy. However, there is no high-quality evidence to support the use of spinal cord stimulation for HIV-SN. Regardless, in refractory cases, spinal cord stimulation may be a reasonable alternative [51].

Postherpetic Neuralgia

Postherpetic neuralgia (PHN) is a neuropathic pain syndrome caused by herpes zoster, "shingles," due to reactivation of the varicella zoster virus. Definitions vary, including pain that persists anywhere from 4 weeks to 6 months after onset of the vesicular rash. The pathophysiology involves abnormalities in both peripheral and central neural processing. Herpes zoster affects one out of three people during their lifetime. Symptoms manifest as a maculopapular rash with vesicles typically along a dermatomal distribution but at times may involve multiple dermatomes and can even be systemic in immunocompromised individuals. The rash is quite painful, and 10% of those affected with herpes zoster will progress to postherpetic neuralgia and chronic neuropathic pain, despite resolution of the rash [52].

The biggest risk factor for progression to PHN after herpes zoster is age. The risk in those under the age of 50 is only 4%, while those over age 80 have a 34% risk of developing PHN after an episode of shingles [53]. Because it is primarily a disease of the elderly, many patients suffering from PHN have limited treatment options due to their comorbidities. It is often quite challenging to manage, and only 50% of patients with PHN have greater than 50% pain relief despite treatment [54].

The severity of pain in herpes zoster (HZ) is also a risk factor for the development of postherpetic neuralgia. Therefore it is imperative to treat HZ aggressively. Certain interventions have been shown to reduce the severity and duration of a HZ outbreak, including antiviral therapy [55], adjuvant corticosteroids [56], antineuropathic medications [57], and procedures such as epidural steroid and paravertebral injections [58]. However, there is no robust evidence to show that any intervention actually reduces the incidence of progression to PHN.

Pharmacologic Management of PHN (Postherpetic Neuralgia)

The pharmacologic management of postherpetic neuralgia is typically grouped together with other neuropathic pain disorders. There is limited literature specifically evaluating the role of pharmacologic management in the treatment of pain related to PHN. Again, the most comprehensive and up-to-date guideline on the treatment of neuropathic pain disorders is the IASP NeuPSIG guidelines. These guidelines recommend gabapentinoids, tricyclic antidepressants, and serotonin norepinephrine reuptake inhibitors as first-line treatments for neuropathic pain disorders, including PHN. However, duloxetine and venlafaxine have not specifically been studied in the treatment of PHN, and the recommendation for their use in this disorder is extrapolated from other neuropathic pain studies such as painful diabetic neuropathy [46].

There is weak evidence for the efficacy of 5% lidocaine and 8% capsaicin patches, and thus these treatments are recommended as second-line agents. However, since topical agents typically have a lower side effect profile than systemic therapies, topical lidocaine may be utilized as a first-line agent in patients

Table 13.2 Weak recommendations for the treatment of neuropathic pain, IASP NeuPSIG 2015 guidelines

Medication	Dose	Recommendations
Capsaicin 8% patches	One to four patches to the painful area for 30–60 min every 3 months	Second line (peripheral neuropathic pain)
Lidocaine patches	One to three patches to the region of pain once a day for up to 12 hours	Second line (peripheral neuropathic pain)
Tramadol	200–400 mg, in two (tramadol-extended release) or three divided doses	Second line
Botulinum toxin A (subcutaneously)	50–200 units to the painful area every 3 months	Third line; specialist use (peripheral neuropathic pain)
Strong opioids	Individual titration	Third line

Finnerup [46]

with multiple comorbidities who may not tolerate other systemic agents. Though there is some evidence to support the use of high-dose capsaicin (Qutenza∗) in postherpetic neuralgia, the long-term effects of high-dose capsaicin are still not known. Though many utilize topical capsaicin in the treatment of PHN, per the **GRADE** classification, evidence for the use of low-dose topical capsaicin is actually inconclusive [46].

Though evidence supports opioids in the treatment of acute pain episodes and in short-term flares of neuropathic pain syndromes, there is no evidence evaluating the efficacy and safety of *chronic* opioid therapy in the treatment of neuropathic pain, including postherpetic neuralgia.

Botulinum toxin A (Botox∗) is recommended as a third-line agent in the treatment of postherpetic neuralgia. Botulinum toxin A is a potent neurotoxin that acts at SNAREs (soluble N-ethylmaleimide-sensitive factor attachment protein receptors) to block presynaptic acetylcholine release at nerve endings. It has shown some analgesic effects outside of its action on muscular activity. The use of botulinum toxin A for neuropathic pain has been most widely studied in peripheral neuropathic pain disorders, which include postherpetic neuralgia. A 2016 review of the available RCTs evaluating botulinum toxin A in the treatment of PHN and trigeminal neuralgia (TN) showed at least moderate evidence to support its use [59]. Based on the available evidence, the NeuPSIG guidelines weakly recommend botulinum toxin A for the treatment of peripheral nerve pain disorders, including PHN. Table 13.2 summarizes the recommendations.

Interventional Management of Postherpetic Neuralgia

Despite comprehensive pharmacologic management, many patients with postherpetic neuralgia continue to experience poorly controlled pain. In these patients, interventional options are considered.

Sympathetic Blocks

There are few nonrandomized trials assessing the efficacy of sympathetic blocks in the treatment of PHN, and no RCTs. A 2004 review evaluated two nonrandomized trials evaluating sympathetic blocks in the treatment of PHN. One study showed improvement in pain scores, but did not distinguish between chronic pain in PHN and acute pain associated with herpes zoster. A second study showed sympathetic blocks to be less effective than somatic blocks at 1 year [58]. Due to paucity of evidence supporting sympathetic blocks in the treatment of PHN, the 2013 IASP NeuPSIG did not recommend sympathetic blocks in the treatment of PHN [41].

Intrathecal Drug Delivery

An exhaustive review by Deer et al. evaluated the evidence supporting intrathecal opioid and nonopioid medications with implantable delivery devices in the treatment of neuropathic pain disorders [60]. Per these guidelines, intrathecal morphine and ziconotide are first-line treatment options when considering intrathecal drug delivery for refractory neuropathic pain conditions. However, there are no studies specifically evaluating intrathecal drug delivery in the treatment of PHN.

Permanent implantation of an intrathecal drug delivery system is not without risk. Due to the lack of strong evidence and potential for adverse events, the IASP NeuPSIG guidelines state intrathecal drug delivery for the treatment of neuropathic pain, including PHN, is still inconclusive [41].

Spinal Cord Stimulation

There are no randomized controlled trials evaluating spinal cord stimulation in the treatment of postherpetic neuralgia. A promising case series evaluating spinal cord stimulation for pain related to postherpetic neuralgia or herpes zoster did suggest improvement in pain scores. Long-term pain relief was achieved in 23 (82%) of PHN patients during SCS treatment confirmed by a median decrease from 9 to 1 on the visual analog scale ($P < 0.001$) [61]. A 2018 review of the literature found 20 reports of spinal cord stimulation being utilized in the treatment of PHN. Of 309 patients with PHN who were treated with SCS, 255 patients went on to permanent implantation, out of which 120 patients had long-term pain relief [62]. SCS appears to be a promising modality for the treatment of refractory pain in PHN, but more studies are needed to continue to support this invasive therapy.

Pulsed Radiofrequency Ablation

A double-blind randomized controlled trial compared pulsed radiofrequency (PRF) treatment with sham therapy in 96 patients with PHN affecting the thoracic dermatomes. PRF treatment of the intercostal nerve at the level of the involved dermatome

and the segments above and below was performed once weekly for 3 weeks. The post-procedure VAS scores in the pulsed radiofrequency ablation group were significantly lower than those in the sham group and lasted for 6 months after treatment ($P < 0.05$) [63]. Similar results have been reported in open-label studies evaluating PRF treatment of the affected cervical, thoracic, or lumbar dorsal root ganglion (DRG) in patients with PHN [64]. These findings are promising, but again, more studies are needed to support pulsed radiofrequency ablation in the treatment of PHN. There were no adverse events in the intercostal pulsed radiofrequency group, and therefore it appears to be a relatively low-risk invasive procedure and is an option in those patients with refractory PHN associated pain.

Peripheral Nerve Injury Pain

Peripheral nerves can be injured traumatically or iatrogenically after surgery or other procedures, including peripheral nerve blockade. Unfortunately, some patients go on to develop chronic peripheral nerve pain after such an injury. Peripheral nerve compression pain disorders (including carpal tunnel syndrome, cubital tunnel syndrome, and tarsal tunnel syndrome) are numerous, and their management is beyond the scope of this chapter.

Pharmacologic Management

Generally, the pharmacologic management of peripheral nerve injury pain is the same as for other neuropathic pain syndromes. First-line agents include gabapentinoids and certain antidepressants (TCAs and SNRIs). For small localized areas of pain, topical therapies such as topical lidocaine, lidocaine 5% ointments, and patches have shown benefit as well.

Interventional Management

Ablative procedures of a large mixed sensory/motor peripheral nerve are typically avoided due to risk of anesthesia dolorosa (pain in absence of sensation) and motor dysfunction. In very rare instances, when only a sensory branch is involved, peripheral nerve ablation may be considered as a treatment for chronic peripheral neuropathic pain [65, 66].

In cases of severe peripheral neuropathic pain related to brachial or lumbosacral plexus nerve root avulsion, some advocate for DREZ lesioning (dorsal root entry zone lesioning). There have been several case series suggesting successful outcomes after DREZ lesioning, but high-quality randomized control trials are absent, and thus the IASP NeuPSIG guidelines on interventional management for neuropathic pain consider the support for this procedure to be “inconclusive” [41].

Management of Complex Regional Pain Syndrome

Introduction

Complex regional pain syndrome (CRPS) is a chronic pain syndrome typically involving the limbs and characterized by severe pain with associated sensory, motor, trophic, and autonomic impairment. The condition can be induced by surgery, major or minor trauma, and sometimes even a period of immobility. It has a varying course and ranges from mild and can resolve without treatment to severe, chronic, and quite disabling [67, 68].

Epidemiology

CRPS occurs most frequently in postmenopausal women between the ages of 61 and 70. There are higher rates among females, affecting females three times more than males. There is an increased rate in the upper limbs compared to the lower limbs, and the most common precipitating event is fracture. Risk factors for CRPS include postmenopausal state, those with a history of migraines, osteoporosis, asthma, and treatment with ACE inhibitors [69–71].

Diagnostic Criteria

CRPS is a clinical diagnosis. The diagnosis is based on symptoms reported by the patient and clinical signs observed by the practitioner. Unfortunately, there is no single objective measure to confirm a diagnosis of CRPS. The most accepted criteria for diagnosis of CRPS are the Budapest clinical diagnostic criteria for complex regional pain syndrome by the IASP (International Association for the Study of Pain) [72]. CRPS can be divided into two subtypes. CRPS type I occurs after an initial noxious event and is not limited to a specific peripheral nerve; the pain is disproportionate to the inciting injury and is associated with vasomotor, sudomotor, and trophic findings in the affected extremity. Severe pain, allodynia, and hyperalgesia are often present in the involved extremity. CRPS type II is only different in that the syndrome occurs after an identifiable injury of a nerve or one of its major branches innervating the involved region. Table 13.3 summarizes the criteria.

Figure 13.1 shows left foot discoloration and swelling associated with CRPS.

Pathophysiology

Despite multiple animal and human studies examining the pathophysiology of CRPS, it is still poorly understood. CRPS is defined as a nociplastic disease process, implicating both inflammatory and neuropathic mechanisms in its development and

Table 13.3 Budapest criteria for diagnosis of complex regional pain syndrome

1. Continuing pain, disproportionate to inciting event
2. Must report at least one symptom in each of the following four categories:
(a) Sensory – reports of hyperesthesia
(b) Vasomotor – reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
(c) Sudomotor/edema – reports of edema and/or sweating changes or sweating asymmetry
(d) Motor/trophic – reports of decreased range of motion and/or motor dysfunction (weakness tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign in two or more of the following categories:
(a) Sensory – evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch)
(b) Vasomotor – evidence of temperature asymmetry and/or skin color changes and/or asymmetry
(c) Sudomotor/edema – evidence of edema and/or sweating changes and/or sweating asymmetry

Harden and Bruehl [72]

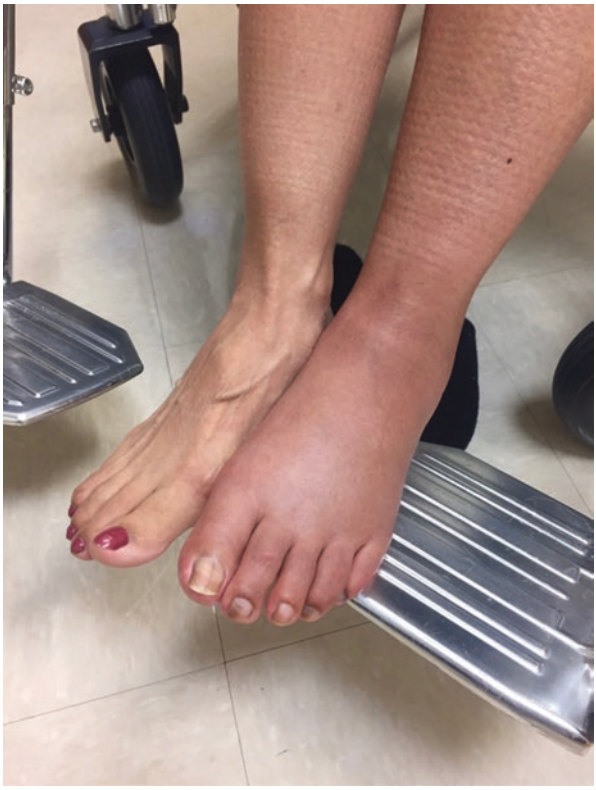

Fig. 13.1 Image of left lower extremity with vasomotor symptoms consistent with CRPS

maintenance. It is a complex disease entity, and three major pathophysiological pathways have been implicated in its development: aberrant inflammatory mechanisms, vasomotor dysfunction, and maladaptive neuroplasticity [73].

Inflammation

During the acute phase of CRPS, the affected limb exhibits pain, edema, erythema, increased temperature, and impaired function, all signs of inflammation. The initial inciting event triggers the release of inflammatory mediators such as IL-6 and TNF-alpha, along with nociceptive neuropeptides including CGRP (calcitonin gene-related peptide), bradykinin, and substance P. These inflammatory mediators trigger extravasation of fluid into the soft tissues and development of edema, warmth, and erythema [73]. However, unlike the normal healing process, those with CRPS go on to display an enhanced neuroinflammatory response, with prolonged pain and dysfunction well beyond the expected healing time period.

Alterations in Cutaneous Innervation

Even when no identifiable nerve injury is found, many believe that some sort of neuronal injury, however imperceptible, is the initial trigger in the development of CRPS. Logically, this can be accepted, because any peripheral injury or trauma will involve some degree of nerve involvement. Studies have shown that there is a reduction in C- and A-delta type cutaneous afferent neuronal fiber density in the CRPS-affected extremity compared to the unaffected limb. These are primarily nociceptive fibers. This decrease in nociceptive fibers was associated with an increase in aberrant nerve fibers, and it has been proposed that the exaggerated pain response in these patients is due to alterations in neuronal fibers [74, 75].

Peripheral and Central Sensitization

As with many chronic pain conditions, peripheral and central sensitization is implicated in complex regional pain syndrome. After injury, release of nociceptive neuropeptides including substance P and glutamate can lead to alteration in nociceptive processing in the central nervous system and increased excitability of central nociceptive neurons in the spinal cord. Research shows that patients with CRPS display greater windup to repeated stimulation of the affected extremity compared to non-affected limbs [76, 77].

Neuroplasticity

Studies have shown evidence of neuroplasticity in those patients with CRPS. Neuroimaging has revealed a decrease in area representing the CRPS affected limb in the somatosensory cortex. The extent of the findings correlates with

the pain intensity, and these alterations have returned to normal following successful CRPS treatment [78–80].

Other Implicated Mechanisms

Alterations in the sympathetic nervous system, autoimmune mechanisms, and genetic mechanisms have all been implicated in the pathophysiology of CRPS as well [81].

Pain Management

Physical and Occupational Therapy

Physical therapy is key, and recommended as a first-line treatment. Due to the severity of pain, many patients develop a fear of using the extremity, which can in turn exacerbate the syndrome, as immobility has been implicated in its development. The goal of physical and occupational therapy is to enable the patient to have the best use of the involved extremity. Modalities include massage, elevation (to reduce edema), desensitization techniques such a contrast baths, transcutaneous electrical nerve stimulation, isometric strengthening exercise, and stress loading. Research has supported the use of mirror box therapy. It has been shown to reduce neuropathic pain in the involved extremity and improve two-point sensation in the CRPS limb [82–84].

Interdisciplinary Pain Management and Psychological Treatments

There are very few studies evaluating the efficacy of an integrated and coordinated interdisciplinary intervention for CRPS. A 2013 Cochrane review of available interventions for CRPS did not review interdisciplinary treatment due to lack of available evidence. A very recent Scandinavian study evaluated the efficacy of a 12-week interdisciplinary treatment program in 10 patients with chronic CRPS. Though the results showed statistically significant improvement in some aspects of function and disability, there were no significant reductions in patients' rest pain, distress, or quality of life [85]. Despite limited evidence to support interdisciplinary treatment programs specifically for CRPS, many experts argue for a multidisciplinary approach because of the complex nature of the condition [86]. Behavioral management techniques utilized in the treatment of chronic pain conditions include cognitive behavioral therapy, relaxation techniques, and biofeedback.

Pharmacologic Management

Anti-inflammatories

Corticosteroids

Inflammation is implicated in the pathophysiology of CRPS. Both randomized controlled trials and case series have shown benefit in pain and range of motion in the affected limb following treatment with corticosteroids [87–89]. However, the overall quality of available evidence to support oral corticosteroids is considered low, and the exact dose and duration of treatment have not been quantified. With some evidence to support its use, it seems a course of corticosteroids may be an option if no significant adverse effects are anticipated.

NSAIDs (Nonsteroidal Anti-inflammatory Drugs)

There is currently no evidence of clinically positive effects following treatment with NSAIDs, and one RCT showed superiority of corticosteroids over piroxicam specifically [90].

Free Radical Scavengers (Topical and Systemic)

DMSO (dimethyl sulfoxide) is a free radical scavenger. Four trials have investigated the topical application of DMSO vs a placebo preparation, one of which reported a negative result on pain. A lower-quality trial reported a positive effect on patient's subjective clinical improvement, but not specifically pain. For these reasons, there is limited evidence to support topical DMSO in the treatment of CRPS. One trial compared IV mannitol to placebo and found no improvement [90].

Vitamin C

Vitamin C has potent antioxidant effects. It is currently established as the most efficacious preventative therapy for the development of CRPS after injury. It is commonly used perioperatively following extremity surgery in an effort to reduce progression to CRPS [90]. Doses range from 200 to 500 mg daily.

Calcitonin

Review of available literature shows there is low-quality evidence to support the use of intranasal calcitonin over placebo but very low-quality evidence which shows that intranasal calcitonin is not superior to paracetamol [90].

Bisphosphonates

CRPS may be associated with localized bone resorption in the affected limb, resulting from osteoclastic hyperactivity. Because bisphosphonates counteract bone resorption, several authors have evaluated the efficacy of bisphosphonates in the treatment of CRPS. A 2009 review of the available literature showed that evidence to support the use of bisphosphonates was still scarce, and there is insufficient evidence to support its use in the treatment of CRPS [91]. A more updated review in 2017 again suggested that bisphosphonates may improve pain in CRPS, but again more evidence is needed prior to supporting its broad application [92]. A 2010 review suggested that bisphosphonates were in fact the only medication available with true benefits in treating CRPS [93].

In light of some evidence to suggest its efficacy, specifically in pain outcomes, it may be a reasonable option in patients with evidence of osteopenia and bone remodeling and refractory pain. However, using bisphosphonates is not without risk. One long-term complication of bisphosphonate therapy is increased risk of pathologic fractures. They are contraindicated in patients with decreased renal function, esophageal motility disorders, peptic ulcer disease, and poor dentition due to risk of osteonecrosis of the jaw.

Gabapentin

Studies evaluating the efficacy of gabapentin in CRPS I have shown improvement in pain reduction [94, 95]. However, a 2013 Cochrane review of the literature found very low-quality evidence showing gabapentin to be *ineffective* in the treatment of CRPS [90]. Due to its overall low side effect profile and significant evidence to support its use in other neuropathic pain disorders, gabapentin may still be a reasonable choice to treat pain in CRPS patients.

Ketamine

Chronic neuropathic pain disorders may lead to upregulation of pro-nociceptive pathways involving NMDA (n-methyl-d-aspartic acid) as a neurotransmitter. Administration of ketamine, an NMDA receptor antagonist, may reverse some of the central sensitization and changes in brain plasticity that occur in CRPS [96]. Ketamine is administered topically or systemically, including IV infusions. Placebo-controlled studies have shown that both topical and intravenous systemic administration of ketamine have reduced pain and even induced remission in some treatment-resistant patients [97–100]. The most recent exhaustive review of ketamine administration for chronic pain conditions states that, for CRPS, there is moderate evidence supporting ketamine infusions (22 mg/hour for 4 days or 0.35 mg/kg per hour over 4 hours daily for 10 days) to provide improvements in pain for up to 12 weeks (grade B recommendation, low to moderate level of cer-

tainty) [101]. However, ketamine is associated with multiple adverse effects, including side effects such as dysphoria, nausea, vomiting, and headaches, and the long-term potential adverse effects of chronic therapy are not entirely understood.

Interventional Management

Sympathetic Blockade with Local Anesthetics

During the initial phase of CRPS, patients exhibit sudomotor symptoms associated with autonomic dysfunction. One therapeutic target is blocking the sympathetic innervation of the involved extremity to reduce sympathetic contribution to pain. The IASP NeuPSIG systematically reviewed the evidence for sympathetic blockade in the treatment of CRPS. A case series of 25 patients who had 3 stellate ganglion blocks at weekly intervals for upper extremity CRPS reported that 40% of patients had complete pain relief, 36% had partial pain relief, and 24% no pain relief over a 6-month period [102]. Although overall the quality of evidence is low, these guidelines state that sympathetic blockade is a reasonable option to consider in patients refractory to pharmacologic and non-pharmacologic treatments, especially early in the disease process [41].

Spinal Cord Stimulation

There is moderate-quality evidence to support spinal cord stimulation in the treatment of CRPS I. Based on the available evidence, the IASP guidelines for the interventional management of neuropathic pain conditions recommend spinal cord stimulation as a "weak recommendation" for the treatment of CRPS I not responsive to conventional medical management. There is a lack of evidence supporting SCS in CRPS II, and thus the recommendation for spinal cord stimulation in the treatment of CRPS II is considered "inconclusive" [41]. A comprehensive 2017 review of the literature found that spinal cord stimulation is a favorable and effective modality for treating CRPS (all types) with high-level evidence supporting its role in improving CRPS patients' perceived pain relief, pain score, and quality of life. However, there is a paucity of evidence supporting functional improvement, resolution of CRPS signs, sleep hygiene, psychological impact, and analgesic-sparing effects, and thus more studies are needed to continue to support this modality in the treatment of CRPS [103].

Intrathecal Baclofen

There are only two small studies showing benefit of intrathecal baclofen for the treatment of dystonia in CRPS. Due to the large number of adverse events associated with intrathecal drug delivery, intrathecal medication for CRPS is given an "inconclusive" recommendation per the IASP NeuPSIG interventional guidelines [41].

Ablative Procedures of the Autonomic Nervous System

Patients with CRPS often have favorable response to local anesthetic sympathetic blockade, but not long-lasting. This has led many practitioners to perform ablative procedures of the autonomic nervous system. Techniques include chemical neurolysis, radiofrequency ablation, and surgical transection. The literature consists of poorly controlled comparison studies and uncontrolled case series [104]. Due to the significant risk of developing post-ablation pain syndromes, sometimes worse than the original pain syndrome, it is recommended that ablative procedures be avoided [41, 104, 105].

Conclusion

Chronic peripheral neuropathic pain can be debilitating to the patient and challenging to the practitioner. While some patients experiencing peripheral nerve pain respond well to first-line treatment approaches, others may require multimodal therapies including not only non-pharmacologic treatments such as physical therapy and behavioral management techniques but also multiple pharmacologic interventions. First-line agents for neuropathic pain typically include the gabapentinoids, serotonin and norepinephrine reuptake inhibitors, and tricyclic antidepressants. There are multiple interventional options available to those patients who do not respond to more conservative management techniques.

Complex regional pain syndrome (CRPS) is a unique syndrome with both nociceptive and neuropathic contributors and thus has been termed a “nociplastic” pain disorder. Due to its unique and complicated pathophysiology, treatment of CRPS often involves multiple interventions, including physical therapy, occupational therapy, medication management, and invasive strategies.

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Chapter 14
Central Nervous System Pain

Hisham Salahuddin and Mehari Gebreyohanns

Central Nervous System Pain

Central pain syndrome (CPS) was first described by a German neurologist, L. Edinger in 1891. CPS is an unpleasant emotional experience due to abnormal processing of information which is initiated or caused by a primary lesion or dysfunction of the central nervous system. Whereas pain provides a protective mechanism, CNS pain is a pathological process which results in continuous or paroxysmal spontaneous pain related to nervous system injury. This injury results in pathological changes at multiple levels due to primary injury of pathways and resulting CNS neuroplasticity. Pain pathways in the CNS are complex and incompletely understood.

Ascending nociceptive information is integrated at the spinal cord level, brain stem, and cortex. Descending pain pathways, mainly from the brain stem, modulate integration of pain at the spinal cord level. The sensation of pain is poorly localized and is due to the processing of pain pathways at multiple regions, leading to the hypothesis of a "pain matrix," first described by Dr. Ronald Melzack. Neuroplasticity at the structural, chemical, and functional levels continuously modulates pain pathways. Due to the complex processes involved in pain processing and comorbid pain conditions, it is challenging for clinicians to predict and diagnose patients who will develop central pain syndromes. Table 14.1 lists important pain terms related to central nervous system pain.

H. Salahuddin · M. Gebreyohanns (✉)
Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas, TX, USA
e-mail: mehari.gebreyohanns@utsouthwestern.edu

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Table 14.1 Definition of important pain terms

Pain: An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage
Neuropathic pain: Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system
Central neuropathic pain: Pain arising as a direct consequence of a lesion or disease affecting the central somatosensory system
Allodynia: Pain evoked by stimuli that is usually not painful (i.e., touch or brush)
Hyperalgesia: An increased response to a stimulus that is normally painful
Paresthesia: An abnormal but non-painful (and not unpleasant) sensation, either spontaneous or evoked
Dysesthesia: An abnormal unpleasant sensation, either spontaneous or evoked
Aftersensation: A sensory impression that persists after the stimulus has ceased
Central sensitization: An increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input

Adapted from H Klit, *Lancet Neurology*, 2009

Table 14.2 Causes of central pain syndromes

Stroke (ischemic or hemorrhagic)
Multiple sclerosis
Traumatic brain injury
Traumatic spinal cord injury
Parkinson's disease
Vascular malformations
Syringomyelia and syringobulbia
Viral or bacterial infection of the brain or spinal cord
Epilepsy

Epidemiology

Central pain can be caused by any pathology affecting the pain processing pathways from the spinal cord to the cerebral cortex. Common causes of central pain syndrome include stroke (most common), spinal cord injury, and multiple sclerosis. Table 14.2 lists causes of central pain syndromes. Central pain syndromes are more commonly seen in men, with the exception of multiple sclerosis-related CPS. The prevalence of central pain syndromes is unknown given the lack of clear diagnostic criteria and large studies.

Neuroanatomical Pathways of Pain

Noxious stimuli in the peripheral nervous system are converted into electrical activity via changes in ion channels of primary sensory neurons. This electrical activity is amplified and transmitted down a neuron which synapses in the spinal cord.

Different peripheral fibers synapse in the spinal cord on second-order neurons. Second-order neurons integrate information from peripheral neurons, descending pathways, and spinal interneurons. Sensory information travels toward the brain stem in three main pathways, the archispinothalamic tract, neospinothalamic tract, and paleospinothalamic tracts.

Peripheral neurons which respond to pain may be specific nociceptive or nonspecific sensory neurons. Nonspecific sensory neurons are polymodal neurons that can be stimulated by non-nociceptive mechanical stimuli as well as by pain stimuli of tactile, muscular, or visceral origin. Nonspecific neurons can be activated by a wide field and have a sensitivity gradient; centrally all mechanical stimuli produce an action potential, while at the peripheral aspects of the field, only nociceptive stimuli produce an action potential. These neurons increase their firing as the intensity of the peripheral stimulus is increased, and the message becomes nociceptive once a specific threshold is exceeded.

Specific nociceptive neurons are specialized primary sensory pseudounipolar neurons comprised of a free nerve ending which is sensitive to noxious stimuli. Thinly myelinated A delta fibers carry sharp, well-localized pain, and unmyelinated slow conducting C fibers carry dull, poorly localized pain, which elicit an affective response. The central processes of these pseudounipolar neurons enter dorsal root ganglion (DRG) with sympathetic and parasympathetic fibers where they form the dorsolateral fasciculus (tract of Lissauer). Second-order neurons course in the spinothalamic (neospinothalamic) pathways or indirect spinoreticular, spinomesencephalic, spinotectal, or spinohypothalamic fibers.

Type A delta fibers synapse in lamina I (posteromarginal nucleus) and lamina V (reticular nucleus). The second-order neurons decussate in the anterior white commissure and ascend in the contralateral anterolateral spinal cord as the lateral spinothalamic (neospinothalamic) tract. Spinal interneurons and descending pathways from the rostral ventral medulla and periaqueductal gray area (PAG) converge on second-order neurons. This tract is responsible for carrying nociceptive, thermal, and crude touch to the ventroposterolateral (VPL) thalamic nucleus. Fibers from the second-order neurons also send collaterals to the reticular formation in the brain stem. Third-order neurons from the ventroposterolateral (VPL) nucleus of the thalamus ascend through the posterior limb of the internal capsule and corona radiata to terminate on the primary and secondary somatosensory cortices.

Similar to the spinothalamic tract, sensory information from the face and dura project to the spinal trigeminal nucleus via the trigeminal nerve (CN 5), facial nerve (CN 7), glossopharyngeal nerve (CN 9), and vagus nerve (CN 10). Secondary neurons from the spinal trigeminal nucleus decussate and project to the ventroposteromedial (VPM) nucleus or intralaminar nuclei of the thalamus. Fibers from here accompany fibers from the ventroposterolateral (VPL) thalamic nucleus carrying sensory information from the body through the posterior limb of the internal capsule to the somatosensory cortex in the postcentral gyrus of the parietal lobe.

Central processes of type C fibers enter the lateral division of the dorsal root with type A delta fibers and synapse on interneurons in lamina II (substantia gelatinosa) and III. Interneurons connect with second-order neurons which arise from laminae

IV–VIII and ascend bilaterally in the spinal cord to form the spinoreticular tract and spinomesencephalic tracts. The paleospinothalamic tract is a polysynaptic tract that transmits nociceptive, thermal, and crude touch information and consists of multiple tracts including the spinoreticular, spinomesencephalic, spinotectal, and spinohypothalamic tracts The paleospinothalamic tract through the mesencephalic reticular activating system formation, intralaminar nuclei of the thalamus, hypothalamus, and limbic cortex (anterior insular cortex, anterior cingulate) work to activate the entire nervous system and are involved in behavioral arousal, descending pain modulation (via the dorsolateral funiculus), and the emotional aspects of pain.

The archispinothalamic pathway is a closely related multisynaptic, diffuse pathway that has its second-order neurons in lamina IV–VII and mainly contributes to visceral, autonomic, and emotional aspects of pain. It projects to the periaqueductal gray (PAG) matter and midbrain raphe in the brain stem and also sends collateral neurons to the hypothalamus and limbic system (via the parabrachial nucleus) through which it can affect the hypothalamic-pituitary axis and stress hormones, descending pain pathways, as well as emotional responses to pain.

The reticular formation, ventral tegmentum, and periaqueductal gray area are involved in modulation of pain perception via ascending pathways to the thalamus and frontal lobes as well as descending pain fibers via the dorsolateral funiculus which exerts inhibitory effects on interneurons in the spinal cord. Endogenous opioids, serotonin, norepinephrine, dopamine, and various other neurotransmitters in the ventral tegmental area and spinal cord contribute to pain processing. Stimulation of the periaqueductal gray matter, raphe nucleus, locus coeruleus, parabrachial area, lateral hypothalamus, lateral reticular nucleus, and nucleus of solitary tract have been shown to provide analgesia.

Ascending information from the spinal cord synapses with the thalamus which is an important location for processing of sensory information. Patients with chronic pain have increased thalamic burst activity. Imbalance between the lateral and medial thalamic nuclei as well as dysfunctional reverberatory feedback loops between the thalamus and cortex (thalamo-cortico-thalamic loop) may play an important role in CPS.

Sensory information from the ventroposterolateral thalamus is relayed to the primary somatosensory cortex (S1) in the postcentral gyrus where properties of pain such as its presence, character, location, and intensity are discriminated. Projections from the primary somatosensory cortex are relayed to the secondary somatosensory cortex (S2) which also receives direct projections from the thalamus. The secondary somatosensory cortex may have a role in distinguishing pain and recollection of previous pain.

Multiple cortical connections between the somatosensory cortex, prefrontal lobe and orbitofrontal cortex, hypothalamus, limbic structures including the amygdala, and cingulate cortex are responsible for emotional responses and further cortical modulation of pain. Pain modulation based on beliefs, expectations, and mental health is modulated through the prefrontal cortical network. The anterior cingulate

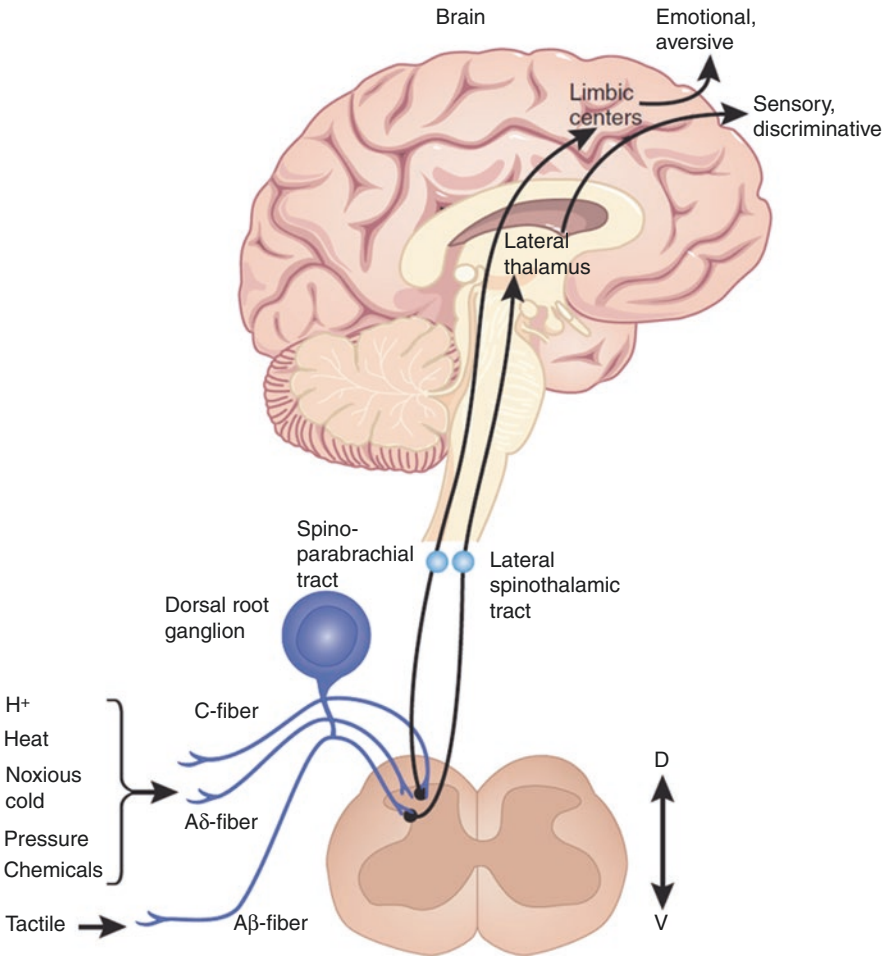

Fig. 14.1 Schematic overview of pain processing pathways. (Adapted from R. Kuner, Nature Medicine 2010)

cortex provides immediate behavioral response to pain and through connections with the amygdala can result in sympathetic activation and physiological responses to pain such as sweating, increased blood pressure and heart rate, and nausea. The dorsolateral prefrontal cortex through connections with the anterior cingulate cortex activates brain stem centers and modulates descending pain pathways which can modulate integration of pain processing via inhibitory interneurons at the spinal cord level. Figure 14.1 shows a schematic overview of pain processing pathways. Figure 14.2 shows possible mechanisms of pain perception and interaction of various pathways. Figure 14.3 shows the main brain regions activated during a painful experience.

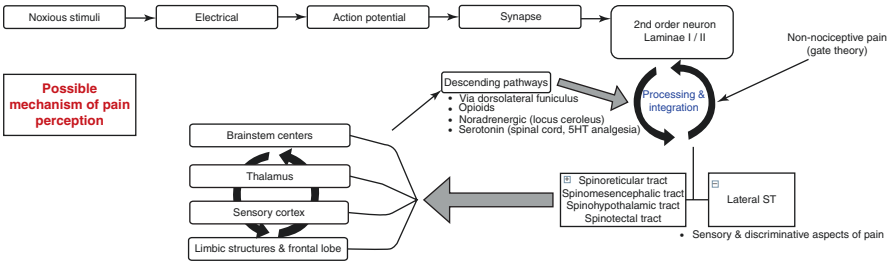

Fig. 14.2 Possible mechanisms of pain perception and interaction of various pathways

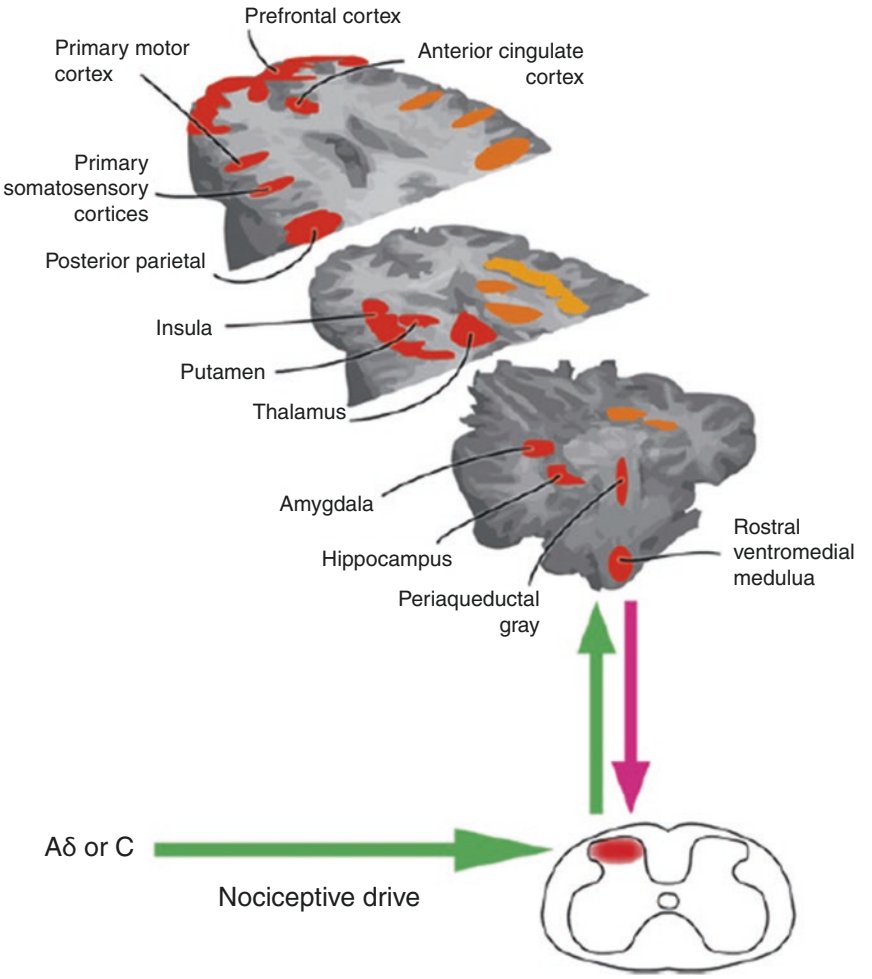

Fig. 14.3 Main brain regions activated during a painful experience, highlighted as bilaterally active but with increased activation on the contralateral hemisphere (orange). (Adapted from Irene Tracy, Neuron 2007)

Central Modulation and Perception

Perception of pain is a combination of outputs from the reticular and limbic systems and is affected by multiple factors including genetics, cultural perceptions, mental and physical health, and age. Augmentation or suppression of sensory input is provided by supraspinal neurons prior to the perception of pain. Modulation of pain occurs at every level of the nervous system allowing for a broad range of pathology which may result in CNS pain.

Multiple mechanisms contribute to CPS and may include decreased thresholds to sensory stimuli, spontaneous impulses from regenerating neurons, nociceptive inflammatory cytokines, alterations in the thalamus, dysfunctional thalamo-cortico-thalamic networks, structural cortical changes, and impaired pain-modulating pathways. The exact pathophysiology of central pain syndrome may vary in individuals based on their mechanism of injury as well as individual characteristics.

Neuroplasticity plays a central role in the pathology of CPS. Dynamic changes in the neural matrix occur at many levels including the molecular, synaptic, cellular, functional, structural, and network levels. Molecular changes include changes induced by phosphorylation and changes in location of molecules by endocytosis or active transport. Synaptic-level changes include potentiation, silencing of synapses, as well as changes in the type, number, and location of receptors. Changes in protein and gene expression, spontaneous discharges, and continued after-discharges of cells are examples of cellular-level changes. Functional and structural changes include degeneration or regeneration of axons, astrocytes, and microglia which can affect nociceptive processing. Network-level changes occur at multiple levels including the spinal cord, brain stem, diencephalic, and cortical levels and may result in central sensitization, changes in emotional responses and sensitivity to pain, as well as changes in the limbic system. Multiple neurotransmitters including histamine, substance P, endogenous opioids (enkephalins, endorphins), serotonin, norepinephrine, endocannabinoids, excitatory amino acids, and neuropeptides at different levels of the central nervous system directly affect the neuroplasticity and threshold of neurons. Figure 14.4 shows disease-induced functional and structural plasticity. Figure 14.5 provides an overview and examples of various levels and types of neuroplasticity.

Clinical Features

CPS often begins in a delayed fashion after the initial injury and may occur months to years later. CPS should be differentiated by central sensitization which is a sequela of chronic pain. Central sensitization is an increased responsiveness of nociceptive neurons in the CNS to their normal or subthreshold afferent input. Central sensitization is often driven by peripheral pain generators, may be associated with early childhood trauma, and may be reversible. Central sensitization often results in sen-

sory changes including allodynia (pain evoked by stimuli that is usually not painful) and hyperalgesia (increased response to a stimulus that is normally painful) which are also seen in central pain syndrome. Central sensitization is discussed further later in this chapter.

CPS is almost always associated with sensory changes of hyperalgesia and allodynia. Dysesthesias are abnormal or unpleasant sensations of touch which often accompany central pain syndromes. Changes in pinprick and temperature are commonly found in the area of CPS on physical examination. Pain is often poorly localized and difficult to characterize and may be continuous or paroxysmal in nature. Common descriptors include burning, prickling, pins and needles, stabbing, and shooting pain. Pain descriptors are not sufficient to identify CPS as they may over-

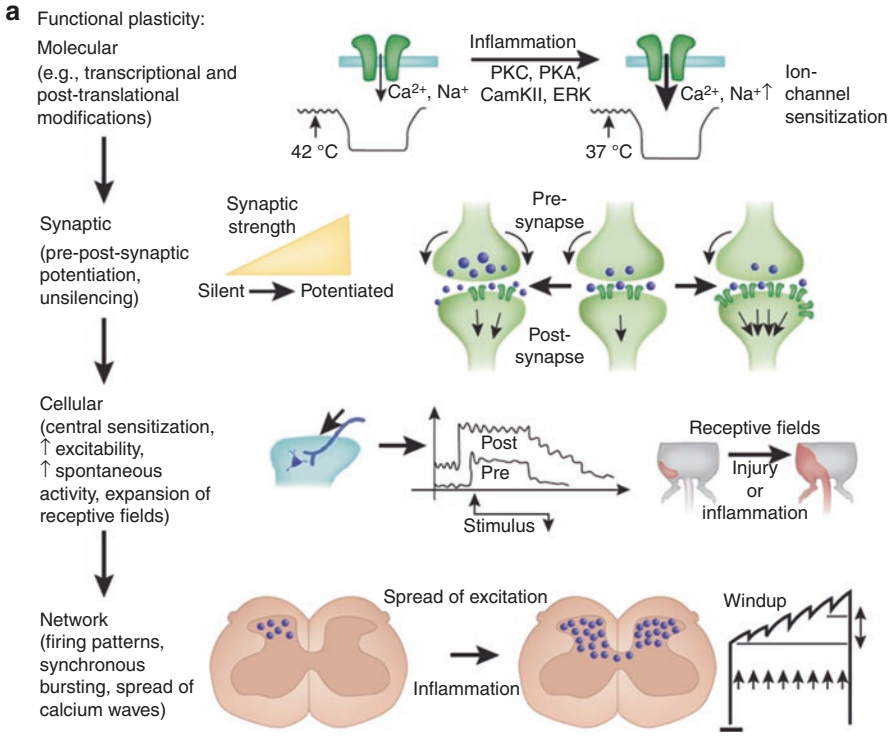

Fig. 14.4 Disease-induced functional and structural plasticity. (**a**) Different levels of activity-dependent functional plasticity. Molecules may become functionally sensitized (top), synaptic transmission may become potentiated by presynaptic mechanisms (second row, arrow to the left) or by postsynaptic plasticity (arrow to the right), cells may respond to noxious stimuli with increased activity and expanded receptive fields after injury (third row), and network function may change so that more cell ensembles respond to noxious stimuli, collectively leading to a higher net spinal output after injury or inflammation (bottom). (**b**) Examples of nociceptive activity-induced structural plasticity. From the top, synaptic spines may increase in size and density; axons may sprout or degenerate; and cells may atrophy (e.g., loss of inhibitory interneurons) or proliferate (e.g., microglia and astrocytes). (Adapted from R. Kuner, Nature Medicine, 2010)

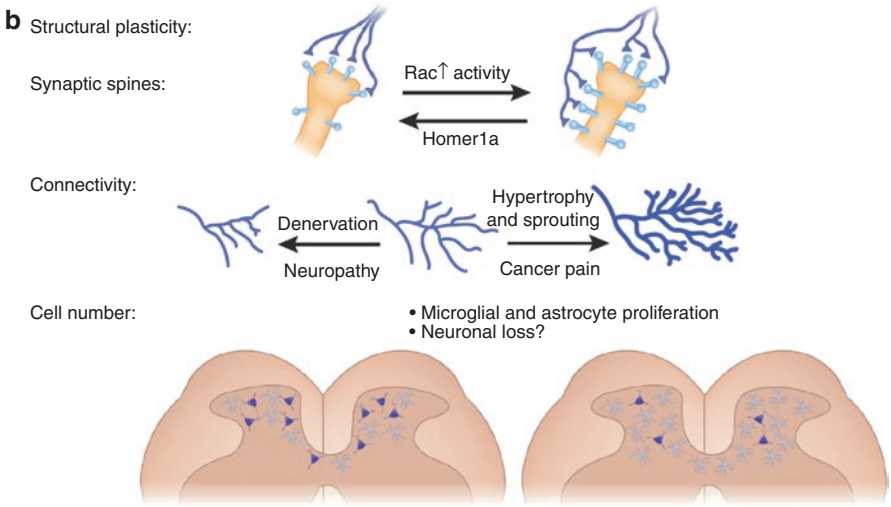

Fig. 14.4 (continued)

lap with other types of neuropathic pain. Pain is typically moderate to severe in onset and may be poorly responsive to a single medication. Pain involves parts of the neurologically affected region and may be limited to a specific area of the body or may be widespread over a large portion of the body. Figure 14.6 shows the relationship between physiological pain and pathological pain associated with allodynia and hyperalgesia.

General Approach to Patients with Central Pain Syndromes

Patients with central pain syndromes need to be approached with a multidisciplinary manner. Patients have different biologic and psychological contributors to pain which should be identified. Perception of pain is due to a culmination of genetic factors, cultural perceptions, patient expectations, mental and physical health, as well as age and gender. All other types of pain should be aggressively treated and minimized with the help of cognitive behavioral therapy, physical and occupational therapy, and exercise regimens. Appropriate treatment of comorbid pain conditions such as shoulder and musculoskeletal pain, muscle spasms, and arthritis can help improve the effectiveness of central pain medications and treatments. Maximizing activities of daily living should be emphasized with the help of aids as needed. Management of psychiatric illness including depression, anxiety, and stress will help improve responses to CPS treatment.

Management of CPS is challenging and often requires extensive trial and error of medications. Treatment for CPS is often unsatisfactory as complete pain control in patients is often infrequent. Combination treatments are required usually at high

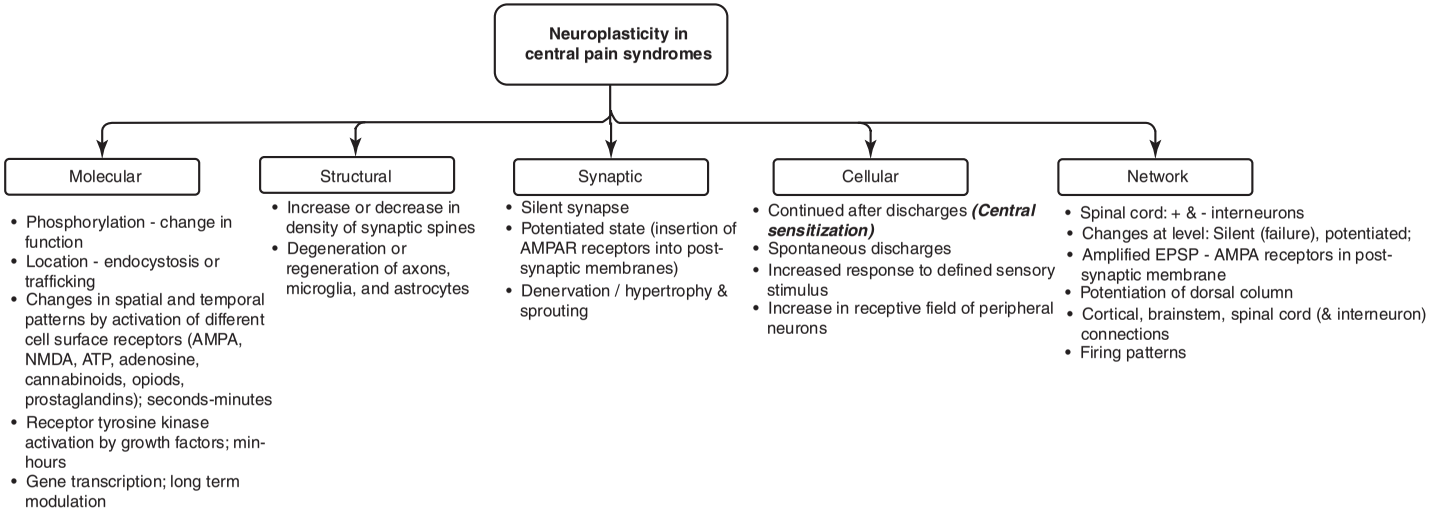

Fig. 14.5 Overview and examples of various levels and types of neuroplasticity in central pain syndromes

doses or until side effects are experienced. Neuromodulation is an option for many patients who do not experience adequate pain relief with medications. Treatment of specific CPS-related conditions is discussed further in the chapter. Table 14.3 summarizes the approach to evaluation and management of central pain syndromes.

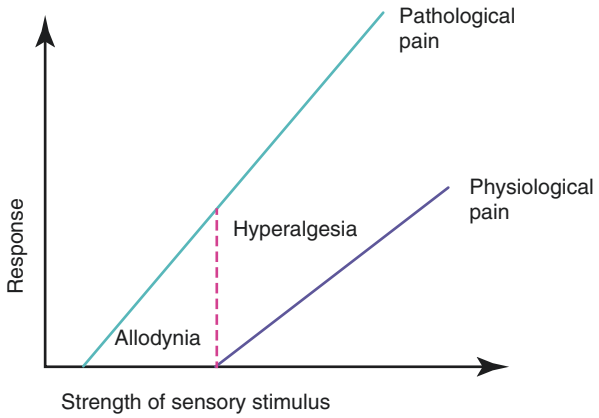

Fig. 14.6 Pathological pain may be associated with allodynia and hyperalgesia. Central sensitization is on the spectrum of pathological pain. (Adapted from R. Kuner, Nature Medicine, 2010)

Table 14.3 Approach to evaluation and management of central pain syndromes

Central pain: Caused by a primary lesion or dysfunction of the central nervous system
History
Social support, mental health assessment, activity of daily living, and exercise assessment
Other comorbid pain conditions
Patient expectations and current impact on daily living
Date of onset of neurological signs/symptoms
Pain features
1. Date of onset of pain
2. Location of pain (use pain drawing preferably), radiation or referral
3. Intensity of pain, maximum and minimum
4. Continuous or paroxysmal, aggravating and relieving factors
5. Temporal features – fluctuations
6. Quality of pain/descriptors – burning, freezing, pressure, cramping, stinging, aching, pins and needles, etc.
Neurological symptoms besides pain
1. Motor (weakness, ataxia, involuntary movements)
2. Sensory changes (hypo- or hyperesthesia, paresthesia, dysesthesia, numbness)
3. Other – speech, visual, cognitive, mood
Examination
Neurological examination – cognitive changes, motor findings, ataxia, spasticity
Sensory exam (start in unaffected area)
1. Tactile (cotton wool, nylon filaments) – allodynia, aftersensations
2. Pinprick and noxious stimuli – hyperalgesia

(continued)

Table 14.3 (continued)

3. Temperature – allodynia (cold, heat)
4. Vibratory sense and proprioception
Investigations
Neuroimaging of the brain and/or spinal cord
Quantitative sensory testing if needed
Other tests as needed – fMRI, SPECT/PET, EMG, regional blocks, etc.
Diagnosis
History suggestive of CNS pathology, onset consistent with diagnosis of central pain syndrome
Pain in an area corresponding to the lesion of the CNS
Other causes of pain such as nociceptive or peripheral neuropathic pain ruled out or unlikely
No relation of pain to movement, inflammation, or other local tissue damage
Allodynia or dysesthesia to touch or cold, hyperalgesia present
Pain descriptors consistent with central pain syndrome
Use of questionnaires if appropriate [e.g., Douleur Neuropathique 4 (DN4), Leeds Assessment of Neuropathic Signs and Symptoms (LANSS)]
Treatment
Appropriate treatment of other causes of pain
Referral to cognitive behavioral therapy, biofeedback, physical and occupational therapy, other adjunctive pain management options
Exercise regimen
Medications (tricyclic antidepressants, anticonvulsants, miscellaneous medications)
Neuromodulatory techniques (deep brain stimulation, spinal cord stimulation, transcranial motor stimulation, etc.)

Stroke

Introduction

Central poststroke pain (CPSP) results from lesions affecting pathways of the central somatosensory system which causes a sensation of pain with minimal or no stimulation of peripheral pain sensors. Dejerine and Rossi initially described eight patients with “severe, persistent, paroxysmal, and often intolerable pains on the hemiplegic side not yielding to any analgesic treatment.” Evaluation of these patients revealed lesions of the thalamus and posterior limb of the internal capsule. With identification of other regions of the brain which may cause central poststroke pain (CPSP), thalamic pain syndrome became known as CPSP.

Damage to the spinothalamic pathway is not always necessary for the development of CPSP, as damage to higher cortical sensory processing areas may also result in CPSP. CPSP occurs in an area of the body affected by stroke which occurs at or after the onset of stroke, and diagnosis is made through a good history and exam along with exclusion of nociceptive pain. Central poststroke pain (CPSP) often develops during improvement and recovery of neurological function. Like other

central pain syndromes, CPSP is characterized by hypersensitivity and dysesthesia and may cause spontaneous intermittent or constant pain.

Evaluation of pain in patients with stroke is important to maximize rehabilitation and neurological function. Poststroke pain has been reported in up to 55% of patients which is manifested in multiple types such as spasticity, shoulder pain/subluxation, and tension-type headache. Diagnosing and controlling these and other nociceptive pain inputs are not only important for a correct diagnosis of CPSP, but it may also reduce the severity of PSCP. Furthermore, treatment of pain in poststroke patients has been shown to reduce poststroke cognitive decline and improve functional outcomes.

Active inquisition about pain after stroke is vital to ensuring that pain has a smaller effect on poststroke depression, suicidality, sleep, cognitive function, quality of life, and final functional outcome. The presence of communication impairments and neglect syndromes contributes to under-recognition of poststroke pain and necessitates individualized approaches to assessment of pain. Elderly patients may not report pain and pain may often be atypical, resulting in underreporting of pain. In patients whom CPSP was identified, one study found approximately two-third of patients had inadequate pain relief and were undertreated. Figure 14.7 shows common types of chronic pain that can occur after stroke.

Epidemiology

*As t*he diagnosis of CPSP is variable and one of exclusion, large prospective studies evaluating the prevalence of CPSP are lacking. Prevalence of CPSP has been reported to be up to 12% in some studies. The first prospective study evaluating CPSP found an 8% incidence of CPSP within a year after stroke. A Finnish study evaluating 824 patients followed for 8.5 years found an incidence of 5.9% of CPSP.

The PRoFESS trial followed 1665 patients with mainly mild strokes (85% had a NIHSS $\leq$5) for 2.5 years and found an incidence of 10.6% of a new chronic pain syndrome. This included 431 patients (2.7%) with CPSP. Younger age of stroke onset, previous depression, current smoking, and increased baseline stroke severity were risk factors for development of CPSP. The presence of a new chronic pain syndrome resulted in greater decline in cognition and final functional outcome.

Localization and Pathology

The likelihood of developing CPSP is related to the location of infarct rather than the size of the lesion or arterial territory involved. Both ischemic and hemorrhagic strokes may result in CPSP. Lesions involving areas responsible for processing of sensory functions and pain are most likely to result in

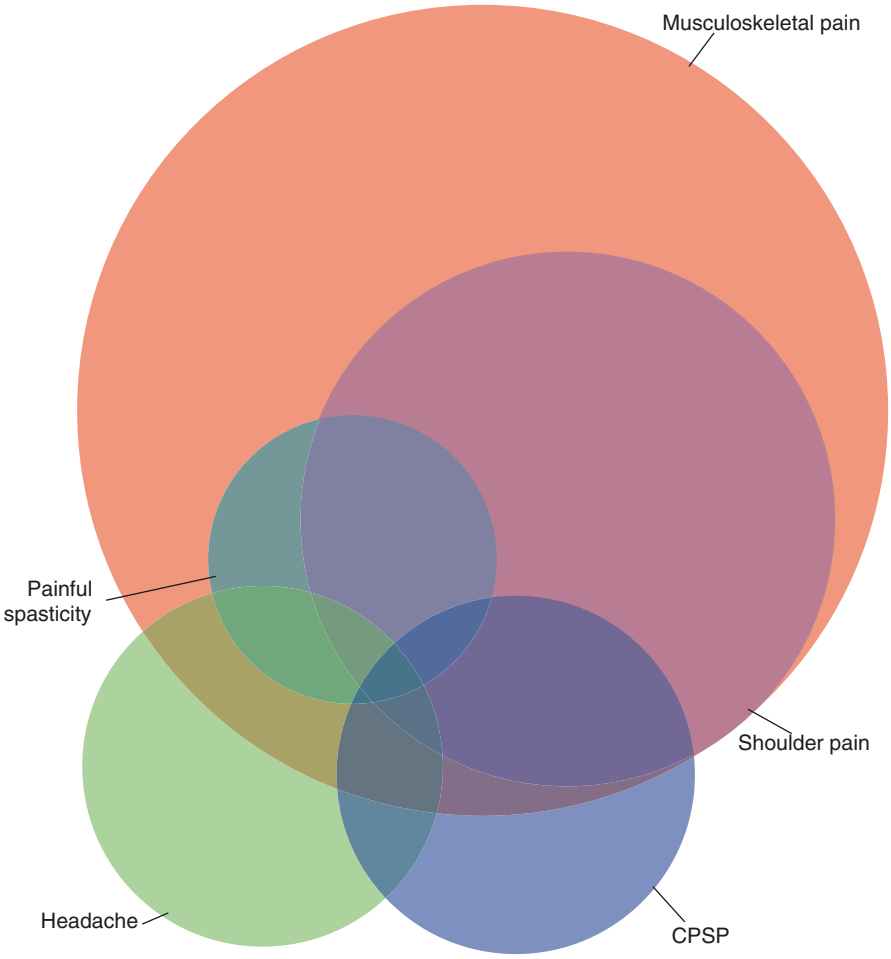

Fig. 14.7 Common types of chronic pain that can occur after stroke. The sizes of circles are approximate to relative frequency (spasticity 7%, headache 10%, central poststroke pain (CPSP) 10%, shoulder pain 20%, musculoskeletal pain 40%). (Adapted from H Klit, Lancet Neurology, 2009)

CPSP. CPSP most often occurs after stroke of the ventroposterior thalamus and lateral medulla.

The pathophysiology of CPSP and central pain syndromes is complex and may be caused by various mechanisms. In patients with spinothalamic lesions, partial damage is more likely to result in CPSP as compared to complete damage.

The PRoFESS trial found an association of small vessel disease and CPSP. This may reflect a higher rate of infarcts in the brain stem and thalamic regions. Damage to brain stem central pathways in the noradrenergic and serotonin pathways may contribute to CPSP and may be responsible for the efficacy of tricyclic antidepressant in CPSP. Wallenberg's (lateral medullary) syndrome has a

high rate of CPSP, up to 44% in some studies. Medial medullary syndrome has a lower rate of CPSP. Development of CPSP in these syndromes may be due to damage of the surrounding periaqueductal gray matter and reticular formation.

A large amount of sensory processing occurs in the thalamus. The ventroposterior aspect of the thalamus processes touch and temperature sensations from the contralateral face (trigeminothalamic tract to ventroposteromedial nucleus) and body (spinothalamic tract to ventroposterolateral nucleus). Damage to the lateral nucleus of the thalamus is thought to interrupt inhibitory pathways and cause disinhibition of the medial thalamus. Changes in the medial thalamus and reticular formation may play a role in maintaining central neuropathic pain. PET studies have shown decreased blood flow as well as increased burst activity in the thalamus in patients with chronic pain syndromes, although it remains unclear whether this is a result of the thalamus being a pain generator or a marker of chronic pain.

The cerebral cortex is involved in modifying input from the spinothalamic tracts and thalamo-cortico-thalamic feedback loops and projects to structures vital for the emotional perception of pain. Lesions in the operculum, insular cortex, and secondary somatosensory cortex most often lead to CPSP. Furthermore, decreased opioid binding to receptors has been noted in the thalamus, insular cortex, secondary somatosensory cortex, lateral prefrontal cortex, and cingulate gyrus in patients with CPSP.

Cortical lesions may also cause CPSP. The insular region and secondary somatosensory cortex are cortical regions most often associated with CPSP. The insular region has been referred to as a "primary pain center" and functions in thermal and nociceptive pain processing. The secondary somatosensory cortex is involved in pain intensity processing, and loss of thalamo-cortico-thalamic connections in the somatosensory cortex, specifically of the right hemisphere, may result in loss of feedback loops. This may result in a disconnection syndrome resulting in denervation supersensitivity of the thalamus leading to abnormal spontaneous and burst activity. Damage to the parietal subcortical region is the most common cause of CPSP. Furthermore, damage to the anterior cingulate and subfrontal cortex determines how pain is perceived and may contribute to CPSP.

Diagnosis

The diagnosis of CPSP is based on history, a thorough sensory examination, brain imaging, and exclusion of other causes. History should include timing of pain onset, quality, and the presence of dysesthesia or allodynia. CPSP may involve large parts of the body or smaller regions but is always located in an area of sensory dysfunction corresponding to the stroke and thus often unilateral. Occasionally unusual distributions such as the periorbital region of the eye or perioral regions may be involved.

Onset of CPSP varies and may occur at the onset of stroke but most often occurs in a delayed fashion, usually within 3–6 months poststroke but occasionally even

years later. Pain is often variable in intensity, averaging 3–6 on the visual analog scale. Pain onset is usually gradual and becomes long-lasting and possibly even lifelong.

The description of pain is not pathognomonic of CPSP but often is associated with allodynia and hyperalgesia. Pain is often described as burning, shooting, electric shock-like, stinging, aching, or pins and needles. Spontaneous pain may be continuous or paroxysmal, whereas evoked pain may be worsened by internal stimuli such as stress or anxiety or external stimuli such as cold objects, touch (allodynia), or pain (hyperalgesia). Nociceptive causes of pain should be excluded or at least adequately treated. CPSP does not worsen with movement or inflammation.

Sensory examination will reveal impaired pinprick and temperature sensation in the area of pain. Bedside testing using a cotton wool for touch, pointed object for pain, and a metal object for cold sensation may be used. Soft brush may be applied to the skin to test for sensory allodynia. In one study, pinprick hyperalgesia was present in 57% of patients with CPSP, allodynia in 40%, and dysesthesia in 51%. Questionnaires such as the LANSS scale may be helpful to determine degree of pain, although many patients may not be able to complete them due to deficits in cognition or communication. In patients where the diagnosis is uncertain, there may be some role of testing somatosensory evoked potentials. Table 14.4 summarizes criteria for the diagnosis of central poststroke pain.

Treatment

Management of CPSP should focus on aggressive management of other peripheral nociceptive and musculoskeletal pain sources, depression, and sleep disorders which can aggravate CPSP. Referral to behavioral psychologists to help identify

Table 14.4 Diagnostic criteria for central poststroke pain

Mandatory criteria for the diagnosis of CPSP
1. Pain within an area of the body corresponding to the lesion of the CNS.
2. History suggestive of a stroke and onset of pain at or after stroke onset.
3. Confirmation of a CNS lesion by imaging or negative or positive sensory signs confined to the area of the body corresponding to the lesion.
4. Other causes of pain, such as nociceptive or peripheral neuropathic pain, are excluded or considered highly unlikely.
Supportive criteria
No primary relation to movement, inflammation, or other local tissue damage.
Descriptors such as burning, painful cold, electric shocks, aching, pressing, stinging, and pins and needles, although all pain descriptors can apply.
Allodynia or dysesthesia to touch or cold.

Adapted from H Klit, *Lancet Neurology* 2009

coping strategies may be helpful, especially if implemented early in treatment during rehabilitation. No successful prophylactic treatments have been identified.

There are no large studies on optimal treatment of CPSP and management. Like other central pain syndromes, treatment is based on patient characteristics, concomitant comorbidities, tolerable dosage, and trial and error. First-line medications may include tricyclic antidepressants, SNRIs, pregabalin, and gabapentin. Anticonvulsants may be considered as second-line agents, although lamotrigine may be considered as a first-line drug as well. Interventional pain management techniques such as deep brain stimulation, motor cortex stimulation, and transcranial magnetic stimulation have also been shown to have some effect on pain relief and should be considered individually.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) increase levels of serotonin and norepinephrine by inhibiting their reuptake at the presynaptic neuron. The first study of amitriptyline was a randomized double-blind crossover, placebo-controlled trial in 15 patients. Amitriptyline was started at 25 mg at night and titrated up to 75 mg daily. Amitriptyline was found to have a significant reduction of pain in 10 of 15 patients when compared to placebo. Patients tolerated the dose well and no dosage reduction was necessary in the study.

Selective norepinephrine reuptake inhibitors (SNRIs) such as duloxetine, nortriptyline, desipramine, imipramine, doxepin, and venlafaxine may be effective in CPSP. Fluvoxamine (25–125 mg) improved pain from 7.7 to 6.0 on the visual analog scale in 28 patients over 2–4 weeks. The effects of antidepressants are thought to be due to changes in the noradrenergic pathways independent of effects of depression. Due to a lack of adrenergic action, SSRIs are thought to be less effective for CPSP compared to SNRIs.

Anticonvulsants

Anticonvulsant medications may work to reduce neuronal hyperexcitability in CPSP. Carbamazepine binds to voltage-dependent sodium channels and extends the inactive phase. It may also depress activity in the nucleus ventralis of the thalamus and was included in the crossover study in 15 patients with amitriptyline, mentioned above. Carbamazepine up to 800 mg/day did not reach statistical significance for reducing pain in this study; however, 4 of 14 patients did report pain relief compared to 1 of 15 in the placebo group. It may be considered as an adjunctive medication in patients with CPSP. Oxcarbazepine, a keto-analog of carbamazepine, may be considered in patients experiencing side effects or take drugs that interact with carbamazepine.

Lamotrigine works by inhibiting glutamate release and inhibiting sodium channel presynaptically. In a double-blind placebo-controlled crossover study in 30

patients, lamotrigine was started at 50 mg daily and titrated up to 200 mg/day. Most patients (90%, 27/30) experienced pain relief significantly more effective than placebo (visual analog score 7 vs 5; $P < 0.01$). Lamotrigine was relatively well tolerated although three patients withdrew due to adverse effects (rash, headache, severe pain). Lamotrigine may have a moderate effect on pain relief in CPSP.

Calcium channels modify the release of multiple neurotransmitters, and calcium channel antagonists such as pregabalin and gabapentin may be effective in relieving CPSP. In a prospective observational study, 84 patients with CPSP treated with gabapentin at 300 mg twice daily had lower posttreatment pain scores after 1 month of treatment. Although other studies have shown gabapentin to be effective in central pain, few studies have specifically evaluated gabapentin in CPSP. Pregabalin was evaluated in a short-term (13 weeks) randomized double-blind placebo-controlled study of 219 patients with CPSP. A dose of up to 600 mg per day was used, and although the study did not show a significant difference in mean pain scores compared to placebo, pregabalin did improve pain scores significantly at 8 weeks, with less pain reduction thereafter. The lack of difference at the end of the study may have been attributed to a high placebo effect, a possible pain reduction ceiling effect, and the fact that other pain-relieving medications such as amitriptyline were allowed in the placebo group. Pregabalin had significant improvement in sleep and anxiety compared to placebo at the end of the study, although 9 patients (8.2%) required discontinuation due to adverse effects.

Phenytoin has also been studied in eight patients with CPSP and improved pain in five patients, although discontinuation worsened pain. Zonisamide was shown to be effective in two patients with CPSP, and one study on topiramate found it to be ineffective in seven patients who were refractory to first-line drugs. In a double-blind, placebo-controlled study lasting over 3 months, levetiracetam was found to be ineffective in 42 patients with CPSP.

Other Medications

Intravenous anesthetics such as lidocaine and its oral analog mexiletine have been studied in CPSP. In a double-blind, placebo-controlled study of 6 patients with CPSP and 10 with spinal cord injury, IV lidocaine improved spontaneous pain in 10 of 16 patients compared to placebo which only improved pain in 6 patients. Patients in the lidocaine group had reduction in brush-induced allodynia and mechanical hyperalgesia, but not thermal allodynia and hyperalgesia. Twelve patients continued on oral mexiletine, and three of these patients experienced 30–50% reduction of pain. Oral mexiletine may be considered as an adjunct to other medications in CPSP but may require high doses (up to 200 mg four times a day) and close blood pressure monitoring for the first 2 days.

Intravenous ketamine, a NMDA blocker, has also been studied in central pain secondary to spinal cord injury and was found to be effective. Intravenous ketamine followed by oral ketamine has been reported to decrease allodynia and hyperal-

gesia in one patient with CPSP. Intrathecal baclofen, a GABA-b agonist, has also been reported to be helpful in a small study evaluating central pain, although oral baclofen has not shown similar results.

Other intravenous medications such as thiopental and propofol have also been studied but have either shown a lack of response or short-lived improvements in pain. Small studies evaluating intravenous morphine, oral levorphanol, and naloxone have not found a large role of opioids in CPSP, although IV morphine has been shown to be effective in reducing allodynia and thermal sensitivity to pain.

Neuromodulation

Deep Brain Stimulation

Deep brain stimulation of the sensory thalamus and periventricular and periaqueductal gray matter by pulse generators was evaluated in 47 patients with chronic neuropathic pain, 18 of whom had poststroke pain. DBS was significantly more effective in improving non-neuropathic pain. In another study of 15 patients with CPSP, 12 achieved adequate pain relief and had permanent pacemaker placement. Seven of these 12 patients (58%) had enough relief to discontinue all oral pain medications. Recently, a prospective study evaluating 85 patients, of which 31 had neuropathic pain after stroke, found an improvement after deep brain stimulation of the periventricular gray matter, thalamus, or both in visual analog scores in 22 patients (30%). DBS remains a consideration for refractory poststroke pain, although the percentage of patients with successful trials and long-term success is lower than that for other indications.

Motor Cortex Stimulation

Motor cortex stimulation has been used in CPSP to activate descending inhibitory sensory pathways as well as inhibitory pathways to the contralateral cortex. Studies on motor cortex stimulation in CPSP have shown variable success rate. A small study of 16 patients with CPSP showed a significant reduction in visual analog scores (8 to 5.3) with motor cortex stimulation. Another retrospective study of 11 patients, of which 8 had CPSP, showed that 75% (6 of 8) patients with thalamic pain experienced significant pain relief. Seizure, infections, and hardware problems are possible complications associated with motor cortex stimulation.

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation is a noninvasive method which applied a weak current that induces an electrical discharge in local areas of the brain. It has minimal adverse effects and has a modest effect on pain relief, although it has been shown to extend pain relief.

In 14 patients with CPSP, TMS reduced pain on the visual analog scale from 4.3 to 3.1 over 3 weeks and improved pain sensation from cold temperature. In another observational study evaluating seven patients with CPSP, four patients (3 moderate pain, 1 severe pain) achieved satisfactory pain relief of 40% or greater. In a randomized, double-blind, sham-controlled, crossover study evaluating 64 patients with neuropathic pain who received daily TMS, of which 52 (81%) had CPSP, there was a modest reduction in visual analog scales in patients who received TMS.

Other interventional pain strategies such as acupuncture have also been shown to have some effect in CPSP in case reports.

There is currently insufficient evidence to recommend interventional strategies such as motor cortex stimulation, deep brain stimulation, and transcranial magnetic stimulation for most patients with CPSP. These strategies may be considered for treatment-resistant cases and should be ideally performed in large-volume neurosurgical centers.

Spinal Cord Injury

Introduction

Traumatic spinal cord injury (SCI) is a devastating neurological injury that may result in severe motor, sensory, and autonomic symptoms at and below the level of injury. Pain in SCI is complex, multifactorial, and usually chronic in nature. Pain may occur immediately after injury or may worsen long after injury. Pain in SCI is associated with reduced quality of life, poorer rehabilitation outcomes, depression, and suicide. Approximately 85% of patients with SCI experience pain, of which one third have severe, excruciating pain. Management of pain in these patients is a significant and unmet need.

Pain after SCI may be of nociceptive, neuropathic, or due to other etiologies. Above-level injury pain may be due to compressive neuropathies or complex regional pain syndrome, whereas at-level pain may be secondary to nerve root compression, syrinx formation, trauma, or ischemia. Neuropathic pain at the level of spinal cord injury is often, but not always peripheral in nature, and most commonly occurs within the first few months after injury. Below-level SCI neuropathic pain is most commonly central in nature. There is a higher frequency of pain below the level of injury (83%), as compared to at-level (50%) or above-level pain (41%). Management of pain in SCI can be challenging due to the variety of pain types related to other factors such as implanted hardware, immobility, and musculoskeletal pain. Table 14.5 describes the associations between the level of pain in patients with spinal cord injury and the causes. Figure 14.8 gives examples to differentiate between different types of pain in patients with spinal cord injury pain.

Table 14.5 Different levels of pain in spinal cord injury

Spinal cord injury pain	
Above-level pain	Compressive mononeuropathies
	Complex regional pain syndromes
At-level pain	Nerve root compression (including cauda equina)
	Syringomyelia
	Spinal cord trauma/ischemia/ compression
	Dual-level cord and root trauma
Below level	Spinal cord trauma/ischemia/ compression

Adapted from PJ Siddal, *International Association for the Study of Pain Newsletter*, 2000

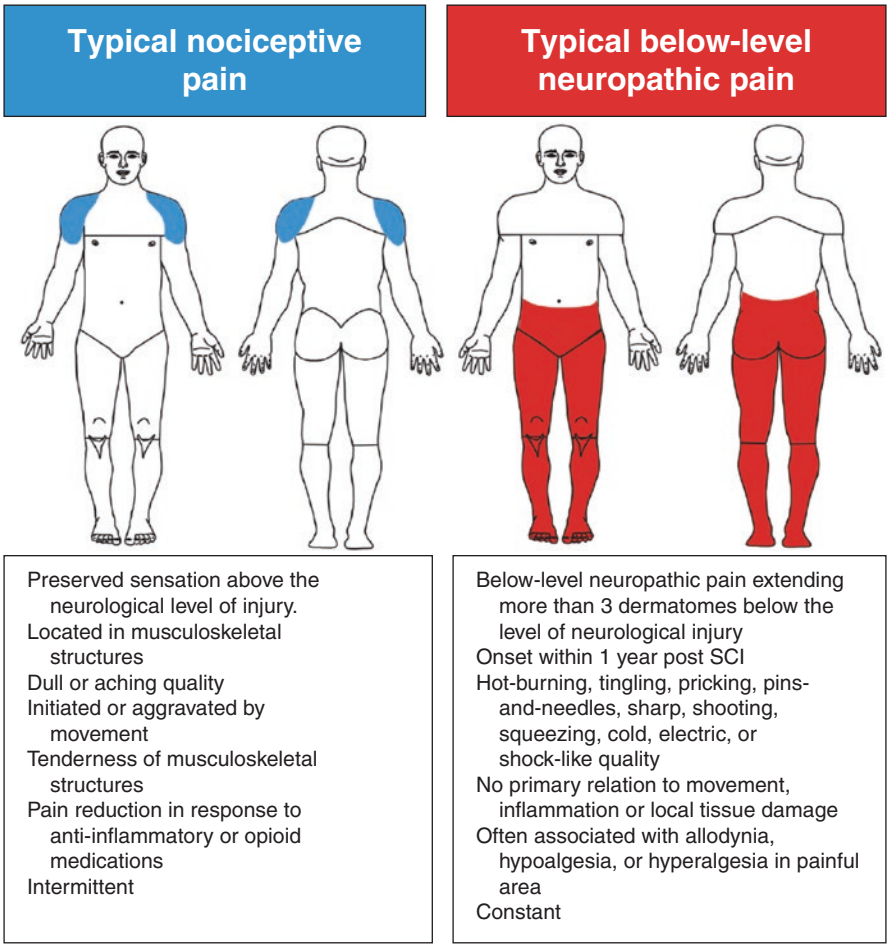

Fig. 14.8 Differentiating different types of spinal cord injury pain. (Adapted from E. Widerstrom-Noga, Drugs, 2017)

Epidemiology

Spinal cord injury occurs in about 54 people per million annually in the United States. Approximately 290,000 live with spinal cord injury in the United States. SCI tends to affect younger males and non-Hispanic whites are the most commonly affected ethnic group. Motor vehicle accidents (38%) are the most common cause of SCI, followed by falls (32%), violence (14%), and sports-related injuries (8%).

Localization and Pathology

Spinal cord injury-related central pain (SCI CP) may have different pathological mechanisms depending on the level and severity of injury in patients with SCI. Level of SCI, completeness of injury, and the integrity of the sensory, motor, and autonomic pathways in the spinal cord determine whether a patient will eventually develop SCI CP.

Central pain in SCI is the result of anatomic, neurochemical, inflammatory chemical changes that produce a hyperexcitable CNS with increased background activity and hypersensitivity to stimuli. Peripheral mechanisms may contribute to the maintenance of central pain by providing abnormal nociceptive inputs to the CNS. Local spinal cord changes, changes in ascending and descending pathways as a result of deafferentation, and cortical and subcortical neuroplasticity all play a role in the development of CP in SCI.

Spinal cord injury results in significant changes in neurochemical and signaling pathways in the spinal cord. Immediately after injury there may be an increase in intracellular calcium, nitric oxide, and peptides such as substance P and dynorphin. Glutamate is released in and around the site of injury along with other toxic neurochemicals, resulting in neurotoxicity. Activation of microglia results in production of cytokines such as TNF-alpha and interleukin 1B and 6 and induces changes in the dorsal horn sensory neurons. Molecular changes result in inactivation of cell signaling pathways, upregulation of sodium channels and vanilloid receptors, changes in glutamate receptors, and inhibition of serotonergic, noradrenergic, opioid, and GABA receptors. The result of these changes includes decreased spinal inhibition, changes in descending pathways, and longitudinal and secondary changes of surviving tissue such as aberrant afferent sprouting of neurons. These changes also contribute to longitudinal extension of spinal cord damage and secondary neuronal injury. These neuropathological pathways may be a target for future neuroprotective strategies to limit secondary cord injury.

The result of neurochemical, cellular, and inflammatory cascades at the site of SCI forms an environment which allows for neuroplasticity and eventual central pain to develop. Loss of inhibitory tone at the level of injury with recruitment of surrounding neurons results in hyperexcitability and pain-generating mechanisms. Furthermore, direct compression of the spinal cord from the primary injury and

abnormal tonic excitatory generators in or around the gray matter may cause ectopic electrical discharges in addition to deafferentation effects. Studies have shown that patients with SCI-related below-level pain have larger spinal cord gray matter lesions than patients without pain. The absence of pain after administration of a spinal anesthetic block indicates that there may be spinal cord pain generators in patients with SCI. Multisynaptic spinal circuits that process, integrate, and transmit sensory information are altered and affect supraspinal pathways and microglial activation.

Cordotomy in some patients with SCI failed to relieve below-level pain indicating a large role of supraspinal generators in SCI below-level pain. Supraspinal neuroplastic changes occur in the thalamus as well as the cortex. Deafferentation and abnormal inputs from the spinal cord likely drive these changes. Bursting activity in the thalamus, imbalance between the medial and lateral thalamic nuclei, and dysfunction of the cortico-thalamic reverberation mechanism are seen in patients with SCI pain. At the cortical level, reorganization of cortical pain processing areas includes the arcuate nucleus and somatosensory cortex. Changes in cortical expression of cholecystokinin, opioid peptides, and precursors have also been demonstrated in patients with SCI-related pain.

The different phenotypes of pain in SCI-related below-level pain are likely due to multiple spinal and supraspinal mechanisms contributing to SCI pain. Hence, treatment for these patients may partially respond to different medications as pain generators may be spinal, supraspinal, or a combination of both.

Diagnosis

The diagnosis of central pain in SCI-related pain may be challenging, as most patients have two or more simultaneous pain types. To help differentiate between nociceptive and non-nociceptive pain, multiple pain-scoring questionnaires and classification systems have been developed.

The Spinal Cord Injury Pain Instrument (SCIPI) was developed specifically for SCI and is the most current questionnaire to help differentiate neuropathic from non-neuropathic pain. The Douleur Neuropathique 4 (DN4) questionnaire is a 10-item questionnaire that also helps differentiate neuropathic and non-neuropathic pain; however validation and reliability in English are currently lacking. The Neuropathic Pain Scale (NPS) helps to differentiate different categories of neuropathic pain and may be helpful in specifically identifying central SCI pain. The Leeds Assessment of Neuropathic Signs and Symptoms (LANSS) uses sensory pain descriptors and a bedside sensory examination and has a good sensitivity (85%) and specificity (80%). Other questionnaires used in SCI include the Neuropathic Pain Questionnaire (NPQ) and the Neuropathic Pain Symptoms Inventory (NPSI).

The International Spinal Cord Injury Pain (ISCIP) classification is the most recent pain classification (2012) developed by SCI pain expert consensus (see

table). It is the first universal classification tool developed at this time but requires further validation and reliability testing. Previous classification systems include the International Association for the Study of Pain taxonomy (developed in 2000, moderate inter-rater reliability), Cardenas SCI pain taxonomy (developed in 2002, substantial inter-rater reliability), and the Bryce-Ragnarsson SCI pain taxonomy (developed in 2002, substantial inter-rater reliability).

Many patients have severe pain within the first 3–6 months of SCI, which may then spontaneously improve. A second increase of pain incidence often occurs 2 or more years after the initial SCI. Incomplete tetraplegia is the most common resulting condition after SCI. Patients with tetraplegia more commonly have neuropathic pain compared to patients with paraplegia.

Clinically, central pain in SCI is commonly described as burning, tingling, pricking, or shock-like. It is usually below the level of injury and associated with sensory allodynia or hyperalgesia. Onset of pain is often months or years after the initial injury and may be more severe with incomplete lesions and thoracolumbar lesions. Pain is in areas of sensory abnormality and may be spontaneous or stimulus evoked. Quantitative sensory testing may occasionally be a helpful adjunct for assessing somatosensory changes in patients with SCI. Similar to other forms of central pain, other features of SCI-related CP include wind-up pain (temporal summation of pain) and aftersensations (pain continuing after stimulation has ceased).

Treatment

Management options for SCI-related central pain include medications such as antidepressants, anticonvulsants, and opioids, in addition to intravenous infusions and surgical options. Unfortunately, due to the small number of patients with SCI compared to other conditions and few large centers, large randomized clinical trials, long-term studies, and head-to-head comparisons evaluating treatment options for SCI-related pain are lacking. Medication recommendations are largely based on small studies in addition to extrapolation from trials for neuropathic pain management.

Because there may be various pain phenotypes in SCI-related CP, individual treatment plans must be made for patients based on their comorbidities, drug side effects, and tolerable dosage. SCI-related pain is difficult to manage with available treatments only being able to reduce pain by about 50% in many cases. A trial of medications is often necessary with dosage adjustments and addition or removal of drugs to achieve maximum pain relief. Some experts have recommended starting patients on an anticonvulsant or tricyclic antidepressant. Second-line agents include SNRIs and weak opioids. Interventional techniques such as spinal cord stimulation, deep brain stimulation, and direct motor cortex stimulation may be considered for refractory cases. Management of nociceptive pain is necessary to minimize pain and referral to behavioral cognitive therapy, and other unconventional techniques such as acupuncture may be used as adjunctive therapies.

Antidepressants

Amitriptyline has been shown to enhance descending monoaminergic pathways and affect spinal and supraspinal inhibitory pathways in patients. Amitriptyline is considered a first-line therapy for SCI-related pain, although it has less evidence than pregabalin. A randomized longitudinal study comparing amitriptyline (25–100 mg) to lamotrigine (25–100 mg) in 147 patients showed a significant difference in pain rating at 3 weeks for both drugs compared to baseline. In a 6-week trial comparing amitriptyline and placebo, there was no significant difference in pain relief between the two groups; however inclusion criteria for this study included patient with musculoskeletal pain as well as SCI-related pain. Another study in 38 patients found improvements in patients receiving amitriptyline compared to lamotrigine and placebo, especially in those patients with concomitant depression. In this study, most patients achieved a dose of 50 mg TID, indicating that higher doses of amitriptyline may possibly have a greater effect. However, anticholinergic and cardiac side effects may limit higher dosing of amitriptyline in a large number of patients. Other tricyclic antidepressants such as nortriptyline, desipramine, and imipramine have not specifically been studied in SCI-related CP.

Besides amitriptyline, only duloxetine and trazodone antidepressants have been studied in SCI CP. Duloxetine did not effectively reduce pain intensity, although was helpful in improving dynamic and cold-induced allodynia. A small study of 18 patients with traumatic myelopathy did not find trazodone to be effective for pain relief. Venlafaxine was studied in patients with SCI pain (not specifically central pain) and depression. The authors of this study concluded that venlafaxine has a limited effect on central pain in SCI. Currently, there is insufficient evidence for use of antidepressants besides amitriptyline for treatment of SCI-related CP; however based on evidence available for other neuropathic conditions, duloxetine may be an option for SCI-related CP.

Anticonvulsants

Among all medications studied for SCI-related CP, pregabalin has the strongest level of evidence for effectiveness (moderate-large) in reducing pain and is a first-line medication in the treatment of below-level SCI pain. The effectiveness of the medication has been demonstrated in three randomized controlled trials, the largest of which enrolled 220 patients. Pregabalin is associated with not only improved pain symptoms but also improvements in anxiety and sleep. A dose of 150–600 mg may provide sustained pain relief which may become evident as early as 1 week after starting therapy in some patients.

Gabapentin can be considered as an alternative to pregabalin in patients with SCI-related CP, given the body of evidence. In a systematic review, gabapentin was found to be less efficacious than pregabalin, although had a lower rate of side effects. In a randomized double-blind placebo-controlled crossover trial in 20 paraplegic patients with neuropathic pain for more than 6 months, gabapentin was found

to reduce both the intensity and frequency of pain. However, a randomized controlled triple crossover trial over 8 weeks comparing amitriptyline, gabapentin, and diphenhydramine (placebo) found no significant difference in pain relief between gabapentin and diphenhydramine. Another prospective, randomized double-blind placebo-controlled crossover study found that gabapentin has some beneficial effects on certain types of pain; however, results were not statistically significant. Given the available evidence, gabapentin should likely be used as an alternative to pregabalin as a first-line medication.

A randomized controlled study has demonstrated effectiveness of lamotrigine in patients with incomplete SCI-related evoked and spontaneous pain. Another study, mentioned above found effectiveness of lamotrigine as well as amitriptyline in improving pain relief compared to baseline pain intensity. Among the anticonvulsants, lamotrigine may be considered a second-line agent for treatment of SCI-related CP.

Levetiracetam at 1500 mg twice daily and valproate have been shown to be ineffective in SCI-related CP. Although topiramate and carbamazepine have been shown to be effective in case reports, there is currently insufficient evidence to recommend anticonvulsants besides lamotrigine for treatment of SCI CP.

Opioids, Intravenous, and Intrathecal Medications

There is limited evidence for the role of opioids, intravenous, and intrathecal medications in SCI CP. Further evidence is needed before the following medications can be recommended for use in SCI-related CP. Intravenous medications are limited by their duration of action and may have a limited therapeutic role in the long-term management of pain in this condition. Some medications, such as intrathecal baclofen, may have potential to worsen SCI-related CP.

Lidocaine

Intravenous lidocaine has been reported to be helpful in reducing SCI-related central pain and allodynia and hyperalgesia. Two studies evaluating intravenous lidocaine at a dose of 5 mg/kg infused over 30 minutes demonstrated significant pain relief over placebo. In another study, intravenous ketamine at 0.4 mg/kg and lidocaine 2.5 mg/kg given over 40 minutes found that ketamine, but not lidocaine, had a significant analgesic effect. Topical 10% lidocaine has also been reported to reduce at- or below-level SCI-related pain.

Ketamine

In small studies, ketamine has been shown to have some effect in SCI-related CP as mentioned above. In one study of 40 patients, intravenous ketamine improved pain intensity up to 2 weeks after injection. Another positive study used an oral 5 mg test

dose of ketamine to select patients for intravenous infusions. Intravenous ketamine combined with alfentanil has demonstrated a significant reduction of continuous pain, allodynia, and wind-up phenomenon.

Opioids

Intravenous morphine was ineffective in the only double-blind placebo-controlled study which included patients with SCI-related pain. In another study, intrathecal morphine or clonidine was not effective in improving pain; however combination intrathecal morphine and clonidine impacted pain symptoms. Drug level in the cervical cerebrospinal fluid correlated with pain relief.

There is some evidence that tramadol may improve SCI-related neuropathic pain, but as with other opioids, substantial adverse effects may limit its use. One small observational study demonstrated pain relief with oxycodone in combination with anticonvulsants. Opioid medications have limited evidence of long-term efficacy, and there may be concerns regarding dependence, adverse effects, and potential for abuse.

Cannabinoids

Whereas cannabinoids have been extensively studied for MS-related CP, there is only one study evaluating cannabinoids in SCI-related pain. Compared to placebo, there was no significant difference in patients with below-level SCI pain taking dronabinol or placebo.

Neuromodulatory Pain Techniques

Neurosurgical and functional modulation therapies have become important alternative strategies to pharmacological therapy of SCI-related CP. Current studies are limited by sample size or quality, with many retrospective studies lacking pain characteristics or level of SCI. Invasive procedures such as deep brain stimulation are not recommended given that they are invasive, irreversible procedures with limited efficacy. Noninvasive neuromodulation may be effective in a subset of the population and needs further research.

Spinal Cord Stimulation

Spinal cord stimulation has been studied extensively for failed back surgery syndrome and complex regional pain syndrome, but studies in spinal cord injury patients with central pain are limited. Spinal cord stimulation is based on Melzack and Wall's gate theory and works by stimulating large dorsal column fibers via electrodes placed in the epidural space. Case series have reported a relatively poor

outcome in SCI patients compared to patients who experience pain relief for failed back surgery. Newer technologies with high frequency and burst paradigms have been reported to be effective for below-level SCI pain, even in cases of complete paraplegia. SCS has been reported to be more effective for incomplete lesions and for at-level pain; however efficacy of SCS often decreases over time. Currently, there remains insufficient evidence to recommend spinal cord stimulation for treatment of SCI-related central pain.

Deep Brain Stimulation

Deep brain stimulation involves implantation of a neurostimulator which targets a specific region of the brain which may potentially cause depolarization of surrounding neurons and mimic lesioning of that brain region. In a systematic review of patients evaluating DBS, patients with SCI-related central pain had poor long-term responses, with 3 of 19 patients (16%) responding to deep brain stimulation. Given the risk of infection, seizures, and intracranial hemorrhage associated with DBS, it is not recommended for treatment of SCI-related CP.

Motor Cortex Stimulation

Motor cortex stimulation has been used to treat SCI-related CP with mixed results. Noninvasive methods of brain stimulation include repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), whereas invasive methods include epidural motor cortex stimulation (EMCS). Repetitive transcranial magnetic stimulation delivers impulses in trains with a constant frequency and intensity, whereas tDCS delivers direct low-intensity electrical currents. Mechanisms of action of these devices are not well understood; however, it has been hypothesized that repetitive currents affect synaptic efficacy and result in long-term potentiation, whereas hyper- or depolarization of neuronal membranes can occur via application of a direct current. Small series of transcranial magnetic stimulation have had mixed results, and a systematic review failed to show a significant difference between TMS and sham. There is evidence that tDCS may reduce pain in the short to medium term and may be a predictor of the effectiveness of ECMS. Motor cortex stimulation remains a promising technique for long-term pain control in SCI-related injury, and further studies are needed.

Other Treatment Modalities

Alternative pain management techniques should be included in treatment of patients with central pain. Referral for educational, cognitive, and behavioral therapies has shown to have various benefits for patients with SCI-related pain. Applied relaxation and meditation techniques reduce muscle tension and improve pain coping.

Cognitive behavior therapy results in decreased pain-related disability, reduced anxiety, and increased participation in activities of daily living. Referral for psychotherapy can help minimize anxiety-related to pain, reduce depression, and improve quality of sleep.

Multiple Sclerosis

Introduction

Multiple sclerosis (MS) is a chronic progressive inflammatory disease which results in demyelination and axonal degeneration in the central nervous system. Pathology of multiple sclerosis involves activation of T-cells, macrophages, and microglia. Multiple sclerosis can result in both peripheral pain related to musculoskeletal pain and spasticity as well as central pain related to primary central neuropathic pain. Primary CNS pain syndromes include continuous pain and intermittent pain syndromes such as painful tonic spasms, trigeminal neuralgia, glossopharyngeal neuralgia, central dysesthetic pain, and Lhermitte's sign. Headache is also a common cause of pain in MS and may be contributed to by central pain mechanisms.

Pain is rarely present at the onset and initial stages of MS, but chronic pain becomes a common problem in MS, seen in over 90% of patients. Chronic pain in MS is more common in primary and secondary progressive types of MS. Risk factors for central pain (CP) in MS include older age and longer duration of illness, higher EDSS scores, concomitant depression or mental disorders, and lower education. Table 14.6 summarizes central pain syndromes in patients with MS.

Table 14.6 Primary central pain syndromes in multiple sclerosis and possible pathophysiological mechanisms

Pain syndrome	Duration of pain	Possible pathology
Central dysesthetic pain	Continuous pain	Deafferentation pain secondary to spino-thalamo-cortical pathways often from plaque in cervical or thoracic spinal cord
Painful tonic spasms	Intermittent pain Less than 2 minutes	Ectopic impulses from axonal damage of neurons in demyelinating plaque in cortico-spinal pathways
Trigeminal neuralgia and glossopharyngeal neuralgia	Intermittent pain Several seconds	Ectopic discharges generated by demyelinating plaques at the interface of the TN nerve entry zone and brain stem and extra-axial mechanical demyelination of the trigeminal primary afferents
Lhermitte's phenomenon	Intermittent pain Few seconds	Ectopic impulses from hypersensitive axons in demyelinated plaques in the posterior column of the cervical spinal cord

Epidemiology

As MS progresses, pain becomes more frequent and may become the dominating problem. Although uncommon, pain in newly diagnosed MS patients is seen in up to 23% of patients. In one study evaluating patients with a known MS diagnosis, all patients had some sort of pain. In another study evaluating 62 patients with MS, more than two thirds had at least two to four pain qualities. Mean pain intensity in a study of 88 patients with MS was 4.5 ± 1.5 on the visual analog scale (2.2 minimum, 6.7 maximum). Pain prevalence in MS is associated with greater disability, disease course and duration, age, depression, and anxiety.

Approximately 30% of patients with MS have MS-related central pain, including about 5% of patients with trigeminal neuralgia. Central pain is the presenting complaint in MS in 1–2% of patients. In most patients, central pain symptoms occur more than a year after the presence of the first sensory and motor symptoms. Central pain in MS most commonly manifests as central dysesthetic pain (18–45%), painful tonic spasms (11–22%), Lhermitte's sign (9%), trigeminal neuralgia (2–5%), and least commonly as glossopharyngeal neuralgia (< 1%). Patients with MS-related CP more commonly have demyelinating lesions in the brain stem compared to spinal cord lesions.

Localization and Pathology

Central pain in multiple sclerosis often leads to hyperexcitability in the CNS due to various mechanisms resulting from demyelination and axonal damage. Ephaptic spread of action potentials from ectopic discharges from demyelinated neurons contributes to hyperexcitability at multiple levels of the central nervous system. Furthermore, supraspinal demyelination and reorganization may contribute to disinhibition of descending pain pathways and dysfunction in pain processing and endogenous pain modulatory systems.

Central pain in MS may result from demyelinating plaques in the thalamus, parietal cortex, cortical regions involved in pain perception, or spino-thalamo-cortical pathways. The presence of central sensitization is evident from experiments using quantitative sensory testing which demonstrated reduced pressure pain thresholds in patient with MS with or without pain. A peripheral deafferentation from lack of normal afferent impulses results in quantitative and qualitative changes in sodium and calcium channels which result in increased neuronal excitability. NMDA and NK-1 neurokinin receptors have also been found to be altered in postsynaptic neurons in the posterior horns of the spinal cord. The CNS has the ability to adapt and reorganize, and the individual variation in pathologico-anatomic localization of demyelinating plaques in MS patients results in a significant variation in the mechanisms and pathways of central pain in these patients.

Diagnosis

Central pain in MS may present as a number of syndromes including trigeminal neuralgia, central dysesthetic pain, painful tonic spasms, and rarely glossopharyngeal neuralgia. Diagnosis of central pain is challenging in MS patients given that many patients may have bilateral pain and that sensory abnormalities may be widespread. Central pain is usually described as a burning, stinging sensation, or a sensory disturbance which poorly responds to standard analgesics and may involve large parts of the body. Pain is usually moderate in intensity but can worsen during relapses. Pain is more likely to involve the lower extremities in MS; however, this may vary depending on the location of demyelination. Given the various types of central pain in MS, clinical characteristics are described separately of each central pain syndrome in MS.

Trigeminal and Glossopharyngeal Neuralgia

Trigeminal neuralgia (TN) is a sudden onset, extremely strong, painful, lancinating type of pain which may last up to several seconds and is often accompanied by a characteristic facial grimace. The painful sensation most often involves the V2 and V3 segments of the trigeminal nerve, although the V1 distribution can be rarely involved.

Estimates of the prevalence of trigeminal neuralgia in multiple sclerosis are about 2–6% and are about 20 times higher in MS patients compared to the general population. Trigeminal neuralgia in MS often occurs later in the disease course and occurs after the onset of non-trigeminal pain. Whereas trigeminal neuralgia in the general population is usually unilateral, the presence of bilateral trigeminal neuralgia occurs more frequently in the MS patients and should alert clinicians to the possibility of MS as a secondary cause.

TN related to MS may be a combination of both peripheral and central pathology. Electrophysiological studies and three-dimensional brain stem lesion analysis have identified pathology in the intrapontine portion of trigeminal pathways in patients with TN related to MS. Peripheral neurovascular compromise, commonly by the superior cerebellar artery, may be a contributing mechanism in these patients as well as ectopic discharges from irritated nerves at demyelinating plaques at the interface of the TN nerve entry zone and brain stem. A study using three Tesla MRI multi-tensor DTI found lower fractional anisotropy in perilesional segments of the trigeminal nerve in patients with MS, indicating differential microstructural changes in the trigeminal nerve in these patients. Studies of neurovascular decompression in MS have resulted in poorer outcomes compared to other patients undergoing neurovascular decompression for TN, likely due to a central component of pathology.

No placebo-controlled trials have evaluated the treatment of TN in MS. TN in MS is treated similarly to isolated TN seen in the general population. First-line

pharmacological treatment consists of carbamazepine, which is the most well-studied medication for trigeminal neuralgia. Doses of 600–800 mg in divided doses are typically needed to control pain associated with TN. However, carbamazepine has side effects which are often poorly tolerated resulting in a need for dose reduction or in some cases discontinuation of the drug. Oxcarbazepine may be an alternative medication in these cases. Other second-line agents include lamotrigine (up to 400 mg daily), baclofen (up to 60 mg daily), gabapentin (up to 2400 mg daily), and topiramate (up to 400 mg daily). Small open-label studies have also evaluated phenytoin, pregabalin, pimozide, levetiracetam, and clonazepam. The prostaglandin E analog, misoprostol, has been specifically evaluated in 18 patients with TN and MS and found to be effective in reducing attack frequency by 50% in 14 of them. One patient discontinued misoprostol due to severe menorrhagia during the study.

For patients who do not respond to pharmacological therapy, onabotulinum toxin A injections may be considered, based on multiple observational studies. In one study evaluating 88 patients, 39% of patients had effective treatment of their TN at 14 months, and 25% of them achieved complete analgesia. Surgical techniques for treatment of refractory TN include microvascular decompression and ablative procedures aimed to interrupt trigeminal pathways. Ablative procedures include rhizotomy with radiofrequency thermocoagulation, mechanical balloon compression, glycerol injection, Gamma Knife radiosurgery, and peripheral neurectomy with a nerve block. Microvascular decompression is the first-line surgical intervention and is associated with high rates of initial pain relief (90%), although pain-free rates decline to approximately 75% at 5 years. Mortality is rare in these procedures, but surgery may be complicated by hematoma formation at the surgical site, infarctions, CSF leaks, and aseptic meningitis. Patients who undergo ablative therapies have similar rates of initial pain relief but lower pain-free rates in the long term. Adverse effects of the surgery may include hypo- or hyperesthesia of the face, decreased corneal reflex, transitory masticatory weakness, and hearing loss. Figure 14.9 shows imaging in patients with MS and trigeminal lesions.

Glossopharyngeal neuralgia (GN) from central lesions may be seen in patients with MS. GN has a higher incidence in patients with MS compared to the general population and has rarely been described as the presenting complaint of MS. It is characterized by severe lancinating, electrical shock-like pain in the posterior pharynx, tonsils, mandibular angle, and base of the tongue. It can be triggered by talking, yawning, coughing, and swallowing. Pharmacological management is similar to that of trigeminal neuralgia. Surgical microvascular decompression most commonly of the posterior inferior cerebellar artery can be considered for refractory cases, as can Gamma Knife radiosurgery.

Lhermitte's Sign

Lhermitte's sign (LS), first described in 1924, is an electrical sensation running down the back and is characteristic of MS, although it has also been reported in patients who received radiation to the neck for cancers. LS is triggered by neck flexion that often lasts less than 2 seconds, with relief of pain upon cessation of

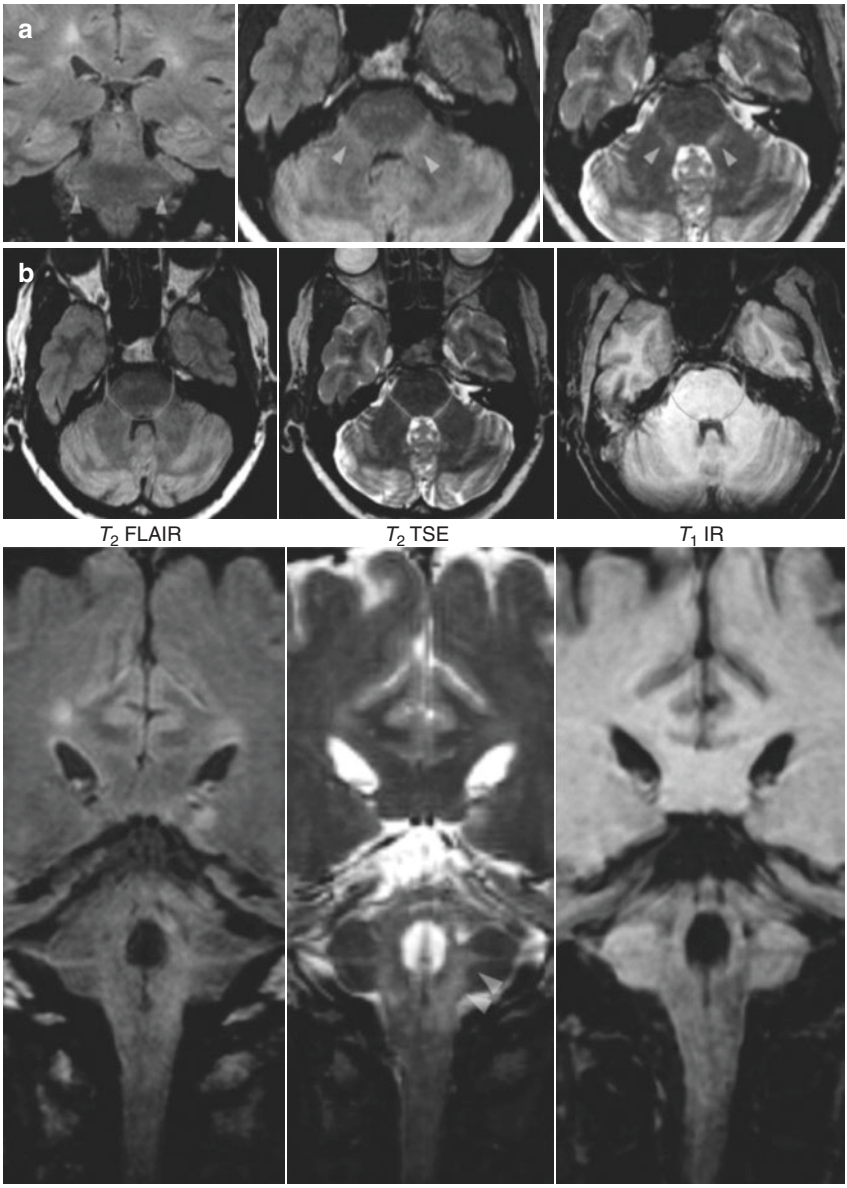

Fig. 14.9 (**a**) Coronal T2 FLAIR (left), axial reconstruction (middle), and corresponding axial T2 TSE axial reconstruction (right) showing bilateral, well-demarcated, linear hyperintense lesions in the trigeminal root entry zones and tracts of otherwise lesion-free pontocerebellar structures. (**b**) Axial T2 FLAIR reconstruction (left), corresponding axial T2 TSE reconstruction (middle), and axial T1 IR reconstruction (right) images from the same subjects as imaged in (**a**). The upper images show the curved plan (green line) in which the lower images were reconstructed. The lower images clearly show abnormal signal extending along the whole transcisternal and intrapontine course of both trigeminal nerves, which become confluent with lesions running rostrocaudally where the pontomedullary trigeminal nuclei would be found (arrowheads). (Adapted from the RJ Mills, British Journal of Radiology, 2010)

neck flexion. It is seen in up to 40% of patients with MS and often seen in the initial stages of disease or during relapses and more frequently in primary progressive MS.

This phenomenon is thought to arise from hypersensitive axons in demyelinated plaques in the posterior column of the cervical spinal cord which can be stretched during neck flexion and result in activation of ascending spinothalamic tracts. LS is present for a few weeks only in about half of patients, whereas they may occur occasionally in the other half of patients. Most cases do not need treatment, although low-dose carbamazepine has been shown to be effective in patients requesting treatment or for persistent cases.

Painful Dysesthesias/Central Dysesthetic Pain

Central painful dysesthesias (CPDs) are the most common type of central pain in MS and has a lifetime prevalence of 12–38% in all MS patients. It most commonly occurs in the primary progressive or secondary progressive type of MS and least commonly in relapsing-remitting MS. Although the exact mechanism of CPD in MS remains unclear, patients with CPD have high rates of plaque formation in the cervical and thoracic cord, as well as the thalamus.

CPD usually affects the lower extremities, although it may involve the head, upper extremities, or trunk. The pain is usually constant, bilateral, and present daily, may be worsened by physical activity, and does not follow a dermatomal distribution. The pain may be worsened by exposure to heat or weather changes. In one study, 97% of patients with CPD had involvement of the lower extremities and 31% in the upper extremities, and 76% had bilateral symptoms.

Treatment of CPD is similar to that of other central pain syndromes, and pharmacological agents used include tricyclic antidepressants (amitriptyline, nortriptyline, imipramine), SNRIs (duloxetine, venlafaxine), alpha-2-delta ligands (gabapentin, pregabalin), and sodium channel blockers (carbamazepine, oxcarbazepine, lamotrigine).

Painful Tonic Spasms

Painful tonic spasms are seizure-like involuntary dystonic spasms that occur on one or both sides in patients with MS. About 11–15% of patients with MS experience painful tonic spasms which are likely related to ectopic impulses from axonal damage of neurons in demyelinating plaque. Neuroimaging of patients with painful tonic spasms has revealed lesions in the basal ganglia, internal capsule, cerebral peduncles, medulla, and spinal cord. Pain may precede painful tonic spasms, indicating that pain is not secondary to the spasms and that mechanism of pain is likely

central in nature. Painful tonic spasms are more common in primary and secondary progressive forms of MS.

Painful tonic spasms may occur several times a day, often are preceded by an aura, and usually last for less than 2 minutes. They are stereotypical, chronic, or recurrent and occur more often at night often resulting in disturbed sleep. They are usually associated with pain or other sensory stimuli such as dysesthesias or numbness. Attacks may last for weeks or months and then spontaneously disappear. Spasms more commonly occur in the lower extremities and are not associated with epileptiform discharges. Painful tonic spasms may respond to lidocaine, mexiletine, duloxetine, cannabinoids, carbamazepine, and gabapentin.

Treatment

Given the difficulty in diagnosis of MS-related CP and lack of randomized, controlled studies or large retrospective studies in MS, much of the therapeutic approach for MS-related CP is based on clinical experience and expert consensus.

Tricyclic Antidepressants

Tricyclic antidepressants such as amitriptyline, clomipramine, and imipramine inhibit presynaptic reuptake of norepinephrine and serotonin and are of proven benefit in patients with MS-related central pain. Although no randomized studies have evaluated amitriptyline in MS-related central pain, evidence from effectiveness of amitriptyline in central poststroke pain, postherpetic neuralgia, and painful polyneuropathy, has led to amitriptyline being considered among the first-line agents for MS-related CP.

SSRI/SNRI

In a randomized placebo-controlled trial in which 18 patients with MS-related CP received the serotonin-norepinephrine reuptake inhibitor duloxetine, there was a significant reduction in the average and worst pain in patients with MS. Four patients discontinued the medication due to side effects; in others the analgesic effect of duloxetine was evident by 4 weeks of treatment. Other selective serotonin inhibitors or serotonin-norepinephrine reuptake inhibitors have not been studied in MS-related CP. Duloxetine and venlafaxine may be effective in the treatment of painful dysesthesias and other central pain syndromes in MS.

Antiepileptics

Carbamazepine is useful in treating trigeminal neuralgia associated with MS as well as painful tonic spasms. In a study evaluating the effect of carbamazepine in 21 patients, the majority of patients achieved effect control of paroxysmal symptoms. High rates of adverse effects and discontinuation have been noted in patients taking carbamazepine requiring dose reduction or switching to an alternative medication. Although oxcarbazepine has not been well studied in MS-related CP, based on evidence available for management of other neuropathic pain conditions, it may be considered in MS-related CP.

Gabapentin was studied in 25 patients with paroxysmal symptoms of MS, of which 12 had dysesthetic symptoms, 6 had painful tonic spasms, 6 had trigeminal neuralgia, and 1 had a neuropathic itch. Seven of the 12 patients with dysesthetic symptoms had complete resolution of their symptoms, and all patients with painful tonic spasms had complete resolution of symptoms within 3 months. A second study evaluating MS-related CP found moderate to excellent relief of pain in a 15 of 25 of patients, with 5 other patients requiring discontinuation due to adverse effects of somnolence or dyspepsia. Given its proven efficacy in MS as well as other neuropathic pain conditions, gabapentin may be considered a first-line agent in the treatment of MS-related CP.

Pregabalin was effective in 9 of 16 patients with paroxysmal pain symptoms at a mean dose of 154 mg. Three patients required discontinuation of the medication due to dizziness or malaise. A smaller case series also demonstrated effectiveness of pregabalin in MS-related pain.

In the only randomized double-blind placebo-controlled crossover study of lamotrigine in patients with central pain in MS, there was no significant difference between lamotrigine and placebo in pain control. Another study conducted in Italy found that lamotrigine may be helpful as an adjunct to painful phenomena in MS, and pain relief may continue to be effective in approximately half of the population after 1 year. Most of the patients in this study requested drug discontinuation after a year. Lamotrigine is possibly helpful in relieving central pain in MS but may have limited efficacy and likely is useful only as an adjunct, based on the available evidence.

Levetiracetam works by modulating neurotransmitter release via binding to the vesicle protein SV2A. It has the benefit of less severe and lower rates of adverse effects compared to most other antiepileptic medications. In a randomized, placebo-controlled trial of levetiracetam in central pain in MS, there was no significant reduction in pain found in 27 patients who received a maximum dose of 3000 mg daily; however patients with lancinating pain or absence of touch-evoked pain showed improvements in pain.

Tiagabine, a selective GABA transporter inhibitor, was successful in treating four of seven patients with painful tonic spasms at a mean dose of 12.8 mg. Other antiepileptics such as phenytoin may also be considered in MS-related CP. Topiramate

has been reported to be effective in treatment of painful tonic spasms in case reports. Overall, antiepileptics are likely at least partially effective in treating central pain in MS. However, intolerable side effects may contribute to difficulty in managing these patients with antiepileptics.

Intrathecal and Intravenous Medications

Intrathecal baclofen given into the L1-2 interspace in four patients with MS spinal lesions was shown to significantly reduce central pain. The use of intrathecal baclofen for central MS pain has limited evidence at this time and is considered experimental.

Opioids

Intravenous morphine has been studied in 14 opioid naive patients with MS-related CP in a non-randomized, single-blind placebo-controlled study. Four of 14 patients had greater than 50% pain reduction at high doses of morphine, indicating that central pain in MS is poorly responsive to intravenous morphine. There are currently no studies that evaluated the effect of other opioids such as tramadol, oxycodone, or hydrocodone in patients MS-related CP.

Anesthetics and Antiarrhythmics

Intravenous lidocaine at 6 mg/kg/h with mexiletine at 300–400 mg daily was very effective in treating 30 patients with painful tonic spasms, neuralgic attacks, and Lhermitte's sign. Effects were not lasting but more efficacious in relieving persistent symptoms as compared to intermittent ones [9].

Cannabinoids

The use of cannabinoids for treatment of various conditions such as treatment-resistant epilepsy has progressed significantly recently. Cannabinoids have been well studied in multiple sclerosis and have shown effectiveness.

A study evaluating a combination oromucosal spray of delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) used quantitative sensory testing and laser-evoked potentials and found that this combination may improve peripheral cold-sensitive receptors in patients with MS-related pain. A double-blind placebo-controlled crossover trial evaluating THC in 24 patients with MS-related CP also demonstrated a modest analgesic effect over placebo.

In a larger randomized study, combination oromucosal THC/CBD was compared to placebo in 66 patients over 5 weeks. At a dose of 10 mg, oromucosal THC/CBD spray improved pain severity but was associated with long-term memory problems. Sixty-four of these patients participated in an open-label extension trial but 46% of patients withdrew in the first year and 24% in the following year. In the 28 patients who completed the trial, mean pain rating at the end of the 2 years was 2.9 ± 0.8 compared with 3.8 of the last week of the 5-week randomized trial. Over 90% of patients experience adverse effects, two of which were severe. The majority of adverse effect was deemed to be mild to moderate in severity; dizziness and nausea were most common.

A phase III placebo-controlled study of cannabinoids in MS-related CP was performed in the United Kingdom in which 339 patients were randomized to THC/CBD oromucosal spray or placebo for 14 weeks, followed by an 18-week randomized withdrawal study. Overall, results of the study were equivocal, although there was an increased time to treatment failure in the THC/CBD group compared to placebo.

The role of cannabinoids in MS-related CP had proven efficacy and likely has a modest effect on pain. Cannabinoids may be considered as an adjunct treatment or for patients with refractory MS-related CP. Cannabinoids have also been shown to be effective in spasticity related to MS and may have multiple pain-relieving actions in a patient with MS.

Surgical and Neuromodulatory Pain Management Options

Small case series have shown that DBS may be effective for the treatment of trigeminal neuralgia in MS as well as MS-related tremor. Transcranial direct current stimulation studied in 16 patients with MS improved pain; however MS-related CP has not been specifically evaluated in studies. Furthermore, transcranial direct current stimulation may have positive effects on cognition, executive function, motor function, and fatigue. Given the limited studies, deep brain stimulation and motor cortex stimulation are not currently recommended for treatment of MS-related CP.

Transcutaneous spinal direct current stimulation studied in 33 patients in a double-blind sham-controlled design found an early effect, lasting greater than 1 month on central pain in MS. Most reports of spinal cord stimulation in MS-related pain have been case reports or small case series. The need for frequent MRIs in MS may hinder the placement of some devices in patients with MS. At the present time, there is insufficient evidence to recommend interventional or surgical techniques for the amelioration of CP in MS.

Alternative Therapies

A systematic review of transcutaneous electrical nerve stimulation (TENS) for patients with central pain in multiple sclerosis found it to be a safe and effective treatment for pain compared to placebo. Unconventional therapies such as tai chi,

psychotherapy (telephone self-management, hypnosis, and electroencephalogram (EEG)), biofeedback, and reflexology do not currently have sufficient evidence to recommend for MS-related CP.

Parkinson's Disease

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder resulting from the degeneration of dopaminergic neurons in the substantia nigra and dysfunction of the basal ganglia network with associated motor and non-motor (cognitive, mood, autonomic, sleep disturbances) symptoms. Multiple types of pain can occur in PD including most commonly musculoskeletal, radicular, or neuropathic pain, dystonic pain, akathitic discomfort, and least commonly central pain. Patients with Parkinson's disease are three times more likely to complain of back pain (74% of patients) and often may have related nocturnal pain related to immobility or restless leg syndrome. Comorbid conditions such as arthritis and lower extremity edema are not uncommon in this population. In a survey of patients with Parkinson's disease, pain was the sixth most troublesome symptom. Table 14.7 is a classification of pain in Parkinson's disease.

Epidemiology

Pain was part of the symptomology initially described in the "shaking palsy" by James Parkinson. Chronic pain affects about 40–60% of patients with Parkinson's disease. Exclusive prodromal premotor symptoms occur in over 20% of patients

Table 14.7 Classification of pain in Parkinson's disease

Pain type	Etiology	Comments
Nociceptive	Musculoskeletal	Rigidity, cramps, should pain
		Non-radicular back pain
		Dystonic pain
Neuropathic	Peripheral	Radicular
		Peripheral neuropathy
	Central	Pain prior to PD diagnosis
		Otherwise unexplained pain, often worse in more severe affected parkinsonian limbs
		Rare unexplained oral, abdominal, or genital pain
Miscellaneous	Akathisia	Off period, drug-induced
	Restless legs syndrome	

Adapted from PJ Blanchet, *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 2018

with PD, with pain being the most commonly reported symptom. Furthermore, in one study, unexplained pain was reported in 20% of patients 2–10 years prior to the onset of motor symptoms in PD. Chronic analgesic prescription use has also been reported to be higher in the Parkinson's disease population compared to the general population (33% vs 20%). In one study, 42% of patients had moderate-severe pain compared to the general European population of which 19% reported moderate to severe pain.

Central parkinsonian pain was first described by Achille Alexandre Souques in 1921. Prevalence of central PD pain ranges from 4.5 to 10%, although some studies have reported as high as 27%. The overall prevalence of central PD pain is likely underestimated as diagnostic criteria are not well defined and pain descriptions overlap with other types of pain seen in PD, specifically musculoskeletal pain. Central PD pain has a larger effect on cognition, communication, and activities of daily living compared to other causes of pain in PD.

Localization and Pathology

Braak's hypothesis of the stages of PD follows a caudo-rostral progression in the CNS with early involvement of the locus coeruleus and nuclei of the raphe. This is followed by involvement of the substantia nigra. Neuronal loss in PD occurs at multiple levels of the CNS and produces various functional changes.

Whereas central pain is a possible premotor symptom of PD, abnormalities in central sensory processing in patients with and without pain have been noted in PD. A study evaluating 20 patients with PD demonstrated functional reorganization of the pain processing matrix in pain-free PD patients. A high prevalence of reduced cold threshold, cutaneous allodynia, and altered pinprick threshold in PD patients with or without pain points to a possible dysfunction of central processing mechanisms in PD. Contrary to these findings, after excluding patients with polyneuropathy, a study comparing patients with PD versus controls found unaltered warmth and thermal thresholds, causing the authors to conclude that there was no specific sensory processing abnormality in early PD. Neurophysiologic studies have demonstrated abnormal nociceptive processing at the spinal level. Central pain may have different phenotypes as a result of variations in pathophysiology, and contribution of each mechanism continues to be investigated.

Premotor symptoms arising from degeneration of the brain stem monoamine system involving the serotoninergic nuclei of the lower raphe system and the locus coeruleus may contribute to early pain in PD. Intraneuronal Lewy bodies have been observed in the vagal nucleus and locus coeruleus in early PD. Additionally, the dopaminergic anti-nociceptive pathway in the ventral tegmental area which projects to the nucleus accumbens also degenerates and may contribute to pain in PD. Descending brain stem analgesic systems include the periaqueductal gray area, parabrachial area, and reticular formation which regulates spinal cord pain centers and is also dysfunctional in PD.

Dopamine has a wide effect on the brain through the cortico-basal ganglia-thalamic circuit and the modulation of the monoamine system. Central pain in PD has multiple possible pathophysiological mechanisms including abnormal supraspinal pain processing, dysfunction of the default mode network, imbalance between the medial and lateral pain systems, involvement of brain stem pain processing areas, and dopaminergic systems and their effect on the opioid system. Dysfunction of the basal ganglia affects the motivational, affective, emotional, and sensory discriminative processing of pain.

Rodent experiments have shown that dopamine is an essential neurotransmitter in the modulation of pain perception. Injections of toxin destroying the dopaminergic system in rats block opioid-induced analgesia, indicating an interaction of the basal ganglia with the opioid system.

Specific neurons in the substantia nigra, neostriatum, and pallidum may respond to nociceptive stimuli. Functional neuroimaging studies have demonstrated a role of the basal ganglia in integrating complex pain aversive maneuvers, emotional, cognitive, and autonomic responses to pain. The basal ganglia affect the emotional experience of pain through the sensorimotor cortex, the thalamus, and the salience network which consists of the dorsal anterior cingulate cortex, anterior insula, amygdala, ventral striatum, and substantia nigra. Some experiments have shown aberrant activation of cortical areas in pain-free PD patients.

Reorganization of pain-related brain areas has been found in PD, and imaging studies have shown a relative cortical thinning in multiple parts of the brain including the dorsolateral prefrontal cortex, orbitofrontal cortex, and posterior cingulate cortex. These areas are associated with the descending pain system, the emotional affective perception of pain, and the lateral sensory system. The medial pain system consists of brain stem regions and the midline thalamic nuclei and is also involved in the autonomic functions and emotional responses. The basal ganglia are connected to both of these systems, and imbalance between the two may be another contributing mechanism to central PD pain. Additionally, the presence of cortical Lewy bodies demonstrates primary pathology can directly affect cortical pain processing areas.

Patients developed higher pain threshold after levodopa administration as measured by the nociceptive flexion reflex, resulting in some to believe that the central PD pain is related to central dopaminergic deficiency. In humans, central PD pain more frequently occurs in “off” periods and may improve with dopamine. The insula, prefrontal cortex, and anterior cingulate cortex has been shown to have increased pain-evoked activity in PD, which can be attenuated by levodopa treatment.

Central pain in PD is likely the result of a combination of neuronal and network dysfunction. However, peripheral axonopathy with cutaneous denervation, off period mobility, and dystonic contractions may contribute to abnormal peripheral input. As with all central pain syndrome, peripheral etiology of pain should always be considered and subsequently treated to help maximize chances of adequate central pain management. Table 14.8 summarizes Lewy body pathology potentially contributing to parkinsonian pain.

Table 14.8 Lewy body pathology potentially contributing to parkinsonian pain

Site	Nuclei	Braak's stage	Comment
Cortex	Dorsolateral prefrontal cortex Orbitofrontal cortex Insula	5–6	Impairment in descending pain modulatory system Impaired emotional evaluation of painful stimuli Abnormal sensory discriminative processing of pain
Medial temporal lobe	Amygdala	4	Impaired emotional evaluation of painful stimuli (with orbitofrontal cortex)
Diencephalon	Intralaminar thalamic nuclei	4	Dopaminergic afferents (from midbrain, PAG, hypothalamus) modulate nociceptive response; connections with rostral anterior cingulate cortex involved in processing and suppression of affective dimension of pain
			Projections to anterior thalamus and cingulate cortex, reticular formation, and spinal cord, and
	Hypothalamus	3–4	Dense orexinergic projection to ventral tegmental area mediating antinociception
Brainstem	Substantia nigra pars compacta Ventral tegmental area	3–4	Ascending dopaminergic projections to medial nucleus accumbens, dorsolateral prefrontal cortex, anterior cingulate cortex; Descending antinociception to spinal dorsal horn
	Parabrachial area serotoninergic nuclei of the lower raphe system Magnocellular portions of the reticular formation	2	Impairment in descending pain modulatory system regulating medullary and spinal nociceptive inputs
Spinal cord	Nociceptive neurons of the dorsal horn (layer 1) Sympathetic and parasympathetic preganglionic neurons (layer 7)	2	Alteration (facilitation) in nociceptive input processing
Cutaneous nerves	Unmyelinated and sparsely myelinated A-delta and C afferent fibers to dorsal horn neurons (layer 1)	Early	Distal axonopathy producing abnormal primary afferent activity

Adapted from PJ Blanchet, *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 2018

Diagnosis

There are no definite criteria for the diagnosis of central pain in PD. The LANSS scale has been used to evaluate 1957 patients in the United Kingdom and is helpful to determine centrally generated pain in PD.

Central pain in PD is of variable quality and location and has occasionally been described as diffuse, aching, burning, or pins and needles. The pain should be unexplained by other causes, may be intermittent or constant, and is frequently localized. Central pain in PD may appear first on the side which motor symptoms first appear, become bilateral, but usually remains worse on the side of more severe motor symptoms. Central PD pain sometimes presents before the onset of motor symptoms but may occur at any time during the disease. Whereas central pain syndromes occur in an area of sensory deficit, this may not always be true in central PD pain. Central pain may be responsive to dopaminergic medication and may in some cases be more severe during "off" periods. Furthermore, central PD pain may be provoked by dopamine or dopamine agonist withdrawal.

Treatment

Management of central pain in Parkinson's disease is based on extrapolation of studies from other conditions and clinical experience. Pain management in PD consists of nonpharmacological agents (physical therapy, occupational therapy, physiotherapy, cognitive behavioral therapy), management of other pain conditions, treatment with adequate dopaminergic agents, pharmacologic agents for central pain, and lastly invasive procedures for pain relief.

First-line treatment of central parkinsonism pain is optimization of antiparkinsonian therapy. Treatment with the dopamine agonist rotigotine found a general improvement in PD-related pain compared to placebo in a study of 267 patients; however this study was not specific for central pain. Dopaminergic medications have been reported to improve the rare cases of genital pain in PD which is hypothesized to be central in nature. Treatment with antiparkinsonian medications is likely to improve musculoskeletal pain related to motor fluctuations and pain in situations where rigidity is driving nociceptive pain. It may be beneficial for patients to identify pain which is maintained or affected by dopamine levels, compared to dopamine-independent pain. Medications for Parkinson's disease include dopamine with peripheral decarboxylase inhibitors (carbidopa-levodopa), dopamine agonists (pramipexole, ropinirole), catechol-O-methyltransferase inhibitors (entacapone, tolcapone), anticholinergics (trihexyphenidyl), monoamine oxidase B inhibitors (selegiline, rasagiline), and NMDA antagonists (amantadine). There is evidence

that deep brain stimulation may be helpful for pain in Parkinson's disease; however this alone is not an indication for deep brain stimulation.

For pain that is not sufficiently controlled by antiparkinsonian treatment, administration of medications used for other neuropathic pain syndromes may be helpful. Anticonvulsants such as gabapentin, pregabalin, lamotrigine, and carbamazepine may be reasonable options in PD-related CP. Gabapentin has been shown to improve rigidity, bradykinesia, and tremor of PD. When selecting antidepressants, preference should be for medications with lower propensity to cause anticholinergic side effects, such as the tricyclic antidepressants nortriptyline and desipramine, or selective serotonin and norepinephrine reuptake inhibitors such as venlafaxine. Duloxetine is the only antidepressant studied for pain related to Parkinson's disease. In an open-label study of 23 patients with PD-related pain, 13 patients reported improved pain with duloxetine. Lastly, opioids may be considered in refractory pain conditions, especially given that central opioid pathways may be affected in central PD pain. Small studies have evaluated cannabidiol and related compounds in Parkinson's disease, but evaluation of central pain in these small studies is lacking.

Patients who have undergone deep brain stimulation for PD have had immediate and long-term improvements in pain. The precise mechanism of pain relief through deep brain stimulation remains unclear; however subthalamic nucleus DBS has been shown to improve pain up to 8 years after initial implantation. Studies evaluating the effect of DBS again did not specifically evaluate central pain, and some pain relief may have been secondary to motor improvements and reduced rigidity. At this time, there is insufficient evidence to recommend deep brain stimulation for central Parkinson's pain.

Ultimately, effective management of central pain in Parkinson's disease relies on optimization of antiparkinsonian's medication, exercise programs, and treatment with anticonvulsants or antidepressants. Exercise may reduce stiffness and postural abnormalities and may recruit inhibitory pain pathways.

Traumatic Brain Injury

Introduction

Traumatic brain injury (TBI) is altered brain function that results from acceleration or deceleration of brain matter inside the skull or from direct penetrating injury. Acceleration and deceleration movements cause stretching and tearing of axons, focal cerebral contusions, and diffuse axonal injury. Repeated head injury has been associated with chronic traumatic encephalopathy in patients who play contact sports or soldiers exposed to blast injuries. TBI can be divided into mild, moderate, or severe based on clinical characteristics including loss of consciousness, amnesia, brain imaging, and the Glasgow coma scale. Immediate effects of a traumatic injury may be related to the primary injury such as hemorrhages, diffuse axonal injury,

countercoup movements, blast waves, and penetrating injury. Delayed or secondary injury occurs later due to disrupted cerebral autoregulation, elevated intracranial pressure, Wallerian degeneration, and hypoxia.

Epidemiology

Approximately 1.7 million Americans suffer from TBI annually. Pediatric TBI (ages 0–4) is commonly due to assault or motor vehicle accidents. Young adults and middle-aged persons are likely to suffer from TBI due to motor vehicle accidents or self-inflicted injuries such as from sports injuries, and older patients (>65 years) are more likely to suffer from falls. Available data indicate that the incidence of central pain in mild TBI may be as high as 68%.

Pathogenesis

Few studies have been performed specifically evaluating central pain in TBI. Altered pain perception and central pain mechanisms in TBI are directly related to the injured area. Multifocal axonal injury, microglial activation, microhemorrhages, amyloid, and tau aggregation all contribute to pathology in TBI. Some evidence indicates that post-concussive headaches after TBI are related to changes in central pain processing areas. Patients with TBI have altered supraspinal pain perception due to dysfunctional pain modulation in the thalamus, pons, anterior cingulate, insular, and dorsal lateral prefrontal cortex. Axonal injury and resulting Wallerian degeneration after mild TBI may contribute to decreased functional connectivity in white matter tracts involved in pain modulation in patients with chronic headaches after mild TBI. Furthermore, patients with mild TBI and persistent headache have also been shown to have hypoperfusion of the basal ganglia.

Involvement of the descending pain pathways from the periaqueductal gray area has also been shown to correlate with central pain following TBI. Release of pain-modulating molecules such as N-acetylaspartylglutamate (NAAG) which is co-expressed with glutamate and inhibits its release plays a protective role against astrocyte cell death and is altered in patients with TBI.

Specific characteristics of central pain after traumatic brain injury is lacking in medical literature. However central pain after TBI has been reported to develop weeks to months after the initial injury and then persists with fluctuating intensity. Evidence of central sensitization phenomena such as allodynia, hyperpathia, and wind-up sensations is often present in patients with TBI-related CP.

Treatment of central pain in traumatic brain injury has not been widely studied. Management approach is similar to that of central pain of other origins. Small studies evaluating neuromodulatory techniques such as transcranial magnetic stimulation indicate the potential use of these approaches in the future.

Treatment Review

Table 14.9 summarizes medications for management of central pain syndromes.

Table 14.10 summarizes neuromodulatory options for management of central pain syndromes.

Phantom Limb Pain

Introduction

Phantom limb pain (PLP) and sensations are feelings that the missing or amputated limb or organ is present and may be related to cortical sensory perception of an amputated body part. It occurs in up to one fifth of patients with congenital limb aplasia. In addition to pain after amputation of a limb, PLP may arise after surgical removal of the eye, tongue, teeth, breast, rectum, penis, or testicles.

Although not a primary central pain syndrome, maladaptive changes in the peripheral and central nervous system occur after amputation which may contribute to pain. It remains unclear why a small proportion of patients remain pain-free postamputation.

Epidemiology

Limb amputations are commonly a result of vascular disease (often diabetes mellitus related), trauma, or cancer. Patients with cancer often lose their limbs at a younger age (average 30 years) compared to those with amputations secondary to dysvascular disease (average 52 years). Patients older than 65 years have a significantly higher risk of amputation, especially related to vascular disease. Pain and depression are the most common secondary results of limb loss. There is a higher rate of depression associated with traumatic amputation compared to patients with dysvascular- or cancer-related causes of amputation.

Pain in the non-amputated limb is most common in patients with vascular disease. Approximately 80% of amputees have PLP, with an average pain level of 5.5 on the visual analog scale, and it significantly interferes with daily living in four fifths of patients. In one study of patients with amputees approximately 10 years prior, nearly all patients experienced some form of amputation-related pain within the last 4 weeks, with PLP being the most common type of pain. Three quarters of patients with amputations over 10 years ago have PLP.

Table 14.9 Summary of medications for management of central pain syndromes

	Efficacy								
Drug	Central pain	Poststroke	Spinal cord injury	Multiple sclerosis	Parkinson's disease	Level of evidence	Mechanism of action	Side effects	Comments
Antiepileptics									
Pregabalin	✓	✓	✓		–	Stroke: 1, 2b SCI: 1 MS: 3	Binds to presynaptic α-2-δ subunit of voltage-gated calcium channels and inhibits release of excitatory neurotransmitters (glutamate, 5HT, NE)	Dizziness, drowsiness, somnolence, edema, weight gain, blurred vision	1st line: Stroke 1st line: SCI, best evidence in SCI MS: Paroxysmal symptoms
Gabapentin	✓	✓	✓		–	Stroke: 2 SCI: 1	As above	Dizziness, drowsiness, fatigue, ataxia, edema, blurred vision	1st line: Stroke
Lamotrigine	✓	✓	✓	–	–	Stroke: 1 SCI: 1 MS: 1	Inhibits voltage-sensitive sodium channels, inhibits release of glutamate, weak inhibitor of 5HT3 receptor	Stevens-Johnson syndrome, nausea, insomnia, drowsiness, dizziness	1st or 2nd line: Stroke SCI: 2nd line 2nd line: TN MS: Consider as adjunct

(continued)

Table 14.9 (continued)

	Efficacy								
Drug	Central pain	Poststroke	Spinal cord injury	Multiple sclerosis	Parkinson's disease	Level of evidence	Mechanism of action	Side effects	Comments
Carbamazepine (may consider replacement with oxcarbazepine)	✓	✓	–	✓	–	Stroke: 1 – not significantly effective ($n = 14$); 2b SCI: 4 MS: 3	Inhibits voltage-sensitive sodium channels, anticholinergic, muscle relaxant activity, decreases synaptic transmission and thalamic potentials	Dizziness, drowsiness, ataxia, nausea, vomiting, dry mouth, Stevens-Johnson syndrome (especially with HLA-B1502), aplastic anemia	Stroke: Adjunct medication 1st line: TN, glossopharyngeal neuralgia, painful tonic spasms
Topiramate	–	×	–	–		Stroke: 4 SCI: 4 MS: 4	Blocks voltage-sensitive sodium channels, enhances GABA activity, antagonizes glutamate receptors, weak inhibitor of carbonic anhydrase	Paresthesia, fatigue, anorexia, memory impairment, metabolic acidosis, renal stones, fetal toxicity, acute myopia	
Zonisamide		✓				Stroke: 4	Stabilization of neuronal membrane via sodium and calcium channel actions, weak inhibitor of carbonic anhydrase	Drowsiness, dizziness, anorexia, headache, nausea	

Levetiracetam	–	×	×	–		Stroke: 1 SCI: 1 MS: 1	SV2A binding modulating neurotransmitter release	Increased diastolic BP, behavior problems, headaches, drowsiness, vomiting	
Valproate		–	×			Stroke: NS SCI: 1	Increases GABA, blocks voltage-sensitive sodium channels	Elevated LFTs, headache, alopecia, nausea, thrombocytopenia, tremor	
Phenytoin		–	–	–		Stroke: 4 SCI: NS MS: 2b	Blocks sodium channels	Cardiac arrhythmia, ataxia, dizziness, confusion, nystagmus	MS: Painful tonic spasms
Tiagabine				✓		MS: 3	Possibly reduces presynaptic reuptake of GABA	Dizziness, drowsiness, nausea, infection, tremor, suicidal behavior	Painful tonic spasms; 12.8 mg mean dose
Antidepressants									
Citalopram (other SSRIs)		×							
Tricyclic antidepressants									
Amitriptyline	✓	✓	✓	✓		Stroke: 1 SCI: 1 MS: 2b	Inhibits reuptake of serotonin and norepinephrine at the presynaptic membrane	Drowsiness, dry mouth, constipation, urinary retention, orthostatic hypotension, sedation, atrioventricular block	1st line: Stroke 1st line: MS 1st line: SCI
Desipramine, imipramine, clomipramine, doxepin	–	✓	–	✓		Stroke: 2b SCI: 2b MS: 2b	As above	As above	Stroke: May be considered SCI: No significant effect

(continued)

Table 14.9 (continued)

	Efficacy								
Drug	Central pain	Poststroke	Spinal cord injury	Multiple sclerosis	Parkinson's disease	Level of evidence	Mechanism of action	Side effects	Comments
Nortriptyline	✓	✓	✓	✓	–	Stroke: 2b SCI: 2b MS: 2b			Stroke: Based on class action
SNRIs									
Venlafaxine	✓	✓	–	✓	–	Stroke: 2b MS: 2b	Inhibitor of serotonin and NE reuptake, weak inhibitor of dopamine reuptake	Insomnia, dizziness, drowsiness, nausea, dry mouth	2nd line: SCI
Duloxetine	✓	✓	–	✓	✓	Stroke: 2b SCI: 1 MS: 1 PD: 2	As above. No anticholinergic activity	Headache, nausea, dry mouth, weight loss	Stroke: May be considered SCI: Some effect, may be considered
Trazodone		–	×			Stroke: NS SCI: 1	Inhibits reuptake of 5HT, blocks histamine and α-1 adrenergic receptors	Drowsiness, dizziness, headache, dry mouth, blurred vision	
Intravenous infusions/miscellaneous drugs									
Lidocaine	✓	✓	✓	✓		Stroke: 2 (n = 16) SCI: 2 MS: 3	Prolongs inactivation of voltage-gated sodium channels	Headache, shivering, cardiac arrhythmia, agitation, seizure	Stroke: IV MS: IV, short-acting effects, more effective for persistent symptoms

Mexiletine	✓	✓	✓			Stroke: 2 (n = 16) SCI: 2	Prolongs inactivation of voltage-gated sodium channels	Cardiac arrhythmia, dizziness, ataxia, GI distress, tremor, nausea/vomiting	Stroke: Adjunct
Ketamine	–	–	✓	–		Stroke: 4 SCI: 1 MS: 4	NMDA antagonist	Cardiac arrhythmia, hypertension, hypertonia, vomiting	Stroke: One case report SCI: Epidural ketamine
Clonidine			×			SCI: 1	A2 adrenoceptor agonist, may affect excitability of dorsal horn neurons	Drowsiness, headache, skin rash, contact dermatitis, dry mouth	Intrathecal may be helpful
Baclofen	–	–	–	–		Stroke: NS SCI: 1 MS: 3	Inhibits mono- and polysynaptic reflexes at spinal cord level	Hypotonia, drowsiness, confusion, seizure	
Tramadol	✓	✓	–	–		Stroke: 3 SCI: 1 MS: NS	Opioid antagonist with effect on 5HT and NE reuptake	Nausea, constipation, dizziness, vertigo, constipation, dry mouth, somnolence, hyperhidrosis	
Morphine		×	×	×		SCI: 1 Stroke: NS MS: 3	Opioid antagonist, more selective for mu receptor	Drowsiness, constipation, headache, urinary retention	Intrathecal may be helpful

(continued)

Table 14.9 (continued)

	Efficacy								
Drug	Central pain	Poststroke	Spinal cord injury	Multiple sclerosis	Parkinson's disease	Level of evidence	Mechanism of action	Side effects	Comments
Thiopental		×				Stroke: 4	Barbiturate: binds chloride channel of GABA-A receptor	Respiratory depression, bronchospasm, shivering, myocardial depression	
Propofol		×				Stroke: 4	Sedative-hypnotic, GABA-A agonist and blocks NMDA receptors	Hypotension or hypertension, apnea, involuntary body movements, hypertriglyceridemia	
Methylprednisolone		✓	×			Stroke: 3 ($n = 8$) SCI: NS	Inhibits inflammation, regulates gene expression; wide variety of actions	Agitation, bradycardia, skin rash, hyperglycemia, fluid retention, hepatomegaly, infections	Stroke: One small study suggested a role
Cannabinoids									
Cannabidiol + tetrahydrocannabinol	–			✓		MS: 1	Bind to CB1 and CB2 cannabinoid receptors, activation of 5HT and vanilloid receptors, antagonize opioid receptors	Weight loss, hematologic changes, somnolence, decreased appetite, elevated LFTs	MS: oromucosal spray studied, adjunct treatment

Tetrahydrocannabinol	–		–	✓		SCI: 3 MS: 1	Bind to CB1 and CB2 cannabinoid receptors	Weight loss, hematologic changes, somnolence, decreased appetite, elevated LFTs	
Antiparkinsonian drugs									
Levodopa	×				✓	PD: 1	Converted to dopamine after crossing blood-brain barrier	Orthostatic hypotension, dizziness, nausea, constipation, dyskinesia	
Rotigotine	×				✓	PD: 1	Dopamine agonist	Hypotension, orthostatic hypotension, drowsiness, dizziness, fatigue	

Level of evidence:
1: One or more randomized controlled trials, meta-analysis or systematic review
2: Open-label trials, prospective studies
2b: Expert opinion/adaptation from other conditions or due to class action
3: Retrospective studies
4: Case reports, small case series; NS: not studied

Efficacy
✓: Likely effective
–: Limited or no evidence, possibly effective, or limited efficacy
×: Should not be used or probably ineffective

Table 14.10 Summary of neuromodulatory options for management of central pain syndromes

	Efficacy					
	Poststroke	Spinal cord injury	Multiple sclerosis	Parkinson's disease	Level of evidence	Comments
Motor cortex stimulation	✓	–	–	–	Stroke: 3 SCI: 1 PD: 3	SCI: Refractory, long-term effectiveness unclear
Transcranial magnetic stimulation	✓	–	–		Stroke: 2	
Direct current stimulation		–	–		MS: 2b	MS: CP pts did not all have MS
Spinal cord stimulation	✓	✓	–		Stroke: 3 SCI: 3 MS: 2	SCI: Refractory cases; most helpful if incomplete lesion Stroke: Experimental MS: Likely effective, MS pts in study did not have specified CP syndrome
Deep brain stimulation	✓	×	×	✓	Stroke: 3 SCI: 1 MS: 4 PD: 2	SCI: Refractory Stroke: PVG, PAG, thalamus MS: Possible role in TN, tremor PD: No studies specifically evaluating pain, CP alone is not an indication for DBS
Transcutaneous electrical nerve stimulation	–	✓	✓	–	Stroke: 3 SCI: 3 MS: 1	
Acupuncture	–	–				

Level of evidence:
1: One or more randomized controlled trials, meta-analysis or systematic review
2: Open-label trials, prospective studies
2b: Expert opinion/adaptation from other conditions or due to class action
3: Retrospective studies
4: Case reports, small case series; NS: not studied

Efficacy
✓: Likely effective
–: Limited or no evidence, possibly effective, or limited efficacy
×: Should not be used or probably ineffective

Localization and Pathology

Pathology of phantom limb pain is not well understood but likely results from a combination of peripheral and central nervous system (spinal cord, thalamus, and cerebral cortex) changes. Modulation of ectopic peripheral impulses from reorganized nerve endings and changes in neuronal thresholds in the peripheral nervous system may drive PLP. Peripheral nociceptor activity from the residual limb or dorsal root ganglion alters pain pathways and results in central sensitization. In one study, brachial plexus anesthesia resulted in partial relief of PLP indicating a central mechanism which likely contributes to PLP as well. Successful improvements in pain with mirror therapy indicate that cortical remapping is an important central mechanism of pain with therapeutic implications.

After amputation of a limb, spinal cord and peripheral nerve sprouting results in changes such as hyperexcitability, enlargement of the receptive field, and increase in neuronal activity. There may be selective loss of C fibers of peripheral neurons. Multiple sprouts can grow out from each cut neuron and travel in many different directions. Many sprouts degenerate, but the few that remain may form a neuroma. These abnormal growths or thickening of nerves may act as a peripheral pain generator and a source of ectopic impulses. Lidocaine injections into these neuromas have been shown to modulate, but not abolish, PLP.

Changes in the synaptic structure of the dorsal horn are induced by activity of peripheral nociceptors. The dorsal root ganglion has been shown to be a site of ectopic discharge. There is also increased synaptic activity between the first- and second-order neurons in nociceptive pathways. Together, net activity from the spinal cord results in downregulation of opioid receptors, increased excitatory signaling mainly of glutamate, and reduced inhibitory signaling mainly of GABA. These changes in addition to deafferentation effects result in central sensitization.

Sympathetic abnormalities and dysregulation have been shown to be associated with PLP, with some evidence of its role in stimulating and maintaining PLP. Electrical and mechanical stimulation of the sympathetic chain has been shown to cause severe pain in the phantom limb. Moreover, emotional distress may trigger increased amounts of epinephrine and increased activity from neuromas.

Cortical remapping of the primary somatosensory cortex in response to maladaptive neuroplasticity plays an important role in PLP. Body image processed by the brain is a dynamic and plastic process that is continually modified and updated. Neuroplasticity results in reorganization of somatic sensory maps due to conflicting visual input from the mental body representation, lack of normal sensory activity of the area involved (deafferentation), and abnormal ectopic peripheral discharges. This results in a redistribution of computational resources of the brain with cortical invasion of the amputated limb by other normal body structures, often by the nearby somatosensory cortex representing the mouth region. Stimulation of the mouth in patients with upper limb amputations has been shown to activate neurons in the somatosensory cortex previously representing the amputated limb. Similar changes in the functional and structural architecture of the primary somatosensory cortex have been demonstrated in monkeys. Multiple, but not all, studies have demonstrated that the extent of cortical reorganization is directly correlated to the degree

of PLP as well as the size of the amputated limb. The efficacy of transcranial magnetic stimulation in relieving pain in PLP provides further evidence of the important role of the somatosensory cortex in PLP.

In addition to cortical remapping, other important central changes are seen in patients with PLP. Gray matter volume is increased in pain processing areas such as the cingulate cortex. Strong cortical connections with the thalamus result in enlarged representation of the residual limb in the thalamus. Studies in monkeys have revealed that cortical changes may be induced by the brain stem and thalamus.

It remains unclear whether the cortical changes represent a "bottom-up" or "top-down" changes. Cortical changes have been reversed by elimination of peripheral input from brachial plexus anesthesia. Acute and chronic PLP possibly have differing mechanisms indicated by the sudden changes in pain ratings within the first year. Ultimately, PLP is a result of structural and chemical changes that may be maintained by varying degrees of abnormal peripheral input from the missing limb and central cortical changes. Figure 14.10 illus-

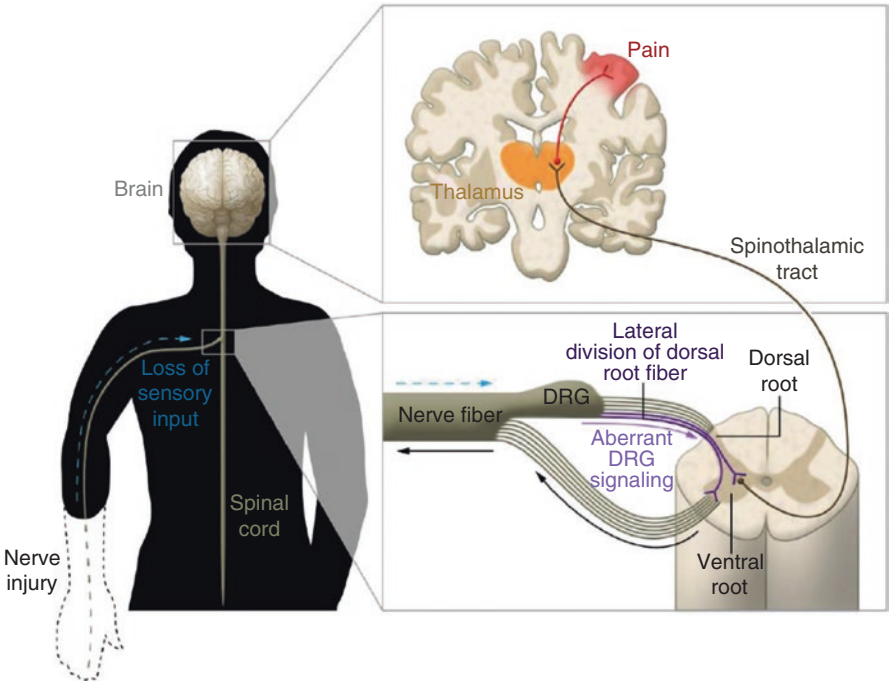

Fig. 14.10 Proposed peripheral contributions to phantom limb sensations and phantom limb pain. When an injury occurs to the nerves, neurons in the dorsal root ganglion (DRG) increase their nociceptive signaling through increases in neuronal excitability and the creation of ectopic discharges. The resulting aberrant signaling through the spinothalamic tract may produce PLP. Pathway: the dorsal root fibers of the DRG split into medial and lateral divisions. The lateral division sections contain most of the unmyelinated and small myelinated axons and specifically carry pain and temperature information. The medial division sections of the dorsal root fibers (not shown) contain mostly myelinated axons that convey sensory information from the skin, muscles, and joints, such as touch, pressure, proprioception, and vibration. (Adapted from KL Collins, Journal of Clinical Investigation, 2018)

trates proposed peripheral contributions to phantom limb sensations and phantom limb pain.

Figure 14.11 illustrates cortical changes associated with phantom pain.

Diagnosis

PLP is very common in patients with amputations with a bimodal incidence days to weeks after the initial injury (45–85%) and approximately 1 year later. Phantom limb sensations are often accompanied with PLP, although they may occur independently. Patients with phantom limb sensations are more likely to develop PLP. Approximately half of amputees have pain in the non-amputated limb, with an average intensity of 4.6 on the visual analog scale. Some studies have reported that PLP dissipates or disappears in some patients, although many studies have reported patients that have high rates of PLP in the long term.

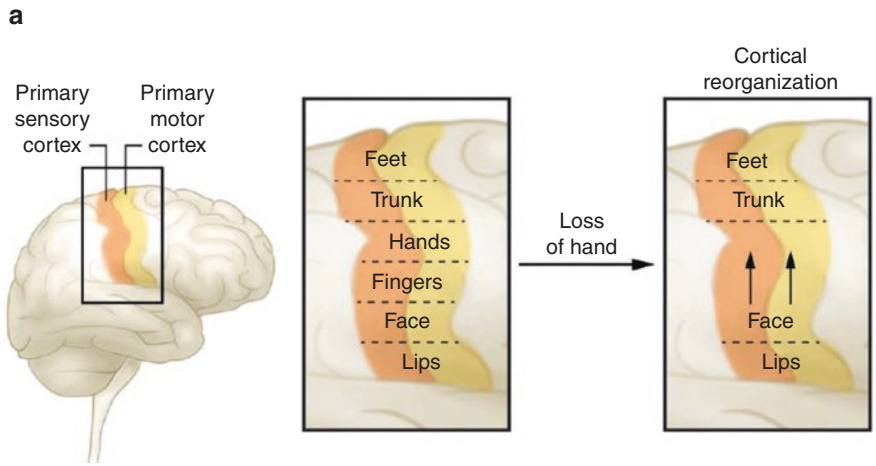

Fig. 14.11 (**a**) Body part sensory and motor representation is laid out in a pattern that forms the cortical homunculus and receives sensory information from different areas of the body. Following amputation, a cortical region that received sensory or motor projections from the amputated limb may begin to receive sensor or motor input, respectively, from neighboring cortical regions, which expand to take over the region that previously controlled the amputated limb. (Adapted from KL Collins, Journal of Clinical Investigation, 2018). (**b**) Assessment of reorganization of the primary somatosensory cortex in an individual with amputation of the arm and phantom limb pain. Neuromagnetic source imaging was used to define the localization of the hand and mouth regions on the cortical hemisphere contralateral to the intact side and of the mouth region on the hemisphere contralateral to the amputation side. Magnetic fields evoked by pneumatic stimulation of the fingers of the intact side and the corner of the mouth on both sides were integrated with structural magnetic resonance images. The localization of the intact hand was then transposed to the side contralateral to the amputation (with the assumption of a symmetrical localization of the somatosensory homunculus) to assess where the former hand region was localized. The mouth representation on the amputated side has completely invaded the hand region. The amount of shift can be identified by calculating the Euclidean distance between the mouth and the hand region. The larger this disease (red arrow) the greater the cortical reorganization. (Adapted from H Flor, Lancet Neurology, 2002)

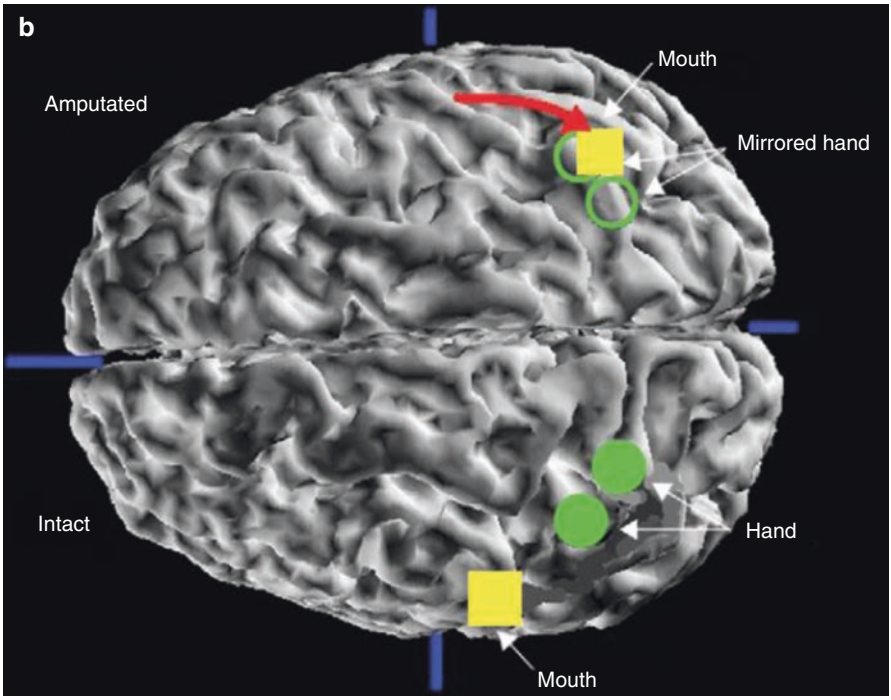

Fig. 14.11 (continued)

PLP is often described as shooting, squeezing, burning, stabbing, pressure-like, or aching pain and often involves distal parts of the missing limb. Pain is often intermittent but can be continuous as well, may vary in intensity, and may have specific triggers such as weather. Risk factors for PLP include female sex, upper limb amputation, and the presence of preamputation pain in the limb.

Treatment

Several studies have shown that current pharmacological treatments for PLP are ineffective in providing significant pain relief. Given the pathophysiology, unconventional treatment methods with the understanding of neuroplasticity and memory formation have been developed to treat PLP. Studies comparing treatments for phantom limb pain have been limited by sample size.

Gabapentin has been studied in a few randomized controlled trials with mixed results. In a crossover placebo-controlled trial of 24 patients, gabapentin produced a meaningful reduction in pain in half of the patients, but there were no significant differences between pre- and posttreatment pain scores. Gabapentin was shown to

be superior to placebo in a smaller study of 19 patients and reportedly also abolished PLP in 6 of 7 children. Additionally, administration of gabapentin prior to amputation in children may have a role in prevention of PLP. Pregabalin has not been studied in PLP.

Although anti-seizure medications are frequently used for PLP, topiramate is the only anticonvulsant that has been studied for PLP, in a case series of four patients. Three of these patients achieved significant pain relief at 14 weeks.

Ketamine, an NMDA antagonist, has also been studied in PLP and may have short-term effects in relieving PLP. Memantine, a NMDA agonist, may also have a role in short-term and subacute PLP but has been ineffective in treating chronic PLP.

Tricyclic antidepressants may be the first line for neuropathic pain, but there are limited studies in PLP. One study compared amitriptyline, tramadol, and a placebo in 94 patients and found excellent and stable phantom limb pain control with amitriptyline and tramadol. Based on this, both amitriptyline and tramadol may be considerations in the management of PLP.

Opiates may affect cortical reorganization in PLP and thus may have a role in the treatment of PLP. Intrathecal morphine and bupivacaine and intramuscular botulinum toxin have limited evidence for efficacy in PLP. Intravenous morphine was compared to lidocaine and mexiletine in two different studies which revealed decrease in intensity of postamputation pain. A randomized controlled study of 60 patients evaluated slow release morphine and found significant pain relief in more than half of patients at 2 months.

Calcitonin has produced mixed results in the treatment of PLP but may have a role in the early postoperative period. Dextromethorphan was also studied in ten patients with PLP secondary to cancer-related amputations, with over half of the patients experiencing benefit from pharmacological therapy.

In cases of elective amputation, therapies to prevent PLP have been investigated. Epidural anesthesia started before and continuing up to days after amputation may confer some protection from PLP, although a few studies have found this to be ineffective. Definitive evidence on the optimal method to prevent or minimize the incidence of PLP is lacking.

Interventional pain techniques such as injection of lidocaine in to the dorsal root ganglion or perineuromal region have been show to transiently relieve PLP. These techniques require continuous infusion or repeated injections to achieve pain relief. However, peripheral block of peripheral nervous system impulses is a potential target for pain relief, given the contribution of PLP by ectopic peripheral discharges. Case reports and a small case series have found transcranial magnetic stimulation to be helpful in improving chronic PLP. Other techniques such as deep brain stimulation, motor cortex stimulation, dorsal root entry zone lesions, sympathectomy, and rhizotomy have limited evidence and are considered experimental.

Given the role of visual input in the development of PLP and memory-based pain, mirror therapy and other forms of sensory-motor training such as motor imagery

have been developed to help relieve PLP. Mirror therapy (MT) is a cheap, noninvasive modality that aims to trick the brain into perceiving movement of the phantom limb when the intact limb is moved and has been extensively studied in PLP. The first randomized sham-controlled study of MT was effective in reducing PLP in 93% of patients. Patients who practiced MT had greater pain relief than patients who only visualized movement of the phantom limb. Furthermore, time to pain relief in MT has been shown to be dependent on initial pain severity. A Cochrane analysis from 2018 concluded that MT reduced duration and intensity of pain and is effective in relieving PLP. Some studies have suggested that MT may reverse postamputation cortical remapping to its original cortical homunculus. Patients with bilateral amputations may benefit from viewing other people's limbs moving in the same way as their phantom limbs. Motor imagery has been shown to be effective in improving pain in PLP as it shares the same neural networks involved in motor execution. It has the added advantage of being cheap and can be practiced anywhere.

Virtual reality provides another avenue for patients with PLP to imagine movement of their limbs. Virtual reality provides a more immersive environment than MT, can be customized, and has been shown to reduce intensity and quality of pain in 14 patients who underwent twelve 2-hour sessions over 6 weeks. Virtual reality may be more effective for PLP related to distorted phantom limb movement and body representations as opposed to typical neuropathic sensations. Visual motor training in PLP seems to be a very beneficial technique in improving pain and, given its effectiveness, should be utilized in all patients with PLP.

Other Syndromes with Central Pain Mechanisms

Multiple conditions can have central pain mechanisms which do not account for the full central pain syndrome. Here, we discuss less well-studied causes of central pain, in addition to conditions which are partly contributed to by central pain mechanisms and central sensitization. Approach to management of central pain remains similar, despite the different etiologies.

Syringomyelia

Syringomyelia, similar to other spinal cord lesions, may result in central pain syndromes. Syringomyelia is a longitudinal fluid-filled cyst within the spinal cord which may be caused by multiple causes, including trauma or tumors of the spinal cord. Evidence indicates that the severity of structural damage, especially white matter in the spinal cord influences the type and intensity of central pain in these patients. Changes in the prefrontal cortex activated by pathological pain suggest that supraspinal pain modulation plays a role of syringomyelia-induced allodynia.

Other Conditions

Central lesions such as acute disseminated encephalomyelitis (ADEM), neuromyelitis optica (NMO), transverse myelitis, spinal and cerebral vascular malformation, abscess, and tumors of the spinal cord and brain may result in central pain syndromes. Understanding the mechanisms of central pain remains a challenge given the significant heterogeneity of the presentation and etiology.

Central pain has been reported to be a manifestation of partial epileptic seizures. However, the exact mechanism of this remains unclear; a study of 127 patients with somatosensory epilepsy found no correlation with painful epileptic seizures. Postoperative central pain has been reported in a patient after spinal cord tumor resection. A diffuse glioma involving the thalamus and extending into the brain stem has also been reported to cause central pain. Abscesses from tuberculous vasculitis, toxoplasmosis, and syphilitic myelitis have also been reported to cause central pain.

Central Sensitization and Its Role in Pain

Central sensitization is an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subnormal input. Central sensitization may be driven by chronic peripheral nociceptive input and from the dorsal root ganglion but is also characterized by reduced inhibition of descending pathways and altered central sensory processing in the forebrain and brain stem. Peripherally, glutamate, substance P, and calcitonin-related gene peptide contribute to hyperexcitability in the dorsal root ganglion. Descending pain pathways may be modulated by levels of vigilance, attention, and stress. Syndromes with central sensitization have been associated with psychiatric conditions and early traumatic life experiences such as mental, physical, and sexual abuse. Given the stress associated with these conditions, dysregulation of the hypothalamic-pituitary axis, autonomic system, and immune system has been noted in patients with central sensitization. Clinical descriptions of central pain and central sensitization are similar. Pathological hyperexcitability of the central nervous system in central sensitization may be on a spectrum with central pain syndrome. Almost all patients with central pain syndromes experience symptoms of central sensitization, but the reverse is not true.

Clinically, central sensitization is characterized by allodynia, hyperalgesia, prolonged pain after the stimulus is abolished (aftersensations), temporal summation of impulses, expansion of the receptive field, dysregulation of the immune system, and structural changes in the central nervous system. This results in abnormal interpretation of pain in the pain centers of the brain including the rostroventral medulla, thalamus, and amygdala. This in turns leads to further stress and

propagation of central sensitization, making pain challenging to treat. Conditions commonly associated with central sensitization include migraine headaches, fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome. Below, we discuss a few of these conditions. (Please see headache chapter on management of migraine headache.)

Herpes zoster is caused by the resurgence of long-standing varicella zoster virus in a dorsal root ganglia. Postherpetic neuralgia is a neuropathic dermatomal pain that persists long after the initial herpetic rash has cleared. It commonly occurs in older patients, immunocompromised patients, and transplant patients. It represents decreased immune activity against a latent virus which may be triggered by emotional stress, changes in weather, or even physical trauma.

Although considered a peripheral pain syndrome, necrosis of the dorsal root ganglia results in downstream deafferentation affects. Ectopic peripheral discharges and inflammation may initiate and maintain central sensitization in these patients. Postherpetic neuralgia patients with sensory loss have increased spontaneous activity in deafferented central pathways. Reorganization of central pathways and decreased activity of white matter areas including the somatosensory cortex, precentral gyrus, amygdala, and parahippocampal region have been demonstrated in postherpetic neuralgia. Treatment options for PHN include gabapentin, pregabalin, topical lidocaine, and tramadol. Opioids, tricyclic antidepressants, and topical capsaicin may also be tried.

Fibromyalgia is another condition with altered central pain processing and central sensitization. It is common in young to middle-aged women and is characterized by widespread musculoskeletal pain and fatigue, which may be accompanied by cognitive dysfunction. Patients with fibromyalgia have chronic pain and are more likely to have other pain conditions such as headaches, TMJ disorder, chronic fatigue syndrome, irritable bowel syndrome, interstitial cystitis, and dysmenorrhea. Primary disturbances in central pain processing and central sensitization likely play a role in the hypersensitivity to pain in fibromyalgia. These conditions may have pathological central sensitization, changes of which are likely on a spectrum of central pain syndrome. Initial management of fibromyalgia includes exercise and a physical therapy program, psychological interventions such as cognitive behavioral therapy, and pharmacological treatment. Medications commonly used for fibromyalgia include amitriptyline, cyclobenzaprine, fluoxetine, duloxetine, milnacipran, tramadol, pregabalin, and gabapentin.

Complex regional pain syndrome also has symptoms consistent with central sensitization. Complex regional pain syndrome is discussed further in the peripheral neuropathies chapter. Figure 14.12 illustrates how chronic early life or adult stress leads to alteration in limbic regulation of the HPA axis.

Table 14.11 lists various wordings used to describe the definition of central sensitization.

Figure 14.14 shows the sites of action for non-narcotic analgesic drugs and techniques.

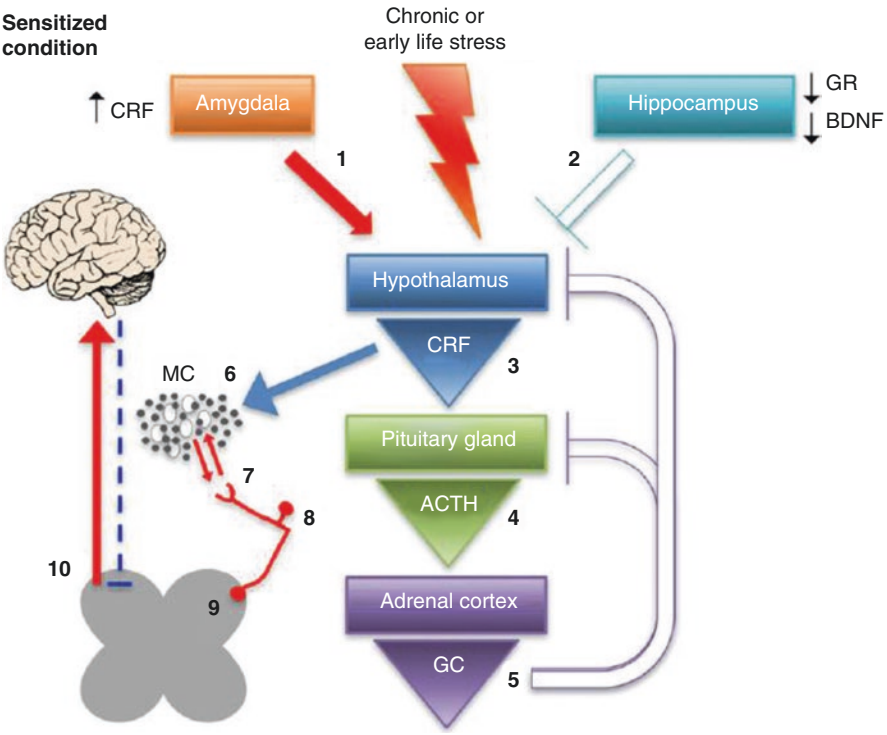

Fig. 14.12 Chronic early life or adult stress leads to alteration in limbic regulation of the HPA axis. This is due to increased CRF expression and drive from the amygdala (1) and decreased glucocorticoid receptor (GR) and brain-derived neurotrophic factor (BDNF) expression in the hippocampus, which dampens inhibition (2). These changes ultimately lead to increased CRF release from the hypothalamus (3), increased and prolonged release of ACTH after cessation of the stressor (4), and increased glucocorticoid (GC) production (5) with decreased negative feedback at higher structures. Increased CRF release leads to greater mast cell activation and infiltration (6) leading to enhanced peripheral nociceptor interaction (7). Increased peripheral drive can lead to hyperalgesic priming (8) and/or wind-up (9), eventually increasing ascending pain signaling, while simultaneously decreasing descending inhibition (10). (Adapted from OC Eller-Smith, Frontiers in Cellular Neuroscience, 2018). Figure 14.13 summarizes the mechanisms contributing to central sensitizations

Table 14.11 Various wordings used to describe the definition of central sensitization

Hyperexcitability
Amplification of neural signaling
Hyperexcitement of the central neurons
Hyperresponsiveness
Enhanced sensitivity or pain perception
Hypersensitivity
Augmented processing of pain
Altered sensory processing
Altered experience of peripheral inputs
Altered pain thresholds
Increased brain activity

Adapted from C den Boer, *Journal of Psychosomatic Research*, 2019

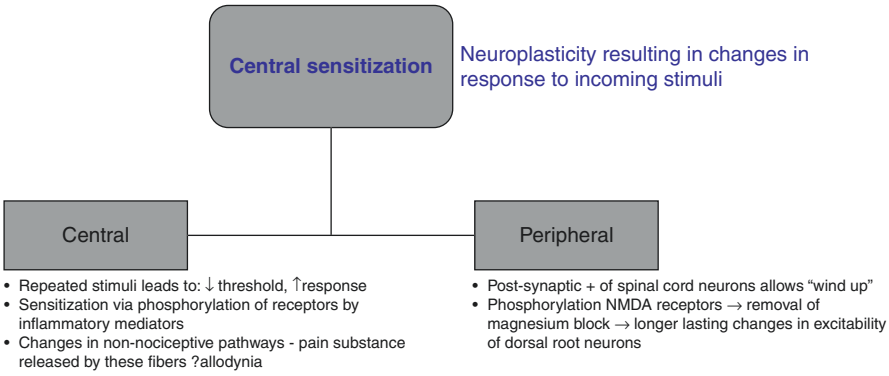

Fig. 14.13 A few of the mechanisms contributing to central sensitizations

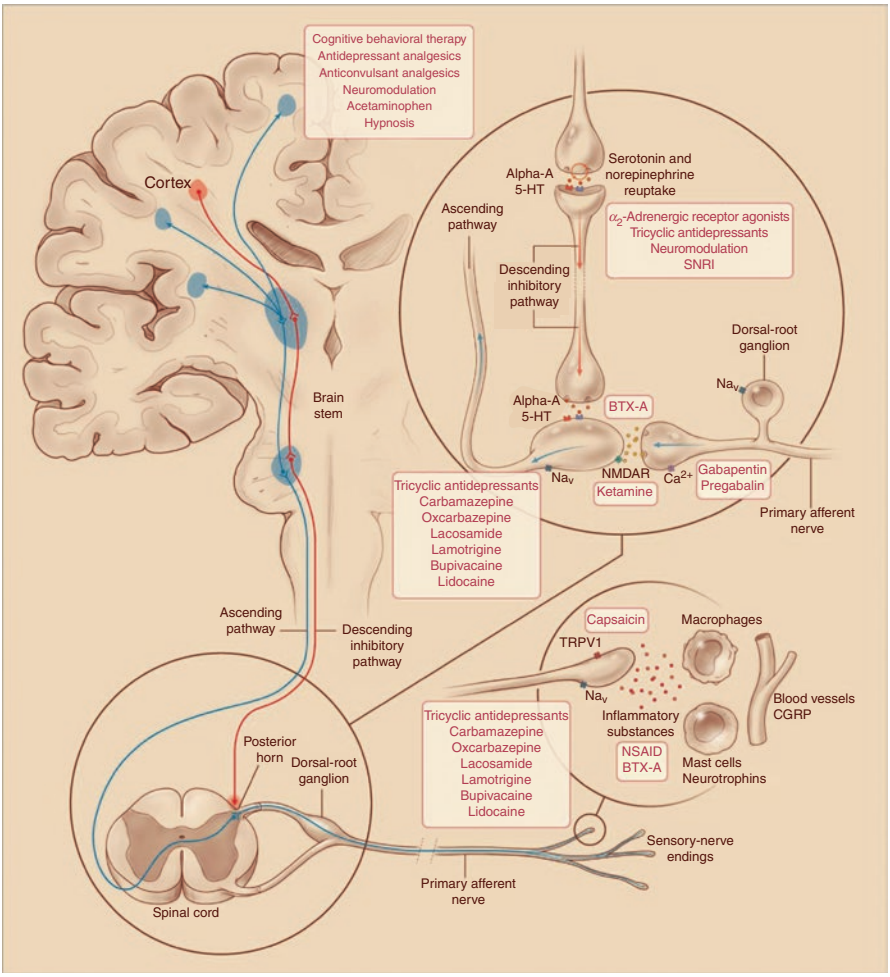

Fig. 14.14 Sites of action of non-narcotic analgesics and other neuromodulatory techniques [369]

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Part IV
Interdisciplinary Evaluation and Treatment

Chapter 15
Behavioral Medicine Assessment and Medication Choice in the Management of Chronic Pain

Aaron Van Wright III and Jennifer L. Nelson

The Need for Behavioral Specialists in Chronic Pain Management

At the time of this writing, there has been a recent opioid epidemic. On average, 130 Americans die every day from an opioid overdose [1]. To stem the tide of opioid death, misuse, abuse, and diversion, pain management specialists have moved away from opioid narcotic use as the mainstay treatment for chronic pain. Pain specialists have increased the use of behavioral medicines and psychotherapeutic interventions to assist in providing safer, alternative treatments to chronic opioid use. Behavioral medicines and therapies employed within an interdisciplinary or multidisciplinary pain management program are relatively low risk compared with other treatments and interventions, such as chronic opioid use or surgery [2]. Thoughtful behavioral assessment and treatment in a comanagement format can enhance the lead pain specialist's effectiveness in dealing with the challenge of chronic pain. The behavioral medicine perspective can lead to a greater understanding of the individual patient's "pain experience" and what is required to achieve an improvement in their condition.

Another compelling reason for behavioral health specialists to be involved in the care of chronic pain patients is the identified comorbid relationship between mood disorders and chronic pain. To fully appreciate this comorbidity between chronic pain and behavioral health disorders, it is helpful to start with the complexity of pain itself. There are many definitions of pain; most of the more comprehensive pain definitions incorporate more than the physical aspects and descriptions of pain. They also include the emotional and cognitive components of the pain experience as

A. Van Wright III (✉)
Department of Psychiatry, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: Aaron.VanWright@UTSouthwestern.edu

J. L. Nelson
Parkland Health & Hospital System, Dallas, TX, USA

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well. One such definition presents pain in terms of three hierarchical levels. The levels include a sensory-discriminative component *(*e.g.*, location, intensity, quality)*, a motivational-affective component *(*e.g.*, depression and anxiety, among others)*, and a cognitive-evaluative component that explores the patient's thoughts concerning the cause and significance of the pain [3]. Each chronic pain experience is unique, and the many facets of a person's chronic pain reveal themselves through thoughtful and careful assessment.

In general, there is an increased probability of finding a diagnosable behavioral or psychiatric condition in the chronic pain patient. Researchers have paired the incidence of occurrence for several behavioral health disorders in the general population without chronic pain complaints vs. the incidence of occurrence in those patients with chronic pain complaints. One of the most prominent mood disorders seen in chronic pain disorders is depression. The incidence of depression is seen to be about 45% in the chronic pain patient versus 5% in the general population without chronic pain [4, 5]. Anxiety disorders demonstrated an incidence of 25% in chronic pain patients versus 3–8% in the general population without chronic pain [4, 6]. The incidence of personality disorders was 51% of chronic pain patients versus 10–18% of the general population without chronic pain [7, 8]. The incidence of substance use disorder was 15–28% in chronic pain patients versus 10% in the general population without chronic pain [4, 7].

Chronic pain patients commonly suffer insomnia. We continue finding sleep quality to be an important factor in many health conditions such as cognitive health, heart conditions, cancer, autoimmune disorders, and pain. Sleep is when the body tries to repair itself, tamp down inflammation, relax muscle tone, and tension. Sleep is also a time for the psyche to "work out" some of the daily issues encountered. In the general community, approximately 20% of the people living with chronic pain report at least one symptom of insomnia compared to only 7.4% in those without chronic pain [9].

Researchers have explored some of the more common chronic pain conditions and the likelihood of association with a comorbid behavioral disorder. There seems to be a lifetime history of depressive disorders reported in about two-thirds of patients with persistent pain conditions. Some of these chronic pain conditions include migraine headaches, back pain, fibromyalgia, pelvic pain, chest pain, irritable bowel, peptic ulcer disease, and functional abdominal pain, among others [10]. Overlooking a comorbid mood problem in these cases can result in problems with compliance, treatment response, higher relapse rates, and decreased patient satisfaction [11].

The Inflammation Connection Between Pain and Behavioral Disorders

The role of inflammation in both chronic pain and mood disorders is an area that has shown promise in furthering our knowledge about this connection between pain and mood. Although acute inflammation can serve a protective function to the body to

remove itself from harmful stimuli and help begin healing, chronic inflammation can lead to more disease and a worsened condition. Chronic inflammation plays a role in heart disease, cancer, Alzheimer's, and diabetes among others. Risk factors for generating and maintaining inflammatory responses include such factors as diets high in saturated fat, obesity, sleep disorders, periodontal disease, smoking, physical, and emotional stress.

According to research, the "Neuroinflammatory Hypothesis of Depression" seeks to explain a link between the inflammatory process and mood disorders. Several of the known inflammatory markers or cytokines such as interleukin 6, C-reactive protein, and tumor necrosis factor are elevated in depressive disorders. Neuroinflammatory conditions such as lupus, multiple sclerosis, and brain injury are associated with higher prevalence rates of major depression [12].

The Neurotransmitter Connection Between Pain and Behavioral Disorders

Neurotransmitters play a vital role in our physical, cognitive, and emotional state of being. Of the numerous neurotransmitters identified, certain ones are believed to be influential in pain perception, modulation, and mood regulation. The most commonly identified neurotransmitters said to play a role in mood regulation are serotonin (5-HT), norepinephrine (NE), dopamine (DA), and gamma-aminobutyric acid (GABA). The neurotransmitters thought to play a role in pain perception and pain modulation include 5-HT, NE, and GABA. Since these chemical messengers are active in pain and mood disorder, one may infer that medicines designed to exact a beneficial change in the condition of depression may have some useful effect in the chronic condition pain. The pharmaceutical companies and their researchers target these chemical messengers to influence the brain's functional ability to alter pain perception and affect mood improvement.

Pathophysiology and the Gate Control Theory of Chronic Pain

It is sometimes helpful to think about a person's pain experience in terms of the "mind-body connection." There have been multiple models created to conceptualize this vital relationship. The "Gate Control Theory" is one such model that was proposed in 1965 by Ronald Melzack and Patrick Wall [13]. In brief, it proposed that as the pain signals travel from the pain site to the brain via the ascending pathways, these chronic pain signals are modulated by action on the descending pathways. In essence, there is a "gate" that can "open or close," effectively modulating or controlling the amount of pain experienced. 5-HT and NE are involved in the signal mediation from the brain to the pain site. The 5-HT neuronal activity or outflow from such brain areas such as the rostroventral medulla and the NE neuronal activity from dorsolateral pontomesencephalic tegmentum act to dampen pain

signals. There are additional connections to emotional centers (limbic pathways) and structures such as the amygdala, hypothalamus, and thalamus that involve stress response, anxiety, and heightened attention. To put the Gate Control Theory into practical terms, there are different things in the biopsychosocial realm identified as factors that "open the gate" to allow the experience of increased pain or "close the gate" to help in attenuating the pain. Conditions and situations found to open the gates and increase the pain experience include medication/illicit drug abuse; the attention paid to pain; belief of pain as mysterious or a catastrophic thing – out of control; imbalances between work, social, and recreational activities; poor support system; poor diet; and other poor health behaviors. Conversely, conditions that have been found to "close the gate" and decrease pain include medication; distracted attention from pain; belief that pain is more predictable and controllable; ability to relax and maintain a stable mood; mindful pacing of activities; healthy balance between work, social, and recreational activities; healthy attitudes; and support from family and friends. As patients go through a comprehensive interdisciplinary program, the discussions involve these biological, psychological, and social aspects of a pain experience along with strategies to help the patient gain confidence and a sense of control over the "gates" of their chronic pain.

The Behavioral Health Assessment Overview

Behavioral medicine specialists command a niche with the perspective they bring to the interdisciplinary and multidisciplinary environment of pain management. Like the often quoted, "No man is an island," no one symptom in an individual exists insulated in a vacuum. To relate this to our topic, we can use a bio-psycho-social framework. Although this model has some fair criticisms leveled against it, we can still use it for simplification and add order to our patient approach.

Since chronic pain can profoundly affect many other aspects of a person's well-being in both mind and body, an excellent behavioral exam should not only capture the classic pain description *(location, duration, character, and other attributes)* but also document the broader "pain experience" of the patient. Pain can affect a person's mind in many different ways. Many emotions associate with pain that range from depression, anxiety, and fear to irritability and anger, among others. Some patients develop a feeling of grief over the loss of physical abilities and the capacity to enjoy and engage in desired activities. The feeling that there may be no escape from pain may heighten anxiety, and lead to isolation and withdrawal from friends, familial relationships, or the world in general. They may eschew beloved hobbies and interests and develop a genuine fear and avoidance of activities out of concern that it will only lead to more pain. The "psychosocial" aspects of a person's pain experience deserve and will often demand attention in conscious and unconscious ways that might affect overall treatment.

Patients are often visibly distressed with their condition and the problems they have encountered in trying to find effective treatment. When anger or frustration is encountered, a useful technique to transition beyond this distress is to "identify the affect." Identifying the affect involves gently identifying – out loud – the patient's real-time bodily display of emotion *(sadness, anxiety, anger)* concerning their pain. This identifying technique serves to help navigate through a potential impasse and acknowledges the patient's struggle in a more complete way. This form of acknowledgment improves the patient-provider relationship through enhanced rapport and furthers engagement of the patient in a more collaborative approach. The biological manifestation of pain may be the patient's primary focus, but it should not end there, especially with the behavioral specialist.

Stigma and the Behavioral Health Assessment

"I am here at a pain management clinic, to be treated for real pain. Why does the pain doctor want me to speak to a behavioral specialist? Do they think the pain is all in my head? Don't they believe me?"

Because of stigma associated with mental illness, some chronic pain patients may have difficulty with the idea of referral to a behavioral health specialist as part of their pain management. This difficulty and feelings about the referral should be dealt with gently. Their emotions may range from taking offense at the referral to a deepened sense of loss with the assumption that a referral to a behavioral specialist represents "the end of the road" and nothing else will or can be done for them from a medical-surgical standpoint. They may even think that they have done something wrong because they have not responded to treatments prior. Some of these feelings may lead a patient to minimize, underreport, or downplay the more emotional aspects of their pain experience. The National Alliance on Mental Illness *(NAMI)* nicely lays out multiple ways to handle some of the stigma associated with mental illness [14]. The NAMI web site emphasizes certain techniques such as educating the patient up front about the purpose of the assessment, speaking openly about mental health issues where suspected while being cautious of language, encouraging equality between physical and mental illness, choosing empowerment over shame, and being honest and open about treatment recommendations. Using these techniques can help the chronic pain patient put some things in a more therapeutic perspective and help "normalize" parts of this referral experience with a behavioral specialist.

Many patients may already intuit some of the possible physical manifestations commonly associated with pain, such as increased muscle tension, inability to relax, restlessness, sleep disturbance, irritability, and limited energy. All of these symptoms can be discussed with the patient in layman's terms as being related to some form of "stress."

The Behavioral Health Assessment Interview

The goal of assessment is not to convince oneself or the patient that they are suffering from a primary psychiatric diagnosis. The objectives should lean toward gathering information, educating the patient, and presenting information as the assessment progresses to demonstrate and affirm the value of the behavioral health assessment. The specialist's approach should help the patient open up, engaged, and feel freer to relate their pain experience in ways that go beyond the usual location, duration, and intensity.

Early in the assessment, the behavior specialist will likely start with open-ended questions and allow the patient to talk about the pain condition and its effect on their life.

Here are a few behavioral assessment sample questions and topics to explore:

- When did the pain start? What makes the pain better, worse?
- What was going on in your life at the time? *(Look for traumas, stress situations, and events beyond one's control)*
- How have you been coping with this condition? How would you describe your mood most days?
- Do you have any feelings of hopelessness or helplessness? Are there thoughts of suicide or homicide?
- What is your sleep routine? How many hours of sleep do you get in a 24-hour period of time?
- Hobbies and interests maintained vs. hobbies and interests that have been given up during this time of pain
- Whom do you consider to be part of your support system?
- Past medical history, behavioral health history, current medication, and previous trials of a psychotropic
- Presence or absence of substance use issues; appropriate use of prescribed medication
- Is there a family history of medical and behavioral health issues?
- Social history to include relationship status, living situation, presently working vs. disability, and possible litigation issues
- Physical and sexual abuse history
- Mental and cognitive status exams

This sample assessment is not exhaustive; it is just a sampling of the different lines of questioning in a behavioral assessment likely relevant to a patient's pain experience. Some articles review the connections between aspects of a person's life such as the quality of a person's support system, job satisfaction, personality traits, coping styles, history of suffering trauma *(physical, sexual)* from childhood to adult, and the likelihood of developing a chronic pain disorder. The mental status and cognitive portions of the exams give the behavior specialist a sense of the patient's insight into their condition and their ability to benefit from the numerous therapeutic behavioral modalities for pain management *(biofeedback,*

cognitive behavioral therapy, and mindfulness, among others discussed elsewhere in this book). Intact memory, concentration, and attention skills are needed to participate actively and fully benefit from many of the therapies offered. It is helpful to note whether or not the patient is experiencing any psychotic symptoms such as auditory and visual hallucinations or paranoid delusional ideas. Some of these symptoms can interfere with the patient's ability to engage in portions of treatment entirely and are contraindicated in some therapies such as biofeedback.

Additional Behavioral Assessment Tools

Psychometric questionnaires are useful tools in the behavioral assessment for screening, providing additional information, measuring severity, and tracking symptoms related to a behavioral disorder. There are numerous patient questionnaires *(Beck Depression Inventory, Quick Inventory of Depressive Symptomatology, and Patient Health Questionnaire-9, to name a few)* related to depression. The questionnaires take an inventory of mood, sleep, appetite, cognition, view of self, thoughts of death and suicide, anhedonia, energy, psychomotor slowing, and/or agitation. Though these screening tools were developed for mood disorders, these questionnaires are used by the behavioral specialist in a pain management environment. There are many items in these questionnaires that can be associated with part of a patient's pain experience. A person who is dealing with chronic pain may have significantly elevated scores on one or more of these items. Some examples of these comorbid shared signs and symptoms between depression and a chronic pain experience are demonstrated in Table 15.1.

Since not every patient that walks into a pain management setting is depressed or in the throes of some other mental health illness, how much should one read into a high score from a pain patient who is presenting for pain and does not endorse any mood disturbance? The concern that an elevated screening could be misleading and could result in diagnosing the pain patient with a psychiatric disorder is legitimate, and questions about the usefulness and validity of the psychometric questionnaire in the chronic pain setting are appropriate. There are review articles that discuss this overlap between depression and that of the pain experience and what it means in terms of valid psychometric questionnaire use in the pain population. The papers explore the question of how much weight to give to the depression scale completed by a pain patient who may not identify themselves as depressed. At this time, the evidence seems to support continued use of the standardized depression questionnaires now available for meaningful assessment in the chronic pain patient. Some researchers contend that there is potentially a more dangerous risk in underestimating depression among chronic pain patients than overestimating. The PHQ-9 was found to be an acceptable choice for screening of depressive symptoms in chronic pain patients [15].

Table 15.1 Comorbid symptom complaint similarities between depression and a chronic pain experience

Depression signs and symptoms	Pain experience
Sleep changes (insomnia or hypersomnia)	May involve poor sleep, but due to the inability to relax, find/maintain a comfortable position. Alternatively, some may use sleep to escape pain if they can
Anhedonia or low interest	May involve avoidance of activity due to pain or diminished ability to enjoy things due to pain
Guilt or feelings of worthlessness	May affect a person's view of themselves and diminish self-esteem and confidence. They may feel vulnerable around others; they may feel they are a burden to family, friends, and co-workers due to limitations in function and level of engagement in work contributions, social, and other obligations
Poor energy	May describe the pain as "exhausting" due to physiological responses such as constant muscle tension and guarding behavior against more pain – the "brace for impact" phenomenon
Poor concentration	May find pain to be "distracting" and inhibiting the ability to concentrate, focus, and make decisions
Psychomotor changes (slowing or agitation)	May endorse slowing in the form of guarded movements as an attempt to avoid exertions that may exacerbate their pain. Conversely, they may be restless, fidgety, pacing due to an inability to find or maintain a comfortable position due to pain
Sadness	May endorse sad mood as a reaction to the pain or difficulty adjusting to the difficulty of pain
Suicide[a] or thoughts of death	May involve hopelessness or helplessness due to the chronicity of pain and feeling "no escape." May involve ruminations about morbidity and mortality. Thoughts of being "better off dead" and holding on to "suicide" as an option to end their suffering with pain

[a]Further behavioral assessment or extended crisis intervention is warranted if suicidality registers on the screening

Diagnostic Considerations for Behavioral Health in Pain Management

Anxiety and depression disorders are the most common mental health disorders. Anxiety affects about 30% of adults at some time during their lives. Twenty-five million people in the United States have had some diagnosable form of anxiety disorder. The numbers of those affected by depression are significant as well. Roughly one in six people (16.6%) experience depression at some point in their lives. One in 15 people (6.7%) can experience depression in any given year. More women than men are likely to experience depression [16]. While some forms of anxiety or depression disorders are comorbid to chronic pain, there are some behavioral health diagnoses more closely associated with a medical problem of which chronic pain may be a feature. In the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), there are a few diagnoses such as "Somatic Symptom Disorder"

and "Psychological Factors Affecting Other Medical Conditions," which are tied to some physical condition such as pain. "Factitious Disorder" is another of these diagnoses that may involve pain. This one, in particular, may be the more difficult one to diagnose and treat.

The DSM-5-recognized condition that specifically mentions pain is Somatic Symptom Disorder. The diagnostic criteria for this list things such as persistent distressing thoughts about one's illness and high anxiety about one's current health and symptoms among other criteria. One of the specifiers in this condition denotes the condition as seen "with predominant pain."

Psychological Factors Affecting Other Medical Conditions is a diagnosis that involves the presence of a medical condition whose course may be adversely affected by psychological or behavioral factors. By definition of this disorder, certain psychological factors may present a problem by – directly or indirectly – interfering with successful treatment in ways such as a patient's poor or inconsistent adherence to treatment recommendation and therapies, ignoring the pain condition and taking a chance on worsening or re-injuring pain sites, and aggravating the pain condition with ongoing anxiety and stress.

Factitious Disorder is when a patient presents him or herself as ill. It is a falsification of physical or psychological illness symptoms. It is not to be confused with malingering *(not a behavioral health diagnosis)* which is also an intentional falsification of illness. The differences between these two presentations reveal themselves in the patient's goal. The goal of a factitious disorder is to play the "patient" or "sick role." This role-playing is done for primary or emotional gain at best. The difference in malingering is that the goal of malingering is one of securing a secondary gain (disability, worker's compensation; avoidance of situation; obtaining narcotics for whatever use).

Behavioral Medication Choices for Chronic Pain

Psychotropic medications have long shown usefulness in easing chronic pain conditions. There are several classifications of psychotropic medications with some showing more use and promise in enhancing the treatment of chronic pain conditions. There are FDA-approved (Table 15.2) and non-FDA-approved but clinically vetted (Table 15.3) antidepressants and other psychoactive medicines for application in the treatment of chronic pain.

The psychoactive medication categories include:

Antidepressants
Anxiolytics
Sedative/hypnotics
Antipsychotics
Stimulants
Antiepileptic drugs (AED)

Table 15.2 FDA-approved psychoactive medication for use in chronic pain

Chronic pain condition	Psychotropic class	Psychotropic medication	Dosage guidelines	Comments
Low back pain	Antidepressants	Duloxetine [17]	Initial: 30 mg once daily for 1 week then increase to 60 mg once daily; max dose: 60 mg/day	Adjunct for patients with inadequate response to nonpharmacologic and NSAID therapy
Headache/migraine	Anticonvulsants/mood stabilizers	Valproic acid (including sodium valproate, divalproex sodium) [18]	Valproic acid: 800 mg/day or 1000–1500 mg/day to maintain plasma concentration above 50 mg/L Divalproex sodium: (ER) 500 mg once a day for 1 week then increase to 1000 mg once daily (DR) 250 mg BID; doses up to 1000 mg/day are sometimes beneficial	Valproic acid has shown benefit in the prophylaxis of episodic migraine and reduced headache frequency (contraindicated in pregnancy)
		Topiramate [19]	IR: 25 mg once daily; may increase by 25 mg daily up to the recommended dose of 100 mg daily in two divided doses. ER: 25 mg once daily; may increase up to the recommended dose of 100 mg once daily	Topiramate (IR and XR) is indicated in the prophylactic treatment of migraine headache (for acute treatment, it has not been studied)
Neck pain		No agent with sufficient supportive information for use identified		
Facial pain	Anticonvulsants/mood stabilizers	Carbamazepine [20, 21]	200 mg/day, gradually increasing in increments of 200 mg/day as needed. maintenance: 400800 mg/day; max dose: 1200 mg/day	Has been shown effective in the treatment of trigeminal neuralgia and has also shown benefit in pain associated with glossopharyngeal neuralgia
Joint pain	Antidepressants	Duloxetine [22, 23]	Initial: 30 mg once daily for 1 week then increase to 60 mg once daily; max dose: 60 mg/day (doses up to 120 mg/day may provide some additional benefit although associated with increased adverse effects)	Duloxetine: For patients with moderate to severe symptoms and an inadequate response to nonpharmacologic interventions and oral NSAIDs are contraindicated. FDA approved for osteoarthritis of the knee (alternative agent)

Neuropathic pain	Antidepressants	Duloxetine [24, 25]	Initial: 30 mg once daily for 1 week then increase to 60 mg once daily; max dose: 60 mg/day (there is no evidence that higher doses provide significant additional benefit)	Duloxetine is recommended as initial treatment of neuropathic pain in diabetes
	Anticonvulsants/mood stabilizers	Pregabalin [21]	(IR) initial: 25–75 mg/day; max dose: 300–450 mg/day (XR): 165 mg once daily; max dose of 330 mg once daily	Pregabalin (IR): Higher doses up to 600 mg/day may have greater adverse effects without additional benefit
Fibromyalgia	Antidepressants	Duloxetine [26, 27]	Initial: 30 mg once daily for 1 week then increase to 60 mg once daily; max dose: 60 mg/day (doses up to 120 mg/day have not shown additional benefit)	Shown to be effective with minimal side effects
		Milnacipran [26, 27]	Initial 12.5 mg once daily titrating to 50 mg BID over 1 week; max dose: 100 mg BID	Milnacipran: reduction in pain noted, small effects on fatigue and disability, no effect on sleep. Of note, milnacipran is not FDA approved for depression but is classified as an antidepressant
	Anticonvulsants/mood stabilizers	Pregabalin [20]	(IR) Initial: 75 mg BID; max dose: 450 mg/day	Pregabalin is recommended for the initial treatment of neuropathic pain in diabetes. Lower initial doses of 25–50 mg at bedtime recommended by some experts
Functional abdominal pain		No agent with sufficient supportive information for use identified		
Central pain syndrome		No agent with sufficient supportive information for use identified		
CRPS		No agent with sufficient supportive information for use identified		

Table 15.3 Non-FDA-approved psychoactive medications for use in chronic pain (presently used in off-label applications)

Chronic pain condition	Psychotropic class	Psychotropic medication	Dosage suggestions	Comments
Low back pain	Antidepressants	Amitriptyline [28]	10–25 mg/day at bedtime; low doses have been found to be effective	Use may be limited by anticholinergic and antihistamine adverse effects
		Doxepin [29]	Mean dose up to 200 mg/day	Use may be limited by anticholinergic and antihistamine adverse effects
		Nortriptyline [30]	Initial dose: 25 mg/day; target dose of 100 mg/day	Use may be limited by anticholinergic and antihistamine adverse effects
	Anticonvulsants/ mood stabilizers	Topiramate [31]	50–400 mg/day	Changes were noted with topiramate in chronic low back pain sensitivity along with health-related quality of life and loss of weight
Headache/ migraine	Antidepressants	Amitriptyline [32]	Initial: 10–25 mg QHS: Max dose:125 mg QHS	Anticholinergic and antihistamine adverse events may limit use. Long-term efficacy has not been established
		Fluoxetine [33]	20–40 mg/day	Found to be moderately effective in the treatment of chronic daily headache, but not effective for migraines
		Paroxetine [34]	20 mg/day	Decreased headache frequency and reduced anxiety
		Venlafaxine XR [35]	(XR) Initial: 75 mg/day titrate to 300 mg/day	Found to be effective for the treatment of tension-type headache
		Mirtazapine [36]	15 mg/day	Was only found effective in case reports
		Phenelzine [37]	15 mg QHS, dose may increase weekly. Max dose: 75 mg/day	Has been shown to be effective for headaches associated with depression, such as tension headaches or migraines refractory to other treatment
	Antipsychotics	Chlorpromazine IV [38, 39]	0.1 mg/kg	Has shown benefit in nausea, photophobia, and phonophobia for migraines. Should not be used to treat non-migraine headaches
		Olanzapine [40]	Between 2.5 mg and 35 mg; most patients received 5 or 10 mg daily	Has shown consistent efficacy in the treatment of headache/migraine, although the data is minimal
	Anticonvulsants/ mood stabilizers	Lithium [41]	300–600 mg/day for the first week then increase to 600–900 mg/day by the fourth week (reduce dose when levels >1.2 mEq/L)	Has been shown to be beneficial for cluster headaches
		Lamotrigine [42]	25 mg/day titrating to a dose of 100 mg/daily	Appears to be effective only in patients with an aura before their migraine

Table 15.3 (continued)

Chronic pain condition	Psychotropic class	Psychotropic medication	Dosage suggestions	Comments
Neck pain	Not applicable			
Facial pain	Antidepressants	Amitriptyline [43]	10–30 mg/day at bedtime	Low-dose amitriptyline has been shown effective in chronic temporomandibular disorder pain for up to 6 weeks and possibly 1 year
Joint pain	No agent with sufficient supportive information for use identified			
Neuropathic pain	Antidepressants	Amitriptyline [44]	10–25 mg/day at bedtime; may increase to 150 mg/day	Strong support for TCAs as first-line treatment, although nortriptyline and desipramine are preferred due to better tolerability
		Imipramine [45]	25–150 mg/day given once daily or in two divided doses	
		Nortriptyline [45]	25–150 mg/day given once daily or in two divided dose	
		Desipramine [45]	25–150 mg/day given once daily or in two divided doses	
		Venlafaxine XR [45]	(XR) 150–225 mg once daily	Reasonably well tolerated and effective for chronic neuropathic pain
	Anticonvulsants/ mood stabilizers	Gabapentin [46]	(IR) 100–300 mg daily to TID. Increase dose to a range of 300 mg to 1.2 g TID (ER) 300 mg QPM. Increase dose to a target dose of 900 mg to 3.6 g daily	Gabapentin compared with placebo significantly increased pain reduction and is recommended for the initial treatment of neuropathic pain in diabetics. An adequate trial of 2 months or more is needed
Fibromyalgia	Antidepressants	Amitriptyline [47, 48]	Initial 10 mg QHS: Maintenance dose: 2030 mg/day. Max dose: 75 mg/day	Anticholinergic and antihistamine adverse events may limit use. Long-term efficacy has not been established
	Antipsychotics	Olanzapine [40, 49]	10 mg/day	Mostly case reports available that showed the beneficial outcomes obscured by its poor tolerability
	Anticonvulsants/ mood stabilizers	Gabapentin [50]	(IR) 100–300 mg once daily at bedtime. Increase dose to a target dose of 1.2–2.4 g/day in divided doses	Changes from placebo were small
Functional abdominal pain	No agent with sufficient supportive information for use identified			
Central pain syndrome	No agent with sufficient supportive information for use identified			
CRPS	No agent with sufficient supportive information for use identified			

Antidepressant Use in Chronic Pain Management

Of all the types of psychotropic medications, antidepressants have long been recognized as helpful in the treatment of some chronic pain conditions. The tricyclic antidepressant (TCA) was discovered in the 1950s. It has been several decades since TCAs were first noted as useful in the treatment of neuropathic pain. Although monoamine oxidase inhibitors (MAOIs) were the first antidepressants in use, it was TCAs that rose to more widespread use in the treatment of specific pain conditions. Beyond initial use in neuropathic pain, multiple clinical studies have found TCAs helpful in other pain conditions such as migraine prophylaxis, facial pain, fibromyalgia, and back pain (Table 15.3). These are all non-FDA-approved uses but well studied and shown useful in clinical practice. Some of the adverse effects and drug interactions are the main drawback in TCA use for some patients. The anticholinergic effects of the drug such as dry mouth, blurry vision, constipation, orthostatic hypotension, and cognitive impairments can prove to be intolerable for some patients. TCAs have an interaction potential with other more traditional pain agents such as opioid narcotics *(including tramadol),* muscle relaxants, and potential cardiac effects with methadone. Care must be taken, but the TCA is generally considered safe and effective for use.

There is some difference in efficacy among the TCAs. Amitriptyline and imipramine are classified as tertiary TCA, and their action is inhibiting uptake of 5-HT and NE. The TCAs nortriptyline and desipramine are secondary amines, and they inhibit uptake of NE mostly. Their impact in terms of analgesic effect is not as pronounced, but they are preferred in some cases as they are better tolerated in regard to side effects.

The quest for better-tolerated antidepressants led to the development of the selective serotonin reuptake inhibitor (SSRI) class of antidepressants in the early1980s. Fluoxetine became the first FDA-approved SSRI in 1987. Although their usefulness in pain management is not as robust as the TCA's, improved tolerability has led to some useful clinical situations such as fluoxetine found somewhat helpful in the treatment of headaches (Table 15.3). Some of the adverse effects of the SSRI include stomach upset, nausea, diarrhea, and sexual dysfunction. The drug interaction concerns are for co-administering with other pain medicines such as triptans, tramadol, aspirin, and nonsteroidal anti-inflammatory drugs. Serotonin syndrome and increased chance of gastrointestinal bleeding are the main concerns with these pain medications.

The more recent class of antidepressants developed, the serotonin-norepinephrine reuptake inhibitor (SNRI), has produced duloxetine, the first FDA-approved antidepressant to treat a pain condition. Other SNRIs such as venlafaxine and milnacipran have proven useful in some conditions such as some headache types and fibromyalgia pain (Table 15.2). The enhancement of both 5-HT and NE by the SNRIs has proven to be a significant benefit in pain management. Duloxetine is particularly helpful in diabetic-related neuropathy (Table 15.2). Some of the adverse effects of the SNRI include dry mouth, nausea, constipation, sedation, increased blood pressure, and sweating. There is some concern for hepatotoxicity with duloxetine. Care is used in those with known liver disease, significant alcohol use, or other conditions affecting the liver. The drug interaction profile is comparable to the other antidepressant classes. There should be careful use with other traditional pain medications such as tramadol, triptans, aspirin, nonsteroidal anti-inflammatory medications, and opioids.

Anxiolytic Use in Chronic Pain Management

Benzodiazepines are a class of medication used to treat anxiety. In chronic pain management, benzodiazepines are sometimes used as muscle relaxants and there is some evidence to support this use. The mechanism of action is thought to be the enhancement of GABA, an inhibitory neurotransmitter that reduces excitability in the motor neuron system and results in relaxation. Clonazepam is a benzodiazepine used in neurological disorders that have associated muscle tension, tremors, and spasms that can be pain generators. It is used in conditions such as multiple sclerosis, dystonia, and Huntington's disease. Despite appropriate use in some conditions, clinicians are finding benzodiazepines as problematic as opioids or at least a close second. Benzodiazepines are addictive, can have dangerous drug interaction effects when used with opioids *(central nervous system depression).* The Centers for Disease Control and Prevention and the National Vital Statistics System note a significant number of deaths involving the combination of opioid and benzodiazepines more than other pairings.

Hypnotic Use in Chronic Pain Management

The sedative hypnotics refer to medication used for insomnia. The older medications in this class are benzodiazepines that have long half-lives and more active metabolites. The discussion for the benzodiazepines would apply here as well. The newer group of hypnotics is non-benzodiazepine. Within this group are three medications sometimes referred to as the "Z-drugs"; these are **z**olpidem, **z**aleplon, and es**z**opiclone. There are a few newer non-benzodiazepines: suvorexant, ramelteon, and Silenor® (the TCA doxepin remarketed). Although they may not have any direct analgesic effects, they can help allow a patient to increase their sleep hours. In the cases where chronic pain has disrupted sleep, this may have an indirect effect in lessening a pain experience due to the importance of sleep to improved physical and psychological functioning overall general wellness. Although the non-benzodiazepines are considered somewhat safer to use long term than the benzodiazepines, some of the side effects are less severe but similar to benzodiazepines, and care should be taken when used with some pain medications. Trazodone or some over-the-counter medication such as melatonin and diphenhydramine may be the safer, more conservative approach when dealing with other potentially precarious medication combinations or concerning comorbidities.

Antipsychotic Use in Chronic Pain Management

Behavioral medicine finds multiple uses for the atypical antipsychotics (AAs) that go beyond the treatment of psychosis. AAs (i.e., olanzapine, aripiprazole, ziprasidone, risperidone, lurasidone, and others) are widely employed as mood stabilizers

and augmentation strategies for depression treatment. Investigators have conducted studies to explore efficacy in chronic pain. Olanzapine has shown some efficacy in the treatment of migraines (Table 15.3). Olanzapine also showed a beneficial outcome in the treatment of fibromyalgia-related pain; however, tolerability has outweighed some benefits (Table 15.3). None of the other AAs reviewed demonstrated evidence of efficacy in headache pain syndromes, although quetiapine has limited evidence of efficacy (Table 15.4).

Table 15.4 Disproven treatments

Chronic pain condition	Psychotropic class	Psychotropic medication	Comments
Low back pain	Anticonvulsants/mood stabilizers	Gabapentinoids [31]	Nonsignificant minimal improvement of pain compared with placebo, with an increase of side effects
Headache/ migraine	Antipsychotics	Quetiapine [40]	Atypical antipsychotics (other than olanzapine) fail to demonstrate efficacy in pain syndromes. Low-quality evidence is available for quetiapine
		Aripiprazole [40]	
		Ziprasidone [40]	
		Risperidone [40]	
	Anticonvulsants/mood stabilizers	Oxcarbazepine [54]	No difference was seen between oxcarbazepine (1200 mg/day) and placebo
		Lamotrigine [42]	Was found to be ineffective for migraine prevention. A small amount of evidence suggests use in migraines with auras only
Neck pain	No agent identified		
Facial pain	Antidepressants	MAOIs [37]	Are not recommended to be used for chronic orofacial pain due to side effects and drug interactions
Joint pain	Antidepressants	Amitriptyline [55]	Studied in combination with NSAIDs, no increased benefit over NSAIDs alone for rheumatoid arthritis patients
Neuropathic pain	Anticonvulsants/mood stabilizers	Topiramate [46]	Was not statistically more effective than placebo in reducing pain scores in three trials
	Miscellaneous	Memantine [56]	Clinical trials have not shown efficacy; current use is not recommended
		Inositol [57]	No change was observed in diabetic neuropathic pain
Fibromyalgia	Antidepressants	SSRIs [26, 58]	Should not be used in the treatment of key symptoms of fibromyalgia. May help improve pain, fatigue, depression, sleep, and quality of life
Functional abdominal pain	No agent identified		
Central pain syndrome	No agent identified		
CRPS	No agent identified		

Although classed as a typical antipsychotic rather than an AA, chlorpromazine has been found helpful in nausea and photophobia associated with migraines (Table 15.3).

Stimulant Use in Chronic Pain Management

Stimulants are gaining more attention for their potential benefit in use for chronic pain conditions. Evidence shows that stimulants such as methylphenidate and modafinil demonstrate some effectiveness in improving the symptoms of fatigue associated with fibromyalgia. Stimulants can potentiate the effect of opioids and reduce some of the effects of analgesic-related sedation and improve cognitive function. Patients with chronic pain have low plasma levels of catecholamine (e.g., DA, NE). The available NE needs adequate level to inhibit the descending pain signal path [51–53].

Antiepileptic Drug and Mood Stabilizers for Use in Chronic Pain Management

Antiepileptic drugs (AED) (i.e., carbamazepine, valproic acid, gabapentin, pregabalin, topiramate, and lamotrigine) have long been used for relief in some chronic pain syndromes, in particular, neuralgias and neuropathic pain. Behavioral medicine employs many of these to help stabilize mood in the case of bipolar disorder and to help in anxiety disorder. The AEDs may dampen the activity of over-sensitized nerves, but the exact mechanism of action is not well understood. Most of the AEDs should be monitored due to side effect profile and a possible effect on bodily organs, chemistry, and blood work. Depending on what agent is used, some of the side effects may be nausea, stomach upset, drowsiness, liver damage, and electrolyte disturbances such as low sodium. Valproic acid, carbamazepine, and pregabalin have FDA approval to treat certain chronic pain conditions (Table 15.2). Table 15.3 summarizes medications that are used “off label” to treat pain. Table 15.4 summarized disproven uses for several medications.

Herbals, Supplements, and Other Alternative Agents Explored in Behavioral and Chronic Pain Management

There are over-the-counter supplements, herbals, and other agents that spark interest in use for treatment of behavioral and chronic pain conditions. The following table (Table 15.5) presents some of these alternative agents. These are helpful to discuss with patients who are looking for more conservative treatments. Some patients are very aware of the problems with chronic opioid use and have taken a 180° turn from narcotic use. Some of the items of interest in Table 15.5 have shown efficacy and are helpful to have in mind for the discussion of more natural remedies.

Table 15.5 Alternative agents

Chronic pain condition	Herbal/OTC product	Mental health conditions	Comments
Low back pain	Cayenne [59]	Depression	Shown to reduce pain more than placebo. Health benefits attributed to the capsaicin. Thought to reduce the amount of substance P which carries pain messages to the brain
Headache/migraine	Valerian root [60]	Anxiety	Thought to relieve headache by its sedative and relaxing properties
Neck pain	No agent with sufficient supportive information for use identified		
Facial pain	No agent with sufficient supportive information for use identified		
Joint pain	Omega-3 fatty acids [61]	Depression	Thought to improve rheumatoid arthritis and may boost the effectiveness of anti-inflammatory medications
	SAMe [62, 63]	Depression	Shown to be equivalent to almost all pain measures when compared to COX-2 inhibitors and NSAIDs in patients with osteoarthritis of the knee
Neuropathic pain	No agent with sufficient supportive information for use identified		
Fibromyalgia	Ginseng [51]	Depression, anxiety	Reduced the number of tender points and improved the patient's quality of life
	SAMe [64]	Depression	Noted to have improvements in pain, fatigue, and quality of sleep
Functional abdominal pain	No agent with sufficient supportive information for use identified		
Central pain syndrome	No agent with sufficient supportive information for use identified		
CRPS	No agent with sufficient supportive information for use identified		

Cannabidiol (CBD)

Lastly, interest in "CBD oils" has grown among pain and psychiatric patients. Cannabidiol (CBD) is one of many different cannabinoids isolated from the *Cannabis* plant. The current evidence is that there is some efficacy in such areas as anxiety, cognition, movement disorders, pain conditions, and epilepsy. CBD acts as a 5-HT_{1A} receptor partial agonist and an allosteric modulator of the mu- and delta-opioid receptors. At this writing, in the United States, it is still classified as a Schedule I drug under the Controlled Substances Act. Production, distribution, and possession are illegal under the federal law [65].

Additional Procedures for Behavioral Health and Pain Management

Electroconvulsive therapy (ECT) is a procedure used to treat severe depression. It is a procedure that involves psychiatry and anesthesiology to administer. This procedure may provide relief in the severe comorbid cases of depression and chronic pain. Some studies also demonstrate the efficacy of ECT in chronic neuropathic pain syndromes where other therapies have failed [66, 67].

Conclusions

Chronic pain management is a complex field that seems to require a multimodal approach for safe and beneficial treatment. Psychotropic medications are an essential class of medication used as an alternative to standard opioid use. The importance of additional information uncovered in a thorough behavioral health assessment can be crucial to the success in treatment. Behavioral interventions in the management of pain go beyond the simple use of medication; it should extend to the use of psychotherapeutic treatment modalities such as CBT for pain, biofeedback, and mindfulness among other therapies covered elsewhere in this publication.

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Chapter 16
Pain and Psychology

Richard C. Robinson and Jeanette Chong

Introduction

Pain, and chronic pain in particular, is a debilitating condition leading to individual suffering and large societal costs. Over 100 million adults in the United States suffer from chronic pain [1], and approximately 20 million Americans report severe enough pain that it impacts their activities in a significant manner daily [2]. Furthermore, the prevalence and expenditures for the most common chronic pain condition – chronic low back pain (CLBP) – are increasing [3]. Specifically, Gaskin and Richard [3] estimate that chronic pain costs $500 – $635 billion dollars a year with regard to medical costs and lost productivity. This is more than the cost of cancer and diabetes with only cardiovascular disease resulting in larger expenses [3].

At its core, pain developed as a biologically adaptive mechanism to notify an individual of physical injury or illness, e.g., a broken leg or infected wound [4]. Pain developed very early in our evolutionary history, and it is influenced by not only primitive brain functions but also portions of the brain that developed later in our species development [5]. As pain persists, the influence of psychological and social factors plays a greater role [4]. However, these psychosocial factors have an influence even on acute, biologically adaptive, pain experiences. Therefore, as discussed by Bushnell and colleagues [5], pain is best conceptualized as "…a complex sensory and emotional experience that can vary widely between people and even within an individual depending on the context and meaning of the pain and the psychological state of the person."

R. C. Robinson (✉) · J. Chong
Clinical Psychology, Graduate School of Biomedical Sciences and Department of Psychiatry, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: Richard.Robinson@UTSouthwestern.edu; Jeanette.Chong@UTSouthwestern.edu

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Conceptualization of Pain: Biopsychosocial

As mentioned, the longer pain persists, the more psychosocial factors play a role in the experience of pain, with biological factors continuing to influence the perception of pain [4]. Definitions of chronic pain have slight variations, but chronic pain is typically defined as pain lasting longer than 3–6 months [6]. This definition is meant to reflect that healing from an injury or illness should have already occurred during this time period. Although this definition is problematic as many disorders continue to influence biologically adaptive pain, this chronic pain definition does not diminish the growing relevance of psychosocial factors as pain persists.

Our understanding of pain continues to be influenced by two models: the traditional biomedical model and the more recent biopsychosocial model [6]. From the traditional biomedical model, pain is conceptualized by the specificity theory – developed by Rene Descartes in the seventeenth century [7]. The specificity theory proposes that the degree of pain should be correlated with the amount of tissue damage [7]. This theory allowed for a distinction between psychological functioning and physical functioning, which continues to influence providers today. For instance, from this theory if pain appears to exceed the amount of tissue damage or physical pathology, or if the source of the pain cannot be identified, then by process of elimination, the pain must be psychological. From this distinction arose the concept of organic vs. functional physical symptoms. Coming to fore toward the end of the nineteenth century, the term "organic" referred to disorders that had "true" physical origins [8]. Functional disorders were those that served some type of intrapsychic function, such as an unconscious mental compromise between unacceptable wishes and the mores of society [9]. For instance, an individual's arm may become paralyzed with no detectable physical pathology to prevent acting on aggressive wishes.

Unfortunately, the specificity theory presents had limitations, but still exists as an active implicit model in the understanding and treatment of pain by some practitioners. In the modern area, Beecher [10] is credited with laying the seeds for the biopsychosocial approach to pain. While serving as a physician in World War II, Beecher observed that only 20% of combat soldiers with serious injuries, and who were not in shock, required morphine [10]. It was hypothesized that the meaning of the injuries, which might lead to no longer serving in combat and returning home, may have influenced their perception [10]. More recently, the influence of psychological factors on the expectation of pain relief was demonstrated by Bingel and colleagues [11] when participants were administered remifentanil, but told they were administered a placebo. During a pain-inducing stimuli, the effects of the opioid were reversed in this study [11].

Based on a growing body of evidence for the importance of psychosocial factors in many chronic conditions, George Engel [12] developed the biopsychosocial approach. With regard to pain, the biopsychosocial approach assumes that pain starts with a biological injury or illness, but that psychosocial factors begin playing

larger roles the longer pain persists [4]. From this model, the distinction between physical and psychological is seen as insufficient and evolves this distinction from physical versus psychological to the extent of psychosocial overlay.

Biopsychosocial and Neuroscience

From a biopsychosocial perspective, we can begin to account for common phenomenon in the experience of pain. For instance, patients are often surprised that they have no "pain" receptors, but rather nociceptors – free nerve endings [13]. Although the stimulation of nociceptors leads to pain, there can be pain without nociception and nociception without pain [13]. For instance, patients with pain intuitively understand this concept with the example of cutting one's self in the garden or garage and not realizing they were injured until they later see blood. However, if they were to have had a similar injury with the same amount of nociceptive stimulation in the exam room, they would likely feel it instantly. Patients also can easily understand the concept of pain without nociception when the example of phantom limb pain is provided. The ultimate experience of pain appears to be dictated by the brain – when the brain translates nociception as "danger" or had been interpreted as "danger" [13].

As discussed, "Pain is a complex sensory and emotional experience that can vary widely between people and even within an individual depending on the context and meaning of the pain and the psychological state of the person" [5]. To better understand this definition, a brief review of the biology of the pain experience is warranted. Although the influence of psychological factors on the experience of pain has been known for quite some time, it was the Gate Control Theory of Pain by Melzack and Wall [14] that began to elucidate the possible influence of psychosocial factors. This "Gate" – an interneuron in the dorsal horn of the spinal column – could be "opened" or "closed" by competing stimuli from the periphery or descending nerve fibers from the brain originating in the periaqueductal gray region and associated with endorphins [14]. Since the development of the Gate Control Theory, researchers' ability to understand the neuroscience of pain has grown with the advancement of neuroimaging techniques.

Nociceptive input that passes through the "gatelike" mechanism flows to many areas of the brain including the thalamus, somatosensory cortex, limbic system, and prefrontal cortex [15]. The thalamus can be conceptualized as the relay station of the brain for sensory input that submits input to the somatosensory cortex and limbic system. The primary and secondary somatosensory cortices provide information to the individual about the location and texture of the pain [15]. However, one could argue that if only the thalamus and somatosensory cortex were activated then an individual might be aware of sensations of varying intensities in certain regions of their body, but the sensations would neither be pleasant nor unpleasant. Rather, the amygdala, basal ganglia, insula, and anterior cingulate cortex are the regions of the limbic system most implicated in the noxious component of the pain experience

[16]. The limbic system assigns relevance and meeting to both internal and external input and is associated with not only pain processing but also with emotional functioning [17].

Nociceptive input is translated as pain by the brain when it is perceived as danger – i.e., physical damage is occurring and some actions are needed [13]. In many ways, anxiety functions in a similar manner to alert us that there is external or internal danger that needs to be addressed. Therefore, it is not surprising that pain and negative emotions are processed in the same region of the brain – the limbic system. Furthermore, it would be anticipated that impacting the activation of the limbic system via the prefrontal cortex and other brain regions would impact the perception of pain. As previously discussed, an individual's emotional state has a significant impact on the experience of pain with negative emotional states correlating with decreased pain tolerance and positive emotional states associated with increased pain tolerance [5].

As part of a series of ingenious experiments that relied on functional magnetic resonance imaging (fMRI), Christopher deCharms, Sean Mackey, and colleagues [18] devised a research paradigm for both individuals with CLBP and healthy individuals. Individuals in both populations were trained in simple pain management exercises and a sophisticated type of biofeedback where they were observing a portion of their limbic system, the anterior cingulate cortex (ACC), with fMRI. Both groups of individuals were trained to decrease the activation of the ACC with simple pain management techniques. Individuals with CLBP were able to decrease their pain by approximately 65%, while healthy individuals who were exposed to stimuli resulting in acute pain were able to decrease their pain by 25% [18].

Along with one's emotional state, the attentional state of an individual is also implicated in the pain experience. It is no surprise that distraction such as involvement in a salient cognitive experience, e.g., giving a talk to a large audience, would impact the pain experience. In fact, Villemure and Bushnell [16] demonstrated that attentional modulation and emotional modulation were related to different parts of brain functioning. For instance, cognitive modulation of pain appeared to be related to the superior parietal lobe, somatosensory cortex, and insula. Emotional modulation of pain appears related to the ACC, prefrontal cortex, and periaqueductal gray. Furthermore, attentional control appeared more related to the experience of pain's intensity and emotional modulation more closely aligned to the unpleasantness of pain [16]. As discussed, one could imagine that if an individual breaks their leg, they may have the experience of an intense feeling in their leg but that the limbic system is what ultimately makes pain unpleasant and thus serves as the warning system of the brain.

Psychological Impact of Pain

As previously discussed, the longer pain persists, the more psychosocial factors play a role in the aggravation and maintenance of pain [4]. An apt metaphor is a pebble being thrown into a still beyond with ever-expanding ripples into a person's

life. Acute pain almost immediately detracts from our ability to attend and concentrate and be physically active. If severe enough, pain impacts our ability to sleep and further compromises attentional abilities. As it persists, and one's roles and functioning at work and interpersonal life become compromised, an individual's sense of identity and agency can also become compromised, contributing to feelings of worthlessness, fear of inability to recover, and potentially to depressive and anxious symptoms. As such, chronic pain becomes a complex condition impacting social and occupational functioning, emotional and cognitive functioning, and identity [4].

As mentioned, attention and concentration as well as processing speed appear to be the most susceptible, and thus the first to be impacted, by pain as well as by medication, lack of sleep, and emotional state. The impact of pain on attention has been seen in self-reports and switching and interference cognitive tests [19]. Along with attention and concentration, working memory is also impacted by pain with regard to both spatial and visual working memory [19]. Furthermore, executive functioning is also impacted, which refers to our ability to problem solve, learn from errors, and organize input as well as our response [19]. Specifically, individuals with chronic pain appear to have difficulty with emotional problem-solving tasks such as the Iowa Gambling Task [20]. As one example, Whitlock and colleagues [21] conducted a large-scale health and retirement study involving 10,065 individuals above the age of 62 for a 12-year period. The investigators found that "Persistent pain associated with accelerated memory decline and increased probability of dementia" (p. 1146). Differences existed among individuals with chronic pain and those without. For instance, average education levels for those with chronic pain were lower, and chronic pain individuals had higher rates of education, hypertension, heart disease, stroke, and depression. However, an increased risk of dementia was still found after adjusting for these covariates [21].

These findings are consistent with the current neuroscience literature in that changes in anatomical structure of the brain have been noted among individuals with chronic pain. Specifically, current evidence reveals decreases in gray matter in certain areas of the limbic system (ACC and insula cortex) and the prefrontal cortex. Furthermore, changes in white matter have also been shown in these areas. One prevalent hypothesis is that neuroexcitation may be responsible for the changes in these areas [5].

Chronic pain impacts our emotional state and our emotional state impacts our perception of pain [5]. Depression and anxiety can be seen as normal reactions to pain that persists and impacts more and more areas of an individual's life. Polatin and colleagues [22] found that 59% of a chronic pain population in a tertiary care facility met current diagnostic criteria for a mental health disorder. Major depressive disorder has been estimated to impact anywhere from 34% to 85% of individuals with chronic pain [22, 23]. Furthermore, individuals who meet criteria for an anxiety disorder have been estimated to be approximately 35% [24].

Testing with the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) has also shown common patterns among individuals with chronic pain. Specifically, cluster analysis has revealed four main profile patterns [25]. Specifically, one group of individuals appear to be expending significant emotional resources coping with

their pain via emotional constriction. Although these individuals are less likely to meet criteria for a major depressive disorder or anxiety disorder, it may come at a cost of increased emotional tension and decrease of positive affect. A second group of individuals produce a profile that suggests that emotional discomfort is being channeled into physical symptomology and are at risk for stress serving to aggravate or maintain their physical complaints. Although individuals in this group may report less symptoms of emotional stress, they may be preoccupied with their physical functioning. The third group is similar in almost all respects to the second, but have higher degrees of emotional distress that is suspected to be related to impaired ability to successfully channel emotional distress into physical functioning. The last group consists of individuals whose coping is either completely overwhelmed or whose coping has been compromised by factors predating the onset of their pain. These individuals typically have long-standing difficulties with their ability to maintain physical or emotional discomfort [25].

Interdisciplinary Care

The longer pain persists, the more areas of a person's life are impacted and the more complex are the psychological, cognitive, and emotional sequelae [4]. The biopsychosocial approach is arguably the best way to conceptualize pain once it becomes chronic, and the interdisciplinary approach to pain management, discussed elsewhere in this book, is arguably the best method to addressing the myriad of consequences and contributing factors to chronic pain [26]. Although detailed elsewhere in this book, a brief review of the elements of an interdisciplinary approach to treatment is warranted with the most attention paid to the role of psychological interventions in the management of pain.

Pharmacological interventions are still considered the first-line treatment for pain. However, it should be noted that the average pain reduction for pharmacological interventions is approximately 33% with regard to opioids and non-opioids [4]. However, opioids have greater increases in an individual's sense of well-being than non-opioids [27]. Along with opioids' ability to decrease pain and increase a sense of well-being, opioids are associated with substance use disorder, endocrinopathy, increased risk of fractures, and death [28]. Furthermore, it comes as a surprise to many individuals participating in chronic opioid therapy (COT) that COT is associated with opioid-induced hyperalgesia, a phenomenon where opioid use leads to decreased pain tolerance [29]. In addition to these risks, the evidence basis for COT is limited, but the evidence for negative effects of COT is clear [30]. In fact, Chou and colleagues [30] concluded, "Evidence is insufficient to determine the effectiveness of long-term opioid therapy for improving pain and function. Evidence supports a dose-dependent risk for serious harms."

A previous role of clinical psychologists in pain management settings was to determine which individuals may be at risk for opioid misuse [31]. However, given the limited evidence for the use of COT, this role has shifted to the treatment of

opioid use disorders or assisting with psychological interventions to help maintain abstinence [32].

Other medical, non-pharmacological interventions, such as surgery, injections, and denervation procedures, are frequently utilized for individuals with chronic pain [33]. According to a review by Chou and colleagues [34], medical interventions for low back pain with some of the strongest evidence include discectomies, laminectomies, and chemonucleolysis and are associated with improvements of back pain with radiculopathy. Other common procedures have weaker evidence, including epidural steroid injections for spinal stenosis and radiofrequency denervation for radiculopathy [34]. From a traditional biomedical model and specificity theory of pain, these findings would not make sense. However, from a biopsychosocial perspective, the amount of physical damage is only one – albeit important – component of what leads to pain [4]. For instance, Jensen and colleagues [35] evaluated 98 individuals who did not report symptoms with back pain. However, 36% of these individuals had some spinal pathology, including bulging discs, protrusions, and even one individual with an extrusion. This is not to suggest that biological factors contributing to pain are unimportant, but rather that the longer pain persists, the more important psychosocial factors become.

Interdisciplinary care involves individuals from multiple disciplines working together in the same setting to address the biological, psychological, and social sequelae of pain as well as the biopsychosocial contributing factors [26]. Pain management pioneers like James Bonica and Wilbert Fordyce developed programs that focused on the decrease of nociceptive input with psychological behavioral techniques to aid individuals in regaining functioning after the development of chronic pain. Fordyce [36] is credited with translating Beecher's finding in a clinically applicable manner.

The hallmarks of an interdisciplinary approach to pain management consist of several elements. First, and most obvious, several disciplines reside in one setting to address the biopsychosocial needs of individual patients. This is in contrast to a multidisciplinary approach where providers reside in different settings; however, the distinction between interdisciplinary approaches and multidisciplinary approaches is often blurred. At a minimum, disciplines involved include physicians, physical therapists, and mental health providers. However, nursing staff, case managers, occupational therapists, and others provide invaluable resources and expertise depending on the population served. Second, interdisciplinary programs provide regular means for formal, as well as informal, communication among providers at the outset of treatment, during treatment, and after treatment. Third, thorough initial evaluations from all providers involved at treatment occur, and systematic monitoring of progress toward goals and biopsychosocial variable of interest ensues [26].

During the evaluation phase, physicians and other medical care providers investigate additional underlying causes of pain and may request additional lab tests and imaging. Furthermore, a review of previous treatments and what has been successful or not is discussed. In addition to other diagnostics, changes in medication regimens may occur, including detoxification from opioids or referrals to providers who are able to manage the detoxification process. Additional referrals may also occur to

specialists in the areas of rheumatology, neurology, internal medicine, etc. In most interdisciplinary settings, the physician leads the interdisciplinary team [37].

Physical therapy is a critical part of interdisciplinary care for multiple reasons. As pain becomes chronic, it is quite common for individuals to develop a fear of movement, kinesiophobia [38]. Physical therapists play an instrumental role in educating patients about the difference between "hurt" and "harm" [4]. In fact, kinesiophobia is now seen as one of the risk factors for acute pain becoming chronic pain [38]. As physical deconditioning sets in, individuals with chronic pain are likely to hurt more as they engage in physical therapy, but this does not necessarily reflect that they are doing additional damage [38]. Physical therapy also helps to address muscle dysregulation through the right types of stretching and strengthening exercises [39].

Nociceptive input can be decreased for many individuals with a graded exercise approach [13]. Prior to an injury or an illness, an individual has a tissue tolerance line and a lower pain line to help prevent tissue damage. Once an individual has an injury or an illness, their tissue tolerance line decreases, in part, due to deconditioning. However, the pain line may decrease even further, and an individual may experience pain well before they are close to experiencing tissue damage. Furthermore, it is helpful to imagine a flare line between the pain line and tissue tolerance line that serves as a type of emergency shutoff for an individual to prevent damage. Therefore, to overcome the changes in the nervous system and the brain that often accompany chronic pain, a graded exercise approach is required [13].

With a graded exercise approach, an individual slowly increases their activity in a step-wise approach, with periodic retreats from previously established intensity or duration levels [13]. For instance, an individual with CLBP may only be able to walk 10 minutes before experiencing significant pain. From a graded exercise approach, this individual may be instructed to start walking 7 minutes a day and slowly increase their walking by 30 seconds to 1 minute per day. However, once this individual reaches 14 minutes, they may notice that they are experiencing more pain or taking longer to recover. As a result, they may be instructed to return to 11 minutes of walking a day until they are able to do this comfortably before increasing the length of their walk. Essentially, an individual is encouraged to take three to four steps forward and then two steps back to retrain their nervous systems, inflammatory system, and pathways of the brain.

Psychological Evaluation

Psychological interventions are also a crucially important component of pain management for several reasons. As previously mentioned, chronic pain becomes a complex condition impacting social and occupational functioning, emotional and cognitive functioning, and identity. Clinical psychologists with pain management expertise can play a role in treating this sequela of chronic pain [40]. As with all components of interdisciplinary care, psychological interventions begin with a

thorough evaluation of an individual [37]. Although assessment is discussed in other areas of this text, a brief discussion of some of the relevant psychological factors is warranted.

Coping style is a relevant construct to understand for individuals – particularly when they are experiencing the stress and sequelae of chronic pain [37]. Coping style simply refers to the typical manner in which a person manages a stressful event or events [41]. Although coping styles have been delineated in multiple ways, understanding coping as an active problem-focused, emotion-focused, and avoidance coping is a common way to delineate coping styles [42]. With an active problem-solving approach, an individual is attempting to engage in activity to address the stressor, such as changing the situation or seeking help from others. An avoidant coping style involves avoiding or minimizing the threat of the stress. However, this coping style may result in inappropriate use of alcohol, drugs, or other less than helpful avoidant behavior. Lastly, an emotion-focused approach involves methods to help manage and tolerate uncomfortable feelings or reframing one's thoughts about the stressor [42]. Carver and colleagues [42] described how individuals with medical conditions who utilize an active problem-solving approach and emotion-focused approach have better emotional outcomes during stressful and challenging medical problems such as cancer and heart disease.

As previously discussed, thoughts have a significant impact on the pain experience with negative thoughts associated with lower pain tolerance and poorer coping [16]. Aaron Beck ushered in the modern era of cognitive therapy with the development of cognitive behavioral therapy (CBT) [43]. From a CBT perspective, thoughts, feelings, and behavior interact with one another and that by changing one of those three elements you impact all three. Of particular interest for CBT practitioners are automatic negative thoughts. These thoughts are often the focus of interventions to change from a thought that may not be entirely rational to a more balanced, objective, and reasonable thought [43]. Turk and Rudy [44] describe two broad factors related to thoughts in individuals with chronic pain, namely, thoughts about the pain, e.g., "It is killing me" or "It's ruined my life," and beliefs about pain and medical conditions, e.g., "If I'm still hurting there is still something that can be fixed."

Several different types of cognitive errors individuals make have been described, one of which is catastrophizing [45]. Catastrophizing is defined as "…an exaggerated negative mental set brought to bear during actual or anticipated painful experience…" and has been noted as a common cognitive error in individuals with chronic pain [46]. It is not surprising that beliefs that pain is causing further damage or indicates that a person is dying would negatively impact the experience of pain. In fact, Wertli and colleagues [47] found that catastrophizing cognitive errors were correlated with worse outcomes in individuals who underwent care for low back pain.

Fear avoidance is another construct that is oftentimes the focus of CBT interventions and has been mentioned previously in this chapter in the context of kinesiophobia. After an individual suffers an acute injury, they might naturally begin to restrict activities that can increase pain [38]. However, as the injury heals, a person may continue to restrict activities for fear of pain or reinjury, but may in fact be

contributing to additional physical deconditioning – muscle weakening and decreased flexibility [48]. Fear of pain that leads to restricted activity is understood as a common barrier for individuals to improve functioning and pain management [38]. The interdisciplinary approach is described in detail elsewhere, but the combination of physical therapy and CBT often works in unison to help individuals learn the difference between hurt (an expected experience when reconditioning the body) and harm (additional tissue damage) [4].

Opioid use disorder represents another area where psychology plays a major role. In 2017, almost two million individuals met criteria for a prescription drug opioid use disorder, and approximately 47,000 individuals died from an opioid overdose. Furthermore, 19,000 died from opioid pain relievers [32]. Current treatment regimens include therapeutic tapering, use of Suboxone, and CBT [32]. However, a gold-standard model for the treatment of opioid use disorder for individuals with chronic pain has not yet reached consensus despite some evidence supporting an individualized, stepped-care model [49].

Psychological Treatment of Pain

Chronic pain is best treated within an interdisciplinary framework [26]. Appropriate medical interventions, pharmacology, physical therapy, and psychological services can be delivered in a systematic and unified fashion. With regard to psychological interventions, CBT remains the gold standard [33], but other evidence-based therapies such as acceptance commitment therapy [50] and emotional awareness and expression therapy [51] have developed a strong evidence basis over recent years. As previously discussed, CBT identifies common cognitive errors and works to promote more adaptive behavior and balanced, objective, and realistic thoughts.

Turk and Gatchel [4] outline several goals for individuals undergoing CBT for chronic pain. First, individuals are assisted in reframing their thoughts about pain sensations, specifically, from something over which they may feel they have no control to something that is far more manageable. Second, patients with chronic pain are provided education about a variety of tools to help them manage their pain, which may include relaxation training, biofeedback training, and mindfulness meditation. The third goal is to help strengthen their coping abilities, especially if they are in a more passive and avoidance stance toward their pain. In this goal, practitioners are attempting to enhance a client's feeling of self-efficacy – that is, an individual learns that they can impact their experience of pain as well as the environment. Fourth, an individual is taught how to monitor and better understand the relationships among their thoughts, feelings, behaviors, and physical sensations. Lastly, the fifth goal is to help patients internalize the ability to apply the skills learned in multiple settings in a manner that is sustainable [52].

The role of psychological interventions in the treatment of chronic pain within an interdisciplinary or multidisciplinary setting can be thought of as occurring at different levels. First, mental health practitioners can treat the common sequelae of

chronic pain including depression, anxiety, sleep disturbance, and substance use disorder. CBT and other evidence-based interventions have proven to be successful treatments for these disorders, but may still require pharmacological interventions. Second, psychological interventions can be utilized to impact positively the experience of pain [4].

With regard to the treatment of pain with psychological interventions, the approach can be best classified as "top-down" and "bottom-up" approaches. Specifically, "top-down" approaches involve skills training and consolidation of such techniques as relaxation training, hypnosis, biofeedback, and mindfulness meditation. These tools can help provide some immediate symptom relief and have a cumulative effect. Specifically, individuals who meditate regularly report better pain management [53].

The "bottom-up" approach, used in unison with the "top-down" skills building approach, involves addressing underlying psychosocial factors that may be serving to aggravate or maintain the pain. As previously mentioned, CBT addresses common cognitive errors regarding pain, particularly catastrophizing, and strengthens adaptive coping and development of more adaptive pain management behavior. Acceptance commitment therapy (ACT) builds upon a CBT perspective with an acceptance approach to managing uncomfortable physical and emotional sensations [50]. The incorporation of mindfulness meditation is an essential element of this approach. Psychoanalytically informed interventions have also been utilized to strengthen reflective functioning and integration of emotions [54].

Conclusion

Chronic pain impacts over 100 million Americans [1] and has large societal costs [3] and leads to individual suffering. Pain is a complex experience and is accurately described as a "…complex sensory and emotional experience that can vary widely between people and even within and individual depending on the context and meaning of the pain and the psychological state of the person" [5]. As pain persists, the importance of psychosocial factors in the aggravation and maintenance of pain increases [4]. Therefore, the biopsychosocial approach first described by George Engel [12] provides the most useful way of conceptualizing, evaluating, and treating pain. From the biopsychosocial approach arose the justification for interdisciplinary pain management, which has proven to be an efficacious and cost-effective treatment for pain [26].

Within an interdisciplinary approach to treatment, biological factors are addressed by medical practitioners through appropriate diagnostic tests and appropriate pharmacological and medical procedures. Physical therapy interventions address physical deconditioning, muscle dysregulation, strengthening/flexibility, and kinesiophobia. Finally, psychological interventions both focus on the common sequelae of pain (depression, anxiety, catastrophizing, fear avoidance, etc.) and instruct patients in pain management skills such as relaxation training, biofeedback, and mindfulness meditation.

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Chapter 17
Physical Therapy for Pain Management

Jason Zafereo

Introduction

Physical therapy is considered a cost-effective, evidence-based treatment option for a variety of medical conditions [1]. Physical therapists are specially trained to analyze and address dysfunctions in the movement system. When pain is believed to be precipitated by, perpetuated from, or having a deleterious effect on movement, a physical therapist can provide skilled interventions to alleviate pain and improve physical function. Evidence suggests that early referrals to physical therapy are vital to a patient's enhanced recovery and to the reduction of overall healthcare utilization related to the presenting condition [2, 3]. More specifically, early physical therapy has been associated with reduced long-term opioid use for shoulder, knee, and low back pain [4, 5].

Physical therapy should not be administered via a protocol-driven, onesize- fits all manner. Rather, physical therapists should consider the unique biopsychosocial factors that contribute to each patient's pain when developing a treatment plan. This process begins with a detailed history and examination, which allows therapists to identify potential biological structures (e.g., the spine) or psychosocial beliefs (e.g., fear avoidance) that may contribute to pain and/or movement dysfunction. Based on the findings from the examination, therapists can then prioritize treatment to the primary impairment(s) to movement, whether they be physical, environmental, or psychological. A detailed description of the clinical reasoning process required to adequately identify and discriminate a patient's primary contributing factors to pain is beyond the scope of this chapter. Truly, it is largely this clinical reasoning process that distinguishes expert from novice clinicians and can account for the variability seen in practice patterns and outcomes between therapists. Taking clinical reasoning aside, the aim of this chapter is to provide an overview of the most common,

J. Zafereo (✉)
Department of Physical Therapy, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: Jason.Zafereo@UTSouthwestern.edu

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evidence-based techniques and approaches used by physical therapists to evaluate and treat patients with pain. The first section on evaluation will include examination techniques, prognosis, and patient diagnosis/classification. The second section on treatment will present management strategies linked to a pain mechanism classification scheme [6–8].

Evaluation

Examination

The physical therapist's examination is primarily concerned with the assessment of movement and its effect on the patient's chief complaint of pain. A distinction is made during the exam between the reproduction of concordant/asterisk sign (related) pain and discordant sign (unrelated) pain. In cases where movement, loading, or sustained postures have no effect on the concordant sign, the role of physical therapy for pain relief is questionable. Physical therapy may in these cases still be appropriate to counteract the deleterious effects of immobilization from pain, such as stiffness, weakness, or functional loss. In cases where the concordant sign is affected by movement, loading, or positioning, the therapist should attempt to differentiate the system(s) involved in the pain and/or movement dysfunction. In the following section, the physical examination will be organized by tests that are performed to uniquely assess the articular, muscular, and nervous systems.

Articular System

Mobility at the spine and extremity joints is fundamental for functional movement to occur. Joint and spinal range of motion (ROM) testing can be performed to assess both osteokinematic and arthrokinematic movements and the effects of pain on each. Osteokinematic movements (e.g., joint flexion) involve active or passive ROM in various planes performed over single or repeated trials. Goniometric measurement is considered a valid and reliable method for the assessment of ROM [9]. Movement that is *limited* actively or passively by pain before the detection of tissue resistance at end range may indicate that *pain* (or *fear* of pain) is the primary impairment to movement. In such cases, care should be taken to avoid vigorous motion testing in the region, so as not to overly exacerbate pain. Active and passive movement that is equally limited, and *accompanied* by pain, suggests that *stiffness* may be a primary impairment to movement, provided that firm tissue resistance is perceptible at the end of the passive ROM. Active movement that is *accompanied* by pain and significantly more limited than passive movement suggests that *weakness* or poor *motor control* may be a primary impairment to movement. In cases where pain accompanies, but does not actually limit motion loss, more vigorous testing is usually tolerable.

When radiating, diffuse pain is present, repeated osteokinematic movements performed in specific planes of motion may be helpful to distinguish the potential

source of the pain and to guide treatment. Centralization is a term used to describe a change in the location of pain from a more distal, referred location (away from the joint/spine) to a more proximal, central location (closer to the joint/spine) [10]. Judgments of centralization are considered reliable and may suggest that a spinal structure, possibly the disc, is a likely source of pain [11, 12]. Furthermore, patients exhibiting centralization of extremity pain with spinal ROM have a favorable prognosis for improvement with the ongoing use of repeated movements in the direction of centralization [13].

Palpation is used to determine the contribution of joint/spine tissues to pain nociception and to assess the passive arthrokinematic mobility of these structures. Passive accessory and physiological motion can be tested to determine whether a joint or spinal segment is moving normally, too much, or not enough. This evaluation can form the basis for treatment decisions, utilizing joint mobilization if hypomobility is perceived at a joint or stabilization exercise when hypermobility is detected with pain [14]. A study by Fritz et al. [14] on patients with low back pain found that the likelihood of treatment failure with spinal mobilization was significantly lower when hypomobility was present (26%) than when hypermobility was detected (83%). In contrast, subjects displaying hypermobility were less likely to fail treatment with an exercise program (22%) compared to mobilization (74%). One limitation to the widespread acceptance and use of spinal accessory motion testing and palpation for pain is the wide range of reliability reported, spanning from poor to excellent [15]. Other issues include questionable validity, as poor agreement has been shown between spinal accessory motion testing and MR imaging [16]. While some may dismiss these forms of testing altogether based on conflicting evidence, most therapists continue to utilize manual palpation of tenderness and arthrokinematic assessments of mobility. When combined with other forms of testing, these assessments can provide meaningful clinical value to identify a concordantly painful structure and/or the desired location, direction, and dosage of manual therapy interventions.

Muscular System

Testing for muscular strength and motor control can take on many forms. While manual muscle testing (MMT), handheld dynamometry, and isokinetic testing can all provide valuable information about muscle strength, motor control may be assessed through observation of the quality, timing, and sequencing of movement. MMT using a 6-point (0–5) grading scale is the most common form of strength testing done clinically, where standardized positions are used to test for force production in the direction of the muscle's primary action. MMT is useful because it can be done quickly and requires no equipment to administer; however, reliability is reduced when grading at the 4 or 5 levels, and substitutions must be avoided when testing so as not to over-grade a weak muscle [17]. For the average, nonathletic patient, a muscle grade of 4/5 should be sufficient for activities of daily living. Patients testing below a 4/5 (nonathletic) or 5/5 (athletic) at muscles in the proximity of pain should be provided with a strengthening exercise program. Motor control exercise programs

may be useful to apply in advance of strengthening programs to ensure proper muscle activation before loading is applied. Motor control exercise programs may also be useful when pain limits the application of muscle strength testing as a means to gradually load the muscle in preparation for strengthening exercise.

Muscle flexibility is an especially important concept in patients with pain. Testing for lower extremity muscle flexibility has been shown to be reliable and, when limited, may predispose a patient to injury or pain [18]. Muscles that cross more than one joint are especially prone to tightness, which may be defined as increased tone in the muscle that can be rapidly overcome with end-range overpressure. Tightness should not be confused with adaptive shortening of a muscle, which does not change rapidly in response to end-range overpressure. Muscles with limited flexibility may also be tender upon palpation. Palpation of muscles may aid in the identification of tender/trigger points along the origin, insertion, or mid-belly of the muscle. Although the reliability of trigger point identification is debated [19], the mere presence of tightness/trigger points may suggest the need for manual therapy techniques to relax the muscle. Exercise options to address limited flexibility may vary based on whether muscle tightness or shortness is identified. While muscle shortness may be addressed with stretching, muscle tightness may be improved with strengthening of muscles in and around the area of the tight muscle.

A hallmark of management for chronic pain is aerobic exercise. Before engaging in this form of treatment, it is important to identify the patient's aerobic exercise threshold. Various forms of submaximal exercise testing may be used in a clinical setting on patients with pain. The Åstrand test; bicycle ergometry; walk tests of 5, 6, or 10 minutes; shuttle walk test; and the modified Bruce treadmill test have all been reported to be valid and reliable in patients with chronic pain, chronic fatigue, and fibromyalgia [20]. Careful monitoring should be performed during testing using a rating of perceived exertion or a heart rate monitor. Testing should be discontinued if the heart rate becomes too fast or slow or if the patient experiences chest pain or other cardiopulmonary signs of distress.

Nervous System

Neurodynamic mobility can be assessed through a series of nerve tension tests. Reflex testing should be performed before doing this type of testing, as neurodynamic excursion should be limited or avoided when nerve compression signs are present [21]. The neurodynamic test most often referred to is the straight leg raise, assessing sciatic nerve mobility from L4 to S2. Femoral nerve mobility can be tested with Ely's test, which assesses nerve roots from L2 to L4. Various upper limb tension tests exist to bias the median, radial, or ulnar nerves and the nerve roots from C5 to T1. Nerve root pain from foraminal stenosis or a herniated disc may also be elicited or relieved with spinal compression or traction testing, respectively. Patients with positive neurodynamic testing may benefit from neurodynamic exercise to relieve pain, while patients with positive traction testing may benefit from manual or mechanical traction application for pain relief.

Quantitative sensory testing (QST) can be useful for determining a patient's prognosis and to provide evidence of the patient's underlying pain mechanism [22]. Using various mechanical, vibratory, thermal, or temperature stimuli, the threshold of sensory detection or pain is reported by the patient at both the site of pain and remotely. Examples of QST include pressure pain threshold testing to detect regional or local hyperalgesia, temporal summation testing with monofilaments to detect the presence of windup, and conditioned pain modulation testing to detect loss of descending pain inhibition. Although these tests are primarily confined to laboratory studies at the present time, some authors have suggested that greater clinical application of an abbreviated, standardized battery of QST testing could improve prognosis formation and treatment of pain in the future [23].

Prognosis

Multiple factors should be considered when determining a patient's rehabilitation potential. Factors that when present may suggest a more favorable prognosis include high self-efficacy and motivation, maintaining an active lifestyle in spite of pain, adequate nutritional intake, and good sleep habits [24–26]. Unemployment, high degrees of disability/pain intensity, and low self-rated health are all considered negative prognostic signs when present in patients with low back pain [27]. Additionally, a host of psychosocial factors such as anxiety, catastrophizing, depression, and fear avoidance beliefs have also been reported in patients with chronic pain, particularly in those exhibiting peripheral or central neuropathic pain [28, 29]. Of these factors, catastrophizing and depression have been identified as the strongest predictors of pain-related outcomes [30, 31]. Multiple self-report questionnaires may be used to assess for the presence of psychosocial factors, including the Patient Health Questionnaire-2, Pain Catastrophizing Scale, and the Fear-Avoidance Beliefs Questionnaire. These assessments have all been reported to have acceptable reliability and validity in patients with various pain conditions [32–34]. Besides requiring a longer course of therapy, or achieving only a partial improvement in pain with rehabilitation, patients presenting with an increasing number of negative prognostic signs may also benefit from multidisciplinary forms of rehabilitation. The STarT Back tool is one example of an assessment that allows providers to stratify patients into those most likely to benefit from education only, traditional (PT), or nontraditional (psychologically enhanced PT) forms of rehabilitation [35]. The following section will expand on the idea of stratified care using a variety of proposed models.

Patient Classification

Physical therapy assessments are typically not based on the pathoanatomical cause of pain, since many times the exact source of pain is not able to be determined. Rather, movement-based classification schemes provide a logical framework on which physi-

cal therapists can base their treatment decisions. The majority of movement-based classification schemes have been developed for the management of spinal pain. These include Mechanical Diagnosis and Treatment (MDT), Treatment-based Classification (TBC), Movement System Impairment (MSI), and O'Sullivan Classification [36]. Movement-based classification schemes allow patients to be placed into homogenous subgroups with the goal of providing treatment to either increase or limit mobility and loading in specific directions. While the reliability for placing patients into homogenous subgroups is generally considered acceptable for all of the aforementioned movement-based classification schemes, the utility of these schemes to improve patient outcomes is debated [37]. No one movement-based classification scheme has been shown to be superior to another, and studies comparing classification-based treatment to traditional/multimodal treatment have yielded mixed results [37–42]. Therefore, new models of classification have been suggested to guide the management of pain.

Pain mechanism-based classification models have evolved along with our rapidly developing understanding of pain science. Physical therapy treatments can be linked to pain mechanisms in much the same way that pharmaceutical treatments are in order to maximize therapeutic benefit. Pain can be classified as nociceptive, neuropathic, or nociplastic (central) according to the preponderance of signs present. Nociceptive pain is localized to the area of injury/dysfunction, proportionate to the aggravating/easing factors, and typically resolves within expected healing timeframes [8]. Neuropathic pain can be described as burning, shooting, or electric, occurring in a dermatomal or cutaneous distribution, accompanied by positive neurodynamic and dysesthesia signs and associated with a history of nerve pathology or compromise [7]. Finally, nociplastic pain is widespread, described as highly irritable and intense, disproportionate to aggravating/easing factors, and associated with diffuse palpation tenderness (allodynia) and psychosocial issues [6]. In addition to sensory discrimination testing with QST, self-report questionnaires may be used to aid in the distinction of a patient's pain mechanism. The painDETECT questionnaire is a reliable and valid tool to identify nociceptive vs. neuropathic mechanisms of pain [43]. Scores below 19 suggest a nociceptive mechanism to pain, while scores at or above this threshold are consistent with neuropathic pain. The Central Sensitization Inventory is a valid and reliable tool that uses a score >40/100 to identify patients with nociplastic pain [44].

In an attempt to bridge the gap between the International Classification of Functioning, Disability, and Health (ICF) model of care, a traditional focus on movement-based treatment, and our evolving focus on pain mechanism-based treatment, Tousignant-Laflamme et al. [45] have proposed the Pain and Disability Driver Management Model for low back pain [45]. In this model, movement-based classification schemes are overlapped with nociceptive mechanisms of pain, which follows a more mechanically based approach to rehabilitation using exercise, manual therapy, and modalities. Multidisciplinary approaches to care, such as psychologically enhanced PT or interdisciplinary treatment, are incorporated for the management of peripheral/central neuropathic pain mechanisms and environmental/behavioral-based contributing factors. The Pain and Disability Driver Management

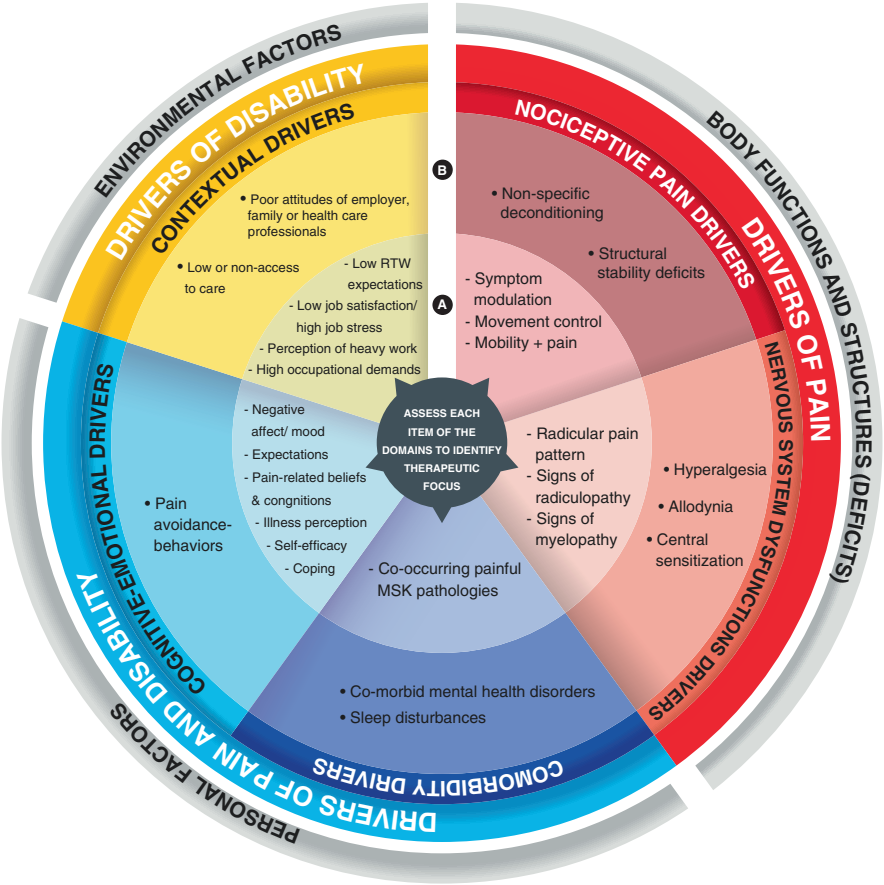

Fig. 17.1 Model for Pain and Disability Driver Management. (From Tousignant-Laflamme et al. [45]. With permission from Dove Medical Press)

Model is among the most comprehensive, biopsychosocial models currently available for the rehabilitation of low back pain (Fig. 17.1). While the current model specifically references treatments for the spine, the principles could be adapted to apply to patients with any type of musculoskeletal pain. The following section will use a pain mechanism model as the basis for discussing physical therapy treatments while also referencing movement/environmental/behavioral-based contributing factors that can be addressed with treatment.

Figure 17.1 shows a model for Pain and Disability Driver Management. Level A includes common elements that are more responsive to individualized treatment. Level B includes complex elements that require an interdisciplinary approach. RTW = Return to work. MSK = Musculoskeletal.

Management

Nociceptive Pain

The majority of published clinical practice guidelines for pain are written to apply to patients who report pain associated with an articular or muscular system impairment. Such is the case for guidelines on the treatment of nonspecific neck or low back pain and lower extremity osteoarthritis [46–63]. While a peripheral nociceptive mechanism is believed to contribute primarily to many of these conditions, a neuropathic or nociplastic mechanism may predominate in some cases [64]. This coexistence of pain mechanisms may explain why some patients with chronic pain do not respond to mechanical, nociceptive-focused treatments which emphasize articular or muscular dysfunction. In cases where nociceptive and non-nociceptive mechanisms are present, a multidisciplinary approach, including treatments described in the neuropathic and nociplastic sections of this chapter, may improve patient outcomes. Multidisciplinary care has been shown to be more effective than standard medical treatment for managing nonmalignant chronic pain conditions such as chronic LBP, fibromyalgia, and mixed chronic pain [65].

Assuming a nociceptive mechanism is predominant, treatments may be selected that address the primary impairment to a patient's movement, regardless of the pathological diagnosis. Using this reasoning strategy, treatment is tied to improving the quality of movement at and around the site of pain, rather than treatment directed at a specific tissue believed to be the source of pain. Regional interdependence is an important concept in this model of treatment, as movement in remote, non-painful areas can influence the degree of pain reported in localized areas [66].

The following section will present a treatment model for nociceptive pain using the core tenants of education, exercise, manual therapy, and modalities to address movement, environmental, and behavioral-based contributing factors. Clinical reasoning is essential to determine which tenant(s) should be emphasized in a particular patient's plan of care, as significant variations can occur in the ordering and grouping of interventions. Supplementary tables are provided detailing the clinical practice guideline recommendations published for spinal pain (Table 17.1) and lower extremity osteoarthritis (Table 17.2).

Education

All patients with nociceptive pain should be educated about their condition and assist in the development of the plan of care for the condition. Education regarding the condition generally includes reassurance about the benign and self-limiting nature of pain from a non-serious pathology. Education about the goals and plan of care should incorporate the patient's preferences where possible. A strong therapeutic alliance is built between the therapist and patient when the patient understands

Table 17.1 Evidence-based recommendations for physical therapy management of acute-chronic neck and low back pain

Treatment for spinal pain	Strength of evidence	Determination
Setting and education		
Inter−/multidisciplinary treatment (chronic)	Low to moderate [46, 48, 49, 52, 82]	Evidence-based treatment
Education, reassurance, and advice to stay active	Low to moderate [48, 49, 51, 53, 82]	
Exercise		
Mindfulness, yoga, tai chi, pilates (chronic)	Low [46, 47, 49, 52]	Evidence-based treatment
Therapeutic exercise: Strengthening, stretching, aerobic, motor control (subacute to chronic)	Low to high [46–49, 51–53, 82]	
Manual therapy		
Manual therapy	Low to high [46–49, 51–53, 82]	Evidence-based treatment
Spinal manipulation (acute)	Low [47, 49, 52, 82]	
Massage	Low to moderate [46, 47, 49, 51, 52, 82]	
Modalities		
Acupuncture	Low to moderate [46, 49, 51, 52, 82]	Evidence-based treatment
Superficial heat or cold (acute)	Moderate [52]	
Low-level laser therapy (chronic)	Low [49, 52]	
Lumbar supports	Low [55]	Accepted but unproven
Kinesiotape	Low [127]	
Therapeutic ultrasound	Low [55]	
Transcutaneous electrical nerve stimulation	Low [55]	
Electrical muscle stimulation	Low [55]	
Traction	Low [47]	Disproven
Pulsed electromagnetic field	Low [131]	Emerging or promising treatments
Cupping	Low [132]	
Whole-body vibration	Low [133]	

their condition and has confidence and trust in the mutually agreed upon plan to address the condition. Evidence suggests that a patient's positive or negative perspectives regarding a specific treatment can positively or negatively affect the outcome of the intervention [67, 68]. Additionally, a strong therapeutic alliance has been associated with improved overall patient outcomes [69].

Education regarding treatment expectations should include advice to remain active and specific recommendations for self-care. Patients reporting increased pain during sustained postures should be asked about external support, including but not limited to footwear (if pain is provoked with sustained standing), chair surfaces (if pain is provoked with sustained sitting), or pillow/bed surfaces (if pain is provoked with sustained lying). Foot orthoses have been shown to provide medium-term pain relief in patients with plantar heel pain [70], while sitting and

Table 17.2 Evidence-based recommendations for physical therapy management of hip and knee osteoarthritis

Treatment for lower extremity osteoarthritis	Strength of evidence	Determination
Education		
Education on activity modification, weight reduction unloading of arthritic joints	Moderate [50]	Evidence-based treatment
Exercise		
Therapeutic exercise for flexibility, strengthening, and endurance	Low to high [50, 54, 57, 58, 60, 61]	Evidence-based treatment
Aquatic exercise for those unable to tolerate land-based treatment	Low [56]	
Functional, gait, and balance training	Low [50, 56]	
Yoga (knee)	Moderate [59]	
Manual therapy		
Joint mobilization (hip)	Moderate to high [50, 54]	Evidence-based treatment
Manual therapy (knee)	Low [57]	Accepted but unproven
Modalities		
Pulsed electromagnetic field (knee)	Low [54]	Evidence-based treatment
Therapeutic ultrasound	Low to moderate [50, 54]	
Superficial heat (hip)	Moderate [50]	
Kinesiotape	Low [128]	Accepted but unproven
Medial compartment unloader brace	Low [57]	
Low-level laser therapy	Low [123]	
Acupuncture	Low [54, 56, 57]	
Transcutaneous electrical nerve stimulation (knee)	Low [54]	Disproven
Lateral wedge insoles (knee)	Low [57]	

sleeping postures have been shown to impact spinal pain [71, 72]. Self-care may also include specific recommendations on a home exercise program (HEP). The HEP should focus on the primary impairment(s) to movement and generally progress from exercises for stretching/mobilization to exercises for strengthening/conditioning. Patients should be reminded about the signs of overload when performing exercises. Since it is common for patients with chronic pain to experience some degree of discomfort during exercise, clear expectations should be communicated about what would be considered an appropriate amount of pain. Pain that is increased during exercise should not be unbearable, should not outweigh the feeling of "work" achieved during exercise, and should begin to decrease within a few hours of completing an exercise (assuming no delayed onset muscle soreness is present). If any of these criteria are violated, the amount of loading for the exercise may be excessive, thus leading to a nonproductive exacerbation of the patient's pain.

Exercise

Exercise is considered the foundation of physical therapy management for multiple painful conditions [46–63]. Exercise has been shown to reduce nociceptor excitability, increase expression of neurotrophins in the muscle, and increase production of anti-inflammatory cytokines [73–75]. Exercise can consist of many forms, including but not limited to ROM/stretching, strengthening, neuromuscular reeducation, aerobic conditioning, and functional training. Additionally, exercise forms can be packaged within different approaches, such as gym/resisted training, spinal stabilization, yoga, pilates, or tai chi. Evidence generally suggests that one exercise approach is not superior to others for the management of chronic spine pain [76, 77]. However, some preference may be given to prescribing a specific form of exercise to specific patient subgroups.

Patients with extremity pain that is being referred from a specific spinal region may benefit from the use of repeated ROM/stretching exercise more than other forms of exercise such as spinal stabilization [78]. Additionally, the direction of the ROM exercise appears to influence the response, as exercise given in the opposite direction to the movement preference did not improve pain as much as exercise matched to the movement preference [79]. The notion of directional preference treatment is well established in the spine and is also now being studied in the extremities [80, 81]. ROM exercises are typically repeated in sets of ten multiple times a day until maximal pain relief has been achieved.

Motor control/stabilization and general exercise programs are each recommended for the rehabilitation of spinal pain [52, 82]. Stabilization programs traditionally include an emphasis on focused, isometric training of core muscles such as the deep neck flexors, transversus abdominis, and multifidus, whereas general exercise programs typically emphasize a mixture of nonspecific muscular stretching and strengthening. While a stabilization program seeks to improve muscular control and coordination, a general exercise program seeks to improve muscular flexibility, endurance, or hypertrophy. In a heterogeneous population of patients with low back pain, evidence suggests that motor control/stabilization and general exercise yield similar benefits in terms of pain and functional improvements. In patients with low back pain and signs of radiographic instability, aberrant movements, or segmental hypermobility, a stabilization/motor control program may be preferred to a general exercise program or to manual therapy [14, 83, 84].

When deciding which form of exercise to select for their patients with either spine or extremity pain, clinicians may consider several factors. In cases where pain is predominant, isometric exercise may be better tolerated than isotonic strengthening exercise for addressing both pain and muscle inhibition [85]. Isometrics can be progressed from low to high intensity, with dosing of hold times being inversely related to the intensity (i.e., submaximal intensity with ≥10-second hold vs maximal intensity with <7-second hold). In patients with predominant movement coordination impairments, an exercise program generally focusing on the correction of aberrant movements and postures, with or without the inclusion of a specific motor control emphasis, may be utilized [86, 87]. Exercise programs for movement coor-

dination impairments typically involve using body weight as resistance, with very high (≥30) repetition dosing and an emphasis on quality of movement. When weakness is predominant, either in areas local or remote to the painful area, a traditional strengthening program emphasizing muscle loading may be beneficial. Physical therapists commonly apply a regional interdependence model to strengthening programs, where thoracic/scapular strengthening is incorporated into cervical and shoulder rehabilitation programs [88] and where hip strengthening is incorporated into low back and knee rehabilitation programs [89]. Using an external load to create muscle fatigue, typical dosing for a strengthening program is to aim for 6–12 repetitions for muscular hypertrophy and >12 repetitions for muscular endurance.

Aerobic conditioning should be recommended as a means of pain modulation, relaxation and stress relief, and cardiovascular/fitness training for all patients with chronic pain [90]. This form of exercise may be most beneficial for patients with deconditioning or fatigue as an accompanying chief complaint to pain [91]. Aerobic conditioning can be effectively performed using a variety of exercise approaches, some of which may include the use of low-impact equipment, low-load environments such as a pool, or the ability to limit movement to non-painful areas. Regardless of the approach, the key element to achieving pain relief is to reach a workout intensity of *at least* 50–60% of one's maximum heart rate [92]. An intensity of 70% of the maximum aerobic capacity has been shown to stimulate endorphin release and activation of descending pain inhibition for up to 30 minutes after exercising [93, 94]. When performed for a duration of 20–30 minutes on at least 2–3 days in a week, patients with a variety of painful conditions can achieve exercise-induced analgesia and improved physical and psychological function [95, 96].

Manual Therapy

Manual therapy may be beneficial to any patient with pain and mobility deficits. Manual therapy can be performed to the joints or soft tissues, delivered using the hands or instruments, via thrust or non-thrust forms of manipulation. Manual therapy has been shown to act through mechanical, neurophysiological, and psychological mechanisms; however, neurophysiological mechanisms have received the most support in the literature [95]. A host of neurophysiological effects have been reported from joint manipulation, including activation of cannabinoid and adenosine analgesic systems, sympathoexcitation, reduced temporal summation, and alteration of muscle tone [97–101]. Additionally, reduced inflammation via altered gene or cytokine expression has been shown with stretching or massage [102]. Short-term improvements in pain have been shown in a majority of randomized controlled trials investigating the use of manual or instrumented massage for treating patients with spinal pain [103].

Regardless of the form used, evidence widely suggests that manipulation is effective for relieving pain and improving function in a number of pain conditions [46–63]. Significant debate still exists, however, regarding the superiority of thrust

vs. non-thrust forms of manipulation, particularly related to outcomes for patients with spinal pain [104, 105]. Clinical prediction rules (CPRs) have been developed to identify patients with neck or low back pain who may benefit more from a thrust form of manipulation [106, 107]. The rules generally suggest that acute-subacute patients with localized pain and segmental hypomobility are likely to benefit from a thrust technique. However, these recommendations should be implemented with caution, as the rules have not been successfully subjected to broad-based validation. Multiple randomized controlled trials have attempted to further clarify the question of thrust vs non-thrust superiority, often with mixed results. Evidence from pragmatic trials generally suggests that thrust and non-thrust techniques yield similar results, while evidence from prescriptive trials more often shows that thrust techniques are superior [108]. For the clinician deciding between these techniques, careful screening must first be performed regarding contraindications to manipulation, particularly at the cervical spine, where adverse events such as arterial dissection can result in permanent disability or death. Manipulation should not be performed in cases of poor or questionable bony or ligamentous integrity, cervical arterial dysfunction, severe or progressive neurological involvement, or cases of non-mechanical pain [109]. Adherence to the contraindications for manipulation, in combination with screening of blood pressure and cranial nerve integrity, can significantly reduce the incidence of a serious adverse event with manipulation [109].

A growing body of evidence suggests that regional interdependence may also be at work in manual therapy, which gives the clinician another option regarding the location of applied manipulation techniques [66]. CPRs have been produced for the use of thoracic spine manipulation for both neck and shoulder pain, lumbopelvic manipulation for patellofemoral pain, and hip manipulation for knee osteoarthritis [110–113]. Based on the results of a validation study for the thoracic manipulation CPR for neck pain, the authors concluded that *all* patients with neck pain may benefit from a thoracic manipulation, not just those fitting the rule [110]. Validation studies have otherwise not been performed for the aforementioned CPRs, but with a low risk and minimal time investment to intervention, an implementation trial of regional manual therapy would seem warranted in many cases. In general, patients with shoulder pain who may benefit from cervicothoracic manipulation include those who are acute-subacute, with limited shoulder flexion and internal rotation ROM, and a negative Neer test [113]. Patients with patellofemoral pain who may benefit from lumbopelvic manipulation include those with increased amounts of foot pronation and ankle dorsiflexion ROM, asymmetry in hip internal rotation, and pain with squatting [112]. Patients with knee OA who may benefit from hip manipulation include those with limited hip flexion and internal rotation ROM and hip/anterior thigh pain that is increased with hip distraction [111].

Since manual techniques are often done passively, they should be considered as a means to an end (with the end being active exercise), and not the end. Multiple high-quality trials suggest that outcomes are improved for neck, back, and shoulder pain if manual therapy and exercise are paired together versus applied as a standalone treatment [114–116]. Non-thrust manipulation techniques are typically per-

formed for up to 30 seconds at a time and repeated until a change in pain or mobility has been achieved. A within-session change in pain or mobility can be expected after a single application of manual therapy and when present, is considered a good indicator of future prognosis with treatment [117].

Modalities

Modalities can serve as a valuable adjunct treatment for pain, whether administered in a home or clinical setting. Home-based treatments such as superficial heat or cold are affordable, accessible, and easy for patients to apply. Cold is generally recommended in the first 48–72 hours after an acute injury to reduce visible signs of swelling and inflammation and for pain control [118]. Beyond 72 hours, patients can use either heat or cold for pain relief, although heating is associated with improved blood flow to an injured area which may aid in tissue repair [118]. Cold application is typically limited to 10 minutes at a time, while heat application can be prolonged if the intensity remains low [119]. Evidence generally supports the use of thermal modalities for pain relief in patients with spine pain and lower extremity osteoarthritis.

Electro-physical modalities such as transcutaneous electrical nerve stimulation (TENS), low-level laser therapy, and therapeutic ultrasound may be administered in a clinical setting to relieve pain and facilitate healing. Significant variability exists in the recommended dosages used for these modalities, which may explain the variability seen in results from clinical outcome trials. While it is beyond the scope of this text to discuss the specific parameters for applying these modalities, a general overview of the physiological mechanisms and clinical outcomes is provided. TENS works at a peripheral level to reduce excitation of the sympathetic nervous system via noradrenergic receptor stimulation and to modulate peripheral sensitization via simultaneous activation of μ-opioid receptors and blocking of substance P production [120, 121]. Despite this reported ability to alter pain physiology, clinical trials do not support the use of TENS for improving pain and function in patients with nonspecific spinal pain or lower extremity arthritis [54, 55]. Low-level laser therapy targets the mitochondria to convert light energy into chemical energy used for DNA/RNA synthesis, mitosis, and cell proliferation [122]. Evidence supports the use of low-level laser therapy for chronic spine pain, but is conflicting for its use in lower extremity arthritis [49, 52, 123]. Finally, therapeutic ultrasound targets the superficial soft tissues to improve metabolism, blood flow, and extensibility [124]. While evidence is conflicting for its effectiveness in patients with spinal pain, support is found for using ultrasound in patients with lower extremity osteoarthritis and calcific tendonitis of the shoulder [50, 54, 125].

Two pain-relieving modalities that have gained popularity among physical therapists over the last two decades include kinesiotaping and dry needling. Kinesiotaping is commonly used among athletes, with a proposed list of benefits including improved circulation/lymphatic flow, normalized muscle function, remodeling of fascial tissue, and improved joint balance [126]. Despite its widespread use, evi-

dence on the effects of taping is conflicting overall, but may show promise for functional improvement in patients with back and knee pain [127, 128]. Dry needling is primarily used to target myofascial pain at various sites throughout the body and can be administered with or without electrotherapy. Dry needling is not synonymous with acupuncture due to differences in the theories, techniques, and training provided. However, some overlap between these modalities can be found in two areas. Both the acupuncture and dry needling literature underscore the importance of neurophysiological mechanisms such as endogenous opioid release and improved descending pain inhibition to explain the immediate and lasting improvements in pain relief achieved with treatment [129, 130]. Additionally, close relationships have been found between trigger points, tender points, and acupuncture points, suggesting that a common mechanism such as sensitized nociceptors may be present. Evidence generally supports the use of acupuncture/electro-acupuncture for chronic spine pain, but is conflicting for its use in lower extremity arthritis [52, 57].

Neuropathic Pain

Patients presenting primarily with a neuropathic mechanism of pain have unique treatment needs compared to patients with nociceptive pain. In particular, evaluation and management of the nervous system is critical for patients with neuropathic pain, whereas a focus on the articular and muscular systems often dominates in cases of nociceptive pain. The following section will discuss a treatment model for neuropathic pain using the same four core tenants previously described and emphasizing interventions that are nervous system-based. One should recognize, however, that patients with neuropathic pain will also likely present with muscular and articular system impairments which may necessitate the use of treatment approaches described in the previous section. Supplementary tables are provided detailing the clinical practice guideline recommendations published for spinal radiculopathy (Table 17.3) and carpal tunnel syndrome (Table 17.4).

Education

Pain neuroscience education (PNE) is the practice of teaching patients how pain processing occurs in the nervous system [134]. Patients gain a practical understanding of such concepts as nociception, spinal inhibition/facilitation, peripheral and central sensitization, and nervous system plasticity. A number of methods can be used to teach PNE, including booklets, videos, and drawings/examples provided by the clinician. A typical example used in PNE is the idea of pain as an alarm system. In a normally functioning nervous system, use of the alarm (pain) is reserved for situations where physical or emotional harm is realized. However, in cases where the nervous system has been sensitized, the threshold for sounding the alarm is lowered. This can make movements or emotions that are well below the threshold of harm be perceived as painful, which can greatly reduce the patient's activity tol-

Table 17.3 Evidence-based recommendations for physical therapy management of cervical or lumbar radiculopathy

Treatment for radiculopathy	Strength of evidence	Determination
Education		
Education on pathology, pain mechanisms, and coping with activity modification	Moderate [51, 53]	Evidence-based treatment
Exercise		
Therapeutic exercise for motor control, graded strengthening, and directional movements	Low [49, 51, 53, 82]	Evidence-based treatment
Manual therapy		
Manual therapy including spinal manipulation	Low [49, 51, 53, 82]	Evidence-based treatment
Massage	Low [49, 82]	Accepted but unproven
Modalities		
Traction	Low [51]	Evidence-based treatment
Transcutaneous electrical nerve stimulation	Low [49]	Accepted but unproven
Acupuncture	Low [49, 82]	
Ultrasound	Low [82]	
Low-level laser therapy	Low [82]	

Table 17.4 Evidence-based recommendations for physical therapy management of carpal tunnel syndrome

Treatment for carpal tunnel syndrome	Strength of evidence	Determination
Education		
Education on immobilization at night with wrist splints	High [155, 156]	Evidence-based treatment
Exercise		
Therapeutic exercise (nerve gliding, tendon gliding, generalized stretching/yoga)	Low [156]	Evidence-based treatment
Manual therapy		
Manual therapy (carpal and soft tissue mobilization)	Low [157]	Evidence-based treatment
Modalities		
Therapeutic ultrasound and ketoprofen phonophoresis	Low [155]	Evidence-based treatment
Low-level laser therapy with transcutaneous electrical nerve stimulation	Low [155]	
Acupuncture	Low [157]	Accepted but unproven
Iontophoresis	Low [156]	Disproven
Magnet therapy (carpal and soft tissue mobilization)	Low [155]	
Polarized polychromatic noncoherent light (Bioptron) therapy	Low [158]	
Cupping	Low [159]	Emerging or promising treatments
Interferential current	Low [160]	
Local microwave hyperthermia	Low [158]	
Continuous shortwave diathermy	Low [158]	

erance. PNE is primarily indicated for patients who are experiencing chronic pain, particularly associated with a neuropathic or nociplastic mechanism. Current evidence supports the use of PNE in chronic musculoskeletal disorders to reduce pain and improve knowledge of pain, improve function and lower disability, reduce psychosocial factors, enhance movement, and minimize healthcare utilization [135].

Exercise

Neurodynamic exercise should be considered in the treatment of patients with neuropathic pain [136]. The potential benefits of this form of exercise may include reduction of nerve adherence, increased neural vascularity, and improvement of axoplasmic flow [21]. Neurodynamic exercise should be based on the results of neurodynamic testing, with expected findings of symptom reproduction and reduced ROM compared to the uninvolved side. A key component of neurodynamic testing is the concept of structural differentiation, whereby movement of a remote area (e.g., neck flexion) alters pain in a primary area (e.g., increased posterior thigh pain) during nerve tension testing (e.g., the straight leg raise test) [21]. When structural differentiation is present, the nervous system (as opposed to the musculoskeletal system) is implicated. Using this concept to inform treatment, tension can also be *reduced* at a remote area while it is being increased across the primary area (e.g., neck extension during a straight leg raise). This type of movement is referred to as a sliding maneuver and is often used as treatment in patients with acute or irritable pain conditions [21]. Neurodynamic exercise should begin with sliding maneuvers on the side of pain or tension maneuvers on the *contralateral* side of pain to reduce forces in the nervous system. Exercises should progressively increase forces in the nervous system through the use of tension maneuvers on the side of pain and through altering the order of applied limb movements so that more painful areas are moved earlier in the neurodynamic sequence [21]. Exercises are generally performed for three to five sets of five to ten repetitions and repeated throughout the day.

Neurodynamic exercise has received support in two recent systematic reviews. Low-level evidence was found for the effect of neurodynamic exercise on reducing intraneural edema in patients with carpal tunnel syndrome [137]. Evidence from randomized controlled trials supports the use of neurodynamic exercise for reducing pain intensity in neck and low back pain and for improving disability in low back pain. The greatest improvements have been found in low back pain, where large effect sizes have been reported for changes in both pain and disability [138]. Lower extremity neurodynamic exercise typically begins with the use of the straight leg raise and progresses to the use of the slump position for maximum loading.

Manual Therapy

Mobilization of the mechanical interface points along a nerve can be an important adjunct intervention to ensure normal neurodynamics. Interface points such as the intervertebral foramen, ligaments, and muscles can become limited in their mobil-

ity, which can in turn limit neural mobility. In patients with radiculopathy, mobilization should begin with positioning or manual techniques to open the neural foramen, including spinal flexion and contralateral sidebending [21]. This form of treatment should continue until the patient can tolerate tension maneuvers on the side of pain, at which time closing techniques into extension, ipsilateral sidebending, or contralateral lateral glide may be implemented [21]. A closing technique referred to as the cervical lateral glide has been studied repeatedly as a treatment for cervical radiculopathy [139–141]. During this technique, patients are supine with the ipsilateral upper extremity placed in some degree of neural tension, while the neck is glided laterally away from the side of pain. Immediate to short-term improvements in pain and disability have been reported for the cervical lateral glide technique in patients with arm pain compared to ultrasound, wait list, and placebo [139–141]. Similarly, a lateral glide technique may be performed at the lumbar spine by placing the patient in sidelying with the involved leg in some degree of neural tension and applying a translatoric force to the spinous process away from the side of pain. A randomized controlled trial comparing the lumbar lateral glide technique with exercise to a program of exercise-only demonstrated significant improvements in pain and disability at short and long term for the group receiving the combined interventions [142].

Patients with carpal tunnel syndrome may also benefit from various manual therapy interventions applied along nerve interface points. A group receiving carpal joint mobilization achieved superior results in pain relief compared to controls, but similar improvements compared to a group receiving neurodynamic exercise of the median nerve [143]. Specific, interface-based massage yielded greater improvements in grip strength compared to the application of general massage at the neck, back, and upper extremity [144]. And finally, similar improvements in nerve conduction velocity, hand function, and symptom severity were reported in a group of patients receiving instrumented, Graston soft tissue mobilization and exercise compared to manual soft tissue and joint mobilization with exercise [145].

Modalities

Modalities for the treatment of neuropathic pain can be grouped into those that are directed at the nerves or their mechanical interfaces. Traction may provide unique benefits for the patient with radiculopathy due to its ability to influence multiple mechanical interface points which impact foraminal opening and intervertebral disc dynamics. While traction is generally not recommended for patients with nonspecific spinal pain, multiple studies have supported the use of traction in patients with radiculopathy, particularly in the cervical spine [146–148]. A clinical prediction rule for the use of cervical traction suggests that patients >55 years old with positive neurodynamic testing, relief of symptoms with traction and shoulder abduction testing, and radiation of symptoms with cervical mobility testing may have the greatest likelihood of achieving a clinical benefit [149]. While this CPR has only been partially validated in a subsequent

study [150], a more recent systematic review supported the widespread application of traction and physical therapy in patients with cervical radiculopathy [148].

Modalities that are directed at the nerve for the management of carpal tunnel syndrome may include ultrasound/phonophoresis, laser/TENS, and splinting. Night splinting is typically recommended as superior to no treatment, although no preference has been found for different splinting styles or wearing regimens [151]. The use of ultrasound with or without phonophoresis provides greater benefits than sham treatment [152]; however, ketoprofen phonophoresis may provide superior benefits over ultrasound alone [153]. Finally, a combination treatment of laser and TENS yielded significant improvements in pain, sensory/motor latency, and provocation tests compared to a sham treatment in patients with carpal tunnel syndrome [154].

Nociplastic pain

The final treatment category is reserved for patients with chronic, complex pain that requires a multifaceted approach to care. Whether physical therapy treatment is administered within an interdisciplinary pain program or not, it should be psychologically enhanced to better influence the cognitive-emotional needs of the patient with nociplastic pain [35, 45]. Interventions may be selected from any of the aforementioned sections, but should also uniquely address the issues of sensory integration and behavioral modification. The following section will emphasize these unique treatment approaches in the context of the four core tenants to physical therapy management. Supplementary tables are provided detailing the clinical practice guideline recommendations published for fibromyalgia (Table 17.5) and complex regional pain syndrome (CRPS), type 1 (Table 17.6).

Education

PNE is considered fundamental in the education provided to patients with nociplastic pain. In addition to learning about pain neurophysiology, patients with nociplastic pain should be informed about brain body maps and the disassociation between pain and a tissue pathology [161]. An image of the brain's homunculus is useful to help explain the concepts of neuroplasticity and cortical smudging. Patients are educated that the internal picture of our body can become warped very quickly when pain is present and that ongoing distortions of this image can result in abnormal movement patterns, decreased coordination, poor body awareness, and heightened nerve sensitivity [162]. The patient is reassured that the body map can be reimaged rapidly and that physical therapy can successfully test for and treat distortions in brain mapping. Additionally, patients are educated that as pain becomes chronic, the timeframe for normal tissue healing has passed away, suggesting that pain is more

Table 17.5 Evidence-based recommendations for physical therapy management of fibromyalgia

Treatment for fibromyalgia	Strength of evidence	Determination
Setting and education		
Multicomponent treatment (≥1 educational or psychological therapy with ≥1 exercise therapy)	Low [54, 181]	Evidence-based treatment
Education to pursue a normal lifestyle using pacing and/or graded activity	Low [181, 185]	
Exercise		
Graduated exercise (aerobic, strengthening, aquatics)	Low to moderate [181, 185, 186]	Evidence-based treatment
Tai chi, yoga, qigong, or Body awareness therapy	Low [54, 181]	
Whole-body vibration exercise training	Low [187]	Emerging or promising treatments
Guided imagery	Low [181]	
Manual therapy		
Myofascial release massage	Moderate [54, 181]	Evidence-based treatment
Chiropractic (massage, stretching, spinal manipulation, education, and resistance training)	Low [181]	Accepted but unproven
Modalities		
Acupuncture	Moderate [54, 181]	Evidence-based treatment
Hydrotherapy	Low [181]	
Low-level laser therapy	Low [188]	Accepted but unproven
Transcutaneous electrical nerve stimulation	Low [189]	
Transcranial magnetic and direct current stimulation	Low [190, 191]	Emerging or promising treatments

a product of a dysfunctional nervous system than it is a dysfunctional tissue [161]. This type of information can be liberating for a patient who has otherwise been told that there is nothing wrong with them or that it is all in their head. In addition to the previously cited outcomes of PNE for improving pain and function, physiological changes have also been observed using FMRI. A single case report found evidence of deactivation at the periaqueductal gray and cerebellum, coupled with activation of the motor cortex, indicating alterations in central pain processing that are critical for the patient with nociplastic pain [163].

Exercise

The term graded motor imagery (GMI) is used to refer to a collection of exercises including left/right discrimination, motor imagery, and mirror therapy to address sensory integration impairments in patients with nociplastic pain [164]. It is critical that any GMI program begins with PNE, as the patient must have a basic under-

Table 17.6 Evidence-based recommendations for physical therapy management of complex regional pain syndrome, type 1

Treatment for complex regional pain syndrome, type 1	Strength of evidence	Determination
Setting and education		
Interdisciplinary treatment with a functional restoration emphasis	Low [169, 184]	Evidence-based treatment
Exercise		
GMI and mirror therapy	Low to moderate [184, 192]	Evidence-based treatment
Tactile discrimination	Low [193]	
Graded exercise and exposure	Low [192]	
Stress loading program	Low [169, 192]	Accepted but unproven
Manual therapy		
Massage and electroacupuncture	Low [184]	Emerging or promising treatments
Manual lymphatic drainage	Low [184, 192]	Disproven
Modalities		
Transcutaneous electrical nerve stimulation	Low [192, 193]	Accepted but unproven
Therapeutic ultrasound of stellate ganglion	Low [184]	Disproven
Low-level laser therapy	Low [184]	Emerging or promising treatments
CO_2 bath therapy	Low [184]	
Pulsed electromagnetic field	Low [192]	

standing of pain neurophysiology to fully buy into this nontraditional "brain" exercise approach. Exercises are introduced on a continuum, where interventions that avoid movement or touch are introduced first. The program begins with exercises on left/right discrimination that are meant to sharpen the mind body maps. Pictures of the affected body part from magazines or mobile apps are shown to the patient, with the goal of having the patient identify whether the image is from a left or right side. Normative data suggests that patients should be able to achieve ≥80% accuracy at an average response rate of ≤2 seconds/image [165]. Patients with extremity pain are more likely to exhibit impairments in left/right discrimination testing than patients with axial pain [166]. The next level of progression is imagery of movements that are considered threatening to the patient. By imaging the movements in a non-limited, non-painful manner, the patient is able to decrease the threat level associated with the activity, which can have rapid effects on pain reduction [167]. Next, patients are ready for gradual exposure to touch and movement. Sensory discrimination training at or around the painful area can take place in many forms, including graphesthesia, localization, desensitization, or two-point discrimination. Regardless of the form selected, tactile stimuli (e.g., shapes drawn on the skin) should be used that will be difficult but not impossible for the patient to accurately identify. Finally, exercise is initiated with the use of mirrors to provide the patient with a non-limited, non-painful image of the affected area moving, when in actuality it is the patient's *opposite* side moving. This form of treatment has been primar-

ily studied in patients with CRPS, with moderate-level evidence suggesting improvements in pain and ROM as a result of mirror therapy [168]. As with any form of exercise, repetition is key for improved performance and outcomes. The recommended dose for imagery and laterality training is 1–2 hours/day which is performed in multiple, short sessions of about 20 images/session. Sensory discrimination and mirror therapy is dosed more similarly to traditional exercise, with two to three sets of ten repetitions performed within a session lasting about 3–5 minutes. Exercise within the GMI framework does not need to be completed in a lockstep fashion, as certain components can be omitted or introduced simultaneously depending on the unique impairments and irritability level of the patient.

Where GMI training may be considered as the means to the end, functional restoration training should be considered as the end goal for patients with nociplastic pain [169]. Functional restoration training utilizes a quota system to encourage improvements in strength, flexibility, and conditioning as the metric for success in an exercise program. With patients focused on improving these physical metrics, as opposed to a focus on their pain response, progressive loading is achieved that results in significant changes in functional capacity. In a graded exercise approach to treatment, quotas are set at the time of baseline testing. Patients who meet their quota receive positive reinforcement and an increase in the quota, while those not meeting their quota are encouraged to meet it during the next exercise session. Examples of graded exercises typically include strength and endurance training, lifting, walking, and cycling. Patients may receive up to 2.5 hours of quota-based activity in a daylong treatment session, which may be repeated on consecutive days within the framework of an interdisciplinary program. Evidence in patients with fibromyalgia suggests that a multimodal program of strengthening and stretching combined with aerobic exercise is superior to a unimodal program of aerobic exercise at improving pain and function, with moderate-large effect sizes reported [170]. Exercise in the moderate- to high-intensity range has been found to be both safe and effective for improving pain, function, and strength in patients with fibromyalgia [171]. Yet, therapists should be aware that patients with central pain processing dysfunction may initially find exercise to be quite irritating due to a loss of descending pain inhibition. In such cases, aerobic exercise may initially be better tolerated than isometric or eccentric exercise, since the latter may elevate nervous system excitability [172]. Furthermore, aerobic exercise may initially be performed at non-painful body regions or, in the case of fibromyalgia, at an intensity below 70% VO_{2max} [173]. Patience, persistence, and adequate recovery between exercise bouts are the key to overcoming these temporary barriers, as the patient's pain response is expected to improve with continued exercise over the course of several weeks [90].

Finally, graded exposure approaches to exercise may be utilized for patients with fear (vs. pain) as a primary impairment to movement. The Fear of Daily Activities Questionnaire is used to identify a patient's level of fear for a particularly limited activity at baseline [174]. Patients are asked to perform the particular activity at a specified intensity and time and then rate their level of fear post-activity. The time or intensity of the activity is subsequently increased if fear is reduced post-activity, while the exercise is left unchanged and repeated if fear is increased or stays the same. Examples of graded exposure activities include walking, sitting, standing,

lifting, and carrying. In a group of patients presenting primarily with work-related chronic low back pain, graded exercise compared similarly to graded exposure for improvements in pain and disability [175].

Manual Therapy

Manual therapy may be beneficial in a subset of patients with nociplastic pain. Joint or soft tissue-based techniques may first be applied locally or regionally to the area of pain as described in the section on nociceptive mechanisms. However, when symptoms are relatively widespread, or when pain limits the application of treatment to the primary area(s), a different perspective may be utilized. In such cases, treating dysfunctions in spinal mobility, even when they are remote to the area of pain, may positively impact neural sensitivity on a systemic level. Spinal manipulation has been performed in a number of conditions associated with a nociplastic mechanism, including fibromyalgia, CRPS, whiplash associated disorder, lateral epicondylitis, and temporomandibular disorder [176]. Additionally, massage has been reported as beneficial for pain relief and functional improvements across a number of pain conditions [177]. Since massage and thrust manipulation have each been shown to work via central mechanisms, these interventions may have greater potential to modulate centrally mediated pain compared to other forms of manual therapy, particularly in patients with fibromyalgia [178–180].

Modalities

A limited number of modalities have been recommended in the management of patients with nociplastic pain. Balneotherapy, which is the therapeutic use of baths, is supported in clinical practice guidelines for fibromyalgia [181]. This hydrotherapy may be delivered at a spa or in the home, via water or mud baths, at a temperature range of 36–45 °C and an average exposure time of 240 minutes over several weeks [181]. Additionally, both acupuncture and dry needling may be beneficial in the treatment of myofascial pain and fibromyalgia [182, 183]. After four weekly sessions of dry needling to the neck and shoulder girdle, patients with fibromyalgia reported significant improvements in a wide range of outcomes, including pain, function, fatigue, anxiety, depression, and sleep quality [183]. Electroacupuncture coupled with massage has also received preliminary support in the literature, making it a promising treatment for patients with CRPS [184].

Conclusion

This chapter provides an evidence-based framework for the evaluation and management of pain by a physical therapist. Using a biomechanical focus to the examination, the therapist should first consider the relative contributions of the articular,

muscular, and nervous systems to impaired movement. Using a biopsychosocial focus to the overall assessment, the therapist should then consider how pain mechanisms and environmental/behavioral-based factors contribute to activity limitations and participation restrictions. Formation of a treatment plan may be viewed like the layers of an onion, with treatments becoming increasingly complex, or layered, as you move further away from the center. Patients with a nociceptive mechanism and fewer environmental/behavioral-based factors are found closest to the center of the onion, making up the "core" of traditional articular- and muscular-based physical therapy treatments. Patients with neuropathic and nociplastic pain are found beyond the core and will require a multilayered approach to management. In addition to traditional treatments, these patients should also receive interventions focused on neurodynamics, sensory integration, and behavioral modification. Regardless of the underlying pathology, the skillful application of layered physical therapy treatment is essential for the successful management of chronic pain.

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Chapter 18
Interdisciplinary Pain Management Programs in the Treatment of Pain Conditions

Danielle M. Brecht, Jessica Stephens, and Robert J. Gatchel

Preface: The Problem of Chronic Pain in America and the Need for an Interdisciplinary Approach

"Pain is a more terrible lord of mankind than even death itself." Dr. Albert Schweitzer's 1931 statement (as cited in [1]) may emphasize the powerful grip a pain condition may have over the well-being of the afflicted. Pain conditions are often ongoing and present with obvious and crippling symptoms. The burden of facing such a condition, or one which is often debilitating to daily functioning and quality of life, may feel insurmountable to some.

It is estimated that 100 million Americans suffer from chronic pain, and an additional1.5 billion people face the problem globally [2]. Moreover, pain is the most common reason Americans report when seeking medical care, thus making it the leading cause of disability and costs to the healthcare system in the USA [2]. More specifically, the substantial cost of chronic pain equates to $2,000 per living US resident, or a massive collective expenditure of $560–$635 billion dollars annually [3]. Other related costs include productivity losses of the 36 million Americans who miss work per year due to substantial pain. This amount is estimated to equate to approximately $299–$325 billion dollars in lost labor and production (i.e., days from work missed, hours of work lost, and lower wages taken related to chronic pain) [4]. These staggering statistics are indicative of the need for understanding how to effectively manage chronic pain conditions in a timely manner. Scientific

D. M. Brecht (✉) · J. Stephens
Department of Psychology, The University of Texas at Arlington, Arlington, TX, USA
e-mail: danielle.brecht@mavs.uta.edu

R. J. Gatchel
Department of Psychology, Center of Excellence for the Study of Health and Chronic Illnesses, The University of Texas at Arlington, Arlington, TX, USA
e-mail: gatchel@uta.edu

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and medical advancements in this area may lead to huge strides in the improvement of life quality and productivity of many millions of Americans and the attenuation of a substantial financial burden on the American economy.

One method of treating chronic pain conditions that has recently emerged, and which continues to accrue gains in popularity, is the use of *interdisciplinary care teams* (ICT) in implementing diversified, affiliative, structured, and highly unified ongoing therapy for pain conditions.

A myriad of pain conditions may be better treated, reduced in diagnostic frequency, and/or diminished in severity by enhancing the research and practical implementation of interdisciplinary practices. Such a change would likely make a highly effective therapeutic avenue for pain care more accessible to the medical community and the pain-suffering masses. Many pain conditions have been, or will be fully illuminated, within this text, but further redundancy and clarity here may be beneficial. Therefore, some of these will be discussed within this Chapter, even if only to give better insight into the merits of interdisciplinary care in treating these pain conditions.

Chronic pain-related illnesses may include, but not be limited to, osteoarthritis, diabetes, cancer, multiple sclerosis, shingles, aids, asthma, hypertension, fibromyalgia, low chronic back pain, coronary artery disease, and other chronic illnesses that can result in chronic pain [5]. For example, if someone has coronary heart disease, they may experience angina. Additionally, those with fibromyalgia commonly report pain sensations such as burning or shooting pains. Furthermore, those with chronic low back pain typically report persistent and aching pain in their lower extremities, commonly due to an inflamed sciatic nerve.

Currently, in the USA every day, 115 people die from overdosing on opioids, and, according to the CDC, the economic burden due to the "opioid crisis" is $78.5 billion [6, 7]. This amount includes estimated cost related to healthcare, lost productivity, addiction treatment, and criminal justice services. How did this problem arise? Specifically, the "opioid epidemic" can be linked to the inconsequential prescribing of opioids in the 1990s, at a time when the health community did not understand how addictive they were [7]. Instead, many physicians prescribing such medications were initially and innocently mesmerized by the instant and substantial relief opioids were providing for many of their patients. Due to this "happy pill" effect, physicians began to increasingly prescribe these powerful narcotics for the treatment of pain conditions, particularly those involving chronic pain. Over time and with continued use, many patients become physically dependent upon such drugs. As such, their bodies rely on the drug to function normally, and they undergo intense cravings and highly uncomfortable physical withdrawals that include severe flu-like symptoms. Still, opioid pharmacotherapy has become the medical "quick fix" for pain suffering, often times being utilized as the first treatment a patient is exposed to, leaving them with little understanding of how to alternatively manage their pain conditions. This and likely other factors have highly influenced epidemic levels of opioid addiction sweeping America in what has been coined the "opioid crisis" [7].

So why do industry professionals continue to use such an emotionally laden term like "crisis" to describe the contemporary issue of narcotic addiction? For a better understanding, it may be helpful to observe some of the statistics. In 2015 alone, for example, an estimated 33,000 Americans died due to opioid overdoses [7]. Furthermore, currently, 21% to 29% of patients prescribed opioids misused these medications, often taking far more powerful doses than medically necessary [7]. Finally, in the Midwestern region of the USA from July 2016 through September 2017, there was a 70% increase in the use of opioids [7]. With a clear problem at hand, the National Institute on Drug Abuse laid out five priorities to alleviate this epidemic: increase access to treatment and recovery, promote overdose reversing drugs, strengthen the understanding of the epidemic, increase research of chronic pain and other causes of opioid usage, and, finally, increase better practices for pain management [6].

In emphasizing the last priority, one of the most successful ways to better manage chronic pain conditions has been through using an interdisciplinary treatment team. In the midst of an opioid epidemic that swept America, the Institute of Medicine [8] concluded that interdisciplinary therapies were the most successful and essential methods for treating pain conditions in contemporary healthcare (as cited by [9]).This may be because individuals suffering from a pain condition who are treated by practitioners who are guided by a comprehensive medical model tend to have improved outcomes over those receiving other forms of pain care [10].

Interdisciplinary Pain Management: An Introduction

We will now turn to a review of what interdisciplinary care is. *IPMPs* are based on a theoretical foundation which supposes that patients need unique and individualized medical care. It is commonly the view of the interdisciplinary team that patient health is based upon a collection of unique circumstances which lead to distinctive treatment needs. In this way, interdisciplinary care is a form of *personalized medicine*.

Pain conditions often take on unique forms within and between individuals. Chronic pain, particularly, may have no known source. Pain conditions also may differ in degree of severity and localization as they develop and unfold. As the characteristics of debilitating and/or long-term pain manifest in diverse ways, a diversified approach may best serve those in need of treatment. *Interdisciplinary* (i.e., integrated) *medicine* may be best understood as a field of health that relies on multiple skill sets, methods, and areas of knowledge. In interdisciplinary medicine, a unified collection of professionals, from several unique areas of expertise, are tasked with using their distinctive views to form understandings and treatment goals to guide patient care [11].

Practitioners of IPMP serve individual patients by following several key methods of practice. These methods include (a) drawing from the skills and knowledge of

their individual backgrounds, (b) forming collective patient plans and treatment strategies, (c) unifying in the execution of the treatment plan they collectively designed, (d) updating each other extensively on all patient notes and progress, (e) holding regular meetings to discuss all patients receiving care, and (f) incorporating each other's relevant ideas and strategies for treatment as the opportunities to do so arise. Lastly, these healthcare professionals nearly always practice in close physical proximity to one another in a true IPMP. In other words, true *interdisciplinary care* is administered by several diverse healthcare advocates who collectively practice in close physical proximity to one another, often under the "same roof," so they may regularly meet [12].

IPMPs are also continuously monitored for efficacy in their approaches. This is commonly done by way of quantifying the aversive and beneficial progress of those undergoing treatments and the costs of operations. While often academically based, they may also be independently owned and operated. IPRP clinics will often emphasize methodological use and effectiveness, professional team dynamic quantification, and details of therapies and other treatment processes in order to reach continued optimization of the program [13].

The most effective IPMPs typically will contain a large collection of professionals who have backgrounds that will allow them to better elucidate the diverse individual cases that present to them. These professionals are typically highly capable of treating all aspects of patient suffering. This is likely because IPMP professionals utilize each other's perspective to form a comprehensive treatment strategy. As such, interdisciplinary teams practice personalized medicine founded in biopsychosocial principles of care when treating pain sufferers [10].

A Foundation for Interdisciplinary Pain Treatment in the Biopsychosocial Approach

The Centers for Disease Control and Prevention (CDC) now recommend that the biopsychosocial model guide medical staff as part of the best practice in treating pain (as cited in [14]). When practicing under the *biopsychosocial* (BPS) *approach*, it is crucial to integrate knowledge of multiple and interrelated facets of patient health in order to view them in a holistic manner. BPS principles are guided by the understanding that patient biology, affect, behavior, cognition, and sociocultural backgrounds influence the cause, course, symptomology, and treatment responsiveness of various health conditions, including those related to pain.

The BPS approach was originally proposed by Dr. George Engel [15], whose conception of health and illness involved an understanding that illness was interacting with biological, psychological, and experiential elements. Engel's ideas were in opposition to the commonly accepted understanding of disease from the biomedical

approach. The biomedical understanding of health placed emphasis on the physical origin and treatment of illness, often at the exclusion of psychosocial elements.

As the mean age of life expectancy for adults in the USA has risen, subsequently the number of adults living with at least one chronic illness is also trending upward. Due to this rise, Engel proposed that chronic illnesses can best be understood and thus managed by applying the biopsychosocial model [15]. This model posits that biological, psychological, and social factors all work together to influence chronic illnesses. For example, if an individual has chronic back pain, biological aspects to be considered include what physiologically is causing the pain (i.e., possibly an inflamed sciatic nerve, central sensitization syndrome, etc.). Psychologically, many patients who suffer from chronic pain become depressed, as well as have pain-related anxiety, or may ruminate on their pain (e.g., pain catastrophizing). All of these psychological factors can magnify one's pain enormously [16]. An individual experiencing chronic back pain may physically withdraw from participating in activities they previously enjoyed (i.e., fear-avoidance behavior – "if I walk it might cause me to be in pain because I was in pain last time,I left my house and went somewhere"). Such actions often cause people to become socially isolated, which may lead to feelings of hopelessness and isolation both of which are strongly associated with depression (i.e., in turn, the more depressed an individual becomes, the more they socially withdraw from activities and therefore ruminate about their pain, and so the cycle continues). It is clear in managing a chronic illness, such as back pain, both biological factors and psychosocial aspects need to be considered.

Loeser [17] elaborated on the work of Engel in describing the BPS understanding of pain conditions. Loeser viewed pain as being based on three things. First to occur in a sufferer was *nociception*, or the natural physical, psychological, and emotional experience of pain. After this, the experience of *suffering* occurred. This was followed by the way in which one *interacted* with their surroundings. It was the belief of Loeser that pain could only be effectively understood and treated if all of these features were taken into account. Approaches to treating chronic pain by way of understanding the BPS approach, and the development of related therapies, began to mature in the latter half of the twentieth century and have recently begun to swell in popularity.

Highly effective and comprehensive treatments for pain conditions require knowledge of the relationship between the symptom expression and all relevant underlying mechanisms of the disease. Currently, the BPS model is one of the best understood and common foundational theories in pain medicine. The BPS design relies on an integrated understanding of the core and tangential features of pain. This is because those who practice with the BPS approach guiding them focus on health, disease, and wellness in a comprehensive fashion, which can be useful in treating a diverse array of symptom expressions found in pain condition sufferers. The BPS serves those treating pain conditions or practicing general medicine, but it should be noted that this model is fundamental to interdisciplinary medicine and IPMP practices [13].

History of Interdisciplinary Pain Management Programs

While programs that integrate the expertise of multiple clinicians under the "same roof" and require their collaboration in designing and executing therapeutic plans may have been utilized for many years, these practices have only been explicitly described as interdisciplinary care beginning in the 1980s [10]. At this point, healthcare advocates began to piece together an understanding that an IPMP offers a comprehensive patient view and treatment plan that is executed by diverse professionals under the same roof. Prior to this, pain sufferers often relied on a general practitioner exclusively to monitor and guide their symptom treatment [13].

In the 1960s and 1970s, Dr. John Bonica of the University of Washington, Seattle, established a multidisciplinary pain management clinic and evolved the techniques within it to match the behavioral modification strategies developed by his collaborator, Dr. Wilbert Fordyce [18]. Dr. Bonica's pioneering clinic offered patients the expertise of eight different fields in the treatment and management of their pain conditions. This program was among the first to integrate the expertise of professionals from multiple backgrounds in treating patients with pain. In 1982, Dr. John Loeser began to head the multidiscipline pain clinic established by Dr. Bonica. Loeser began to strengthen the reliance on concepts of team care and behavioral alterations in treating pain. Thus, the multidisciplinary clinic began to more closely resemble an interdisciplinary clinic, as an interactionist approach among the specialists began to take on a key role in the success of the facility [18].

Several pioneers in the IPMP approach have fine-tuned the methods of best practice for treatment. Mayer et al. [19] and Mayer and Gatchel [20] were among the first to utilize multiple treatment professionals under the same roof in guiding pain therapy. In developing the *Functional Restoration Program*(FRP), a concise, comprehensive, and cost-effective intervention could be used for the long-term management of pain in injured workers. FRPs incorporated interprofessional teams to provide care in one setting and therefore be in constant communication among one another. This made functional restoration among the first pain treatment programs to ever offer interdisciplinary treatment by design.

Mayer [20] discussed three separate studies which addressed the outcomes and efficacy of FRPs. It was concluded that FRPs not only have high accuracy (89%) in identifying who is most at risk at not returning to work following a severe injury but also are highly efficacious in returning patients to work (87%) and preventing future pain surgeries (5%), compared to other treatment program outcomes. Patient self-reports of pain and progress indicated that FRPs outperformed primary physician-based care. FRPs were also determined to have halved the recurrence of pain injuries in these workers (6%) and nearly halved the healthcare utilization needed by these individuals (34%). Finally, FRPs tend to be highly cost-effective as well [21].

An important feature of chronic pain that should be kept in mind when formulating treatment strategies for new patients is the uncertainty regarding how they might respond to treatment. This may even be the case for a so-called *gold standard treatment* method, which implies it is the most common and effective treatment available.

Individuals who share a common diagnosis of chronic pain often respond differently to the same treatment [10]. For example, medical history must be considered by a physician before prescribing a patient medication. An individual complaining of chronic low back pain is asked then if they have a previous history of substance abuse and recovery. If they do have a positive history of substance abuse, then this would likely lead to a physician determining that this patient cannot be considered a candidate for opioid treatment of their pain condition.

Interdisciplinary and Multidisciplinary Pain Management Similarities and Distinctions

Multidisciplinary and interdisciplinary pain programs share many commonalities, including a reliance on a comprehensive view of health, previously discussed as the BPS approach. Thus, multidisciplinary pain management programs (MPMs) and IPMs include cognitive, behavioral, and social aspects of pain conditions and symptoms in patients. Interdisciplinary programs often include team meetings with the professionals (i.e., physicians, nurses, and rehabilitation specialists), establishing a collective goal of maintenance, and continuous and regular collaborative communication, decision-making, and updating [21].

MPMs typically involve an assortment of clinicians, each with distinctive expertise in a given treatment area, working together to treat a patient, just as interdisciplinary treatment professionals might. Professionals, such as nurses, general practitioners, mental health professionals, anesthesiologists, and physical and occupational therapists, might be involved to the same degree and duration for MPM or IPM therapies. Background and expertise of each professional might be similarly suited to counterbalance the other professionals collaborating with them. These professionals will also commonly be in continued communication with one another under either approach [11].

However, multidisciplinary practitioners are often not in close physical proximity to one another. MPM professionals may be separated by buildings, or entire cities, states, or countries in some cases. Furthermore, the professionals executing an MPM program commonly have treatment goals that are centered around their expertise and remain un-unified with the other professionals on the team. The therapies developed in MPM may not be as comprehensive, cohesive, and/or continuously and collectively updated as is commonly the case in an IPM program [22].

While nuanced, the differences in how goals are formulated and executed can make a great deal of difference to patient outcomes in MPM and IPM programs. First of all, professional hierarchies are common in MPM teams. Rather than equal participation in the design of a treatment plan, one or more physicians may take the helm and direct the majority of orders for those other professional team members beneath them. Further, the goals set forth by each professional may be unique, with collaboration in the design and execution of pain treatment goals sometimes taking

a "back seat" to personalized plans formulated by each member of the team. Because this treatment is typically less coordinated, it may be redundant or oppositional to the treatments by other members of the team. This is something that may be less likely to occur in IPM treatment teams.

Multidisciplinary teams may be limited in that the unit might be less capable of developing a cohesive care plan. Each MPM team member uses his or her own expertise to develop individual care goals. In contrast, IPM team members rely on the construction of care plans as based on each other's expertise. A fundamental tenet of the IPM program is to tap the knowledge and abilities of diverse experts in order to create and achieve superordinate and shared goals. Therefore, it may be most crucial to distinguish these fields with the following clarification: multidisciplinary teams work as individual members collectively, while interdisciplinary teams engage in collective work. Thus, it should now be apparent that there is a substantial difference between multidisciplinary and interdisciplinary treatment programs. Unfortunately, one of the current problems faced within the healthcare system is that many do not agree upon the definitions, as well as the different nuances between these two approaches [23].

Professional Roles in an Interdisciplinary Team

Because the management of a chronic pain condition is multifaceted (i.e., biological, psychological, social aspects must be managed), a variety of healthcare providers are needed to address each aspect. This makes employing an interdisciplinary care team approach the most viable treatment option. Additionally, because chronic pain conditions vary from individual to individual, a tailored approach is preferred and is also accomplished through an IDT. The various roles each healthcare professional plays in the management of a chronic illness will be discussed next.

The first role that will be discussed as being part of an interdisciplinary care team will be that of a physician. It is important to note here again the difference between a multidisciplinary and an interdisciplinary care team. One major difference is that in a multidisciplinary care team, the physician is seen as the ultimate authority in charge of the care team. However, with regard to the interdisciplinary care team, the physician is seen as being equal to the other health providers and not operating in a hierarchical manner [23, 24]. Also, it is important to understand that there are two types of physicians that can legally practice in the USA, medical doctors or allopractioners (MD) and osteopathic doctors (DO). Both of these professionals complete a 4-year undergraduate degree, 4 years of medical school, and a 5-year residency and then must pass the US Medical Licensing Exam following a 3-year fellowship where they then become certified in a specific discipline of medicine [25]. Another major difference between these types of doctors is that, for individuals educated in an osteopathic medical school, they focus on a more holistic approach to practicing medicine utilizing the biopsychosocial model. In particular, they are educated in osteopathic medical treatments, such as body manipulation or

other homeopathic remedies [26]. On the other hand, individuals who complete traditional medical schools are taught to adhere to the biomedical model, using an allopathic approach to treating diseases. Due to such differences, because they are initially schooled using a holistic framework, a DO might be more suited to work as part of an IDT, as compared to an MD. However, both physicians complete similar roles, including conducting an initial evaluation and then developing an overall medical care plan, such as determining what other medical professionals (e.g., psychologist, physical therapist, occupational therapist, case manager, etc.) a patient needs to meet with [25]. The physician is also responsible for ordering diagnostic procedures such as MRIs, CT scans, PET scans, etc., as well as prescribing medications [23].

Physical therapists, like physicians, must obtain a Doctor of Physical Therapy, as well as hold a professional license and often times complete a residency after completing their DPT to specialize in a certain area of care, such as the management of chronic pain [27]. In regard to being part of an IDT, PT's role as a practitioner includes the following: general reconditioning; decreasing fear-avoidant behaviors; gradually incorporating new activities into a patient's therapy sessions; stretching exercises; improving a patient's level of cardiovascular conditioning; and improving overall strength, such as using resistance bands/weight training [28]. Additionally, PTs might educate patients on how to conduct a self-massage, increase their body awareness, as well as guide patients in how to engage in daily activities focusing on how to manage chronic pain [29]. Also, PTs serve to provide continued evaluations of current and prospective levels of physical functioning, evaluate musculoskeletal pain, conduct gait analysis, develop personal exercise regimens, and fit patients for necessary devices (i.e., braces, a walker, cane, etc.) and can apply TINS therapy as a non-pharmaceutical option in helping to alleviate pain [30]. Finally, PTs initially prescribe exercise programs, but other individuals, such as a physical therapy assistant, may monitor patients during weekly sessions or educate patients in areas that contribute to increase physical functioning, such as yoga, progressive muscle relaxation, activity-rest cycles, and how to properly schedule various activities [31]. Again, such activities ultimately operate within the oversight of a physical therapist.

Occupational therapists (OTs), like PTs, typically hold a doctoral level certification (DOT) Specifically, OTs focus on vocational issues, as well as techniques managing pain while involved in activities related to one's work [23]. OTs also educate and hold group sessions on topics such as bathroom safety, cleaning, driving, home safety, time management, yardwork training, and creating a schedule to balance activities away from therapy sessions [28]. A growing number of OTs are also trained in biofeedback and conduct therapy sessions implementing diaphragmatic breathing and muscle relaxation strategies [32]. Finally, OTs focus on postural biomechanics and teach proper communication skills and proactive problem-solving [33].

Psychologists, like other professionals, also must obtain a doctoral level of education and hold a professional license to practice. In a recent article, clinical psychologists were recognized as playing a critical role in helping "difficult" patients who often are patients suffering from chronic pain illnesses [33]. For one thing, the

clinical psychologist can make more time to devote to individual patients compared to a physician. This extended time allows the psychologist to reflect on barriers that may cause decreased treatment adherence, such as a patient having had a previous negative experience involving healthcare, cultural factors, or familiar problems [33]. Psychologists can address specific patient concerns, as well as individually encourage and hold patients accountable to adhering to treatment regimens as prescribed by other providers on the team. Such a role ultimately helps to alleviate the burden for other providers and creates a more tailored approach for an individual focusing on patient's overall goals, motivations to change, self-efficacy, and how to properly and professionally interact with other healthcare staff, address issues creating anxiety or depression, and incorporate non-pharmacological therapies (i.e., CBT and acceptance and commitment therapy; ACT) which may be more cost-effective than pharmacotherapy [33].

More specifically, the psychologist can utilize cognitive behavioral therapy, focusing on activity pacing/scheduling, relaxation training, cognitive restructuring, developing mindfulness skills (such as engaging in valued activities/focusing on the present moment), as well as educating patients about the neurophysiology of chronic pain and how to make healthy lifestyle choices as related to the management of chronic pain [29]. Also, as a working part of an IDT, the psychologist may conduct group therapy sessions covering a plethora of topics related to chronic pain management, including anger management, anxiety, assertiveness, behavioral changes, central sensitization syndrome, cognitive coping, depression, chronic pain cycles, distraction therapy, drug interventions, fear, forgiveness, problem-solving, relationships, relaxation, increasing self-esteem, improving self-efficacy, sleep, stress, and social withdrawal [28]. Also, as related to CBT, psychologists play a critical role in helping patients understand the impact that depression and anxiety can have, such as exacerbating chronic pain, as well as one's mood and other psychosocial factors that relate to the intensity of pain [34]. The ultimate goal of such therapy is to identify maladaptive thought patterns/behaviors related to chronic pain. More specifically, such therapy targets openness, awareness, and committed actions and has been shown effective in significantly improving the physical and mental health of patients [35]. Finally, it is important to note that, in certain situations, such as a parent who has a child suffering from cancer, a clinical psychologist will meet with parents to discuss how it is best for them to interact with their children regarding their child's medical condition. For example, parents are taught not to ask about their child's pain, but rather to focus on their child's functioning [33]. In other situations, such as a patient in hospice, a psychologist can help with grief counseling and processing emotions that may impact a patient's overall quality of life.

Pharmacists also play a critical role in the management of chronic pain in working as part of an interdisciplinary care team. To practice, a pharmacist must obtain a doctoral level of education (Pharm. D) and successfully pass a board licensing exam [36]. Their specific roles include identifying the most effective drug therapies, assisting with prescribing proper medication dosages, reducing opioid consumption for those with chronic pain (e.g., prescribing naloxone), as well as brainstorming alternative pharmacotherapies such as medications that are more cost-effective for a

patient or a medication that has less side effects (i.e., chronic constipation, dry mouth, drowsiness, headaches, dizziness, etc.) [37]. Pharmacists also educate patients on properly adhering to the prescribed medical regiment [29]. In addition, many patients dealing with chronic pain often suffer from poor sleep quality which acts as a catalyst for other problems (e.g., impaired physical healing of damaged tissue), so the pharmacist may prescribe medication that improves a patient's overall quality of sleep [33]. Finally, a clinical pharmacist plays a critical role in reviewing legal ramifications within their state of practice as well as prescription monitoring programs and managing lab screenings [38].

Nurses, like other healthcare professionals, must hold a professional license to practice (registered nurse, RN). As part of the IDT, nurses are unique because they typically spend more time with patients compared to physicians, as well as are trained to have proper bedside manner; this allows them to build better rapport with a patient [39]. Due to positive patient rapport, a patient may disclose more information to the nurse. This allows the nurse to be able to better manage symptoms, complete ongoing health assessments, and obtain an understanding of the daily routines of their patients [39]. For example, a nurse will understand the side effects of medications, such that it may be better for a patient to be awake during certain hours of the day. Additionally, nurses' roles include assisting the physician by providing follow-up procedures (i.e., giving an injection or medications as requested by the physician), becoming a case manager for the patients (i.e., coordinate future care once outside of a program), maintaining communication among all healthcare professionals on the IDT, as well as taking charge of managing and tapering addictive pain medications (e.g., oxycodone) as requested, again, by a physician [23, 28].

It is important to keep in mind that the role of various healthcare providers as laid out above does not include an exhaustive list. For example, several other professionals play a crucial role as part of an IDT. Other roles include job counselors; chiropractors (i.e., perform acupuncture and education on myofascial release techniques); registered dietitians (i.e., conduct an initial intake assessment of food, drinks, supplements, and medications, as well as coordinate proper diets for those with certain allergies, observe eating patterns, ask about religiously motivated food behaviors, and make individualized nutrition plan); social workers; support staff; volunteers; safety risk managers; administrative specialist; information technology staff; patient representatives; nurses aids; physician's assistants; nurse practitioners; and potentially other support roles [25, 40, 41].

Other Features of Interdisciplinary Pain Management Programs

In summary, ICT teams consist of the following: patient, significant other, physician, physician assistant/advance nurse practitioner, nurse, psychologist, physical therapist, occupational therapist, recreational therapist, job counselor, pharmacist, registered dietitian, social worker, support staff, volunteers, and others [42]. In

IPMPs several of these professionals work in tandem to tackle the significant and multidimensional aspects of managing chronic pain (i.e., dealing with the physical pain reported possibly using medication, emotionally coping with being in pain, getting back to work while managing pain, maintaining social relationships, etc.). Chronic pain itself is not considered a pathological disease, because it varies with each person; but, there are a myriad of chronic conditions that typically results in a patient reporting being in chronic pain. Chronic pain-related illnesses may include osteoarthritis, diabetes, cancer, multiple sclerosis, shingles, aids, asthma, hypertension, fibromyalgia, low chronic back pain, coronary artery disease, and other chronic illnesses that can result in chronic pain [5]. For example, if someone has coronary heart disease, he/she may experience angina, or those with fibromyalgia often report pain sensations such as burning or shooting pains, while those with chronic low back pain often report aching persistent pain in their lower extremities, typically due to having an inflamed sciatic nerve. Because pain is multidimensional, it creates the inherent need for a variety of health professional to manage such illnesses.

Those who practice interdisciplinary care may do so in order to benefit diverse populations. Prior to characterization and administration of an IPM therapy, a battery of assessments may be given to an individual believed to be suffering from a pain condition. These tests may involve scoring qualities regarding pain experiences and psychological and occupational functioning [43].

It is common for an interdisciplinary team to practice on both children and adult sufferers and those who have various symptoms of pain manifestation [11]. Interdisciplinary professionals may treat pain that is characterized as being diffuse or localized, long term, acute, or intermittent, and/or even pain which is expressed secondarily as a symptom outcome of another treatment, such as chemotherapy [44].

Interdisciplinary teams and clinics were said to share many core foundational features including working in a close-knit and collaborative fashion and maintaining a positive productive team environment [45]. Stanos [13] discussed other features common in IPM facilities in his review of integrated pain programs. IPM facilities were said to sometimes be structured uniquely from one another in some areas. Often, this is done in order to best serve relevant local patient populations, such as with areas with high prevalence of cancer or those with high instances of occupational injuries. Some interdisciplinary pain centers may be structured in order to emphasize individual or group care, vocational or personal physical rehabilitation, nursing or psychological professional oriented pain treatment, etc.

Additionally, IPM clinics may be more inclined to emphasize a patient-oriented treatment approach (as opposed to a goal-oriented approach). Patient-centered facilities typically emphasize concern for the well-being of the individual receiving treatment above all else. Patient-oriented clinics, like IPM clinics, typically are careful to understand what the patient wants, and needs, over the entire course of treatment. Conversely, goal-oriented programs that offer interdisciplinary care may emphasize the outcome and progress of the patient more so than patient-oriented programs.

Cognitive behavioral therapy (CBT) has also been utilized in the treatment of pain conditions in IPM programs. Ehde, Dillworth, and Turner [46] found that CBT

could be useful in improving the health and functioning and reducing the severity of pain in those with pain conditions. Clinical trials have found proven efficacy for CBT in reducing the long-term and debilitating effects of multiple pain conditions in populations spanning in age from childhood to adulthood. This is likely why treatment on an IPM team almost always relies, in part, on the utilization of mental health and/or cognitive behavioral specialists.

Case and Efficacy Studies of Interdisciplinary Care

The efficacy of an IPMP in treating those with opiate addiction was the focus of a longitudinal retrospective study by Huffman et al. [47]. Therein, 120 patients diagnosed with pain and therapeutic opioid addiction conditions completed a yearlong interdisciplinary pain rehabilitation program. Even though patients were simply encouraged not to use opioids in treatment, the results of the program were highly effective in curbing opiate use. In the posttreatment 12-month assessment, patients resumed use at a rate of 22.5%. Furthermore, patient depression levels seemed to play the most substantial role in determining the likelihood of opioid relapse after treatment. Patient depression status appeared more crucial in determining 12-month posttreatment opioid recurrence then, even whether the patient initially was administered opioids, as medically instructed, or was diagnosed as an addict.

As an example of how an interdisciplinary care team works, one can examine a case study [48]. Patient L. is a 48-year-old male who was referred to an interdisciplinary chronic pain program due to complaints of daily headaches, depression, and anxiety and lost his job ultimately because he was not able to manage his chronic pain. Patient L. ‘s chronic headaches were results from experiencing physical assault, as well as from having a previous brain tumor. Having been referred to the interdisciplinary chronic pain program, he was first evaluated by a psychiatrist who asked about his pain levels. Specifically, patient L. complained of pain in the frontal and temporal regions of his head, as well as reported feeling pain radiating throughout his neck and chest. As a consequence of his pain, patient L. expressed suicidal ideation, avoided housework, lost his job which significantly increased his levels of stress due to financial strain, and was taking five prescription medications.

For the physical evaluation portion of his initial assessment into the pain program, it was reported that patient L. had a rounded shoulder posture with forward head movement, as well as presented guarding, had high levels of anxiety related to his pain, and reported overall poor sleep quality. Furthermore, it was suggested patient L. be involved in outpatient therapy encompassing physical therapy and occupational therapy, as well as work with a psychologist to manage his stress (i.e., biofeedback training and mindfulness), as well as continue his pharmacotherapy. As required for joining the program, patient L. met with a physical therapist, occupational therapist, as well as a psychologist once a week; he also attended several group sessions throughout the week. The group sessions focused on breathing techniques, progressive muscle relaxation, guided imagery, as well as applying such

techniques to activities of daily living in managing pain. Some of the group sessions educated the patient on chronic pain cycles, emotional stress and distress related to pain, dysfunctional attitudes, increased stress associated with pain, and the adoption of healthy attitudes such as acceptance and resiliency. It was also noted that he met once a week with a psychiatrist to adjust his medications. In working with the physical therapist, patient L. focused on stretching, cardiovascular conditioning, functional balance, postural reeducation, and body mechanics and participated in aquatic exercises. With the occupational therapist, he worked on pacing techniques, as well as journaling activities to review pain management strategies learned from the group sessions. In total, patient L. completed 87.5 hours of the interdisciplinary pain program. The program was a success! For instance, by the end of the program, he was on no pain medications, had increased sleep quality, was able to get a new job, had a significant decrease in headaches, and reported a substantial decrease in pain and a more stabilized mood. At a 1-year follow-up, patient L. was continuing to perform well at his job and was still successfully using his pain management strategies [49].

Another recent example of the efficacy of an IPMP implementation should also be mentioned. An interdisciplinary care team approach was applied to the emergency department [7]. Specifically, 14 patients who frequently visited the ER due to chronic pain received interdisciplinary care that consisted of an initial evaluation where an individualized care plan was then uploaded to that patient's electronic medical record where it could be accessed by multi-healthcare professionals. The interprofessional pain assessment program (IPA) was made up of pain specialists, a physician, a nurse, a social worker, and a health psychologist. For patients who were on high doses of an opioid, they worked with an addictive medicine specialist. Initially, patients in the program were evaluated in the ER and then met one time a week in person with the psychologist and a psychiatrist. Also, patients met two times a week with the other healthcare specialist on the ICT, and a nurse was available via phone if they needed more interaction than what was provided biweekly. Overall, significant improvements were reported, including a decrease in pain, improved physical function, decreased visits to the emergency room, reduced symptoms of depression and pain catastrophizing, improved sleep quality, increased health-related quality of life, and decreased risk of future opioid use [7].

In a study investigating the short-term efficacy of an interdisciplinary care team approach, patients suffering from post-laminectomy syndrome, who had previously gone through unsuccessful spinal cord stimulation to alleviate their pain, completed an interdisciplinary pain rehab program [48]. This program utilized the biopsychosocial model as evidenced in the incorporation of CBT, physical reconditioning, biofeedback, relaxation training, stress management, chemical education, activity moderation, and cognitive restructuring as to avoid pain catastrophizing/pain-related anxiety. Patients also worked with a physical therapist and completed various exercises including stretching, aerobic conditioning, and low weight resistance training. In working with an occupational therapist, they were taught how to restructure activities, moderate their activity efforts, overcome fear-avoidance behaviors, as well as learn functional independence. In total, all 31 patients who completed the

program were tapered off NSAIDs, benzodiazepines, muscle relaxers, supplements, and antidepressants. In terms of physical functioning, all patients showed improvement in their 6-minute walk test and reported decreased pain scores. Psychosocial improvements included reports of increased life control scores, as well as increased self-efficacy, and decreased depressive symptoms and pain catastrophizing scores [48].

In a separate study, length of treatment received was examined using an interdisciplinary approach for women with fibromyalgia [50]. Specifically, there were two groups of patients; one group completed a 2-day interdisciplinary team program, and the other participated in a series of ten sessions. In both conditions pain levels and physical functioning were measured at the first appointment and at a 6-month follow-up appointment. The interventions for both groups covered the same material, but just in different amounts of time. Patients were educated about the definition of disease and clinical signs and symptoms of fibromyalgia, exercises to help manage chronic pain (i.e., aerobic and strength conditioning, as well as stretching) were reviewed, and CBT was implemented via a psychologist. Results of those who took part in the 2-day interdisciplinary clinic reported decreased levels of pain/tenderness and had improved scores for physical functioning. For those who completed the long-term approach, they also reported the same results as those in the short-term program but, in particular, had more effectiveness in reducing their chronic pain [50]. These results indicate that, while a short-term approach is helpful, in order to receive the maximum benefit of an interdisciplinary care team approach, a longer program is better. A program consisting of 6–8 weeks might be preferred over a few days clinic because it takes time to recondition someone physically and, when engaging in new behaviors, habits must form through the process of cortical restructuring and, again for this to occur, it takes extended time and repetition [50].

Not only has the short-term efficacy of interdisciplinary care teams been shown in a variety of contexts, with varying pain conditions, but this treatment approach has also found to have excellent short-term efficacy among a variety of ages. In the first two examples, these studies had average ages of patients including 64 and 38, but, in another study, researchers focused on the effects of care for patients aged 9–18, with an average age of 14. In this study, an interdisciplinary care team approach was offered to those diagnosed with pediatric joint hypermobility syndrome (PJHS) [33]. Over a 6–8-week period of treatment, these patients and their parents underwent educational, exercise, and medication management sessions. The IDT encompassed a physical therapist, occupational therapist, a physician, and a psychologist who offered counseling. For the patients completing the program, they reported improvements in pain, depression and anxiety related to their chronic pain, social functioning, and physical functioning. The parents of the children with PJHS also showed improvements in depression, anxiety, catastrophic thinking, self-blame, helplessness, leisure functioning, and parental behaviors [33]. While these results of the efficacy of implementing an interdisciplinary approach in managing chronic pain encompass a myriad of factors, as the old adage goes "the proof is in the pudding." Thus, long-term efficacy of this type of an approach must also be considered.

In a recent publication, the long- term efficacy (i.e., data were collected over an 8-year period) of an interdisciplinary care team approach for spinal cord injury patients was successful [51]. Specifically, if patients were taking large doses of opioids to manage their chronic pain, then they were deemed eligible for participation in the treatment program. The care team consisted of a physical therapist, an occupational therapist, a recreational therapist, a vocational therapist, and a physician who specialized in pain. The results of this program were significant in that opioid use decreased from 39% to16%, or from 2.5 to 1.5 prescriptions per person [51].

In another study, researchers analyzed the efficacy of an IDT for patients suffering from chronic pelvic pain by checking in with these patients for 1 year [52]. Pain measures, quality of life, health utilization, and other psychosocial factors were measured. Specifically, patients participated in pain workshops that reviewed ways to manage chronic pain, including mindfulness, meditation, breathing, guided visualization, and progressive muscle relaxation. Also, these patients completed counseling, CBT, and physical therapy two times a week. The physical therapy sessions encompassed calm breathing techniques, addressing the fear of movement, proper posture, pacing/grading activities, and exercises focusing on their abdominal muscles and hips. Dietary changes were also addressed if needed. Overall, patients reported pain scores that had decreased by an average of two points, had improved functional movements, and frequented the ER significantly less [52]. Also, through this study, researchers concluded that high amounts of pain were associated with pain catastrophizing.

Having examined the treatment efficacy of an interdisciplinary team approach, considering both short- and long-term examples, it is apparent that, in successfully managing a chronic pain condition, the biopsychosocial model should be the guiding theoretical framework applied as it calls for all areas of an illness to be addressed and therefore ultimately has given way to the creation and utilization of interdisciplinary teams. To reiterate, because chronic illnesses are multifaceted, treatment must also be multifaceted to be the most effective.

Modern Interdisciplinary Pain Management Program Variations

Functional Restoration Programs

As discussed previously, FRPs typically address psychological, biological, and social components of pain ailments. A psychologist is often employed to help the patient by establishing and treating any underlying psychosocial distress or conditions that may impact their pain and recovery process, by providing mental healthcare and guidance, as needed. Cognitive behavioral and multimodal disability therapies are common provisions of such programs and are often provided along

with personalized treatment and recovery plans. A patient's physical needs are commonly addressed through ongoing and up-to-date health assessments completed by a medical practitioner, nurses, and a physical therapist. This team would be implemented to address their physical complaints. Socially, patients are also introduced to others within the Functional Restoration Program and encouraged to build a trusting social support system with these individuals and the staff of the FRP.

Interdisciplinary Pain Rehabilitation Programs (IPRPs)

Interdisciplinary Telemedicine

Telemedicine programs involve the use of technology in order to check in on patients who prefer, or are required, to be homebound for some or all of the time that they undergo therapy for their condition(s). This approach is sometimes referred to as interdisciplinary ehealth treatment. This form of treatment allows for the patient and specialists treating him or her to communicate with one another regularly, often at the same time. The Internet does provide the ability for individuals to communicate who have incompatible schedules or obligations by leaving email or instant message communications which may be viewed and responded to by the patient or ehealth team member at a future time [53].

Telehealth has been assessed for patient adherence and acceptability by Kim et al. [54] in an examination of the link between the adoption of telemedicinal treatments and scores on the Technology Acceptance Model (TAM). The TAM was developed by F.D. Davis [55] as a tool for the assessments of self-reported approval and practical ease of use of technological systems on a five-point Likert-type scale. Results of a factor analysis indicated that groups could be meaningfully separated by general health practices, with good health behaviors represented in Group 1 and poor health behaviors represented in Group 2. It was determined that Groups 1 and 2 were meaningfully distinguished by ease of use perceptions (i.e., Group 1 scoring higher standardized path coefficient of 0.65 than Group 2).

A patient suffering from severe pain conditions may make trips to a hospital or other health setting uncomfortable, inconvenient, and/or impossible to make. Due to this, some interdisciplinary teams enact their forms of therapy and rehabilitation in the common environment of the patients' dwelling.

Interdisciplinary Home Visit Programs

Interdisciplinary home visit programs involve individuals from diverse health professionals providing care to patients at their own place of residence. Typically, these specialists visit the home at the same time as a collective unit and then provide their

own form of specialized care to suit the needs of the patient contemporaneously, though with the hope of being unobtrusive. The collective and simultaneous team therapy is often used in order to minimize the inconvenience to the patient and to maximize effective collaboration and communication between the professionals and the individuals they are treating [56]. These programs have been found to be highly cost-effective and reduce the number of future hospitalizations that patients incur after therapy concludes [56]. It is the hope of professionals who utilize these programs to keep patients comfortable and to minimize further injury and symptom exaggeration.

Mayo Clinic Pain Rehabilitation Programs (MCPRP)

Sletten et al. [57] discussed the history and design of the MCPRP established in Minnesota and Florida. The MCPRP in Rochester, Minnesota, was established in 1974 and has since served over 5,000 patients dealing with pain conditions. Since then, the Florida MCPRP opened and now serves approximately 4,000 patients in a given time. These clinics are examples of comprehensive interdisciplinary pain treatment centers. The methods used typically involve physical rehabilitation and fitness therapies, chiropractic services, cognitive-emotive-behavioral treatment, opioid prescription use attenuation, and education-based programs to enhance wellness attitudes and behaviors. Interdisciplinary programs like these have been found to reduce costs associated with treating pain in health settings by approximately 59%. The MCPRPs offer inpatient and outpatient treatment services and regular treatment events. Patients in the Mayo Clinic Pain Rehabilitation Program receive a structured calendar of continuous therapeutic events for patients. This gives them a regimen to follow that is dictated by the hour within each day of the week, something that allows for them to have structure, to make plans, and to monitor regular progress [13].

Interdisciplinary Pain Rehabilitation Programs (IPRPs) for Veterans

The Veterans Affairs Administration is the largest publicly funded and fully integrated healthcare team having an established interdisciplinary pain clinic since 2015 [14]. This team consist of a primary care provider, a psychologist, a pharmacist, and a physical therapist. Overall for those patients in the program, the average daily opioid dose significantly decreased after 90 days of interdisciplinary care, as compared to a control group (i.e., veterans who did not receive interdisciplinary care), and, at 180 days, daily opioid use was reduced by 103% [14]. As might be expected, veteran populations report higher levels of pain than nonveterans, and this pain tends to have many harmful secondary effects on their lives, including

higher levels of stress and PTSD, higher reliance on narcotic painkillers, greater healthcare use and costs accrued, and higher levels of debt and related financial troubles [29]. Likely due to these common veterans' issues, the IPRP for veterans has been implemented in San Francisco and Florida. At these sites, the veteran IPRPs have initiated a National Pain Management Strategy which was founded on the BPS approach in helping alleviate the suffering in relevant veteran patient populations. This strategy is described as using interprofessional expertise in order to provide optimal pain therapies for veterans across America. Anamkath et al. [29] found that these programs substantially reduced the instances of pain disability in the veteran populations monitored and significantly alleviated the strength of aversive psychological symptoms commonly experienced in them, namely, depression and catastrophizing.

The Chicago Center for Pain Management

The Center for Pain Management (CPM), a part of the Chicago-based Shirley Ryan AbilityLab, was awarded the "Center for Excellence" in 2009 by the American Pain Society [58]. The patient-oriented care at the facility is said to be modeled to provide patients with long-term care strategies that they may use to maintain high-quality health and wellness over the lifetime. Furthermore, the CPM aims to fully recover patients to their former occupational ability and status, provide them with psychosocial and emotional support and therapy, instill positive and productive coping strategies, and include the inner familial circle in giving patients and those closest to them the tools needed for ongoing recovery. They offer care for a wide variety of pain diagnoses, including complex regional pain syndrome, a difficult to treat condition that often afflicts young adults in their 20s and 30s, and may involve faulty pain nerve signaling to localized area such as an appendage. Once a patient is enrolled in the program, typical interdisciplinary care is provided, along with more specialized care that is aimed to address an array of unique patient concerns. These include sleep disturbance, walking dysfunction, a desire to be trained in relaxation techniques, and enhancing body posture, position, and mechanical ability.

Current Challenges for Practitioners of Interdisciplinary Care

While the efficacy of IPMPs may be clearer to the reader, that does not mean that the future of using interdisciplinary medicine in treating pain conditions is absent of adversity. For one, there is not a lot of agreement as to what specific disciplines should be part of an IDT [23]. For example, some of the studies reviewed had IDTs that included a physician, physical therapist, occupational therapist, and health psychologist, while other programs included a chiropractor, a registered dietitian, etc. There is also a lack of understanding as to why the biopsychosocial model is needed

in managing a chronic illness. Traditionally, the line of thought in the field of medicine has encompassed the biomedical model which focuses solely on a cure, and, therefore, health was seen as a lack of disease, rather than the management of various chronic illnesses. As mentioned previously, one significant advantage of using the biopsychosocial model is that, through ICTs, individualized care treatment plans are created. This is important because different people recover at different rates; thus, a uniformed approach may not be the most effective [23].

Another barrier that must be discussed includes the fact that some insurance companies, including Medicare, will not cover IDT programs because it involves more "upfront" costs since they have to pay a team of specialists, versus one individual healthcare provider [59]. Due to this, it has been suggested that an interdisciplinary approach may be the most cost-effective for those patients who are considered "high risk." Such patients have been labeled super-utilizers by some researchers and are often times low-income patients who make up 20% of the US population; but they account for 20% of all healthcare expenditures [59]. In accounting for such factors, a *socio-biopsychosocial* model has been proposed [60]. This model accounts for all the aspects of the biopsychosocial model, but through the lens of socioeconomic status (SES) and other social disparities. These factors, also known as cultural capital, are important to think about because they often put some individuals at risk for having compromised behaviors that can lead to chronic illnesses [60]. For example, in a narrative, a homeless woman discusses how she would manage her chronic pain in a more cost-effective manner in her point of view by using crack cocaine. While this is one example, the reality is that there are several socially disadvantaged people who continue to fuel the opioid epidemic [60].

Along the same lines in terms of thinking about how SES might affect those who have chronic illnesses, many of these individuals work blue collar jobs which are associated with more injuries resulting from work. Since this is the case, it is important to point out that most IDTs are paid through workers' compensation, and this processing creates a logistical barrier financially [23]. Other barriers as noted in a recent study include not having easy access to patient information due to having multiple databases with patient information [61, 62]. This type of problem is multifaceted because, in order to advance technology, new databases must be created which have the ability to communicate with other systems while not compromising patient information, and current employees must also undergo extensive training such as how to operate new information systems. This again cuts into current productivity, as well as has a substantial cost associated with it.

Another barrier to implementing IDTs is that, in many programs, future healthcare professionals are not taught how to properly collaborate with others and, therefore, lack the knowledge of how to work as part of an interdisciplinary team. In working toward a solution to this problem, one program utilized an online video game (PAIN ME FREE) to educate nursing and medical students on how to work with others collaboratively [63]. Nursing students, in particular, demonstrated improved knowledge regarding interdisciplinary care of pain management for geriatric patients, as did the medical students that participated in this program. The students also reported that the online game was interactive and very informative

[63]. While implementing training for future members of an IDT while still in school is ideal, most programs do not provide their students with this type of knowledge resulting in many current health professionals lacking such knowledge. One educational intervention held 12, 30-minute sessions with the aim being to improve interdisciplinary knowledge for healthcare professionals providing pain relief to cancer patients [64]. This program (Oncology Provider Pain Training) entailed providing examples of the provider's role in pain management and reviewing the National Comprehensive Cancer Network guidelines, opioid therapy principles, and other therapies for cancer pain syndromes. Overall, this program was successful in that the healthcare providers who took this course showed marked improvement in their interdisciplinary pain techniques for cancer patients [64]. Finally, in a separate training, healthcare providers participated in a 2-day workshop acquiring knowledge about pediatric pain management techniques [65]. Specifically, a nurse was asked to invite a physician to complete the program with them. The program addressed healthcare providers' knowledge and attitudes regarding pain, and those who took the course displayed improved knowledge in this area. For instance, one participant commented, "I like that it was interactive and that we got to talk to other people from different institutions about things they did for pain" [65]. It is important that to successfully implement IDTs, healthcare providers must have knowledge concerning how to properly implement this approach as acquired while in school or by attending a workshop/conference.

In summary, due to astronomical expenses associated with healthcare for those suffering with a chronic pain condition, a more holistic approach to managing such illnesses is warranted; specifically, the care team of various healthcare providers, such as a physician, nurse, occupational therapist, physical therapist, health psychologist, and other professionals that are needed, plays an important role in addressing particular facets of pain conditions. Now, more than ever, in wake of the opioid crisis, it is imperative that "high risk" or "super-utilizers" get the proper help they need. As reviewed above, IDTs have shown to have reliable short- and long-term treatment efficacy. This is important in providing a solution to reduce healthcare expenditures. While this solution is the most viable, as reviewed above, there are still several barriers to overcome in making an interdisciplinary care team approach the preferred standard of treatment nationwide.

Future Directions for IPMP Programs

Future IPMPs may place more emphasis on pain treatments for nontraditional patients, such as young children. Upcoming IPMPs may be in need of addressing a lack of offerings for the large number of pediatric patients in need of treatment for a chronic pain condition. These chronic pain sufferers are undergoing intense emotional and physical stress, often to the detriment of normal functioning, and the number of children presenting with these types of conditions appears to be growing [66]. A meta-analysis of interdisciplinary treatments for children with chronic pain

concluded that symptoms leading to disability, severity of pain, and affective depression were alleviated [66].

Dorflinger et al. [67] utilized a Rapid Process Improvement Workshop (RPIW) to elucidate new advances and improvements to integrate care that could be implemented in future programs. Care provider surveys, completed by pain specialists, nurses, and physicians (n = 127) in IPMP settings, were examined regarding future improvements. The study specifically monitored those patients who were less responsive to integrated healthcare services than other cohorts. It was determined that several implementations could improve patient outcomes provided by interprofessional treatment. Primarily, future programs would do well to detail an integrated program clinic. This would allow for an even more streamlined process of treating pain conditions, as patients would potentially be visiting and keeping records at only one site.

Additionally, it was noted that opioid therapies have complicated traditional pain care in many populations in America. Future IPMPs will benefit from providing all staff members with thorough training on how to properly care for individuals without reliance on narcotic painkillers. In addition to this, all members of the interdisciplinary team should know how to handle patients who may be using or misusing narcotic painkillers regularly or intermittently and how their patients may be withdrawing from such medications.

Future programs may also benefit from eliminating some of the problems that have plagued patients and staff of contemporary professional pain management programs in the past. These issues included inconvenient consultation processes, such as those that were redundant, required multiple visits, and/or were overly complicated and lengthy. Issues of consultation may also lead to problems with getting the most fastidious access to pain care services, which may be a pressing need for a pain sufferer. Additionally, miscommunication issues between the head physician, which is typically the primary care practitioner, and other members of an interdisciplinary team may occur and lead to problems in care. A lack of access to the most "state-of-the-art" pain treatments at a facility may occur if the facility is underfunded. Finally, a poorly constructed and/or implemented individual patient plan has also been highlighted as a potential pitfall that should be avoided at future IPMP locations. It was noted that the most beneficial IPMPs offer continuous management strategies and care for pain sufferers, rather than seeking to cure them. It was also noted that acute or symptom-targeted treatments (i.e., prescription opioids) tended to be less useful than cohesive and ongoing therapies for treating patient populations. Such comprehensive strategies, like a focus on regular physical and psychological therapy, may be more effective at reducing symptom severity in a long-term fashion [67].

Furthermore, interdisciplinary care may be given to more Americans in the future in order to continue to be enhanced as an effective form and field of pain treatment. Currently, comprehensive disciplinary therapies may not be implemented as widely as is needed for the 10% of individuals in America who are believed to be suffering from a chronic pain condition [68]. Individuals suffering from pain conditions may be facing several hurdles that are in need of addressing by future professionals practicing interdisciplinary medicine. Individuals who may benefit most from

interdisciplinary care likely include benefitting from better pain care in the future,particularly if they reside in rural areas with poor access to healthcare facilities.

It may also be important for quality of life to become a focus of those who are receiving treatment for pain conditions. Those suffering from chronic pain typically suffer from reduced quality of life, which is a degree of well-being that is commonly assessed when determining BPS functioning [68]. Variables that were commonly reported in pain sufferers included an extended time spent suffering from pain symptoms; reduced social, spiritual, emotional well-being; and altered perceptions of pain and health. Quality of life is not often measured in those undergoing interdisciplinary care, and it is not often studied in those who are diagnosed with pain conditions. In the future though, programs may be improved substantially by including this measure in analyses of patient outcomes.

All, Fried, and Wallace [68] examined quality of life in those receiving pain therapy and found that they reported a reduced quality of life rating, as compared to those who had no treatment for their pain. This is surprising and may be due to a small or isolated sample. Still, it is worth further examining in order to determine if quality of life ratings in patients suffering from pain conditions may be better accounted for after interdisciplinary pain treatment, as compared to the current standard methods offered.

Concluding Thoughts

In bringing this Chapter's discussion full circle, it may be important to readdress that many patients suffering from chronic pain are primarily treated via pharmacotherapy (e.g., prescription opioids). With a rise in those suffering from chronic pain conditions, there has also been a recent subsequent rise in opioids prescribed. This practice in part has fueled the opioid epidemic. When fighting a large wildfire, it would be trivial to use a water gun. Instead, drastic measures must be taken to not only contain the fire but also eradicate it completely. The same analogy applies to the fight against the opioid epidemic. The upsurge in treating chronic pain using an interdisciplinary care approach is certainly a step in the right direction. However, the flames are still burning, lives are still being lost, and more help and sophisticated techniques need to be utilized. As chronic pain can never be cured, but rather only managed, utilizing multiple therapies (i.e., pharmacotherapy, psychotherapy, physical therapy, occupational therapy, etc.) should also utilize a myriad of disciplines. One recommendation is that interdisciplinary care should expand to other disciplines, such as legal professionals, computer engineers/scientists, artists, and other disciplines. Each of the professions listed above, whether it is evident or not, plays a substantial role pertaining to the opioid epidemic.

For example, due to the help of legal professionals, recent legislation was passed, [Opioid Crisis Response Act 2018 (OCRA)] in fighting this epidemic. This bill encompasses many things, such as increased help by the Centers for Disease Control and Prevention (i.e., continued research on opioid addiction and alternative thera-

pies in alienating chronic pain), providing more state funding for programs monitoring the use of illegal drugs such as heroin and cocaine, and increased grants for providing comprehensive opioid recovery centers which specifically bolsters an interdisciplinary approach to the opioid crisis [69]. One way an interdisciplinary approach is being established is through the National Health Service Corps. Through funding received as part of the OCRA, they can award money to newly graduated healthcare professionals such as medical doctors, social workers, nurses, and other related specialist up to $75,000 in student loan debt forgiveness [70]. Such debt forgiveness requires that these individuals must work in a substance abuse facility in an underserved area for a minimum of 3 years. The purpose of this commitment parameter is so that these health professionals can be properly trained in holistically treating patients suffering from opioid addiction, which they may not receive otherwise in their traditional programs of study.

Another area in need of continued aid by legislators is that of holding and regulating how much accountability and agency pharmaceutical companies have and will continue to keep in fueling this epidemic. In a recent study in JAMA by Scott et al. [71], they found that nearly $40 million dollars was spent by various companies to promote the use of specific opioids to physicians. Such promotions included paying for meals and trips and providing consulting fees. In analyzing data from 2013 to 2015, it was concluded that for every three extra payments pharmaceutical companies compensated doctors with per 100,000 people, at a 1 year later follow-up, there was an 18% increase in the overall death rates involving prescribed opioids. Additionally, this study found that this type of practice was the most prevalent in the Northeast part of the USA (i.e., Virginia and Washington) and least prevalent in the Midwest. This specific finding highlights the need for a cultural shift in how the marketing of various drugs is handled and can best be reformed through the continued work of legal specialist.

Another recent article published by *POLITICO* brought attention to the notion that unconsented data are being "mined" and then applied to newly formulated algorithms that calculate a patient's "risk score" [72]. This score then indicates an individual's risk for abusing opioids on a scale of 0–1 and is directly uploaded into a patient's electronic health record. Accordingly, there is no current law against such practices, and data are often collected blindly from patients in the exam rooms or from other sources (i.e., insurance claims, digital health records, housing records, information about friends and family, etc.). Justification provided for this practice not being outlawed is that it is an ethical practice as it may be saving lives. Currently in America, daily, 130 lives are lost due to opioid-related overdoses. However, several cautions are extrapolated concerning such a practice including the following. First, there is no absolute certainty that the algorithms formulated are accurate and as a result may lead to overestimating "abuse risk," resulting in some patients not being prescribed opioid therapy and therefore suffering in pain. Second, overtime reliance on such programs may decrease physicians' intuitions of prescribing medications (i.e., they do not rely on "head knowledge" and experience; rather, they allow a computer to think for them). Finally, algorithms are standardized such as a "one-size-fits-all" approach. As discussed above, a primary advantage to managing chronic pain using an interdisciplinary approach is that it allows patients a tailored

treatment plan, which again does not align in using a standardized algorithm. The final verdict for this type of technology is still to be determined and ultimately needs more evidence-based outcomes in proving its efficacy. Due to a lack of such knowledge, this is most certainly a future direction that is recommended that all research scientists from all disciplines need to investigate further.

Another occupation that has had an impact in combating this epidemic is that of an artist. In a local program, the *Opioid Spoon Project*, an 800-pound heroin spoon was crafted out of bronze with the name of a pharmaceutical company [73]. The artist commented that his intent in creating this piece was twofold. First, he pointed out that this project called attention to holding pharmaceutical companies accountable for the role they play and will continue to have in resolving the opioid epidemic. Second, the statue symbolizes that this problem is large scale and, as such, affects everyone involved including a person's entire family. This brings to light the need for future research to focus on not just individuals managing chronic pain, but rather taking a broader approach to include examining the relationships that circumvent this crisis in its entirety.

Clearly it can be concluded that managing chronic pain, and thus fighting for the lives of those who are overdosing in response to such pain, requires an interdisciplinary approach. Such a tactic should include nontraditional disciplines (i.e., those not automatically associated with healthcare). If we want to abolish this crisis in its entirety, then multiple disciplines need to be put into action. To quote Hippocrates, "the greatest medicine of all is to teach people how not to need it," including excessive amounts of opioids! The only way this will happen is through the continued implementation of interdisciplinary care teams in managing chronic pain.

Unique personal attributes, environments, ability levels, and health history collectively influence one's experience of illness and rehabilitation. Therapeutic approaches aimed at addressing a patient's distinctive needs and characteristics as potential moderators of their treatment plan are crucial in order to provide the most effective and affordable care possible.

Interdisciplinary care is guided by the practices emphasized in the BPS approach. As such, IPMPs typically aim to holistically treat the patient by uncovering the potential biological, psychological, and socioenvironmental promoters of the onset, course, and possible attenuation of symptoms under what is called the BPS model. When an interdisciplinary care team approach is taken, many patients may find the burden of living with a debilitating disease is lifted and their quality of life is substantially improved. "Unity is strength… When there is teamwork and collaboration, wonderful things can be achieved" – Mattie Stepanek [74].

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Part V
Medical Treatments

Chapter 19
Office Procedures for Pain

Kavita Trivedi

Introduction

Office procedures for pain can be a good option to help patients with various musculoskeletal issues that cause pain and functional impairment. Musculoskeletal pain is pain that is caused by a disorder of a bone, muscle, tendon, or ligament. Depending on the length of time that it affects an individual, musculoskeletal pain can be acute or chronic. Acute pain is caused by a specific disease or injury and is associated with skeletal muscle spasm and activation of the sympathetic nervous system [1]. Chronic pain, on the other hand, can be considered a disease state and outlasts the normal time of healing if it is associated with a disease or injury [1]. Acute pain is generally considered pain that lasts for less than 3 months. A study exploring the definition of acute low back pain found that outcomes for patients with 2–4 weeks of symptoms were similar to patients having 4–12 weeks of symptoms [2].

The indication for an in-office pain procedure is to relieve pain, reduce inflammation, and improve mobility by injecting corticosteroid into articular, periarticular, or soft tissue structures [3]. These procedures have both a diagnostic and therapeutic value. Therefore, success of the procedure depends on knowing the right diagnosis and performing the correct procedure [3]. Just as important as knowing the indications for an in-office procedure, it is crucial that the provider is aware of contraindications as well. Some of these contraindications include broken skin at the injection site, known hypersensitivity or allergy to any of the injectable agents, fracture at injection site, severe joint destruction, skin infection at the injection site, and unstable coagulopathy [3].

K. Trivedi (✉)
Department of Physical Medicine and Rehabilitation, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: Kavita.Trivedi@UTSouthwestern.edu

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These injections often consist of two types of medication: local anesthetic and corticosteroid. Local anesthetics help provide faster pain relief. They also add volume to the injectate and help to distribute corticosteroid within the joint space [3]. Corticosteroids help decrease inflammation by acting directly on nuclear steroid receptors and interrupting the inflammatory and immune cascade at several levels [4]. The injectable corticosteroids that have a current Food and Drug Administration (FDA) label for intra-articular injections consist of methylprednisolone acetate, triamcinolone acetate, betamethasone acetate, betamethasone sodium phosphate, triamcinolone hexacetonide, and dexamethasone [4]. In the United States, methylprednisolone acetate (Depo-Medrol) is the most commonly used intra-articular steroid, followed by triamcinolone hexacetonide and triamcinolone acetonide [5]. While there is evidence that suggests the advantage of using non-particulate steroid when doing epidural steroid injections in the spine [6], there are no definite guidelines or evidence that recommends the use of a specific steroid based on the type of office procedure or injection. As with the choice of corticosteroids, the choice of local anesthetic for injection is based more on clinical preference than evidence [3].

Other injectable agents for office procedures include botulinum toxin, platelet-rich plasma, and hyperosmolar dextrose (prolotherapy). Botulinum toxin (BTX) is a presynaptic neuromuscular blocking agent that triggers chemical denervation by temporarily suppressing secretion of acetylcholine at motor nerve endings. Therefore, BTX injections have traditionally been useful for diseases with increased involuntary muscle activity or tension [7]. There is preclinical and emerging clinical evidence of an antinociceptive mechanism of action of BTX [8]. An evidence-based review of BTX for osteoarticular pain found short-term efficacy of an injection of BTX in relief of pain and, in some cases, improvement of function and quality of life. However, more clinical trials are needed to better define the clinical use of BTX injections for the treatment of refractory osteoarticular pain [8]. Platelet-rich plasma (PRP) is defined as a platelet concentration higher than the physiologic platelet concentration found in healthy whole blood. PRP contains growth factors and bioactive proteins that influence the healing of tendon, ligament, muscle, and bone [9]. A systematic review of the literature of studies that investigated the effectiveness of PRP in knee osteoarthritis concluded that larger randomized studies of good quality and low risk of bias are needed to test whether PRP injections should be a routine part of management of patients with osteoarthritis (OA) of the knee [10]. Prolotherapy is a technique that involves the injection of an irritant, usually a hyperosmolar dextrose solution, in the treatment of chronic painful musculoskeletal conditions [11]. Introducing an irritant solution to the site of painful and degenerated tendon insertions, joints, ligaments, and adjacent joint spaces during several treatment sessions promotes the growth of normal cells and tissues [12]. A major goal of prolotherapy in chronic musculoskeletal conditions is the stimulation of regenerative processes in the joint that will facilitate the restoration of joint stability by augmenting the tensile strength of joint stabilizing structures, such as ligaments, tendons, joint capsules, menisci, and labral tissue [13]. A systematic review of prolotherapy found limited high-quality data supporting the use of prolotherapy in the

treatment of musculoskeletal pain. However, further investigation with high-quality randomized controlled trials with noninjection control arms in studies specific to musculoskeletal conditions is necessary to determine the efficacy of prolotherapy [14].

The technique for office procedures can be image guided, such as with an ultrasound, or landmark guided, which is performed by using anatomical landmarks alone. Several studies have been performed to determine if image guidance is necessary for office procedures. The results from these studies vary. For example, a randomized clinical trial study in 2016 was performed in patients with shoulder impingement syndrome. This study concluded that ultrasound-guided injections increase accuracy but they do not have a significant impact of efficacy, especially in cases where there are limitations to ultrasound [15]. Another study comparing the functional outcomes in patients with shoulder pathology found a difference in pain and abduction between landmark-guided injections and ultrasound-guided injections; however, these differences were small and may not represent clinically useful differences [16]. A more recent review concluded that while current studies indicate that ultrasound guidance improves efficacy and cost-effectiveness of many injections, these studies are limited and more research is needed [17].

As with any procedure, obtaining informed consent from the patient is essential. Informed consent in medical care is a process of communication between a clinician and a patient that results in the patient's authorization or agreement to undergo a specific medical intervention. According to The Joint Commission, informed consent is the agreement or permission accompanied by full notice about the care, treatment, or service that is the subject of the consent. A patient must be apprised of the nature, risks, and alternatives of a medical procedure or treatment before the physician or other health-care professional begins any such course. After receiving this information, the patient then either consents or refuses such a procedure or treatment [18]. Emphasis should be placed on the fact that informed consent is a communication process between the health-care provider and the patient with the patient understanding the risks, benefits, and alternatives to the proposed treatment. For informed consent, the patient must have the capacity to make the decision, the medical provider must disclose information on the treatment including the expected benefits and risks, the patient must comprehend the information, and the patient must voluntarily grant consent without coercion or duress [19].

The injection procedure has the same basic steps for most in-office pain procedures. After determining the diagnosis and indication for the procedure, written and verbal informed consent is obtained. A timeout is then completed which includes confirming patient identifying information including name and date of birth, reviewing any patient known allergies and sensitivities, as well as asking the patient to verbally state what procedure is being done including laterality. Procedure preparation is then done which includes obtaining the appropriate medications, needles, and syringes. Using sterile technique, the syringes are prepared with the appropriate medications. The landmarks are then identified and properly marked on the patient. Then, this area is cleaned with isopropyl alcohol, povidone-iodine, or chlorhexidine gluconate. Ethyl chloride spray or a cooling spray can be used as needed for patient

comfort after the area is prepared with the cleaning agent. A syringe containing 1% xylocaine is attached to the appropriate length and gauge needle. Often for intra-articular in-office procedures, a 25-guage 1 1/2-in. needle will be adequate. The needle is gently guided into the intra-articular space or soft tissue depending on the injection being done. After negative aspiration, 1% xylocaine is injected. The needle tip is secured and the syringe is removed. Then, the syringe containing the physiologic solution is attached to the needle. After negative aspiration, the physiologic solution is slowly injected. The medication should be injected without resistance. If resistance is encountered, slightly reposition or rotate the needle so that the physiologic solution is able to be injected freely and without resistance. After the solution has been injected, remove the needle and apply a bandage. Post-procedure counseling should include potential complications that the patient might experience. The most common complications after a corticosteroid injection include an elevation in blood sugars for diabetic patients, post-injection flare, skin atrophy, and fat atrophy. Other less common complications include facial flushing, infection, and hypersensitivity reaction [3].

Shoulder

The human shoulder represents a complex dynamic relationship of many muscle forces, ligament constraints, and bony articulations. Static and dynamic stabilizers allow the shoulder the greatest range of motion of any joint in the body [20]. The shoulder consists of three bones and four joints. The three bones of the shoulder include the humerus, scapula, and clavicle. The joints of the shoulder are the glenohumeral joint, acromioclavicular joint, sternoclavicular joint, and scapulothoracic joint. Joint stability is provided by static stabilizers and dynamic stabilizers. The static stabilizers include the labrum, capsule, and ligaments, while the dynamic stabilizers include the rotator cuff, deltoid, and scapular stabilizers [20]. The rotator cuff muscles consist of the supraspinatus, infraspinatus, subscapularis, and teres minor muscles. The shoulder joint can be affected by various pathologies that result in shoulder pain and dysfunction. These can include rotator cuff tendinopathy, subacromial bursitis, impingement, adhesive capsulitis, labral tears, disorders of the long head of the bicep tendon, and osteoarthritis. It is important to have a diagnosis before deciding what treatments to offer the patient. The proper diagnosis can be reached by obtaining a focused history and performing a physical exam. Imaging can sometimes also provide information that helps to confirm a diagnosis. Depending on the cause of the shoulder symptoms, different types of office procedures can be considered especially after conservative treatments including activity modification, physical therapy, and medications, particularly nonsteroidal anti-inflammatory drugs, and have been tried.Glenohumeral joint injections can be considered for osteoarthritis, adhesive capsulitis, and rheumatoid arthritis. The glenohumeral joint is the third most common large joint affected by degenerative joint disease [21]. Glenohumeral osteoarthritis is characterized by degeneration of articular cartilage

and subchondral bone with narrowing of the glenohumeral joint. The onset of stiffness is progressive over many years and will cause significant functional deficit, typically presenting in patients over 60 years of age [22]. Adhesive capsulitis, or frozen shoulder, starts with a painful phase which leads to stiffness suggesting an initial inflammatory response which evolves into a fibrotic reaction [23]. Rheumatoid arthritis affecting the shoulder region is a progressive disorder that results in pain, loss of range of motion, and functional disability. The inflammatory response results in synovitis, pannus formation, and articular destruction [24]. Glenohumeral joint injections can be done from an anterior or posterior approach. The needle for the anterior approach should be placed just medial to the head of the humerus and 1 cm lateral to the coracoid process. The needle is directed posteriorly and slightly superiorly and laterally. The needle for the posterior approach should be inserted 2–3 cm inferior to the posterolateral corner of the acromion and directed anteriorly in the direction of the coracoid process [25]. Figure 19.1 shows the posterior approach to glenohumeral joint injection. In terms of the injectate volume, to date, no study has directly compared relative injectate volumes in the glenohumeral joint on the effect of clinical outcomes. Various studies have used total injectate volumes ranging from 1 mL to 16 mL, with no obvious pattern of superiority associated with a particular volume [26].

Subacromial injections can be considered for subdeltoid bursitis, shoulder impingement, rotator cuff tendinopathy, and adhesive capsulitis [39]. Subacromial impingement syndrome encompasses a spectrum of subacromial space pathologies including partial thickness rotator cuff tears, rotator cuff tendinosis, calcific tendinitis, and subacromial bursitis [28]. The subacromial bursa lies beneath the deltoid muscle and extends from the upper portion of the muscle to the undersurface of the acromion process. It separates the greater tuberosity of the humerus from the deltoid muscle, and its floor is in close contact with the supraspinatus and infraspinatus muscles [29]. Some studies suggest that inflammation of the subacromial bursa does occur in patients with rotator cuff disease [30]. The rotator cuff complex is defined as a group of tendons that envelope the humeral head, arising from four muscles that

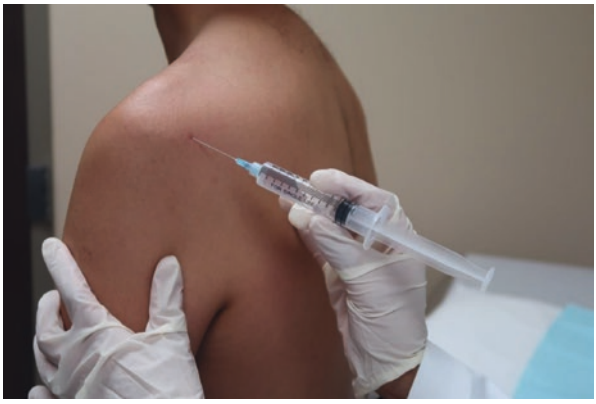

Fig. 19.1 Posterior approach to glenohumeral joint injection

have their origin on the scapula. These muscles, subscapularis, supraspinatus, infraspinatus, and teres minor, act in synergy as the glenohumeral joint is utilized to allow positioning of the hand in space for function [31]. Signs of impingement may include painful overhead reaching, an inflamed subdeltoid bursa, or positive special tests meant to provoke symptoms [32]. Two common tests used for the diagnosis of impingement are the Hawkins' test and the Neer's test [25]. The Hawkins' test elicits pain with the shoulder passively flexed to 90 degrees and internally rotated [33]. The Neer's test elicits pain with passive abduction of the shoulder to 180 degrees [34]. Partial rotator cuff tears are defined as tears involving less than 50% of the muscle, while full thickness tears are usually due to chronic degeneration [32]. Patients with partial rotator cuff tears commonly present with reduced shoulder function (dyskinesis, weakness, pain, and stiffness) as well as pain at rest, night pain, or a painful arc [35]. A tendinopathy is an overuse condition that manifests itself as pain in and around the tendons [36]. This painful condition is associated with tendon disorganization and thickening that reduces its physical properties, which causes the tendon to fatigue, further exacerbating the painful condition with ultimate failure [37]. Rotator cuff tendinitis is a term used to describe chronic and acute conditions that involve the inflammatory process [38]. A prospective, randomized, controlled, double-blind study concluded that subacromial injection of corticosteroids is an effective short-term therapy for the treatment of symptomatic subacromial impingement syndrome, and the use of such injections can substantially decrease pain and increase the range of motion of the shoulder [39]. Another study found that subacromial corticosteroid injections in the acute or subacute phase of subacromial impingement syndrome provided additional short-term benefit without any complications when used together with nonsteroidal anti-inflammatory drugs (NSAIDs) and exercise [40]. A meta-analysis found that subacromial injections of corticosteroids are effective for improvement of rotator cuff tendonitis up to a 9-month period [41]. Subacromial injections are generally performed with the patient sitting up. Figure 19.2 shows the subacromial injection approach. The distal, lateral, and posterior edges of the acromion are palpated. The needle is inserted just inferior to the posterolateral edge of the acromion and is directed toward the opposite nipple [25]. No study has directly compared relative injectate volumes in the subacromial space on the effect on clinical outcomes. Various studies have used total injectate volumes ranging from 1 mL to 11 mL, with 10 mL being the most common volume. No obvious pattern of superiority associated with a particular volume is evident [26].

Acromioclavicular (AC) joint injections are indicated for osteolysis of the distal clavicle and osteoarthritis [42]. The AC joint provides a structural connection between the scapula and clavicle that facilitates support of the shoulder complex on the thorax [43]. Osteolysis of the distal clavicle is characterized by the insidious onset of a dull, gnawing pain with increasing limitation of normal shoulder movements. In most cases, there is a report of a previous injury to the same shoulder [44]. In addition to trauma to the shoulder, osteolysis of the distal clavicle is also seen in weight lifters. Push-ups, dips, military press, and any throwing motion exacerbate the pain [45]. Primary osteoarthritis more commonly affects the AC joint than the

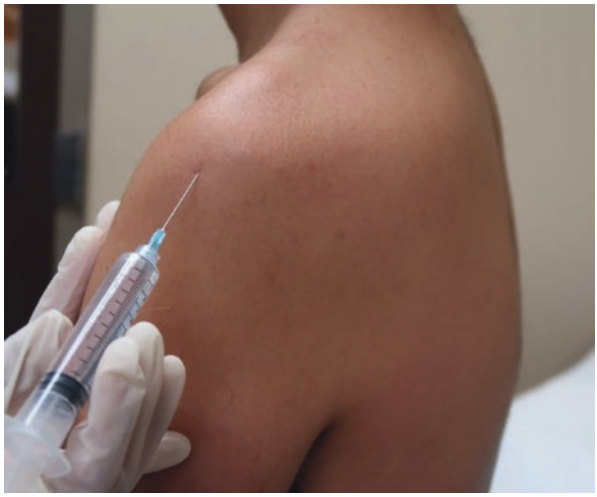

Fig. 19.2 Subacromial injection

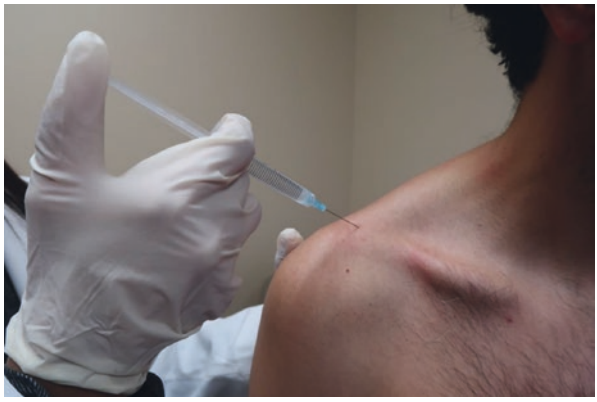

Fig. 19.3 AC joint injection with patient sitting

glenohumeral joint [47]. A study demonstrated 54–57% of elderly patients have radiographic evidence of degenerative arthritis of the AC joint [48]. A case-control study found that AC joint injections remain a valuable technique as they have a low cost, minor risk of complications, and a high diagnostic value [49]. AC joint injections can be done with the patient seated or supine. The AC joint is identified by palpating the clavicle distally to its termination at which point a slight depression is felt at the joint articulation. The needle is inserted from the superior and anterior approach into the AC joint and directed inferiorly [25]. Figure 19.3 shows the approach for AC joint injection with patient sitting.

One study evaluating AC joint injections used a total of 3 cc volume for the injectate for AC joint injections. This consisted of 2 mL 0.25% bupivacaine and 20 mg triamcinolone. They found that injecting higher volumes in a small joint, which is further reduced by pathology, is not possible [50].

Disorders of the long head of the biceps (LHB) tendon can exist in conjunction with several other shoulder pathologies. The LHB tendon travels through the bicipital groove to insert on the head of the humerus [51]. The LHB tendon may be affected by tendinopathy, dislocation, and partial or complete tears. Disorders of the LHB tendon are associated with rotator cuff tears in up to 90% of cases [52]. The function of the LHB tendon at the shoulder is incompletely understood. Evidence suggests that the LHB tendon may contribute passively to glenohumeral stability [53]. Pathologic disorders of the LHB tendon can be divided into three categories: inflammatory/degenerative conditions, instability of the biceps tendon, and superior labrum anterior to posterior (SLAP) lesions/biceps tendon anchor abnormalities [53]. A common finding for biceps tendon pain is point tenderness over the bicipital groove [54]. Yergason's test of resisted supination causing anterior shoulder pain may be specific for biceps pathology but tends to lack sensitivity [55]. Speed's test is considered positive if pain is localized to the proximal biceps area and is caused by resisted shoulder forward flexion with the elbow extended and the forearm supinated. A study found that Speed's test is moderately specific [56]. An LHB tendon injection can be administered with the patient seated or supine. The bicipital tendon is identified in the bicipital groove. The point of insertion is marked as the most tender area over the bicipital groove. The needle is directed parallel to the groove and should enter the skin at 30 degrees [25]. Figure 19.4 shows the approach for LHB tendon injection. It is vital to ensure that the injection is not into the tendon itself because of the risk of rupture [57]. The most frequently used corticosteroid in biceps tendon sheath injections is triamcinolone acetonide 5–10 mg. Other corticosteroids including methylprednisolone 5–10 mg, dexamethasone 0.8–2.0 mg, and betamethasone acetate 1.5–3.0 mg can also be used [57].

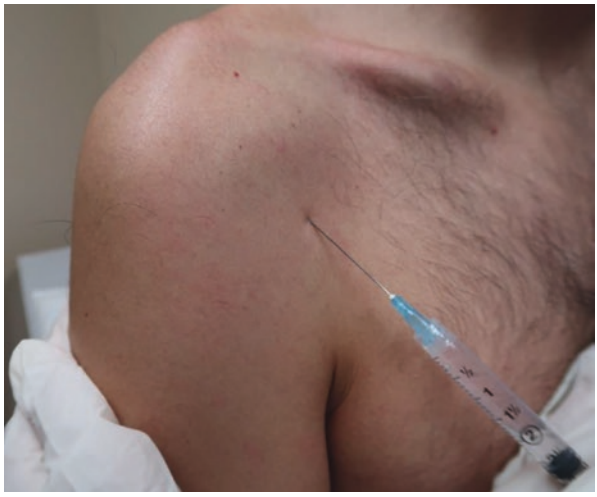

Fig. 19.4 LHB tendon injection

Elbow

The elbow joint is a complex structure that provides an important function as the mechanical link in the upper extremity between the hand, wrist, and shoulder. The elbow's functions include positioning the hand in space for movements, powerful grasping, and serving as a fulcrum for the forearm [58]. The elbow joint is composed of three bones which form four articulations. The three bones of the elbow, the ulna, radius, and humerus, articulate to form the humeroulnar, humeroradial, superior radioulnar, and inferior radioulnar joints. Static stabilization is enhanced by the ulnar collateral ligament, the lateral collateral ligament, and the elbow joint complex. There are 23 muscles that are directly associated with the elbow joint, and they provide dynamic stabilization to the elbow and enable the hand to perform precise motions [59].

Elbow pain can be seen as a primary presentation in the outpatient setting. Pathology can arise from any component of the joint including the tendons, bursae, bones, or nerves. Tendinopathies (mainly lateral and medial epicondylitis) can arise from playing sports or various activities of daily living. Arthritis can also affect the elbow including rheumatoid, post-traumatic, and primary osteoarthritis [50]. Tendinopathies are one of the most common disorders of the elbow in the outpatient setting. Lateral epicondylitis of the elbow has an estimated prevalence of 1–3%, peaks at age 45–54 years, and is more common in men than in women [60]. It is described as a chronic symptomatic degeneration of wrist extensor tendons involving their attachment to the lateral epicondyle of the humerus. The extensor carpi radialis brevis (ECRB) is the most commonly affected muscle, but the supinator and other wrist extensors can be involved [61]. Any activity involving excessive and repetitive use of these muscles (e.g., tennis, playing an instrument, typing, manual work) may cause tendinosis [62]. Medial epicondylitis of the elbow is characterized by pathologic changes to the musculotendinous origin at the medial epicondyle [63]. Medial epicondylitis occurs less frequently than lateral epicondylitis. Lateral epicondylitis has been diagnosed seven to ten times more often than medial epicondylitis [64]. Medial epicondylitis occurs predominantly in the fourth and fifth decades of life, male and female prevalence rates are reportedly equal, and 75% of patients are symptomatic in their dominant arms. The primary etiology is repetitive stress or overuse of the flexor-pronator musculature. Degenerative changes in the musculotendinous region of the medial epicondyle are the result of chronic repetitive concentric and eccentric contractile loading of the flexor-pronator group. Most often changes are seen in the pronator teres and flexor carpi radialis muscles, although larger diffuse tears can occur in other flexor/pronator muscles [63]. Activities that involve excessive and repetitive use of these muscles (e.g., pitching in baseball, golf, bowling, racquetball, football, carpentry, plumbing, and meat cutting) can cause medial epicondylitis because they require repetitive forearm, wrist, and hand motions [65]. Degenerative joint disease of the elbow is another painful condition of the elbow that can be seen in the outpatient setting. Arthritis of

the elbow is either due to inflammatory disease (most commonly rheumatoid) or degenerative changes within the elbow joint (osteoarthritis) [66]. Primary osteoarthritis is less common than post-traumatic arthritis of the elbow [67]. Primary osteoarthritis is most commonly seen in men with a history of heavy manual labor. On the other hand, post-traumatic arthritis may occur after any traumatic insult to the elbow regardless of the patient's age, sex, or severity of joint damage [66]. Rheumatoid arthritis is a chronic inflammatory disease characterized by peripheral polyarthritis. One or both elbows are involved in 20–65% of rheumatoid patients [68]. Olecranon bursitis is another cause of elbow pain. The olecranon bursa is the only bursa of the elbow joint. It is positioned subcutaneously on the extensor aspect of the elbow over the olecranon process of the ulna [69]. Olecranon bursitis occurs particularly when there is a prominent olecranon process or bone spur and when the elbow is subjected to recurrent trauma [70]. Other less common causes of elbow pain include posterior interosseous nerve syndrome, radial tunnel syndrome, cubital tunnel syndrome, and ulnar collateral ligament injury and triceps tendinopathy [71].

The physical examination for the elbow starts with inspection for any redness, swelling, asymmetry, or deformity. A shoulder and neck examination should be done to rule out any referred pain to the elbow due to radiculopathy or referred pain from the neck or shoulder. When palpating the joint, tenderness to palpation just anterior to the medial epicondyle signifies medial epicondylitis. Point tenderness anterior to the lateral epicondyle is diagnostic of lateral epicondylitis [50]. Range of motion testing should include active and passive movements. Restriction of full extension is diagnostic of osteoarthritis [50]. Olecranon bursitis is characterized by an abnormal increase in the volume of fluid within the bursal cavity [72].

Injection of the elbow can be a useful diagnostic and therapeutic tool in an outpatient setting. Corticosteroid injection is an accepted treatment option for medial and lateral epicondylitis. Olecranon bursa aspiration and injection are useful when the olecranon bursa is inflamed [73]. Localized corticosteroid injections yield moderate symptomatic relief in short term but do not demonstrate benefit on long-term follow-up for medial and lateral epicondylitis [74]. A prospective, randomized, double-blind study concluded that the local injection of steroids provides short-term benefits in the treatment of medial epicondylitis [75]. PRP has also been shown to be an effective treatment for chronic lateral elbow epicondylitis in the short term [76].

The most common approach to performing an in-office elbow injection is with the patient in the supine position. For lateral epicondylitis, the affected arm should rest at the side with the elbow flexed to 45 degrees and the wrist pronated. Figure 19.5 shows the approach for lateral epicondylitis injection with patient supine and hand pronated. For medial epicondylitis, the affected arm is resting comfortably abducted and the hand is supinated. Figure 19.6 shows the approach for medial epicondylitis injection with patient supine and hand supinated. The most tender point of the epicondyle is identified by gentle palpation and marked. The area is then sterilized with the appropriate cleaning solution. A 25-guage 1-in. needle is inserted at 90 degrees down to the level of the bone and pulled back 1–2 mm. Then, after negative aspiration, the medication consisting of 1 mL corticosteroid (betamethasone 6 mg/mL, methylprednisolone 40 mg/mL, or triamcinolone 40 mg/mL) mixed with 2–3 mL of 1% lidocaine, 0.25% bupivacaine, or 0.5% bupivacaine is injected slowly. The nee-

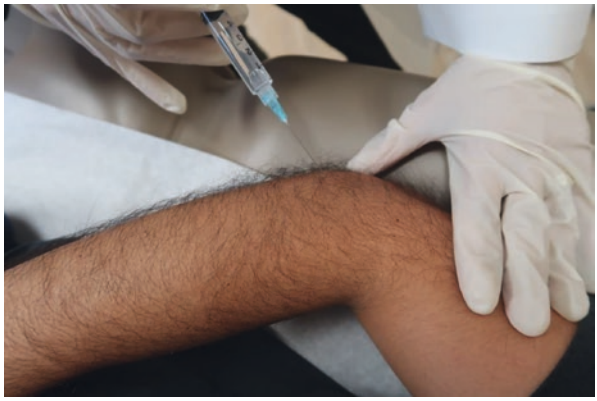

Fig. 19.5 Lateral epicondylitis injection with patient supine and hand pronated

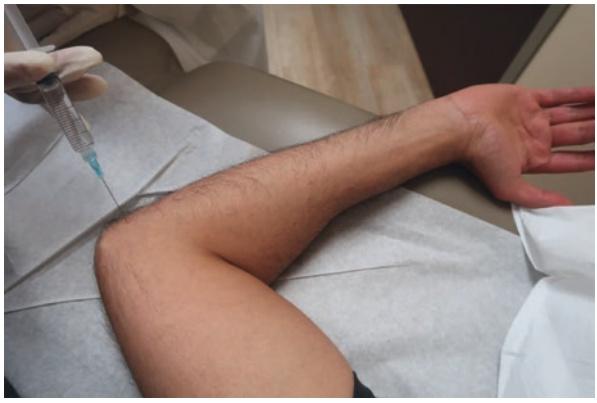

Fig. 19.6 Medial epicondylitis injection with patient supine and hand supinated

dle is then withdrawn [73]. For the olecranon bursa injection, the patient is placed supine with the elbow flexed as much as the patient can comfortably tolerate. The area over the olecranon process is palpated for fluctuance. After cleaning the area with the appropriate cleaning solution, a 22-guage 1-in. needle attached to an empty 10-mL syringe is inserted directly into the bursa and fluid is aspirated. After the fluid has been aspirated, the needle is held in place with a hemostat while the syringe is changed. A syringe containing 1 mL corticosteroid (betamethasone 6 mg/mL, methylprednisolone 40 mg/mL, or triamcinolone 40 mg/mL) mixed with 3 mL of 1% lidocaine, 0.25% bupivacaine, or 0.5% bupivacaine is injected slowly. The needle is then withdrawn [73].

Hip

The hip joint is a "ball and socket" synovial joint with articular cartilage and a fully developed joint capsule allowing movement in all three body planes [77]. These planes include the transverse axis, which allows for flexion and extension,

the longitudinal axis, which allows for internal and external rotation, and the sagittal axis, which allows for abduction and adduction. The flexor muscles include the iliopsoas, rectus femoris, pectineus, and sartorius muscles. The hip extensor muscles include the gluteus maximus and hamstring muscle groups. Smaller muscles, such as the gluteus medius and minimus, piriformis, obturator externus, and internus and quadratus femoris muscles, insert around the greater trochanter, allowing for abduction, adduction, and internal and external rotation [78]. This joint provides an articulation site for the head of the femur with the acetabulum of the pelvis and mainly functions to support the weight of the body in both dynamic and static positions [79]. The acetabular labrum is a fibrocartilaginous ring that surrounds the bony acetabulum and blends inferiorly with the transverse acetabular ligament. It increases the joint surface area by adding depth to the acetabulum and thereby reduces mechanical stress on the articular cartilage [80]. During normal ambulation, the human hip undergoes cyclic loading that can place forces three to five times those of body weight, and during more strenuous activity, such as running or climbing, the joint is exposed to much greater forces – as much as 12 times those of body weight [81].

Self-reported hip pain affects about 14% of the population over the age of 60 years [82]. Musculoskeletal sources of adult hip pain can be divided into posterior, lateral, and anterior categories [46]. Posterior hip pain can be due to numerous pathologies including piriformis syndrome, ischiofemoral impingement, sacroiliac joint dysfunction, lumbar radiculopathy, and vascular claudication [78]. Piriformis syndrome is defined as sciatica caused by compression of the sciatic nerve by the piriformis muscle. Signs specific for piriformis syndrome include external tenderness over the greater sciatic notch, internal tenderness of the piriformis muscle on vaginal or rectal examination, Freiberg test, Pace test, Beatty test, tonic external rotation of the hip, and pain with the FAIR (flexion-adduction-internal rotation) maneuver [83]. A positive Freiberg test consists of pain reproduced with passive internal rotation of the hip in extension [84]. The Pace test was first described in 1976 and is pain reproduced when the clinician provides resistance to hip abduction by holding the sitting patient's knee [85]. For a positive Beatty test, the patient has pain while holding the flexed hip in abduction against gravity while lying on the unaffected side [86]. The treatment for piriformis syndrome includes (but is not limited to) physical therapy, medications, and injections. Piriformis muscle injections can be done in the office if they are ultrasound guided. Because the piriformis muscle lies deep to the gluteus maximus muscle, it is difficult to perform an accurate piriformis muscle injection without image or electrophysiologic guidance. Clinicians have reported successful applications of electrophysiologic technique, fluoroscopy, computed tomography, and magnetic resonance imaging to improve the accuracy of needle placement into the piriformis muscle. Musculoskeletal ultrasound has shown promise as a visual guidance tool for piriformis injections [87]. The piriformis muscle is best examined using ultrasound with the patient in the prone position. A curvilinear transducer is placed in a transverse orientation to identify the sacral cornua and is then moved toward the greater trochanter until the lateral edge of the sacrum is observed. The piriformis muscle will appear as a

hyperechoic band lying between the lateral edge of the sacrum and the greater trochanter and deep in the gluteus maximus muscle. A 21-guage needle is preferred for piriformis muscle injection because it is more rigid compared to a 23-guage needle [88]. One study investigating a technique for piriformis injections used 40–60 mg methylprednisolone or 40 mg triamcinolone in 5–6 mL normal saline. The needle was then pulled back 3–8 mm and placed in the belly of the piriformis muscle, and additional injectate consisting of 40 mg methylprednisolone or 40 mg triamcinolone in 7–10 mL 1% lidocaine was injected [6].

Another cause of posterior hip pain is ischiofemoral impingement (IFI). IFI is a fairly rare cause of hip pain. IFI is defined by a narrowing of the space between the lateral aspect of the os ischium and the lesser trochanter of the femur [89]. Although this is usually found in patients who have a history of trauma or prior hip surgery, rare cases have been reported in patients with no history of trauma or surgery. Imaging is usually required for diagnosis confirmation; however, the ischiofemoral impingement and long-stride walking tests have been found to be highly accurate to help identify those with or without IFI [90]. The long-stride walking test is considered positive if the posterior pain is reproducible lateral to the ischium during extension with long strides, whereas pain is alleviated when walking with short strides. The IFI test is performed with the patient in a lateral position. This test is intended to provoke impingement in extension with a neutral or adducted hip and relieves the impingement pain in extension with an abducted hip [90]. No definite treatment has been recommended for IFI other than excision of the lesser trochanter [91]. However, some cases of infiltration of the ischiofemoral space with a combination of local anesthetics and steroids have been reported to be useful [92]. In the office, this injection can be done with ultrasound guidance. The ultrasound-guided technique uses the proximal hamstring tendons as a landmark for injection into the ischiofemoral space [92]. The patient is placed prone, and the ultrasound probe is placed on the affected side. It is moved laterally to visualize the bony acoustic landmark of the lesser trochanter. The quadratus femoris muscle and sciatic nerve are then visualized. A 22-guage 3.5-in. spinal needle is inserted from lateral to medial until the needle tip is in the quadratus femoris muscle. A total of 4 mL consisting of 1 mL triamcinolone, 1 mL 1% preservative-free lidocaine, and 3 mL of ropivacaine is then injected [93].

Lateral hip pain can be caused by tendinosis of the gluteus medius and minimus, thickening of the iliotibial band, trochanteric bursitis, external snapping hip, and neuropathy of the iliohypogastric or lateral femoral cutaneous nerves [46]. Greater trochanteric pain syndrome (GTPS) encompasses a range of causes including gluteal medius and minimus tendinopathy/tears, trochanteric bursitis, and external coxa saltans [94]. External coxa saltans is a term used to describe palpable or auditory snapping with hip movements. Extra-articular snapping may be caused laterally by the iliotibial band or anteriorly by the iliopsoas tendon [95]. The most common form of coxa saltans is the external extra-articular variety which involves either the posterior iliotibial band or the anterior aspect of the gluteus maximus as they travel over the greater trochanter during hip flexion and extension or internal and external rotation [96]. Greater trochanteric pain syndrome is a clinical diagnosis

with a typical presentation of chronic intermittent lateral hip/thigh/buttock pain, aggravated with activity and affected side lying positions [97]. Treatment in the initial stages encompasses a range of conservative measures including physiotherapy, local corticosteroid injection, PRP injection, shockwave therapy, activity modification, pain and anti-inflammatory medication, and weight reduction [97]. A cure rate with such conservative interventions, administered independently or in combination, can be expected to exceed 90% [98]. A randomized trial comparing injection therapy and usual care (consisting of analgesics as needed) found an additional value of injection therapy in patients who have clinical signs of greater trochanteric pain syndrome. The application of corticosteroid injections made no difference in the long-term resolution of pain, but the injection gave patients early relief [99]. A greater trochanteric bursa injection is performed with the patient lying in the lateral recumbent position with the affected side up. The landmark is found by palpating the femur from the mid-shaft proximally until the area of bony protrusion is reached. The injection site is the point of maximal tenderness or swelling. Figure 19.7 shows the approach for greater trochanteric bursa injection with patient in the lateral recumbent position. A 25-guage 1 1/2-in. needle (longer if patient is obese) is inserted perpendicular to the skin. The needle should be inserted directly down to the bone and then withdrawn 2–3 mm before injecting. A total of 4–6 mL is injected consisting of 3–5 mL of 1% lidocaine (or 0.25% or 0.5% bupivacaine) and 1 mL betamethasone sodium phosphate and acetate (or 1 mL methylprednisolone) [100].

Anterior hip pain can be caused by osteoarthritis of the hip joint, hip labral tear, femoroacetabular impingement, iliopsoas bursitis, occult or stress fracture, transient synovitis, septic arthritis, and osteonecrosis [78]. Patients with anterior hip pain often will localize the pain to the anteromedial thigh (inguinal region) with what is known as the "C" sign at physical examination [46]. The osteoarthritis (OA) process involves progressive loss of articular cartilage, subchondral cysts, osteophyte formation, periarticular ligamentous laxity, muscle weakness, and possible synovial inflammation [101]. The American College of Rheumatology has established crite-

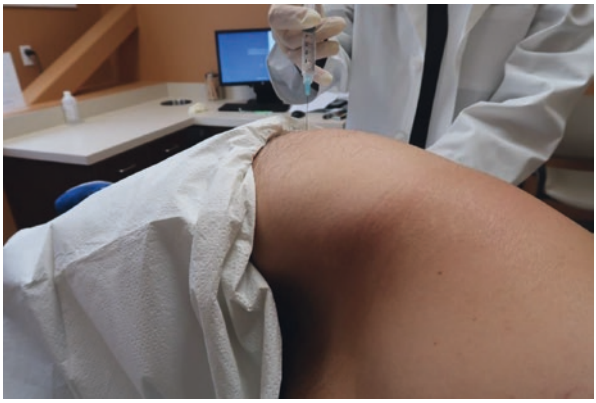

Fig. 19.7 Greater trochanteric bursa injection with patient in the lateral recumbent position

ria that are used in the diagnosis of hip OA in clinical practice. Components of this criteria include hip pain, pain with hip internal rotation, morning stiffness of the hip less than 60 min, age over 50 years, and certain radiographic findings such as joint space narrowing and femoral/acetabular osteophytes [102]. There is evidence that intra-articular corticosteroid injections offer symptomatic relief in hip OA [103]. The guidelines currently recommend the use of intra-articular corticosteroid injections as an adjunct to other treatments for pain relief in hip OA [104]. Intra-articular hip injections can be done in the office with ultrasound guidance. The patient is positioned supine with the hip slightly abducted and internally rotated. A low-frequency curvilinear transducer is used to visualize the hip joint and target the anterior synovial recess. Initially, the probe is placed in a transverse plane parallel to the inguinal ligament and used to identify the femoral artery and vein above the femoral head. The probe is then moved laterally to just above the hyperechoic femoral head and rotated to an oblique sagittal position so that the probe marker is aimed toward the umbilicus. The femoral head, femoral neck, anterior capsular recess, and iliofemoral ligament should be visualized. A 25-guage 3.5-in. standard spinal needle is guided to the anterior capsular recess until the needle tip is clearly visualized in the joint space [105]. One study investigating the technique of hip injections used a total of 7 mL injectate consisting of 2 mL betamethasone with 5 mL 1% lidocaine [106].

Hip labral tears can be caused by trauma, femoroacetabular impingement, capsular laxity/hip hypermobility, dysplasia, and degeneration [107]. Patients will usually present with anterior hip or groin pain. On physical exam, a Trendelenburg gait may be observed. If the hip is affected, the weight is lowered carefully on the affected side, and the knee bends to absorb the shock [108]. On examination of hip range of motion, the combined movement of flexion and rotation causes pain in the groin. Certain maneuvers may also produce clicking and locking sensations [109]. Although conservative treatment options including rest, restriction of weight-bearing, nonsteroidal anti-inflammatory medications, and physical therapy are tried first, surgery is considered the main treatment line for labral tears [110]. There is limited evidence showing the efficacy of therapeutic hip intra-articular cortisone injections for the treatment of labral tears. A 2014 study found that in patients with symptomatic labral tear, intra-articular cortisone injection has limited clinical benefit as a therapeutic modality. However, anesthetic-only intra-articular injections for patients who may be candidates for hip arthroscopy can be a useful diagnostic tool [111].

The iliopsoas bursa is the largest bursa in the body and lies between the iliacus muscle and iliopsoas tendon and the anterior surface of the hip joint capsule and pectineal eminence [112]. Iliopsoas bursitis is often associated with hip joint pathologies (mostly degenerative and in a lesser degree inflammatory arthropathies) and snapping hip syndrome or may appear as a result of repetitive trauma or sport activities that affect normal hip joints [113]. The inflammation of the bursa results in disabling pain in the groin region, with the hip kept in flexion and external rotation [114]. There is some evidence that patients can benefit from corticosteroid injections into the iliopsoas bursa. Sonography-guided iliopsoas bursal injections can

provide relief to patients with iliopsoas tendinitis/bursitis [115]. These injections are done with the patient supine. A linear or curvilinear transducer is used, depending on the patient's size. The tendon is visualized in short axis at the iliopectineal eminence of the acetabulum. If fluid is present, a 20- or 22-guage needle is then positioned in plane with the transducer by using a lateral approach into the bursa. If the bursa is not visible, then the needle is positioned between the tendon and the hip capsule. If the needle is placed accurately and fluid is injected, bursal distention should occur [116]. A total of 5 mL can be injected consisting of 1 mL triamcinolone (40 mh/mL), 2 mL of 1% lidocaine, and 2 mL of 0.25% bupivacaine [117].

Knee

The knee joint is a synovial joint that connects the two largest bones of the body, the femur and the tibia. It is a complex modified hinge joint with the greatest range of movement in flexion and extension about the sagittal plane, as well as varus and valgus rotation about the frontal plane [118]. It consists of two bony articulations; the articulation between the femur and tibia bears most of the body weight, while the articulation between the patella and femur creates a frictionless transfer over the knee of the forces generated by contraction of the quadriceps femoris muscle [119]. The two main joints of the knee are the femorotibial joint and the patellofemoral joint. The tibiofemoral joint is a hinge joint between the distal femur and proximal tibia. The patellofemoral joint is a diarthrodial plane joint that consists of the posterior surface of the patella and the trochlear surface of the distal anterior femur [120]. The knee joint depends on the ligaments and muscles that surround it for its strength and stability, not on its bony configuration [121]. Primary knee stabilization is achieved through knee ligaments, while muscles around the knee play a secondary role, although both work congruently to help the knee function reliably [118]. On the medial side of the knee, the ligament supporting structures include the medial collateral ligament (both superficial and deep) and the posterior oblique ligament, which blends with the posterior capsule. The lateral ligament support consists of the lateral collateral ligament and structures, including the popliteus and posterolateral capsule that make up the arcuate ligament complex. In addition, the iliotibial band supplies some lateral support [122]. Another set of ligaments, the cruciate ligaments, is essential in their contribution to stability in the knee. The anterior cruciate ligament originates behind the anterior tibial spine and passes upward and backward to insert over the back of the lateral femoral condyle. The posterior cruciate ligament is somewhat stronger compared to the anterior cruciate ligament. The posterior cruciate ligament originates from the posterior aspect of the tibia and passes forward to insert into the medial femoral condyle in the intercondylar area. These cruciate ligaments control stability in the anteroposterior plane [122]. In addition to the ligament, the menisci of the knee are also important for joint function. The lateral and medial menisci of the knee joint are crescent-shaped wedges of fibrocartilage that provide increased stability to the femorotibial

articulation, distribute axial load, absorb shock, and provide lubrication to the knee joint [123].

Knee pain affects approximately 25% of adults, and its prevalence has increased almost 65% over the past 20 years [124]. Pain and functional disability are the principal reasons why patients with chronic knee pain seek medical treatment [125]. Potential causes of knee pain in an adult include meniscal tears, ligament sprains, contusions, patellofemoral dysfunction, bursitis, and osteoarthritis. Knee osteoarthritis is one of the major causes of pain and physical disability in older adults [126]. Risk factors for developing knee osteoarthritis include obesity, previous knee injury, selected physical activities, the presence of hand OA (Heberden's nodes), and a family history of the disease [127]. A Framingham study found that a decrease in body mass index of 2 units or more over the 10 years before the examination in the study decreased the odds for developing osteoarthritis by over 50% [128]. Ten mechanism-based injury patterns have been recognized for knee injuries including pure hyperextension, hyperextension with varus, hyperextension with valgus, pure valgus, pure varus, flexion with valgus and external rotation, flexion with varus and internal rotation, flexion with posterior tibial translation, patellar dislocation, and direct trauma [129]. Injuries to the menisci are the second most common injury to the knee with a high incidence of meniscal tears occurring with an injury to the anterior cruciate ligament [130]. Plain radiography remains a mainstay in the diagnosis of osteoarthritis [131]. The Kellgren-Lawrence classification is typically applied specifically within the context of knee osteoarthritis. Each radiograph is assigned a grade from 0 to 4, which correlates to increasing severity of osteoarthritis, with Grade 0 signifying no presence of osteoarthritis and Grade 4 signifying severe osteoarthritis [132].

The physical examination of the knee can be grouped into three aspects: (1) patella-femoral joint/extensor mechanism, (2) articular (meniscal and chondral lesions), and (3) knee instability [133]. Each of these groups has specific physical exam signs and tests that can be used to help further evaluate the knee. The patella-femoral joint can be further assessed by evaluating the Q angle, patellar tilt and glide, patella tracking, and the J sign [133]. The Q angle is formed by the intersection of two lines that cross at the center of the patella: one going from the anterior superior iliac spine (ASIS) to the center of the patella and the other from the anterior tuberosity of the tibia to the center of the patella [134]. The larger the Q angle is, the greater the lateralization force on the patella, which increases retropatellar pressure between the lateral facet of the patella and the lateral femoral condyle. This can give rise to patellofemoral pain syndrome and eventually lead to degeneration of the joint cartilage of the patella [135]. The patellar tilt test assesses for tightness of lateral structures. It is performed with the knee extended, and the patella is grasped between the thumb and forefinger. The medial aspect of the patella is then compressed posteriorly while the lateral aspect is elevated. If the lateral aspect of the patella is fixed and cannot be raised to at least the horizontal position (0 degrees), the test is positive and indicates tight lateral structures [136]. The glide test is performed with the knee flexed at 30 degrees: if the patella glides laterally over 75% of its width, a medial laxity is diagnosed; while when it glides less than 25%, lateral restraint tightness is

predicted [137]. Patellar tracking is defined as the motion of the patella relative to the femur or femoral groove on knee flexion and extension. Abnormalities of tracking are thought to relate to many disorders of the patellofemoral joint [138]. The J sign indicates excessive lateral patellar shift in terminal extension [139]. Meniscal and chondral lesions of the knee can be evaluated by meniscal palpation tests such as the McMurray and Bragard's tests and meniscal rotation tests such as Apley's, Bohler's, squat, duck walking, and Thessaly tests. According to the McMurray test, a medial meniscal tear is suspected if a clicking sound is elicited when the knee is slowly extended after the knee has been completely flexed and the leg has been externally rotated as far as possible. A lateral meniscal tear is indicated if a clicking sound is elicited when the leg is internally rotated as far as possible [140]. In Bragard's test, external tibial rotation and knee extension bring the meniscus more anterior: if tenderness is felt along the joint line palpation, an articular surface irregularity (i.e., chondral lesion) or a meniscal tear is suspected [133]. To perform Apley's test, the patient is in a prone position and the tibia is rotated over a fixed femur, while the knee is alternatively compressed and distracted to elicit pain. This differentiates pain due to a meniscal lesion (worse on compression) from pain due to other soft tissue injuries (worse on distraction) [141]. In Bohler's test, a varus stress and a valgus stress are applied to the knee: pain is elicited by compression of the meniscal tear [133]. The squat test, duck walking test, and Thessaly test consist of several repetitions of full weight-bearing flexions on the knee, in different positions (squatting, walking and full flexion, and at 5 degrees and 20 degrees flexion, respectively) [133]. A 2009 study assessed the validity of the Thessaly test as a means of detecting meniscal tears of the knee by comparing arthroscopic findings to a clinical examination finding. They concluded that the Thessaly test is a valid and reproducible physical examination technique for predicting meniscal tears [142]. The third group of physical examination tests assess for knee instability. These tests include stress tests, slide tests, and pivot shift tests [133]. The standard stress tests for the knee include valgus (abduction) and varus (adduction) tests. The valgus stress test performed at 30 degrees of knee flexion with the tibia in external rotation evaluates the stability of the medial collateral ligament. This test is performed with the patient placed supine and the hip of the affected limb is slightly abducted and the knee flexed to 30 degrees over the side of the table. The examiner positions one hand over the lateral aspect of the knee and grasps the ankle with the other hand. A valgus stress is applied. This is then repeated with the knee in extension [143]. The test is then graded based on the amount of medial joint opening and the quality of the endpoint. Grade I is assigned to knees with 5 mm or less of joint opening and a solid endpoint. Grade II corresponds to 6–10 mm opening with a good endpoint, and grade III represents a >10 mm opening and a soft endpoint [144]. The varus stress test is used to detect lateral collateral ligament laxity. This test is performed with the patient placed in a supine position with the tibia held in gentle internal rotation. The examiner places one hand on the medial aspect of the thigh and the other on the proximal tibia. The involved knee is flexed to 30 degrees; a varus force is applied across the joint line. The test is then repeated with the knee in full extension [145]. Grading the varus stress test is similar to the valgus stress test with incorporation of

the amount of medial joint opening and the quality of the endpoint. The medial and lateral collateral ligaments are important in knee stability. An analysis of varus and valgus stresses found that the collateral ligaments are the load-bearing structures and their absence would substantially increase primary laxities, coupled axial rotations, forces in cruciates, and articular contact forces [146]. The slide tests for knee instability include the anterior and posterior drawer test and the Lachman test. In vitro and in vivo analyses indicate that the Lachman test is the clinical examination of choice for detection of anterior cruciate ligament insufficiency and that the Lachman test places more strain on the anterior cruciate ligament than the anterior drawer test [143]. The Lachman test is performed with the patient supine and the knee flexed to 30 degrees. The examiner stabilizes the anterolateral distal femur with one hand and uses the other hand to exert firm pressure on the posterior aspect of the proximal tibia in an attempt to induce anterior displacement. Proprioceptive and/or visible anterior translation of the tibia beyond the femur with a "mushy" or "soft" endpoint represents a positive test result [147]. The posterior drawer test has been reported to be a sensitive test in the evaluation of an isolated posterior cruciate ligament injury [27]. This test is performed with the patient supine and the affected knee flexed to 90 degrees. In this position, a normal anatomical relationship between the tibia and femur is established. Next, a posterior force is applied to the proximal tibia. Tibial posterior translation and quality of the endpoint are evaluated [143]. The pivot shift test is a test of anterolateral rotatory instability and is done by subluxation and reduction of a loaded joint. The knee is placed in 10–20 degrees of flexion, and torque is placed on the tibia while rotating it internally and applying valgus stress to the knee joint. If there is anterior subluxation of the lateral tibial plateau underneath the femoral condyle, then this represents a positive test [138].

The most common indication for an in-office knee injection is osteoarthritis. The injectate for an intra-articular knee injection can be corticosteroid, hyaluronic acid, or platelet-rich plasma. For knee osteoarthritis, intra-articular injection (corticosteroids, viscosupplements, blood-derived products) is preferred as the last nonoperative modality, if the other conservative treatment modalities are ineffective [4]. A meta-analysis concluded that intra-articular injections of corticosteroid improve symptoms of osteoarthritis of the knee and effects were beneficial up to 2 weeks and at 16–24 weeks [41]. Viscosupplementation is an intra-articular therapeutic modality for the treatment of knee osteoarthritis and is based on the physiologic importance of hyaluronan in synovial joints. Its therapeutic goal is to restore the viscoelasticity of synovial hyaluronan, decrease pain, improve mobility, and restore the natural protective functions of hyaluronan in the joint [148]. A Cochrane review analysis supported the contention that the hyaluronan and hylan class of products is superior to placebo in the treatment of knee osteoarthritis. The analysis also supports that hyaluronan and hylan products have more prolonged effects than intra-articular corticosteroids [148]. In terms of blood-derived products, autologous platelet-rich plasma (PRP) contains a pool of growth factors and appears to offer an easy solution for delivering multiple growth factors needed for tissue repair [149]. A randomized study concluded that PRP treatment for patients with knee osteoarthritis had beneficial effects in regulating inflammatory factors and alleviating joint

inflammation, cartilage destruction, and bone damage [150]. In addition to corticosteroid, viscosupplements, and blood-derived products, stem cell injection is an emerging therapy for knee osteoarthritis. The aim in using stem cells is to support the self-healing process of the knee joint cartilage which results in relief from osteoarthritis symptoms [151]. A 2017 systematic review of stem cell injection studies for knee osteoarthritis found level 3 or level 4 evidence for the use of stem cell injection of different types in the treatment of knee osteoarthritis. However, all studies were found to be at high risk of bias, and the study concluded that stem cell therapy for patients with knee osteoarthritis is not recommended [152].

There are many approaches to performing in-office knee intra-articular injections. Landmark-guided knee injections at the superolateral patella were the most accurate [153]. A systematic review found that landmark-guided intra-articular knee injections were reasonably accurate, in particular at the lateral injection sites. Although the use of needle guidance improved the accuracy of intra-articular knee injections, there was insufficient evidence to suggest that increased accuracy of knee injections resulted in improved therapeutic outcome [153]. The knee injection is best performed with the patient supine with the knee bent to about 45 degrees. One way to achieve this bend in the knee is to place a pillow under the knee in the popliteal area so that the knee bends slightly. The superior lateral aspect of the patella is palpated, and the skin is marked one fingerbreadth above and one fingerbreadth lateral to this site. Figure 19.8 shows the superolateral approach to intra-articular knee injection with patient supine. After cleaning the area with the appropriate cleaning solution, a 25-guage 1 1/2-in. needle is used to anesthetize the area with 1% xylocaine. If there is an effusion or swelling of the knee, a 22-guage 1 1/2-in. needle attached to a 5 or 10 cc syringe is directed at a 45-degree angle distally and 45 degrees into the knee, tilted below the patella. Once the needle is inserted, aspiration is performed, and the syringe should be filled with fluid. Once the syringe is filled with fluid, a hemostat can be placed on the hub of the needle, and the syringe can be disconnected. Then, a syringe filled with corticosteroid medi-

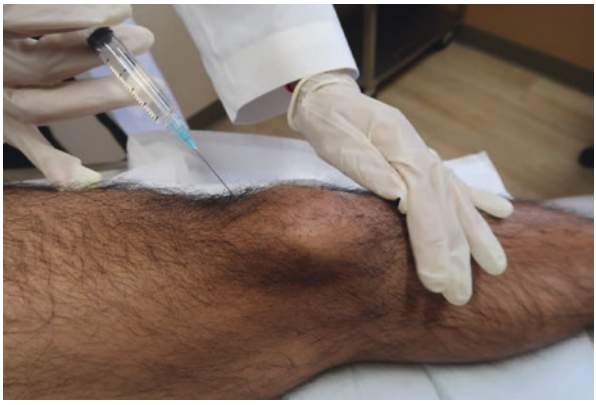

Fig. 19.8 Superolateral approach to intra-articular knee injection with patient supine

cation can be attached to the needle. The corticosteroid medication should consist of 1 mL of the corticosteroid (betamethasone 6 mg/mL, methylprednisolone 40 mg/mL, or triamcinolone 40 mg/mL) mixed with 3–5 mL of 1% lidocaine. If there is no swelling of the knee, then a 25-guage 1 1/2-in. needle attached to a syringe filled with the corticosteroid medication with lidocaine can be inserted in the same location where the 22-guage needle is inserted for aspiration. After negative aspiration, the corticosteroid medication can be injected. After injection of the medication, the needle and syringe are withdrawn [154].

Myofascial Pain

Myofascial pain syndrome is a common, painful musculoskeletal disorder characterized by the presence of trigger points [155]. Myofascial pain syndrome arises from the muscle and is composed of symptoms from the sensory, motor, and autonomic systems [156]. This is different from fibromyalgia syndrome, which involves multiple tender spots or tender points [157]. A myofascial trigger point is a discrete, hyperirritable nodule in a taut band of skeletal muscle which is palpable and tender during physical examination [158]. Clinically, myofascial trigger points are defined as active or latent [159]. An active myofascial trigger point is recognized as eliciting spontaneous pain as well as pain, referred pain, and motor or autonomic symptoms on palpation [160]. An active trigger point causes pain at rest [161]. In contrast, latent myofascial trigger points upon palpation/compression cause pain, a local twitch response, and referred pain [162]. A 2015 study proposed a preliminary set of diagnostic criteria. This study found that the majority of clinicians did not consider there to be any signs or symptoms that were judged as being essential to the diagnosis of myofascial pain syndrome. However, more than a quarter of surveyed clinicians reported local muscle pain, decreased pain pressure threshold, soft tissue pain, non-focal neurologic exam, and regional pain as essential [163]. Patients who have trigger points often report regional, persistent pain that usually results in decreased range of motion of the muscle [161]. The muscles commonly involved include muscles used to maintain body posture including the upper trapezius, scalene, sternocleidomastoid, levator scapulae, and quadratus lumborum [156].

In-office trigger point injections can be offered as a treatment modality for patients with myofascial pain and trigger points. Therapeutic injections have generally been used for treating pain associated with myofascial trigger points [164]. The mechanism of action of trigger point injections is thought to be disruption of the trigger points by the mechanical effect of the needle or the chemical effect of the agents injected, resulting in relaxation and lengthening of the muscle fiber [155]. For the injection, the patient should be placed in a position to produce muscle relaxation, most commonly prone or supine. The overlying skin over the trigger point is cleansed with alcohol. Then, the trigger point is isolated by pinching it

between the clinician's thumb and index finger. Using sterile technique, a 22-guage 1.5-in. needle is inserted 1–2 cm away from the trigger point so that the needle can be advanced to the trigger point at an angle of 30 degrees to the skin [161]. Before advancing the needle into the trigger point, the clinician should warn the patient of the possibility of sharp pain, muscle twitching, or an unpleasant sensation as the needle contacts the taut muscular band [165]. After negative aspiration, a small amount of anesthetic (such as 1% lidocaine) should be injected once the needle is inside the trigger point. The needle is then slightly withdrawn and redirected in different directions, repeating the needling and injection process in each direction until the local twitch response is no longer elicited [161]. The needle is then completely withdrawn.

Table 19.1 lists in-office procedures that are considered "evidence-based treatments" for which there are studies that suggest effectiveness of the above treatments. The references for these procedures have been discussed in the text of this chapter.

Table 19.2 lists in-office procedures that are considered "emerging treatments" for which there is conflicting evidence for the efficacy of the above-listed treatments [152, 166–175].

Table 19.1 Evidence-based treatments for in-office procedures

Musculoskeletal disorder	In-office procedure
Glenohumeral joint osteoarthritis	Glenohumeral joint corticosteroid injection
Adhesive capsulitis of the shoulder	Glenohumeral joint and subacromial corticosteroid injection
Rheumatoid arthritis of the glenohumeral joint	Glenohumeral joint corticosteroid injection
Subdeltoid bursitis	Subacromial corticosteroid injection
Shoulder impingement	Subacromial corticosteroid injection
Rotator cuff tendinopathy	Subacromial corticosteroid injection
Acromioclavicular joint osteoarthritis	Acromioclavicular joint corticosteroid injection
Osteolysis of distal clavicle	Acromioclavicular joint corticosteroid injection
Long head of the biceps tendinopathy	Long head of the biceps corticosteroid injection
Piriformis syndrome	Piriformis muscle corticosteroid injection
Ischiofemoral impingement	Ischiofemoral space corticosteroid injection
Greater trochanteric bursitis	Greater trochanter bursa corticosteroid injection
Hip osteoarthritis	Hip intra-articular corticosteroid injection
Iliopsoas bursitis	Iliopsoas bursa corticosteroid injection
Knee osteoarthritis	Knee intra-articular corticosteroid injection
Lateral epicondylitis	Lateral epicondyle corticosteroid injection
Medial epicondylitis	Medial epicondyle corticosteroid injection
Olecranon bursitis	Olecranon bursa corticosteroid injection
Myofascial pain with trigger points	Trigger point injection with local anesthetic

Table 19.2 Emerging treatments for in-office procedures

Musculoskeletal disorder	In-office procedure
Knee osteoarthritis	Stem cell injection
Knee osteoarthritis	Platelet-rich plasma (PRP) injection
Lateral epicondylitis	PRP injection
Rotator cuff tendinopathy	PRP injection
Plantar fasciitis	PRP injection
Greater trochanteric pain syndrome	PRP injection

Conclusion

There are many different in-office procedures that are helpful to patients with various musculoskeletal issues that might be causing pain and functional impairment. These procedures can be considered in an acute or chronic pain situation. In-office pain procedures can help in relieving pain, reducing inflammation, and improving mobility. It is imperative for the clinician to make the correct diagnosis prior to performing an in-office procedure. This can be achieved by obtaining a good history, performing a thorough physical exam, and getting the appropriate imaging. In addition to understanding the indications for an in-office procedure, it is important to recognize situations where a procedure might be contraindicated. Such situations include infection, skin breakdown at the potential injection site, unstable coagulopathy, and allergy to any of the injectable agents. If recommended in the appropriate situation, an in-office procedure can be helpful in improving a patient's mobility and quality of life.

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Chapter 20
Interventional Pain Management Procedures

Gabor Bela Racz, Gabor J. Racz, and Tibor A. Racz

Introduction

In this chapter, we will incorporate much of the information gained from the clinical experiences of the past 30 years and incorporate interventional pain research, teaching, and practice. The recognized patterns of complications that have been recognized from over 300 medical/legal reviews have also been included.

The field of pain management is very technical. The good outcomes are a consequence of knowledge, evidence, and technique. Similarly, the undesirable and bad outcomes are the consequence of obsolete knowledge, technique, and absence of delivery of information that can prevent these complications. We intend to remedy this by providing as much relevant information as possible so that the practitioner can utilize the information to improve their ability to treat patients.

Interventional pain management is a wonderful area of medicine where the physician must obtain the highest level of qualifications. One must complete a fellowship or a fellowship equivalent and pass the board exams. The American Board of Anesthesiologists and the American Board of Medical Examiners' certification are becoming more important in terms of credentialing for hospitals and health plans. Beyond that, the highest level of international qualification is the Fellow of Interventional Pain Practice (FIPP) and/or the American Board of Interventional Pain Physicians (ABIPP).

G. B. Racz
Department of Anesthesiology, Texas Tech University Health Science Center, Lubbock, TX, USA

G. J. Racz (✉)
Epimed International, Dallas, TX, USA
e-mail: gabor@epimed.com

T. A. Racz
Optimal Pain Doctors, Addison, TX, USA

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One of the most important points is the recognition that no single injection or procedure can lead to long-term favorable outcomes unless one considers functional restoration. Therefore, in the patient suffering from failed back surgery, a single injection will not lead to the long-term outcome that the patient or the doctor anticipates without rehabilitation.

Blunt Needle Injections

Sharp needles are not recommended for most advanced interventional procedures. Placing blunt needles through the skin to the target is virtually impossible, and a two-needle technique using an introducer and the procedure needle are necessary. The techniques outlined in this chapter show how to place the blunt needle close to the target by taking a safe path to the final placement area.

Akins concluded that after 100 passes, an 18 g blunt needle did not penetrate the renal artery of experimental animals [1]. In addition, blunt needles do not penetrate nerves. Blunt needles used for intrathoracic sympathetic blocks at T2, T3 level have not been followed by pneumothorax. Sharp needle techniques have a predictable pneumothorax rate. The incidence of intra-arterial and intraneural injection-related complication is estimated to be 1 in 7000–10,000. This is based on reviewing numerous depositions and the numbers of procedures physicians are performing. The incidence of vascular and neurological disasters along the spinal canal when sharp needles are used is significant. The number of procedures performed using blunt needles is estimated to be more than 750,000, and thus far, there has not been a single blunt needle-related injection disaster reported. Some confuse venous runoff as arterial injection. These two vascular injections are completely different. The first may lead to paralysis, and the second could lead to cardiovascular consequences if a sufficient dose of local anesthetic has been given. Particulate steroid may have undesirable consequences if injected intra-arterially. Thus far, transforaminal injection-related disasters have been associated with the use of open-ended sharp needles. Selander, Akins, Heavner, and Racz conducted studies evaluating the vascular and nerve penetration of blunt needles [2, 3]. Doug Selander concluded that in an experimental animal, injecting 0.1–0.2 mL over 1 minute in the sciatic nerve could generate up to 750 mm mercury of peak pressure and spread into the thoracic spinal cord and, in rare instances, to the cerebellum. There is no safe volume of local anesthetic. Heavner and Racz evaluated sharp vs. blunt needles in anesthetizing dogs [4]. They concluded that 100% of the time, blunt needles with sizes ranging from 20 to 25 g could not penetrate nerves or arteries. With the use of a blunt needle, there has not been a reported cord injury from intraneural or intra-arterial injections. To utilize a blunt needle, an introducer needle must be used to make blunt needle placement safe, fast, and close to the target site.

Fluoroscopic Positioning

Fluoroscopy is critical for performing interventional pain procedures safely and effectively. Procedures should not be attempted until optimal fluoroscopic images are obtained by the combination of patient positioning, C-arm positioning, and

radiological technique. A skilled professional technician and a modern C-arm are needed for proper interventional pain practice.

The basic imaging views are anterior-posterior (A/P), lateral, and oblique angles (Fig. 20.1). Figures 20.2, 20.3, and 20.4 show the posterior lower lumbar spine anatomy, C-arm and patient position, and anterior-posterior image for a lumbar spine, respectively. Figure 20.5 shows oblique lumbar spine anatomy. The oblique image is obtained by rotating the C-arm from position A (anterior-posterior) to position B (oblique) (Fig. 20.6). Figure 20.7 shows the patient and final C-arm position for an oblique view (Fig. 20.7).

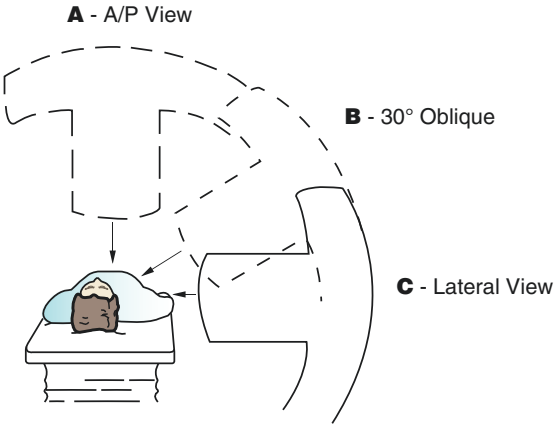


Fig. 20.1 The three most common C-arm positions for correct visualization and needle placement (**a**) A/P view. (**b**) 30° Oblique. (**c**) lateral view

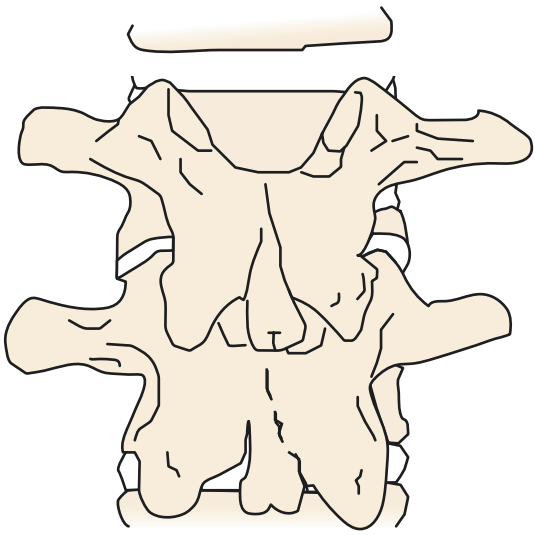


Fig. 20.2 Anterior-posterior lumbar spine anatomy

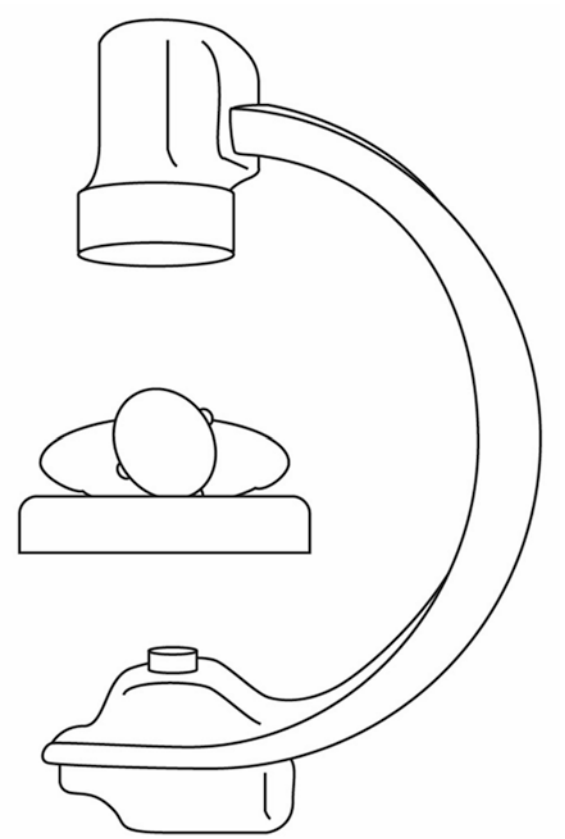


Fig. 20.3 C-arm position for anterior-posterior image

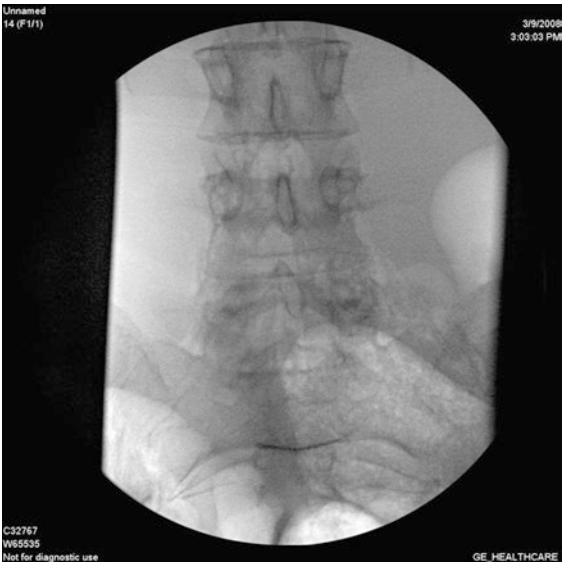


Fig. 20.4 Anterior-posterior fluoroscopic image

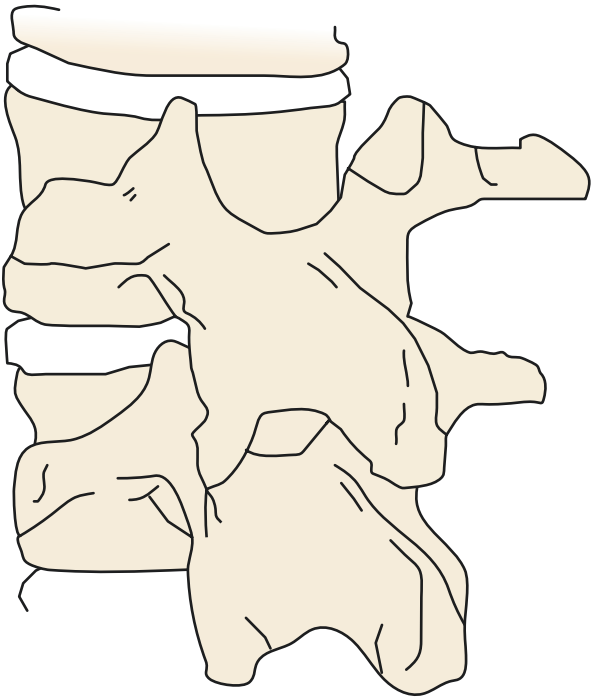


Fig. 20.5 Oblique lumbar spine anatomy

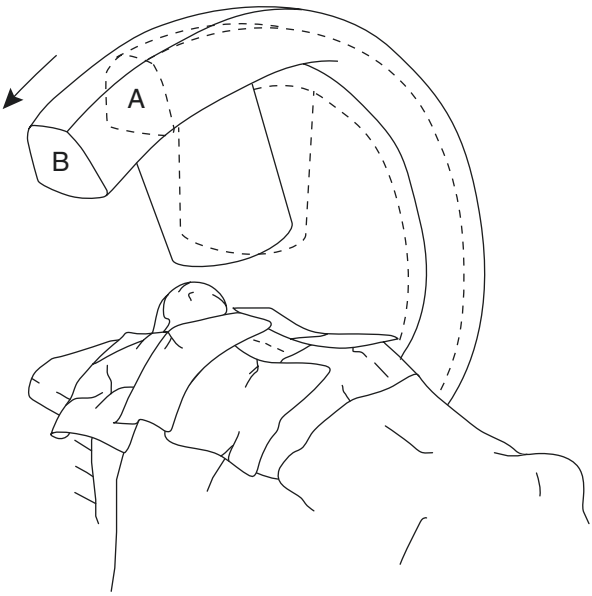


Fig. 20.6 Oblique C-arm rotation

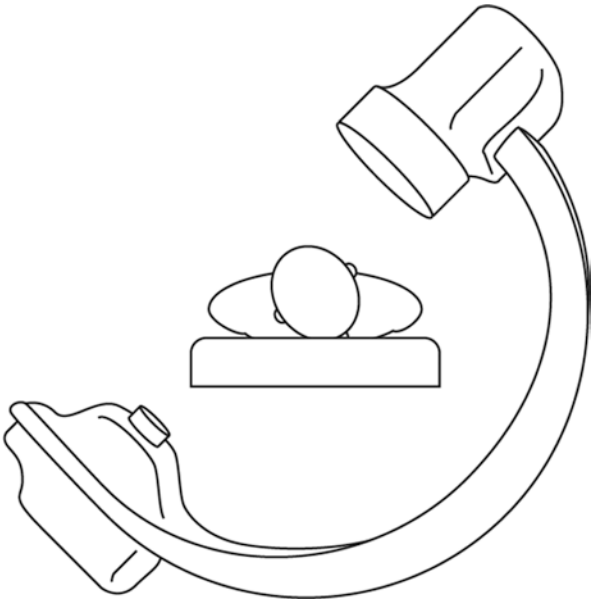


Fig. 20.7 Oblique C-arm position

Lumbar Transforaminal Blunt Coudé® Needle Placement

Oblique rotation of C-arm unit from the anterior-posterior view will move the spinous process to the opposite side in order to visualize the "Scottie dog" image. Figure 20.8 shows the C-arm rotation to the cephalad-caudad position (Fig. 20.8). Figure 20.9 shows the cephalad/caudad tilt lumbar spine anatomy. To optimize the view for transforaminal injection, the cephalad/caudad tilt of the C-arm is adjusted such that the superior articular process (SAP) or the ear of the "Scottie dog" appears to move in the opposite direction until the superior pars (Scottie dog's ear) is superimposed over the disk space (Figs. 20.10 and 20.11). For lumbar transforaminal technique, the target is the tip of the superior articular process (SAP) (also known as the ear of the Scottie dog). With an oblique fluoroscopic image, the ear of the "Scottie dog" should be superimposed over the disk. The SAP is a safe bony target that is posterior to the nerve root. without using an introducer needle, it is very difficult to place a blunt needle close to the target. The introducer is placed toward the superior articular process (Fig. 20.12a, b). The metal needle of the introducer cannula is removed, so that the blunt Coudé® needle can be advanced. The arrow marker on the hub of the needle corresponds with the direction of the tip of the curved blunt needle. The arrow marker is oriented medially, and the needle is advanced until it contacts the tip of the SAP (Scottie dog's ear) (Fig. 20.13a, b). Once bony contact is made with the ear of the "Scottie dog" (superior articular process (SAP)), the needle should be rotated 180° laterally (Figs. 20.14a, b). Once this has been done, advance the blunt

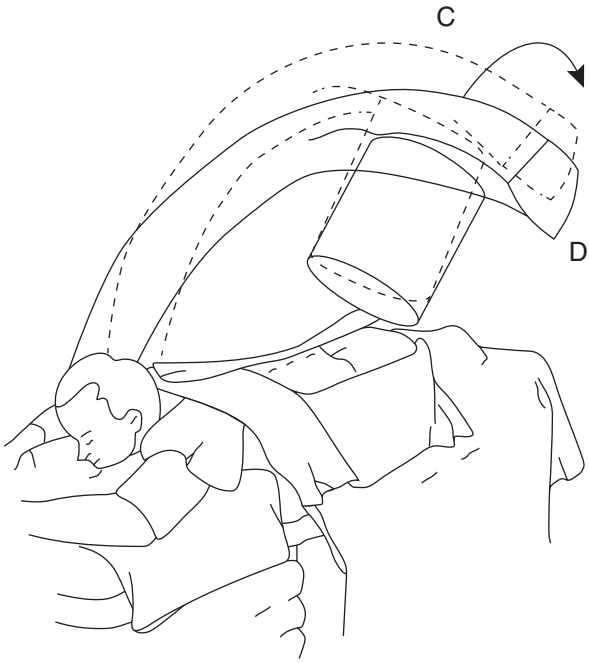


Fig. 20.8 Cephalad/caudad tilt of the C-arm

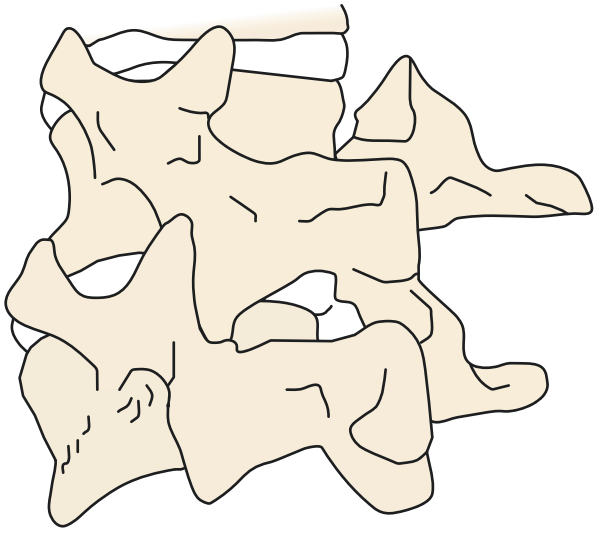


Fig. 20.9 Cephalad/caudad tilt lumbar spine anatomy

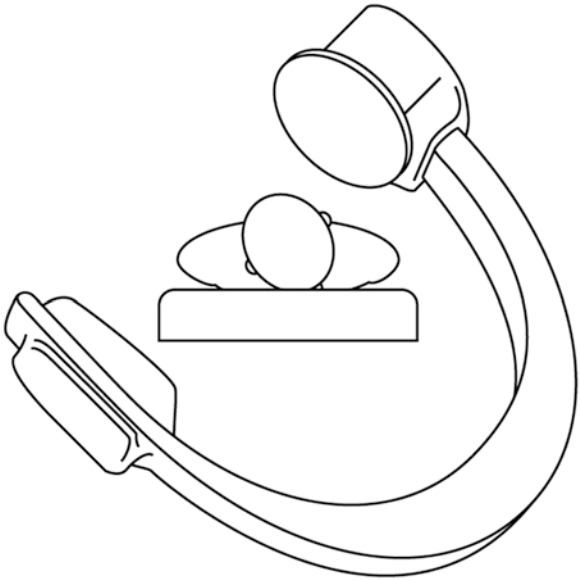


Fig. 20.10 Cephalad/caudad C-arm angle in oblique position

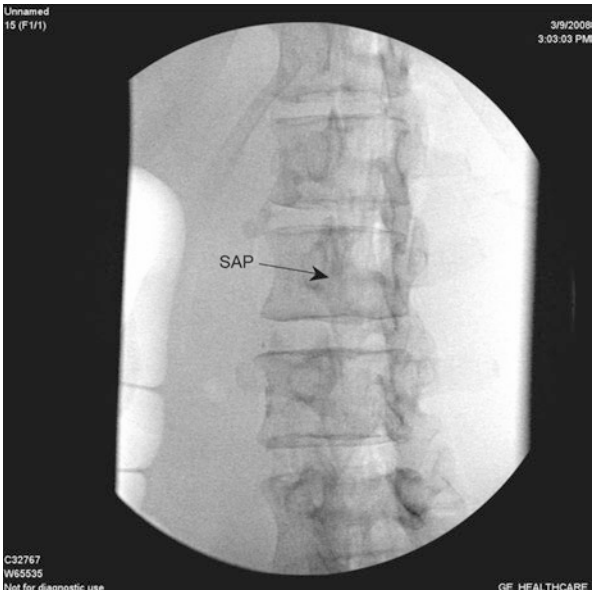


Fig. 20.11 Cephalad/caudad C-arm angle in oblique position. The arrow points to the superior articular process (SAP)

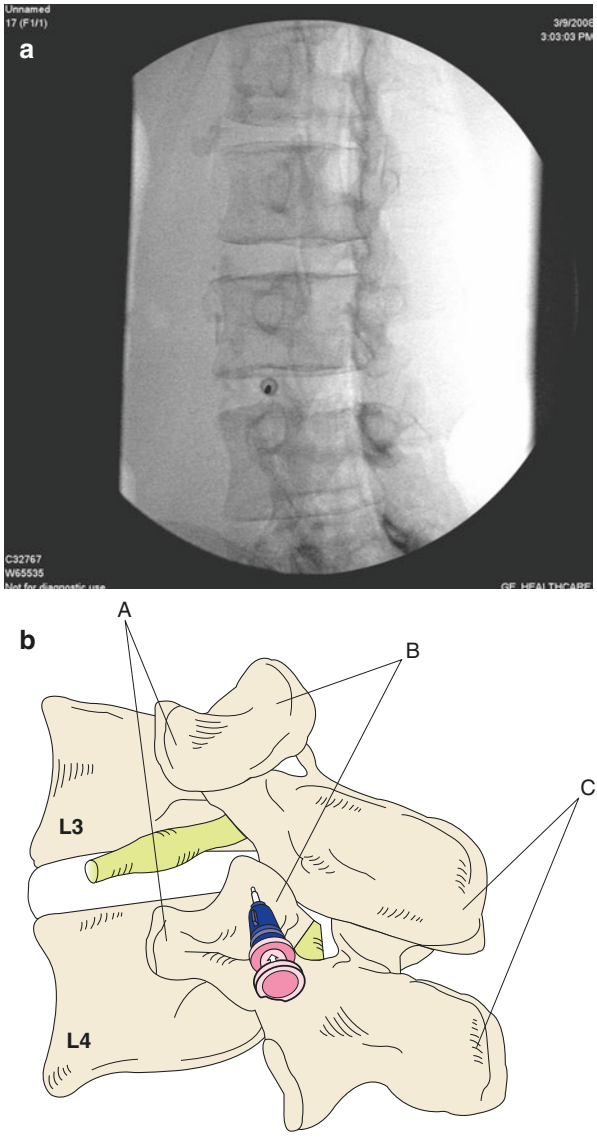


Fig. 20.12 (**a**) The ear of the Scottie dog is superimposed over the disk space. The tip of the superior articular process is the bony target for the introducer needle (**b**) A. Transverse process, B. superior articular process, C. spinous process

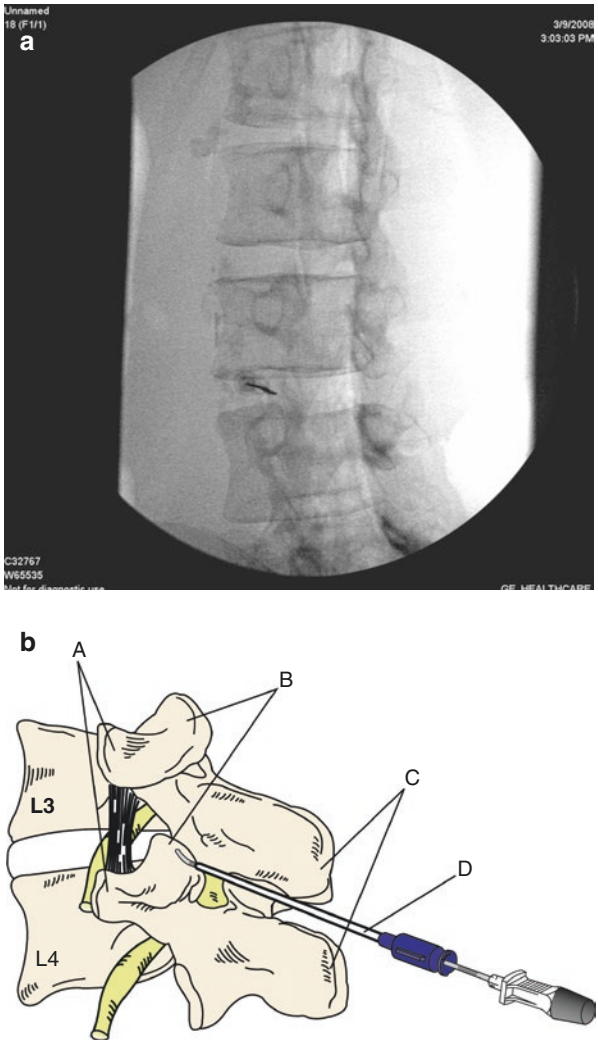


Fig. 20.13 (**a**) The metal needle of the introducer cannula is removed, and the blunt Coudé needle is placed with the arrow marker on the hub facing medially until the blunt Coudé needle contacts the tip of the Scottie dog's ear, the superior articular process. (**b**) Blunt Coudé needle in medial direction. A. Transverse process, B. superior articular process, C. spinous process, D. Introducer

needle just past the SAP (Fig. 20.15a, b). Once anterior to the ear of the "Scottie dog" (SAP), the needle hub should be rotated 180° medially. The C-arm is rotated to give a lateral view (Fig. 20.16). The needle is advanced through the intertransverse ligament until it pops through (Fig. 20.17a, b). The needle tip will enter the neural foramen with enhanced safety, as the blunt needle is less likely to penetrate nerves or arteries (Fig. 20.18). The needle tip can be rotated to reposition, without withdrawing and readvancing, as is done with a straight needle. Needle position is confirmed with A/P and lateral fluoroscopic visualization. Contrast is injected in the AP view using digital subtraction and/or continuous fluoroscopy to rule out arterial injection. Contrast spread along the nerve root or inferior to the pedicle helps to confirm adequate placement for a successful block. This is followed by injection of a test

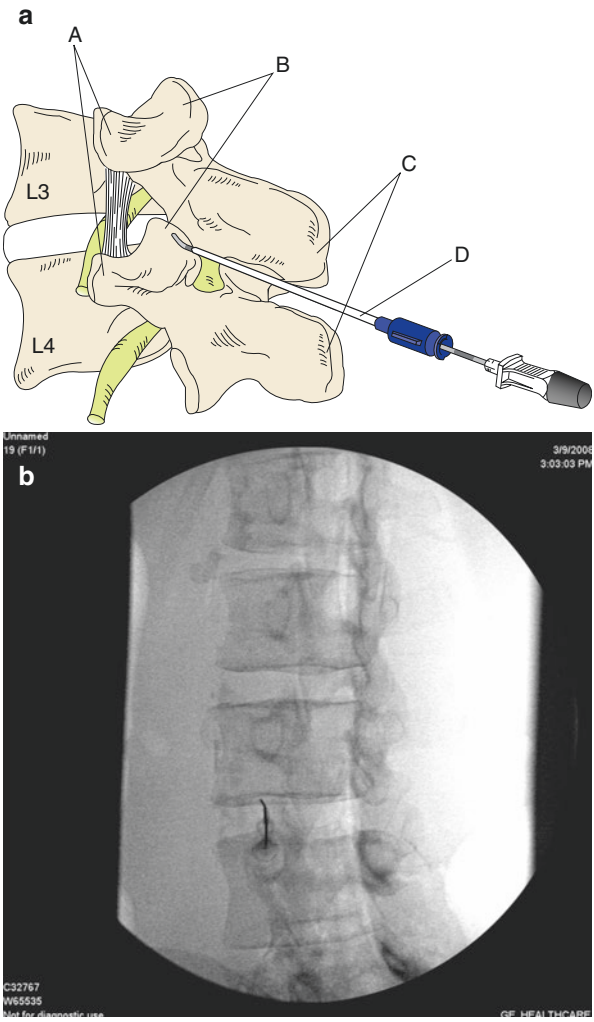


Fig. 20.14 (**a**) Blunt Coudé needle after rotation 180° with arrow marking on the hub facing laterally. A. Transverse process, B. superior articular process, C. spinous process, D. Introducer. (**b**) Fluoroscopy image with blunt Coudé needle after rotation 180° with arrow marking on hub facing laterally

dose of local anesthetic (1% preservative-free lidocaine, 1 ml.). After observation, non-particulate steroid (10 mg dexamethasone) may be injected. The needle tip may be placed to the ventral lateral bony structure of the neural foramen. Needle position will still be confirmed with A/P and lateral fluoroscopic visualization. Contrast is injected to verify the spread followed by injection of local anesthetic and steroids. Contrast injection in the lateral imaging view is recommended for visualization if there is venous runoff, and if there is, redirect the needle and verify that there is no vascular (venous) spread. Venous injection may be visualized on lateral view, and accumulation of contrast can be seen in the vena cava as a thin line parallel to the vertebrae. Most of the larger veins are located at the inferior neural foramen (disk) area.

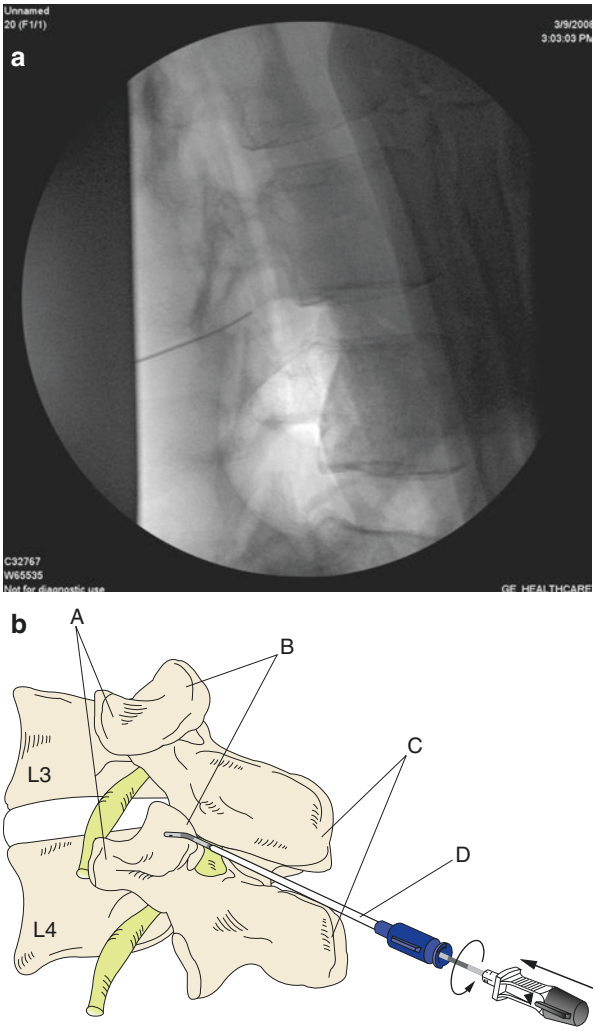


Fig. 20.15 (**a**) The blunt Coudé needle is advanced just passed the superior articular process and then rotated medially. (**b**) The blunt Coudé needle is advanced just passed the superior articular process and then rotated medially

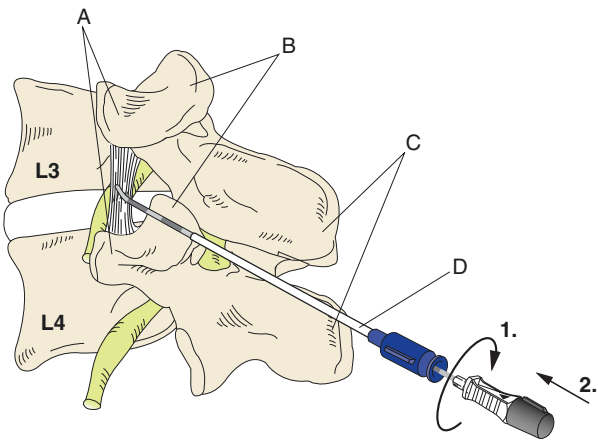


Fig. 20.16 The C-arm is rotated to a lateral position

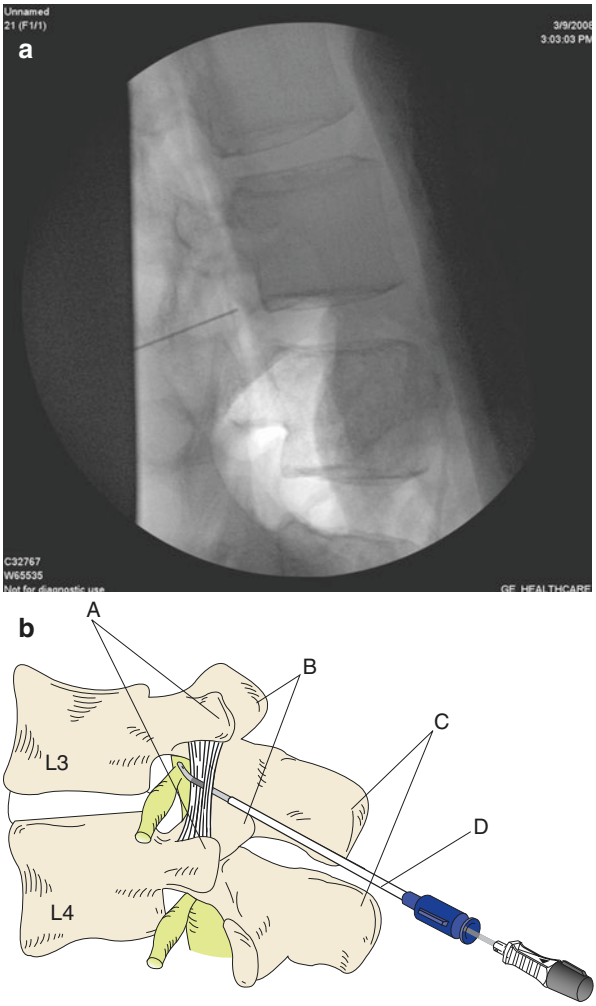


Fig. 20.17 (**a**) The blunt Coudé needle is advanced through the intertransverse ligament until a "pop" is perceived (**b**) The Blunt Coudé needle is advanced through the intertransverse ligament. A. Transverse process, B. superior articular process, C. spinous process, D. Introducer

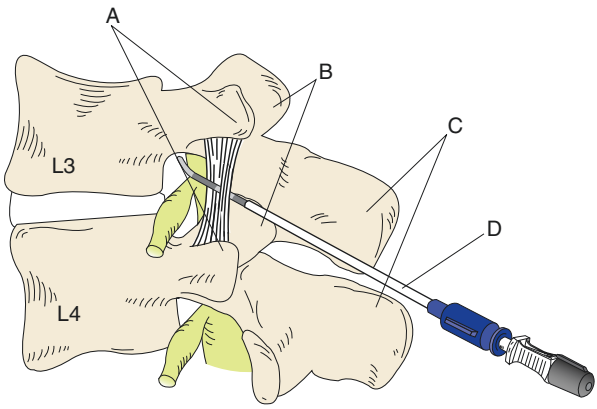


Fig. 20.18 The blunt Coudé needle is advanced to the foramen. A. Transverse process, B. superior articular process, C. spinous process, D. Introducer

Cervical Blunt Coudé® Needle Nerve Sleeve Injection

Cervical transforaminal injections using a sharp needle have been the most common causes of intraneural and intra-arterial injection-induced cord injuries. Consequently, many practitioners have converted to catheter-based techniques for single shot cervical injections. When performing a cervical blunt needle nerve sleeve injection, the 3D technique (direction, depth, and direction) is utilized. The tip of the needle is navigated, at the most, half way across the width of the facet joint into the neural foramen so that injected fluid can escape the neural foramen along the track of the needle rather than loculate in the epidural space. It is also imperative to look for the perivenous counter spread (PVCS) where injected fluid spreads to the opposite side and loculates. If there is loculation, the patient will experience pain followed by numbness and weakness. This can lead to paralysis. If loculation occurs, pressure buildup can cause spinal cord ischemia. Lateral runoff through the neural foramina is necessary to both prevent and treat this. If loculation occurs unilaterally, hemiplegia can occur. If loculation occurs bilaterally, quadriplegia can occur. Central loculation may result in syrinx formation. The chin to shoulder, left to right flexion rotation maneuver needs to be performed to open the neural foramina and dissipate the pressure in the cervical epidural space. See the discussion about this topic included in the section about cervical lysis of adhesions [22, 31].

The third cervical nerve root lies more posterior relative to the lower cervical nerve roots. Care needs to be taken to avoid using parallax views on fluoroscopy images to guide needle placement. The neural foramen on the wrong side may be mistaken for the targeted foramen and result in needle placement that is too anterior. The left and right C3 neural foramina must be superimposed on the lateral image to avoid complications including injuring the 3rd cervical root.

In the mid-cervical spine, while variations are common, the vertebral artery usually passes anterior-medial to the neural foramina (Fig. 20.19). For the procedure, place the patient in supine position and palpate the posterior lateral border of the cervical spine. Using a marking pen, place a mark on the posterior border of the lateral masses (Fig. 20.20). Under fluoroscopy, find the target neural foramen using a 30° oblique fluoroscopic view (Fig. 20.21).

Place a Kelly hemostat or metal pointer over the target site (neural foramen) (Fig. 20.22a, b). Mark the level on the previously placed line, outlining the posterior border of the lateral mass, which will be the entry site for the introducer cannula.

After infiltration of local anesthetic at the needle entry site, place the C-arm in the lateral position (Fig. 20.23). Advance the introducer cannula to the target site at the posterior border of the lateral mass and stop when bony contact is encountered (Fig. 20.24). Rotate the C-arm to the anterior-posterior positon (Fig. 20.25). Verify the lateral spine position of the introducer needle tip on the anterior/posterior view of the C-arm (Fig. 20.26a, b). Rotate the C-arm to the anterior-posterior position (Fig. 20.27). At this point, the inner metal needle portion of the introducer cannula should be withdrawn for introduction of the blunt Coudé® needle. Maintain the lateral C-arm position and introduce the blunt Coudé® needle through the flexible cannula making sure the arrow of the curved needle tip is facing posteriorly. Advance

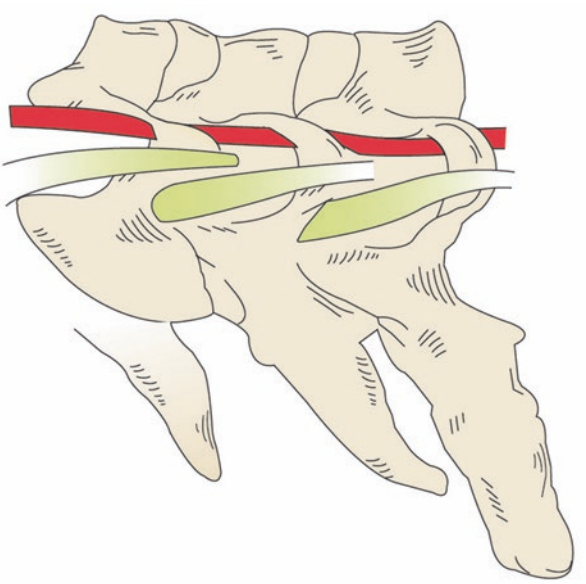


Fig. 20.19 Cervical anatomy showing the vertebral artery passing anterior-medial to the neural foramina in the mid-cervical area

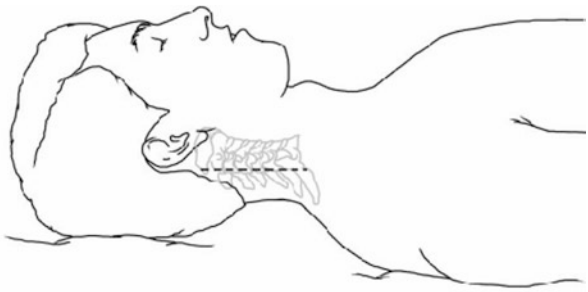


Fig. 20.20 Palpate and mark the lateral masses

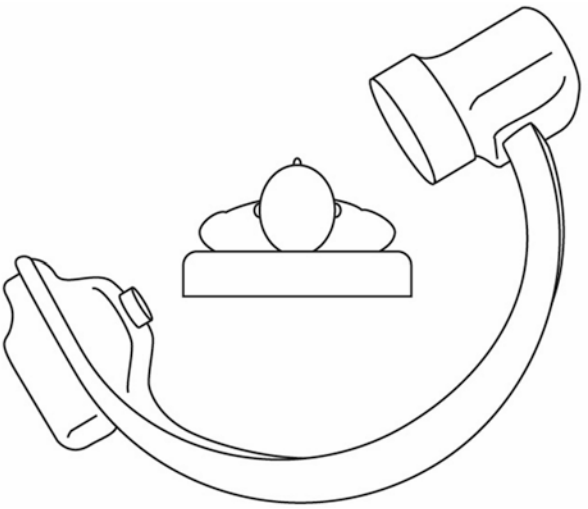


Fig. 20.21 The oblique view is initially used for cervical transforaminal injections

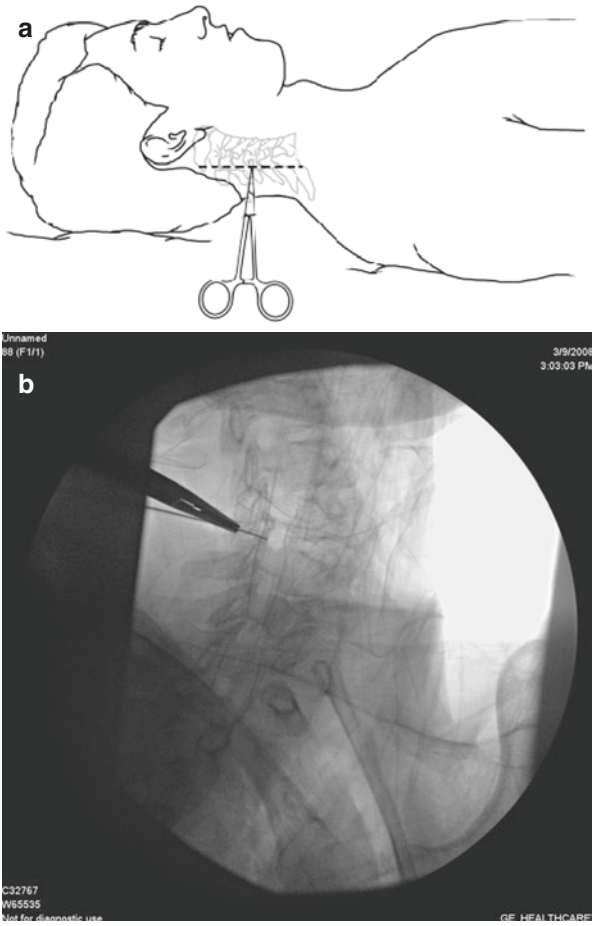


Fig 20.22 (**a**) Identify the target neural foramen using a radiopaque object. (**b**) Identify the target neural foramen using a radiopaque object

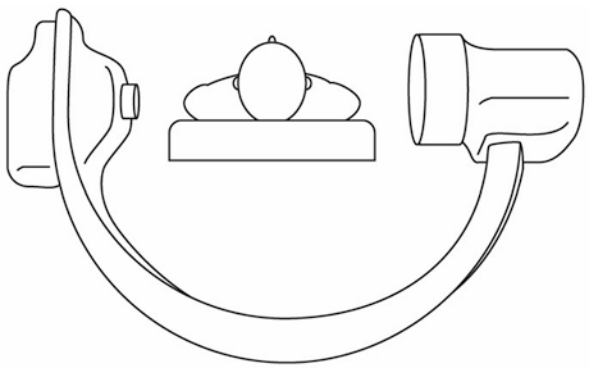


Fig. 20.23 The C-arm is rotated to the lateral position

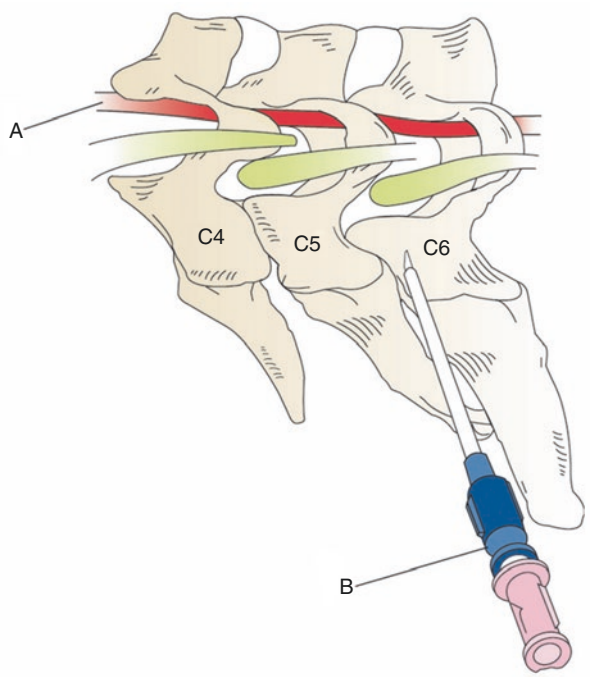


Fig. 20.24 The introducer is placed using the lateral view to make bony contact

the blunt needle until you experience bony contact on the lateral border of the lateral mass (Fig. 20.28). Rotate the C-arm to the 30° oblique view from horizontal (Fig. 20.29). Rotate the blunt Coudé® needle 180° to the anterior position, having the marker arrow readily visible (Fig. 20.30).

Slightly advance the Blunt Coudé® needle until it is fluoroscopically visible in the neural foramen.Rotate the Blunt Coudé® needle back 180° to a posterior direction and advance allowing for the needle to slide on bone if the ventrolateral epidural space is the target (Fig. 20.31a, b). The C-arm is then rotated to the A/P position (Fig. 20.32). The needle is advanced no more than half way into the facet joint line within the neural foramen if a transforaminal block is performed (Fig. 20.33). If a selective nerve root block is adequate, the needle need not be inserted into the foramen. Contrast is then injected using digital subtraction and/or continuous fluoroscopy to verify the absence of intravascular injection. In many cases, contrast injection outside the foramen shows adequate distribution for a selective nerve root block. Once this has been verified, a test dose of local anesthetic (preservative-free lidocaine 1%, 1 ml) is injected. After an observation period to rule out anterior spinal artery syndrome, vertebral artery injection, and other possible adverse effects of local anesthetic, non-particulate corticosteroid may be injected (dexamethasone 10 mg). If arterial injection or other problems are suspected, steroid is not injected.

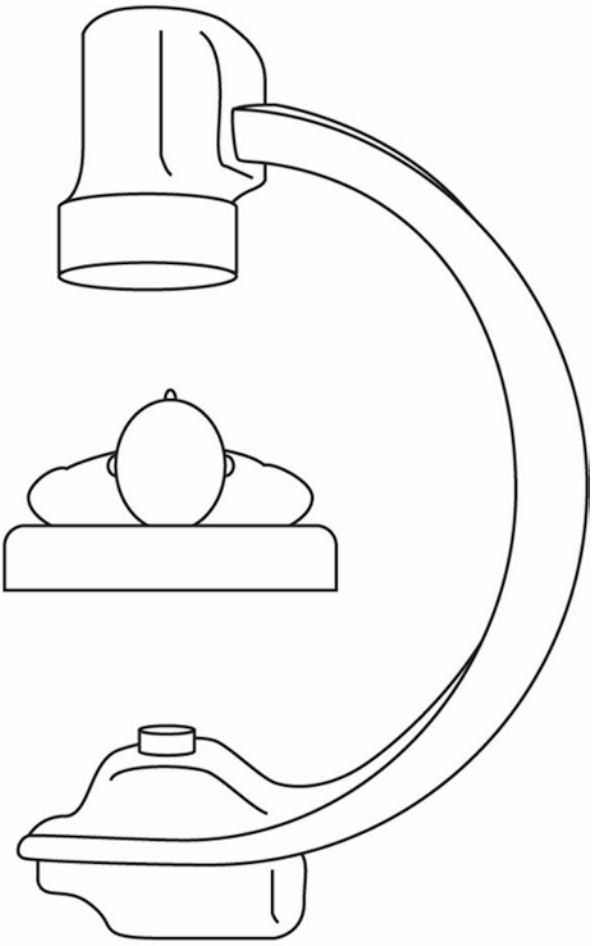


Fig. 20.25 After placing the introducer using the lateral view and making bony contact, rotate the C-arm to the anterior-posterior view to verify position

Lysis of Epidural Adhesions

Epidural lysis of adhesions employs site-specific catheter placement to the desired ventral lateral epidural space and verifies that the space is opened up at the symptomatic level to achieve freeing up of the nerve root. If this is not achieved, placement of a transforaminal catheter to open up the symptomatic level is performed. Lysis of adhesions with the local steroid and hypertonic saline sequence is performed either as a 1-day procedure or as three separate injections. Lysis of epidural adhesions was developed as a 3-day technique with injections each day. The technique has been adapted to a shorter treatment using injections at least 6 hours apart over a day and a half. Once the lysis procedure has been completed, the patient begins neural flossing exercises. Because the pulling forces with exercises are relatively small, the physical lysis of adhesion by fluid dispersion in the tissue plane is

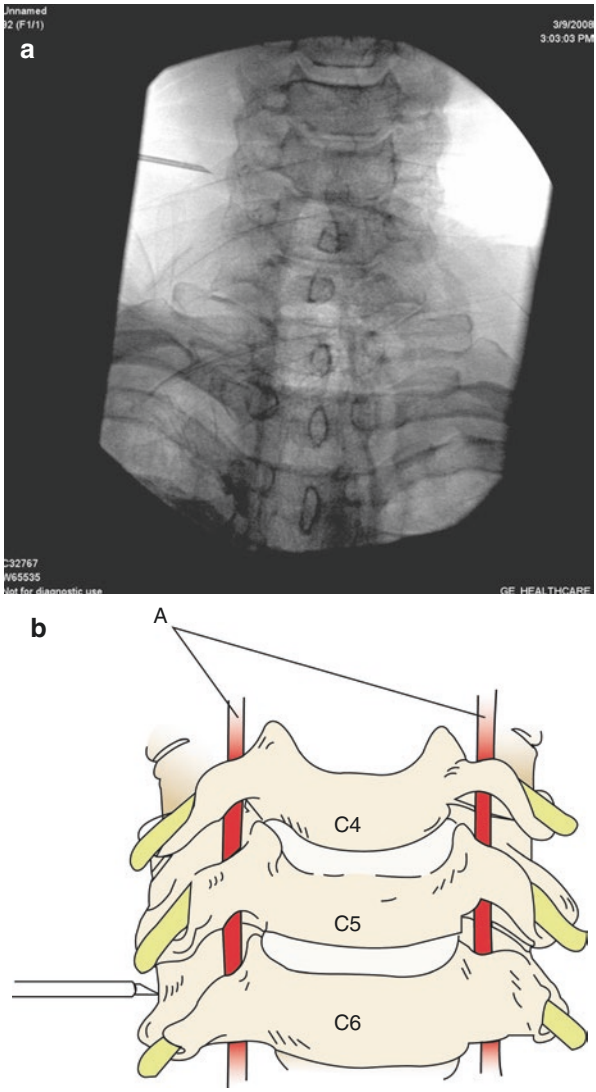


Fig. 20.26 (**a**) Anterior-posterior image. (**b**) Anterior-posterior diagram. The vertebral arteries are labeled A

a crucial aspect of this technique. Because the most significant innervation to the spinal canal component of the disk is the sinu-vertebral system, it responds very well to the use of hypertonic saline. Hypertonic saline has long-term analgesic effects when used in the epidural space for lysis of epidural adhesions. The recovery of action potentials in myelinated neurons has been demonstrated after application of hypertonic saline [5]. Birkenmaier studied hypertonic saline in a human fibroblast cell culture but did not study recovery of action potentials [6]. Heavner et al. performed a prospective, randomized blinded trial of lesion-specific epidural adhesiolysis on 59 patients with chronic intractable low back pain [7]. The combination

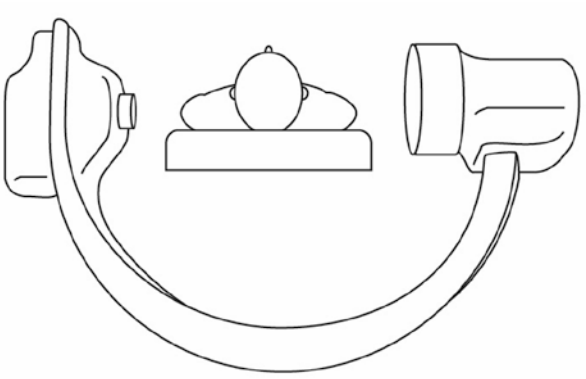


Fig. 20.27 The C-arm is rotated back to the lateral position

of hypertonic saline and hyaluronidase has provided the best results with epidural lysis of adhesions. Hyaluronidase enhances the spread of injected medications in the epidural space and has an inhibitory effect on neutrophil infiltration [8].

In the epidural space, these medications are safe and effective, but epidural placement must be confirmed with radiographic imaging and local anesthetic test doses to rule out subdural or other placement. However, facet-mediated pain is common in these patients, and a part of the treatment algorithm is the evaluation of the patient for pain originating from the facet joints at the 1-month follow-up visit following lysis of adhesions. Diagnostic medial branch blocks are performed at the affected segments. If the patient reports excellent pain reduction, the block can be repeated once or twice more a couple of weeks apart. If the pain recurs, then consider radiofrequency thermocoagulation of the lateral branch as well as the posterior primary ramus or medial branch on the transverse process.

Lysis of Epidural Adhesions via Caudal Approach

The sacral hiatus allows direct access to the sacral epidural space (Fig. 20.34). The RX™ Coudé® epidural needle has a specialized tip to allow for catheter repositioning without shearing the catheter. The RX™ Coudé® allows for multiple passes of the catheter to achieve the optimal tip placement. The RX™ Coudé® tip is designed to reduce the chance of catheter shearing. The opening of the needle tip is completely round allowing free passage of the catheter, unlike the oval tipped Tuohy needles or conventional spinal cord stimulator needles. The needle tip and catheter

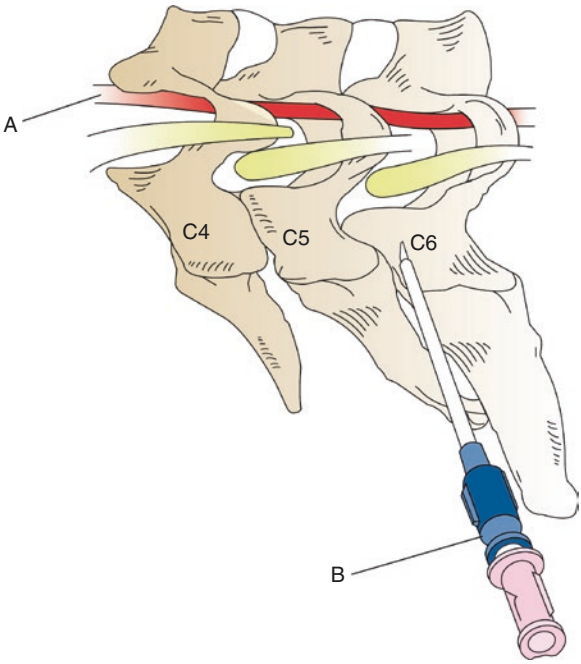


Fig. 20.28 The introducer needle is removed, and the blunt Coudé needle is placed with the arrow mark on the hub facing posteriorly, to make bony contact on the lateral mass

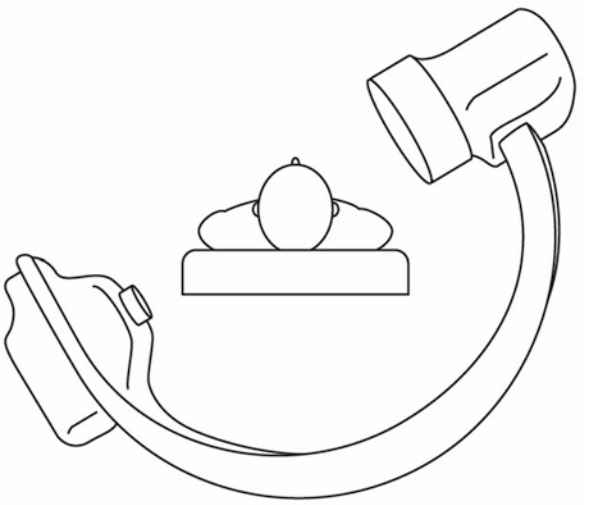


Fig. 20.29 The C-arm is rotated to the oblique view

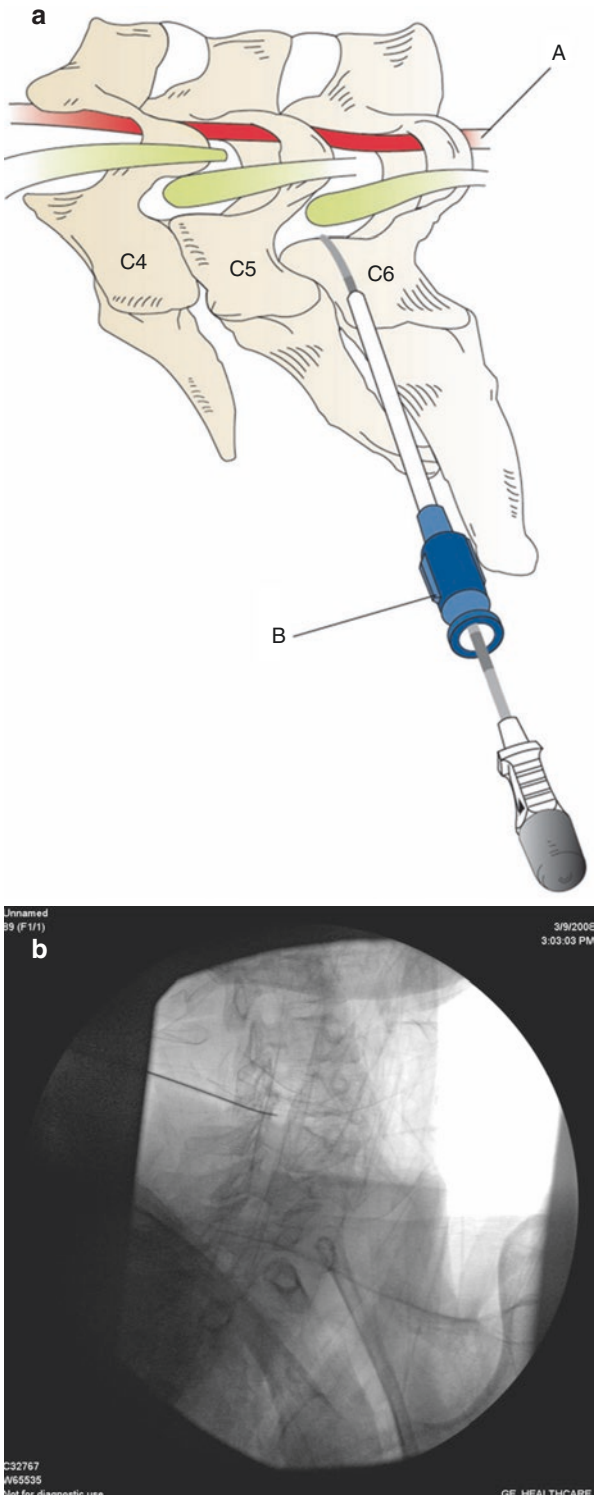


Fig. 20.30 (**a**) The blunt Coudé needle is rotated 180° and is advanced to the foramen for a selective nerve block. (**b**) The blunt Coudé needle is rotated 180° and is advanced to the foramen for a selective nerve block

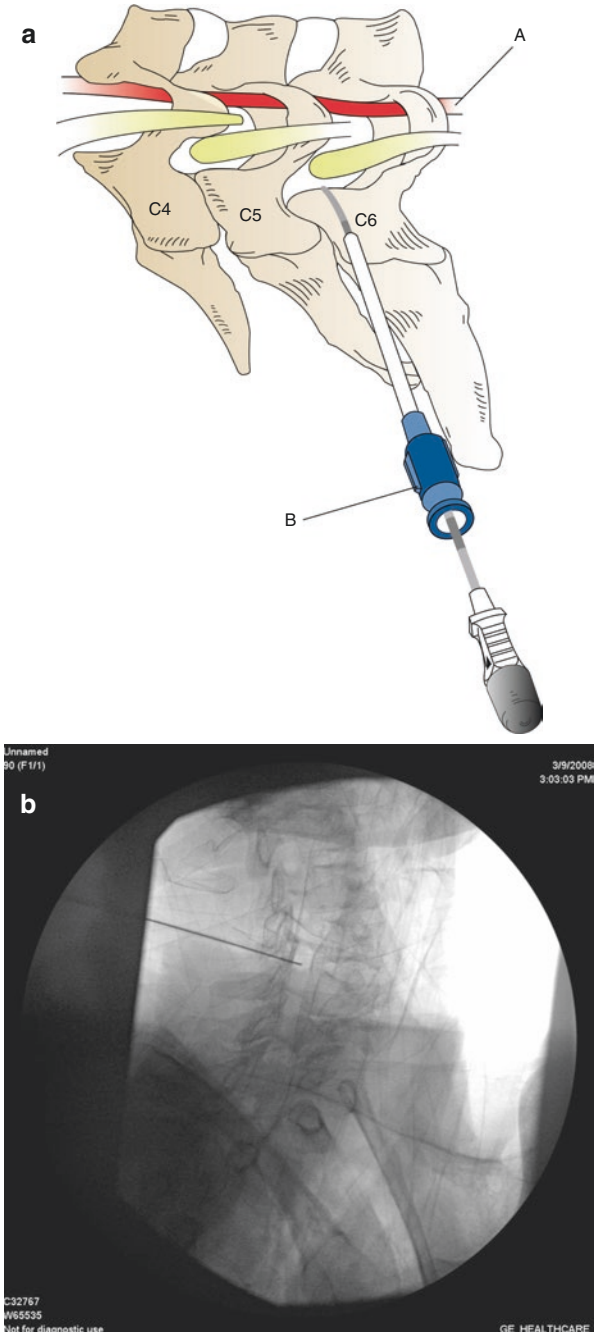


Fig. 20.31 (**a**) The blunt Coudé needle is rotated 180° to advance into the foramen if the target is the ventrolateral epidural space. (**b**) The blunt Coudé needle is rotated 180° to advance into the foramen if necessary

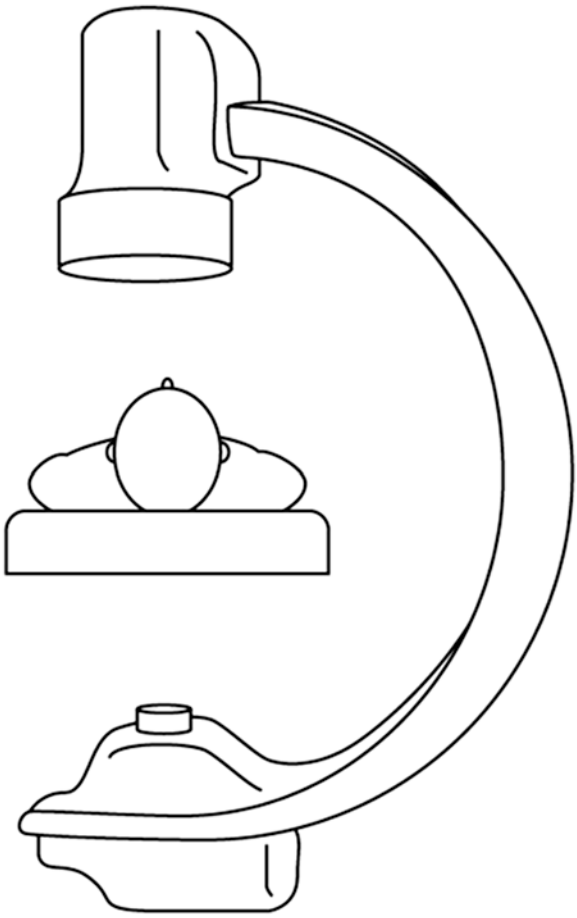


Fig. 20.32 The C-arm is rotated to the anterior-posterior position to advance the blunt Coudé needle into the foramen

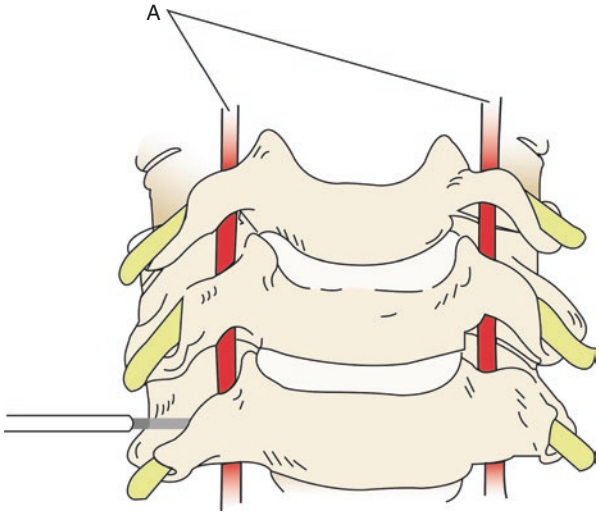


Fig. 20.33 The C-arm is rotated to the anterior-posterior position to advance the blunt Coudé needle into the foramen if adequate contrast distribution cannot be accomplished with more external placement

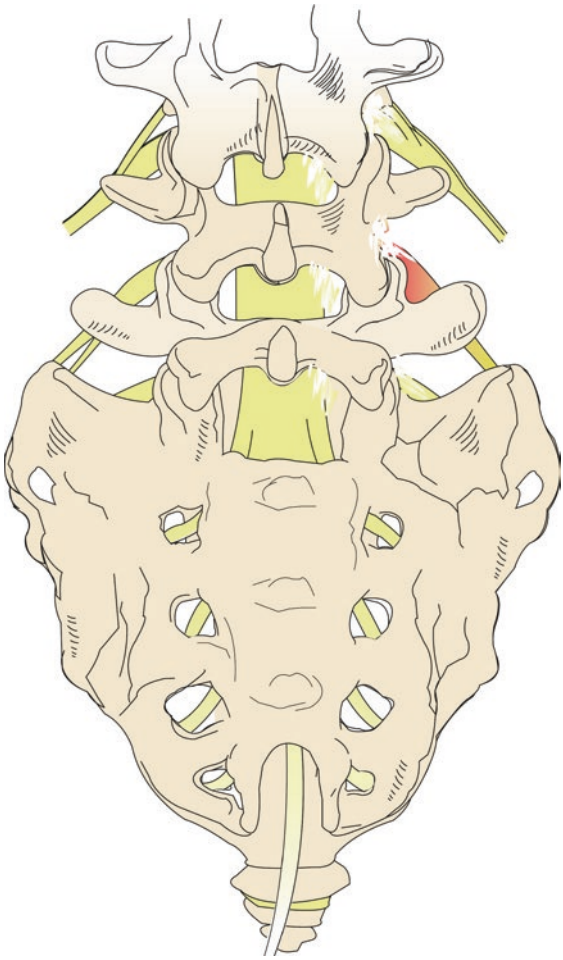


Fig. 20.34 Posterior lumbosacral anatomy with sacral hiatus

bend must be positioned in the same direction. The catheter used has a wire coil construction with a special coating to prevent kinking and vascular penetration. The Racz® catheters are radiopaque and can be steered in the epidural space to the level and side of pathology in the ventrolateral epidural space. Site-specific injections are far superior to blind non-specific delivery of medications. The ventral lateral epidural space is unique in that fluid injected under pressure follows the path of least resistance and will spread into the scarred perineural space and "free up" the nerve roots. When the target cannot be reached, it is clearly visible on the lateral fluoroscopic views. Subsequent treatment using the transforaminal approach for catheter placement and lysis can further reduce back pain and/or radiculopathy from involvement of the structures that are the most richly innervated by the sinu-vertebral nerve system. For 1-day lysis procedures, the skin entry point for needle access may be close to the sacral hiatus in the midline for easier placement. For the 3-day technique and repeat injections or continuous infusion therapies, the skin entry is 2 inches inferior and 1 inch lateral to the gluteal cleft on the contralateral side to the

pain. This second approach places the skin entry away from the sacral hiatus in order to reduce the chance of infection and allows easier catheter placement on the affected side.

Patient Inclusion Criteria

- Chronic low back pain of 3–6-month duration and failed conservative treatment options
- Back pain with or without radiculopathy
- Radiating lower extremity pain with provocative straight leg raising test
- Failed back surgery syndrome
- Radiographic evidence of pathology such as spondylosis
- Spinal stenosis
- Osteophyte and radiculopathy
- Lateral recess stenosis and radiculopathy
- Disk herniation and radiculopathy
- Spondylosis and radiculopathy (magnetic resonance imaging (MRI), computed tomography (CT))
- Radiculopathy due to epidural fibrosis (on enhanced MRI)
- Discogenic back pain and back spasm
- Failed neuromodulator (Spinal cord stimulator, spinal narcotics)
- 18 years of age or older (no specific contraindication by age)

Patient Exclusion Criteria

- Spinal instability
- Spinal cord syrinx
- Local infection, unresolved spinal infection
- Chronic infection
- History of gastrointestinal bleeding or ulcers
- Drug addiction and/or uncontrolled major depression or psychiatric disorders
- Arachnoiditis
- Arteriovenous malformation
- History of adverse reaction to local anesthetic, steroids, contrast, or other
- injected medications
- Uncontrolled or acute medical illnesses including coagulopathy, renal insufficiency, chronic liver dysfunction, progressive neurological deficit, urinary and sphincter dysfunction, infection, increased intracranial pressure, spinal fluid leak, pseudotumor cerebri, intracranial tumors, unstable angina, and severe chronic obstructive pulmonary disease
- The use of anti-platelet medications or anticoagulants, e.g., aspirin, Plavix, NSAIDs, gingko, ginseng, vitamin E, garlic, Coumadin, fish oil, Mobic, etc.

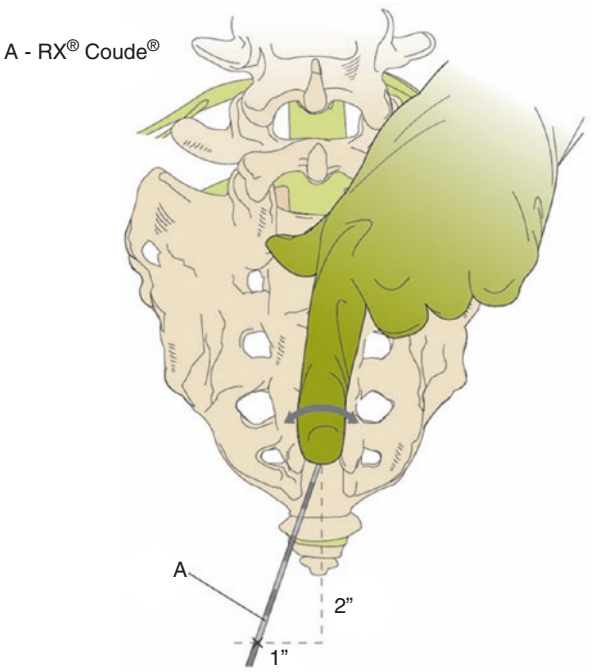


Fig. 20.35 The sacral hiatus is identified by palpation, and a skin puncture site is contemplated approximately 2 inches inferior and 1 inch lateral to the hiatus. Skin puncture site is labeled as an X, inferior to the sacral hiatus to allow entry of the RX Coudé needle. The puncture is made off the midline on the side contralateral to the pain in order to direct the catheter to the affected side

(laboratory measurements for bleeding and clotting to be in the normal range following discontinuation for appropriate duration)

- Pregnant or lactating women

Palpation with the index finger is used to locate the sacral horns (cornua) of the sacral hiatus to determine the entry point for the 15ga. or 16 ga. RX™ Coudé® needle (Fig. 20.35). The entry point is 2″ below the sacral hiatus and 1″ from midline (gluteal cleft). The anterior-posterior C-arm position may be used to confirm the location of the sacral hiatus (Fig. 20.36). The finger is rolled medially and laterally to confirm the location, and the finger is maintained at the sacral hiatus as a guide. A lateral fluoroscopic view should be obtained after skin penetration to avoid needle advancement too anteriorly into the bowel (Fig. 20.37).

After confirming epidural placement, rotate the needle 90° toward the target area (Fig. 20.38a, b). Anterior-posterior and lateral view and injection of contrast confirms good needle placement. Needle tip placement should be below the S3 neural foramen to avoid the thecal sac. Midline catheter placement in the sacrum can result in subdural placement by penetrating the inferior dural sac at the S3 level. This is avoided by catheter placement off the midline when using the caudal

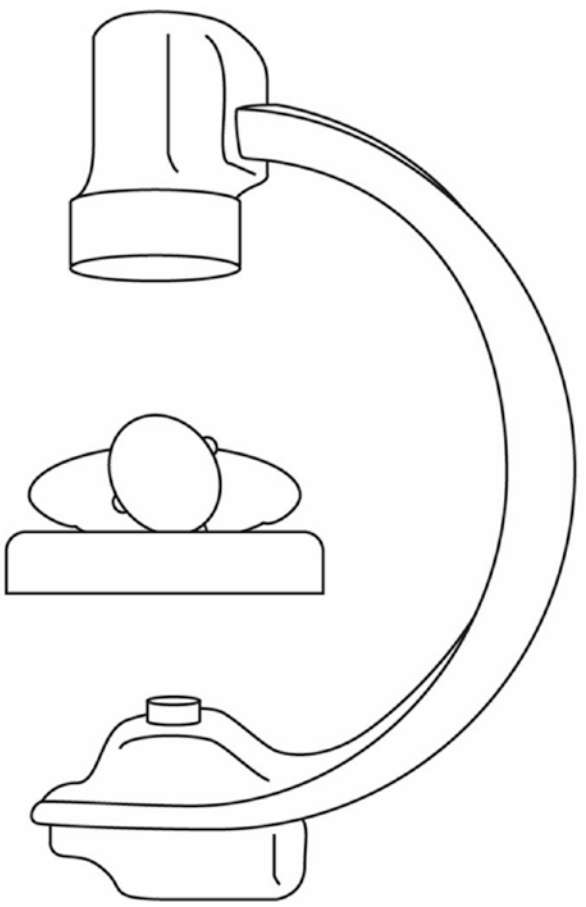


Fig. 20.36 The C-arm position is anterior-posterior to maintain needle position superficial to bony sacrum and coccyx

approach. It is important to make a bend at the Racz® bend marker on the catheter 1 inch (second marker on the catheter) proximal to the catheter tip at a 15–20° angle for optimum steering (Fig. 20.39). With the XL tip catheter, the stylet needs to be close to the tip for enhanced steering. If the bend is too short, the catheter tends to buckle. If the bend is too long, it is much harder to steer. The C-arm is rotated to the anterior-posterior position (Fig. 20.40). In order to direct the catheter to the ventral lateral epidural space, the catheter advancement should be slow, keeping the catheter near the midline and the point on the bend medial to the tip. This allows the catheter to be steered anteriorly in the epidural space (Fig. 20.41a, b). The tip of the RX Coudé needle should be oriented toward the target (Fig. 20.42). The technique is described in more detail elsewhere [9]. Cases with long-term outcomes are also reported [10].

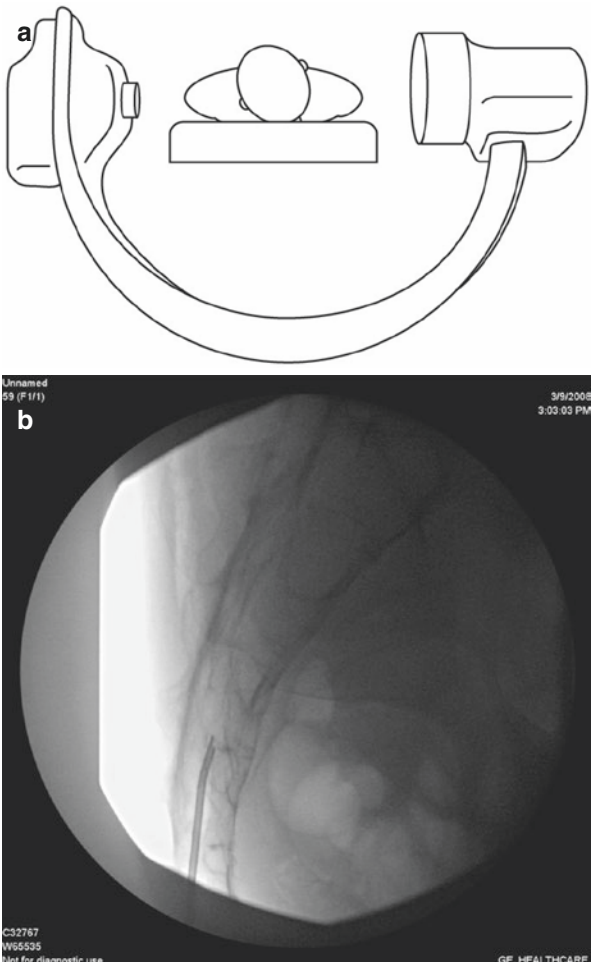


Fig. 20.37 (**a**) The C-arm is rotated to the lateral position to confirm placement. (**b**) The lateral image confirms placement

The technique for securing the catheter is shown (Fig. 20.43).

Advanced Catheter Fastening Technique Steps

1. Make a full twist in the catheter to form a loop.
2. Place loop over the neck of the connector.
3. Pull the catheter until it is secured around the connector body.
4. Use tape to secure the device.
5. Attach a bacterial 0.2-micron filter to maintain sterility.

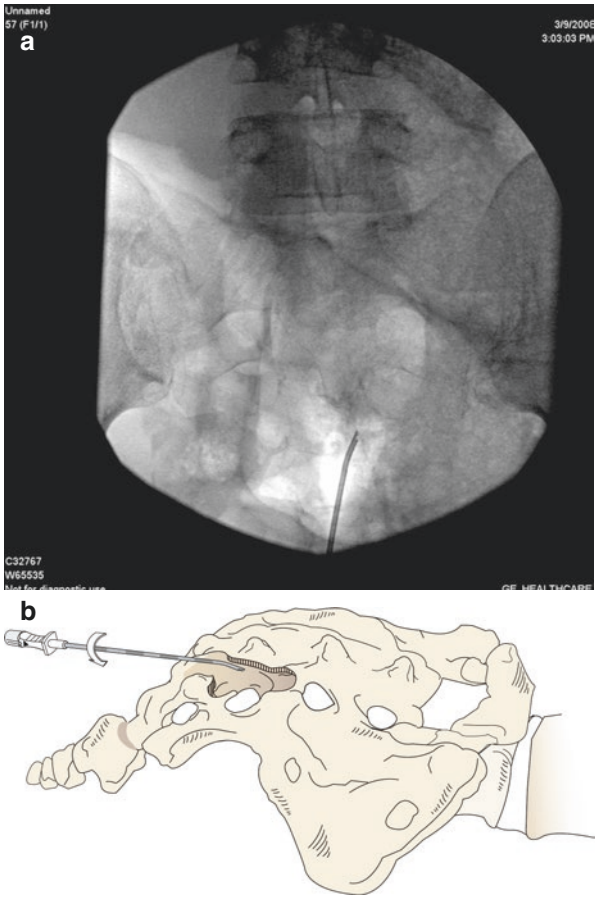


Fig. 20.38 (**a**) The RX Coudé needle is placed into the caudal canal and rotated toward the target. (**b**) Cutaway diagram of RX Coudé needle placement. The RX Coudé needle is rotated toward the painful side to facilitate catheter placement at the target area

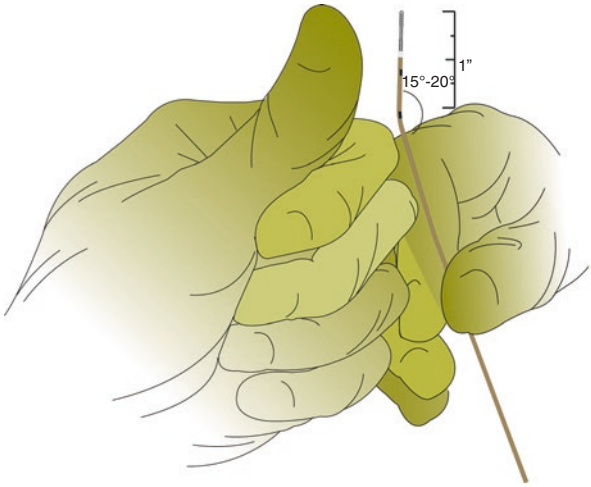


Fig. 20.39 A 15–20° bend is made at the insertion end of the catheter to facilitate steering

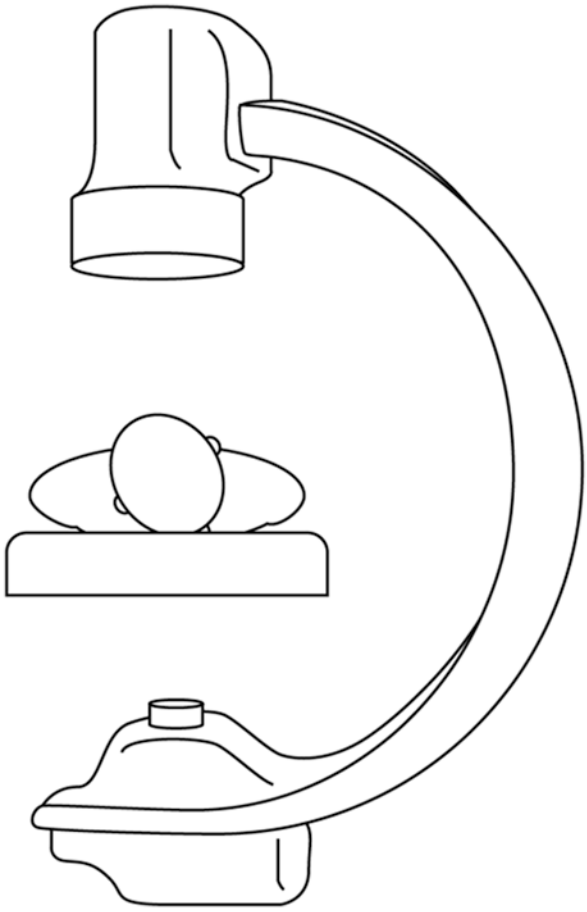


Fig. 20.40 The C-arm is rotated to anterior-posterior position

The connector is attached to the catheter for connection to a syringe (Fig. 20.44).

The C-arm is rotated to the lateral view (Fig. 20.45). Contrast injection is performed, showing contrast in the ventrolateral epidural space (Fig. 20.46).

Subsequent injections result in the lysis of epidural adhesions (Fig. 20.47).

Anterior-posterior image shows contrast in the epidural space and contrast that has flowed out of the epidural space through the neural foramen (Fig. 20.48).

Epimed's Stingray™ connector design allows for a fastening technique that changes pulling force direction to prevent disconnects. The Stingray™ connector when compared to four other connectors for grip and strength was found to be the best; however, for repeat injections or prolonged use, the following additional measures further enhance safety [11]. Using this technique, the force to separate the catheter is more than doubled. Bacterial filters are recommended in all instances when more than one injection is used or the catheter is left in place for prolonged period. When there is a disconnection of the catheter and the connector, the system should be removed from the patient. This is an essential precaution to prevent

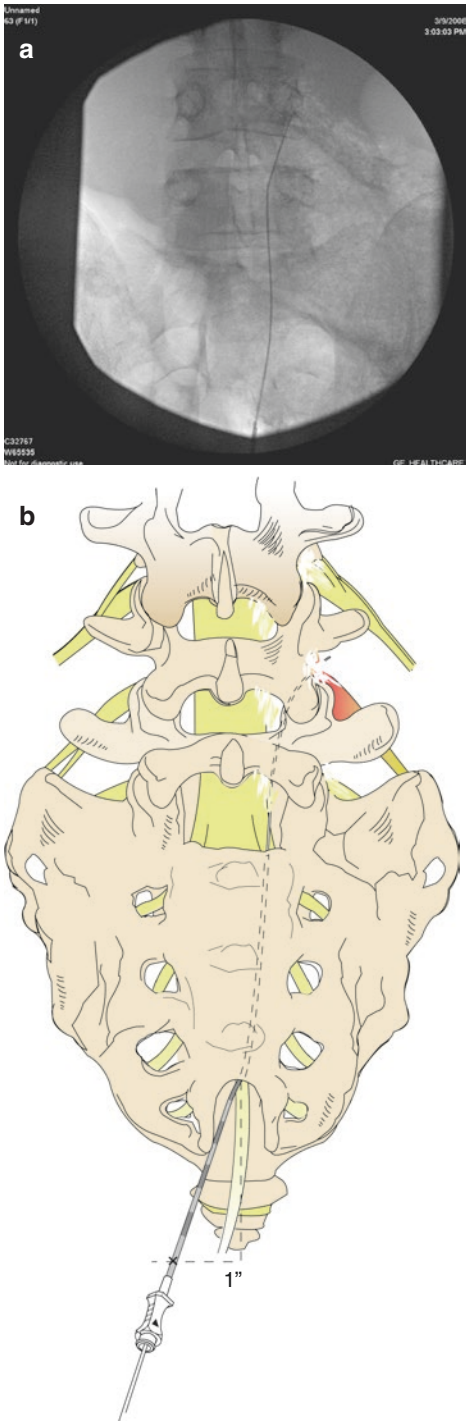


Fig. 20.41 (**a**) The catheter is passed to the target, L4 on the right, in this case. (**b**) The catheter is passed to the target, L4 on the right, in this case

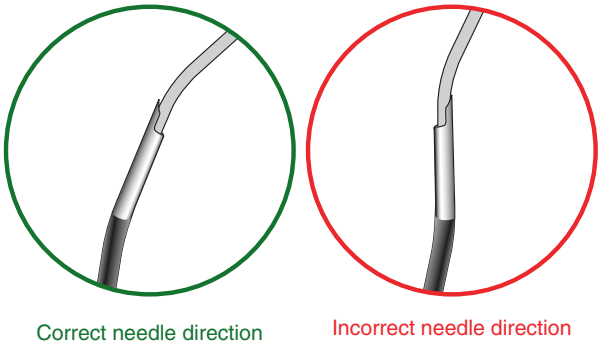


Fig. 20.42 The tip of the RX Coudé needle should be oriented toward the target to make placement easier. This also prevents shearing if the catheter needs to be withdrawn and redirected

Fig. 20.43 Advanced catheter fastening technique steps. (1) Make a full twist in the catheter to form a loop. (2) Place loop over the neck of the connector. (3) Pull the catheter until it is secured around the connector body. (4) Use tape to secure the device. (5) Attach a bacterial 0.2-micron filter to maintain sterility

infection. After the catheter tip is placed in the proper location (ventral/lateral), attach Stingray™ connector to inject the target site. Always use bacterial filter.

Physicians use this technique during a 3-day lysis series or post-procedure injection of hypertonic saline in the recovery room for the 1-day procedure. It is also useful when prolonged or postoperative infusion is utilized.

In order to simplify the procedure, several tips are offered:

1. Slow down.
2. Go near mid-sacral canal.
3. Make a 15–20° bend at the 1-inch Racz® bend marker and steer only when the catheter is being advanced.

Table 20.1 summarizes medications and doses for the procedures.

Discharge criteria include ambulation and voiding. If patients have difficulty, they should be observed until recovery is complete. Spine surgery patients may have

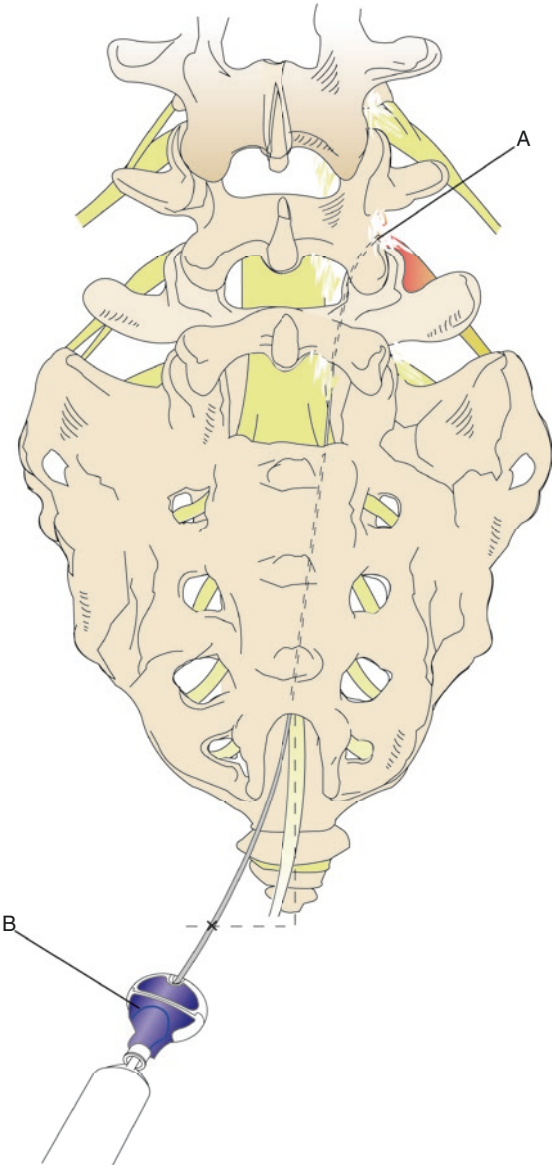


Fig. 20.44 The connector is attached to the catheter for a syringe

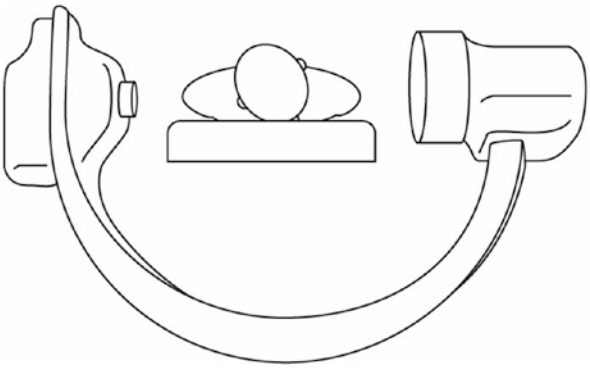


Fig. 20.45 The C-arm is rotated to the lateral view

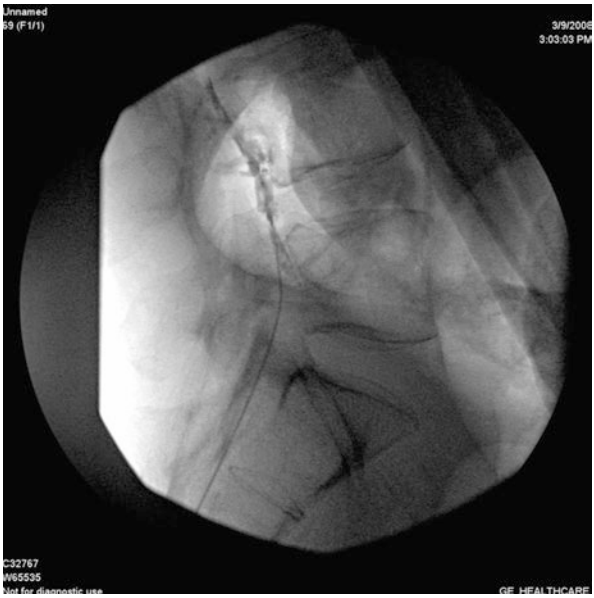


Fig. 20.46 Contrast injection shows placement in the ventrolateral epidural space

dural tears and need to be monitored for subdural blocks. Also, patients with dense scar may develop recurrent scarring within 3 months, and lysis can be repeated in 1 month to prevent this from occurring.

A variation of the series of three injections is the 4 day, single injection period, technique.

The medications used are outlined below.

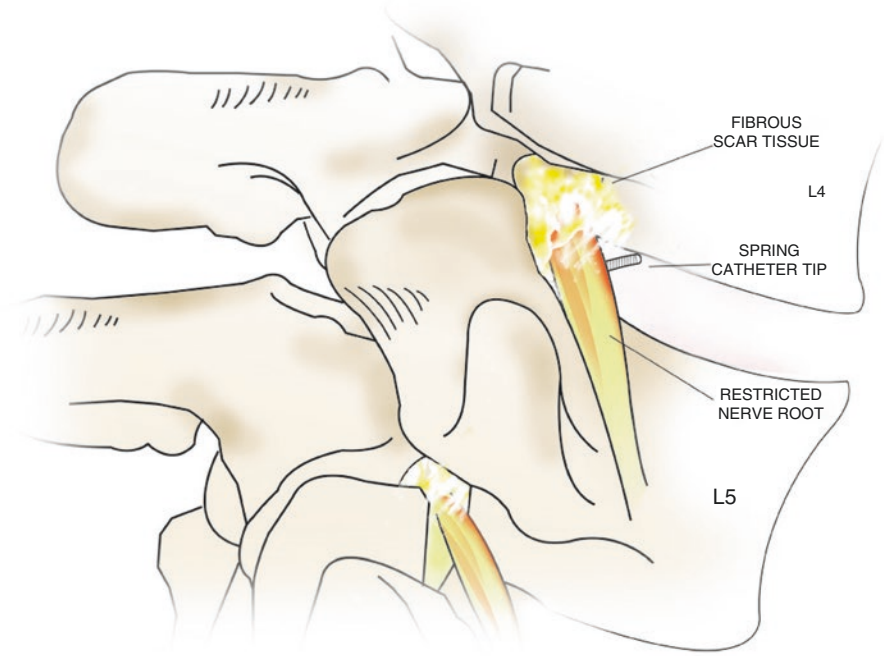


Fig. 20.47 Schematic of the lysis procedure. The catheter is placed in the ventrolateral epidural space, and fluid is injected to open scar around the nerve root

Day Lumbar Lysis

1. Diagnostic: 5–10 mL Omnipaque™ 240 – outline filling defect and place catheter to target site.
2. To show runoff and absence of loculation, contrast 4–5 mL Omnipaque™ 240∗ is injected through the catheter.
3. 2–3 mL Omnipaque™ 240∗ through catheter for verification of enzyme effectiveness.
4. Spreading factor: Hylenex® 150–300 units (human recombinant) diluted in 10 mL of preservative-free saline.
5. Steroid injection: 4 mg dexamethasone or 40 mg triamcinolone.

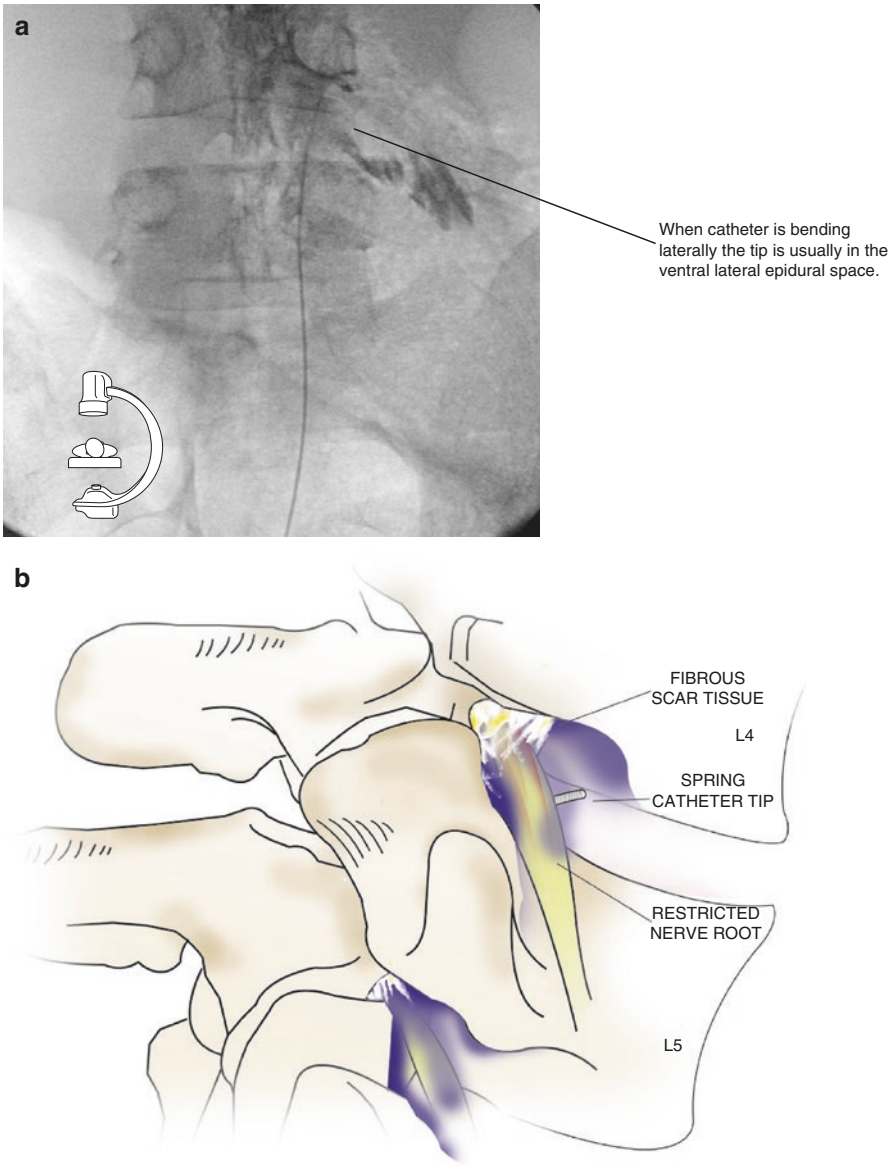


Fig. 20.48 Anterior-posterior image showing contrast in the epidural space and contrast that has flowed out of the epidural space through the neural foramen

Table 20.1 Pain-free hypertonic saline volumes and pharmacological adjustments

1st series injections	2nd series injections	3rd series injections
Caudal catheter 1. 10 mL caudal epidural Omnipaque 240 contrast 2. 10 mL PF normal saline w/ 150 units hyaluronidase 3. 0.25% bupivacaine with 40 mg triamcinolone under fluoroscopic A/P and lateral observation. Lateral view (essential to rule out intravenous or subdural injection or spread through a partial surgical tear). Observe the patient for 20–30 minutes for delayed onset of motor block that would indicate subdural placement – *Abandon procedure if motor block develops due to subdural spread* Subdural motor block usually develops in 14–15 minutes later. Shorter observations not recommended Start flexion-rotation exercises *NEW*-20–30 minutes later. Lidocaine 1% 1.5 mL injection, followed by 2–3 minutes later 10 mL of 10% sodium chloride in 0.6% lidocaine injected in 1 mL increments fairly rapidly, over 3–5 minutes. The small volume, pre-hypertonic lidocaine, seems to cover the periphery of the injection site, therefore no pain from the hypertonic. Remember to flush at the end with 1 mL PF saline Frequent check for motor function-postoperative observation requirements, maybe 2–4 hours *Transforaminal catheter* Volumes are reduced to 5 mL (local and hypertonic)	*Caudal catheter* Usually same day, 4 hours later 1. 10 mL of bupivacaine 0.125% No motor block →Wait 20–30 minutes If no motor block 2. 1.5 mL – 1% lidocaine → Wait 2–3 minutes 3. Inject 10 mL (6 mL 1% lidocaine, 4 mL of 23.4% NaCl) = 10% sodium chloride in 0.6% lidocaine, fairly rapidly, over 3–5 minutes Flush after observing the patient for 30 minutes *Transforaminal catheter* Volumes are reduced to 5 mL. (local and hypertonic). Pre-hypertonic lidocaine: 1% 1 mL If there is no motor block and the patient is able to ambulate, the patient can go home in 45–60 minutes. Cost saving	*Caudal catheter* Usually same day, 4 hours later 1. 10 mL of bupivacaine 0.125% No motor block →Wait 20–30 minutes If no motor block 2. 1.5 mL – 1% lidocaine → Wait 2–3 minutes 3. Inject 10 mL (6 mL 1% lidocaine, 4 mL of 23.4% NaCl) = 10% sodium chloride in 0.6% lidocaine, fairly rapidly, over 3–5 minutes Flush after observing the patient for 30 minutes *Transforaminal catheter* Volumes are reduced to 5 mL. (local and hypertonic). Pre-hypertonic lidocaine: 1% 1 mL If there is no motor block and the patient is able to ambulate, the patient can go home in 45–60 minutes. Cost saving

The drugs and doses for caudal and lumbar transforaminal lysis are summarized in the table
Lidocaine 1% has been used successfully in multiple centers to prevent pain from hypertonic saline flowing into newly opened areas after successful lysis of epidural adhesions. The protocol has been modified since no cases of catheter migration have been reported. This allows for lower concentrations of bupivacaine to be used because a subdural block does not need to be excluded prior to the 2nd and 3rd series of injections
Also, the second and third hypertonic series related observation times are 75% reduced from 4 hours to 1 hour to meet discharge criteria allowed by the local anesthetic reduction (i.e., able to walk and void). This has produced significant cost savings

6. Local anesthetic: 10 mL of 0.2% ropivacaine or 10 mL of 0.25% bupivacaine. Patients seem to respond to bupivacaine better than ropivacaine.
7. Depending on the physician's lysis technique, wait 20–30 minutes. Evaluate for motor block with a voluntary straight leg raise. If no motor block is present, with the patient's painful side down, inject 8–10 mL of 10% hypertonic saline over 20–30 minutes. If the patient experiences pain, inject 2–3 mL of local anesthetic.

After injections have been completed, the patient's motor function should be evaluated by testing hip flexion with the knee extended. If there is a motor block, stop the procedure. Be sure to attach bacterial filter to the Stingray™ connector to guarantee sterility of the catheter. Wait 20–30 minutes. Place the patient with their painful side in the gravity-dependent position. Flush catheter with 2–3 ml normal saline solution. Once the nerve root is freed, the "neural flossing" exercises are started. Patient education about the exercises is an important component. Very commonly, patients also have facet joint arthropathy that requires additional treatment.

Several tips are very useful. The catheter should be advanced with slow movements, and rotation should be performed while advancing the catheter, not by twirling the catheter in place.

In order to make the catheter easier to steer for cervical and thoracic procedures, a Racz® bend is made at the 1/2-inch mark from the tip. For caudal procedures, the bend is made at the 1-inch mark. When the catheter is in the ventrolateral epidural space, the catheter will bend laterally.

Most epidural scar formation occurs in the ventral and lateral recess. Fluid injection under pressure opens up the perineural space. The process is "compartmental filling" – where the injected fluid flows along the path of least resistance in the scar and then overflows into the adjoining "compartment."

After the initial injections have been completed, the introducer needle must be withdrawn from the patient to allow for repeat bolus injections. Before removing the introducer needle, it is important to stabilize the catheter's position (Fig. 20.49a–c).

The sequence of steps is:

A. Stabilize catheter to prevent catheter tip displacement.
B. Withdraw introducer needle while holding catheter in place.
C. Remove introducer needle.

Once the introducer needle has been carefully extracted from the patient's body, secure the catheter body at the exit site. At this point, the introducer needle should be withdrawn completely from the catheter. Bacterial filters are

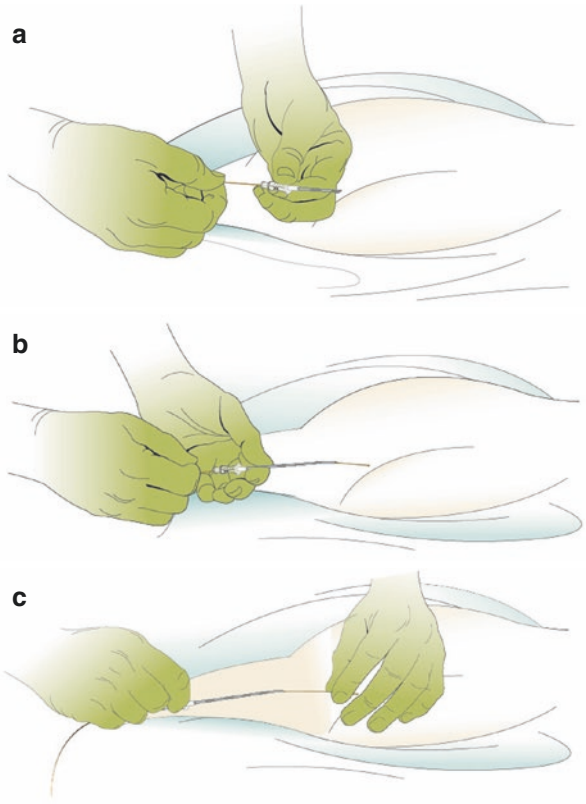


Fig. 20.49 (**a**) Needle removal without dislodging the catheter is critical. The sequence of steps is: Stabilize the catheter to prevent catheter tip displacement. (**b**) Withdraw introducer needle while holding the catheter in place. (**c**) Remove introducer needle

recommended in all instances when more than one-time injection is used or the catheter is left in place for prolonged period. When there is a disconnection of the catheter and the connector, the system should be removed from the patient. This is an essential precaution to prevent infection. The importance of securing an intact catheter cannot be overemphasized. The technique that has been developed is described next.

Catheter Tape Down Technique

- Place suture and tie loose loop (Fig. 20.50).
- Wrap around catheter two times and tie surgical knot (Fig. 20.51).
- Apply antibiotic ointment around skin entry and place two-split 2 × 2” gauze to keep antibiotic in place (Fig. 20.52).

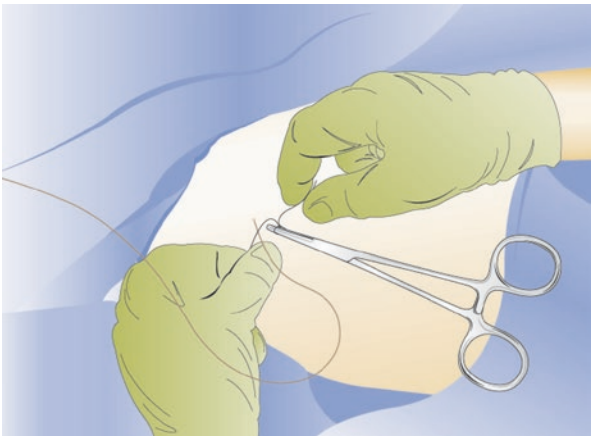


Fig. 20.50 Catheter tape down technique. Place suture and tie loose loop

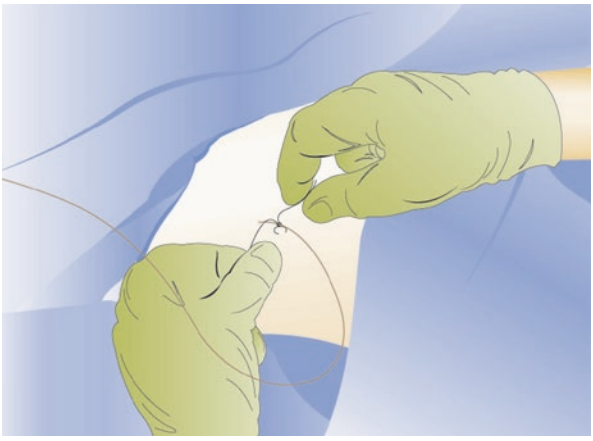


Fig. 20.51 Catheter tape down technique. Wrap around catheter two times and tie surgical knot

Fig. 20.52 Catheter tape down technique. Apply antibiotic ointment around skin entry and place two-split 2 × 2” gauze to keep antibiotic in place

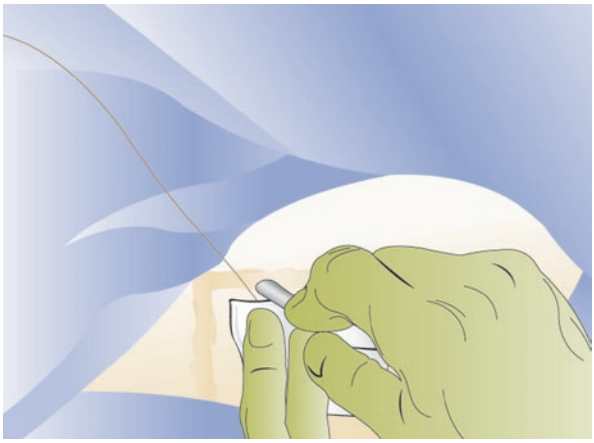


Fig. 20.53 Catheter tape down technique. Apply adhesive, i.e., tincture of benzoin, around the gauze

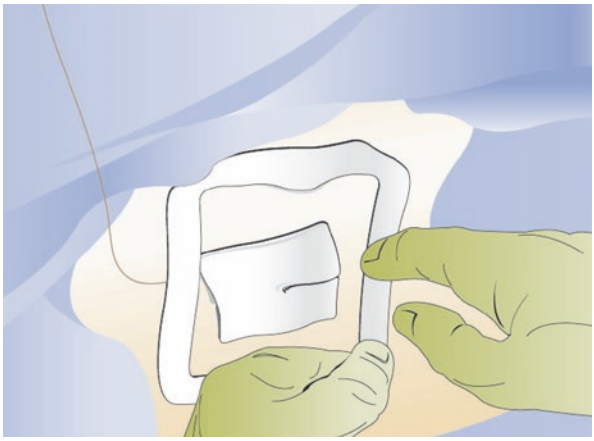


Fig. 20.54 Catheter tape down technique. Place one loop on catheter and transparent dressing, i.e., Opsite

- Apply adhesive, i.e., tincture of benzoin, around the gauze (Fig. 20.53).
- Place one loop on catheter and transparent dressing, i.e., Opsite (Fig. 20.54).
- Connect bacterial filter and four pieces of sweat-resistant Hypafix tape (Fig. 20.55).

After completion of the procedure, cut suture and gently remove the catheter. If resistance is detected, do not forcibly pull on the catheter to avoid catheter shearing. Reposition the patient and attempt to remove the catheter. Simultaneously pushing and twisting the catheter allows removal (Fig. 20.56). The use of wide-open RX™ Coudé® needles reduces the incidence of shearing.

After injections have been completed, the patient's motor function should be evaluated by testing hip flexion with the knee in extension. If there is a motor block, stop the procedure. Be sure to attach bacterial filter to the Stingray™ connector to reduce the infection risk. Observe for 20–30 minutes. Place the patient with their painful side in the gravity-dependent position.

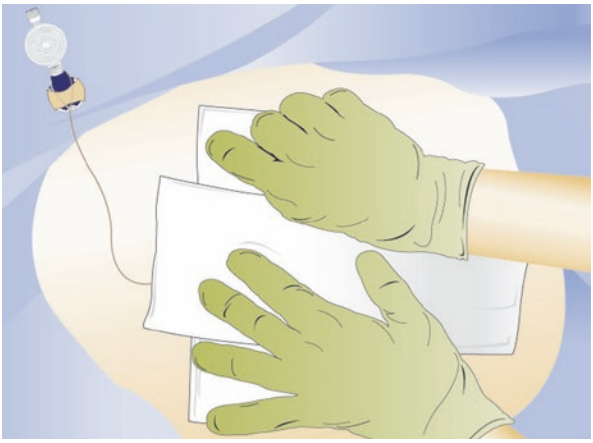


Fig. 20.55 Catheter tape down technique. Connect bacterial filter and four pieces of sweat-resistant Hypafix tape

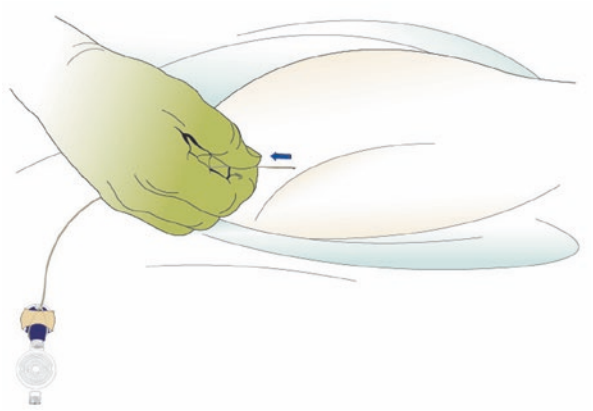


Fig. 20.56 Catheter removal with tip intact

Lumbar Transforaminal Catheter Placement

The RX™ Coudé® epidural needle and Racz® catheter are used. Oblique lumbar anatomy is shown in Fig. 20.57. The C-arm is rotated to the oblique position (Fig. 20.58). First, rotate the C-arm until the ipsilateral spinous process appears to move to the contralateral side of the spine. Second, adjust the cephalad-caudal tilt until the superior pars is superimposed over the disk space. An approximately 30° oblique angle is used while viewing the SAP or the ear of the "Scottie dog" as the needle target. Rotate the C-arm in the cephalad/caudad plane so that the ear of the "Scottie dog" (SAP) is superimposed over the disk space. These two steps can be accomplished faster than the much lengthier process of trying to square the end plates. The RX™ Coudé® needle is steered to come in bony contact with the tip of the superior pars (Fig. 20.59). Advance the RX™ Coudé® needle until the tip comes in contact with the superior articular process (SAP). Once bony contact is made,

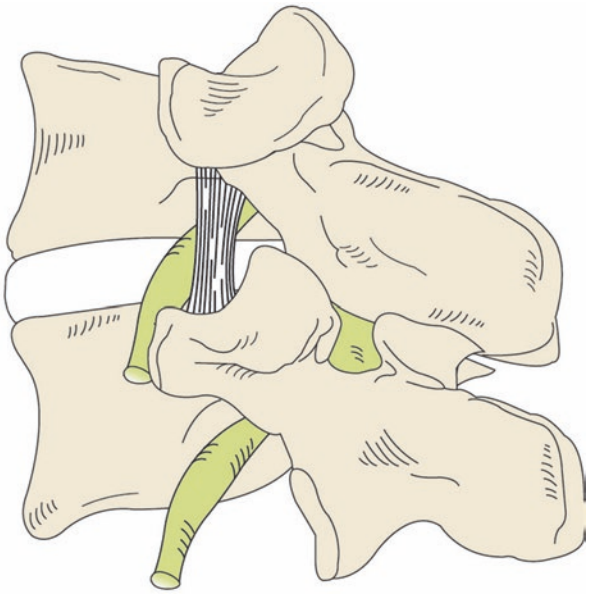


Fig. 20.57 Oblique lumbar spine anatomy

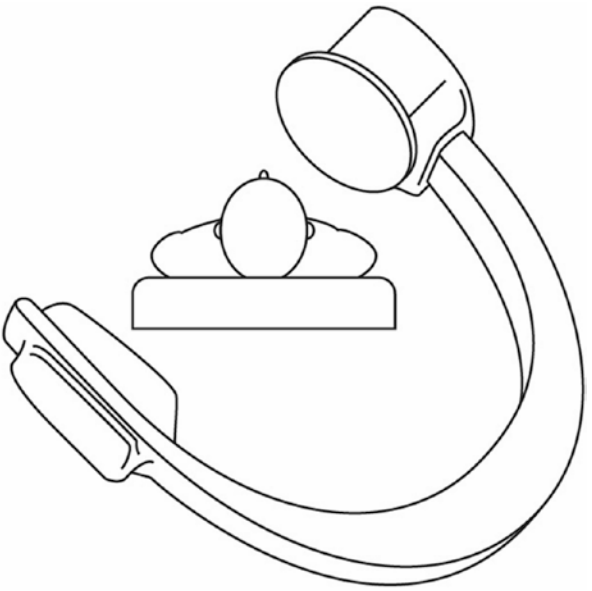


Fig. 20.58 C-arm is in oblique position

rotate the RX™ Coudé® needle 180° counterclockwise to orient the needle laterally (Figs. 20.60 and 20.61). Rotate C-arm to give lateral view (Fig. 20.62). Using a lateral fluoroscopic view, the needle tip is navigated around the SAP (Fig. 20.63). Advance the needle to slide past the superior articular process. Change the C-arm to the lateral position and advance the RX™ Coudé® needle until you feel it "pops"

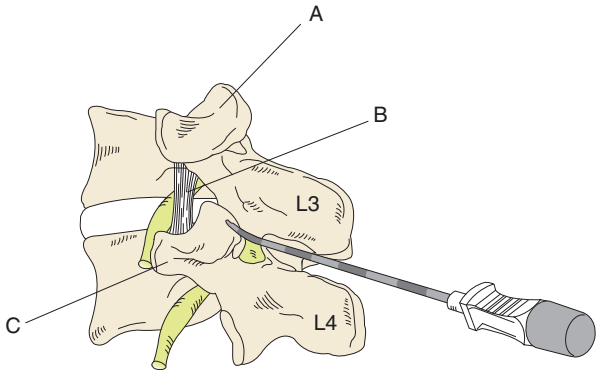


Fig. 20.59 The RX Coudé needle is advanced to make bony contact with the superior articular process posterior to the target foramen. (**a**) Superior articular process. (**b**) Intertransverse ligament. (**c**) Transverse process

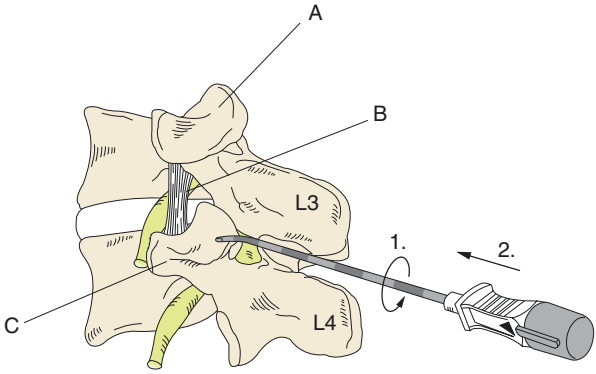


Fig. 20.60 The RX Coudé needle is rotated to a lateral orientation to allow navigation around the superior articular process. (**a**) Superior articular process. (**b**) Intertransverse ligament. (**c**) Transverse process

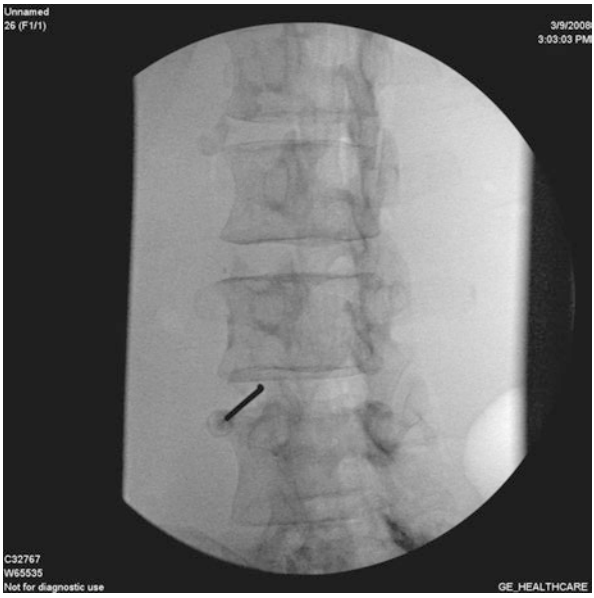


Fig. 20.61 The RX Coudé needle is rotated to a lateral orientation to allow navigation around the superior articular process

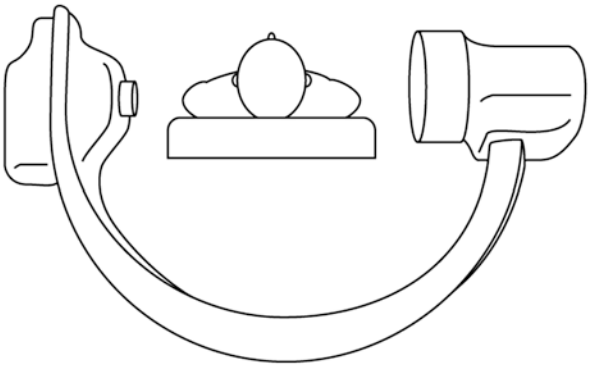


Fig. 20.62 The C-arm is rotated to the lateral position

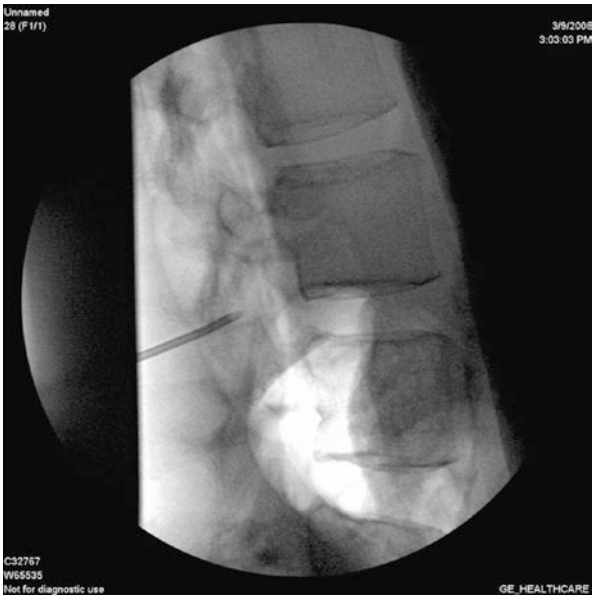


Fig. 20.63 The RX Coudé needle is advanced lateral and around the superior articular process

through the intertransverse ligament (Fig. 20.64). Rotate the RX™ Coudé® needle back 180° clockwise allowing the needle to curve back in the direction of the foramen (Fig. 20.65). The RX-2™ Coudé® needle has a second stylet that protrudes 1 mm beyond the needle tip to convert the needle to a blunt probe. Needle advancement is stopped at this point. The RX™ Coudé® advancement should stop before the nerve root is reached. There should be no paresthesia or sharp nerve pain. When using the VERSA-KATH®, it is important to make a half inch 10–15° bend in the catheter for optimum steering ability (Fig. 20.66). With the XL tip catheter, the stylet needs to be close to the tip for enhanced steering. If the bend is too short, the catheter tends to buckle. If the bend is too long, it is much harder to steer. The use of a wide-open RX™ Coudé® needle reduces the incidence of shearing. A Racz® catheter will readily be passed in the ventral epidural space to mid-canal position

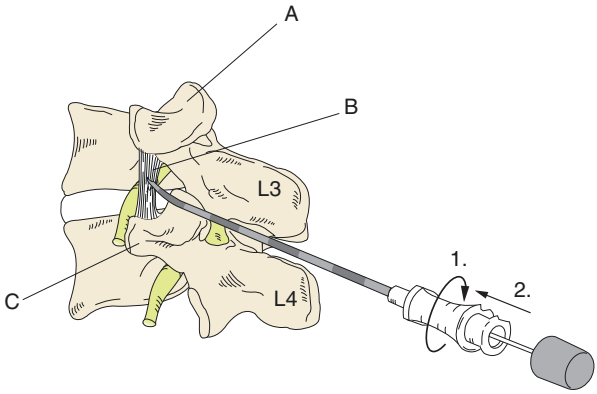


Fig. 20.64 The RX Coudé needle is advanced through the intertransverse ligament using the lateral view to avoid anterior placement. (**a**) Superior articular process. (**b**) Intertransverse ligament. (**c**) Transverse process

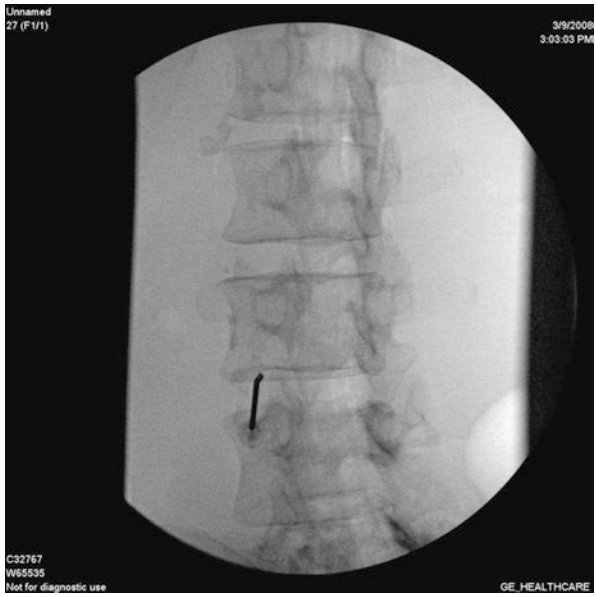


Fig. 20.65 The RX Coudé needle is rotated to the medial orientation to facilitate catheter placement

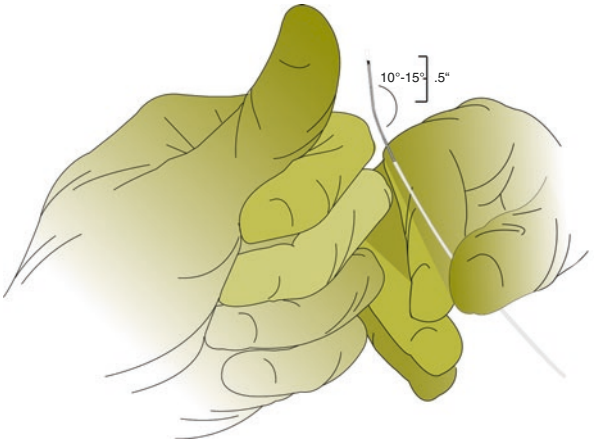


Fig. 20.66 A 10–15° bend is made ½ inch from the catheter tip to facilitate steering

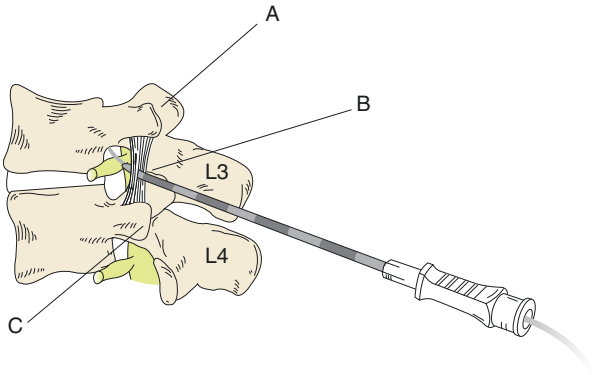


Fig. 20.67 Catheter placement, lateral anatomy (**a**) Superior articular process. (**b**) Intertransverse ligament. (**c**) Transverse process

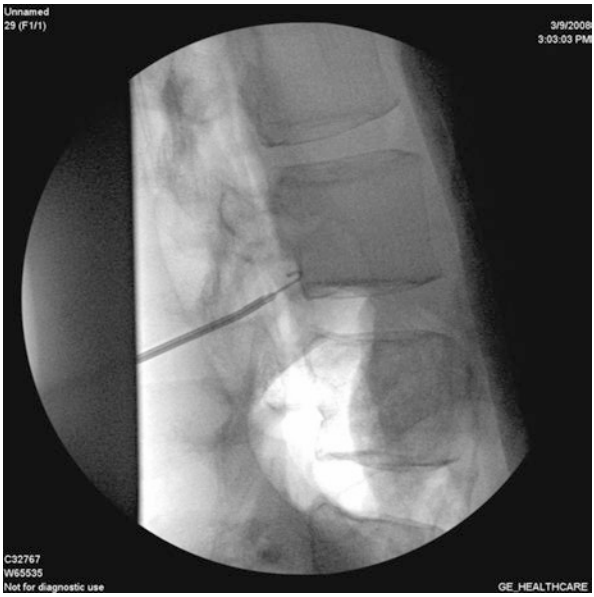


Fig. 20.68 Catheter placement in lateral image

(Figs. 20.67, 20.68, 20.69, and 20.70). A test dose of local anesthetic is administered, and the patient is monitored for 15 minutes to ensure a subdural block is not produced. Using a sharp epidural needle for catheter placement may produce a puncture or laceration of the dural sleeve. Safely introduce a Racz® catheter to the ventral/lateral epidural space and halfway into the spinal canal. The optimal catheter placement should be halfway or less into the epidural space of the spinal canal, without crossing the midline. If perivenous counter spread (PVCS) is observed during injections, flexion and rotation exercises must be performed to reduce pressure by opening the neural foramina and allow fluid to escape through the foramina. Bacterial filters are recommended in all instances when more than one-time injection is used or the catheter is left in place for prolonged period. When there is a disconnection of the catheter and the connector, the system should be removed from the patient. This is an essential precaution to prevent infection. The catheter cannot be cleaned and reconnected if it becomes contaminated.

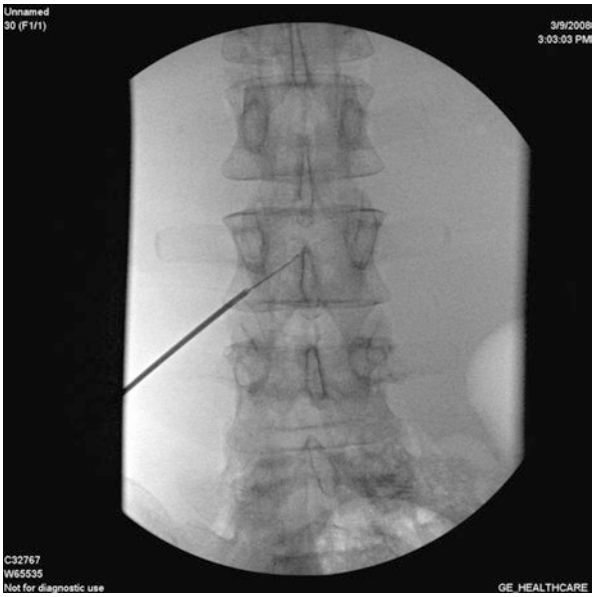


Fig. 20.69 Catheter placement in anterior-posterior image

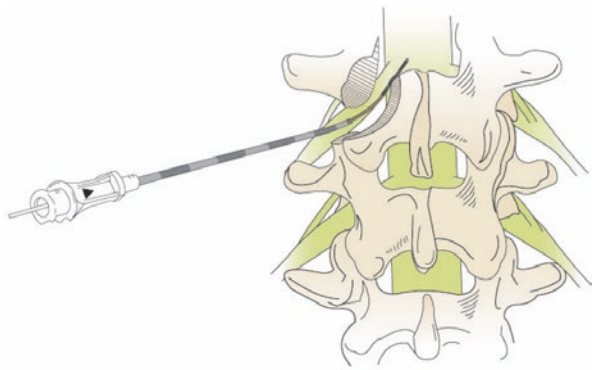


Fig. 20.70 Catheter placement in anterior-posterior cutaway schematic drawing

Steps to secure the catheter are as follows:

1. Make a full twist in the catheter to form a loop.
2. Place loop over the neck of the connector.
3. Pull catheter until it is secured around the connector body.
4. Use tape to secure the device.
5. Attach a bacterial 0.2-micron filter to maintain sterility.

Epimed's Stingray™ connector design allows for a fastening technique that changes pulling force direction to prevent disconnections. The Stingray™ connector is designed to have more grip strength on the catheter. This is essential for repeat injections or prolonged use. Using this technique more than doubles the catheter pull strength resistance. This technique is used for a 3-day series of injections for lysis or post-procedure injection of hypertonic saline in the recovery room for the 1-day

procedure. It is also useful when prolonged or postoperative infusion is utilized. Bacterial filters are recommended in all instances when more than one injection is used or the catheter is left in place for prolonged period. When there is a disconnection of the catheter and the connector, the system should be removed from the patient. This is an essential precaution to prevent infection. The catheter tape down technique, described previously, is used. After completion of the procedure, cut the suture and gently remove the catheter. If resistance is detected, reposition the patient and attempt to remove the catheter. At times, pushing and twisting the catheter allows removal.

Sacral Foraminal Catheter Placement

The scarring triangle is a common location that requires lysis. A recent observation is that patients develop scarring in the L5-S1 dorsal root ganglion area that may be associated with ankle weakness or foot drop. This area is difficult to enter using a catheter. Teske described the space as the scarring triangle (Fig. 20.71) [12]. The space measures 0.9–1.1 mL on each side. The boundaries are medial to the L5 nerve

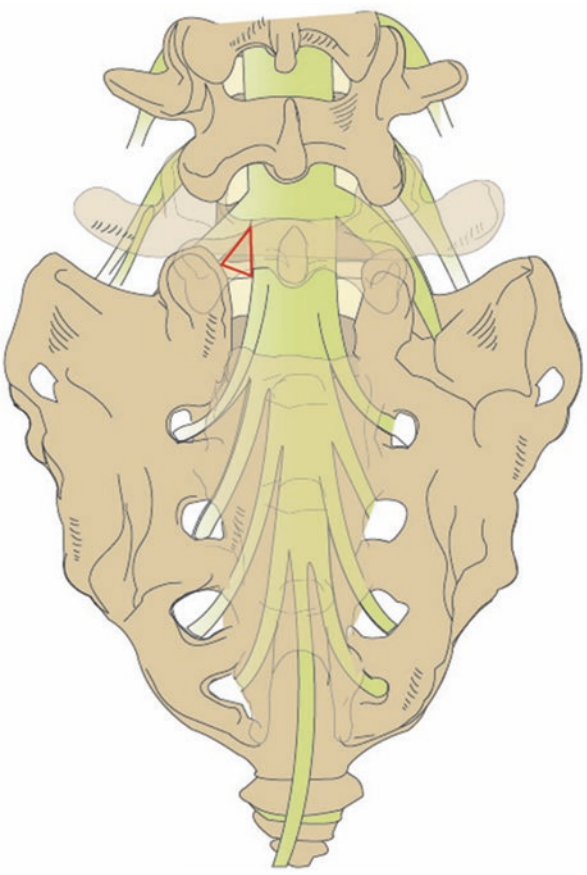


Fig. 20.71 Posterior lumbosacral anatomy, cutaway schematic showing the scarring triangle in red

root and lateral to the S1 nerve root, and the base of triangle is above the disk of L5-S1. This space is large enough to accept the average loose disk fragment. It tends to collect leaky disk material or the scars because of trauma and/or surgery. Due to the curvature of the sacrum and the formation of dense scarring, this area blocks catheters and scopes from entering into the ventral epidural space. Regular epidural catheters and scopes have not been able to enter this scarred area. Matsumoto described the use of a 21-gauge VERSA-KATH® using a transforaminal approach [13]. Matsumoto realized that coming from the posterior S1 neural foramen with an 18-gauge RX-2™ Coudé® needle and then rotating it, the curved tip allows ventral epidural projection of a 21-gauge VERSA-KATH®0.2 The VERSA-KATH® is x-ray visible and steerable as long as rotation coincides with the advance of the catheter.

Place patient in prone position. The corresponding ventral and dorsal foramina are not at the same plane, but the posterior neural foramina are more proximal (Fig. 20.72). The 18-gauge needle has a curve near the tip, but one still needs a gentler angle to allow cephalad advancement of the catheter. The starting point will be the lateral side of the S2 posterior neural foramen (Fig. 20.73). Rotate the C-arm in a cephalad direction until the S1 ventral and dorsal neural foramina align. A slight lateral rotation helps separate the ventral and dorsal neural foramina. The needle entry point is from the S2 aiming toward the medial side of S1. Apply topical anesthesia and advance the needle through the skin. Curve the needle down to touch the bone between the S1 and S2 on the sacrum (Figs. 20.74, 20.75, and 20.76). The RX Coudé needle is rotated to orient the tip superiorly, and the needle is advanced toward the first sacral foramen (Fig. 20.77a, b).

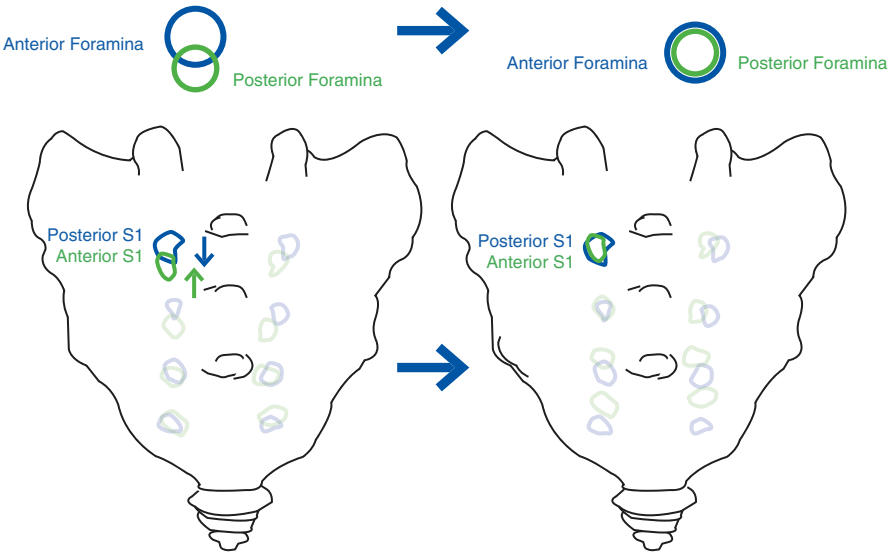


Fig. 20.72 The posterior and anterior foramina of the first sacral segment are not aligned in the anterior-posterior fluoroscopic image. In order to visualize the posterior foramen, it is helpful to rotate the C-arm in a cranial-caudal direction to facilitate foraminal entry

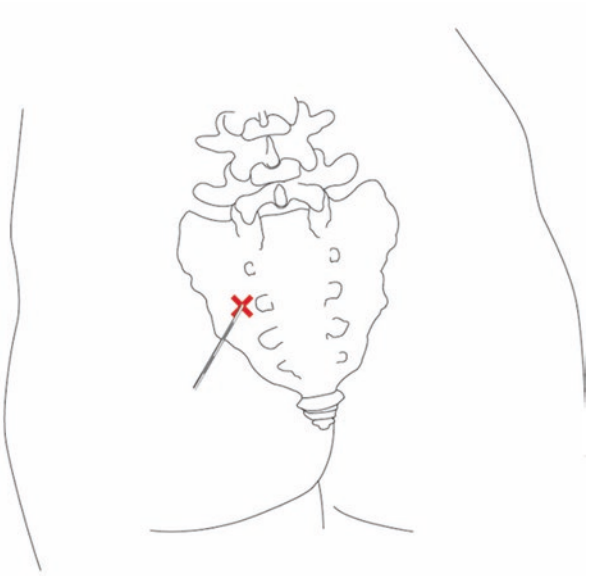


Fig. 20.73 The skin entry is inferior and lateral to the first sacral foramen at the level of the second sacral foramen

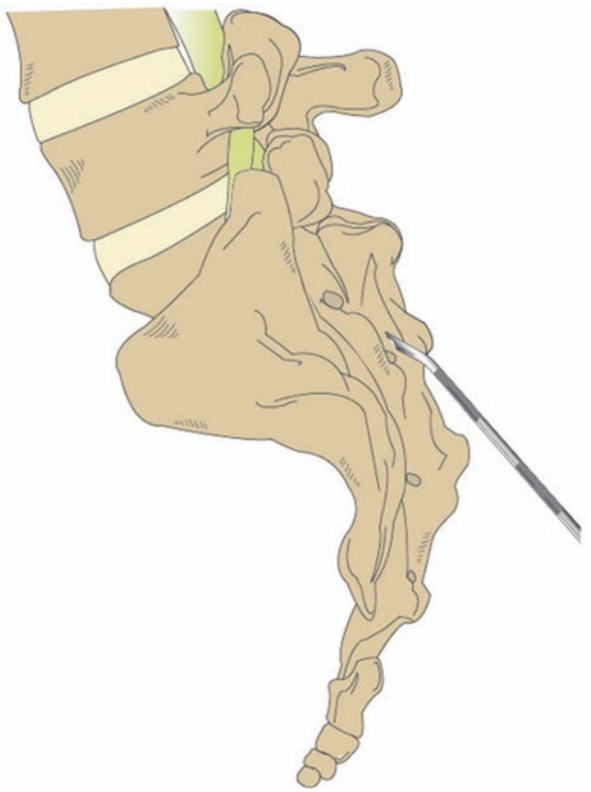


Fig. 20.74 The RX Coudé needle is advanced with the tip oriented in the anterior position to make bony contact between the first and second posterior sacral neural foramina

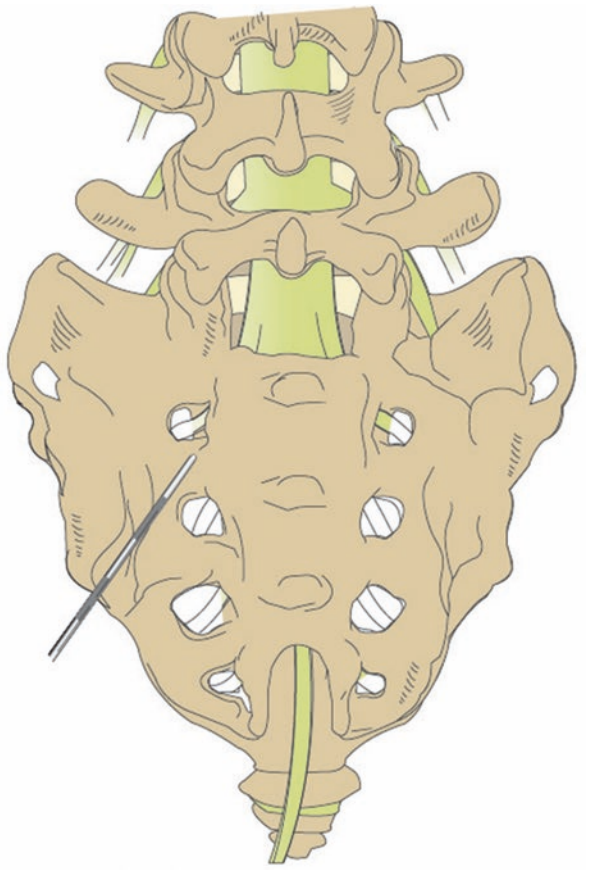


Fig. 20.75 The RX Coudé needle is advanced to make bony contact between the first and second posterior sacral neural foramina

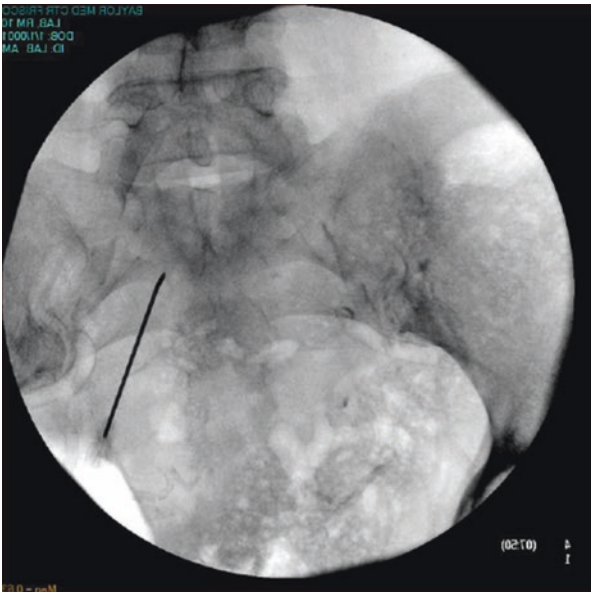


Fig. 20.76 The RX Coudé needle is advanced to make bony contact between the first and second posterior sacral neural foramina on anterior-posterior fluoroscopic imaging

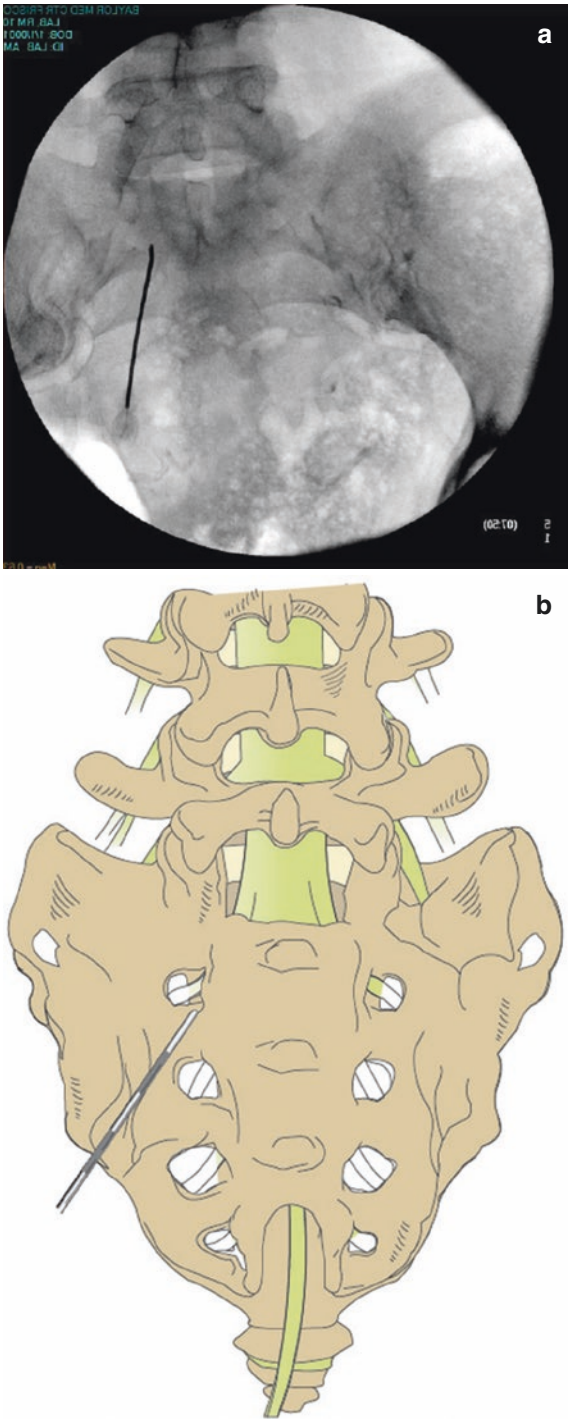


Fig. 20.77 (**a**) The RX Coudé needle is rotated to orient the tip superiorly, and the needle is advanced toward the first sacral foramen. (**b**) The RX Coudé needle is rotated to orient the tip superiorly, and the needle is advanced to the first sacral foramen

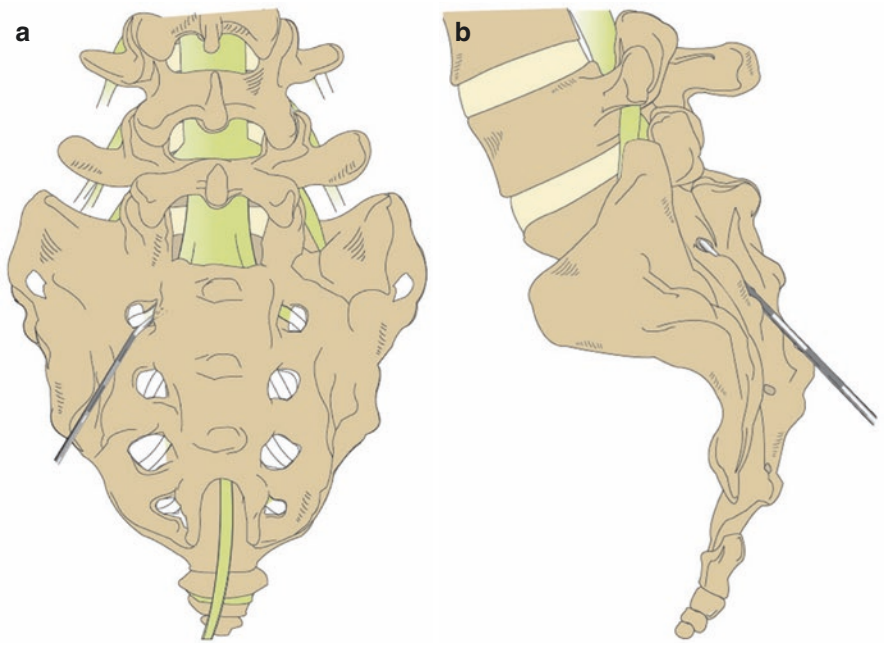


Fig. 20.78 (**a**) The RX Coudé needle is rotated to the medial tip orientation and advanced toward the medial foramen. (**b**) The RX Coudé needle is rotated to the medial tip orientation and advanced toward the medial foramen

Rotate the needle tip to navigate and become visible in the S1 fluoroscopic view (Fig. 20.78a, b).

Rotate the needle tip ventrally and elevate it while it is advancing to pop into the sacral canal (Fig. 20.79a, b). At this point, lateral fluoroscopic visualization will help advance the needle after rotation with the second stylet in place (Fig. 20.80). Rotate the C-arm into the anterior/posterior position with a cephalad tilt to avoid radiation exposure of the operator's hand. Only the needle tip is visible. With the stylet in place, advance the VERSA-KATH® within the sacral canal under fluoroscopic visualization. The catheter needs to cross the disk space and advance within the scar approximately near the top of the L5 neural foramen, not medial nor lateral in the imaginary triangle between L5 and S1 (Fig. 20.81a–d). It is possible to navigate the VERSA-KATH® by rotation during advancement.

S1 Catheter Injections

1. Connect the Stingray® connector and inject 10 cc of Omnipaque™ 240 within the scarred area. Injection of contrast may require significant pressure for a complete spread due to its viscosity.

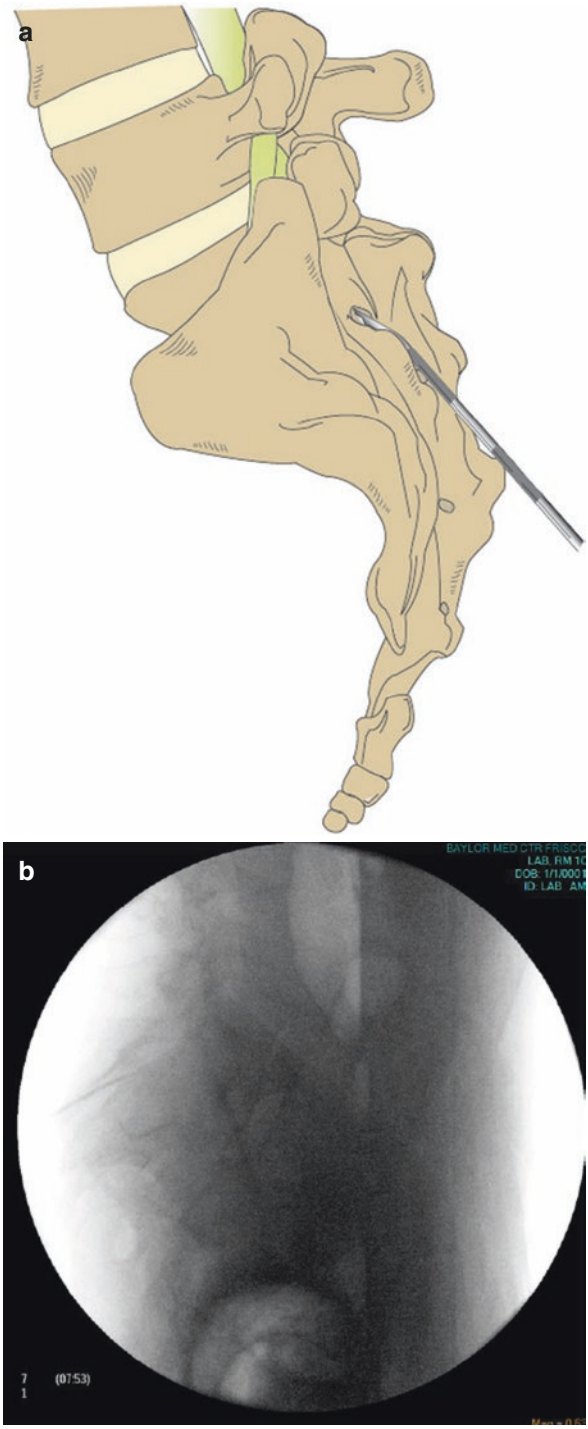


Fig. 20.79 (**a**) The RX Coudé needle is rotated to orient the tip anteriorly, and the needle is advanced to the first sacral foramen. (**b**) The RX Coudé needle is rotated to orient the tip anteriorly to enter the posterior first sacral foramen

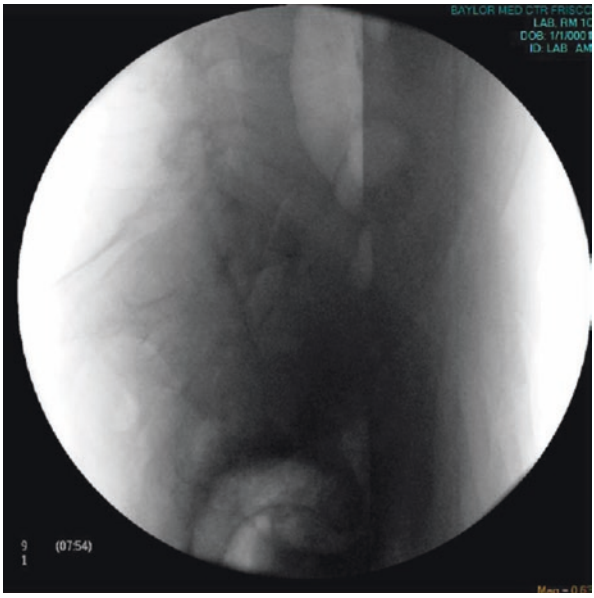


Fig. 20.80 The RX Coudé needle with the blunt stylet is rotated to the superior tip orientation and advanced into the epidural space

It will open up the ventral epidural space, slowly crossing over, and spread from L4 down to S2 bilaterally.

2. Inject a mixture of 10 cc of preservative-free saline and 150 units of Hylenex®; this will disperse the contrast. Carefully observe for a potential spread into the subdural and subarachnoid spaces, especially in failed surgery cases where the possibility of a dural tear may exist.
3. Slowly inject a mixture of 10 cc of 0.2% ropivacaine and 40 mg triamcinolone. Ask the patient to move their feet and to report any pain at any time other than during injection. Subdural injectate accumulation in the scarred area may produce bilateral pain and have atypical appearance. If subdural loculation occurs, it can be aspirated with an interlaminar needle placement.
4. After local anesthetic injection, observe the patient for 20–30 minutes and make sure they are able to perform a 90° straight leg raise without any evidence of motor block.
5. Infuse 10% NaCl over a 15-minute period. Then flush with local anesthetic or normal saline at completion.
6. If the patient develops a motor block, he or she may need to be admitted to the hospital for observation.
7. A one-time injection into the scarring triangle is effective for a short period of time; however, three repeat injections, 6–8 hours apart, have been reported as more effective for many months to over a year.
8. Instruct the patient to perform neural flossing exercises for the sciatic area. There are also separate instructions for the upper lumbar area.

Apply the Stingray® connector and inject 10 cc of Omnipaque™ 240 within the scarred area. Contrast is viscous, sticky, and hard to inject. Injection of contrast

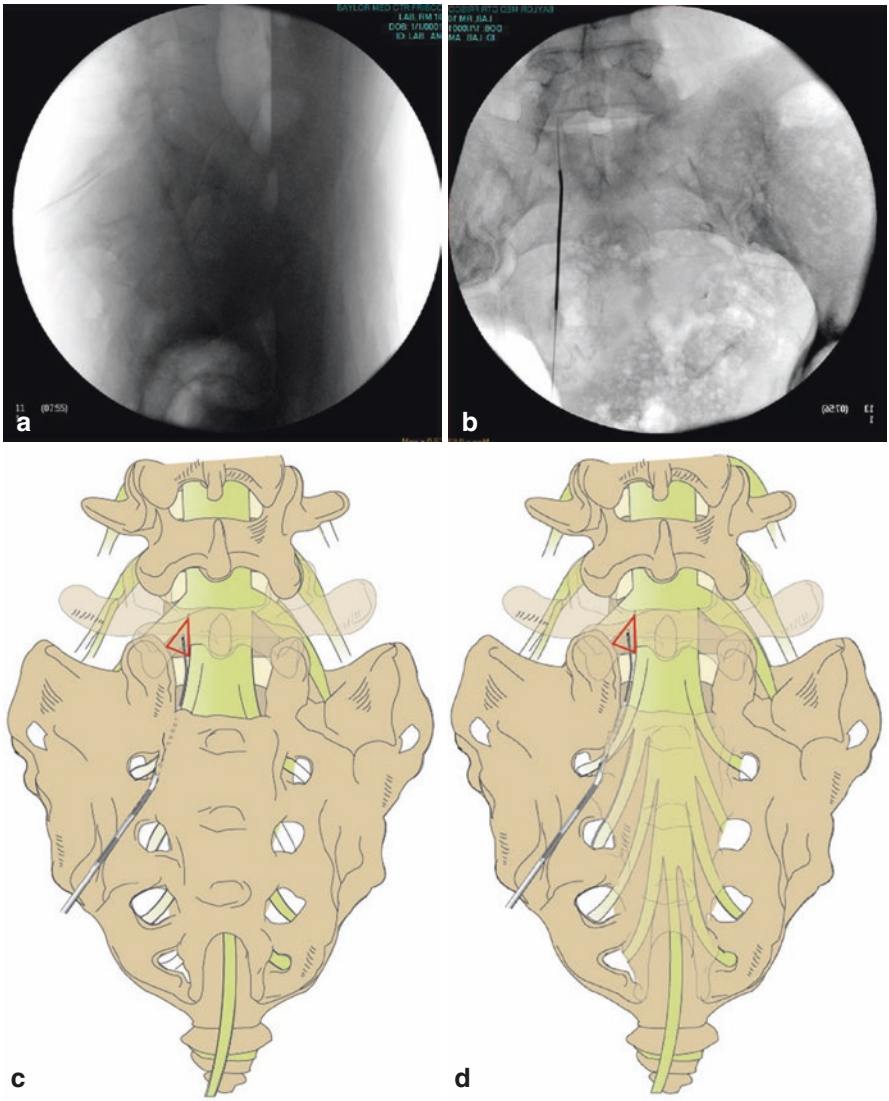


Fig. 20.81 (**a**) The RX Coudé needle tip is rotated to the superior orientation for catheter placement. (**b**) The RX Coudé needle tip is rotated to the superior orientation for catheter placement. (**c**) The RX Coudé needle tip is rotated to the superior orientation for catheter placement. The scarring triangle is indicated by the red triangle. (**d**) The RX Coudé needle tip is rotated to the superior orientation for catheter placement. The scarring triangle is indicated by the red triangle

requires significant pressure from the syringe. It will open up the ventral epidural space, gradually crossing over, and may spread from L4 all the way down to S2 bilaterally. Next, inject a mix of 10 mL of preservative-free saline and 150 units of Hylenex®. It will disperse the contrast. Carefully observe potential spread into the subdural and subarachnoid spaces, especially in failed surgery cases where

the possibility of a dural tear exists. Slowly inject a mix of 10 cc of 0.2% ropivacaine and 40 mg triamcinolone. Ask the patient to move their feet bilaterally and report any continuous pain at times other than during injection. Subdural accumulation in the scarred area may produce bilateral pain and have atypical appearance. If subdural loculation occurs, it can be aspirated with an interlaminar needle placement. So far, subdural spread has not been observed or reported except during a midline caudal catheter placement. Observe the patient for 20–30 minutes post local anesthetic injection and make sure they are able to do a 90-degree straight leg raise without any evidence of motor block. Infuse 10% NaCl over 15 minutes and flush with local anesthetic or saline at completion. Results appear significantly better when three repeat infusions are performed 6–8 hours apart. If the patient develops a motor block, they may need to be admitted to the hospital for observation. Indications include positive dural tug reproducing back pain and hip pain, L5-S1 radiculopathy, and foot drop. We have seen a bladder dysfunction recover following an unavoidable complication from a surgical laminectomy for spinal stenosis. Lower lumbosacral nerve root scarring and stretch injuries appeared responsible for foot drop after unsuccessful surgical procedures. Patients with spinal stenosis, in addition to radiculopathy, also need a mid-canal transforaminal second catheter at the maximum stenotic area. In addition, each injected volume of contrast, hyaluronidase, and local anesthetic steroid, followed by 10% hypertonic saline, is reduced to 5 mL. If pain is experienced during the hypertonic infusion, it may be necessary to top off 2–3 cc of 1% lidocaine. A one-time injection to the scarring triangle is effective for a short period, whereas three repeat injections have been reported to be more effective for many months to over a year.

Finally, instruct the patient to perform neural flossing exercises for the sciatic area and provide a handout. There are also separate instructions for the femoral upper lumbar area.

1. Start with the skin wheal needle technique to numb the entry point area of the introductory needle – RX™ Coudé® needle.
2. Diagnostic: 5–10 mL Omnipaque™ 240∗ – outline filling defect and place catheter to target site.
3. To show runoff and absence of loculation, contrast 4–5 mL Omnipaque™ 240∗ is injected through the catheter.
4. Spreading factor: Hylenex® 150–300 units (human recombinant) diluted in 10 mL of preservative-free saline, or hyaluronidase bovine compounded 1500 units diluted in 10 mL preservative-free saline.
5. Steroid injection: 4 mg dexamethasone or 40 mg triamcinolone. Local anesthetic: 10 mL 0.2% ropivacaine or 10 mL of 0.25% bupivacaine
6. 2–3 mL Omnipaque™ 240∗ through catheter.
7. Depending on the physician's lysis technique, wait 20–30 minutes. Evaluate for motor block with a voluntary straight leg raise. If no motor block is present, with the patient's painful side down, inject 8–10 mL of 5–10% hypertonic saline over 20–30 minutes. If the patient experiences pain, inject 2–3 mL of local anesthetic.

Critical note: Make sure to use non-ionic water-soluble dye. Some physicians also use 5–10 mL of ISOVUE-M 200.

Cervical Interlaminar Epidural Catheter Placement

Cervical interlaminar epidural RX-2™ Coudé® needle and catheter placement is an advanced technique for cervical radicular pain. The use of the RX™ Coudé® needle with its second stylet allows atraumatic needle movement with reduced chance of complications. Any movement of a sharp needle in the epidural space has a hazard of cutting the dura or high-pressure veins. Hematoma formation is rare but must be kept in mind with needle placements into the upper thoracic epidural space. Symptoms can be delayed several hours later, which include back pain, bladder dysfunction, numbness, weakness, and paralysis. Immediate MRI followed by emergent surgical evacuation can prevent permanent cord injury. The cause of potential pressure buildup in the absence of lateral runoff is perivenous counter spread (PVCS). Perivenous counter spread (PVCS) occurs in the presence of increased epidural pressure and becomes an indicator of possible spinal cord compression. If not sedated, the patient will complain of bilateral pain secondary to cord ischemia. During PVCS, the injected fluid spreads outside of the ventral epidural veins (perivenous) to the opposite side from the injection. If there is no lateral neural foraminal runoff, epidural pressure can increase lateral to the cord, on the opposite side (Fig. 20.82).

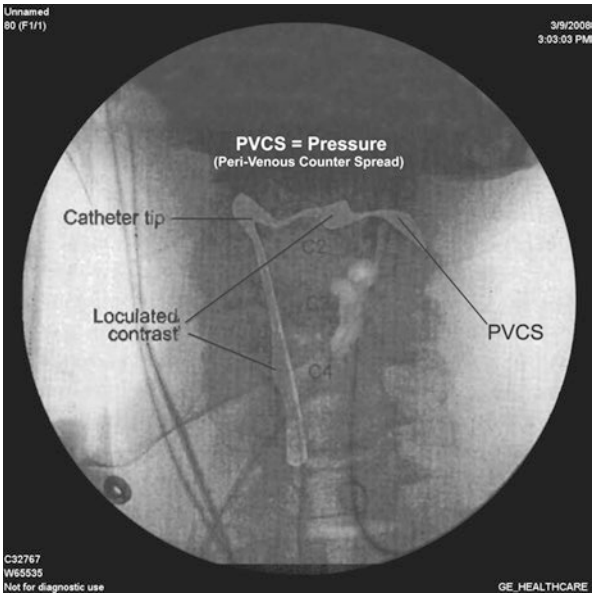


Fig. 20.82 Perivenous counter spread can occur with cervical injections and requires prevention and treatment with chin to shoulder maneuvers to open the cervical neural foramina and allow injected fluid to spread through the foamen, thus decompressing the epidural space

This leads to cord compression and is reported by the patient as bilateral arm and chest pain.

Repetitive chin to shoulders flexion rotation enlarges the neural foramina, facilitates decompression, and allows lateral runoff. Recognition of PVCS is especially important if patient is given sedation and is unable to report pain from ischemia. Rotation of the head is safe when the catheter is in place as the needle entry sites C7-T1, T1-T2, and T2-T3 do not move during rotation. If not recognized and/or patient is sedated, the patient will have postoperative pain, weakness, bladder problems, and paralysis. MRI does not detect the problem. Remember that cervical spine does not have fixed foramina diameters. They can be opened by flexion and rotation, and pressure can be reduced by lateral runoff.

Enlarging of Neural Foramina by Flexion Rotation and Chin to Shoulder Maneuver

During flexion, the inferior pars slides forward over the superior pars, making the neural foramen larger (Fig. 20.83). During extension, the inferior pars slides backward over the superior pars, making the neural foramen smaller. During injection,

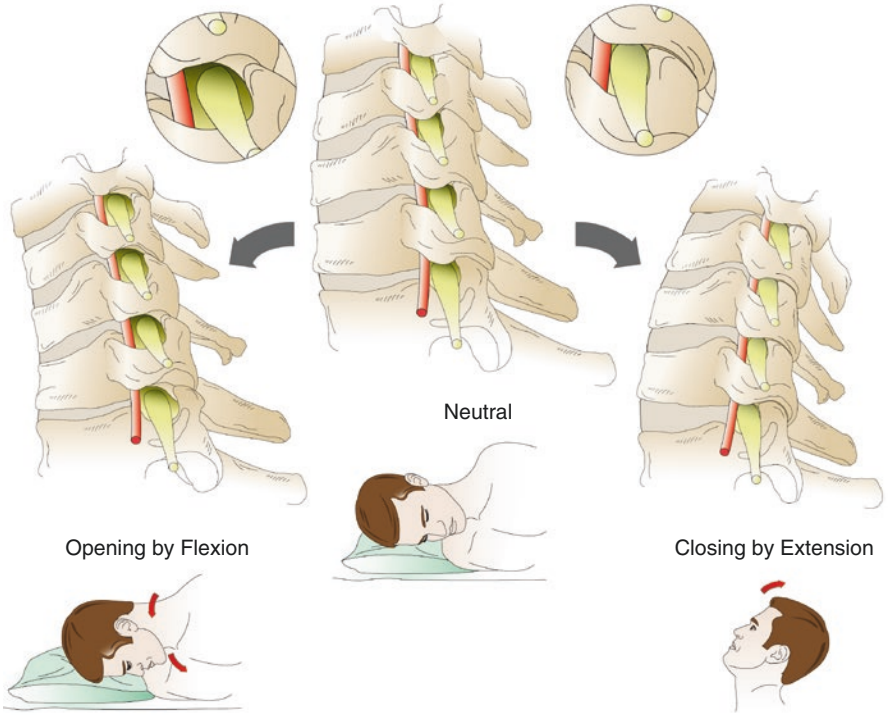


Fig. 20.83 Flexion widens the neural foramen allowing pressure to be released by fluid flowing out of the foramen. Repeating the maneuver is important to prevent spinal cord compression

the patient should flex and rotate the head from left to right to facilitate lateral runoff through the neural foramina. The opening and closing of the neural foramen will help in the assurance of fluid runoff, decreasing the probability of increased pressure in the epidural space (PVCS). Flexion and lateral rotations of the spine will change the size of neural foramen, making lateral runoff possible. This allows for reduced pressure created by fluid runoff, which will prevent loculation. The indication for pressure buildup in the absence of lateral runoff is better known as a perivenous counter spread (PVCS). During flexion, the inferior pars slides anteriorly over the superior pars, making the neural foramen larger. During extension, the inferior pars slides posteriorly over the superior pars, making the neural foramen smaller [14]. During injection, the patient should flex and rotate the head from left to right. The opening and closing of the neural foramen will help in the assurance of fluid runoff, decreasing the probability of increased pressure in the epidural space (PVCS). Flexion and lateral rotations of the spine will change the size of neural foramen, making lateral runoff possible. The fluid runoff outside the foramina results in reduced pressure for the loculation. The maneuvers should be continued until signs and symptoms resolve. Perivenous counter spread (PVCS) occurs in the presence of increased epidural pressure and becomes an indicator of possible spinal cord compression. If not sedated, the patient will complain of pain secondary to ischemia. The fluid spreads outside the ventral epidural veins to the opposite side. If there is no lateral neural foraminal runoff, epidural pressure can also increase lateral to the cord. This leads to cord compression reported by the patient as bilateral arm and chest pain. Repetitive chin to shoulders flexion rotation enlarges the neural foramina, facilitates decompression, and allows lateral runoff. Recognition of PVCS is especially important if patient is given sedation and is unable to report pain from ischemia. Rotation of the head is safe as the needle entry site C7-T1, T1-T2, T2-T3 does not move during rotation. If not recognized and/or patient is sedated, the patient will have postoperative pain, weakness, bladder problems, and paralysis. MRI will show nothing. Remember that cervical spine is not fixed; it is variable! The pressure can be reduced!

Cervical Interlaminar Epidural RX™ Coudé® Needle and Catheter Placement

The posterior cervical anatomy is shown in Fig. 20.85 (Fig. 20.84). With the patient in the prone position, the C-arm is rotated into the cephalad direction compensating for the patient's spinal kyphosis helping to optimize and enlarge the C7-T1 interlaminar target site. The Bromage grip should be used for needle advancement. The Bromage grip includes bracing the knuckles of the nondominant hand against the patient's back or neck. The needle is advanced with the fingers, so if the patient moves toward the needle, the hand and the needle move as well so that the needle does not penetrate deeper. Following local anesthetic injection, the RX™ Coudé® needle is introduced with the tip facing anterior medially. Using a paramedian

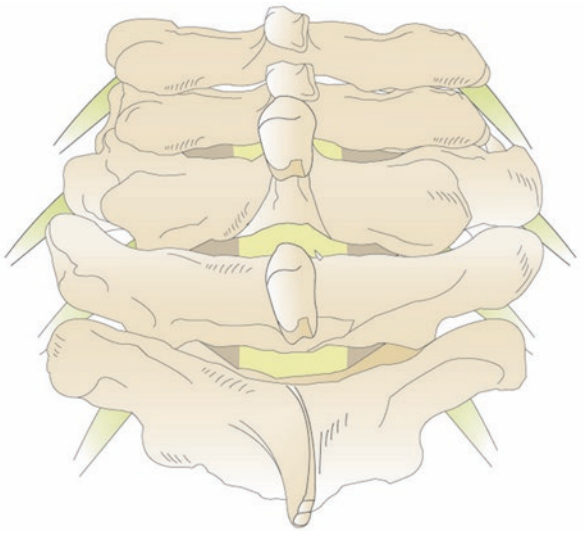


Fig. 20.84 Posterior cervical spine anatomy

approach allows the smooth passage of the RX™ Coudé® needle to the midpoint of the interlaminar space. The point of entry is slightly medial to the pedicle at the level below the chosen interspace. The skin entry point is 1.5 segments below the target interspace and 0.5″ lateral from the spinous process (Fig. 20.85a, b). Orient the needle tip medially while crossing the interspace. Curving the needle medially crossing the interspace, rotate the needle tip down interiorly, and bony contact is made with the lamina aiming toward the midpoint; the needle tip is steered until the edge of the lamina is reached. When the tip of the needle crosses the proximal end of the T1 lamina, the C-arm is rotated to the lateral view (Fig. 20.86). (The base of the spinous processes forms a straight line on fluoroscopic imaging.) The ligamentum flavum is in direct extension between the straight lines. Rotate the needle anteriorly and advance to the ligamentum flavum (Fig. 20.87a, b). The needle is rotated so that the tip is now parallel with the ligamentum flavum. The lateral view is utilized on fluoroscopy. The needle is advanced to be in line with the "straight line." The straight line is the enhanced bony outline of the bony cortex of the inside and the outside of the bifurcating lamina. The needle is positioned so that the bevel is parallel with the ligamentum flavum. The ligamentum flavum should be penetrated in the midline. The stylet should be removed, and a (LOR) syringe is attached to the hub of the needle. The needle is advanced with the "loss of resistance" or "loss of bounce" technique until a loss of resistance is felt which indicates entry into the epidural space. With this technique, the plane of the needle bevel tip is parallel to the plane of the dura, reducing the chance of penetration (Fig. 20.88a, b). The needle

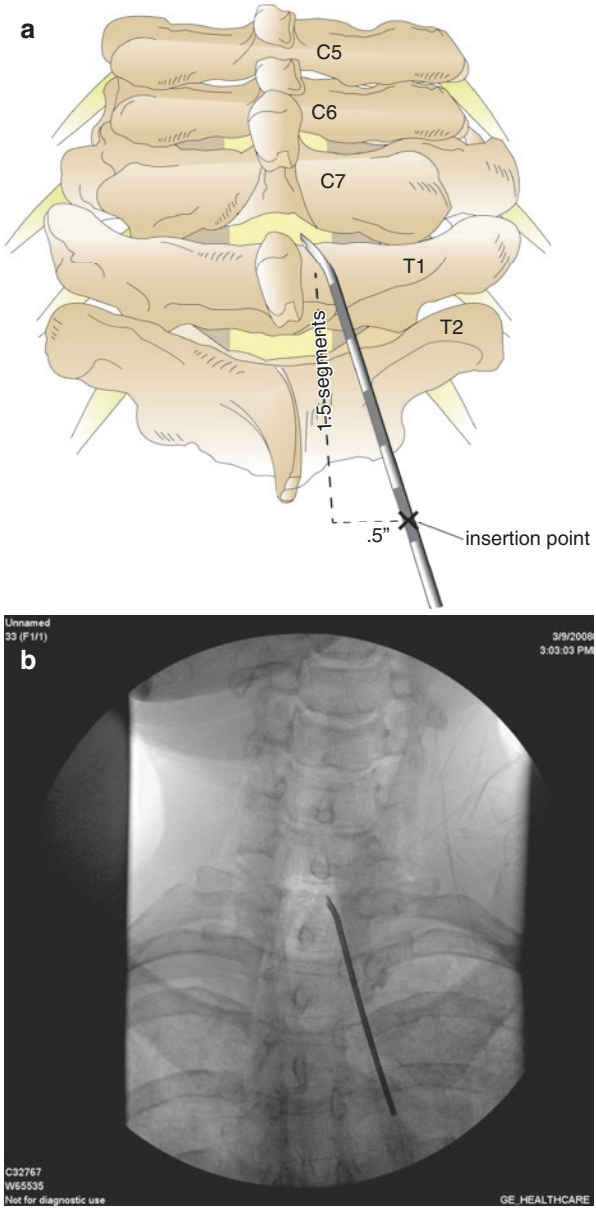


Fig. 20.85 (**a**) The skin entry point is 1.5 spinal segments inferior to the target interlaminar interspace. A paramedian approach is used with the RX Coudé needle tip in the medial orientation position. The seventh cervical–first thoracic interspace is used to avoid higher levels for needle puncture. (**b**) The skin entry point is 1.5 spinal segments inferior to the target interlaminar interspace

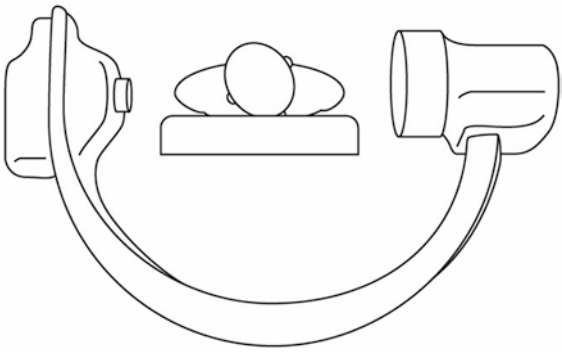
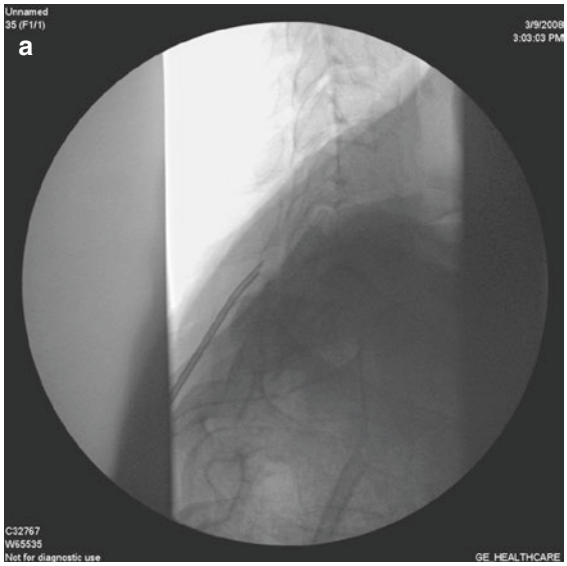


Fig. 20.86 The C-arm is rotated to the lateral position



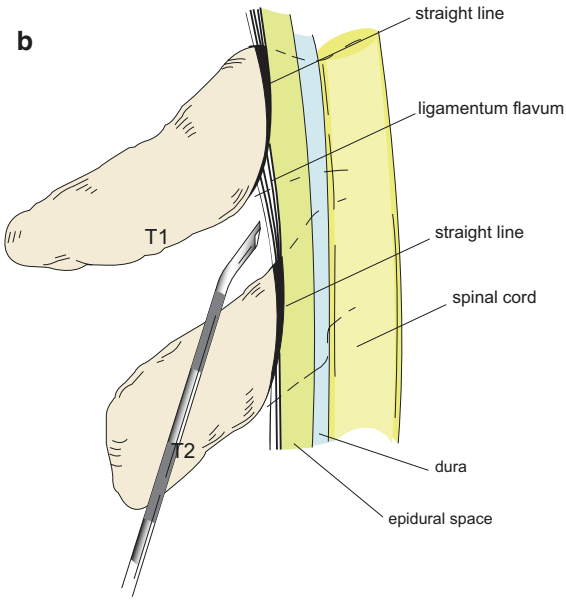


Fig. 20.87 (**a**) The RX Coudé needle is advanced using the lateral image. (**b**) The RX Coudé needle is advanced using the lateral image

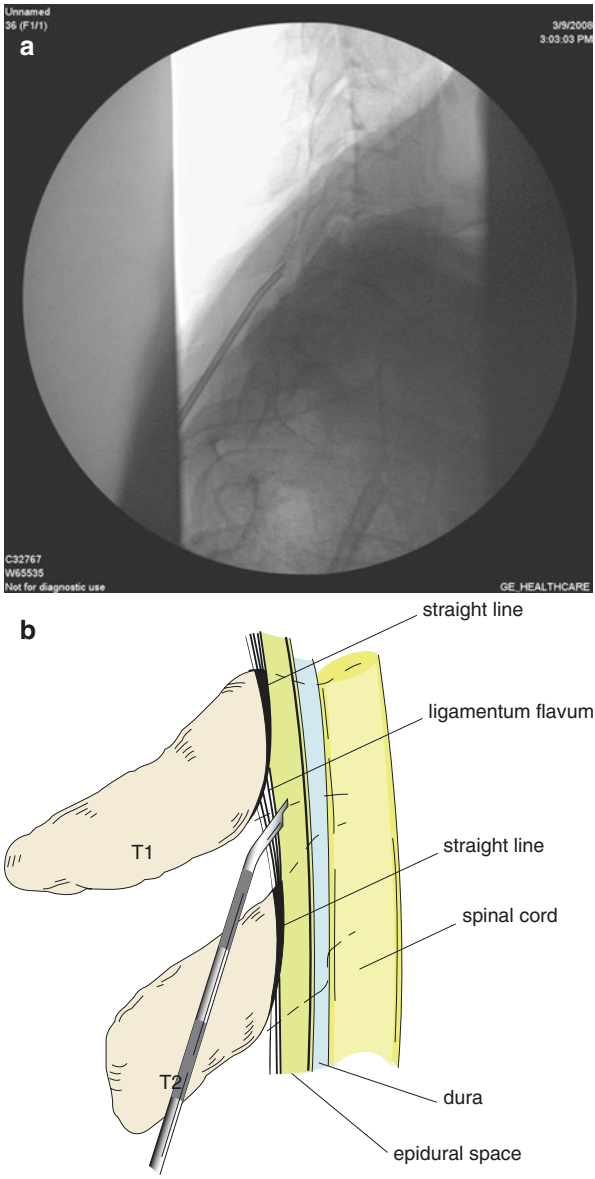


Fig. 20.88 (**a**) The loss of resistance technique is used to complement the lateral fluoroscopic image for identifying the epidural space. (**b**) The loss of resistance technique is used to complement the lateral fluoroscopic image for identifying the epidural space

is advanced with the "loss of resistance" technique until a loss of resistance is felt which indicates entry into the epidural space. Small volumes of contrast injection can confirm epidural placement on lateral and AP view. The RX-2™ Coudé® needle features an additional threaded interlocking blunt stylet that protrudes a short distance beyond the RX™ needle tip. The second stylet protrudes approx. 1 mm beyond the tip to convert the needle to a blunt probe. At this point, the second stylet is placed (Fig. 20.89a). This allows the rotation of the curved needle toward the direction of the area where the catheter needs to be directed. The blunt tip safely pushes the dura away. The needle should only be rotated with the blunt protruding

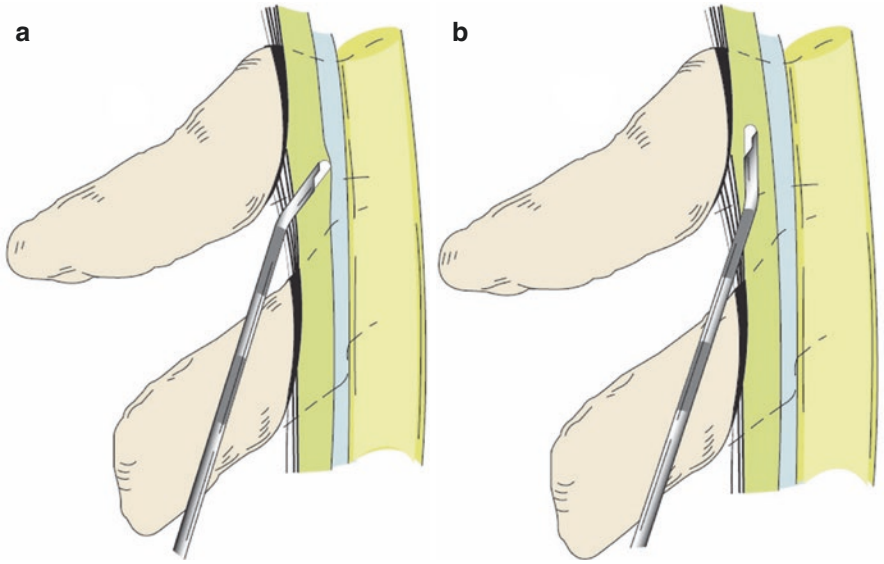


Fig. 20.89 (**a**) The blunt stylet is placed to prevent dural laceration or puncture. (**b**) The RX Coudé needle is rotated to the superior tip orientation with the blunt stylet in place to prevent dural or vascular laceration

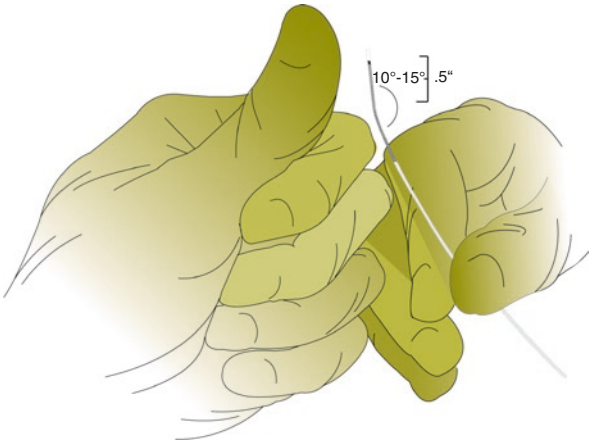


Fig. 20.90 A 10–15° bend is made one half inch from the catheter tip to facilitate steering

stylet in place. In this configuration, redirection (or rotation) of the needle tip is possible. Any needle directional rotation may cut the dura and lead to cerebrospinal fluid (CSF) leak and spinal headache. The RX-2™ protruding stylet prevents this. After the RX-2™ Coudé® needle has been rotated in the direction of the target, remove the extended blunt stylet (Fig. 20.89b). It is important to make a half inch 15° bend in the catheter for optimum steering ability (Fig. 20.90). With the XL tip catheter, the stylet needs to be close to the tip for enhanced steering. If the bend is too short, the catheter tends to buckle. If the bend is too long, it is much harder to steer. Insert the catheter into the RX™ needle that will safely place the catheter

parallel to the dura. Following the RX™ Coudé® entry into the epidural space, the soft tipped catheter is placed for a short 1/4″–1/3″ distance beyond the tip of the needle to push the dura away. This allows the rotation of the needle toward the intended target. This reduces the chance for the rotation of the needle tip from cutting the dura. When the RX™ Coudé® needle is rotated in the direction of the target, the catheter is placed parallel to the dura. The RX™ Coudé® needle should always point in the direction of the target. The incorrect needle orientation is shown in Fig. 20.91a, b. After rotation, the catheter or electrode becomes easier to direct

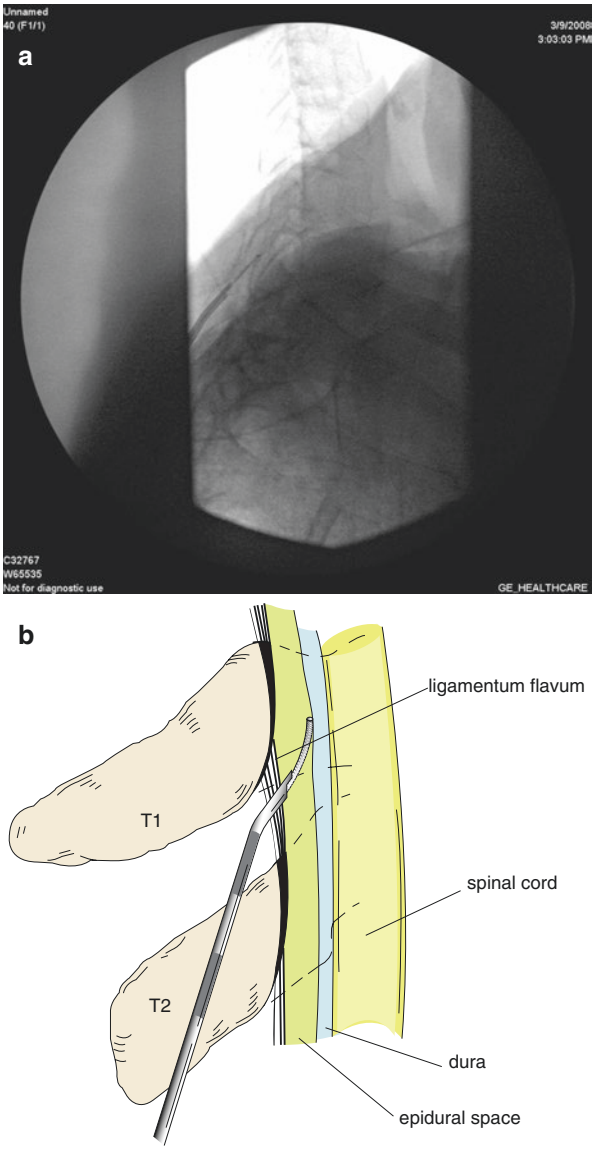


Fig. 20.91 (**a**) Incorrect needle position for catheter placement. The needle is in the anterior orientation position, and so the catheter projects toward the dura. (**b**) Incorrect needle position for catheter placement. The needle is in the anterior orientation position, and so the catheter projects toward the dura

and parallel to the plane of the dura (Fig. 20.92a, b). The C-arm is rotated to the anterior-posterior position (Fig. 20.93). The catheter tip is placed toward the C6 ventral-lateral epidural space (Fig. 20.94a, b). Any movement of a sharp needle in the epidural space has a hazard of cutting the dura or high-pressure veins. Hematoma formation is rare but must be kept in mind with needle placements into the upper thoracic epidural space. Symptoms can come some hours later that include back pain, bladder dysfunction, numbness, weakness, and paralysis. Early MRI followed

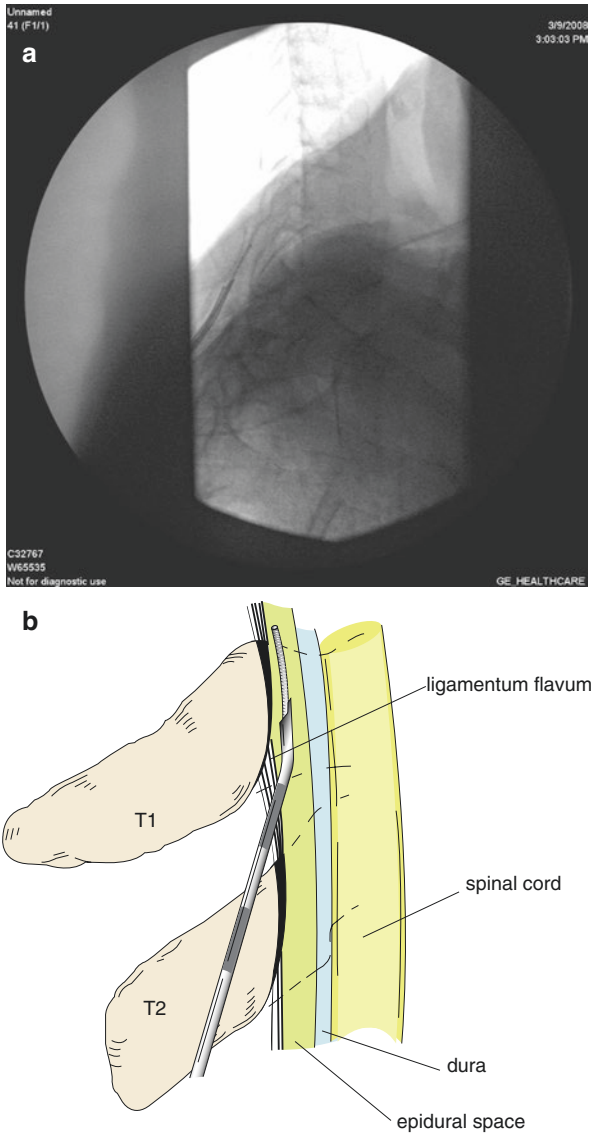


Fig. 20.92 (**a**) Correct needle orientation to allow catheter passage without dural compression. (**b**) Correct needle orientation to allow catheter passage without dural compression

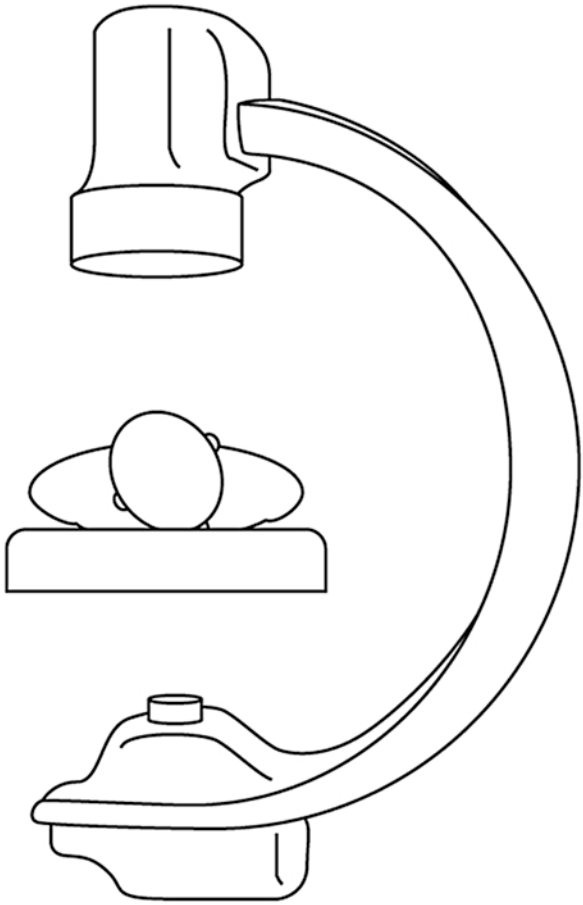


Fig. 20.93 The C-arm is rotated to the anterior-posterior position

by surgical evacuation can prevent permanent cord injury. The second stylet of the RX™ Coudé® needle makes needle movement atraumatic with reduced chance of above-mentioned complications. Bacterial filters are recommended in all instances when more than one-time injection is used or the catheter is left in place for prolonged period. When there is a disconnection of the catheter and the connector, the system should be removed from the patient. This is an essential precaution to prevent infection.

The advanced catheter fastening technique is strongly recommended.

Advanced Catheter Fastening Technique

1. Make a full twist in the catheter to form a loop.
2. Place loop over the neck of the connector.
3. Pull the catheter until it is secured around the connector body.
4. Use tape to secure the device.
5. Attach a bacterial 0.2-micron filter to maintain sterility.

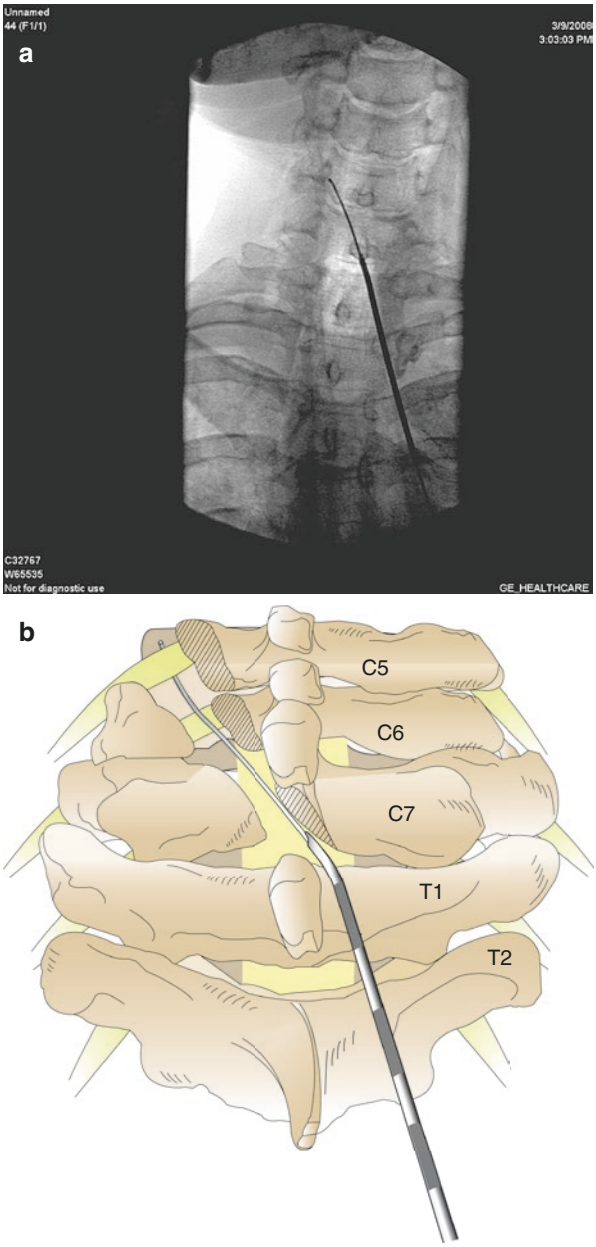


Fig. 20.94 (**a**) The catheter is placed to the target location. (**b**) Cutaway diagram – The catheter is placed to the target location

Epimed's Stingray™ connector design allows for a fastening technique that changes pulling force direction to prevent disconnects. The Stingray™ connector when compared to four other connectors for grip and strength was found to be the best; however, for repeat injections or prolonged use, the following additional measures further enhance safety. Physicians have been known to use this technique during

a 3-day lysis series or post-procedure injection of hypertonic saline in the recovery room for the 1-day procedure. It is useful when prolonged or postoperative infusion is utilized. The force required to separate the catheter from the connector is more than double that of other connectors. Bacterial filters are recommended in all instances when more than one injection is used or the catheter is left in place for prolonged period. When there is a disconnection of the catheter and the connector, the system should be removed from the patient. This is an essential precaution to prevent infection.

Catheter Tape Down Technique

- Place suture and tie loose loop.
- Wrap around catheter two times and tie surgical knot.
- Apply antibiotic ointment around skin entry and place two-split 2 × 2" gauze to keep antibiotic in place.
- Apply adhesive, i.e., tincture of benzoin, around the gauze.
- Place one loop on the catheter and transparent dressing, i.e., Opsite.
- Connect bacterial filter and four pieces of sweat-resistant Hypafix tape.

The 10-Step Approach to Safer Cervical Catheter Placement Using RX™ Coudé Needle

1. Point of entry is one and a half segment below the target 1/2 inch from midline.
2. Cross interspace – curving medially.
3. Curve down to lamina to touch the bone (lamina).
4. Curve medially and advance the needle to the edge of lamina in the midline.
5. Rotate C-arm to lateral view and look for the straight line.
6. Advance the needle to just below straight line and remove stylet.
7. Use loss of resistance or loss of bounce technique to enter the epidural space.
8. Reduce dura perforation from tip movement by either:

   A. Advancing the catheter short distance beyond the tip of the needle to push dura free from the tip of the needle
   B. Placing protruding RX-2™ stylet and making sure interlocking cap is rotated clockwise, pushing the dura from the tip of the needle

9. Rotate the needle toward the desired target side.
10. Put 1/2 inch 15-degree bend at the Racz® bend mark on the distal tip of the catheter and thread the catheter to the lateral cervical epidural space at the target nerve root.

Equipment Options

1. 18-gauge RX™ Coudé® needle and 21-gauge VERSA-KATH® with Stingray™ connector and bacterial filter if multiple injections are anticipated

   (a) Observe safety recommendations about taping, filter, and volumes of injections.

2. 15- or 16-gauge RX™ Coudé® needle and Brevi-XL™ with a similar 15° bend for one- time use or Tun-L-XL™/24 catheter if re-injections are anticipated

   (b) Both catheters connect to the specific gauged Stingray™ connector with or without the bacterial filter.

Cervical Injections

1. Diagnostic: 1–2 mL Omnipaque™ 240∗ – outline filling defect and place the catheter to the target site.
2. To show runoff and absence of loculation, contrast 0.5–1 mL Omnipaque™ 240∗ is injected through the catheter.
3. 1–2 mL Omnipaque™ 240∗ through catheter for verification of enzyme effectiveness.
4. Spreading factor: Hylenex® 150–300 units (human recombinant) diluted in 5 mL of preservative-free saline.
5. Steroid injection: 4 mg dexamethasone or 40 mg triamcinolone.
6. Local anesthetic: 6 mL 0.2% ropivacaine or 10 mL of 0.25% bupivacaine.
7. Depending on the physician's lysis technique, wait 20–30 minutes. Evaluate for motor block. If no motor block is present, with the patient's painful side down, inject 5 mL of 10% hypertonic saline over 5–10 minutes. If the patient experiences pain, inject 2–3 mL of local anesthetic.

The 10-Step Approach for Safer Cervical Catheter Placement Using RX™ Coudé® Needle

1. Point of entry is one and a half segment below the target 1/2 inch from midline.
2. Cross interspace – curving medially.
3. Curve down to lamina to touch the bone (lamina).
4. Curve medially and advance the needle to the edge of lamina in the midline.
5. Rotate C-arm to lateral view and look for the straight line.
6. Advance the needle to just below straight line and remove stylet.
7. Use loss of resistance or loss of bounce technique to enter the epidural space.
8. Reduce dura perforation from tip movement by either:

   A. Advancing the catheter short distance beyond the tip of the needle to push dura free from the tip of the needle
   B. Placing protruding RX-2™ stylet and making sure interlocking cap is rotated clockwise, pushing the dura from the tip of the needle

9. Rotate the needle toward the desired target side.
10. Put 1/2–3/4 inch 15-degree bend in the catheter and thread the catheter to the lateral cervical epidural space at the target nerve root.

Equipment Options

1. 18-gauge RX™ Coudé® needle and 21-gauge VERSA-KATH® with Stingray™ connector and bacterial filter if multiple injections are anticipated

   (a) Observe safety recommendations about taping, filter, and volumes of injections.

2. 15- or 16-gauge RX™ Coudé® needle and Brevi-XL™ with a similar 15° bend for one-time use or Tun-L-XL™ 24 catheter if re-injections are anticipated

   (b) Both catheters connect to the specific gauged Stingray™ connector with or without the bacterial filter

Epidural lysis of adhesions procedures are techniques for which there are CPT codes and virtually uniform reimbursement. Lysis is a technique that saves money, reduces the incidence of surgery, and even in the presence of failed back and neck surgery is much more beneficial and effective than repeated surgeries. It improves the effectiveness of spinal cord stimulation where the intensity of the pain may be too much for the spinal cord stimulator to reduce. We now see evidence of nerve function recovery following the use of the lysis of adhesions technique [15].

Table 20.2 summarizes cost-effectiveness for different treatments for back and radicular pain.

Suboccipital Compartment Injection

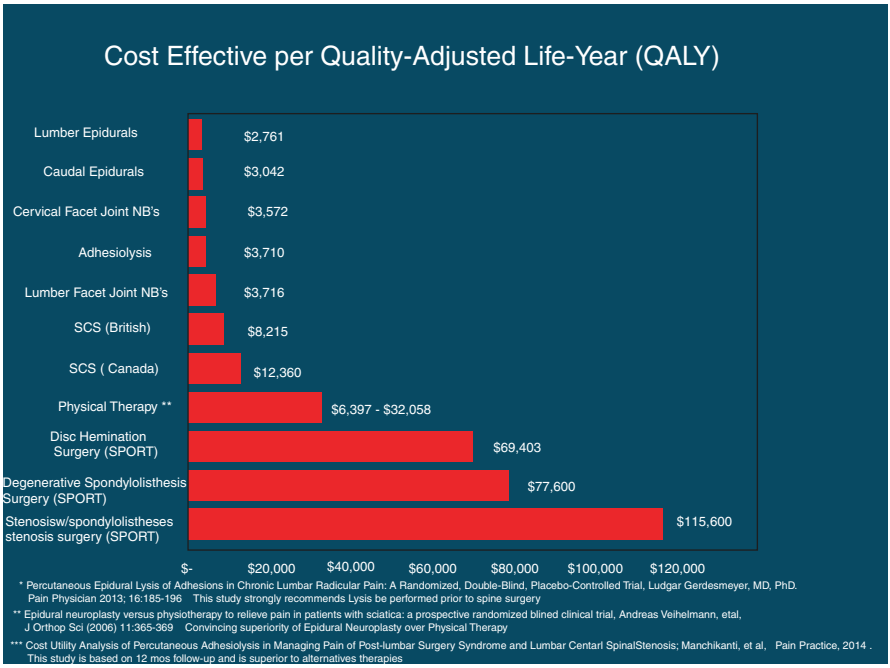
Stealth™ Needle System is used for the suboccipital compartment injection technique.

Intractable occipital nerve entrapment headache has been treated with the suboccipital compartment injection technique. Alternative techniques such as occipital nerve blocks may provide relief for 2 weeks. Botulinum toxin injections may last 12 weeks. In contrast, suboccipital injections provide 24 weeks of relief.

Sharp needles are not used because intraneural injection can spread retrograde along the C2 root to the cord. This has resulted in a “locked-in phenomenon” and a brain stem dissection by the injectate spreading to the C2 area of the spinal cord. The technique described in this chapter is a safer way to help patients suffering from one of the most common headaches, which is the greater, lesser, and third occipital related cephalgia. The greater occipital nerve travels through multiple muscle layers and can be entrapped and compressed (Fig. 20.95). The most proximal compression occurs at the inferior oblique muscle between the first and second cervical vertebrae (Fig. 20.96). The suboccipital compartment injection is performed using a bullet-tipped side ported Stealth™ needle with a curved tip for steering.

The Stealth™ needle prevents intraneural injections. If sharp open-ended needles are used for injection, intraneural injection can be followed by “locked-in” phenomenon where the patient is awake but cannot move or breathe. Unless ventilator support is provided, cardiopulmonary collapse can occur to be followed by brain injury. This is extremely rare but necessitates the procedure being done with

Table 20.2 Cost-effectiveness per QALY



A study comparing the cost-effectiveness per quality-adjusted life year (QALY) found that lumbar lysis of adhesions was less expensive than commonly used treatments including physical therapy and surgery. $3710 for epidural lysis of adhesions, which has been proven to be a cost-effective therapy that improved quality of life and has long-lasting effects

Advanced Cardiac Life Support personnel and equipment. Patients need monitoring and support until recovery occurs.

Intraneural injection should be avoided. When performing this procedure, the Stealth™ needle will pass inferior to the occiput, anterior to the trapezius and semi-spinalis muscles. The injection area is a semi closed compartmental space that has a number of important structures including the greater, lesser, and third occipital nerves, as well as the occipital artery and other vessels.

The Stealth™ needle injection site is just below the level of the nuchal line, one fingerbreadth lateral to the midline and inferior to the palpable occipital notch but still over the occiput (bony structure) (Fig. 20.97). The point of entry is slightly inferior to the nuchal line, one fingerbreadth lateral to the midline. Following local anesthetic injection, just below the nuchal line, a skin puncture is made to allow the passage of the bullet-tipped Stealth™ needle (Fig. 20.98). Using a cutting needle, make a skin puncture to enable the needle to pass through the muscle layers in the direction of the superior pars at the C2 level (Fig. 20.99). After the second "pop,"

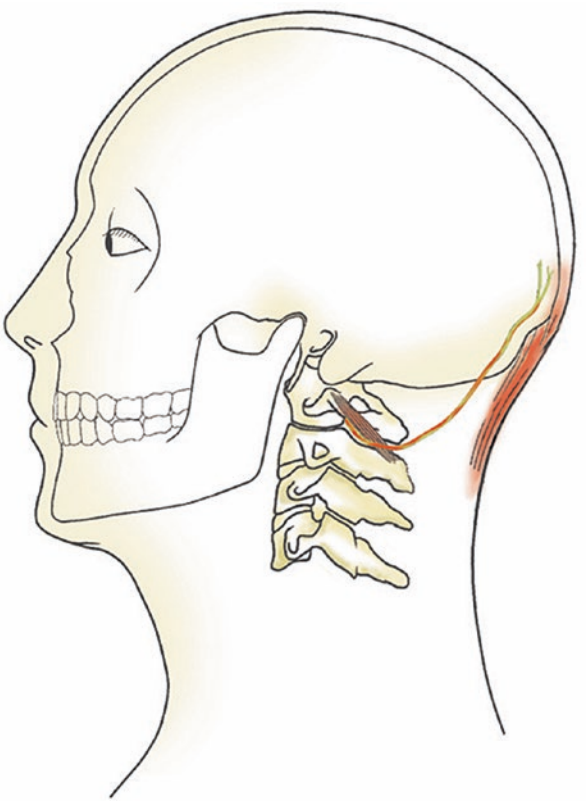


Fig. 20.95 Occipital nerve anatomy

the advancement is stopped. The C-arm is rotated to the lateral position (Figs. 20.100 and 20.101).

Following the removal of the cutting needle, the Stealth™ needle should follow the needle track to the suboccipital compartment (Fig. 20.102).

On lateral view fluoroscopy, the needle tip is pointed slightly inferior to the arch of the first cervical vertebra (Fig. 20.103). Contrast injection is used to confirm that the injectate is not tracking along the nerve sheath toward the spinal cord (Fig. 20.104a, b). This is followed by 8–10 cc dilute local anesthetic and corticosteroid mixture on each side. This technique will also block the lesser occipital and third occipital nerves that may be entrapped as well. Under lateral fluoroscopic visualization, the Stealth™ needle should never be advanced beyond the spinous process. Contrast injections are to be carried out with continuous lateral fluoroscopic imaging. The lateral fluoroscopic view of the contrast injection will show the spread under the suboccipital muscle layers (trapezius and semispinalis muscles). Filling the suboccipital compartment will open up the entrapment of the suboccipital

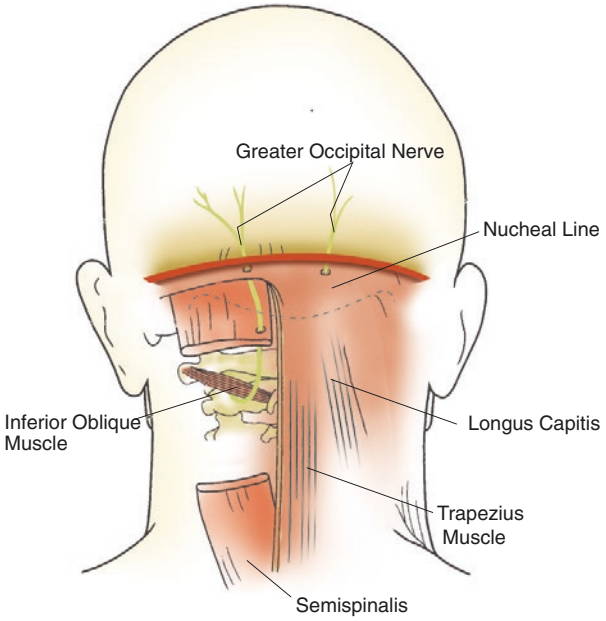


Fig. 20.96 Muscles of the suboccipital compartment

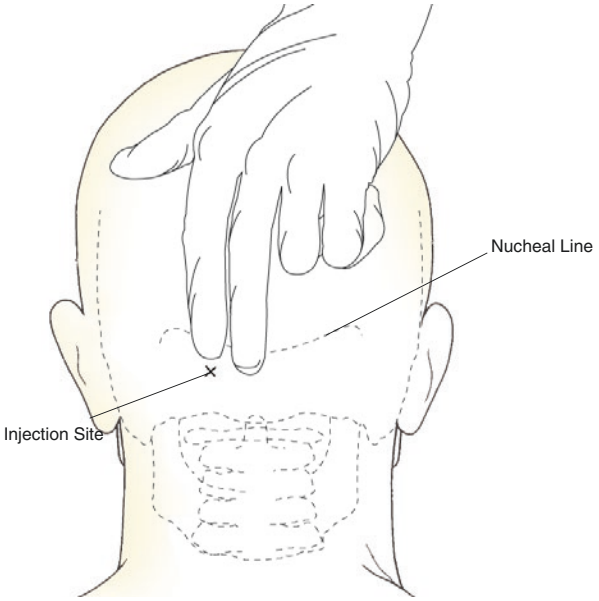


Fig. 20.97 The skin puncture site for the Stealth™ needle is just below the level of the nuchal line, one fingerbreadth lateral to the midline and inferior to the palpable occipital notch

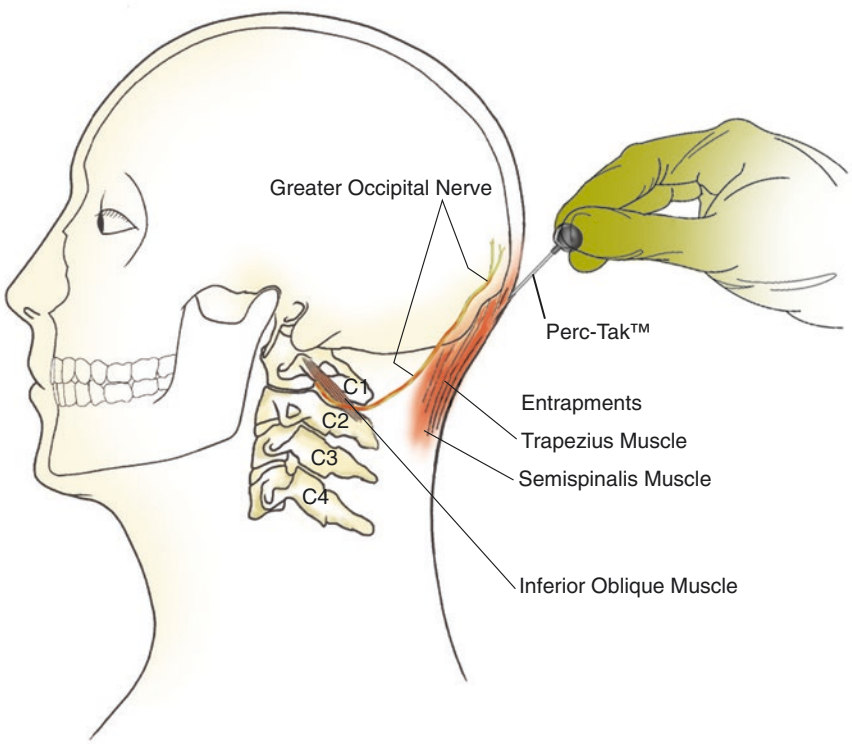


Fig. 20.98 A skin puncture is made to allow the Stealth™ needle to pass

nerves. Contrast should not be infiltrated into the muscles but should fill the suboccipital compartment. The injection port is on the inside of the curvature in the direction of the greater occipital nerve. The dye spread should flow laterally from the needle and will be within the suboccipital space or compartment. If the needle tip is directly below the occipital bone and above the arch of C1, intravenous injection is more likely to occur.

Post-procedure exercises for stretching and relaxing the inferior oblique muscle are an important component to the procedure. Starting from the neutral position and moving the chin and head backward, stretch the inferior oblique muscle, lessening the entrapment of the greater occipital nerve (Fig. 20.105). For enhanced efficacy, the exercises are performed in sets of ten repetitions and repeated 8–10 times a day.

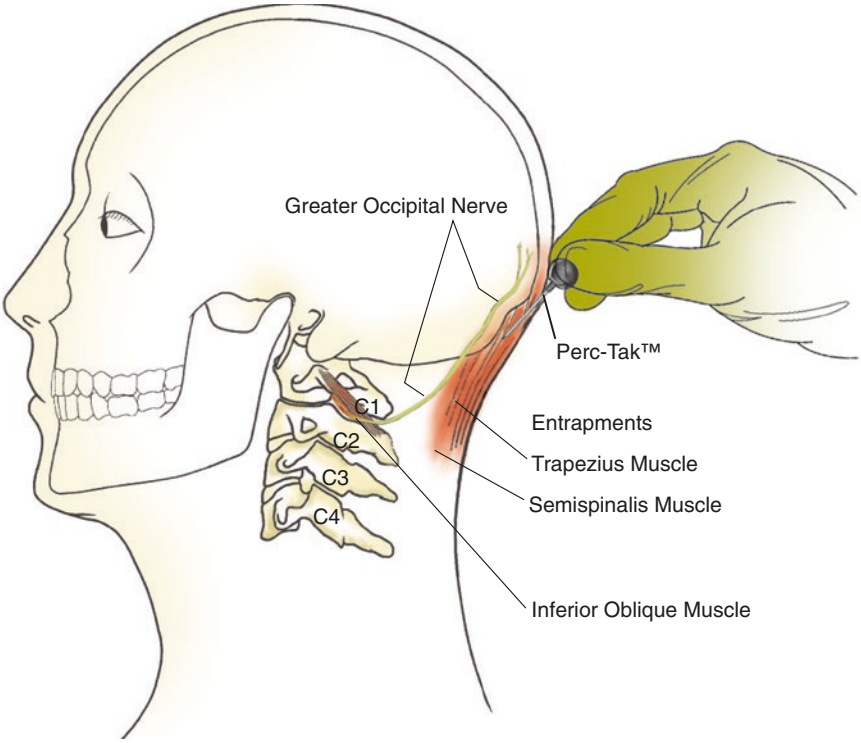


Fig. 20.99 A skin puncture is made to allow the Stealth™ needle to pass

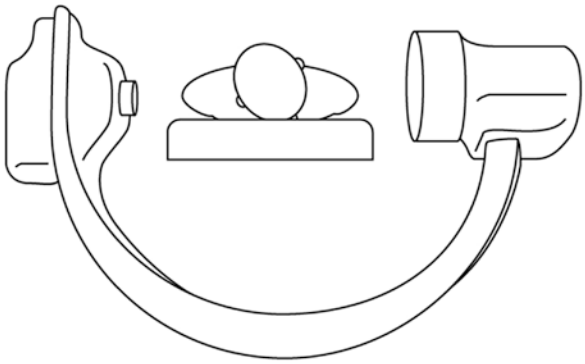


Fig. 20.100 The C-arm is rotated to the lateral position

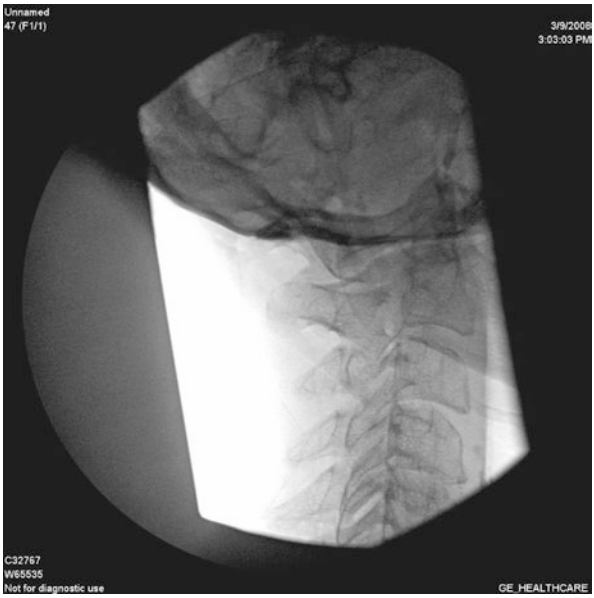


Fig. 20.101 The C-arm is rotated to the lateral position

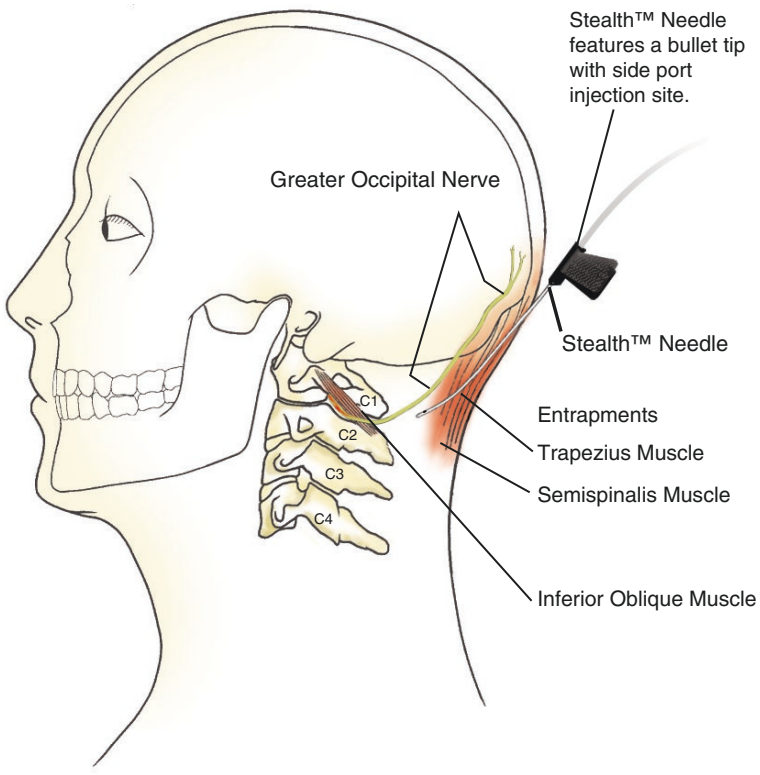


Fig. 20.102 The Stealth™ needle is placed into the suboccipital compartment

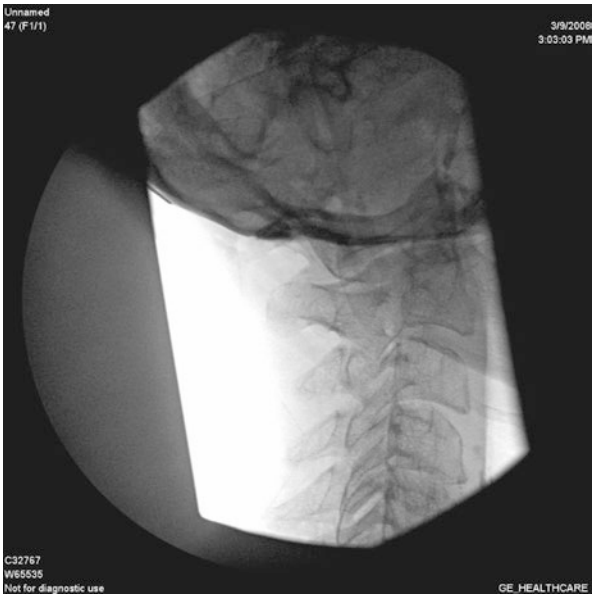


Fig. 20.103 The Stealth™ needle is introduced into the tract created by the skin puncture

This is one of the most successful headache procedures involving the occipital nerves [16].

Stellate Ganglion Injection

Stellate ganglion injections have been associated with seizure, respiratory arrest, quadriplegia, and death when performed at the transverse process of C6. A safer and better technique is described in this chapter where the needle tip placement, through a special needle. The needle need not be moved once the ventral lateral side C7 is reached, and the direction of the injection is toward the stellate ganglion from the ventral lateral part of the body of C7.

Multiple techniques are used for stellate ganglion injections; however, the least hazardous technique uses the ventral lateral side of the C7 vertebral body as the target in order to avoid the vertebral artery, nerve root, and pleura. The Bella-D® needle has a directional side port that allows for injection toward the lateral stellate ganglion located at the C7-T1 level (Fig. 20.106). The needle tip is sealed so injection of local anesthetic and steroid occurs through a side port proximal to the tip and anterior to the longus colli muscle. This needle is designed to be site specific for this procedure and increases the probability of injecting in the tissue plane containing the ganglion. The rationale of the historical technique of injecting at the base of the C6 transverse process at the Chassaignac tubercle is to prevent pneumothorax; however, there are numerous cases of seizures from vertebral artery injection, infarctions from injections of local anesthetic with particulate steroid, and respiratory and cardiac arrest from intraneural injection leading to deaths. The target is the ventrolateral C7 vertebral body, not Chassaignac's tubercle. Once bony contact is made,

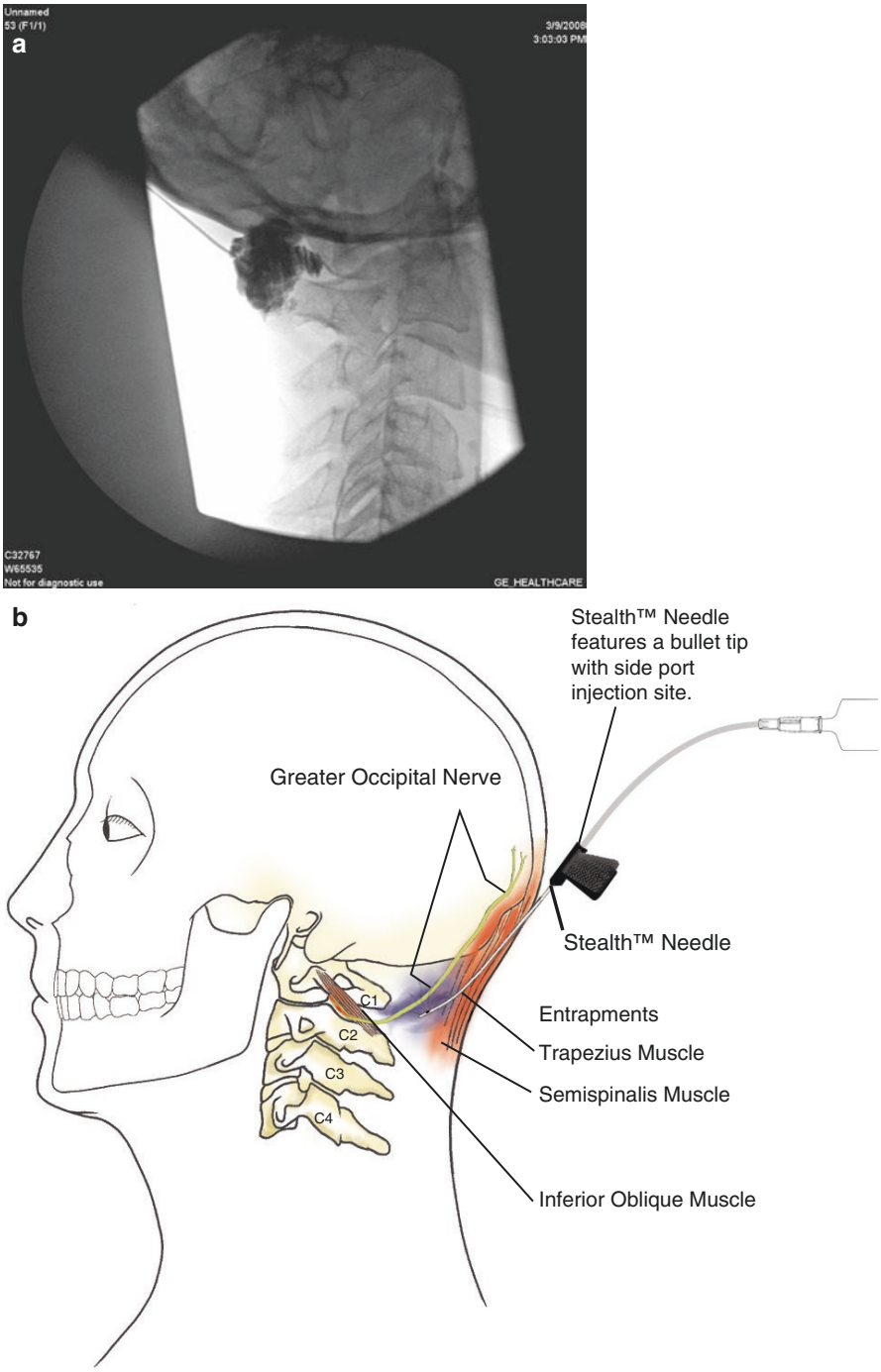


Fig. 20.104 (**a**) Contrast injection in the suboccipital compartment is performed to ensure that contrast does not track retrograde toward the spinal cord along the second cervical nerve root. (**b**) Contrast injection in the suboccipital compartment is performed to ensure that contrast does not track retrograde toward the spinal cord along the second cervical nerve root

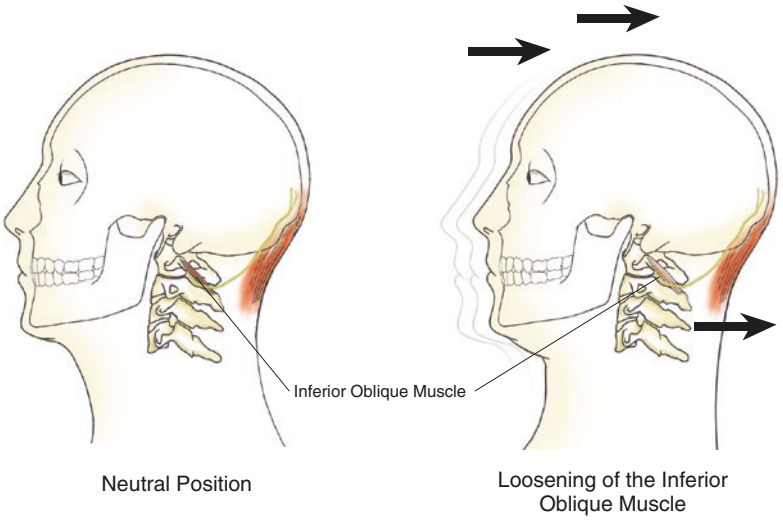


Fig. 20.105 Exercises are a critical part of the technique

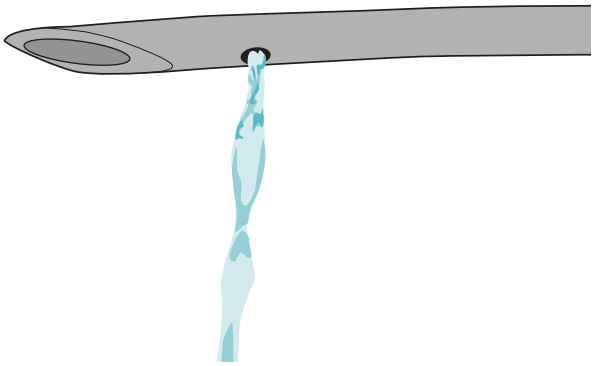


Fig. 20.106 Bella-D® needle with sealed tip and side port for directional injection

the needle should be stabilized. This avoids the complications related to moving with needle. The side port is proximal to the tip, so local anesthetic will be deposited in the tissue plane. Orientation of the side port to the lateral position will ensure that injected material is directed to the stellate ganglion. However, the use of the Bella-D® needle reduces the risk of intraneural and intra-arterial injections.

It is designed to direct injection toward the stellate ganglion. The needle tip is sharp and has side port in the direction of the wing. Figure 20.107 shows the anterior neck anatomy. The point of skin entry is one fingerbreadth inferior to the cricoid cartilage (Fig. 20.108). Gentle pressure is applied between the trachea and carotid artery. The carotid artery pulsation is felt with the finger, and the needle is aimed

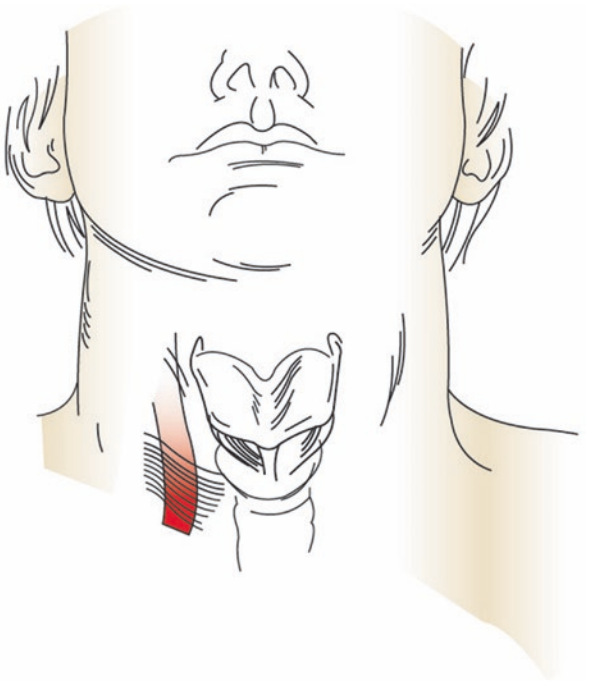


Fig. 20.107 Anatomy for stellate ganglion block showing trachea and carotid artery

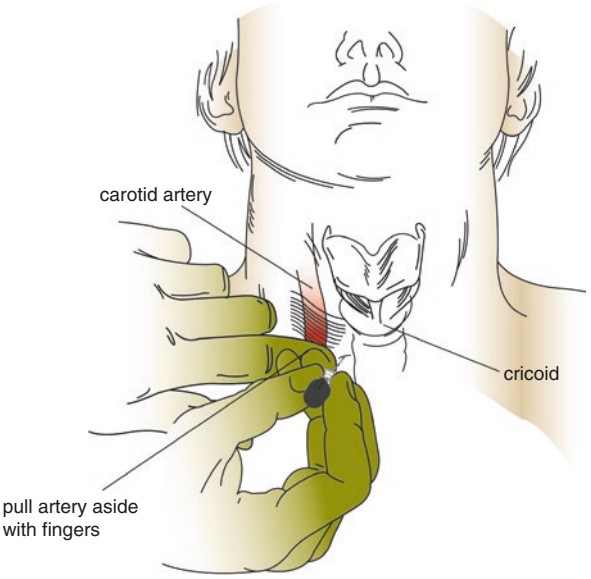


Fig. 20.108 The point of skin entry is one fingerbreadth inferior to the cricoid cartilage

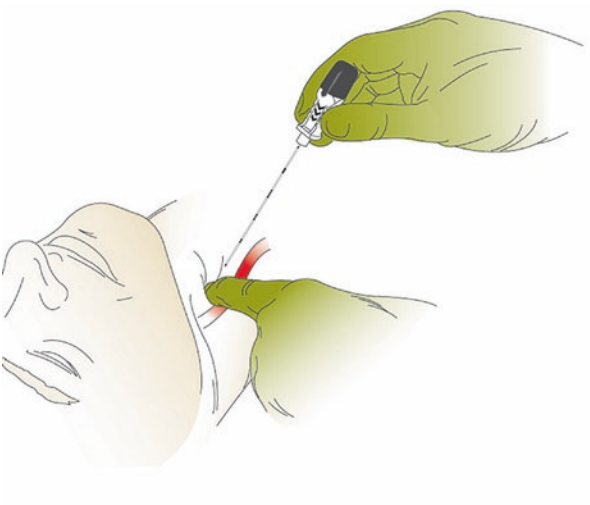


Fig. 20.109 Gentle pressure is applied between the trachea and carotid artery. The carotid artery pulsation is felt with the finger, and the needle is aimed slightly medially

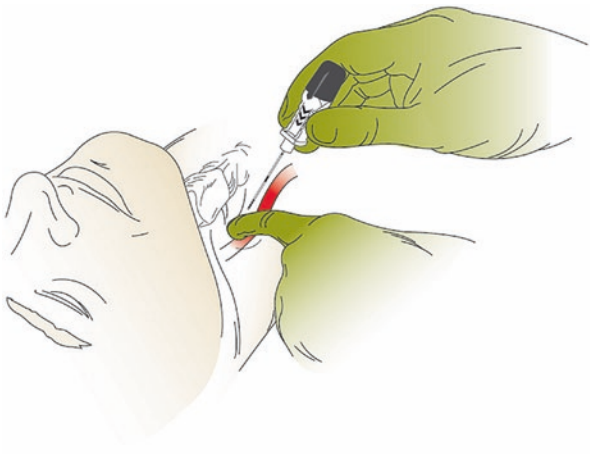


Fig. 20.110 The needle passes between the carotid sheath and the trachea

slightly medially (Fig. 20.109). The needle passes between the carotid sheath and the trachea (Fig. 20.110). The neck is maintained in a neutral position. The C-arm is in the anterior-posterior position (Fig. 20.111). The Bella-D® needle is advanced to make bony contact and is rotated to position the side port to face laterally toward the ganglion. The needle tip final position is ventrolateral body of C7 (Fig. 20.112). The injecting side port injects laterally to the stellate ganglion. The injection spread should be anterior to the lateral aspect of C7-T1 where the stellate ganglion is located. For pain in the radial or median distribution, the lateral injection position should be used to block the stellate ganglion. If pain is present in the ulnar distribution, the side port should be oriented 45° inferiorly from the straight lateral in order to spread local anesthetic inferiorly and block upper thoracic sympathetic nerves. Once the needle touches the bone (body of C7), ensure it is at the anterolateral C7 vertebral body. Following aspiration testing, contrast is injected (1 ml) and needle tip is held firmly against the bone. The injected fluid comes out through the side port

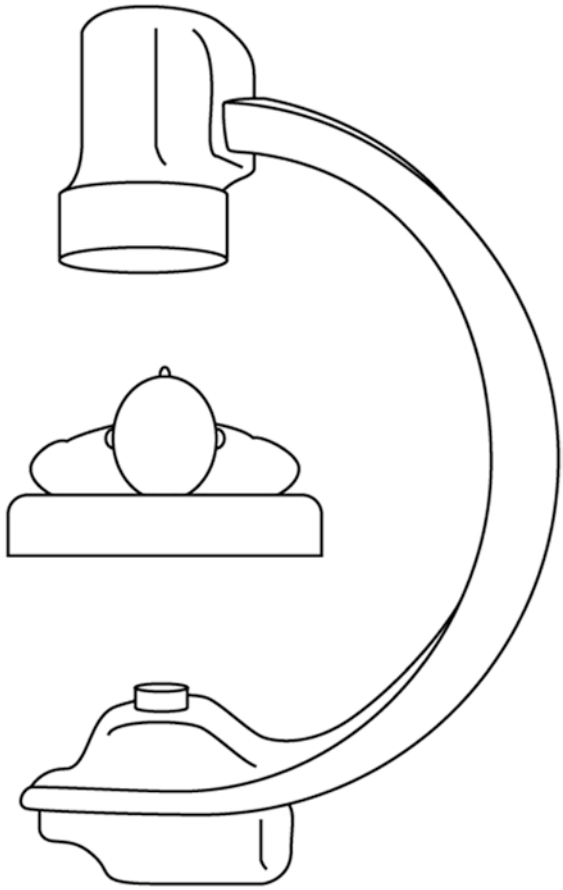


Fig. 20.111 The C-arm is in the anterior-posterior position

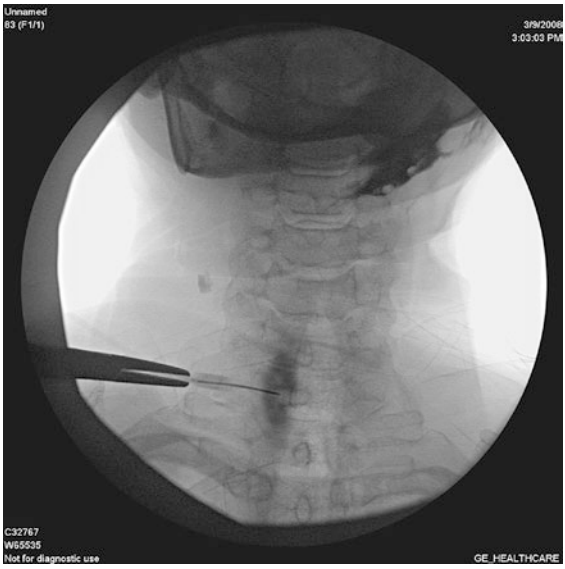


Fig. 20.112 The needle is secured with a large hemostat to allow the hand to increase distance from the fluoroscopy beam. Contrast injection is used to confirm placement

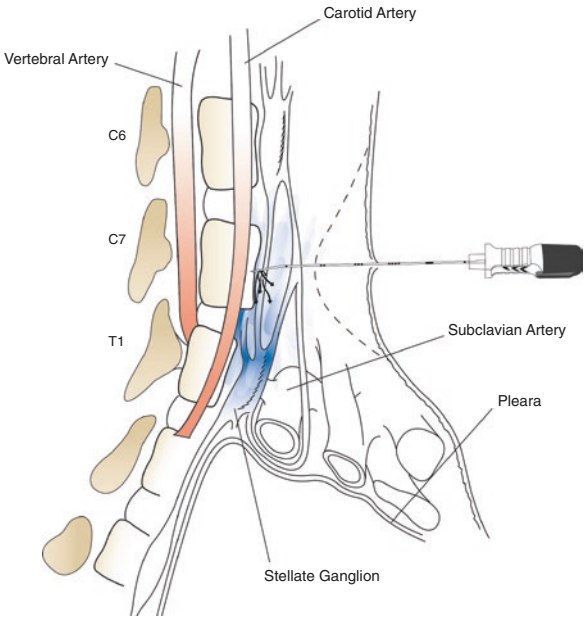


Fig. 20.113 Lateral schematic of stellate ganglion block showing Bella-D® needle and injected fluid in blue

of the needle in the direction of the wing, i.e., lateral, to the stellate ganglion (Fig. 20.113). The firm wing of the Bella-D® needle is held by a hemostat in a position that does not obstruct the fluoroscopy image.

Usual Injection: 1 ml Omnipaque™ 240

Local Anesthetics

- 4–5ml 0.2% ropivacaine
- 4–5ml 0.25% bupivacaine

Steroids

- 40 mg Depo-Medrol®
- 10 mg dexamethasone
- 40 mg triamcinolone

Discogram with the Day Needle and Introducer

There are a number of medical/legal cases from simple discograms. Figure 20.114 shows the relation of the L5 nerve root and L5 disk (Fig. 20.114). The discogram needle perforates the L5 nerve root, and the patient ends up with worse pain.

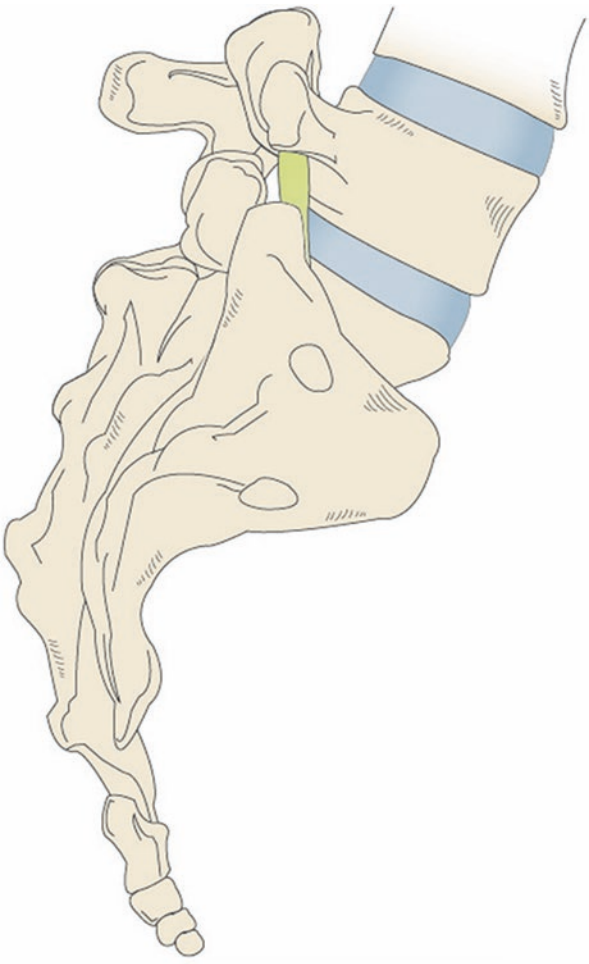


Fig. 20.114 Lumbar spine anatomy

This problem has led to the development of the steerable bullet-shaped curved tip or straight tip Day needle and introducer. The needle is steered in small movements under fluoroscopic guidance to the desired target. If the Day needle meets the nerve root, it will simply push it aside, yet it allows penetration of the annulus to reach the middle of the disk to carry out the discogram. This is a simple technique but a major step forward when one considers the paresthesias and cut fibers when sharp needles are used. When one looks at the tip of a sharp needle under a microscope, it is like a sharp knife. When nerves are cut, neuromas may form and lead to persistent pain and unfortunate long-term undesirable outcomes.

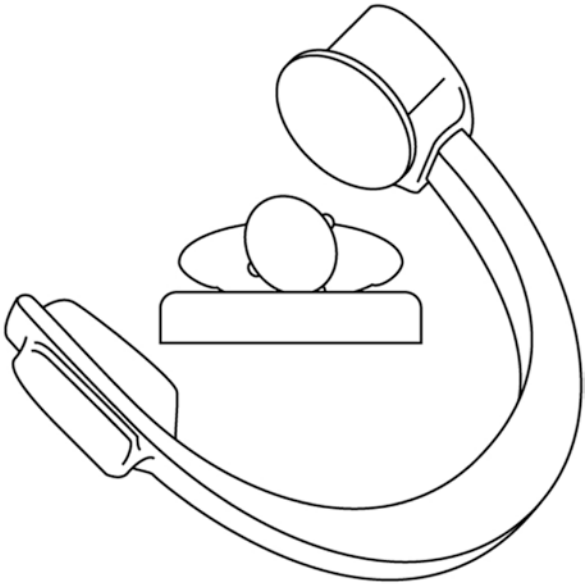


Fig. 20.115 The C-arm is rotated to the oblique position and also rotated in the cranial-caudad position

The Day needle is a bullet-tipped side ported needle. It is produced as a straight needle or with a curved tip. Fluoroscopic guidance is used to make a view by rotating the fluoroscope until the ipsilateral pedicle is superimposed over the mid-body of the vertebra. The fluoroscopy tilt is adjusted until the base of the superior pars is superimposed at the inferior margin of the target disk (Fig. 20.115). An introducer needle is advanced with a tunnel view to be close to the target (Fig. 20.116a, b).

The C-arm is rotated to the lateral position (Fig. 20.117). The Day needle is passed through the introducer slowly to avoid the L5 nerve root (Fig. 20.118a, b) The Day needle is navigated to enter the disk (Fig. 20.119a, b). The tip of the Day needle is steered using both anterior-posterior and lateral views. The target is the middle of the disk. The advantage of the Day needle is that it has no cutting edge that can permanently injure the nerve root by formation of neuromas. If a paresthesia occurs, the Day needle can be steered around the nerve root without permanent injury. The iliac bone must be avoided in order to place the needle. In the lateral view, the Day needle is advanced in to the mid-disk position. The C-arm is rotated to the anterior-posterior position to check the final position (Fig. 20.120). The final position is the mid-disk (Figs. 20.121 and 20.122). The non-cutting needle tip safely passes inferior to the nerve root. Small movements allow steering of the curved tip to the middle of the disk on anterior-posterior and lateral fluoroscopic images.

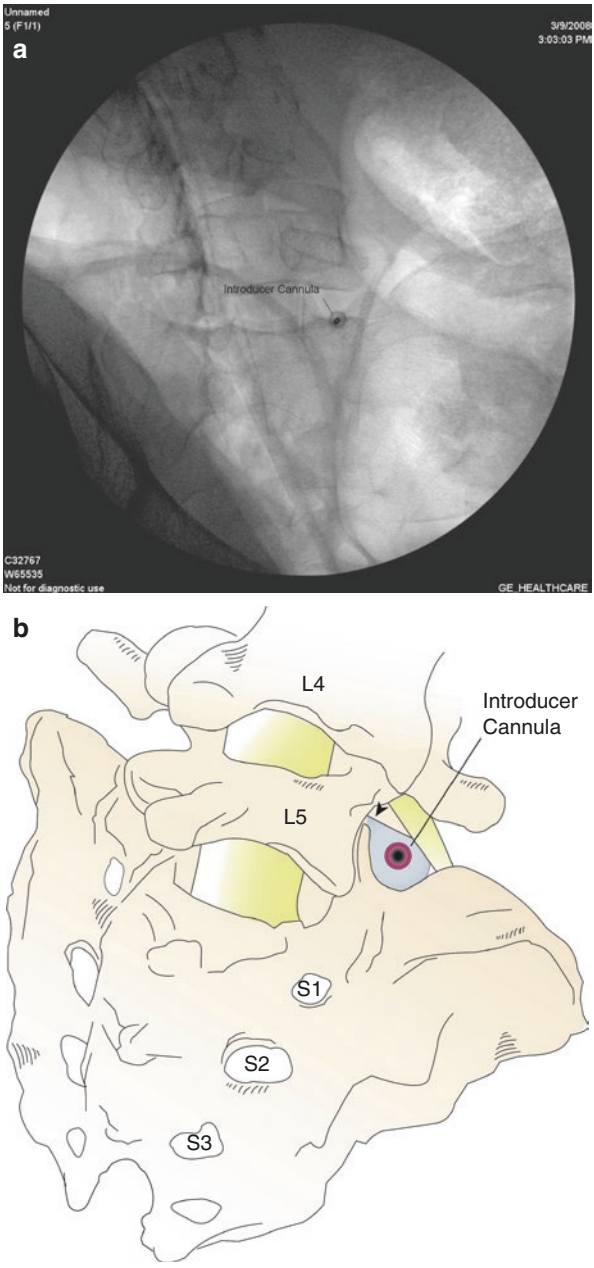


Fig. 20.116 (**a**) The introducer cannula is introduced from an oblique and superior point from the target disk, the L5-S1 disk in this case (**b**) The introducer cannula is introduced from an oblique and superior point from the target disk, the L5-S1 disk in this case

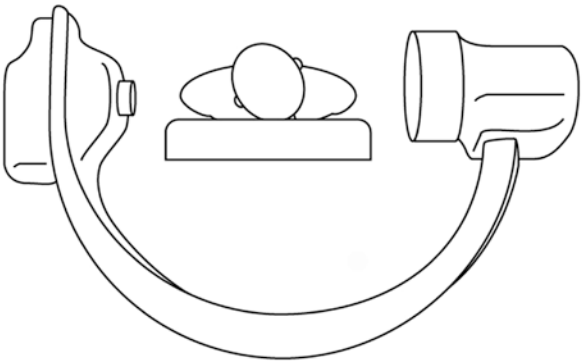


Fig. 20.117 The C-arm is rotated to the lateral position

Hypogastric Plexus Block

The superior hypogastric plexus block is used for treating pelvic pain of malignant and non-malignant origin. The superior hypogastric plexus is located in the retroperitoneal space at the level of the lower half of the fifth lumbar vertebrae and extending inferiorly to the upper part of the pre-sacral area. It is a mixed plexus with ascending and descending fibers. The plexus contains sympathetic and parasympathetic pre- and post-ganglionic as well as pain fibers. The plexus extends superiorly to the anterior left side of the aorta and communicates with the celiac ganglion. The pelvic division of the superior hypogastric plexus contains pre-sacral and lateral branches. Since a larger volume of injectate is used for a diagnostic block, compared to a neurolytic block, the local anesthetic will spread toward the near midline location of the superior hypogastric plexus over the L5-S1 junction. Venous runoff is common using the original lateral approach. In patients with advanced pelvic cancer pain, pain with palpation of the ischial tuberosity (Racz sign) is helpful in determining which side should be blocked [17]. The lateral approach of neurolytic blocks, because of concern of distant spread over to the ureters, has led to reduced volume use and shorter duration long-term pain relief. Following successful pain reduction from repeat local anesthetic blocks, a reduced volume of 4–5 ml 6% phenol in saline by the L5-S1 transdiscal approach has provided an increased duration of pain relief. Utilizing contrast injection of 3–4 ml and observing the lateral spread has increased safety by reducing the injected volume if lateral spread is observed. The main technical problem has been related to the narrow space between the L5 transverse process and the sacral ala. It is difficult to reach the lower end of the anterior border of the L5 vertebral body with straight sharp needles. A significant technical advance came from the use of the blunt-tipped Percutaneous Navigation Device (PND). It is placed through an introducer cannula posterior to the L5 nerve

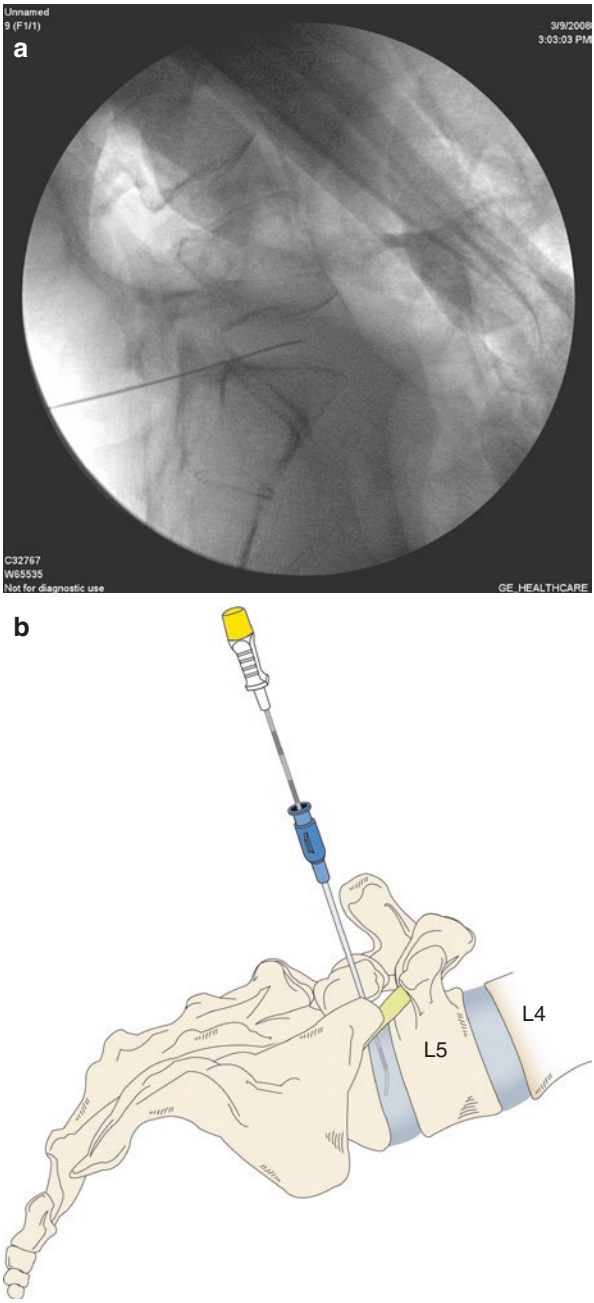


Fig. 20.118 (**a**) The Day needle is passed through the introducer slowly to avoid the L5 nerve root. (**b**) The Day needle is passed through the introducer slowly to avoid the L5 nerve root

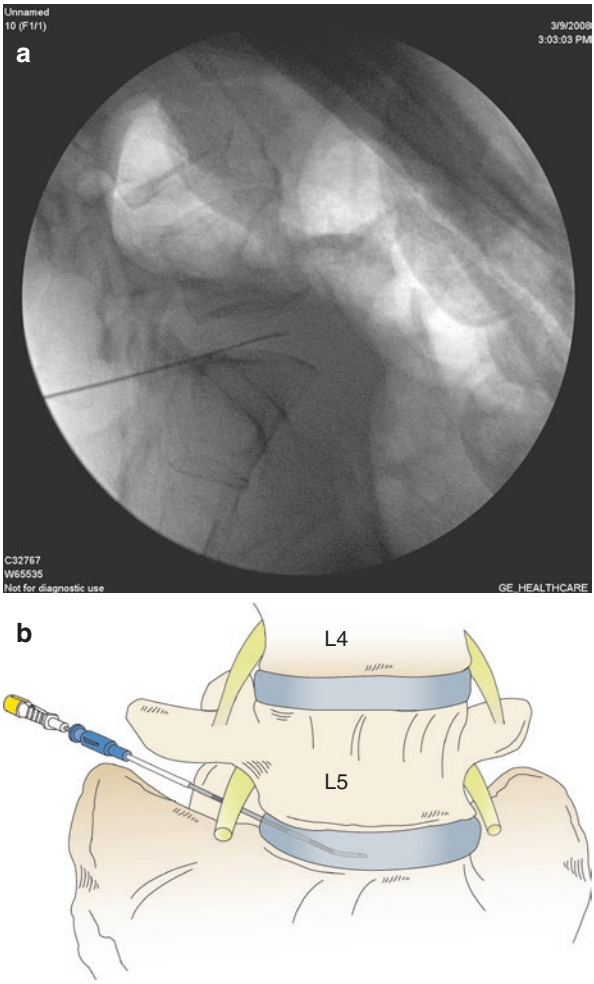


Fig. 20.119 (**a**) The Day needle is placed into the disk. (**b**) The Day needle is placed into the disk

root and lateral to the neural foramen. Prior to the use of the PND, it was extremely common for patients to complain about paresthesias secondary to L5 nerve root injury during and after the procedure. The PND can be steered to the target and avoid nerve injury and intravascular injection.

Technique: The patient is placed in the prone position. The C-arm is tilted cephalad to open up the space between the L5 transverse process and the sacral ala; next rotate the C-arm in an ipsilateral direction until the L5 vertebral body comes into view as a vertical line (Fig. 20.123).

The vertebral body on the medial side, the transverse process superiorly, and the sacral ala are the boundaries of the triangle. The posterior superior iliac spine should not enter this view. Local anesthetic infiltration is carried out as lateral and as inferior in this triangle as possible. The 16-gauge 2.5–3-inch introducer cannula (blunt access cannula (BAC)) should be directed to this triangle (Fig. 20.124).

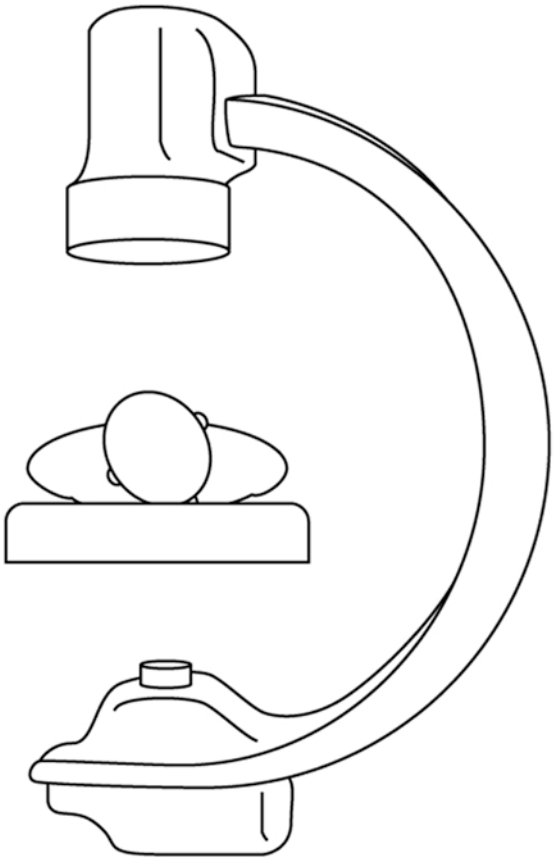


Fig. 20.120 The C-arm is rotated to the anterior-posterior position

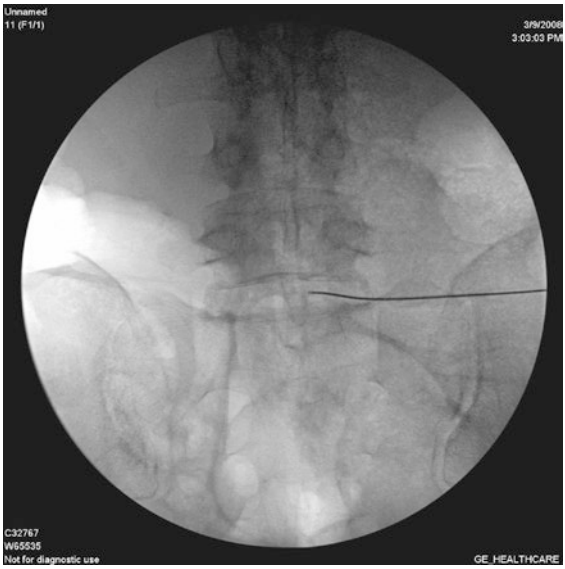


Fig. 20.121 The anterior-posterior fluoroscopic image shows the tip of the Day needle in the mid-disk position

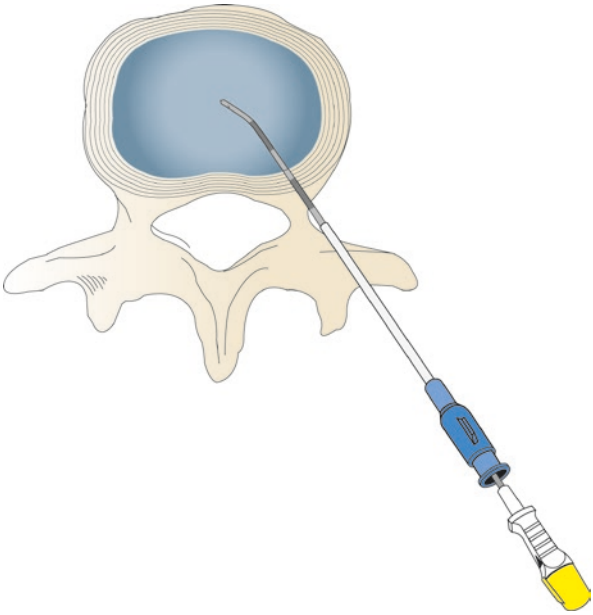


Fig. 20.122 Drawing of the final position with the tip of the Day needle in the mid-disk position

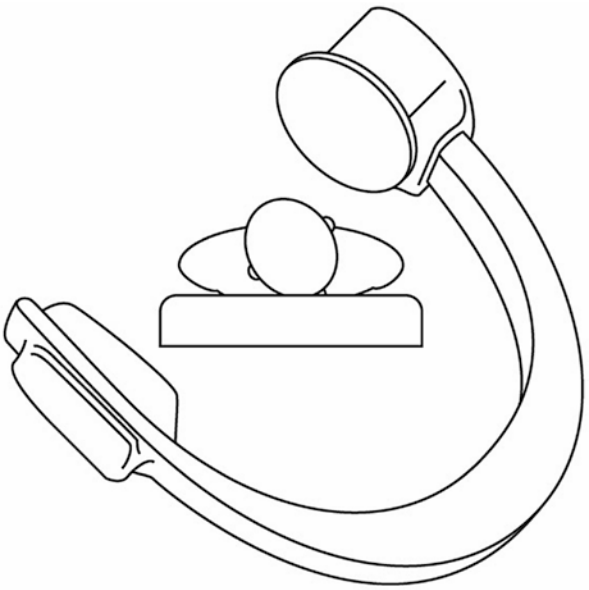


Fig. 20.123 The C-arm is positioned in an oblique and cephlad-caudad position to visualize the space inferior to the L5 transverse process and superior to the sacral ala

When the triangle is reached, the C-arm needs to be turned for a lateral view, and the introducer cannula should be advanced to be posterior to the L5 neural foramen. The needle is removed from the BAC, and the 15-cm PND is steered to the lower end anterior border of the L5 vertebral body (Figs. 20.125 and 20.126a, b). Bony contact must be perceived as the hypogastric plexus is in a tightly retroperitoneal space. Three to 4 cc of Omnipaque 240 is injected followed by 10 ml of 0.2%

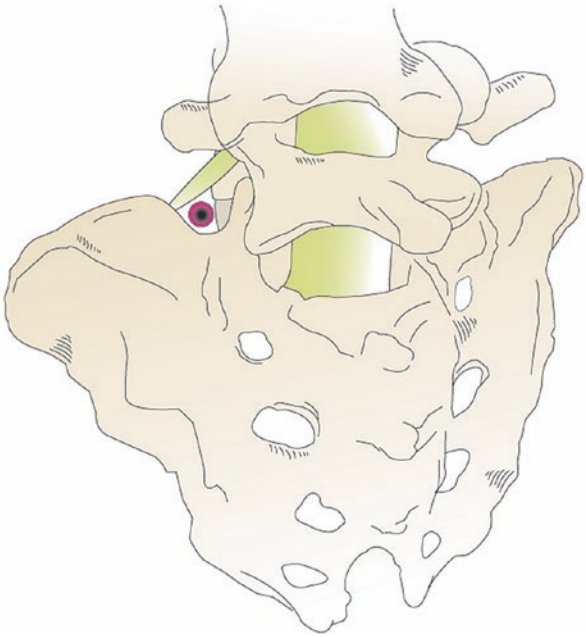


Fig. 20.124 Diagnostic hypogastric plexus blocks are performed using an introducer to guide the percutaneous navigational device past the L5 nerve root and lateral to the spine

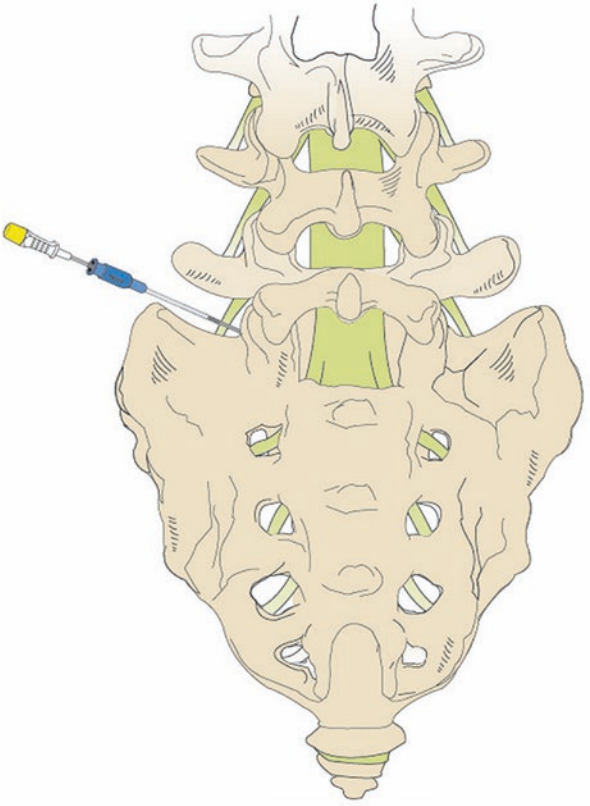


Fig. 20.125 The posterior lumbosacral anatomy with the introducer and percutaneous navigational device in position for hypogastric plexus block

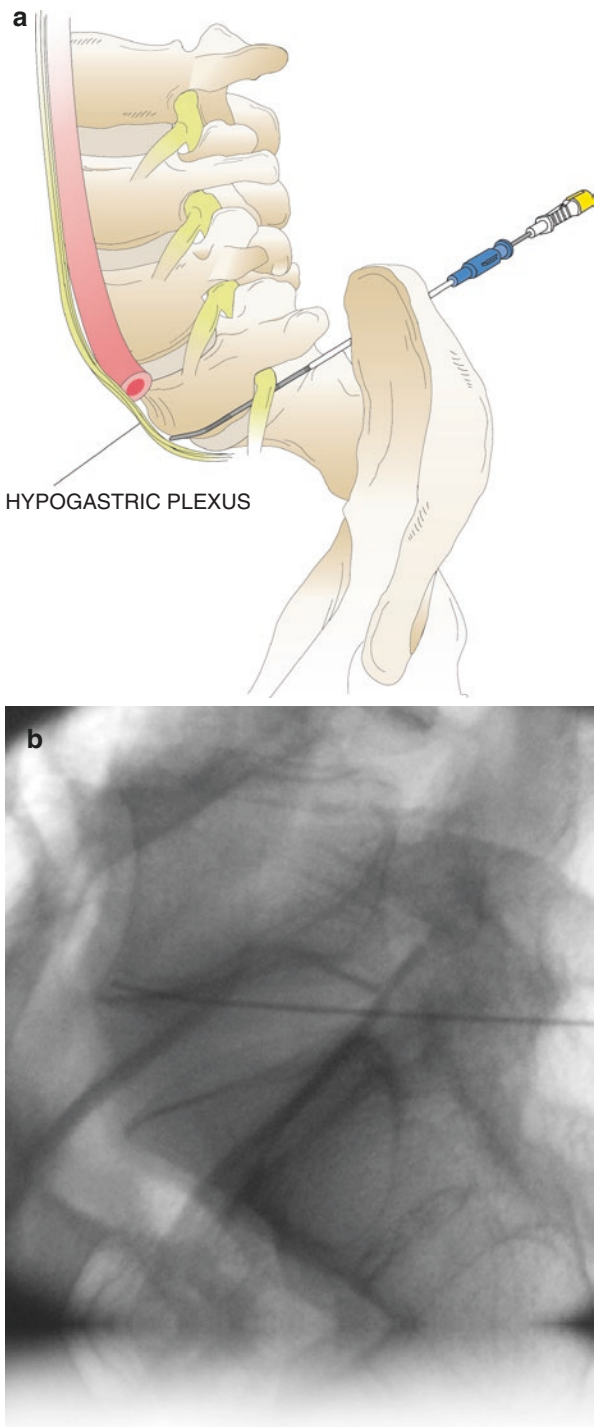


Fig. 20.126 (**a**) The percutaneous navigational device is used to avoid the L5 nerve root and curve around the body of the L5 vertebra. (**b**) The percutaneous navigational device is used to avoid the L5 nerve root and curve around the body of the L5 vertebra

ropivacaine or 0.25% bupivacaine. Using the above technique avoids perforation of the nerve root and intravascular injection making the procedure safer and quicker. With experience, one pass is adequate to reach the target, thus reducing radiation exposure and time requirements.

Equipment Required: 15-cm Day Needle and Introducer

The vertebral body on the medial side, the transverse process (superiorly), and the sacral ala (inferiorly) are the boundaries of the triangle. The posterior superior iliac spine should not be superimposed into the tunnel vision view for this approach. Local anesthetic infiltration is used as lateral and as superior in this triangle as possible for skin entry to allow the best angle to reach the target. The blunt access cannula (BAC) is made of a plastic introducer containing a sharp needle to allow easy placement of the BAC close enough to the target to allow the blunt percutaneous navigational device to be placed at the target. The 16-gauge 2.5–3-inch introducer cannula should be directed to this triangle, when the triangle is reached, the C-arm is turned for a lateral view, and the introducer cannula is advanced to be posterior to the L5 neural foramen. The needle is removed from the BAC, and the 15-cm percutaneous navigational device (PND) is steered to the inferior and anterior border of the L5 vertebral body. The PND, with its curved leading tip, can be positioned around the vertebral body, rather than being limited to a linear trajectory. Bony contact must be perceived during needle placement to avoid other structures as the hypogastric plexus is in a tightly occupied retroperitoneal space. Three to 4 cc of Omnipaque 240 is injected followed by 10 ml of 0.2% ropivacaine or 0 0.25% bupivacaine. This technique avoids perforation of the nerve root and intravascular injection, so the procedure is safer and easier to perform. With experience, a one-pass technique is possible, thus reducing radiation exposure and time requirements.

Neurolytic Hypogastric Plexus Block

In advanced pelvic cancer pain such as carcinoma of the cervix, rectal carcinoma, pre- and post-surgery, and post-radiation pain, the ischial tuberosity sign (Racz® sign) is helpful in determining which side to do the first diagnostic block. Because larger volume is used for the diagnostic block, the local anesthetic spread is able to reach the near midline location of the superior hypogastric plexus block over the L5-S1 junction when the lateral approach is used. The lateral approach of neurolytic blocks, because of concern of distant spread to the ureters, has led to reduced volume use and shorter duration long-term pain relief. Following successful pain reduction from repeat local anesthetic blocks, a reduced volume of 4–5 ml 6% phenol in saline by the transdiscal approach through the L5-S1 disk has given increased duration of pain relief. Utilizing contrast injection of 3–4 ml and observing the lateral spread has increased the safety by reducing the lateral spread.

The main technical problem has come from the narrow available space to reach the lower end of the lower and anterior border of the L5 vertebral body with the commonly used straight sharp needles. Significant technical advance came from the use of the blunt-tipped PND (percutaneous navigation device) placed through an introducer cannula verified to be posterior to the L5 nerve root and lateral to the neural foramen on lateral and anterior/posterior fluoroscopic visualization. Prior to the use of the PND, an extremely common patient complaint was paresthesia secondary to L5 nerve root injury during and after the procedure. The PND can be steered to the target and avoid nerve injury and intravascular injection. With the above technique and attention to detail, the procedure has a good record of safety but may need to be repeated. Potential complications include damage to the nerve root, intra-arterial injection leading to paralysis, bowel or bladder dysfunction, and distant spread and damage to ureters.

The dispersal spread of the dye will indicate any unusual spread or vascular runoff.

Equipment Required: Day Needle and Introducer

For the neurolytic hypogastric plexus block, a transdiscal approach is used. The patient is placed in the prone position. Fluoroscopy is used to identify the triangular space between the L5 transverse process (superiorly), the posterior superior iliac spine and the iliac crest (laterally), the sacral ala (inferiorly), and the facet joint complex (medially). After marking the inferior lateral portion of this triangular space, local anesthetic is infiltrated, and a 16-g 2.5″ intravenous cannula is passed in the direction of the lateral inferior L5 vertebral body. The skin entry is made using a point as lateral as possible on the fluoroscopic image within this rather small triangular space. The initial fluoroscopic visualization is similar to the technique for the local anesthetic hypogastric plexus block except that the point of skin entry is closer to the base of the inferior pars (Fig. 20.127a, b). As an oblique view of the fluoroscopic image is obtained, the iliac bone must not block the approach toward the lower end of the L5 vertebral body. The target is to reach the level of the transverse process along with the sacral ala and not to enter the L5 nerve root area. The L5 nerve root travels in a variable path from the foramen. If a paresthesia is caused by the passing of a sharp needle, a long-lasting L5 neuropathic pain may result. Therefore, the technique has been completely modified to avoid all sharp needle approaches to the hypogastric plexus. Instead, the needle of choice is a 15-cm or 6-inch long blunt Coudé needle. The next step is to remove the metal needle from

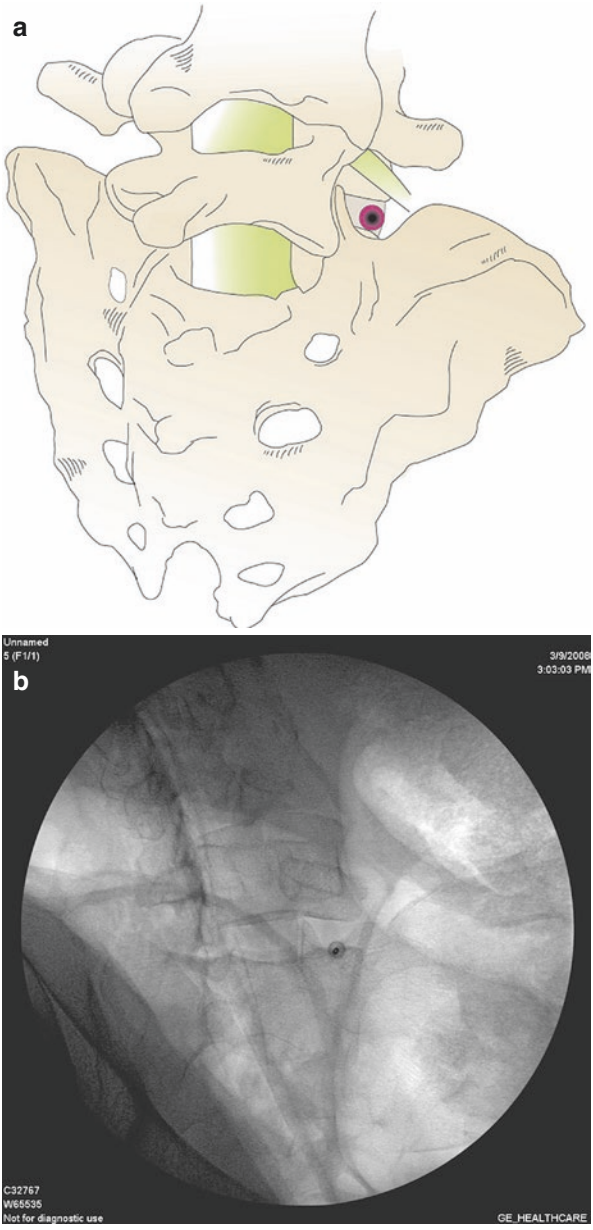


Fig. 20.127 (**a**) The neurolytic hypogastric block is transdiscal, and the introducer is used to guide the percutaneous navigational device past the L5 nerve root and into and through the disk. (**b**) The neurolytic hypogastric block is transdiscal, and the introducer is used to guide the percutaneous navigational device past the L5 nerve root and into and through the disk

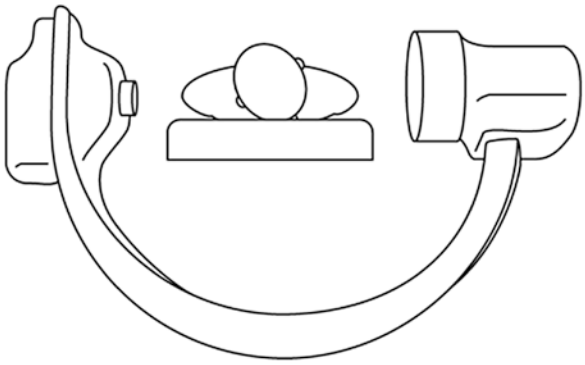


Fig. 20.128 The C-arm is rotated to the lateral view

the cannula and pass the curved blunt needle in the direction of the lower one-fourth of the L5 vertebral body. The C-arm is rotated to the lateral view (Fig. 20.128). The next step of the procedure is done using a lateral fluoroscopic view while steering the tip of the needle to avoid injuring the L5 nerve root and avoid entering veins and passing the needle to the lateral inferior L5 vertebral body end plate or lower one-fourth. The needle utilized to enter the L5-S1 disk is the 20-gauge 15-cm bullet-tipped Day needle (Fig. 20.129a, b). The needle is passed through the disk, steering it to the target site on the symptomatic side near the anterior mid-position of the disk (Fig. 20.130). When the needle perforates the anterior annulus of the disk, there is a loss of resistance. The C-arm is rotated to the anterior-posterior position (Fig. 20.131). The anterior-posterior image shows final placement (Fig. 20.132). The final position is shown in Figs. 20.133 and 20.134. Injection of 4–5 ml of contrast (Omnipaque 240) should indicate contrast spread on the surface of the iliopsoas muscle and spread toward the midline of the L5 vertebral body. Omnipaque 240 is followed by 4–5 ml of 6% phenol. The dispersal spread of the contrast will indicate any unusual spread or vascular runoff. A series of local and neurolytic hypogastric blocks reports that the best outcomes are from the transdiscal approach and the neurolytic block may provide 9 months of pain relief. Our technique is modified for neurolytic hypogastric plexus injections. The approach targets the L5-S1 disk, rather than the lower end of the L5 vertebral body. The introducer cannula is similarly aimed at the base of the superior pars of the S1 sacral area, and the needle again is either the 15-cm blunt Coudé or the 15-cm Day needle, which has a bullet tip to allow for easier penetration of the disk. The needle is advanced slowly through the disk on the lateral view, and frequent A/P lateral visualization is carried out until the needle is steered by rotating it left and right to exit the anterior portion of the L5-S1 disk in the midline position. The density of the annulus fibrosus is easily recognised once it has been reached, loss of resistance is used and it is pushed through the annulus to the pre-vertebral space where the hypogastric plexus is located. At this point, we inject 1–2 ml of Omnipaque 240 to rule out intraneural or intravascular spread of contrast. Following evaluation, inject 4–5 ml's of 6% phenol in saline in 1/2 ml increments in the direction of the painful side by needle rotation.

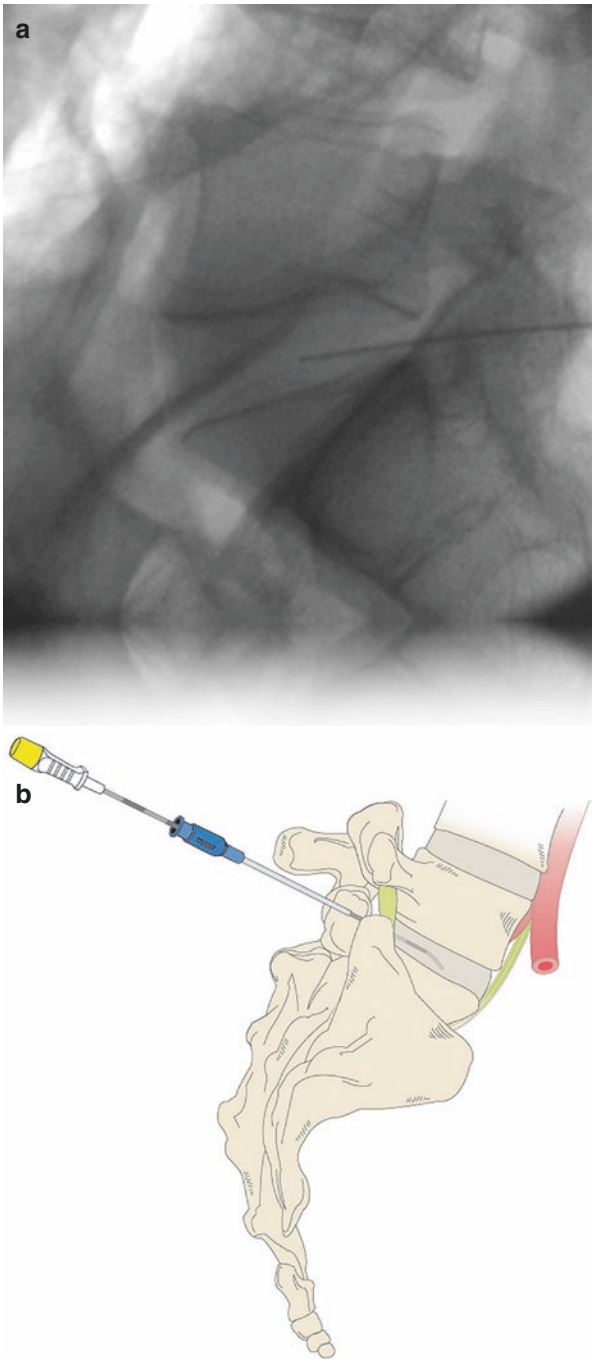


Fig. 20.129 (**a**) The percutaneous navigational device is advanced slowly past the L5 neural foramen and into the disk using lateral fluoroscopic imaging. (**b**) The percutaneous navigational device is advanced slowly past the L5 neural foramen and into the disk for the transdiscal neurolytic hypogastric plexus block

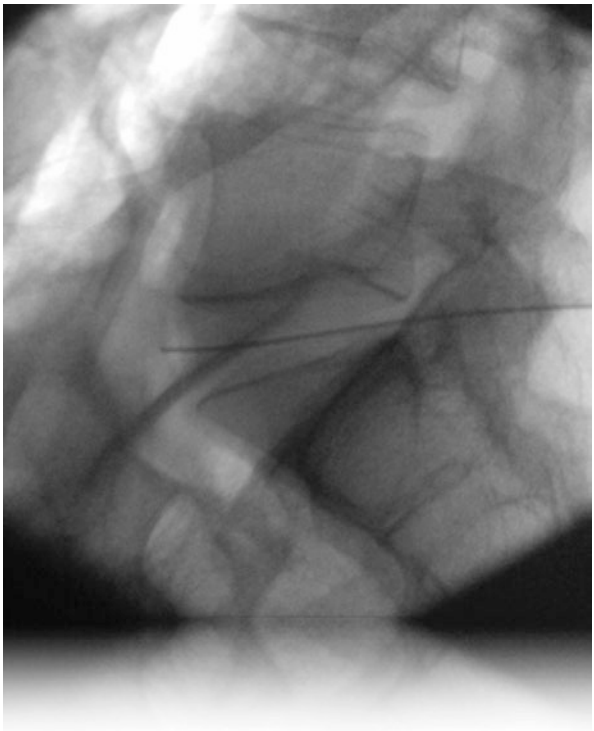


Fig. 20.130 The percutaneous navigational device is positioned anterior to the disk for the neurolytic hypogastric plexus block

The most common indications for hypogastric plexus have been pain secondary to cancer of the cervix and abdominal perineal resection. Post-radiation pelvic pain may respond. Non-malignant conditions have been successfully treated including groin pain, dyspareunia, rectal pain, scrotal pain, bladder pain, perineal pain, ischial tuberosity pain, coccydynia, vaginal pain, prostate pain, and buttock pain. Contraindications are few but severe infection in the vicinity and bleeding and dysesthesias, or patients on anti-coagulants would be relative contraindications. It is remarkable how simple, pain-free, and problem-free this technique has been, so long as the curved blunt needle is utilized. Intravenous injections have been reduced dramatically with this technique. Aspiration should always be performed prior to injections. If paresthesia is encountered, the needle is rotated to avoid the L5 nerve root. This does not lead to permanent L5 radiculopathy as a rule; at least we have not seen radiculopathy as a complication of the procedure. The injection of contrast helps to verify that the tip of the needle is not in a vein, and the injection needs to be performed under continued fluoroscopic visualization, to verify that the contrast and neurolytic substance are not spreading into the venous system. Local anesthetic is used for diagnostic blocks, and the transdiscal approach is avoided. The transdiscal approach is reserved for neurolytic blocks. Thus far, we have not experienced a single serious complication from the above-described technique. Bilateral neurolytic blocks should not be performed on the same day due to possible bladder,

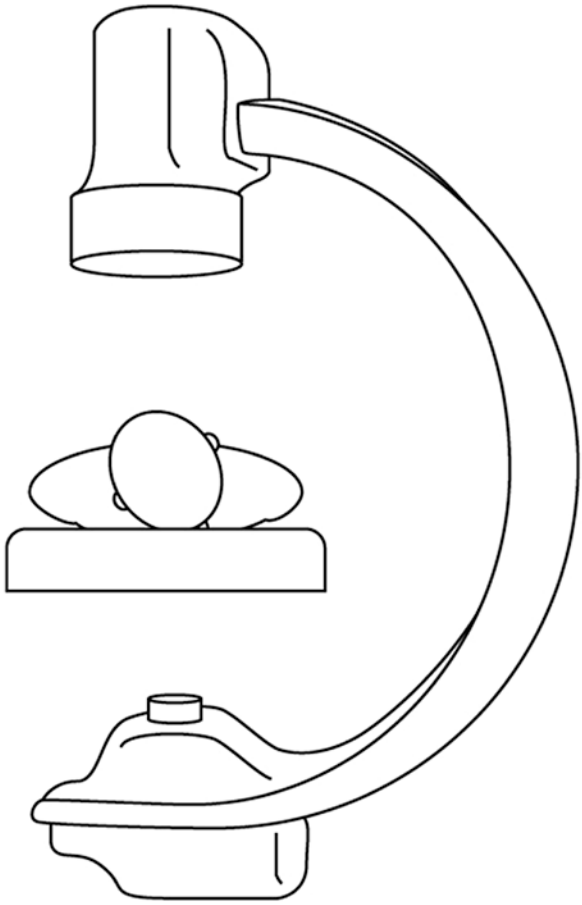


Fig. 20.131 The C-arm is rotated to the anterior-posterior position

bowel, or sexual dysfunction. In the early learning phase, we used the originally described technique by Plancarte, which is 7 cm lateral from the L4–5 interspace, aiming 45° inferiorly and 45° medially. With sharp, straight needles, more intravascular related injection-type problems occurred. We have abandoned this approach in favor of the two techniques that have just been described.

Celiac Plexus Block

Anatomy – The celiac plexus is the autonomic nerve ganglion to the abdominal organs (liver, pancreas, spleen, gall bladder, stomach, kidneys, small bowel, and two-thirds of the large bowels). The celiac ganglia are located anterior to the aorta at L1 surrounding the celiac artery behind the vena cava and anterior to the pancreas.

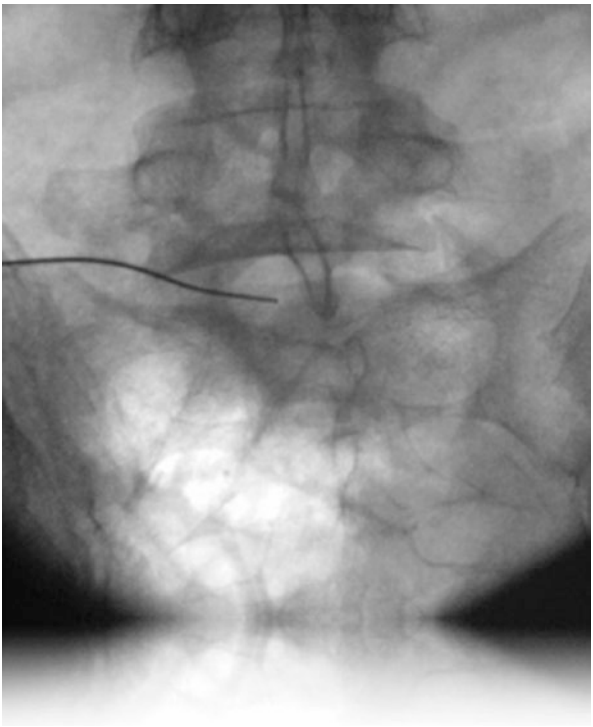


Fig. 20.132 The anterior-posterior image for hypogastric plexus block

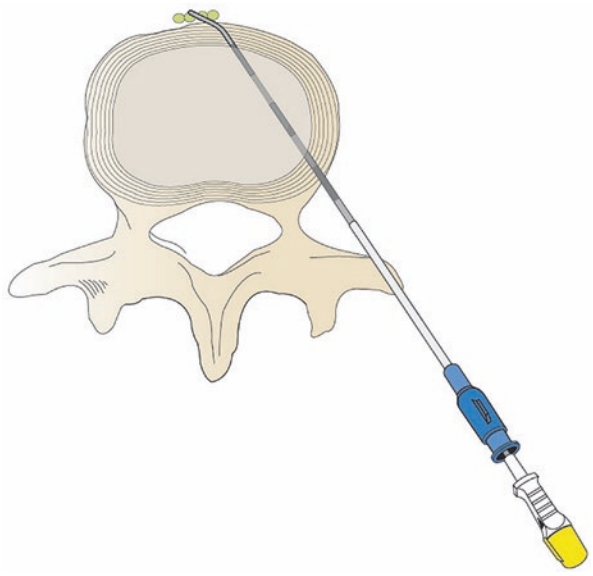


Fig. 20.133 The percutaneous navigational device is positioned through and anterior to the disk for the neurolytic hypogastric plexus block

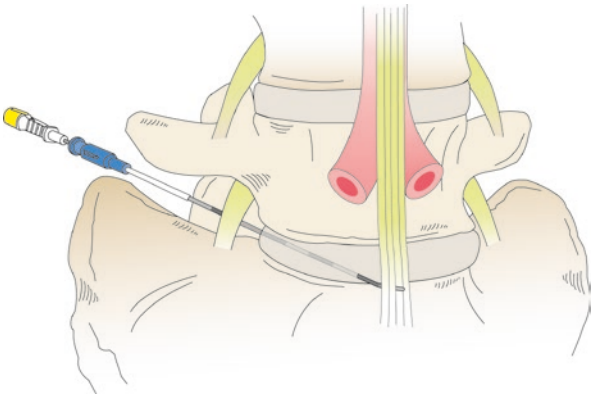


Fig. 20.134 The percutaneous navigational device is positioned anterior to the disk for the neurolytic hypogastric plexus block

The parasympathetic nerves originate from the left and right vagal trunks. The sympathetic nerves arise from thoracic spinal levels. The greater splanchnic is from T5-T6 to T9-T10, the lesser splanchnic is from T10 to T11, and the least splanchnic is from T11 to T12.

- Indications: Pain originating from intra-abdominal organs
- Chronic pain, chronic pancreatitis – use only local anesthetics
- Cancer pain of abdominal organs

- Contraindications: Patients on anti-coagulants that can cause a bleeding hazard
- Acute or chronic infection, unstable or large aortic aneurism

- Equipment used: 2.5–3-inch 16-gauge IV cannulas
- 20-gauge 6–8-inch blunt Coudé PND needle
- 3-ml syringe with 25-ga 1.5-inch needle
- 22-ga 1.5-inch needle
- 20 ml 0.2% ropivacaine
- Two 10-ml syringes; for neurolytic, add two 20-ml syringes

Patient may develop significant hypotension because of the sympathetic block; therefore, there is a need for hydration.

Dehydrated patients may need to be hydrated prior to the procedure to avoid hypotension after the block.

Complications:

- Hypotension
- Diarrhea

The risk of complications is reduced by the use of the blunt-tipped PND and short distance introducer. These include bleeding from arteries and the aorta, intravascular or intra-nerve injection, and perforation of organs with abscess formation.

Paraplegia from injection into spinal arteries may be avoided using this technique. Other complications include lumbar nerve root damage and retrograde spread and sexual dysfunction, especially ejaculation from sympathetic nerve block.

Technique

The procedure is done under fluoroscopy with the patient in the prone position using minimal sedation. Intravenous lines are started for hydration and intravenous access. Bony landmarks are used to plan the skin entry location (Fig. 20.135). Tips of L1 and L2 spinous processes are identified and marked. The tip of the 12th rib is identified and marked just medial and below to it. These marks are interconnected to form a large triangle. Fluoroscopy is used to confirm the locations. The entry point is infiltrated with local anesthetic, and the 16-gauge introducer cannula is passed along the marked line toward the mid-lateral body of L1 (Fig. 20.136). The introducer needle is inserted along the outline of the marks and is not advanced anterior to the neural foramina. The introducer cannula is passed along the line between the tip of T12 and L1. Once the introducer is through the posterior abdominal wall, before you reach the L1 nerve root, the introducer stylet is removed. The curved blunt needle is inserted into the introducer cannula and is steered passed the foramina area (Fig. 20.137). The needle is then advanced to the point just anterior to the L1 vertebral body. The 15-cm (6-inch) percutaneous navigational device (PND or blunt Coudé needle) is steered in front but lateral to the aorta (Fig. 20.138a, b). The PND is passed directing the tip to the desired target (celiac plexus) which lies anterior to the aorta. Figure 20.139 shows

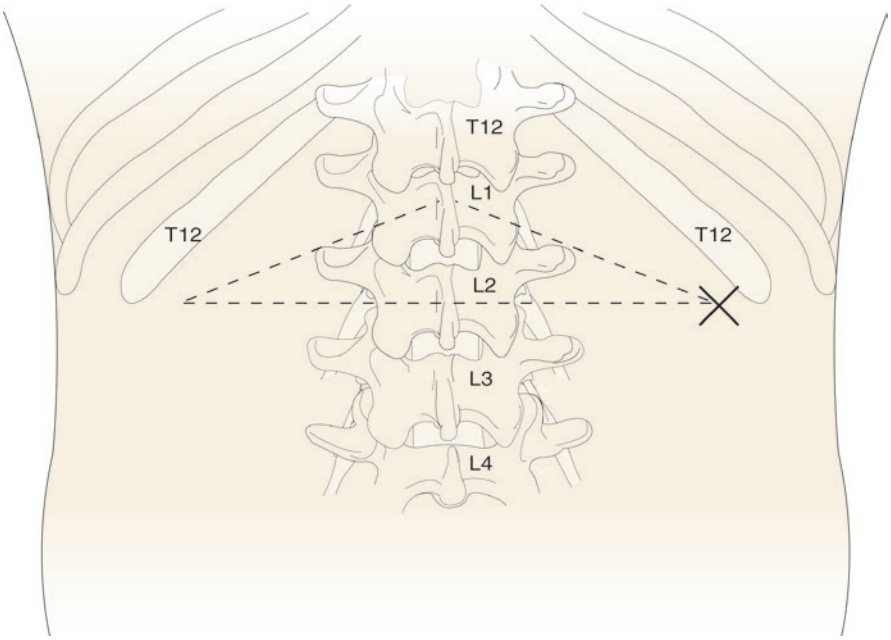


Fig. 20.135 Landmarks for celiac plexus block. X marks the skin entry point for the right side

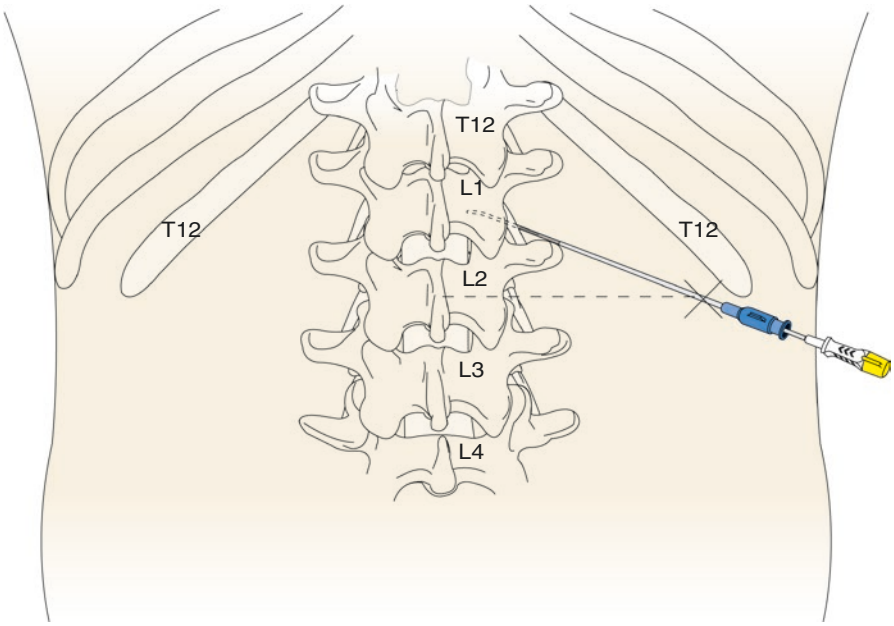


Fig. 20.136 The introducer is placed and directed in a medial and superior direction toward the anterior-lateral aspect of the L1 vertebral body

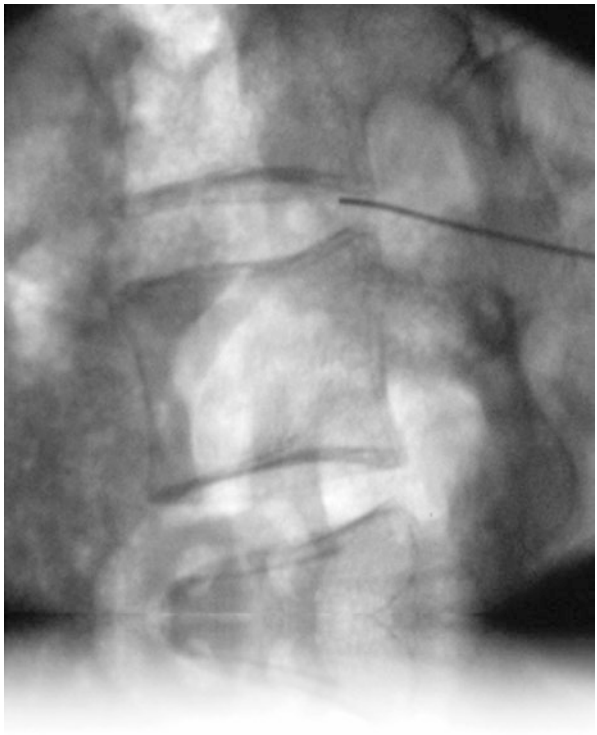


Fig. 20.137 The lateral view is used to slowly advance the curved blunt needle past the foraminal zone

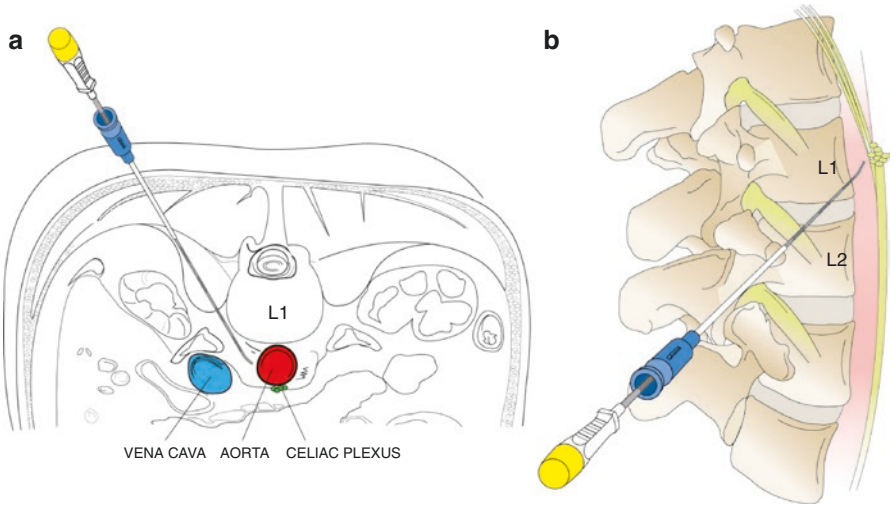


Fig. 20.138 (**a**) The curved blunt needle is advanced to the lateral aortic area. (**b**) The curved blunt needle is advanced to the lateral aortic area

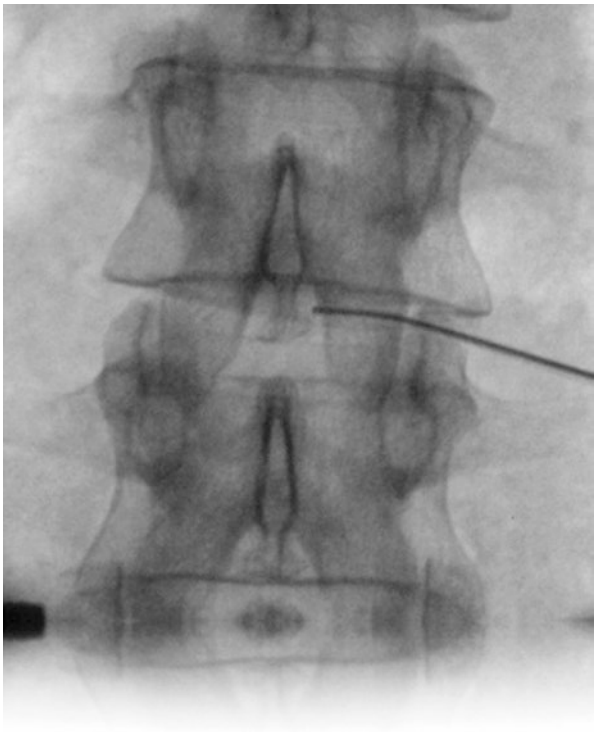


Fig. 20.139 The C-arm is rotated to the anterior-posterior position to confirm placement

the anterior-posterior image of the needle in final position (Fig. 20.139). The blunt tip of the PND reduces the chance for nerve root injury and bleeding from the aorta or abdominal organs. When the tip of the curved blunt needle touches the aorta, pulsation maybe felt and the needle is steered around to the anterior border of the aorta where the celiac ganglion is located. Contrast is injected and dye spread will be visible in this area including across to the celiac plexus on the surface of the aorta. The procedure is repeated similarly bilaterally. A/P and lateral fluoroscopic visualization is used to verify PND tip position followed by injection of 4–5 ml of contrast to verify placement. For local anesthetic block, 10 ml of 0.2% ropivacaine or 10 ml of 1% lidocaine is used. For neurolytic block, 5 ml of 6% phenol in saline plus 5 ml of 0.2% ropivacaine is used. For neurolytic block, the classic Seattle approach is 50% final concentration of alcohol in saline, 25 cc total on each side. The procedure has been done many times without any fluoroscopic guidance; however, fluoroscopic guidance is used now with AP, oblique, and lateral views. Local anesthetic diagnostic blocks may be repeated two to three times before attempting neurolytic block. Oftentimes, patients will respond to a series of local anesthetic blocks, and the risks of a neurolytic block may be avoided. The area experiencing acute pain may be injected at the time of surgery for postoperative pain relief.

Splanchnic Diagnostic Block and Radiofrequency Thermocoagulation

These procedures are intra-thoracic and should not be done bilaterally due to the risk of pneumothorax. This is especially important if the patient travels a distance post-procedure. Pneumothorax is always possible, and every effort must be made to prevent it. Since the development of the technique, we have had only one pneumothorax that needed to be treated with chest tubes. That was a case where sharp needle was used! Our routine practice has been to use an introducer needle through the posterior chest wall and only blunt Coudé needles inside the thoracic cavity. The blunt Coudé needles were developed by Gabor Racz, MD, and Philip Finch, MD (RF needle), and are produced by Epimed International.

The splanchnic nerves follow a posterior superior direction from the celiac ganglion where the course of the three nerves crosses the superior, anterior one-third of T12 and the middle one third of the T11 inferior endplate. There are two targets for splanchnic nerve block, one at the upper anterior 1/3 of the T12 vertebral body and the second at the inferior and middle 1/3 of T11. The nerve roots exiting the foramen are the common obstacle encountered while attempting to reach the targets.

For the procedure, the patient is in the prone position. The kyphosis and lordosis of the spine may require cephalad or caudad tilt of the C-arm to open the view of the interspace between the T11 and T12 ribs. C-arm is locked and rotated obliquely

toward the target side until the vertebral body comes into view. That usually occurs when the spinous process appears to reach the opposite side. The fluoroscopic view reveals a small access passageway above the T12 rib, lateral to the vertebral body. Local anesthetic infiltration is used for anesthesia. An introducer cannula is used, and in a tunnel view approach, the needle is advanced toward the superior aspect of the T12 vertebral body. The introducer is placed just superior to the rib below to avoid the intercostal nerve and vessels. A paresthesia is avoided by advancing the introducer cannula slowly. The metal needle stylet is removed, and the curved blunt 10- or 15-cm length, 20-g needle is popped through the remaining fascia and on lateral view (Fig. 20.140). The tip of the needle is navigated following bony contact with the lateral vertebral body steering the tip of the needle away from the bone. The needle can be advance to the superior anterior one-third of T12 vertebral body on the lateral view for the injection of contrast followed by local anesthetic (Fig. 20.141). The advancement of the needle is done by contact of the vertebral body and navigating or steering the needle tip to the anterior superior one-third. The active tip for the splanchnic RF needle is 15 mm. A double-lesion technique is used by rotating the curved blunt RF needle 180° after the first lesion and repeat lesioning at 80 degrees Celsius for 90 seconds, which will create a larger "Butterfly" lesion (Figs. 20.142 and 20.143). For the second level of the splanchnic nerve block at T11, the lateral rotation of the fluoroscope is maintained with the patient in the prone position. Local anesthetic infiltration is used for introduction of the cannula. The needle is advanced superior to the T11 rib making sure no paresthesia is obtained. The metal needle is removed, and the 10–15-cm-long blunt Coudé needle is popped through the fascia and navigated to the inferior middle one-third of the T11 vertebral body (Fig. 20.144). Proximity to the splanchnic nerves is verified by bony contact of the

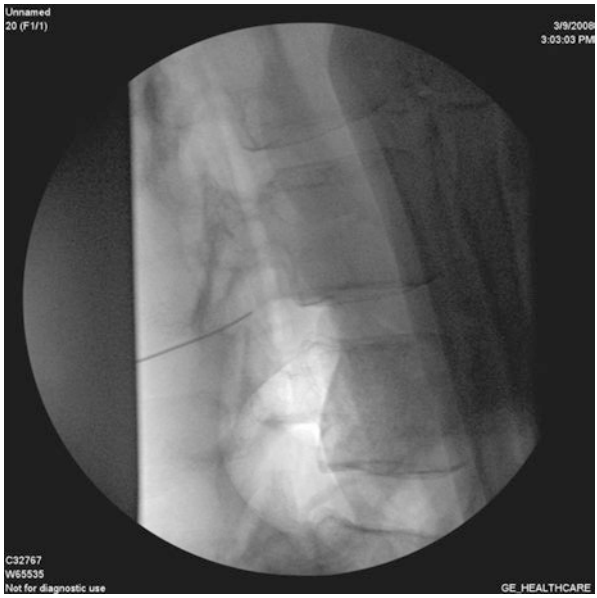


Fig. 20.140 The curved blunt needle is advanced slowly past the neural foramina area

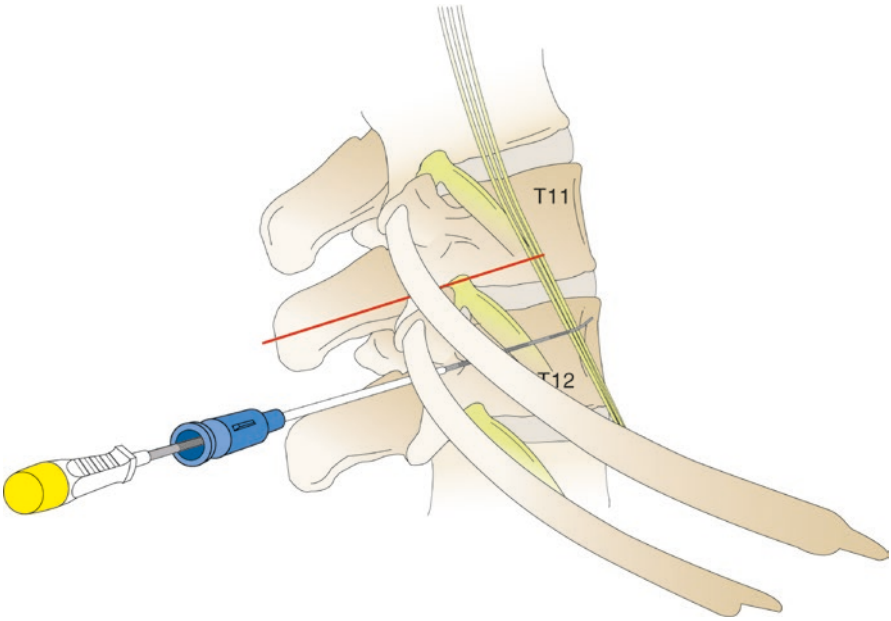
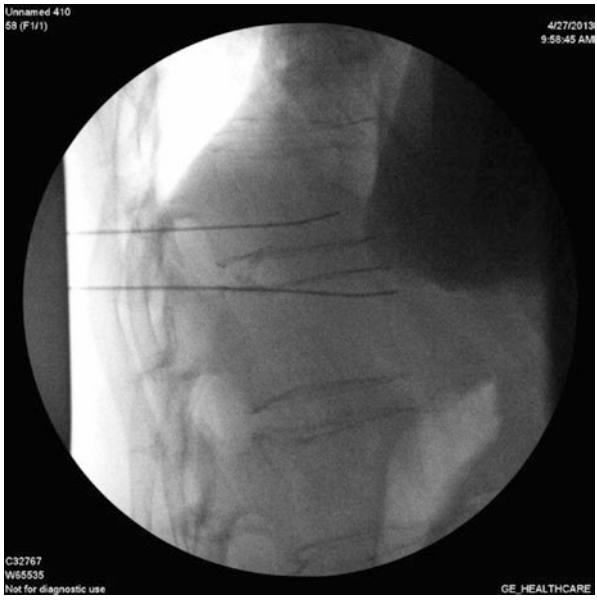


Fig. 20.141 The introducer is placed at the T12 level, and the curved blunt needle is advanced toward the target position

Fig. 20.142 The needles are positioned for the first lesion



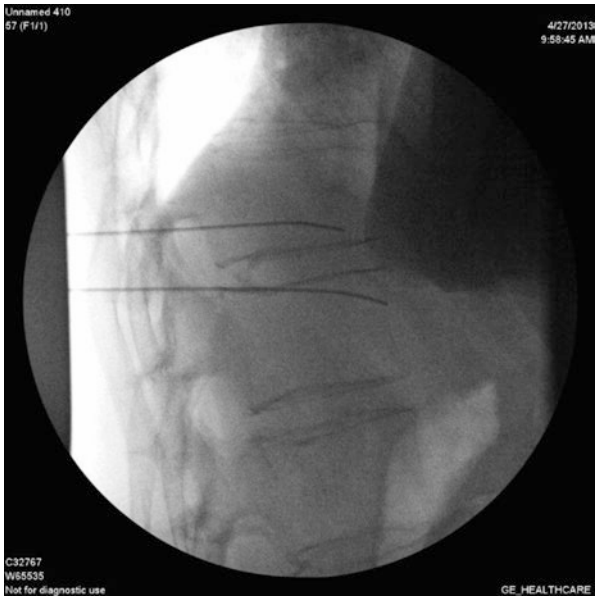


Fig. 20.143 The needles are rotated 180° for a second lesion in order to lengthen the lesion

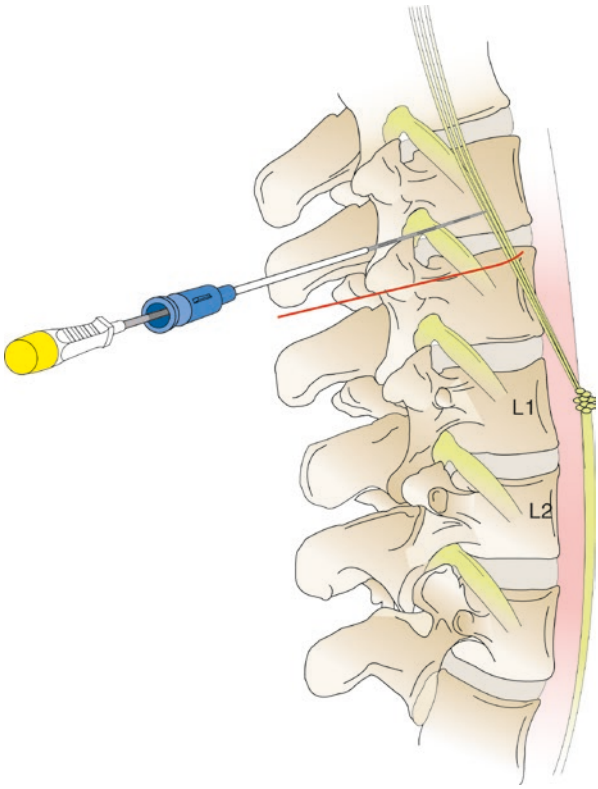


Fig. 20.144 The introducer is placed for the T11 level, and the curved blunt needle is advanced toward the target position

T11 vertebral body. This contact is often painful, and the patient needs to be warned that this may be painful and some sedation is required. The fluoroscopy positions for the procedure are AP oblique and lateral view. The volume of injection is 2–3 cc of contrast and 5–6 cc local anesthetic and steroid at each side. Because the introducing sharp needle cannula remains outside the thoracic cavity, the incidence of pneumothorax is extremely low. Although one perforates the parietal pleura, the visceral pleura is gently pushed away by the advancing blunt needle. The patient needs to be warned regarding the possibility of pneumothorax and that the onset of pneumothorax maybe multiple hours later. Therefore, long distance travel or air travel is something that should be discouraged, and the patient should be evaluated for safety and comfort the following day. The procedure is usually done on one side to eliminate the possibility of bilateral pneumothorax.

Sphenopalatine Block

The sphenopalatine ganglion is a collection of cells that make up an important role in communication between the autonomic nervous system and different branches of the trigeminal nerve (Fig. 20.145). The trigeminal nerve mediated pains particularly the first and second division often involve the sphenopalatine ganglion. The third division, the mandibular division, rarely involves the sphenopalatine ganglion. There

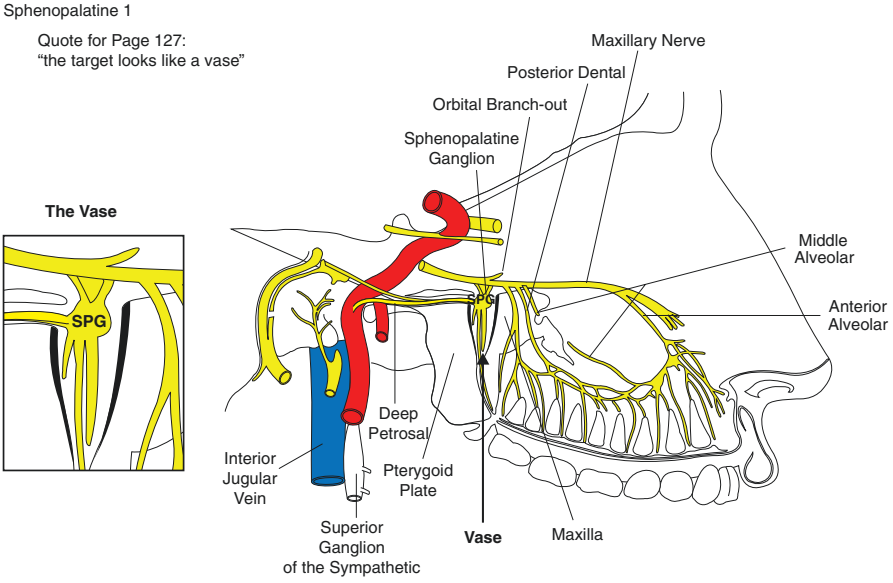


Fig. 20.145 Anatomy for sphenopalatine block

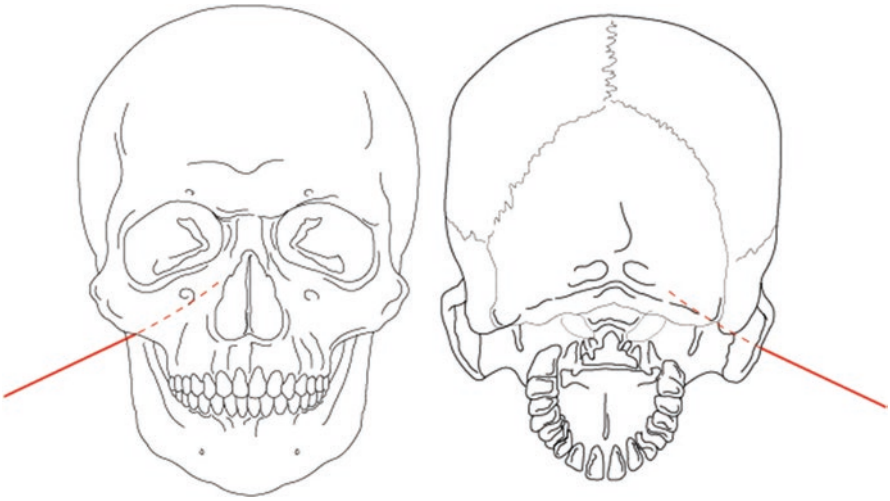


Fig. 20.146 Schematic drawing for sphenopalatine block

is communication between the sphenopalatine ganglion, the sympathetic nerves, the seventh nerve, and the first and second division of the fifth nerve. Sphenopalatine ganglion mediated pains are often associated with ipsilateral lacrimation and nasal congestion. The pain behind the eyes is a common hallmark of sphenopalatine ganglion mediated pain. The ganglion is located in the posterior superior aspect of the pterygopalatine fossa and is surrounded by significant arteries and nerves. The medial side of the ganglion is near the lateral wall of the nasopharynx, approximately 5 mm deep from the mucosa. Reaching the sphenopalatine ganglion has been attempted using multiple approaches. The lateral approach is from inferior to the zygoma aiming to the superior/anterior portion of the pterygoid plate using a curved/Coudé® needle through an introducer (Fig. 20.146). The needle tip is navigated to the interior aspect of the pterygoid plate, right on top of the sphenopalatine ganglion. The pterygopalatine fossa appears on fluoroscopy in the shape of an inverted vase where the stem of the vase broadens out to accept the sphenopalatine ganglion. Complications using the lateral approach include significant hematoma formation. If the lateral approaching needle perforates the mucosa, nosebleed may occur. This has been a moderately common complication because of the difficulty to stop the bleeding once an artery has been lacerated with the tip of a cutting sharp needle. Trans-nasally, local anesthetics have been deposited on the posterior lateral wall of the nasopharynx. Four percent cocaine is an excellent topical local anesthetic for this procedure, but diversion has curtailed the use.

Positioning of the C-arm and the sterile draping of the patient's face and forehead are important. The C-arm in lateral view is used to identify the target of the needle. The left hand is placed on the patient's forehead, and the head is slightly rocked left to right to line up the back end of the maxilla and front of the pterygoid plate in order to avoid the distortion of the view or parallax. The inferior border of

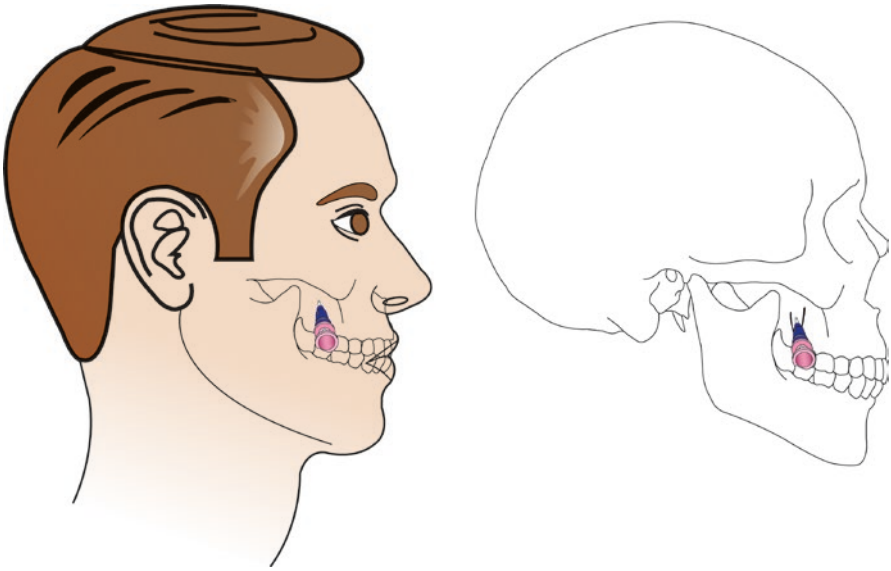


Fig. 20.147 The inferior border of the zygoma is palpated slightly interior to the target, and local anesthetic infiltration is used with a small gauge needle. The 16-gauge introducer cannula is passed through the skin a short distance, just enough to be anteromedial to the zygomatic arch and avoid the mandible

the zygoma is palpated slightly interior to the target, and local anesthetic infiltration is used with a small gauge needle. The 16-gauge introducer cannula is passed through the skin a short distance, just enough to be anteromedial to the zygomatic arch and avoid the mandible (Fig. 20.147). The metal needle is removed and the 10-cm-long 20-gauge blunt Coudé® needle is passed in small incremental moves with jabbing-type advancing movements (Fig. 20.148). The needle is then navigated to the target, which is the posterior superior part of the fossa that resembles an inverted vase on the fluoroscopic image (Fig. 20.149). The blunt needle is thus navigated percutaneously to the target by rotating the tip. When the tip of the needle meets the sphenopalatine ganglion, pain may be elicited and often ipsilateral tearing is seen (Figs. 20.150 and 20.151). Radiofrequency lesioning is used for longer duration of pain relief. When an insulted blunt Coudé needle is used, the approach will be similar through an introducer cannula. When the needle is brought to be in the superior posterior aspect of the pterygopalatine fossa, sensory stimulation at 50 Hz is performed. If the needle tip is too distal below the targeted sphenopalatine ganglion, the palatine nerve will be stimulated, and the patient shall experience paresthesia in the hard palate. If the tip of the needle is too anterior, closer to the maxillary nerve, paresthesia in a maxillary nerve distribution will be observed. The optimal needle placement from the lateral approach will curve around the sphenopalatine ganglion posteriorly and possibly superiorly. This position will elicit a buzzing-like paresthesia behind the nose with 50-Hz stimulation. Pulsed radiofrequency lesions

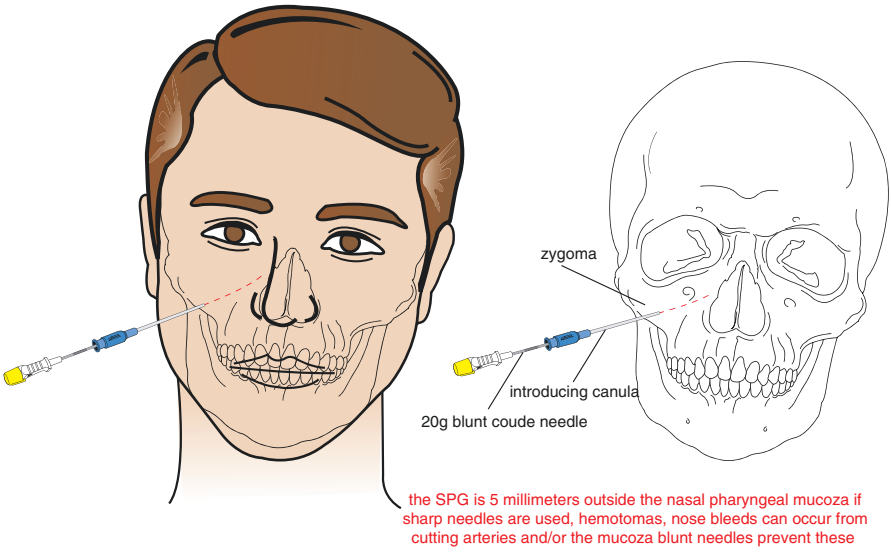


Fig. 20.148 The curved blunt needle is advanced through the introducer toward the sphenopalatine ganglion

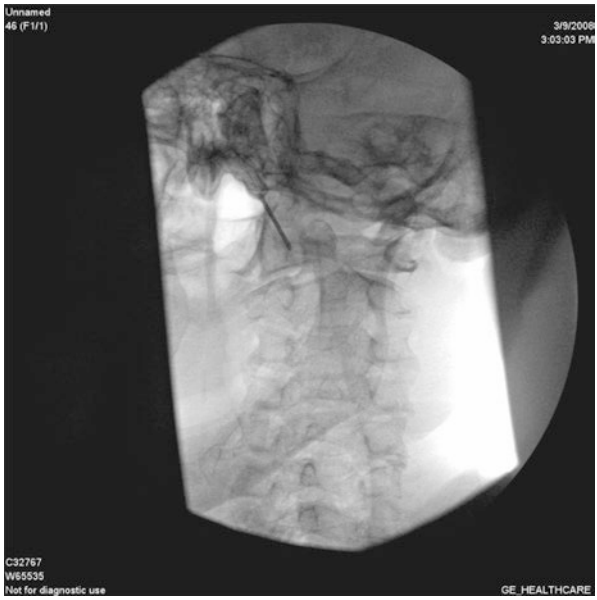


Fig. 20.149 The metal needle is removed, and the 10-cm-long 20-gauge blunt Coudé® needle is passed in small incremental moves with jabbing-type advancing movements. The needle is then navigated to the target, which is the posterior superior part of the fossa that resembles an inverted vase on the fluoroscopic image. The blunt needle is thus navigated percutaneously to the target by rotating the tip. When the tip of the needle meets the sphenopalatine ganglion, pain may be elicited and often ipsilateral tearing is seen

may produce good relief of post-head injury pain and atypical facial pain in distribution of the first and second trigeminal division [18].

The pulsed technique employs a couple of 42° centigrade for 6–8 minutes total duration. The facial pain relief is less predictable, but the use of the post-radiofrequency is consistently helpful. An additional point is the use of a curved

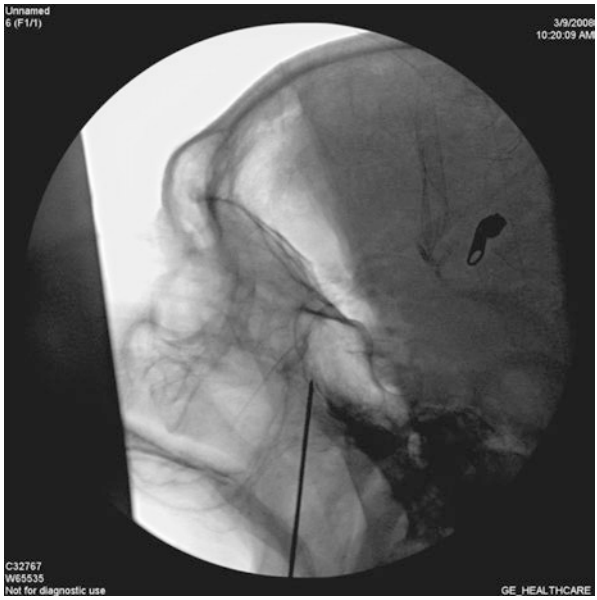


Fig. 20.150 Lateral image

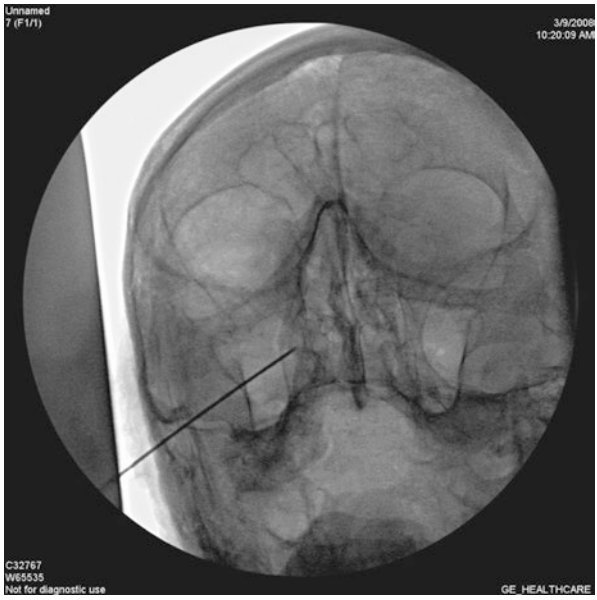


Fig. 20.151 Anterior-posterior image

blunt needle for radiofrequency thermocoagulation. A 90-second duration 80° centigrade lesion is used. The most common indication is frontal headache and pain behind the eye and first and second trigeminal division mediated pains. It is necessary to tell the patient that some of the hazards with radiofrequency lesions are injuries to the nerves near the lesion. Therefore, there may be profound numbness in the

usual second division distribution, the side of the nose, the upper lip, and the hard palate. The duration of the numbness may be months or longer, and the pain relief is not guaranteed. The incidence of hematomas and nosebleeds since we have switched to the use of curved blunt needles has dropped to zero in our practice. Similarly, the only medical legal cases that I have been involved with have been related to sharp needle-related complications. The problem with using oblique views is the possibility of misplacing the needle into the orbit. A case of monocular blindness has occurred after thermocoagulation as a result. It is important to maintain the pterygoid plate and posterior maxilla in parallel on the fluoroscopic image. Using the technique described above and performing sensory trial stimulation, before the lesion and injecting local anesthetic prior to thermocoagulation is effective. Our practice is to add steroids through the needle after thermocoagulation to reduce the inflammatory changes. The curved/Coudé® blunt needle is not a typical needle but is a percutaneous navigational device (PND) that allows maneuvering around obstacles and important structures to reach targets, such as the sphenopalatine ganglion, safely.

Neural Flossing Exercises

Before beginning the neural flossing exercises, the patient is given an instructional guide, available for both cervical and sciatic nerves. Femoral nerve stretch exercises are important for upper lumbar pathology. Practical experience supports sustained stretching, such as straight leg, raises over a 20–30 second time span. This changes the stretching of the nerve to sliding of the nerve, thus regaining the mobility of the previously scarred nerve root. Clinical experiences show that physical therapy by itself does not free up a scarred nerve root very readily. Veihelman compared neuroplasty to physical therapy and reported that neuroplasty was more effective [19].

However, in failed neck surgery patients, patients respond to lysis of adhesions manifested by reducing radiating pain. Continuation of cervical neural flossing exercises can result in complete resolution of pain and spasm up to 2 years after the lysis procedure (two to three times per day with 30 second sustained hold). Patient involvement is essential. The cervical exercises are shown as component moves in Figs. 20.152, 20.153, and 20.154. The combined exercises are shown in Fig. 20.155.

A recent observation after the lysis procedure is that patients may develop pain in the absence of positive straight leg raising. In these cases, the epidurogram shows scarring of the dorsal root ganglion (DRG) area. The nerve root has stretched, and the ganglion and lateral recess area developed scarring. Movement-related pain is not present. Repeat lysis, especially with Hylenex, works and needs to be repeated. An important concept is the approach to treatment of scarred nerve roots. The problem begins with degenerative disk disease when the nucleus pulposus material leaks into the epidural space. This produces an inflammatory response leading to radiculitis secondary to inflammation and scar tissue, scarring of the nerve root, and movement-related pain. The work of Indahl et al. shows that discogenic impulses can lead to back spasms [20]. Disk height and facet joint alignment are changed at the same time. Pain generation arises from the disc, nerve root, facets, and the muscles in the back and

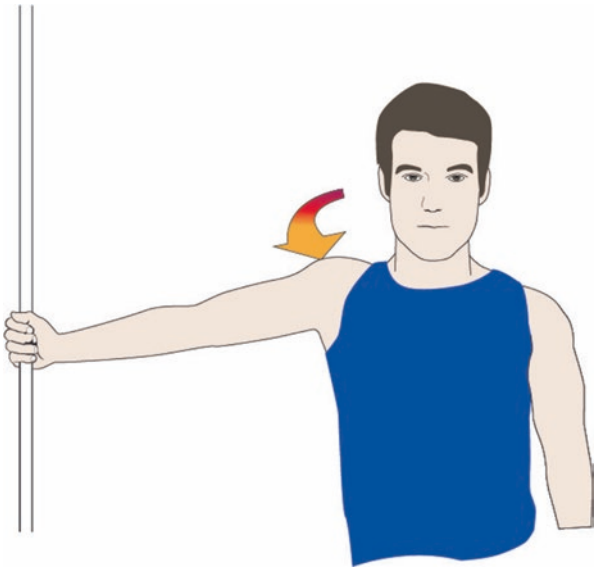


Fig. 20.152 Component move of cervical neural flossing 1

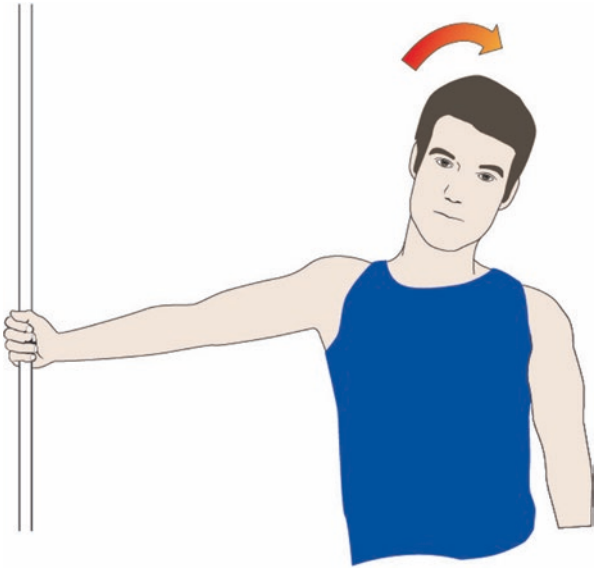


Fig. 20.153 Component move of cervical neural flossing 2

iliopsoas muscles. Patients suffering from upper lumbar back pain may develop significant back spasm and groin pain. To stretch out the back spasm, the patient may do the exercise in a reclining position where they need to curl up both knees and pull up to the chest and hold their head in a straight position (Fig. 20.156). This can stretch the muscles that are in spasm. This stretching motion can be repeated multiple times during the day, but the crucial aspect is that it should be held for 22–30-s. After a period of rest, it can be repeated several times. Additional exercises are also performed

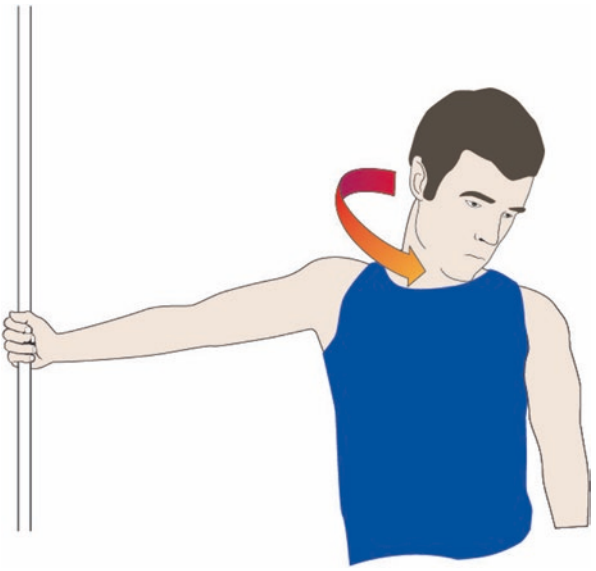


Fig. 20.154 Component move of cervical neural flossing 3

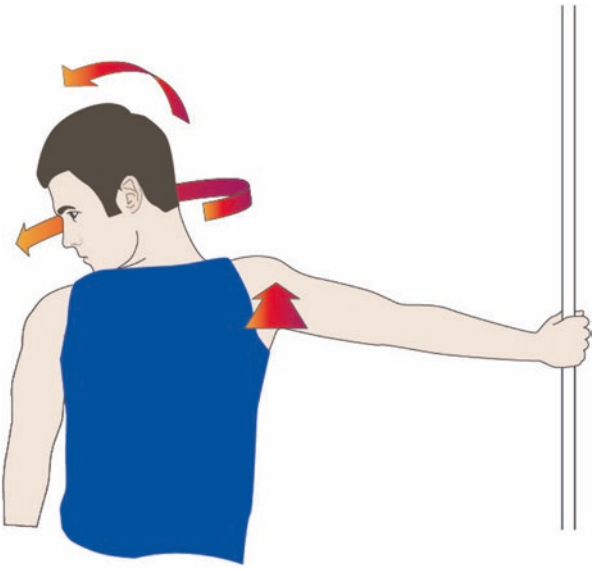


Fig. 20.155 Combined moves for chin to shoulder neural flossing maneuver

(Figs. 20.157 and 20.158). When there is femoral nerve involvement and back spasm as secondary feature, often there is a thigh pain. If the patient is unable to do the exercise in a standing position, the exercise can be performed on a comfortable mattress in the lateral position with the asymptomatic side in the dependent position. The ankle of the symptomatic leg is pulled to stretch the quadriceps femoris muscle as much as possible for 30 seconds. The neck and back should be extended to stretch the second and third lumbar nerve roots. This movement also loosens the large intra-abdominal psoas muscle that is involved in patients suffering from back pain from the upper

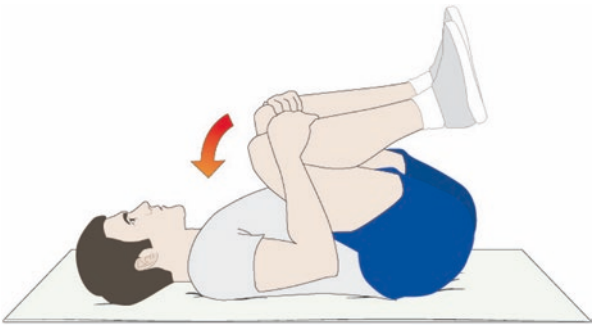


Fig. 20.156 Reclining lumbar neural flossing maneuver 1

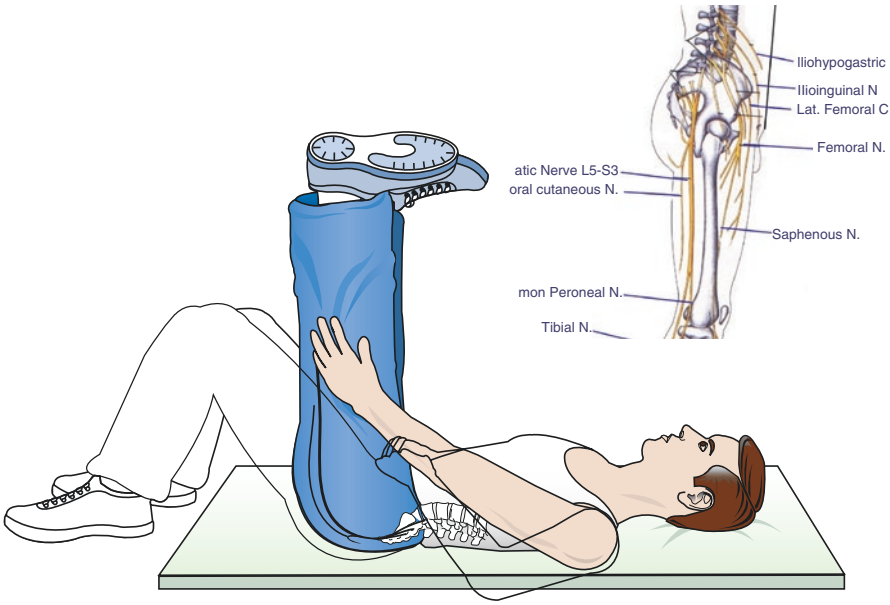


Fig. 20.157 Reclining lumbar neural flossing maneuver 2

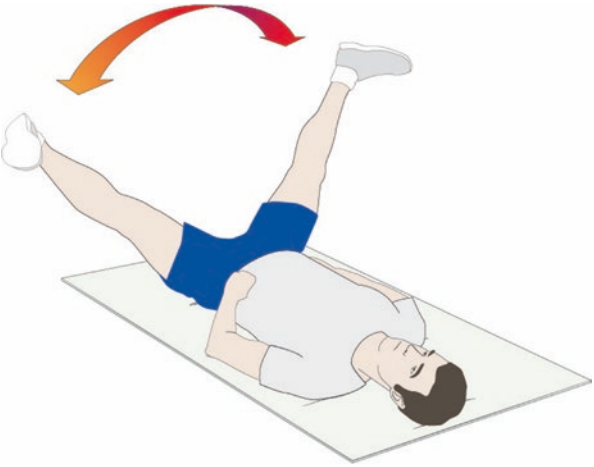


Fig. 20.158 Reclining lumbar neural flossing maneuver 3

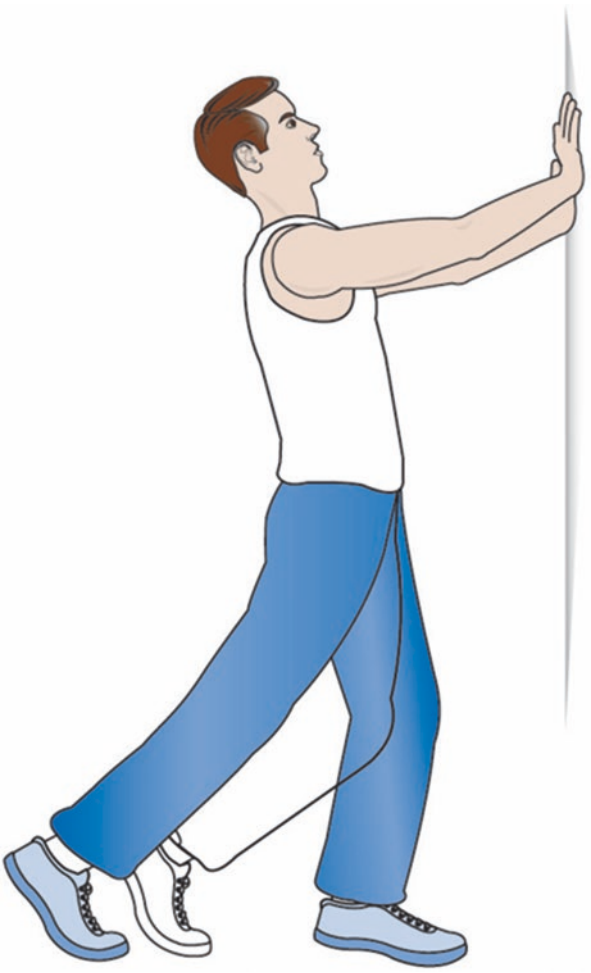


Fig. 20.159 Standing lumbar maneuver 1

lumbar nerve roots. These exercises should be performed two to three times a day, and repetitions have been found to be helpful. Femoral stretch exercises may be done standing. This exercise is primarily for patients suffering from upper lumbar back pain and radiating pain involving the lower extremity but specifically the anterior thigh area. The femoral nerve primarily comes from the second and third lumbar nerve roots, and they join together to form the femoral nerve. The femoral nerve exists through the front of the upper thigh from the abdomen and innervates the main muscles of the upper thigh and supplies sensory innervation down to the inside of the lower leg to the level of the inside or medial ankle. The patient suffering from back pain also develops severe muscle spasms in the iliopsoas muscle. Patients that have hip replacement are at risk for subluxation of the hip joint. These patients may gently perform femoral stretch exercises in a standing position, leaning against a wall and extending at the hip to move the leg slowly back in a straight stretching position (Fig. 20.159).

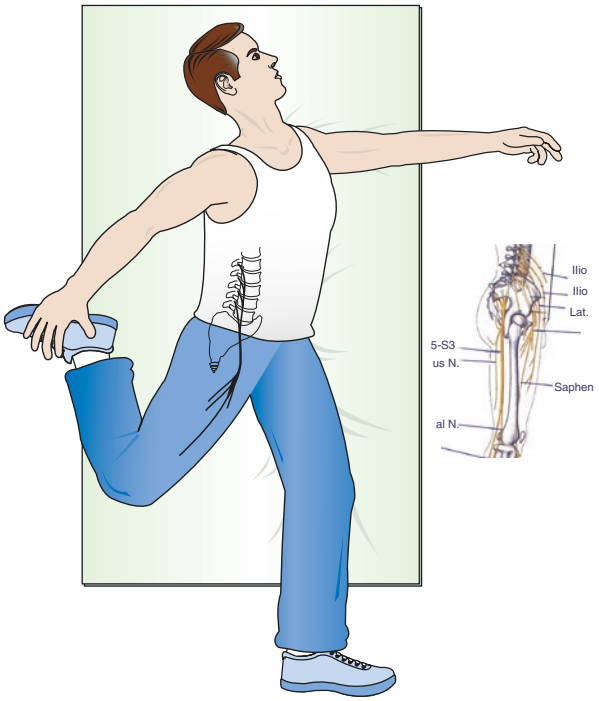


Fig. 20.160 Femoral stretch

This will stretch the iliopsoas muscle as well as the femoral nerve roots and will mobilize the femoral nerve. Once the leg is moved back to maximally obtainable position, the stretch can be exaggerated by leaning and pushing backward from the wall and maintaining this position for 22–30s, and this helps to reverse significant spasm. An alternate exercise for patients that have no hip joint issues is to stabilize against the wall and hold the lower part of the foot. The leg may be forcibly pulled back while leaning backward again achieving significant stretching of the muscle and spasm, and this helps to mobilize the femoral nerve (Fig. 20.160). Again the stretching position should be maintained for 20–30s, and the stretching can be repeated many times whenever the pain is significant.

Medicolegal Complications

Complications occur despite the best of training and technique. The information we have gained regarding complications and disasters does not come from prospective randomized studies but has come from the busy practitioner's daily work and experience in the medical/legal arena. Unfortunately, many of these complications have not been published because they have failed to become public information and either the patient or the physician did not give consent for the information to become public. We need more evidence. We need more studies. However, one noteworthy aspect of published studies is the lack of reported complications. The studies do not

teach us what we must avoid in order to spare our patients and ourselves from the stresses and hazards of undesired outcomes and complications. However, this information must be shared. Denial of complications or pretending that complications can be avoided by following one's imaginary procedural guidelines amounts to misleading posture and wishful thinking. I am not aware of any physician who gets up first thing in the morning with the idea that "I am going to hurt somebody today." It is in the training, in the fiber, in the blood of the physician the concept of "Primum non nocere," in other words, "First, do no harm, which has been around for centuries. The development of the techniques for these procedures has been evolving because there have been disasters, deaths, and paralyzed patients. This is not due to the physician being careless and negligent or who failed to follow instructions. Having reviewed over 300 medical malpractice cases, one cannot miss when a similar scenario presents itself repeatedly. This pattern may mean that there is information not generally known for avoiding the development of this pattern that leads to the complication.

The ten-step approach for cervical needle and catheter placement described in this chapter will lead to significant reduction in problems encountered where the patient may end up quadriplegic and paraplegic or suffer from hemiplegia or Brown-Sequard syndrome. The techniques described represent years of experience. Optimizing the speed in which procedures are carried out will dramatically reduce the complications that we are forced to defend in the medical/legal arena. The problems related to the use of sharp needles and intraneural injections have been elegantly studied by Doug Selander [3, 4].

The number of legal cases is increasing at a steady constant rate. Spinal cord injury from interscalene injection is a growing problem. The most likely explanation is intraneural injection and local anesthetic spreading with a very high pressure at the spinal cord causing myelopathy. Another case is related to loculation from an interlaminar single needle injection. The concept of treating perivenous counter spread (PVCS) could possibly lead to prevention of permanent cord injury; the diameters of the cervical spinal canal and foramina are not static. Flexion and rotation of the cervical spine lead to enlargement of neural foramina and facilitate runoff from the cervical epidural space. This runoff may very well be lifesaving in that the pressure is reduced, blood supply is reestablished to the spinal cord, and a major disaster for the patient and a major lawsuit for the doctor may be averted. Another case involved a disaster from a cervical C6 transforaminal injection where a sharp needle was used. Penetrating the vertebral or radicular artery or injection of the nerve root can lead to a serious complication. Embolization had occurred or an intraneural high-pressure injection led to myelopathy. Another case of cord injury is from a posterior approach for a C2-C3 cervical facet injection. A sharp needle reached the C3 nerve root, the most posterior of the cervical roots, and intraneural injection is followed by permanent cord injury. A number of cases of interlaminar, small gauge Tuohy needle injections have been associated with complications. The tip of the Tuohy needle simultaneously ends up in the epidural and subdural space, and local anesthetic injection leads to delayed cardiovascular collapse. Tuohy needles in the cervical area can go through a gap in the ligamentum flavum and end up

in the spinal cord. Scanlon et al. have recommended that the way to reduce cervical vascular injury and complications is to use blunt needles [21]. The pattern of symptoms that should be recognized is bilateral arm pain, chest pain, and even leg pain. Pain, numbness, and then weakness are the sequence of symptoms in PVCS. Emergent communication with colleagues has been an effective way to help manage complications in this situation [23].

Informed Consent

Informed consent is very important as these procedures have significant risk and are often of limited efficacy. In Texas, state law requires specific language in written consent forms for neuroaxial procedures, peripheral and visceral nerve blocks and/or ablation, and implantation of pain control devices:

Neuroaxial Procedures (Injections into or Around Spine)
- Failure to reduce pain or worsening of pain
- Nerve damage including paralysis (inability to move)
- Epidural hematoma (bleeding in or around spinal canal)
- Infection
- Seizure
- Persistent leak of spinal fluid, which may require surgery
- Breathing and/or heart problems including cardiac arrest (heart stops beating)

Peripheral and Visceral Nerve Blocks and/or Ablation
- Failure to reduce pain or worsening of pain
- Bleeding
- Nerve damage including paralysis (inability to move)
- Infection
- Damage to nearby organ or structure seizure

Implantation of Pain Control Devices
- Failure to reduce pain or worsening of pain
- Nerve damage including paralysis (inability to move)
- Epidural hematoma (bleeding in or around spinal cord)
- Infection
- Persistent leak of spinal fluid which may require surgery

Outcome Studies and Conclusions

Positive randomized trial studies of transforaminal and selective nerve root blocks are limited to the lumbar region. Selective nerve blocks with bupivacaine and betamethasone have been shown to reduce the surgery rate (8/28) compared to blocks

with bupivacaine alone (18/27) during follow-up of 13 to 28 months [24]. However, after long-term follow-up, the surgical rate between the two groups was not significantly different [25]. Lumbar transforaminal injections are used for radicular pain. In an early study, after 15-month follow-up, the success rate was 84% versus 48% [26]. In another study analyzing transforaminal injections versus interlaminar versus caudal epidural steroid injections, transforaminal injections were considered the best [27]. Lumbar epidural lysis of adhesions had been studied in a randomized, sham controlled trial, and the results show significant improvement of pain and function in the active treatment group [28]. Long-term follow-up of lumbar epidural lysis of adhesions shows positive results [29]. In a study of cervical percutaneous neuroplasty versus epidural steroid injections, the cervical percutaneous epidural neuroplasty group had better outcomes 6 months after treatment for cervical disk disease [30]. In addition, contrast runoff correlates with improved outcome [30]. Sub-compartmental occipital blocks and pulsed radiofrequency treatment have been shown to be more effective than conventional nerve blocks [32, 33]. The sympathetic blocks have been studied in patients with complex regional pain syndrome and vascular disease. Cervical sympathetic blocks have been studied in reflex sympathetic dystrophy. A small double-blind crossover study showed an analgesic effect with local anesthetic [34]. Thoracic sympathetic block showed a significant long-term effect in patients with complex regional pain syndrome [35]. The analgesic effect observed long term was not present in the short term, and the mechanism for this observation is not understood. Lumbar sympathetic blocks and cervical sympathetic blocks were performed in a crossover study in patients with complex regional pain syndrome. The local anesthetic treatment was associated with a longer duration of analgesia compared to saline [36]. Another trial in children showed a positive effect of lumbar sympathetic block [37]. Phenol lumbar sympathetic blocks have been shown to be effective for vascular ischemic rest pain [38]. Radiofrequency thermocoagulation has been compared to phenol block [39]. The radiofrequency technique required modification to increase lesion size and effectiveness [40]. A randomized trial showed that radiofrequency treatment was effective and radiofrequency treatment is potentially safer than phenol injections [41]. Hypogastric plexus block has been studied as treatment for pelvic pain. A randomized trial in patients with pain after abdominal hysterectomy showed positive results [42]. Celiac plexus block has been studied in several trials, and in patients with pancreatic cancer, celiac blocks have been shown to reduce opioid requirements and medication-related side effects [43–45]. Celiac block for pain that is not specifically attributable to the pancreas is less effective; however, a case report has been published describing success in a patient with metastatic colon cancer [46]. Splanchnic block has been compared to celiac block. In patients with upper abdominal tumors, splanchnic block was superior [47]. Another trial comparing medical management with celiac block or thoracoscopic splanchnicectomy showed no difference in pain relief between the three groups [48]. Sphenopalatine block has been used to treat migraine and reduces headache days, pain severity, and medication use and improves quality of life [49]. Another trial in emergency room patients with headache was negative [50].

Sphenopalatine block has also been used for postoperative pain after palatoplasty in children [51]. Interestingly, sphenopalatine block may have a role in treating hypertension [52].

Interventional pain management procedures are safe and effective alternatives to opioids for a number of common pain problems. Patient selection and proper technique can reduce the risk of complications and repeat procedures. Informed consent is an important method for engaging patients in the decision-making process.

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Chapter 21
Clinical Use of Opioids for Chronic Pain

William G. Brose, Daksh Datta, and Justin Kromelow

Introduction

Opioids are an expansive class of psychoactive drugs with many major medical uses, including the treatment of pain. They are among the most potent and effective analgesics known to the medical world and are used primarily to relieve human suffering. The value of these medications has been recently affirmed by the addition of one of its group members to the World Health Organization's 2011 list of the 100 most important medications in the world [1]. These medications also possess a potent activation of pleasure centers within the human brain that paradoxically can lead to suffering through their illicit use, resulting in dependency, abuse, and addiction.

The term "opiate," derived from the Latin *opium*, refers to natural or slightly modified components purified from opium such as morphine, codeine, and heroin. The term opioid was introduced initially to describe the synthetic analogs such as oxycodone and fentanyl but has since expanded in usage to refer to the entire class of compounds that are agonists at the opioid receptor. This class contains over 20 other alkaloids. This includes endogenous opioid peptides as well, such as enkephalins, dynorphins, and endorphins, as these molecules bind to the same receptors as the opioid receptor agonists and antagonists mentioned above. Any natural or semisynthetic substance with morphine-like effects can be characterized as an opiate. There are many clinically available opioids in the United States at the time of publication (Table 21.1). The continued pharmaceutical development of new opioids

W. G. Brose (✉)
Department of Anesthesia, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, CA, USA
e-mail: WBROSE@BROSEMD.COM

D. Datta · J. Kromelow
Opos Solutions, Opos Inc, San Mateo, CA, USA
e-mail: justin@kromelow.com

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Table 21.1 List of clinically available prescription opioid pain and cough medicines

Generic name	Found in brand name(s)
Alfentanil	Alfenta®
Buprenorphine	Belbuca®, Buprenex®, Butrans®
Butorphanol	No brand name currently marketed
Codeine	Fioricet® w/ codeine, Fiorinal® w/ codeine, Soma® Compound w/ codeine, Tylenol w/ codeine, Prometh® VC w/ codeine (cough), Triacin®-C (cough), Tuzistra® XR (cough)
Dihydrocodeine	Synalgos-DC
Fentanyl	Abstral®, Actiq®, Duragesic®, Fentora®, Ionsys®, Lazanda®, Sublimaze®, Subsys®
Hydrocodone	Anexsia®, Hysingla® ER, Lortab®, Norco®, Reprexain®, Vicodin®, Vicoprofen®, Zohydro® ER, Flowtuss® (cough), Hycofenix® (cough), Obredon® (cough), Rezira® (cough), Tussicaps® (cough), Tussigon® (cough), Tussionex®, Pennkinetic® (cough), Vituz® (cough), Zutripro® (cough)
Hydromorphone	Dilaudid®, Dilaudid®-HP, Exalgo®
Meperidine	Demerol®
Methadone	Dolophine®
Morphine	Astramorph ®PF, Duramorph® PF, Embeda®, Infumorph®, Kadian®, Morphabond®, MS Contin®
Oxycodone	Oxaydo®, Oxycet®, Oxycontin®, Percocet®, Percodan®, Roxicet®, Roxicodone®, Xartemis® XR
Oxymorphone	Oxymorphone ER, Oxymorphone HCI extended
Pentazocine	Talwin®
Remifentanil	Ultiva®
Sufentanil	Sufenta®
Tapentadol	Nucynta®, Nucynta ER
Tramadol	Conzip®, Ultracet®, Ultram®, Ultram ER

List of Prescription Opioid Pain and Cough Medicines from - CVS-Caremark, https://www.caremark.com/portal/asset/DSAAUTPDF2016_123.pdf, last accessed April 27, 2019
This is not a comprehensive list

stands as a testament to the imperfect effects of all members of the class in the clinical treatment of human pain.

This list is illustrative of the clinically available opioids.

Opioid variability is wide and deep. They can be classified based on their potency, chemical similarity, derivation, receptor affinity, and even abuse potential. Perhaps the most clinically important classification is abuse potential as described by the US Drug Enforcement Administration (DEA), who oversees the sale and distribution of legally manufactured opioids within the country. It is this governmental organization that registers physicians and pharmacies charged with the prescribing and distribution of the medications. This classification identifies higher abuse potential as Schedule 2 and Schedule 3 with a slightly lower potential. At the time of printing for clinical purposes, only codeine and buprenorphine remain as Schedule 3 drugs with virtually all remaining controlled substances being characterized as Schedule 2.

History

The early history of opium begins with growth and use around 3400 BC by the Sumerians in lower Mesopotamia. They referred to the bright red poppy flowers as *Hul Gil*, the "joy plant" [2]. The Sumerians of ancient Iraq cultivated poppies and isolated opium from their seed capsules around 3000 BC. This extract was initially given with hemlock to put people to a quick and painless death. The Sumerians soon passed it on to the Assyrians, who in turn passed it on to the Egyptians. Mentions of opium, which comes from the plant *Papaver somniferum*, have been recorded throughout history [3].

Before being discovered for its analgesic properties, opium may have been grown for its poppy seeds instead. It has been used in civilized society since ancient Greece and is even described in Homer's Odyssey. The Greek philosopher Theophrastus also spoke of opium poppy extracts, then called meconium.

Opium spread east when Arab traders in the eighth century AD brought it to India and China. Records of drug abuse first appeared in the sixteenth century in Turkey, Egypt, Germany, and England among other nations. It started after the spread from the Middle East to Europe and East Asia. It was an especially large problem in China, as the practice of smoking opium began in the early 1600s. China received opium from Europe in return for tea through the East India Company. As the addictive properties of opium were uncovered, the Opium Wars occurred between Britain and China. A victorious Britain was ceded Hong Kong, leading to the opening of Chinese ports to opium trade and the legalization of opium importation. This led to the spread of opium to the USA alongside the immigration of Chinese laborers. The Harrison Narcotics Act of 1914 was responsive to the expanding threat of opioid dependency, leading to the social marginalization of opioid use and the development of heroin addiction, which remains a growing crisis in America to this day [4].

Opioid Receptors

Opioid analgesic targets within the central nervous system appear to be G-protein-coupled receptors. Pain relief from opioids has been reported for centuries. Pain is defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [5]. Pain occurs when noxious pressure, chemical, or heat energy is transduced from a peripheral stimulus to pain-sensitive tissues. The electrochemical signal created is transmitted via peripheral nerve fibers to the spinothalamic tract and eventually to the somatosensory cortex. Opioid analgesia is thought to be achieved through the binding of an opioid with an opioid receptor along this pathway.

Opioid receptors are present in both the central nervous system (CNS) and peripheral tissues throughout the body. Three receptors are largely responsible for

the opioid mechanisms of analgesia and adverse effect profiles: μ, κ, and δ receptors [6].

- μ-Receptor activation leads to supraspinal analgesia and well-known opioid adverse effects (respiratory depression, sedation, euphoria, and decreased gastrointestinal motility). The gene coding for the μ receptors, OPRM1, is highly polymorphic, with more than 100 variants identified.
- κ-Receptor activation leads to spinal analgesia and similar adverse effects (respiratory depression, sedation, and dysphoria).
- δ-Receptor agonism likely leads to dysphoria and psychomimetic effects.

All opioids are μ-receptor agonists and vary in their degree of κ and δ agonism. Some opioids, such as tramadol and methadone, have additional non-opioid receptor–based sites of action.

The involvement of opioid receptors in the mediation of analgesia has led to hypotheses and derivative research to determine if a certain type of receptor activation would confer a certain type of pain relief.

More detailed and recent research suggests that the concepts of receptor-mediated effects are too simplistic. In his 2013 review, Kelly has described that a clear understanding of affinity, efficacy, and potency of each opioid with the resulting ligand bias would be a prerequisite for predicting unique drug receptor-related responses [7]. The continued work on unraveling an adequate understanding of the mosaic that is the elusive opioid receptor appears to be a future achievement. As a result, and in parallel, continued efforts at drug development without a singular unique target are ongoing.

If Not the Perfect Pain Receptor, Maybe the Perfect Drug?

Since the first isolation of morphine by F.W. Serturner in 1803, the search for the best opioid has been ongoing [8]. Serturner named his discovery “morphine” after the Greek god of dreams, Morpheus. Pierre Jean Robiquet later isolated codeine from opium as well. In the 1850s, the first hypodermic syringe was made, and morphine started to be used in minor surgeries for chronic pain. Heroin was first championed as a more potent and less addictive opiate when compared to morphine in 1898 [2]. In 1939, meperidine was first synthesized, and in 1946, methadone, both of which have similar properties to morphine but different structures. Today, opiates are used throughout the world for pain relief and are abused to a degree worthy of a national epidemic [9]. The development of meperidine, hydrocodone, oxycodone, oxymorphone, methadone, levorphanol, and the entire fentanyl 4-anilinopiperidine family of drugs occurred in pursuit of the elusive best drug.

The variability in opioid responses among individual patients and specific drugs has given rise to intensive research and development over the last century. Better

understanding of the pharmacology of this group of substances has offered promise of more predictable results from the prescription of opioids to treat pain, but no clear best drug or dose has emerged to date. Even with this disappointment, the use of these medications to relieve pain is a daily activity for many physicians. As a consequence, some knowledge of opioid pharmacology may be useful while the search for the best opioid continues.

Pharmacokinetics, Pharmacodynamics, and Pharmacogenomics

As the target of opioid analgesic drugs remains partially obscured and the drugs themselves a mixture of better and suboptimal as determined on an individual basis, some focus has turned to the search for optimal dosing of the available medications through better understanding of the drugs' distribution characteristics. Research funded by the National Institutes of Health (NIH) investigated the unique pharmacokinetic and pharmacodynamic properties of one of the opioids, methadone, in order to determine whether an analgesic drug concentration achieved within the body of patients with pain could result in a predictable analgesic response [10, 11]. The research demonstrated that even with real-time Bayesian forecasting employing population kinetic parameters then iterated with individual kinetic responses, predictability was unachievable. The study of pharmacokinetic variability, pharmacodynamic variability, and receptor neuropharmacology raised more questions than answers. It appears that knowledge of the kinetic and dynamic variables for each drug is a necessary prerequisite for predicting the drug response, but that response will be determined on an individual basis and therefore becomes a much more daunting problem. The search for predictability and reliability in opioid pain relief continues.

The advent of pharmacogenomics is the newest area of investigation to help organize the anticipated interpatient variability. As the heterogeneity of human pharmacokinetic, pharmacodynamic, and receptor neurobiological influences has been revealed, the need for even more basic understanding of this variability has been established [12].

The complexity of unraveling these combinations and genetic encoding promises years if not decades of ongoing research [13].

The zeal of pharmaceutical researchers and the improving tools at their disposal will likely provide genomic testing to identify the unique receptor and kinetic/dynamic determinants necessary to make a safer and more effective analgesic. However, the long and complex detailing of these pharmacogenetic variants is literally just unfolding [14]. As the tools necessary to understand interindividual variability are developed, the current focus needs to be on the clinical application of currently available medications to treat the pain of those patients physicians are privileged to serve.

The Imperative for Treatment

The ubiquitous experience of pain continues day in and day out across the globe. The demand for relief of human suffering has resulted in national and international calls for pain relief as a human right [15]. In responding to these demands, the clinician today must use the best of current pharmacology, neurobiology, and empirical clinical pain practice to weave a complex matrix of care to palliate pain in the world.

Modern Evolution of Prescribing Practices

The promotion of opioid prescribing for chronic, non-cancer pain began in the late 1980s with the publication of peer opinion of Dr. Russell Portenoy and Kathleen Foley [16]. Their publication describes the results of successful opioid treatment of 38 patients with the statement, "We conclude that opioid maintenance therapy can be a safe, salutary and more humane alternative to the options of surgery or no treatment in those patients with intractable non-malignant pain and no history of drug abuse." This endorsement in the absence of balanced presentation of concern over complications such as addiction or opioid-related accidental death heralded the promotion of opioid prescribing.

In the State of California, the promotion of opioid analgesic treatment of pain combined with a Liberal State political system to promote opioid prescribing. The availability of a promising, powerful solution (opioids) and a public demand for pain relief led to the adoption of the Intractable Pain Treatment Act in 1990. The timeline illustrated below in Fig. 21.1 depicts the course of events from 1990 to the current time establishing the clear pro-opioid prescribing practices of the early part of the twenty-first century. California's bellwether position was reinforced by the simultaneous intractable pain treatment act in Texas the same year and subsequent pro-prescribing regulatory changes describing treatment of intractable pain in Arkansas, Colorado, Florida, Iowa, Louisiana, Missouri, Montana, North Dakota, Nevada, Ohio, Oklahoma, Rhode Island, Oregon, and West Virginia during the years that followed. The powerful and long-lasting medical and cultural swing toward opioid treatment of pain was underway [17].

In California, as evidence of the pro-opioid treatment, the MBC revised their 1994 guidelines for prescribing controlled substances in 2007 with the unanimous adoption of the revisions to the Business and Professions Code 2241.5c, stating "No physician and surgeon shall be subject to disciplinary action by the board for prescribing or administering controlled substances in the course of treatment of a person for intractable pain." During the 2007–2014 period, the MBC had no opioid dose ceiling or dose-related risk of opioid-induced death included in their provider guidelines.

These regulatory responses supporting the medication treatment of pain joined a rapidly growing marketing campaign for opioid prescribing that had been gaining

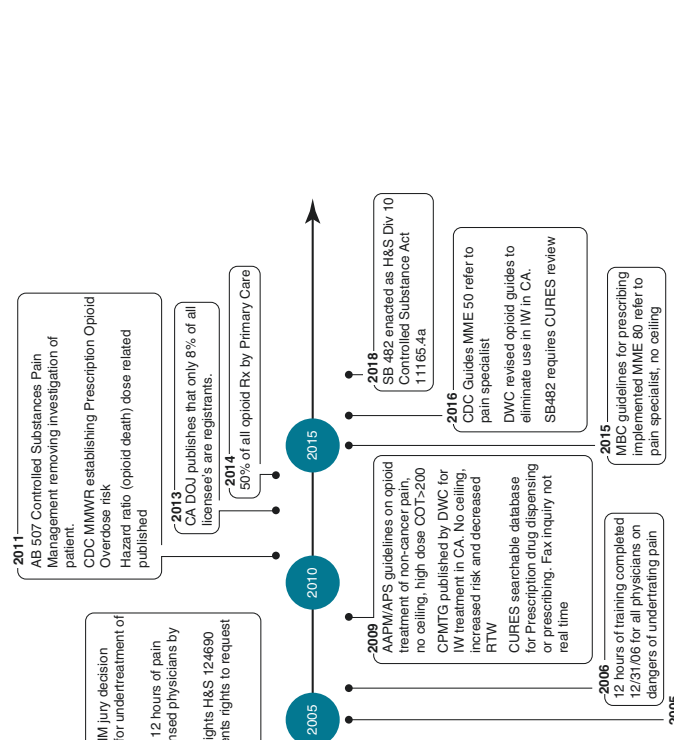


Fig. 21.1 These foundational events illustrate the consumer-led demand for pain relief that was prominent in the 1980s, 1990s, and early 2000s. The Rich review provides but one of many opinions about the Standard of Care at this time. In 2001, Assembly Bill 487 was introduced in the wake of a court decision in the Eden Medical Center case where a provider was punished for the undertreatment of pain to enforce pain treatment. The resulting demand for providers to treat pain medically was so pervasive that all licensed providers were required by the Medical Board of California (MBC) to complete 12 hours of Pain Specialty training to prevent pain undertreatment. The result was a compelling message for a more liberal prescribing of opioids from the literature, judiciary, and clinical guidelines

momentum since the 1996 product launch of OxyContin by Purdue Frederick. Indeed, the next decade of pharmaceutical "detailing" of providers created a shift from pain specialists as the major prescribers of opioids to primary care physicians as the dominant prescribers of these potent medications.

Figure 21.2 provides a graphic representation of the evolution of opioid sales during the decade that followed the introduction of OxyContin. The pharmaceutical company marketing initiative combined with the consumer demand and the regulatory revisions as an impetus to steep increases in drug sales.

As the impact of all of the pro-opioid prescribing periods evolved toward a zenith, a gradual progression of published reports describing risks of opioid side effects began to emerge. However, the first real warning of fatal consequences published on a large-scale basis was provided by the Centers for Disease Control and Prevention (CDC) in November of 2011 [9].

This announcement heralded the recurrent publication of opioid deaths on an annual basis. This mortality data has combined the death rate from medical use with that from illicit use. Review of the annual mortality data has shown continued increases in overall deaths despite increasing awareness of the problem. The data has included an observational link between the prescribed dose of opioid and the risk of death. Whether illicit or prescribed, the use of increasing opioids and the combination of opioids with central nervous system depressants, including benzodiazepines and alcohol, have been the subject of increasing investigation and regulation.

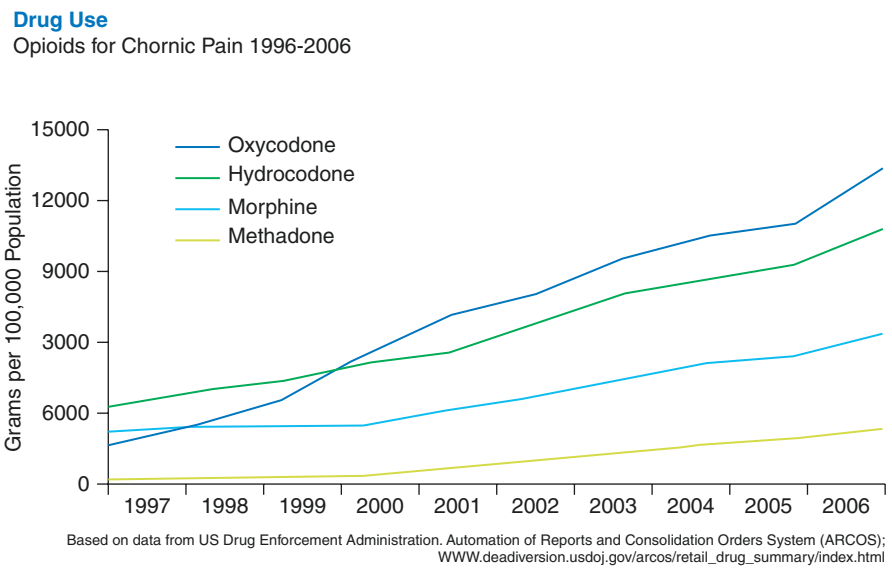


Fig. 21.2 This illustration depicts grams of each opioid sold per year in the United States based on information from the DEA. The trendlines for methadone shown in light green are described by the DEA as reflecting a fivefold increase in the prescribing for this medication alone over this 10-year period

Observational studies linking opioid dose and risk of death were published in 2011 [18]. To accomplish this task, dose equivalency tables and calculators were designed to allow different drugs to be compared on a common scale. This process of developing a conversion table utilized epidemiologic data (rather than clinical data) to enable lumping of patients into potentially comparable groups based on dose of opioid consumed. This lumping into groups allowed hazard ratios to be constructed based upon the observed death rates in the patient groups. The result of this effort has been a promotion of these quasi-scientific dose equivalency tools to be applied and often misused in the clinical treatment of patients [19]. However, from this data, dosing ceilings emerged. Over the ensuing years, many groups integrated the concepts of opioid dose-related risk and dose ceilings to help reduce risk of overdose death. This work moved toward a medication equivalency formula allowing the creation of a "Morphine Equivalent Daily Dose" (MEDD) from the various prescribed opioids of differing potencies and doses that required several years for acceptance. Unfortunately, these opioid equivalency tables and calculators are without an accepted pharmacologic foundation and are broadly employed out of a sense of urgency and obligation rather than accuracy in trying to communicate relative overdose risks. As the opioid deaths grew in 2012 and 2013, the concern and confusion of the particular contributions for each drug and drug dose for an individual patient was abandoned in favor of using a relative MEDD measurement [20].

In the ensuing months and years, the trend away from opioid prescribing has been clear. The awareness of physician prescriber involvement in the increased prescribing of opioids has been made public. The lay press and regulatory responses have been clearly focused on reducing the use and quantities of these pain relievers. However, the first evidence of such evolution in provider guidelines with prevailing authority suggesting dose limitations in California was the April 2014 California Division of Workers' Compensation publication of draft opioid treatment guidelines for the California Workers' Compensation system. In November of 2014, the MBC adopted separate guidelines, and following this, the CDC published specific guides in March of 2016.

More recent publications of opioid prescription information have demonstrated a very clear decline in prescription opioid amounts nationally. The prescribed amount reached a peak in 2012 with gradual declines since that time (Figs. 21.3, 21.4, and 21.6).

This decline likely represents a combination of CDC publications of risk information repeatedly during the 8 years that have elapsed since the 2011 MMWR notification combined with guidelines and regulatory and judicial influences leading to a change in the Standard of Care with regard to this opioid prescribing. This change has been heralded as a success in the battle against prescription opioid deaths, but the continued monitoring of the opioid death rate shows a clear separation of prescribing versus illicit drug use as the death rate continues to rise.

More recently, the CDC has modified their message, moving away from describing the opioid death epidemic as a prescription-led epidemic to a series of three

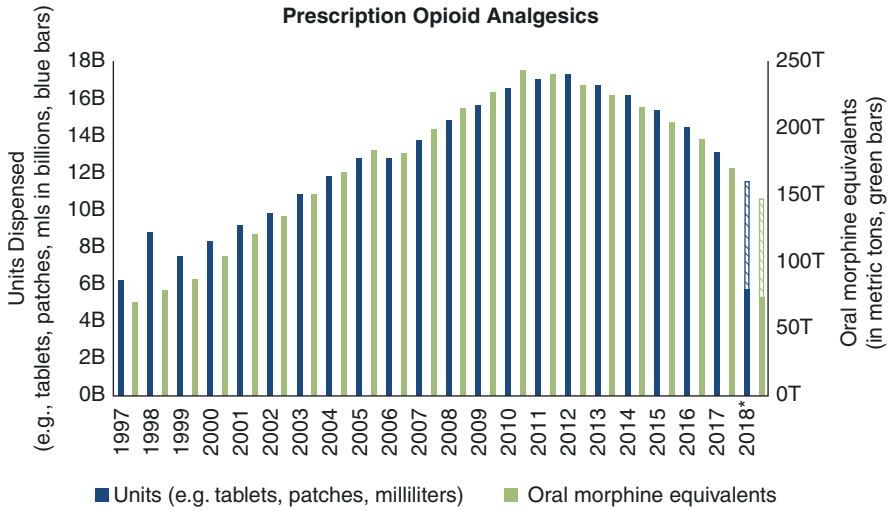


Fig. 21.3 The graphic representation of opioids prescribed per year in tons beginning in 1997 through 2018 (projected). The zenith of the opioid prescriptions appears in 2012. This change was approximately a year after the 2011 CDC announcement of the prescription opioid overdose epidemic

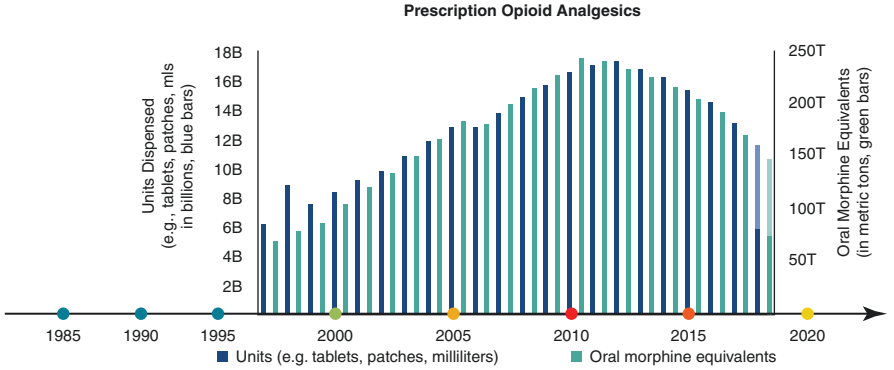
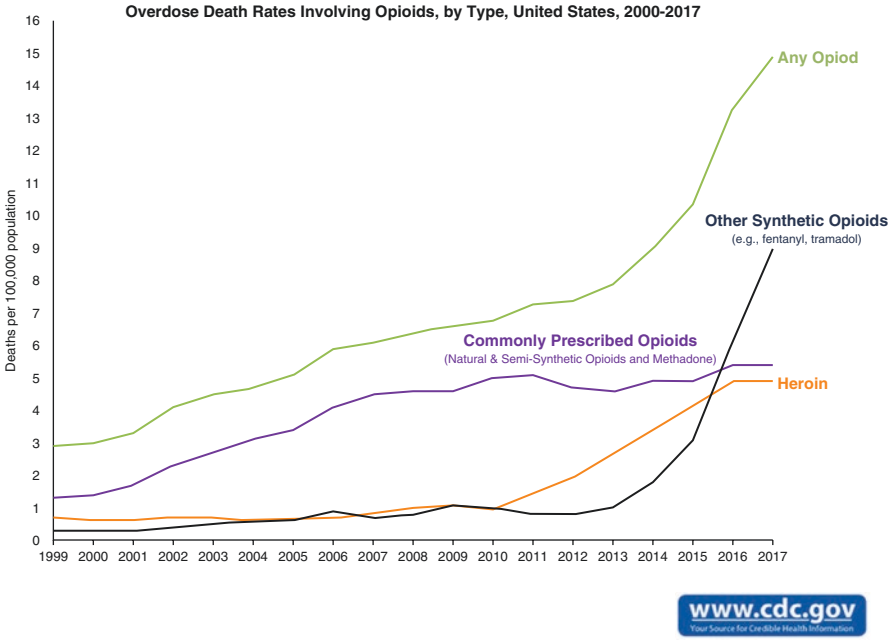


Fig. 21.4 This illustration applies the 5-year time epochs established in Fig. 21.1 to the opioid prescription data from Fig. 21.3. The colored dots moving from green to yellow to red reflect the spread of the pro-prescribing influences on the prescription amounts, and the subsequent decline in prescribing following the 2011 CDC announcement is illustrated in a transition down from red to orange and now yellow reflecting the caution that now pervades the prescribing behavior

loosely connected waves, as illustrated in Fig. 21.5. The first of these waves was clearly described as due to prescribed medications, the second wave appeared to have involved a return to illicit heroin, and the third has been the emergence of illicit fentanyl compounds with their lower cost and increased potency leading to the most rapid rise in death rates (Fig. 21.6).



SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2018. https://wonder.cdc.gov/.

Fig. 21.5 The CDC illustrates the rapidly escalating death rate in the United States associated with opioids (light green). This rise is a combined effect of prescription and illicit drug use. The relative tsunami of increased deaths is from separate loosely related opioid sources. The leveling off of the prescribed opioid deaths in 2011–2015 (purple) reflects a clear downturn of risk contributed from the prescribed opioids. The 2010 resurgence of heroin as an alternative to prescribed opioids emerges (goldenrod) as an illicit threat. This wave is then followed by the acceleration of the death rate in 2013 from illicit fentanyl, creating a third wave which has continued to grow nonlinearly to the latest reported year in 2017 (dark green). (Source: CDC/NCHS, National vital statistics system, mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2018. https://wonder.cdc.gov)

This figure clearly shows the continued rise in opioid-related deaths when the corresponding decrease in prescribed opioids would have predicted a declining threat if opioid-related pain care was the primary contributor. As hoped, a focus on education about the risk benefit of opioids and promotion of alternatives to opioids for treatment of chronic pain have impacted the therapeutic demand of patients for opioids. Simultaneously, the regulatory scrutiny about overprescribing and concerns about opioid overuse have led to large numbers of physicians choosing to "just say no" to the requests of patients for this type of pain treatment.

The lessons learned from the close scrutiny of opioid prescribing seem to include a perception that the death rate from *prescription* opioids can be reduced with best practices and that the use of these substances illicitly carries an increasing risk of death. Figure 21.7 depicts the projected death rates from opioids based upon model-

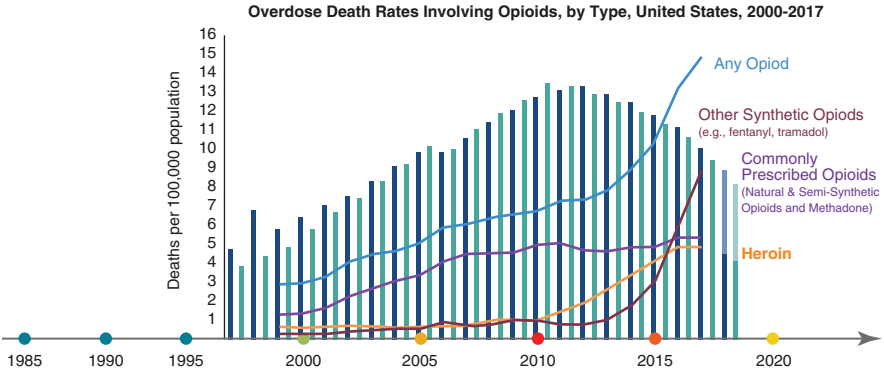


Fig. 21.6 This figure overlays the timeline and opioid dosing information depicted in Fig. 21.3 with the mortality data from Fig. 21.4. This composite allows the simultaneous comparison of public sentiment reflected by the colored dots in the *x*-axis with the dosing information from prescribed opioids illustrated by the yearly bar graphs of prescribed drugs with the line drawing of deaths. This overlay is provided to reinforce the separation of the prescribing opioid rate from the opioid death rate. As the first wave of the opioid epidemic has passed, the impact of the resulting development in guidelines, regulatory changes, and provider awareness of risk has clearly led to a decline in prescription-related deaths while the simultaneous impact of our culturally reinforced illicit drug market is threatening increased lives with each passing year

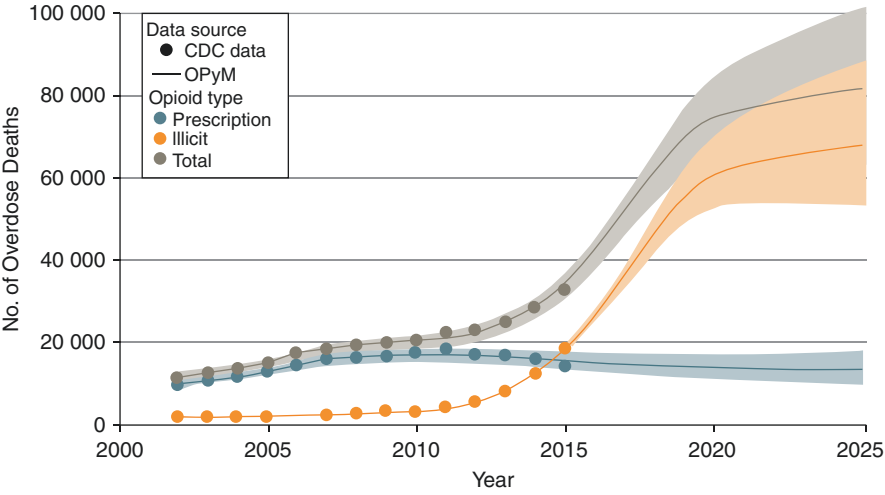


Fig. 21.7 This figure combines the death rate from opioids as reflected in Fig. 21.5 and expands them with predicted modeling of death rates for each of the three waves contributing to the epidemic. As the death rate from prescription-related deaths continues to fall, the death rates from illicit heroin and fentanyl continue to escalate. The importance of understanding this shifting threat is made more clear as we observe the lifesaving benefit of opioid education and regulation, which is that it improves the safety for prescribed drugs while simultaneously having no apparent impact on overall opioid deaths

ing from historical trends. The primary focus on prescribed medications has shown some success.

In retrospect, while the contributions of prescription opioids to the opioid-induced death rate in America appear clear, the evolution of more careful and reduced prescribing of these drugs has now lowered the prescription opioid death rate. Speculation and anecdotes of patients losing access to prescribed drugs may still be leading users to shift to illicit drugs with greater risk of harm, but the concept that prescription drugs are the gateway to illicit drug use is without evidence. One unintended and perhaps unrecoverable consequence of a reduction in demand and supply of prescription opioids may be the increasing abandonment of chronic opioid-using patients by a growing number of physicians no longer willing to prescribe them. This impact does not explain the continued growth of first-time users of illicit drug. There is an increasing opioid death rate in America, and it is no longer being caused by the prescription drug overdoses first identified in 2011. The current threat is a much more concerning one that is outside the scope of this chapter. This is the threat of an illicit marketplace that is unregulated where the scientific knowledge and safe practices developed for prescription opioid are not valued and cannot be shared to impact the behaviors of illicit use to curb the exposure.

As clinicians, our focus needs to shift from the pro-prescribing days of the late 1990s and early twenty-first century to a better informed and safer prescribing based upon the individualization of opioid treatment planning that evaluates risk and monitors safe use in order to provide access to reduced pain and suffering for those who can benefit from these medications and limit opioid-related harms to those who cannot. Those patients who are at low risk for opioid-related harms and who have no access geographically or economically to pain treatment alternatives should be offered these drugs under safe prescribing Standards of Care. For those patients who are at high risk, a continued search of risk reduction through alternative medications or treatment processes must be encouraged.

Outpatient encounters have traditionally provided the means to monitor and manage these complex issues. This has proven to be a questionable means based on a study of Veterans Health Administration patients who experienced unintentional prescription opioid overdoses [21].

In this population, it was observed that 33% of patients were seen in outpatient settings 1 week prior to their overdose and 62% within 1 month of their overdose. Only 15% of the patients received an opioid prescription during the visit prior to their accidental overdose or death.

Clinical Practice Guidelines

The opioid conquest of pain first suggested in 1986 by Dr. Portenoy and Foley in their well-intended but unsupported promotion of these drugs for chronic pain sufferers has provided tens of thousands of patient reminders of the risks of these drugs. Within the United States, risks of escalating prescription opioid deaths from

respiratory depression [9] and motor vehicle fatalities [22] while taking opioids has been shown. Additionally, the risk of substance use disorder including, but not limited to, addiction has developed in response to therapeutic use of these medications in growing numbers of patients [23, 24].

The problems of opioid-related adverse effects must be addressed. The problems of opioid tolerance, opioid hyperalgesia [24], opioid-induced endocrinopathy, constipation, and renal insufficiency can be managed and communicated to the opioid consumer as a part of the informed consent obtained for the use of chronic opioid therapy (COT) [24]. However, the management of those problems for the appropriately chosen patient still requires increased attention. The detailed discussion of these problems and risks is beyond the scope of this chapter but remains a valuable and ongoing dialogue between provider and patient for COT. These consequences are providing a growing incentive to identify the risk factors that determine the patients who will develop these adverse effects so that those effects can be predicted and either avoided or mitigated.

Enter practice guidelines, informed partially by evidence and partially by opinion, establishing a new labyrinthian framework that promises improved safety while adding incalculable burden to the therapeutic use of these medications. The goal appears to be an evolution in the Standard of Care for medical pain treatment and the use of opioids in particular [23]. Urine drug monitoring, prescription drug monitoring programs, fixed length-fixed format self-administered questionnaires, controlled prescription quantities, entangling opioid treatment agreements, and careful monitoring practices are the tools of these guidelines. It should be noted that the focus of the guidelines centers around the outpatient encounter relating to prescribing opioid refills and not necessarily during routine follow-up care.

In general, most guidelines in place today address a similar set of recommended practices. These recommendations are generally performed as part of the prescribing or refill process which may not necessarily occur on usual or regular timeframes. The more confusing and controversial of these guidelines are reviewed below.

Table 21.2 provides a comparison of the Medical Board of California and CDC guidelines revealing a large amount of overlap. These recommendations are in part based on evidence provided by risk reduction research and also contain what is currently promoted as the safest practice to avoid accidental death.

Urine Drug Testing

Perhaps the first and potentially most overused of the new tools of treatment guidelines is urine drug testing. Urine drug testing (UDT) offers evidence of analgesic use adherence while simultaneously assessing risk from illicit use. By identifying predicted metabolites in the urine of those who were prescribed medications, prescribers can be offered some reassurance that those who were prescribed these controlled substances are using them. While current science does not support the rendering of an absolute indemnification from diversion, as partial drug diversion

Table 21.2 Comparison of the documentation requirements between the Medical Board of California and the Center for Disease Control guidelines

Guideline requirement	CA MBC guideline	CDC guideline
Documented diagnosis		
MED factor calculation		
Opioid risk assessment		
Review of concurrent medications and conditions		
Functional goal setting		
Functional monitoring		
Pain score monitoring		
Documented optimization of non-opioid therapies		
Assessment of side effects and aberrant behaviors		
At least quarterly office visits		
At least quarterly PDMP review		
At least quarterly patient education about opioid risk and access to non-opioid and non-medication treatments for chronic pain		
At least yearly urine drug testing order and review		
At least yearly medication weaning attempts		
Naloxone prescription consideration		
Other clinical monitoring as needed (e.g., for methadone, risk assessment for QT prolongation and consideration of ECG)		

with partial use would provide identical to no diversion results, it does offer a partial protection from this concern. This benefit allows many patients and providers alike to feel confident that there is objective evidence supporting the prescribed use of the drugs at least in part for their intended purpose.

A second concern described in a subset of COT patients is combined risk from concurrent illicit or combined opioid and sedative use that would escalate the risk of harm. This testing has been largely applied from the forensic testing of body fluids that accompanied the required monitoring of US Department of Transportation registered drivers who must maintain an exclusive prohibition of controlled substances and alcohol from their bodies to maintain their licensing for work. The recommendations for random nature of the testing and the rigorous analysis of the specimen to establish origins of any unexpected findings have been incorporated into the application of UDT for clinical opioid prescribing practice. This forensic evaluation for compliance testing was quickly endorsed by prescribers and regulators suspicious of concurrent illicit use.

Perhaps because of the very objective end points, UDT has emerged as a recommended random assessment in most guidelines on at least an annual basis to establish the security of prescribed drugs from potential diversions which could harm other unintended consumers of the prescribed medications. This benefit combined with the reduction of potential harm to the intended therapeutic user choosing to consume illicit or other sedative prescribed medications without the provider's knowledge has been driving this adoption.

At present, the current state-of-the-art testing includes witnessed random testing of urine with a point-of-care device employing immunoassay methodology to allow for instantaneous results that establishes both the presence of anticipated drug metabolites and the absence of unexpected drugs in the consumer's body. Limitations of an immunoassay screen, however, include having a high threshold of detectability and only providing qualitative information about a select number of drug classes. Because of these restrictions, clinicians should understand that immunoassay screens have high false-positive and false-negative rates. Despite these limitations, the results can assist the clinician with making preliminary treatment decisions. Unexpected results in these point-of-care tests then trigger a formal analytical chemistry review of the UDT findings to allow more careful forensic analysis with possible details confirming the findings. The lower threshold of detectability and combined qualitative and quantitative information of a laboratory test offer complementary advantages to the use of this tool in clinical practice. A laboratory urine drug test's greater degree of specificity allows for a relatively low false-negative and false-positive rate in contrast to an immunoassay screen. Like any other diagnostic test, an immunoassay screen and a confirmatory urine drug test both possess limitations.

Unfortunately, like many tests, UDT can be overused. Some practices have chosen to apply such tests at every visit and associate such testing even in low-risk individuals with increased charges for testing, an interpretation when no such frequent testing is warranted. Other more entrepreneurial physicians choosing to invest in testing equipment and staff to operate locally at their in-office lab also establish a conflict of interest with the development of prescribing policies. These policies mandate such testing on a frequent interval while failing to communicate the conflict of interest in such operations which may be secret and pecuniary when evaluated from a billing perspective. I anticipate that this area of opioid monitoring may benefit from further development of evidence-based guidelines and the application of appropriate antitrust review to avoid conflicts of interest.

Prescription Drug Monitoring Programs

Concern over doctor shopping by drug-addicted patients where a single patient would be prescribed opioid medication by several different physicians simultaneously led to a demand for a prescription drug monitoring program for the use of prescribing physicians. The hope was that by identifying these at-risk patients, prescribers would reduce the risk of self-harm by them and diversion of their prescribed drugs to other unintended consumers. The logic of developing such programs has led to nearly complete adoption of prescription drug monitoring programs (PDMPs) across America [25]. The increasing regulatory obligation of providers to check the available information resident within the PDMPs seems ongoing while increasing the burden on the prescribing physician with anticipated rejection of the prescribing role continues.

Controlled Prescription Quantities

The demand for monitoring of opioid use profiles across large segments of the population for epidemiologic purposes led to the development of concepts of Morphine Equivalent Daily Dose (MEDD) and Morphine Milligram Equivalent (MME). These epidemiologically derived dose equivalencies developed for studying populations have allowed for the identification of opioid dose-related risks of sudden death [21]. Application of these data to the population being prescribed medications has allowed the establishment of lower risk and higher risk patient groups where specialty provider input and oversight may be needed. While the level at which higher risk of sudden death necessitates pain specialty review differs across guidelines, most guidelines have adopted a daily dose-related risk qualifier. As an illustration in the State of California, the Medical Board of California (MBC) Guidelines for controlled substance prescribing cites an MME of 80 as the transition point for engaging a pain specialist, while the CDC establishes the transition at MME = 50 [9].

While the intention of such dose-related risk assessments are unquestioningly benevolent, the implementation of those guidelines has been restrictive and possibly punitive to the patient using opioids for pain control. A retrospective 5-year analysis of the impact of Ohio prescribing guidelines for ED clinicians showed a 39.7% decrease in total number of prescriptions and a 28.3% decrease in prescriptions of more than 3 days of opioids [26]. Not surprisingly, in the United States, where payer systems define access to specific benefits, the application of payer-specific regulations to these well-intended guidelines has created a fracturing of the Standard of Care for patients using these medications on a therapeutic basis. The "Standard of Care," defined as "what a reasonably prudent physician of the same specialty would choose to do under the same or similar circumstances," is being disrupted by the application of payer-specific quotas, monthly prescription limits, lack of covered alternatives, and other restrictive policy procedures and processes [27].

Consequences of the Regulatory Interference

There has been a reported decline in the number of prescriptions and an estimated reduction in the number of prescribing physicians [28]. There has also been a decline in prescription opioid-related deaths that appears responsive [29]. There have been no widespread published estimates of any corresponding increase in reported pain or limited access to opioids from pain patients, but it has been recognized that the CDC opioid prescribing guidelines advice has been misused in ways that can harm patients, specifically with respect to the application of recommended dosages, duration thresholds, hard limits, rapid tapering, and sudden discontinuation [30]. Numerous anecdotal examples and patient accounts of chronic pain management adversely impacted by reduced prescribing can be found by performing a Google search on "patients harmed by opioid restrictions." It has been noted that patients "may be increasingly unable to access safe amounts of opioids when needed for pain control" [28].

These later changes are likely to be a result of the labyrinthine implementation of new rules, regulations, and hassles regarding the prescription of opioids to patients regardless of their need. Providers who are interested in continuing the prescribing of these medications to assist those in pain who are at low risk and showing long-term benefit from them are facing the implementation of new policy, procedure, and process in their practice to comply with the guidelines.

The increase in direct cost for guideline compliance to a practice is a concern. But this must be balanced with escalating malpractice insurance cost defending both administrative accusations from the Medical Board (MBC Death Certificate Project) and potential malpractice and criminal liabilities from overprescribing. The public shaming of providers who face accusation of intentional harm to patients that they were intending to help is perhaps the most concerning impact. If we can retain the prescribing physicians and empower them with cost-effective tools to identify, analyze, and manage the risks to their patients, we may be able to prevent the loss of access to these important tools in the United States.

The increased cost of these tests and systems and the increase in patient and provider time in compliance with these new guidelines are changes that will continue to impact healthcare until an ideal practice can be implemented. Today, more than 50% of opioid prescriptions are written by primary care physicians to address the needs of the large population affected by chronic disease [31]. Typically, primary care physicians do not have the time or expertise to meet the compliance requirements of the prescribing guidelines for opioid therapies [32]. Pearson found that among primary care prescribers, the majority of respondents (over 60%) did not feel confident managing patients with chronic pain, including opioid prescribing, but had increased confidence following an opioid therapy protocol for managing opioids and the capability to identify patients at risk for opioid misuse.

Today, 60% of US adults have one or more chronic conditions that are typically managed in primary care [33]. For adults aged 65 years and older, 81% are afflicted with two or more chronic diseases. For adults aged 40–64 years, 50% are afflicted with two or more chronic diseases. Opioids are not necessarily prescribed for diagnosis limited to chronic pain and are often used to manage pain associated with symptoms related to other chronic conditions. This can include diabetes, hypertension, mood disorders, coronary atherosclerosis and other heart diseases, inflammatory joint disorders, arthritis, upper respiratory disorders (chronic laryngitis, chronic sinusitis), anxiety disorders, asthma, and neuropathic and rheumatic conditions. Twenty-nine percent of opioid prescriptions between 2006 and 2015 were written without an accompanying diagnosis of pain or other indication [34]. Daily opioid use in these chronic conditions has been demonstrated to improve physical function, decrease pain, and improve overall health compared to no opioid therapy [35] (Fig. 21.8).

Opioids are commonly used to treat pain associated with chronic disease. Chronic opioid use in hypertension is estimated at almost 30%, and hypertension with systemic inflammatory diseases is almost 50% [36]. Chronic opioid use in peripheral vascular disease was found to be almost 25–30% [37]. According to Sodore, “adults living with type 2 diabetes are suffering from incredibly high rates of pain and non-

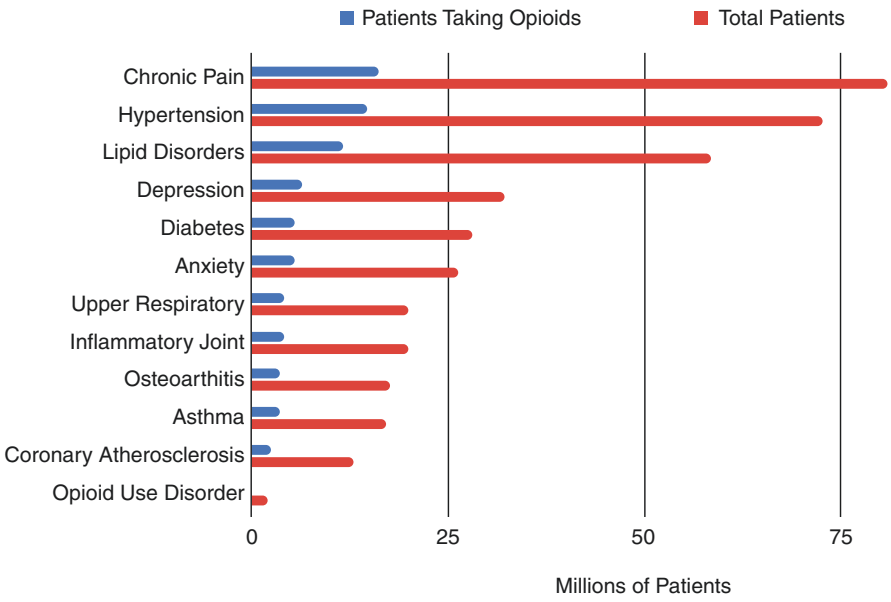


Fig. 21.8 This figure illustrates long-term opioid use across a range of chronic diseases. This figure shows that each chronic condition has roughly 20–30% of the afflicted population receiving long-term opioid therapy

pain symptoms, at levels similar to patients living with cancer" [38, 39]. Across many of these conditions, there may be between 20% and 30% of patients receiving long-term opioid therapy as a component of disease management [36, 37, 40–44]. It is clear that opioid reliance in primary care is likely to remain. This may reflect a practical approach to palliative symptom management based on the aging demographics that reflect a high prevalence of multiple chronic conditions. Most of the population is either geographically or economically restricted to these therapies due to custom and practice. A rational approach to the treatment of pain in the coming decade needs to include opioids.

A Case for Technology

A recent trend in chronic disease monitoring is the remote monitoring and self-monitoring that exist outside of the outpatient setting. The objective of these models is to manage chronic disease by focusing on preventative measures employing more continuous monitoring instead of emergency care and hospital admissions. There are demonstrable cost savings using this approach [45]. There is also evidence that a patient's willingness to self-monitor might be associated with disease control [46]. Early work in this area continues to demonstrate that remote monitoring shows promise in improving clinical outcomes for patients [47]. While there has been

demonstrated success with hypertension, diabetes, and other chronic diseases, there are currently no remote monitoring applications for the monitoring of opioids as part of a chronic disease treatment plan. It is not hard to imagine that 1 day we will see the development of safety and outcomes remote patient] monitoring solutions that measure patient function and satisfaction and can detect accidental overdose, sleep apnea, and other patient safety threats. Development of these systems would allow automation of the information collection and adherence monitoring to the many opioid prescribing guidelines.

As society moves into an era of self-monitoring, enabled by smartphones, activity trackers, fitness sensors, and sleep monitors, each person will become a silo of their "big data" [48]. The challenge will be how to apply all of this information to answer the following questions: "Does this patient receive a functional benefit from the current opioid therapy? Is the patient compliant? Is it within an acceptable margin of safety for the patient?" Clearly, it would be very easy to overwhelm the prescriber with vast amounts of patient data, and it would be difficult to know how to interpret the data within the timeframe of a clinical encounter. Artificial intelligence (AI) has the promise of monitoring and analyzing all of this data to provide an assessment and interpretation for the clinician. AI has already demonstrated the capability to measure impairment as well as detect alcohol consumption episodes using smartphone accelerometer data [49]. The same smartphone can also be used to detect human emotions, detect fall activities, recognize human activities, and detect overdose in real time [50–52]. As the features mature, there can be no doubt that they will be integrated into single applications capable of alerting and presenting necessary information to prescribers to determine patient risk and opioid efficacy. In the not-too-distant future, AI may provide the oversight and monitoring that will enable prescribers to utilize opioids in a safer and more effective manner with their patients.

While the magnitude of the unmet chronic pain problem in the United States has not improved under high-dose chronic opioid therapy, these treatments remain a valuable tool for some patients. The disadvantages of opioid-related cognitive impairment, addiction, dependence, tolerance, hyperalgesia, endocrinopathy, constipation, renal insufficiency, and pruritus have however taught prescribers and patients valuable lessons about the safe and effective use of opioids in selected patients. While Karl Marx may be correct that "religion may remain the opioid for the masses," opioids have an important clinical place for large numbers of suffering patients. The application of current evidence-based practice guidelines with technology-assisted education, monitoring, and analysis offers optimization with access to high-quality, predictable, safer, and affordable opioid pain treatment that virtually no other pain therapy can offer. At a time where the promise of genomic testing of individuals may offer pharmacogenomic matches of the best opioid to treat a patient's pain, we must implement these time-proven but risky tools rather than abandon them. Care providers are called to continue pursuing the best treatment for patients with pain. As a society, we need to strive for better drugs, better information, and best practices that allow for these agents to be broadly employed with both care and compassion in order to maximize their effect on the treatment of our patients.

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Chapter 22
Opioid Alternative Medication and Clinical Dilemmas

Stephen T. Krazit

Opioid Alternative Medications and Clinical Dilemmas

Chronic pain is one of the most common reasons for patients to seek medical care. There are numerous ways in which this pain can be addressed through medication. Chronic pain is difficult to treat as conditions that can cause pain are not uniform and cases are not always responsive to specific treatments. Currently, there is great interest in providing pharmaceutical analgesia without the use of opioid medications. There are many well-established options that can be used as alternatives to opioid medications. The aim of this chapter is to provide examples of treatment options that have been supported by research and evidence, as well as to highlight options that are emerging.

We will briefly discuss the general initial recommendations for the treatment of neuropathic and nociceptive pain, as these conditions may be more receptive to differing medications. These two conditions can overlap and may not always fully describe complex types of pain.

Neuropathic Pain

When confronted with a patient with neuropathic pain, the primary goal should be to establish a diagnosis if possible. If a diagnosis can be ascertained, then a specific treatment may be pursued [1]. When choosing pharmacologic management, the choice of an initial medication may be led by individual patient factors, including

S. T. Krazit (✉)
Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: Stephen.Krazit@utsouthwestern.edu

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comorbidities, symptoms, medication interactions, and pain pathophysiology among other variables. Sometimes, there are well-known medications for specific causes of neuropathic pain, such as carbamazepine which is a first-line treatment for trigeminal neuralgia.

Although there have been multiple evidence-based guidelines published [2–6], possible shortcomings exist including lack of head-to-head drug comparison, limited available evidence, short study length, and variation in specific drug recommendations for the pharmacologic treatment between multiple guidelines. Many studies of pharmacologic therapy have focused on monotherapy for a specific etiology, such as postherpetic neuropathy, which may not be applicable to other neuropathic pain conditions.

There is general consensus about the classes of drugs that have proven efficacy and should be considered for first-line or subsequent therapy [2–7]. This consensus states that initial pharmacologic treatment of neuropathic pain should involve either antidepressants (tricyclic antidepressants or selective serotonin norepinephrine reuptake inhibitors) or calcium channel alpha 2-delta ligands. Topical therapy may be utilized when pain is localized [1, 8].

Multimodal therapy is often required as less than half of patients with neuropathic pain will respond to a single agent [9]. However, there is not much evidence regarding the efficacy and safety of combination treatment.

Nociceptive Pain

The pharmacologic approach to nociceptive pain primarily involves non-narcotic analgesia. Medication is commonly used in conjunction with nonpharmacologic therapies and approaches to relieve the source of the pain.

Primary pharmacotherapy treatment for nociceptive pain tends to be either acetaminophen or oral nonsteroidal anti-inflammatory drugs. Acetaminophen is typically recommended as first-line therapy for pain related to osteoarthritis [10, 11] and chronic low back pain [12]. However, acetaminophen may be less effective than nonsteroidal anti-inflammatory drugs (NSAIDs) [13, 14], which is also a first-line agent for mild-to-moderate chronic low back pain or osteoarthritis [15, 16].

This chapter discusses individual medications and classes, their indications, and possible contraindications as far as disease concerns or clinical dilemmas.

Acetaminophen

Acetaminophen is the most widely used analgesic in the United States [18] and is included as a component in many prescription and nonprescription pain medications. Acetaminophen is typically recommended as first-line pharmacotherapy for nociceptive pain related to osteoarthritis [10, 11] and chronic low back pain [12]; however, it has been used for many different types of pain that may be of somatic origin.

Clinical Concerns

The main concern for a potential clinical dilemma involving acetaminophen is the potential for hepatotoxicity [18]. In patients who have hepatic impairment or chronic alcohol use, caution should be exercised with this medication. Overdose can lead to severe hepatotoxicity and is the most common cause of acute liver failure in the United States [19]. Even at therapeutic doses, the possibility of hepatotoxicity exists, especially in patients with chronic alcohol use or liver disease [20]. Some studies have shown that at therapeutic doses, four or more days of treatment with acetaminophen may lead to asymptomatic increases of blood hepatic aminotransferase concentrations [18], although these increases do not necessarily suggest an increased risk of progression to acute liver failure.

Heavy alcohol use or significant liver disease may be considered a relative contraindication to acetaminophen use. Maximum safe dose in this patient population is thought to be lower than in healthy patients.

Other possible adverse effects that have been associated with acetaminophen include chronic kidney disease, hypertension, and peptic ulcer disease.

NSAIDs

The other class of first-line agent in nociceptive pain is an oral nonsteroidal anti-inflammatory drug (NSAID) [15, 16]. NSAIDs are primarily indicated for mild-to-moderate pain, particularly of somatic origin, although a number of newer compounds carry an indication for severe pain. As with acetaminophen, they are frequently used for soft-tissue injury, headaches, and arthritis. They also exert synergy when paired with opioids, producing a dose-sparing effect.

A systematic review of NSAIDs for the treatment of low back pain found that NSAIDs were more effective than placebo for pain relief [21]. Although several guidelines recommend oral NSAIDs as a first-line therapy in selected patients [11, 12], for patients with localized pain in specific joints, topical NSAIDs may be a reasonable option for a trial of therapy [22, 23].

Within the NSAID medication, a category exists consisting of selective cyclooxygenase 2 inhibitors (COX-2 inhibitors), such as celecoxib. Based on a systematic review and meta-analysis, these COX-2 inhibitors were found to be equal to nonselective NSAIDs for treating soft-tissue pain following injuries with less gastrointestinal adverse effects than NSAIDs [24]. Many NSAIDs exist; however, little literature exists that shows improved efficacy of one NSAID over another [21].

Clinical Concerns

There are many clinical concerns with the administration of NSAIDs in terms of adverse effects. These adverse effects mainly include inhibition of platelets, gastrointestinal insult, renal insult, and adverse cardiovascular effects. The risk of adverse

effects due to NSAIDs may be enhanced by increased drug dose, drug–drug interactions, and medical comorbidities [28]. Due to common mechanisms of action and the effects of the other factors that increase risk of adverse effects, there may not be a "safest" medication in the NSAID family. Increasing the dose of any NSAID is associated with an increased risk of most related toxicities.

Additionally, there is potential drug interaction with medications commonly prescribed to patients with heart disease, most notably antihypertensive drugs [25], warfarin [26], and low-dose aspirin [27]. Regular NSAID use should be avoided in patients taking low-dose aspirin for cardiovascular protection as most NSAIDs interfere with platelet aggregation with the exception of the selective COX-2 inhibitors [31]. This interference means that NSAIDs decrease the cardioprotective effect of aspirin in patients with heart disease, potentially exacerbate heart failure, and may raise blood pressure. Chronic and short-term uses have been shown to increase risk for adverse cardiovascular events including myocardial infarction and stroke [29, 30]. NSAIDs have some prothrombotic effects and are relatively contraindicated in patients with a history of venous thrombosis. In patients with or at risk for cardiovascular disease, NSAIDs should be used in the lowest effective dose, for the shortest duration necessary.

The potential gastrointestinal side effects include dyspepsia and gastric ulceration. Patients who are at high risk for peptic ulcer disease or its complications have a relative contraindication to the use of an NSAID. The risk of gastrointestinal toxicity is increased by a history of a gastrointestinal ulcer or hemorrhage, advanced age (over 60), high dosage of an NSAID, the concurrent use of glucocorticoids, and the concurrent use of antiplatelet agents and anticoagulants [32]. Food and antacids may help patients with less dyspepsia tolerate NSAIDs. In addition, protection against gastroduodenal toxicity can be achieved with a proton pump inhibitor. Untreated *Helicobacter pylori* infection [33] and the use of selective serotonin reuptake inhibitors (SSRIs) may also increase the risk of bleeding or perforation.

Nephrotoxicity is also associated with NSAID use, and this includes reversible renal insufficiency due to renal vasoconstriction, acute interstitial nephritis, and a predisposition to acute tubular necrosis in patients with low renal perfusion [34]. The risk of acute renal failure is increased in patients with existing renal disease, hypercalcemia, and hypovolemia. They should be avoided in patients with congestive heart failure and cirrhosis. NSAIDs can also lead to fluid retention and should be prescribed with caution in patients with hypertension or renal insufficiency.

Although rare, the primary pulmonary reactions that can occur with NSAID use include bronchospasm (which can be severe) and, rarely, pulmonary infiltrates with eosinophilia. Nonselective NSAIDs may also precipitate acute exacerbations of airway inflammation in patients with aspirin-exacerbated respiratory disease (AERD). In contrast, the selective COX-2 inhibitors are much less likely to trigger AERD in patients with this syndrome.

A small increased risk of nonunion in patients with bone fractures has been reported with the use of nonselective NSAIDs or COX-2-selective agents. A relationship of causation has not been proven, and the effect of these drugs on fracture heal-

ing in humans is uncertain. In rodent studies, both nonselective and COX-2-selective NSAIDs can interfere with normal fracture healing, an effect that appears to be mediated by the inhibition of COX-2 [35, 36]. A 2010 systematic review and meta-analysis found that the degree of risk for nonunion was significantly elevated in NSAID-exposed patients with long-bone fractures or spinal fusion [37]. However, when only the high-quality studies were considered, a significant increase in risk was not observed.

In terms of effects on tendon injury, animal studies suggest a theoretical adverse impact of some nonselective and COX-2 selective NSAIDs on healing from tendon and ligament injuries [38, 39]. However, there are no published human data demonstrating such effects.

NSAIDs should be used cautiously in older adults and generally for a limited duration, given the increased risk of toxicity in this population, including gastrointestinal bleeding, renal impairment, and heart failure.

Antidepressants

Both tricyclic antidepressants (TCAs) and serotonin norepinephrine reuptake inhibitors (SNRIs) possess analgesic qualities, while the evidence for the effectiveness of selective serotonin reuptake inhibitors (SSRIs) is weaker [40].

Multiple studies have found that antidepressants provide effective pain relief in neuropathic pain conditions [41–44]. Antidepressants may also be effective for other painful conditions such as fibromyalgia or chronic back pain.

Analgesic antidepressants may provide pain relief separate from their antidepressant effects as analgesic effects may occur earlier and at lower doses than for antidepressant effects. In addition, the analgesic efficacy of antidepressants in neuropathic pain has been established in nondepressed patients.

Pain may also worsen concurrent depression. A 2014 review found consistent evidence suggesting that treatment of pain can improve response to treatments for depression [45]. In patients with concurrent depression and musculoskeletal pain, severity scores in both pain and depression may be decreased with treatment of antidepressants [46].

TCA

Tricyclic antidepressants (TCAs) are pharmacological mainstay in a variety of chronic pain states, with or without coexisting depression. TCAs are believed to have independent analgesic effects as well as an ability to relieve the depressive symptoms associated with chronic pain.

Of the tricyclic antidepressants, amitriptyline has been the most widely studied TCA in chronic pain [47, 48]. Amitriptyline and nortriptyline have been shown in

randomly controlled trials to relieve numerous neuropathic pain syndromes, including central poststroke pain, postherpetic neuralgia, painful diabetic and nondiabetic polyneuropathy, and postmastectomy pain syndrome. Less convincing results have been seen in spinal cord injury pain [49], HIV neuropathy, or phantom limb pain [50]. A number of other TCAs, including doxepin, imipramine, and desipramine, also have been used with success. Systematic reviews have also corroborated this evidence, consistently showing in placebo-controlled the efficacy of TCAs in the treatment of patients with neuropathic pain [51].

Secondary amine TCAs (nortriptyline and desipramine) are preferred because they are better tolerated than tertiary amine TCAs (amitriptyline and imipramine) but have comparable analgesic efficacy [51].

TCAs are typically prescribed at lower doses for chronic pain as opposed to depression, although higher doses have provided superior analgesia in some studies. Some patients respond only as the dose is steadily increased. The onset of analgesia may be after 1 week and typically occurs at lower doses than needed for the treatment of depression [6].

Clinical Concerns

TCAs are associated with multiple undesirable adverse effects that vary depending on the medication. These adverse effects include anticholinergic effects, antihistaminergic effects, alpha-1 adrenergic receptor blockade, and cardiac effects. Additionally, TCAs can cause sedation.

TCAs should be avoided in people who have cardiac conduction system disease [53] as TCAs have been associated with heart block, ventricular arrhythmias, and sudden death. Patients should have ECG screening done if they are over 40 years old or have a positive history of cardiac conduction system disease [6]. Patients with coronary artery disease or at risk may benefit from a non-TCA medication although this is not a universally accepted [54].

TCAs are recommended as a second-line medication among chronic kidney disease patients if gabapentin or pregabalin is not effective. This is due to the side effects of TCAs being more common. The aforementioned tachyarrhythmias are also a concern among CKD patients, given the high burden of cardiovascular disease in CKD.

TCAs may also lower seizure threshold in patients with a history of seizures, with traumatic brain injury, with alcoholism, or in any other therapy.

The possible anticholinergic effects of TCAs should be a cause of caution for use in patients with decreased GI motility, increased intraocular pressure, narrow-angle glaucoma, or urinary retention. The anticholinergic effects are less pronounced in secondary amine TCAs.

When patients are using other antidepressants such as SSRI and SNRIs, one should be aware of potential QT-interval prolongation as well as serotonin syndrome. The use of TCAs in a patient with bipolar disorder may precipitate mania or hypomania.

Based on the side effect profiles, the use of the secondary amine TCAs is recommended over the tertiary amine TCAS in older patients.

SNRI

Venlafaxine, desvenlafaxine, duloxetine, and milnacipran are the four serotonin norepinephrine reuptake inhibitors (SNRIs) that are available in the United States. Duloxetine and venlafaxine have been studied in peripheral neuropathic pain, while milnacipran has been studied only in fibromyalgia.

Serotonin and norepinephrine reuptake inhibitors such as duloxetine and venlafaxine have been shown to have effect in painful polyneuropathies, more-so than tricyclic antidepressants [44].

For postherpetic neuralgia, there are similar results for the SNRI and TCA [55].

Duloxetine has been shown to be effective in the treatment of painful diabetic polyneuropathy (DPN), fibromyalgia, as well as chronic lower back pain and osteoarthritis [55–57], leading to approval by the US Food and Drug Administration for the treatment of these types of pain.

A systematic review found evidence that duloxetine was more effective than placebo with response rates suggesting efficacy similar to other antidepressants [58]. Additionally, in patients with chronic low back pain, duloxetine has been reported with a reduction in pain greater than placebo [59–61]. However, all trials were sponsored by the drug manufacturer, differences were small, and patients were more likely to discontinue duloxetine compared with placebo due to adverse effects. Significantly greater pain relief has also been seen in painful DPN compared with placebo [55].

Venlafaxine is an SNRI that inhibits serotonin reuptake at lower dosages and both serotonin and norepinephrine reuptake at higher dosages. Efficacy was demonstrated in patients with painful polyneuropathies including DPN [62, 63].

Desvenlafaxine has been found by some trials to be effective for DPN [64], while milnacipran is FDA approved for the treatment of fibromyalgia.

Clinical Concerns

SNRIs have a generally favorable side effect profile. Nausea is the most common side effect, but it occurs less frequently with initiation of low dosages and gradual titration increase. Other side effects include dry mouth, insomnia, drowsiness, constipation, fatigue, and dizziness.

SNRIs should be avoided in patients with hepatic or severe renal insufficiency. Gradual tapering is recommended at discontinuation to avoid withdrawal symptoms.

In trials, only venlafaxine has been shown to occasionally lead to ECG changes [65] and blood pressure increases have been reported. In patients with cardiovascular risk factors, caution with prescribing should be exercised and monitoring is recommended in this patient population.

SSRI and Other Antidepressants

The SSRIs citalopram and paroxetine showed limited evidence of efficacy in RCTs in painful DPN but fluoxetine did not [66, 67]. Based on the results of these trials, bupropion, citalopram, and paroxetine are options for patients who have not responded to an adequate trial of a TCA or SNRI when additional treatment with a medication with analgesic and antidepressant effects is being considered.

Analgesia with SSRIs may be associated with the primary relief of depression, especially in somatically expressive instances of depression. In many of these patients, effective treatment of the primary depression can ameliorate or even resolve the complaint of chronic pain. In patients with chronic pain that may lead to depression, a favorable response to an SSRI may greatly relieve the subjective experience of distress linked to their experience of physical pain [69].

SSRIs have been studied as possible therapy for fibromyalgia. Trials of fluoxetine have shown mixed results [70, 71], and small trials of citalopram [72], paroxetine [73], and fluvoxamine [74] have been inconclusive. A 2015 systematic review and meta-analysis of randomized trials of SSRIs found that more patients showed a 30% pain reduction in pain with SSRIs compared with placebo and significant global improvement [75]. Levels of depression also decreased in the treated patients, and the drugs were well tolerated. Thus, in some patients, a trial of these agents may be warranted. In particular of the SSRI studied: with fluoxetine, fixed lower doses may not be superior to placebo [71], but with dose escalation, fluoxetine may be significantly more effective than placebo [70]. Like the SNRIs, the effect on pain was independent of change in mood. In a trial of paroxetine, some fibromyalgia patients had an improvement compared with those receiving placebos. Fluvoxamine and citalopram studies have had inconsistent results [72, 74].

In small trials of bupropion (a norepinephrine and dopamine reuptake inhibitor), some efficacy in relieving various peripheral and central neuropathic pain conditions has been observed [76].

Clinical Concerns

The SSRIs tend to be better tolerated than tricyclic antidepressants [77] and have similar side effect profiles [77] although certain medications may be more likely to cause specific side effects. Nausea and sedation may be more likely to occur with paroxetine and fluvoxamine, diarrhea with sertraline, and activation may be more likely to occur with fluoxetine and sertraline [79]. Therefore, some patients who cannot tolerate one SSRI may do well with another [78].

SSRIs can prolong the corrected QT interval [80]. The SSRI with the highest value for QTc prolongation was citalopram. Therefore, caution should be used in prescribing these medications in patients with cardiac conduction disease.

Multiple meta-analyses of observational studies suggest that SSRIs are associated with an elevated risk of upper gastrointestinal bleeding [81]; however, the absolute

risk is low [82]. The risk increases when SSRIs are given in conjunction with NSAIDs. Based on these findings, discretion should be exercised in patients who may be at high risk for bleeding or are also taking NSAIDs.

Several observational studies suggest that SSRIs are associated with new-onset stroke; however, many randomized trials indicate that SSRIs may offer protective effects for patients who have suffered a stroke [83]. The absolute risk of any stroke in patients using SSRIs was thought to be very low [83]. Most evidence suggests that SSRIs do not increase the risk of death in patients with strokes.

Many observational studies have found an association between SSRI use and bone fractures, although these studies have not shown causality [84, 85].

SSRIs may also increase the risk of serotonin syndrome, and one should be cognizant if they are used with other serotonergic medications.

Gabapentin and Pregabalin

Gabapentin and pregabalin bind to the voltage-gated calcium channels at the alpha 2-delta subunit and inhibit neurotransmitter release. When examined against placebo, they have been shown to be efficacious in several neuropathic pain conditions [6, 8, 86].

Gabapentin has primarily been studied and found effective for the treatment of postherpetic neuralgia and painful diabetic neuropathy [87]. Several large trials have documented moderate effect on pain and quality of life measures, including mood and sleep disturbance in mixed neuropathic pain states, postherpetic neuralgia, painful diabetic neuropathy, and spinal cord injury.

Some studies have shown that the efficacy of gabapentin in the treatment of painful diabetic neuropathy is similar to amitriptyline [88]. Gabapentin in addition to antidepressants such as SNRIs may have a synergistic effect on pain improvement as opposed to single medication therapy [89].

Pregabalin may provide analgesia more quickly than gabapentin, as some trials have shown that it was efficacious at a lower initial dose with less time needed to titrate to a full dose [90]. A systemic review has shown pregabalin to be more effective than placebo in patients with postherpetic neuralgia, painful diabetic neuropathy, central neuropathic pain, or fibromyalgia [91]. The response rates may be lower for patients with central neuropathic pain or fibromyalgia as compared to postherpetic neuralgia or painful diabetic neuropathy.

Clinical Concerns

Although efficacy and toxicity profiles appear to be similar, gabapentin tends to me more widely used than pregabalin because it is generally the less expensive agent. Both gabapentin and pregabalin can produce dose-dependent dizziness and sedation that can be reduced by starting with lower doses and titrating slowly.

Pregabalin and gabapentin should be administered cautiously to patients who are receiving other analgesics and sedatives. In patients receiving prescription opioids, concomitant prescription of pregabalin was associated with a dose-related increase in the risk of opioid-related mortality [92]. Similar results have been reported for co-administration of opioids and gabapentin [93]. The data regarding both respiratory depression and abuse potential with both drugs are evolving. Due to potential abuse, potential caution should be exercised when prescribing these drugs to gabapentinoid-naïve patients [94, 95]. Pregabalin has been reported to cause euphoria and is classified as a Schedule V controlled substance in the United States.

Gabapentin is cleared by the kidney, and elimination is reduced in patients with low glomerular filtration rate (GFR) [96]. As a result of this, CKD patients are at an increased risk for side effects such as neurotoxicity and acute kidney injury secondary to rhabdomyolysis [97]. In this population, doses should be reduced based on GFR. Lower dosing may also be utilized in older patients or those with only mild neuropathic pain.

Similarly, there have been case reports of neurotoxicity when using pregabalin in CKD patients [98]. As with gabapentin, dosing should be reduced based on kidney function. Despite this, in patients with severely reduced GFR, both medications may have a beneficial effect on the other common symptoms present with end-stage renal disease (ESRD), such as pruritus, restless legs syndrome, and poor sleep.

Other Anticonvulsants

The use of carbamazepine has been found to be effective for trigeminal neuralgia and is the first-line treatment [99]. There is limited evidence suggesting that carbamazepine is moderately effective for other chronic neuropathic pain, including painful diabetic neuropathy and poststroke pain [100]. However, due to its adverse side effect profile, other drugs may be a better choice for pain syndromes other than trigeminal neuralgia. Based on randomized controlled trials, oxcarbazepine and carbamazepine may have a comparable analgesic effect; however, there may be fewer side effects during oxcarbazepine [102].

Limited data have shown that phenytoin had a positive effect on painful diabetic neuropathy although some studies have shown no analgesic effect. In patients with acute flare-ups of various neuropathic pain conditions, intravenous phenytoin had a significant pain-relieving effect [103].

Systemic reviews of lamotrigine and levetiracetam have suggested that these medications should not be utilized for pain control, especially in light of more effective therapies [69, 104].

A review found topiramate without evidence of efficacy in diabetic neuropathic pain, the only adequately tested neuropathic condition for that drug. Additionally, the presence of adverse events is much higher with active treatment than placebo control [105]. However, significant pain improvements have been seen in migraines compared with placebo [103].

A complete blood count and baseline liver function tests should be obtained prior to starting patients on these anticonvulsants. Blood tests are recommended during initiation of therapy and routinely afterwards. Although blood levels do not generally correlate with efficacy, they may be helpful in determining compliance during dose escalations. Generally, doses are gradually titrated upward until pain symptoms are improved or adverse effects occur.

NMDA Antagonists

Ketamine

While recent consensus guidelines on the use of intravenous ketamine have found evidence supporting its use in chronic pain, many studies are limited with variation of pain condition, dosage, and frequency, as well as study size and blinding [106]. The guidelines did reference use of oral ketamine as a potential pain control modality.

Although oral ketamine has been evaluated in several placebo-controlled trials [107–110], the studies generally show no significant benefit, although there may be an opioid-sparing effect [109]. Oral ketamine tends to have poor bioavailability, and oral doses are much lower than that of IV administration. In a study utilizing oral ketamine following inpatient infusion therapy, it was found that oral ketamine was at least partially effective in the majority of patients and some experienced an opioid-sparing effect in the absence of pain reduction. However, it was found that most of the patients in this study had neuropathic pain, and those receiving opioids fared better than individuals not receiving opioid therapy [111].

Another placebo-controlled trial in a small number of patients with neuropathic pain responsive to IV ketamine, oral ketamine resulted in significantly better pain relief than placebo [112].

Compared to oral ketamine, intranasal ketamine has a higher bioavailability. It has been studied in several randomized trials in individuals with chronic pain, with results showing efficacy for breakthrough pain for a variety of chronic pain conditions in individuals with opioid tolerance [113], neuropathic pain [114], and migraines [115]. However, the analgesia was short lived, lasting less than a few hours.

In general, the use of other nonketamine NMDA-receptor antagonists has shown mixed results. High-dose dextromethorphan may have a clinically relevant effect in painful diabetic polyneuropathy but seems to lack efficacy in other neuropathic conditions. Amantadine and memantine have also shown conflicting results for neuropathic pain and possibly other chronic pain conditions that may involve central sensitization. Results of riluzole have been mostly negative [116, 117].

Overall, the guidelines found that there is low-level evidence to support the use of oral ketamine and other NMDA-receptor antagonists and moderate evidence to support intranasal ketamine as a treatment for breakthrough pain [106].

Clinical Concerns

Multiple disease concerns exist with regard to ketamine use. Ketamine should be avoided in patients with ischemic heart disease or conduction abnormalities. Additionally, in patients with severe liver disease or prone to liver disease, caution should be practiced as ketamine can cause transient changes in liver function tests. There is an addiction or abuse risk with ketamine, and it should be used very cautiously in patients with the potential for abuse. As far as psychiatric comorbidities, people with active psychosis should not take this medication. Another issue that should be considered is the potential for accidents, as ketamine may cause hallucinations and impairments in judgment, visual and perceptual functions, and psychomotor ability. This may be particularly relevant for motor vehicle collisions.

Muscle Relaxants

Many pain conditions can be present with painful muscle spasm, and muscle relaxants can be useful in treating this aspect of the patient's symptoms. Skeletal muscle relaxants are divided into two categories: antispastic (for conditions such as cerebral palsy and multiple sclerosis) and antispasmodic agents (for musculoskeletal conditions). Baclofen is the only antispastic drug indicated by the FDA for muscle spasm [118]. There is conflicting evidence on baclofen use for chronic pain; however, it may be useful in acute lower back pain [119].

Antispasmodic Agents

A systematic review found insufficient evidence to determine whether skeletal muscle relaxants are effective for subacute or chronic low back pain [120]. While short-term use may be utilized as adjunctive therapy in patients with acute exacerbations lower back pain, there are insufficient data to recommend their use for chronic stable low back pain [120]. Furthermore, available literature shows skeletal muscle relaxants are better than placebo, but not more effective than NSAIDs in patients with acute back pain. So, while acetaminophen and NSAIDs remain first-line agents for acute low back pain, skeletal muscle relaxants may be reserved as an alternative treatment option especially in patients with renal disease or at risk for gastrointestinal bleeding [12].

Of the skeletal muscle relaxants, cyclobenzaprine is the most heavily studied medication showing effectiveness [120, 122]. A meta-analysis comparing cyclobenzaprine with placebo for back and neck pain found cyclobenzaprine to be moderately more effective than placebo, despite more adverse effects [123]. Overall,

studies appear to routinely show that cyclobenzaprine has the greatest benefit during initial and not chronic treatment [122, 123].

Literature has shown that skeletal muscle relaxants are more effective as adjunctive therapy to analgesics in treating acute low back pain and that the use of combination therapy has been supported in quickening recovery. For example, in using cyclobenzaprine with naproxen, one study showed statistically significant decrease in muscle spasm and tenderness compared with naproxen alone [124]. Another review showed that tizanidine plus analgesics was more effective in providing pain relief and decreasing muscle spasm than analgesics alone [120]. This same review, however, did not show differing outcomes between drugs of this class.

Cyclobenzaprine has also been studied in treating fibromyalgia. A limited meta-analysis has found that cyclobenzaprine moderately improved sleep and pain, but long-term benefits were unknown. Additionally, even though cyclobenzaprine was better than placebo in the treatment of fibromyalgia, it was inferior to antidepressants [125].

Despite not having sufficient data as with the muscle relaxants listed thus far, metaxalone and methocarbamol may be useful in patients who cannot tolerate the sedative properties of cyclobenzaprine or tizanidine [126].

Clinical Concerns

The adverse effects of the skeletal muscle relaxants have been well publicized, with their primary effects on the central nervous system typically as dizziness and drowsiness [120]. Secondary to weak evidence for comparable effectiveness, selection of an agent should be based on side effect profile, patient preference, abuse potential, drug interaction potential, and other characteristics of the individual drugs [126]. Because drowsiness and dizziness have been noted with the muscle relaxants, concern should be used in patients receiving other sedative medications due to risk of respiratory depression.

Carisoprodol is metabolized to meprobamate (a class III controlled substance) and has been shown to produce psychological and physical dependence [127]. Therefore, carisoprodol and diazepam should be reserved for last-line therapy because of their abuse potential and lack of superiority to other skeletal muscle relaxants.

All skeletal muscle relaxants should be used with caution in older patients, and especially, diazepam should be avoided in this population or in patients with significant cognitive or hepatic impairment.

Cyclobenzaprine has an anticholinergic effect and should be avoided in older patients and those with glaucoma. It also may cause rare cardiac effects such as arrhythmias or myocardial infarctions, so it should be contraindicated in patients with cardiac conduction disease, recent myocardial infarction, or congestive heart failure. Seizures have been reported with concomitant use of tramadol.

Metaxalone should be used in caution in patients with liver disease as it may cause increases in liver function tests. Tizanidine should not be used in patients using CYP1A2 inhibitors, CNS depressants, or chronic alcohol use [126].

Benzodiazepines

While diazepam has been used for muscle spasms as mentioned above, there is very little evidence to show that it is an effective treatment for musculoskeletal pain [128]. While benzodiazepines may be utilized in patients who would benefit from anxiolysis, there are many adverse effects that make it a poor choice for an analgesic – chiefly, the addictive potential of this class of drug in addition to sedative effects and respiratory depression with the use of other sedative medications. In a study of patients with noncancer pain on long-term opioids, concurrent benzodiazepine use was associated with greater pain severity, higher prescription doses of opioids, substance use, and greater mental health comorbidities [129].

Topical Agents

Multiple topical agents have been utilized for analgesia. The advantages that these medications may have over systemic drugs include local delivery, lower initial rates of systemic absorption, fewer systemic effects, and patient preference. However, significant systemic concentrations can result with topical application, and systemic side effects are possible.

Topical Lidocaine

In a systemic review of topical lidocaine as a treatment for neuropathic pain, although there is little evidence to support the use of topical lidocaine to treat neuropathic pain, results from individual studies and clinical experience suggest that it can be effective in some patients [130].

The 5% lidocaine patch has shown efficacy and excellent tolerability in trials involving patients with postherpetic neuralgia and multiple types of peripheral neuropathic pain [131, 132]. Efficacy has been shown with the less expensive lidocaine gel (5%) in these conditions as well [131]. Topical lidocaine is most appropriate for patients with well-localized neuropathic pain, and even though it can be used as monotherapy, it can also be utilized as an adjunct to systemic medication.

Capsaicin Cream

Capsaicin is an alkaloid derived from chili peppers. Capsaicin is available as a cream (0.025% or 0.075%) and as a high concentration patch (8%). A systematic review found that capsaicin had moderate-to-poor efficacy for relief of chronic musculoskeletal or neuropathic pain; however, it may be beneficial as an alternative in patients unresponsive to other treatments or as an adjunct [133]. This medication may take up to 6–8 weeks of repeated daily application before optimal pain relief can be achieved. The higher concentration patch is applied over 60 minutes under clinical supervision. Some possible side effects of capsaicin are burning, stinging, and erythema at the site of application with intolerance in up to one-third of patients.

Topical Nonsteroidal Anti-inflammatory Drugs

Topical nonsteroidal anti-inflammatory drugs (NSAIDs), in the form of a gel, spray, or cream, have been found to provide modest relief for acute musculoskeletal pain [134]. Topical NSAIDs tend to be more effective for acute pain over chronic low back pain, widespread musculoskeletal pain, and peripheral neuropathic pain [135]. A systematic review showed that topical diclofenac was well tolerated and more effective than placebo in the relief of osteoarthritic pain knee pain [136]. A systematic review found that response rates for topical salicylates are lower than for topical NSAIDs for chronic pain [137].

Topical Doxepin

Topical doxepin, usually indicated for treatment of pruritus, had only minimal effect on pain reduction in one small trial [138].

Compounded Topical Medications

There has been interest in using topical compounded medications as part of chronic neuropathic pain treatment. There are some studies conducted on the efficacy of topical ketamine, clonidine, gabapentin, baclofen, and amitriptyline among other medications for peripheral neuropathic pain. These medications can be used alone or in combination with other formulations. Effectiveness has not been fully elucidated, but these medications tend to be safe. More studies are needed; however, the topical agents have the potential to be helpful as complementary medications [139, 140].

Cannabis and Cannabinoids

Cannabis and cannabinoid use for chronic pain is controversial. Systematic reviews and meta-analyses of trials have found some formulations of cannabis and cannabinoids efficacious for treatment chronic pain [141–146]. One meta-analysis found limited low-strength evidence that cannabis might alleviate neuropathic pain in some patients, but insufficient evidence for other types of chronic pain [146]. Another review found that inhaled cannabis is consistently effective in reducing chronic noncancer pain more-so than oral formulations while being more easily tolerate with more predictable effects [147].

Clinical Concerns

Adverse effects of cannabis and cannabinoids may include dizziness, somnolence, nausea, euphoria, confusion, and hallucination [141]. The long-term effects of medical cannabis are not known. One prospective cohort study found no difference in serious adverse events between the users and nonusers. However, the medical cannabis group had a higher rate of nonserious respiratory adverse events [148]. Cannabis use has also been associated with adverse psychosocial effects, and caution may be needed in patients with concomitant opioid or benzodiazepine use.

Low-Dose Naltrexone

Naltrexone and naloxone are classical opioid antagonists. In lower than standard doses, they exert different pharmacodynamics. Low-dose naltrexone (LDN), a daily dose of 1–5 mg, has been shown to reduce the glial inflammatory response and systemically upregulate endogenous opioid.

Clinical reports of LDN have demonstrated possible benefits in diseases, including fibromyalgia, Crohn's disease, multiple sclerosis, and complex-regional pain syndrome [149, 150]. LDN is inexpensive and well tolerated for use in daily therapy. The use of LDN for chronic disorders is still highly experimental, and there is limited publication of trails [150].

Ultra low-dose naltrexone/naloxone (ULDN) less than 1 μg per day may potentiate opioid analgesia and has been of use in postoperative control of analgesia by reducing the need for the total amount of opioids following surgery, as well as ameliorating certain side effects of opioid-related treatment [149].

Very low-dose naltrexone (VLDN), dosing range between 1 μg and 1 mg, has been used experimentally as an adjunct treatment for boosting tolerability of opioid-weaning methadone taper [149].

Table 22.1 Evidence-based treatments

NSAIDs	Musculoskeletal pain
Acetaminophen	Musculoskeletal pain
TCA	Neuropathic pain
SNRI	Neuropathic pain/musculoskeletal pain
Gabapentin/pregabalin	Neuropathic pain
Carbamazepine	Trigeminal neuralgia
Muscle relaxants	Acute musculoskeletal pain
Topical agents	Localized neuropathic and musculoskeletal pain

Table 22.2 Emerging treatments

Low-dose naltrexone	Neuropathic pain/musculoskeletal pain
Compounded topical medications	Neuropathic pain/musculoskeletal pain
Oral/intranasal ketamine	Neuropathic pain/musculoskeletal pain
Cannibis/cannabinoids	Neuropathic pain/musculoskeletal pain

Table 22.3 Accepted but unproven treatment

SSRI/bupropion	Neuropathic pain
Anticonvulsants (topiramate/valproic acid/phenytoin)	Neuropathic pain
Nonketamine NMDA antagonists (memantine, dextromethorphan)	Neuropathic pain

Table 22.4 Disproved treatment

Lamotrigine/levetiracetam

The use of naltrexone in the low-dose formats is still fairly new in practice, and further research is needed; however, they tend to be well tolerated.

Table 22.1 summarizes evidence-based medications for chronic and neuropathic pain. Table 22.2 summarizes treatments that are emerging as promising agents. Table 22.3 summarizes treatments that are commonly used but are unproven. Table 22.4 summarizes drugs that have been shown to be unhelpful for chronic pain.

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Chapter 23
Pain and Addiction

Ivanshu N. Jain, Adriane dela Cruz, and Sidarth Wakhlu

Substance Abuse Terminology

To understand treatment strategies for patients with addictive disorders, physicians need to understand substance abuse terminology. The terms physical dependence and tolerance have been inappropriately used in the past to define addiction. Physical dependence is defined as development of a physical withdrawal syndrome following abrupt dose reduction. Its presence does not indicate the presence of addiction, but rather it is a normal physiologic response to chronic use of opioid analgesics. Tolerance likewise is not indicative of addiction but can be defined as a normal physiologic response at the cellular level to the chronic use of opioid analgesics that results in requiring more drug to elicit the same physiologic response. Physical dependence and tolerance to opioids are normal and predictable physiologic events that are the natural consequences of chronic opioid use. Their development can be expected after extended use of these drugs (several days to a few weeks) and does not imply the presence of addiction.

Addiction Addiction is a chronic brain disease characterized by chronic, relapsing disorder that has been characterized by (a) a compulsion to seek and take drugs, (b) loss of control over drug intake, and (c) emergence of a negative emotional state (e.g., dysphoria, anxiety, and irritability) that defines a motivational withdrawal syndrome when access to the drug is prevented [1]. The occasional, limited, recreational use of a drug is clinically distinct from the loss of control over drug intake and the emergence of compulsive drug-seeking behavior that characterize addiction.

I. N. Jain (✉) · A. dela Cruz · S. Wakhlu
Department of Psychiatry, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: Sidarth.Wakhlu@UTSouthwestern.edu

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Tolerance Tolerance is defined as a decrease in pharmacologic response following repeated or prolonged drug administration. It is either innate or acquired. Innate tolerance due to pharmacogenetic makeup of the patient and is usually evident after the initial dose administration. Acquired is due to repeated exposure to opioids and is considered due to pharmacokinetic, pharmacodynamic, or learned mechanism [2]. Pharmacokinetic mechanism occurs as a consequence of drug being inducer or inhibitor of metabolic enzyme or transporter system. Diminishing response of intrinsic opioid receptor system over time results in pharmacokinetic tolerance. Finally, learned tolerance is either behavioral or conditioned learning and is attributed to learning, either behavioral or conditioned. Behavioral tolerance occurs when an individual learns to function despite repeated exposure to a drug. Eventually incremental amount of opioid is needed to produce pleasure comparable to that provided in previous drug use episodes.

Dependence and Withdrawals Altered physiological state characterized by manifestation of opposite physiological effects of drug when it is removed. It is intricately associated with tolerance, and the adaptive changes associated with tolerance predominate and become profoundly nonadaptive when drug levels drop below certain threshold. In human brain, the locus ceruleus (LC) is responsible for release of noradrenaline (NA), which in turn is responsible for effects including breathing, wakefulness, blood pressure modulation, and alertness. Opioid intake via linking to mu receptors on LC suppresses the release of NA and resultant decrease in alertness, respiratory drive, and blood pressure. With time, this suppression is offset by the augmented activity of LC brain cells. When opioids are not present, this enhanced activity is postulated to be causative of withdrawal symptoms like agitation, anxiety, muscle cramps, and diarrhea due to excess of NA [3].

Hyperalgesia It is defined as a state of nociceptive receptor sensitization caused by exposure to opioids. The condition is described as a paradoxical increase in pain perception after prolonged use of opioids whereby patient becomes more sensitive to certain pain stimuli.

Allodynia Allodynia is pain due to a normally innocuous stimulus that does not usually provoke pain. Stimuli could be mechanical or thermal in nature. It is caused by peripheral and central sensitization of receptors, which is described later in this chapter.

Understanding Stages of Pain

As per Task force on taxonomy of the International Association for the Study of Pain (IASP), pain is "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Below mentioned are physiological processes involved in generation of pain and sensitization.

Stage 1: Nociception It is the ability to feel pain, caused by a noxious stimulus (mechanical, chemical, or thermal); if strong enough or repetitive, it causes depolarization of nociceptors or afferent pain fibers (A-delta and C fibers). This message is transmitted from peripheral tissue to dorsal horn of spinal cord and then to second-order neurons, which send the message rostral to the lateral and medial thalamus. Thalamic projections to somatosensory cortex convey localization and intensity information, resulting in the conscious perception of pain, and limbic system is responsible for the emotional aspect of pain [1].

Stage 2: Peripheral Sensitization Intense and prolonged tissue damage, inflammation, and cell death cause stimulation of the previously dormant nociceptors, which may spontaneously discharge and become more sensitive to peripheral stimulation. Inflammatory mediators like bradykinin, prostaglandins, serotonin, and histamine activate secondary messenger system, which causes phosphorylation of receptors, influx of calcium ions, and release of chemicals like substance P, which furthers continued release of inflammatory mediators. Several receptors including opioid, γ-aminobutyric acid (GABA), bradykinin, histamine, serotonin, and capsaicin have also been identified on the surface membrane of sensory axons [1].

It is important to understand the consequences of peripheral sensitization at this point. Now spontaneous or subthreshold would be enough to cause depolarization of primary afferent pain fibers, leading to firing without a noxious stimulus present. This codes for an increase in the pain signal to the spinal cord and brain, causing increased pain from a given noxious stimulus—this is termed *hyperalgesia*. Also, normal light touch or stimulus (that does not usually provoke pain) would cause pain due to peripheral sensitization and is termed as *allodynia*.

Stage 3: Central Sensitization Persistent noxious stimulus enhances the responsiveness of neurons in dorsal horn, and it is independent of primary afferent drive which leads to secondary hyperalgesia and allodynia. Multitude of neurotransmitters are responsible for this process, including excitatory amino acid glutamate, substance P, calcitonin gene–related peptide, vasoactive intestinal peptide, somatostatin, and others. Inhibition of this nociceptive circuit is mediated by 5-hydroxytryptamine, GABA, and glycine as well as neuropeptides such as enkephalins. This manifests as chronic pain states generally characterized as maldynia or bad pain. Maldynia is exaggerated intensity of pain, which is spontaneously triggered by innocuous physical or physiological stimuli. It is still not clear whether genetic, cognitive, or emotional factors play a role in stage 3 pain [1].

Neuroscientific View of Addiction

Addiction to opioids and pain share the common neurochemicals and neuropathways in the brain. Addiction affects mood, behavior, physical health, and social aspects of life, and it worsens the quality and perception of pain. Their relationship is pretty complex as opioids are attributed to cause both analgesia and hyperalgesia.

Brain abnormalities resulting from chronic use of opioids are underlying causes of opioid dependence (the need to keep taking drugs to avoid a withdrawal syndrome) and addiction (intense drug craving and compulsive use). Brain changes that produce dependence appear to resolve after detoxification, within days or weeks after opioid use is stopped. The changes that produce addiction, however, are more wide-ranging, complex, and long-lasting [3]. Interaction of environmental effects can occur between stress, the social context of initial opiate use, and psychological conditioning, and a genetic predilection in the form of brain pathways that were abnormal even before the first dose of opioid was taken. These interactions can precipitate craving that might steer future relapse months or years after the individual is no longer opioid dependent [1].

Standard diagnostic criteria for opioid or other drug and alcohol use rely on physiologic responses to chronic drug use, behavioral consequences as loss of control over drug use, and significant disruptions in social and occupational functioning.

Active addiction goes through three stages: (1) binging and/or intoxication, (2) withdrawal/negative affect, and (3) preoccupation/anticipation. It has been hypothesized that both classical conditionings and operant conditioning play a significant role in addiction. In addition, social psychology (self-regulation failure framework) and neurobiology (counteradaptation and sensitization frameworks) can be superimposed on the stages of the addiction cycle. These processes are enmeshed with each other and intensify with time, leading to a pathological state called *addiction* [1].

Agonist activity at mu-opioid receptors (MOR) provides a robust and unfailing analgesia and, hence, makes them the most powerful and effective treatment for pain known to man. Opioid analgesics bind to mu-opioid receptor (MOR) on opioid neurons. One such area of the brain that gets activated by opioids is the mesolimbic (midbrain) reward system. This system generates signals in a part of the brain called the ventral tegmental area (VTA) that results in the release of the chemical dopamine (DA) in another part of the brain, the nucleus accumbens. DA is the same neurotransmitter that rewards people with feelings of pleasure when they engage in activities that promote basic life functions, such as eating and sex. When opioids, prescribed for pain, activate these reward processes in the absence of significant pain, they can motivate repeated use of the drug simply for pleasure. Amygdala and other areas of the brain create a lasting record or memory that associates these good feelings with the circumstances and environment in which they occur. This positive conditioning often leads to the craving for drugs when the user reencounters those persons, places, or things, and they drive users to seek out more drugs in spite of many obstacles [3].

When without drug, the addicted individual suffers from negative symptoms such as anhedonia, prolonged dysphoria, and irritability, which have been attributed to dopamine-depleted state in the reward pathways and also to recruitment of the brain stress or antireward systems. The antireward system triggers the release of chemicals like corticotropin-releasing factor (CRF), norepinephrine, and dynorphin, producing aversive or stress-like states. Simultaneously, within the positive

motivational circuits of the ventral striatum and extended amygdala, reward function is weakened, resulting in a powerful negative reinforcement that perpetuates a compulsive drug-seeking behavior and long-term addiction. Evidently, the negative feeling states associated with drug withdrawal can augment the subjective discomfort associated with pain. Interestingly, as many research studies have pointed out, anticipation of pain and pain in itself can create a negative emotional state that can intensify the negative emotional state of addiction and vice versa. In order to maintain a homeostatic level of reward system activity, antireward systems are recruited to counteract drug effects, which become stronger with each exposure of the drug and extinguish more slowly than the original response. Opioid addiction worsens over time, is influenced by environmental factors, and leaves a neuroadaptive trace that allows rapid "readdiction" even after detoxification and years of abstinence [1].

Long-term opioid use may have a drug opposite response such that the euphoria associated with acute opioid effects is lost and a negative mood response prevails, much like the drug opposite effect with opioid-induced hyperalgesia [4], which is further discussed in the next section.

Risks and Associations

Depression is a risk factor for prolonged opioid treatment for postoperative pain. The self-loathing factors (past failure, guilty feelings, self-dislike, self-criticalness, suicidal thoughts, and worthlessness) on the Beck Depression Inventory-II are most predictive of continuing opioid use [5]. In a 16-week trial of opioids for chronic back pain, higher doses of opioids were associated with improved anxiety, depression, irritability, and pain [6]. Results of another study show that opioids may contribute to depression in patients with chronic pain who are treated with opioids [7], which contradicts the above findings. Opioids have a dose-dependent association with depression, and duration of opioid exposure is correlated with depression. Opioids are associated with antidepressant failure, and opioid dose reduction is associated with mood improvement.

Opioid overdoses increased 30% from July 2016 through September 2017 in 52 areas in 45 states [8]. Fifty-one percent of opioid prescriptions are prescribed to patients with depression or other mental health condition [9]. Suicide is a significant factor in the death rate associated with the opioid overdose epidemic [10]. Prescription pain reliever overdose deaths among women increased more than 400% from 1999 to 2010, compared to 237% among men. Forty-eight thousand women died of prescription pain reliever overdoses between 1999 and 2010. It has been discovered that overdose and suicide have shared risk factors [11]. In one study, suicidal ideation is reported in 36.5% of patients with chronic pain who were treated with opioids. 16.4% and 2.5% had made an attempt in their lifetime and within the past 12 months, respectively [12]. The risk of suicide by any means and by overdose with opioids is dose dependent. The risk doubles from doses

below 20 MME and above 100 MME [13]. An alarming study reported that more than half of overdoses occur within 90 days of starting opioids and one third of overdoses occur on doses below 50 mg of morphine equivalents per day [14]. It is important to note that as per one of the study, the overdose death risk is highest among patients with substance use disorder compared to the groups of patients with cancer pain, chronic pain, and acute pain [15]. It is all the more important that the physicians should be trained in assessing opioid use during every visit if patients are on controlled substance prescription. On the contrary, physicians are not trained to screen patients who are high risk for opioid treatment. One study showed that physicians identified only 5% of patients as high risk in a population of exclusively high-risk patients [16]. One study showed that 91% of patients were prescribed opioids again after a nonfatal overdose [17]. Finally, in a study of chronic opioid users, it was found that most patients on chronic opioid therapy began opioids after surgery or trauma [18].

Current State of Opioid Addiction

The misuse of and addiction to opioids including prescription pain relievers, heroin, and synthetic opioids such as fentanyl are a serious national crisis that affects public health as well as social and economic welfare [19]. The current opioid epidemic has had three waves. The first wave began with increased prescribing of opioids for chronic pain in 1990s followed by a heroin wave in 2010, which resulted in increased overdose deaths [20]. The third wave has been illicit fentanyl use started in 2013, which again spiked overdose death numbers. According to the 2015 National Survey on Drug Use and Health (NSDUH) [21], the majority of people (87.2%) who take prescription pain relievers do not misuse them and the most common reason for their last misuse was to relieve physical pain (63.4%) [22]. It has been noted that 4.2% of the total US population misuses opioids and 92% of the people who misuse are taking prescription opioids either legally or illegally [23]. The risk of opioid-use disorder is dose dependent and increases by a factor of 15 on low doses, 29 on moderate doses, and 122 on high doses [24]. Every day, more than 130 people in the United States die after overdosing on opioids [25]. According to another study published in *Journal of International Association for the Study of Pain*, roughly 21–29% of patients who are prescribed opioids for chronic pain misuse them [26]. Between 8% and 12% of patients develop an opioid use disorder [27–29]. An estimated 4–6% of patients who misuse prescription opioids transition to heroin [27–29]. Paradoxically, patients who should not be prescribed opioids are more likely to be prescribed opioids. Patients with a history of substance use disorder have been able to obtain prescription opioids during the opioid epidemic [30]. It has been shown that longer duration of initial opioid therapy prescribed is associated with an increased risk of long-term opioid use [31].

Management Strategies

Medication-assisted treatment (MAT) for opioid-use disorders is the use of medications in combination with behavioral therapies. There are several FDA-approved medications for opioid-use disorders, that is, methadone, buprenorphine/naloxone combination, buprenorphine monotherapy, and naltrexone, both as oral tablets and monthly injectable preparation. MAT has been shown to improve patient survival with decrease in or complete elimination of illicit opioid use, increase retention in treatment, increase patients' ability to gain and maintain employment, and improve birth outcomes among pregnant women addicted to opioids.

Methadone is a full mu agonist, NMDA antagonist, and an SNRI. It usually exists as a racemic mixture of its two enantiomers, S-methadone (d-isomer) and R-methadone (l-isomer). The d-isomer (S-methadone) antagonizes the NMDA receptor and prevents 5-hydroxytryptamine and norepinephrine reuptake, while the l-isomer has significant opioid agonist properties.

Methadone's oral bioavailability is approximately 80% (range 40–99%), which is three-fold that of oral morphine. Methadone appears to be extensively distributed throughout peripheral tissues, perhaps related to its high degree of lipophilicity. Likewise, its volume of distribution has been reported to be high. Given its large volume of distribution (mean 6.7 l/kg), the plasma elimination of methadone usually occurs slowly (mean half-life 26.8 hours). Methadone's slow clearance from the body (mean 3.1 ml/min/kg) provides the rationale for dosing it once per day in methadone maintenance therapy, thereby preventing the onset of opioid withdrawal syndrome for 24 hours or more. Unfortunately, prolonged pain relief is not similarly sustained. Methadone undergoes a biphasic pattern of elimination, with an alpha-elimination phase persisting 8–12 hours and a beta-elimination phase ranging from 30 to 60 hours. The alpha-elimination phase equates to the period of analgesia that typically does not exceed 6–8 hours. Initial dosing for analgesia may need to be frequent, because steady-state kinetics are required for reaching the biphasic profile. Although the 30- to 60-hour beta-elimination phase can prevent withdrawal symptoms, it is usually subanalgesic. Thus, the biphasic elimination probably accounts for the dissociation between the brief analgesic effect and the longer plasma-elimination half-life.

This likely underscores why methadone is prescribed every 24 hours for opioid maintenance therapy and every 4–8 hours for analgesia. Unlike morphine and other opioids whose breakdown products are associated with neurotoxicity, methadone has no known active metabolites.

Buprenorphine is a semisynthetic highly lipophilic opioid that is derived from the baine, one of the alkaloids in raw opium. Buprenorphine is a partial agonist at the mu-opioid receptor and a weak antagonist at the kappa opioid receptor. Being a partial mu agonist, buprenorphine has a higher safety profile compared to full mu agonists, especially with regard to respiratory depression. Buprenorphine has higher affinity at the mu-opioid receptor as compared to other full mu agonists.

The only exception being fentanyl. Induction with buprenorphine requires a patient to be in at least mild opioid withdrawal, premature induction with the full mu agonist still occupied to the receptor site will cause a precipitated withdrawal. Because of its high affinity, it offers an "opioid blockade" to other opioids that typically lasts in excess of 24 hours. Oral bioavailability of buprenorphine is low because of extensive first-pass hepatic metabolism. The administration of buprenorphine by the sublingual route allows for bypassing of the first-pass hepatic metabolism, thus increasing bioavailability. Buprenorphine is well-absorbed sublingually, with 60–70% of the bioavailability of intravenous doses. It is highly bound to plasma proteins and is inactivated by enzymatic transformation via N-dealkylation and conjugation. Buprenorphine is mainly metabolized to inactive conjugated metabolites (80–90%), but norbuprenorphine, a product of N-dealkylation by the cytochrome P450 3A4 enzyme, has more potent respiratory depressive effects than the parent drug. The combination product contains buprenorphine and naloxone in a 4:1 ratio. The tablets are available in 8 and 2 mg and the films in 12, 8, 4, and 2 mg. The naloxone is poorly absorbed sublingually and may precipitate a withdrawal if the combination product is administered parenterally, thus reducing the risk of misuse and diversion. The monoproduct contains buprenorphine only. In 2016, FDA approved the first buprenorphine subdermal implant and the next year the monthly buprenorphine injection, which is administered subcutaneously in the abdomen.

A clinical challenge is how to treat pain in a patient who is on MAT for their opioid use disorder. Pain can be categorized as anticipated acute pain, unanticipated acute pain, acute pain superimposed on chronic pain, and chronic pain.

Anticipated Acute Pain

Painful procedures such as elective surgery can be anticipated. This is an opportunity for both the patient and the treatment team to plan and optimize the management of this acute pain [32]. If the elective procedure is associated with mild-to-moderate pain, the dose of methadone or buprenorphine can be titrated upward with TID dosing. If the postoperative pain is severe, patients can be maintained on the same dose of methadone/buprenorphine and a high-potency full mu agonist like hydrocodone or hydromorphone can be added to the treatment regimen until the acute pain resolves.

Unanticipated Acute Pain

Some patients may experience pain secondary to trauma such as a motor vehicle accident or other acute, surgical emergencies. If the pain is mild-to-moderate pain, the dose of methadone or buprenorphine can be titrated upward with TID dosing. If the pain is severe, patients can be maintained on the same dose of

methadone/buprenorphine and a high-potency full mu agonist like hydrocodone or hydromorphone can be added to the treatment regimen until the acute pain resolves.

Acute Pain Superimposed on Chronic Pain

If patients with a history of opioid-use disorder and chronic pain syndrome on methadone or buprenorphine TID dosing experience acute pain, a high-potency full mu agonist like hydrocodone or hydromorphone can be added to the treatment regimen until the acute pain resolves.

Chronic Pain

Patients on MAT who are taking methadone or buprenorphine once daily dosing and who experience chronic pain may divide the total dose and take it on a TID dosing schedule. Then, like any other chronic pain patient, the dose of methadone or buprenorphine is titrated to effect.

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Chapter 24
Surgical Causes of Back Pain

Michael Van Hal

Introduction

Back pain is ubiquitous. In fact, a majority of adults in the United States and the world at large will experience back pain in their lifetime [1, 2]. Back pain can run the spectrum in terms of severity. Back pain can be relatively acute and benign or it can be debilitating. There is relatively little known about why some patients suffer debilitating back pain and why some patients are mostly unaffected outside of the acute episode [3]. Back pain is always a symptom of something else. At times, it can be a symptom of a more systemic process, including infections, metastatic disease, and systemic inflammatory conditions, which should be considered and ruled out in the majority of cases with a proper history and physical examination [4]. The majority of cases of back pain are due to intrinsic spinal disorders. Most of these have nonspecific causes. However, it is the clinician's duty to rule out these specific causes, such as a fracture, herniation, or stenosis. If no specific cause can be found, then the back pain is diagnosed as nonspecific. The chronic disorders we will deal with are in two larger categories of degenerative conditions and deformities (Fig. 24.1).

Infectious etiologies are a concern because they can present with back pain. These include spondylodiscitis and osteomyelitis. Classically, these infections can occur from three sources: hematogenous spread, direct infection, and spread from continuous sources. In children, the discs have a blood supply, but in the adult, the discs are avascular [5]. This avascular environment is a prime target for an infection to relatively hide from the host's immune system. Most spinal infections are not readily apparent and necessitate a high index of suspicion regarding when to work up a potential infection. Infections can be thought of as a spectrum from discitis, to osteodiscitis, and epidural abscess. Unless there is destruction of the vertebral

M. Van Hal (✉)
Department of Orthopedic Surgery, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: Michael.vanhal@utsouthwestern.edu

C. E. Noe (ed.), *Pain Management for Clinicians*,
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1. Systemic diseases:
    I. Infectious etiologies
        i. Discitis/osteomyelitis
        ii. Epidural abscesses
    II. Neoplastic disease
        i. Primary bone cancers
        ii. Metastatic disease
    III. Systemic inflammatory arthropathies
        i. Rheumatoid arthritis
        ii. Lupus spines
            1. Ankylosing spondylitis (AS)/diffuse idiopathic skeletal hyperostosis (DISH)
2. Spinal intrinsic diseases:
    I. Acute disorders:
        i. Traumatic fractures
        ii. Back strain/sprain
        iii. Disc herniation/acute annular tear
    II. Chronic disorders:
        i. Degenerative causes:
            1. Spondylosis
            2. Stenosis
            3. Facet arthropathy
            4. Spondylolisthesis
        ii. Deformity
            1. Scoliosis
                a. Congenital scoliosis
                b. Neuromuscular scoliosis
                c. Idiopathic scoliosis
                d. Degenerative scoliosis.

Fig. 24.1 Surgical causes of back pain – chapter outline

column, stenosis with neurological symptoms, unremitting symptoms, or failed conservative treatment, most of these infections are best treated with antimicrobials alone [6].

Epidural abscesses were historically considered a surgical indication, but now most have been shown to be better treated with antibiotics without surgery [7]. Due to a lower complication profile and better outcomes, surgical intervention is generally reserved for osteomyelitis that is refractory to antibiotics, epidural abscesses that cause neurological impairment or that cause progressive deformities (kyphosis, scoliosis, etc.) [7–9].

Neoplastic disease to the spine can mimic nonspecific low back pain [10]. These include primary bone cancers like sarcomas, multiple myeloma, aggressive hemangiomas, or osteoid osteomas. Alternatively, metastatic disease frequently spreads to the spine which is the most common site of bone metastases due to a robust blood supply and a venous system without valves in the lumbar Batson plexus [11, 12]. Fortunately, cancer as a cause of low back pain is quite rare, with less than 1% of those presenting with low back pain [10, 13]. There is no definitive test that would rule out cancer as the cause of back pain. Red flags for cancer have been debated regarding their use in screening. These questions include a history of cancer, unexplained weight loss, greater than 50 years of age, and pain that lasts more than a month. These questions can help direct when one should obtain more advanced imaging studies but cannot be completely replaced by good clinical judgment for when to do a more complete work up of back pain [13].

Systemic disorders can also be associated with back pain. These do not usually constitute a surgical indication but rather rely on the treatment of the underlying disorder. Examples include rheumatoid arthritis, lupus, and spondyloarthropathies. Of note, rheumatoid patients may actually not have more back pain than the general population possibly because they have other pain that masks the back pain, or alternatively, they may have less disability given their already limited functional demands. Surgical intervention is generally reserved for the same indications such as neurological impairment or deformity of the vertebral column. One specific exception to this general rule is when minor trauma occurs in a fused spine such as ankylosing spondylitis (AS) or diffuse idiopathic skeletal hyperostosis (DISH). When even minor trauma occurs in these patients, the spine is very susceptible to catastrophic injury (given the lack of flexibility). Thus, minor or minimal trauma can result in very unstable fractures. Thus, any patient with back pain and a history or imaging that is consistent with AS or DISH should have advanced imaging to rule out a fracture. Plain radiographs are insufficient to rule out a fracture in these patients. There is frequently a delay in diagnosis for these injuries, and a high index of suspicion is needed to avoid preventable neurological injuries [14].

The majority of this chapter will deal with intrinsic spinal disease leading to back pain. These include both acute disorders and chronic conditions. The acute disorders are traumatic fractures, disc herniations, acute annular tears, and muscular strain/sprains.

After ruling out a systemic disease process with a good history and physical examination, a majority of acute low back pain conditions can be managed nonsurgically. Spinal fractures are always a concern when there is a history of trauma. They can also be present even in low-energy situations if there is a pathological reason for the bone to be weak such as a systemic disease which we addressed earlier or if the bone is inherently weak such as osteoporosis. These bones are susceptible to failure even with a normal physiologic stress. High-energy traumatic histories should be investigated with imaging, as the potential for missing an injury is high given the limitations of a relatively nonspecific physical examination.

In most cases, however, the acute back pain is not associated with a traumatic history. These cases, therefore, are best managed without imaging. Recommended

treatments continue to include conservative treatment with oral medications, early mobilization, and physical therapy. A majority of these back strains and/or sprains will resolve with time and conservative measures alone [4] [15].

Imaging of back pain is only recommended when the symptoms are persistent and fail to improve over 6-week minimum [15, 16]. Obtaining imaging earlier can be associated with worse outcomes as imaging in the acute setting can be diagnostically confusing since a significant percentage of asymptomatic patients less than 40 years had abnormal MRI findings [17].

Disc degeneration is a common cause of acute back pain. The disc is the physiological entity that meets the somewhat conflicting demands of both motion and stability in the spine. This dual nature is seen in the thick outer annulus and the gelatinous center of the nucleus pulposus (Fig. 24.2). This disc can degenerate due to several factors that influence the health and longevity of the disc. These include age-related, genetic, nutritional, metabolic, infectious, traumatic, or mechanical factors [18]. Traumatic disc herniations can and do occur, but a majority of cases are not associated with a single traumatic event. Disc degeneration and herniation may occur along a spectrum of degeneration that weakens the outer annulus which can fail completely in a full herniation. Other times, the disc can just bulge backward through a relative weak area in the annulus [18]. Regardless of the integrity of the annulus, all types of degeneration from minor annular tears to full disc herniations can be associated with back pain and/or radicular symptoms. The exact mechanism of disc degeneration and pathological symptoms are not completely understood or accepted [19].

Most cases of acute disc degeneration/herniations will resolve with time alone. Managing the pain/symptoms until the body has time to recover is the goal of treatment, and it can be difficult to achieve when symptoms are sometimes severe and debilitating. Surgical intervention should be reserved for those cases which fail to improve after at least 6 weeks of conservative treatment [20, 21]. Conservative options range from over the counter medications, prescription medications, physical

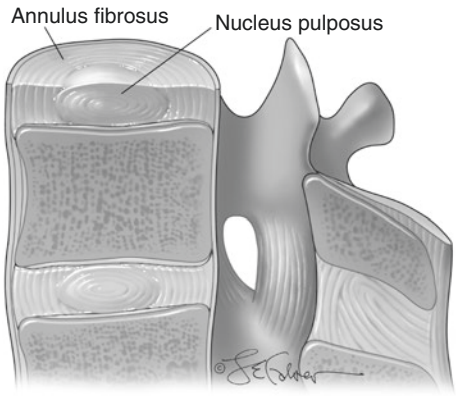

Fig. 24.2 Drawing of the intervertebral disk showing the outer annulus fibrosus and inner nucleus pulposus

therapy, and injections. Acute back pain that is associated with radicular components also responds to conservative treatment and should be attempted first prior to surgical intervention [21, 22]. Potential surgical complications include bleeding, infection, worsening neurological function including motor weakness, cerebral spinal fluid leaks, and persistent symptoms. Given these risks, the surgical indications for acute disc herniations should be reserved for those cases with unrelenting symptoms despite conservative treatment for a minimum of 6 weeks or for those cases associated with neurological loss such as weakness, progressive numbness, or bowel and bladder dysfunction.

Surgical outcomes for disc herniations have excellent outcomes and show superiority to conservative treatment if the patient has failed to improve with conservative treatment. This benefit from surgery is maintained for years after the surgery [20, 23].

Spondylosis, which is defined as a degenerative condition of the spine, is an extremely common condition of the lumbar spine given the mechanical demands placed on it and the relative mobility of the lumbar spine when compared to the thoracic and sacral spine. This combination of load and mobility makes it a common place for degeneration or spondylosis. Spondylosis, given its progressive degenerative nature, is a difficult entity to cure. Treatment revolves around managing the progression of the disease. Surgical intervention for spondylosis alone has not been very successful [24]. Surgical intervention is more reliable at relieving extremity symptoms rather than axial symptoms. Most cases of spondylosis without neurological impairment are best treated conservatively [24].

Spondylosis can lead to stenosis or narrowing of the spinal canal due to a complex process that is thought to be adapting to the degenerative changes in the lumbar spine by trying to stabilize the spine. This leads to secondary changes in the spine with facet joint hypertrophy, ligamentum flavum hypertrophy, and disc degeneration. This stenosis or narrowing can lead to impingement on the canal centrally, in the lateral recess near the facet joints, or in the foramen as the nerves exit the spinal canal. Impingement in the foramen or the lateral recess can lead to radicular symptoms. Impingement centrally can lead to neurogenic claudication symptoms.

Radicular symptoms due to stenosis secondary to spondylosis have good outcomes from surgical intervention [25]. Nerve root radicular symptoms improve in the majority of cases by removing the stenosis from the lateral recess or the foramen.

Central stenosis can lead to neurogenic claudication, which is a clinical entity that is characterized by progressive loss of walking tolerance or standing tolerance. This is demonstrated clinically by patients describing the ability to walk for a certain length of time or distance and then needing to stop and sit down (usually bending forward) in an attempt to increase the diameter of the central canal by forward flexion of the lumbar spine. This is also seen as a relative ease of walking uphill (forward flexion) rather than downhill (extension) or using supportive devices to lean forward upon (such as a shopping cart). This entity also responds well to surgery if it fails to improve with conservative care [20, 25]. Conservative care for

lumbar spinal stenosis with neurogenic claudication can improve with a walking program [20, 25]. Outcomes from surgical intervention show improvement in functional outcomes although this is somewhat controversial, but the effect of surgery does seem to diminish with time [20, 25].

Spondylosis can have subtypes of facet degeneration or facet arthropathy. This entity causes pain in a similar fashion that most arthritic joints generate pain. The facet joints are a synovial joint with articular cartilage and as such can form synovial cysts. This facet arthropathy from the joints can be a source of back pain [26]. Additionally, the synovial cysts can form inside the spinal canal and contribute to impingement on the neural structures. Synovial cysts can be a difficult clinical entity to treat, and some can respond to aspiration attempts, but many reoccur (>50% in some studies) [26, 27]. Surgical excision is successful as well but also have a higher failure rate given the nature of the arthritis joint producing another cyst. Fusions for facet arthropathy are also a viable treatment and show good success at relieving the radicular pain and the back pain [26].

Spondylolisthesis, which is defined as one vertebra displaced relative to the distal vertebra, can have several different types, including degenerative, isthmic, traumatic, iatrogenic, and congenital. All these different types can lead to back pain. These types of spondylolistheses can be treated conservatively and have some good success at back pain relief. Many patients with spondylolisthesis are asymptomatic [28]. For purposes of this chapter, we will discuss the two most common types: degenerative and isthmic. Degenerative spondylolisthesis (DS) is spondylolisthesis that is a result of spondylosis. Isthmic spondylolisthesis usually develops in childhood and is associated with spondylolysis or a pars defect [28].

There is controversy regarding the surgical management of spondylolisthesis. Those patients with degenerative spondylolistheses that were deemed unstable by radiographs were traditionally treated surgically. Recently, there is evidence that there is not a perfect correlation between radiographic instability and functional instability [29]. Isthmic spondylolisthesis, if refractory to conservative care, also can benefit from surgical intervention with a fusion (either posterolateral alone or with an interbody). For both types, surgical intervention with stabilization/fusion can provide lasting relief [25, 30].

Deformity can cause back pain due to asymmetric disc degeneration and abnormal back mechanics. Frequently patients with alignment outside of the normal physiologic range suffer from increased back pain due to increased muscle fatigue when the spine is out of alignment in what is known as the cone of economy [31, 32] (Fig. 24.3). This is where the spinal alignment is relatively located over the pelvis/hips in such a way that the body does not have to exert excessive energy to hold the trunk and head upright. This is similar to not struggling to hold an object close to the trunk but having a much more difficult time holding the same object at arm's length.

Deformity in spine is not limited to a coronal imbalance (scoliosis) or a sagittal imbalance (lordosis or kyphosis). Spinal deformities are a complex three-dimensional orientation that leads to an abnormal posture [33].

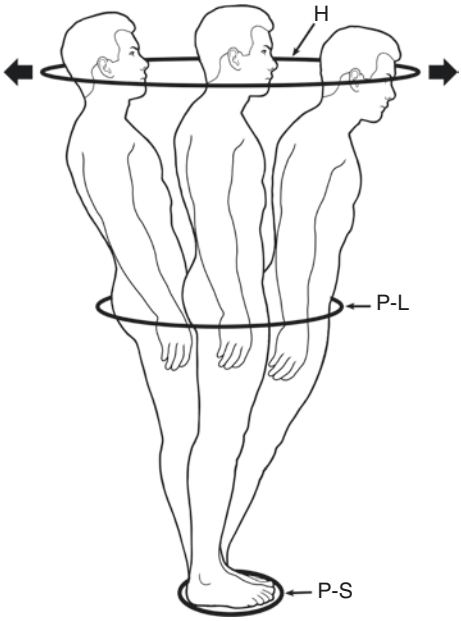

Fig. 24.3 Drawing of the zone of economy. H head, P-L pelvic level, P-S polygon of sustentation

Scoliosis is defined as any coronal imbalance in the spine >10 degrees. Patients with scoliosis experience more back pain than the general population [34]. The mechanism of this increased pain is not clearly known [34]. Scoliosis has several different subtypes including congenital, neuromuscular, idiopathic, and degenerative. Most of these are pediatric types of scoliosis, but the degenerative scoliosis is becoming a more defined and important clinical entity especially as the population ages and the concept of spinal parameters are better understood [35, 36].

Management of scoliosis depends on the type and the severity. In congenital scoliosis, this is typically a surgical condition and very little conservative management is recommended as the deformity is usually progressive since it is due to abnormally segmented or abnormally fused vertebra which typically worsen the curve as the child grows. Surgical intervention involves fusion to arrest the growth development of the abnormal segment [37].

Neuromuscular scoliosis is a deformity that develops due to muscular imbalances frequently due to intrinsic musculoskeletal or neurological disorders such as Duchenne's muscular dystrophy or cerebral palsy.

Adolescent idiopathic scoliosis is more common in females, and it can be treated with a brace if caught early enough which has been shown to be effective at halting the progression of the disease, obviating the need for surgical correction [38]. If the curve is caught late or if unresponsive to bracing, then surgical intervention to cor-

rect the deformity and or halt the progression is recommended. Determining which curves will benefit from surgical intervention is controversial and has been the topic of much debate on the subject. There have been several attempts to classify and predict which curves will progress and, therefore, benefit from surgical arrest and correction [39].

Degenerative (or adult onset) scoliosis is an ever-increasingly important clinical entity as the average life expectancy is increasing and as elderly patients are healthier and placing higher functional demands on their spine [36]. Functional outcomes in degenerative scoliosis do appear to be correlated with an alignment that fits into a cone of efficiency that allows movement at a relatively low metabolic cost [35]. The indications for surgical intervention in this patient population are being debated and refined. However, there are some classification systems that predict which patients do more poorly and, therefore, are recommended for surgery [35].

In summary, there are many causes of back pain. While low back pain is nearly ubiquitous, fortunately most acute episodes are self-limited. Back pain can be divided into systemic disease with back pain as a symptom of a more diffuse condition. However, the vast majority cases of back pain in the adult are intrinsic spinal disorders. These can range from acute strains to more chronic and complex problems of spinal deformity. Surgical intervention, in general, is reserved for those cases refractory to conservative treatment or when spinal stability or neurological dysfunction is significant or progressive.

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Chapter 25
Peripheral Nerve Compression and Pain

Shelby R. Lies, Dennis Kao, and Jonathan Cheng

Nociceptive pain stimulus is sent from peripheral nerve receptors through the spinal cord to the brain for interpretation and response. Acute pain from direct physical trauma involves essentially four processes: transduction, transmission, perception, and modulation [1]. Nerve endings in skin, muscle, bones, and joints sense stimuli ranging from lacerations and ischemia to fractures or dislocations. The types of pain fibers responding affect the timing of transmission and quality of perceived pain once it reaches the brain. The brain then interprets and refines the signal within the somatosensory cortex and responds via autonomic/motor and emotional feedback. Modulation is effected by an endogenous hormonal response, which can vary by patient physiologic makeup. For example, when compared to the general population, a professional boxer will respond quite differently to a right hook because of occupational experience.

Chronic pain results from prolonged transmission of pain with an uncontrolled modulatory response. Repetitive minor insults will lead to a central sensitization that exaggerates from normal response. Once the mind loses grip of the reality of stimuli outcome, the response can be catastrophic. Without proper coping mechanisms, many patients have recalcitrant courses. The incidence of migraine headaches theorized as a trigeminal sensitization has correlated with carpal tunnel syndrome infliction [2], which indicates a common biochemical milieu for the central sensitization pathway.

S. R. Lies (✉) · J. Cheng
Department of Plastic Surgery, University of Texas Southwestern Medical Center, Dallas, TX, USA
e-mail: Shelby.Lies@utsouthwestern.edu; Jonathan.cheng@utsouthwestern.edu

D. Kao
Department of Plastic Surgery, University of Texas Southwestern, Dallas, TX, USA

Department of Surgery, University of Washington, Seattle, Washington, USA

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Nerve pain can arise from direct injury or inflammation around an involved nerve, leading to ischemia or compression. Peripheral nerves traverse through soft tissue compartments via specific anatomical tunnels, where they are susceptible to compression neuropathy. Common sites in the upper extremity include carpal tunnel, cubital tunnel, and radial tunnel. Common sites in the lower extremity include piriformis, fibular neck, and tarsal tunnel. These sites are amenable to surgical decompression; however, if left unchecked, chronic neuropathic pain may ensue. Multiple compression points along the course of a single neural pathway can be involved through the "double crush" phenomenon [3]. For example, patients with cervical radiculopathy are more susceptible to distal peripheral nerve compression in the upper extremity. The presence of multiple sites of compression along the same neural pathway can also exacerbate the severity of compressive symptoms at each of the anatomical locations when compared to any single site of compression in isolation.

The description of pain quality correlates with the severity and duration of compression. The pathophysiology of nerve compression includes dynamic ischemic insult, demyelination, axonal loss, and most commonly a mixed type with elements of each of the above [4]. The Sunderland classification depicts the histological degree of nerve injury, and is relevant to chronic nerve compression and to acute nerve trauma where it is more commonly referenced [5]. The degree of damage will affect the timing of nerve recovery and clinical indications for intervention. The rate of recovery after appropriate treatment will be rapid for ischemia resolution, more gradual for myelination, and steadily slow with a rate of improvement dependent on the quantity of axonal injury. The mixed phases result in a stair-step improvement in functional recovery with time-marks at roughly 1 month, 3 months, and 6 months following decompression, finally reaching a plateau at around 12–18 months. These time points correspond with the improvement in ischemia, myelination, and axonal regeneration following release.

Complex regional pain syndrome (CRPS) is a disproportionately profound response involving autonomic dysfunction and functional impairment. Type 1 CRPS, or reflex sympathetic dystrophy, has no clearly identifiable lesion, whereas type 2 CRPS, or causalgia, is classified as dystrophic changes with a diagnosable peripheral nerve injury. Some would argue that we just have not pinpointed the responsible nerve in type I, and clinically should probe further. Peripheral nerve exploration may discover a missed site of compression or neuroma from prior trauma or surgery.

Quantifying Pain and Functional Assessment Tools

We are all familiar with single-item rating scales for assessing pain intensity such as the visual analog scale. Significant work has been achieved to build on multidimensional measures of patient-reported hand pain and function, including the Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire, Michigan Hand Outcomes

Questionnaire (MHQ), Australian/Canadian Osteoarthritis Hand Index (AUSCAN), and the Patient-Rated Wrist/Hand Evaluation (PRWHE). Each of these tools has evidence supporting the reliability and validity of score metrics and will aid clinicians and researchers in tracking outcomes using patient self-reported measures.

History, Physical Exam, and Diagnosis

Careful history and physical examination allow hand and peripheral nerve surgeons to localize a lesion as a source of generating pain. There are many examination maneuvers and diagnostic tools to aid in identifying potential sites of nerve compromise.

Most clinic visits will start with a handshake. Avoidance of the injured hand can be a subtle sign of the patient's pain modulation and coping response, when compared with the anatomic severity of the problem. Catastrophizing may be evident during history-taking, and has been shown to correlate with poor outcomes regardless of correct treatment [6]. In many cases where nerve decompression surgery has already been performed while pain persists, precise history-taking can be particularly revealing because the timing of improvement, worsening, or lack of change following prior injury or surgery can be indicative of particular anatomic causes related to acute trauma, compression neuropathy, or iatrogenic injury [7].

The patient should be observed carefully for pain-related posturing, disuse atrophy, and motor deficits. Autonomic clues of CRPS include edema, shiny skin, sweating, and skin color and temperature changes. Muscle mass should be assessed, particularly in the first dorsal interosseous, the thenar eminence, and the hypothenar muscles. A hollowing at the radial side of the thumb metacarpal can indicate atrophy of the abductor pollicis brevis, which is usually the thenar muscle most commonly seen to atrophy in severe carpal tunnel syndrome.

Next, sensation is tested by asking the patient to provide a number out of ten (Strauch "ten test") in response to light touch of the fingertips compared to the contralateral normal digits [8]. Other tests, such as moving and static 2-point discrimination and Semmes-Weinstein monofilament exam, can provide further objective demarcation.

Provocative nerve testing should come after the subtler tests of sensibility, as physical exam perturbation can alter sensation for a period of time afterward. A Tinel's sign is positive when manual percussion over the expected area of compression causes shooting and tingling sensations in the distribution of the underlying nerve. This can also signify the location of a neuroma or regenerating axonal front after nerve injury. If there is a strong Tinel's sign within an area of known or visible scar, this may point to a cut or tethered nerve. A local anesthesia block can aid in the diagnosis of painful neuroma, with relief reported within the hour. In carpal tunnel syndrome, another example of provocative testing is the modified Phalen's maneuver, similar to Durkan's test, which involves an examiner providing extrinsic manual compression of the carpal tunnel during wrist flexion. This maneuver can

reproduce sensory symptoms (numbness and tingling) in the median nerve-innervated digits and typically will spare the small finger due to its ulnar-only sensory innervation. The examiner should keep in mind that when the patient has prolonged diabetes with neuropathy or extremely chronic compression neuropathy present for several years or decades, strong provocative signs may not always be present and further electrodiagnostic study is warranted.

By manually testing motor strength and sequentially comparing with the contralateral side, the examiner can differentiate subtle weakness. For example, ulnar nerve compression at the elbow may cause weakness in distal interphalangeal joint flexion (ulnar-innervated flexor digitorum profundus) of the ring and small fingers. A claw deformity results from poor metacarpophalangeal (MP) joint flexion due to lack of lumbrical function, most frequently exhibited in low ulnar nerve palsy. Froment's test can demonstrate weakness of the first dorsal interosseous muscle through compensatory overactivation of the flexor pollicis longus muscle, which is a late finding in ulnar neuropathy, and is often manifested as an easily visible sunken-in first dorsal webspace in neglected cases.

The scratch collapse test (SCT) can further delineate both common and uncommon sites of compression and is a useful adjunct for patients with otherwise equivocal physical exam findings [9]. The patient is seated with his arms at the side and elbows flexed at 90 degrees. Then, the patient externally rotates his shoulders against examiner resistance after the soft tissue overlying the suspected area of nerve compression is palpated or "scratched." When positive, the affected limb collapses into the belly due to inability to oppose the internal rotation force of the examiner's hand. This is theorized to be a primitive protective neuromuscular reflex which exists to avoid threatened damage to an already embarrassed limb [10].

Electromyography (EMG) and nerve conduction studies (NCS) utilize precise measurements of conduction velocity, distal onset latency, insertional activity, and motor unit action potentials, among other parameters, to diagnose and grade severity of peripheral nerve compression. Though not always indicated with classic symptoms, these studies can help to guide the surgeon where and when to operate on patients with atypical nerve compression findings. Motor unit action potentials (MUAPs) are a sign of intact motor innervation, and their complete absence will incline a surgeon to perform peripheral nerve reconstruction for the affected nerve-muscle unit if the patients presents within a 9–12-month window after acute denervation. The electrodiagnostic report also helps to document pre- and post-operative findings. It is possible to have false-negative nerve conduction studies, particularly with cubital tunnel syndrome [11]. Campbell et al. provide a useful review of the diagnostic parameters and sensitivity/specificity of ulnar nerve conduction studies [12]. When history and clinical signs of nerve compression are consistent, the absence of significant electrodiagnostic findings should not preclude the surgeon from proceeding with nerve decompression.

Ultrasonography studies have quantified ratios and nerve caliber measurements to signify localized nerve swelling proximal to sites of compression neuropathy. Ultrasound provides real time visualization proximal and distal to sites of compression and affords a preoperative view of the hourglass nerve constriction, which is

otherwise only visualized in the region of compression at the time of surgery. A minimal risk profile makes ultrasound use strongly encouraging, but the adoption of this diagnostic modality has not been uniform partially due to variability in technical experience of sonographers.

Magnetic resonance (MR) neurography is especially useful in visualizing nerve continuity or lack thereof and can provide valuable preoperative estimation of gap distances for planning reconstruction following nerve injury. In proximal nerve compression, MR may demonstrate changes in the bulk and appearance of affected muscles which correlate with distinguishable trunk level patterns. Furthermore, the relative length of remnant proximal stumps in ruptured brachial plexus nerve roots following traction injury can help the surgeon preoperatively to determine conditional suitability for nerve graft versus distant nerve transfer reconstruction.

Medical Management

This section broadly reviews the basic pharmacologic therapies available to treat neuropathic pain.

Most medications that successfully treat neuropathic pain with long-term results require considerable time to titrate to effect. Doses need to be tailored to the patient, and generally should be started low and increased slowly to the point of symptom relief and acceptable side effects. Chronic pain is frequently associated with depression and anxiety; therefore, many medications that are initiated are chosen to address both.

Tricyclic antidepressants (TCAs), including amitriptyline, nortriptyline, and desipramine, have been shown to be efficacious for neuropathic pain in many placebo-controlled trials. The clinician should be wary of serotonin syndrome when using antidepressant medications to treat neuropathic pain, especially in patients taking SSRIs. Furthermore, patients started on TCAs should be screened for prolonged QT interval, due to the inherent risk of developing torsades de pointes. Duloxetine and venlafaxine are selective norepinephrine and serotonin reuptake inhibitors (SNRIs). Generally, these are less effective for neuropathic pain, although with less cardiac toxicity than TCAs.

Gabapentin and pregabalin are considered first-line treatments for neuropathic pain. Gabapentinoids act via modulation of voltage-gated calcium channels, inhibiting release of pro-nociceptive neurotransmitters. Pregabalin can be used when gabapentin fails due to inadequate pain relief or unacceptable side effects.

Most patients benefit from a combination of multimodal analgesia in lieu of opioids, given the misuse potential. Opioid intake has actually been associated with greater pain intensity and decreased satisfaction with pain control after fracture surgery [13]. Topical treatments may also provide benefit for some patients with cutaneous allodynia or hypersensitivity. Lidocaine gel or patches can provide localized skin analgesia in affected areas, and capsaicin may ultimately impart desensitization. The value of Vitamin C supplementation is unclear, as disputed studies demonstrate decreased risk of developing CRPS after wrist fracture [14].

Hand Therapy

The hand is very sensitive and constantly used; thus, any injury to the upper limb can significantly impair a patient's function and quality of life. Effective treatment of any hand condition requires a comprehensive rehabilitation strategy. The patient must cognitively understand and sense that the pain is manageable in order to foresee favorable outcomes. Therapists provide edema management and range of motion exercises for stiffness, and perhaps more importantly, guide the patient with goal-setting and positive expectations.

Manual exercise is well supported by the literature for improving neuropathic pain. Stress loading is an effective example [15]. Stress loading therapies apply progressive vibration and static and dynamic loading of muscles and joints, which are theorized to activate the dorsal column system and mitigate the spinothalamic-mediated pain pathways. For similar reasons, splinting of hands with neuropathic pain is typically avoided due to the loss of muscle and joint input, which can result in worsening of pain. It is common to address postural imbalances with therapy, for example, using scapulothoracic strengthening exercises to modulate proximal compression neuropathies at the level of the brachial plexus [16]. Mirror therapy and graded motor imagery are additional strategies available to address neuroplastic central sensitization changes [17].

Modalities such as heat, therapeutic ultrasound, transcutaneous electrical nerve stimulation, and laser therapy have been utilized with variable success. Cognitive behavior therapy is helpful for managing psychosocial variables before, during, and beyond tissue response in rehabilitation. Assessing patients' understanding, beliefs, and reinforcing the importance of therapy can provide better outcomes. Involving the patient with communication early on and emphasizing education of the patient are two important keys to success.

Surgical Intervention

The first step in curing nerve pain is identifying the injured nerve that is responsible for generating said pain. Accidental transection of a cutaneous nerve from injury or surgery can cause painful neuroma formation. By approaching the injured nerve well outside of the zone of injury, the surgeon can completely resect a neuroma to healthy appearing fascicles. When a distal nerve target is identifiable, a nerve graft is used to reconstruct the gap. Interpositional nerve graft, when performed correctly, eliminates misdirected axonal sprouting and aberrant axonal escape that may lead to recurrent neuroma. If and when there is no distal target, the proximal end of divided nerves is buried into muscle [18–20]; or, more purposely, the nerve end can be reconnected into an adjacent muscle efferent pathway through targeted muscle reinnervation (TMR). Promising evidence is amassing that TMR significantly improves phantom limb pain and may facilitate more dexterous control of bioprosthetics via enhanced access to motor control signals [21]. Prior reports have

also described connecting the proximal end of divided nerves to long "wandering" nerve grafts, which redirect regenerating axons proximal to the level of injury into a less anatomically vulnerable location [22].

As mentioned previously, peripheral nerves travel through soft tissue compartments where they are susceptible to compression and can cause compressive peripheral neuropathy. These anatomical tunnels can become targets of surgical decompression if clinical symptoms do not improve with nonsurgical treatment.

Nerve decompression is very successful and provides great relief for patients. We discuss the presentation of the most frequently encountered neuropathies in the neck and upper and lower extremity. We will review the common points of compression by tight ligaments or fascial bands, and the appropriate surgical treatment to relieve them.

Brachial Plexus: Thoracic Outlet Syndrome

Neurogenic thoracic outlet syndrome is irritation or compression of the brachial plexus along its course from the neck into the axilla through the thoracic outlet. It is much more common in women and often presents as pain in the neck and shoulder region that radiates down to the hand, as well as numbness and sometimes weakness in the arm and hand. Symptoms may be exacerbated by certain activities or arm positions. Unfortunately, most of these findings are subjective and cannot be demonstrated objectively using EMG or NCS. Physical examination by an experienced clinician is critical to making an accurate diagnosis of thoracic outlet syndrome, as both cervical radiculopathy and more distal nerve compressions can confound the examiner's ability to pinpoint the anatomic origin of the patient's symptoms.

The thoracic outlet consists of three sequential triangular spaces that allow the passage of the brachial plexus from the neck into the axilla: interscalene space, costoclavicular space, and subcoracoid space. The borders of the interscalene space consist of the anterior scalene muscle anteriorly, the middle scalene muscle posteriorly, and the first rib inferiorly. The borders of the costoclavicular space consist of the clavicle superiorly and the first rib inferiorly. The borders of the subcoracoid space consist of the pectoralis minor muscle anteriorly, the rib cage posteriorly, and the coracoid process superiorly. Of the three triangular spaces, the interscalene space is the most common area of brachial plexus compression.

Management of neurogenic thoracic outlet syndrome begins with physical therapy and postural modification. However, when symptoms fail to improve after 12 months, surgical treatment may be considered. Currently, the most common surgical approach includes scalene release with or without first rib resection. The incision is designed 1 cm superior and parallel to the clavicle on the symptomatic side. This approach allows access to perform the anterior and middle scalene muscle release, inspection and neurolysis of the brachial plexus, as well as first rib resection. A literature review demonstrated equivalent outcome of scalene release alone when compared with scalene release with first rib resection [23].

Upper Extremity

Median Nerve: Carpal Tunnel Syndrome

Median nerve compression at the wrist, otherwise known as carpal tunnel syndrome, is the most common compression neuropathy in the upper extremity. Patients with carpal tunnel syndrome present with numbness and tingling of the tips of the thumb, index finger, middle finger, and ring finger. In severe cases, they also exhibit thenar muscle atrophy.

Diagnosis can be confirmed by NCS, with the presence of prolonged sensory/motor latency, as well as by EMG, with signs of thenar muscle denervation. MR neurography can demonstrate neural hyperintensity, loss of deep carpal fat, indentation at the site of compression with or without proximal nerve enlargement, and distal flattening in the carpal tunnel, as well as variant anatomy such as early branching or bifid median nerve. Secondary changes of muscle denervation can be seen in more severe cases.

The carpal bones are arranged geometrically in such a way that they form a central concavity on the volar side. With the transverse carpal ligament (TCL) spanning the volar carpal bones and enclosing their central concavity, the so-called carpal tunnel is formed with the TCL as the roof. Ten structures typically traverse this tunnel, with nine flexor tendons (one flexor digitorum profundus and one flexor digitorum superficialis for each of the four fingers, and one flexor pollicis longus for the thumb) and the median nerve. The ulnar nerve and the wrist flexors are not encompassed within the carpal tunnel. The median nerve is located just beneath the TCL and represents the most superficial structure in the carpal tunnel. The proximal edge of the TCL is continuous with the antebrachial fascia of the distal volar forearm, which can be quite thick and may contribute to compression of the median nerve.

Although wrist splinting and cortisone injection can provide temporary symptomatic relief in patients with mild carpal tunnel syndrome, surgical decompression remains the most effective long-term treatment. Currently, the two main techniques for carpal tunnel decompression are open and endoscopic. The open technique involves making a longitudinal incision in the palm and releasing the TCL directly through this external approach. This allows direct visualization of the median nerve and the opportunity to perform tenosynovectomy if proliferative tenosynovitis (which can cause carpal tunnel syndrome by mass effect) is seen, such as with rheumatoid arthritis or amyloidosis. The distal several centimeters of the antebrachial fascia are also divided under direct vision through the palm incision, as this structure can cause recurrent carpal tunnel symptoms if not adequately addressed during carpal tunnel release.

The endoscopic technique involves making a transverse incision in the distal volar forearm hidden in a wrist flexion crease. The distal portion of the antebrachial fascia is then divided through this incision, with a rationale like that described above for open carpal tunnel release. The carpal tunnel endoscope, specifically designed for carpal tunnel release with an integral retractable blade for dividing the TCL, is

inserted into the carpal tunnel through this forearm incision. The TCL is visualized from its undersurface and is divided incrementally in a distal to proximal fashion as the endoscope is withdrawn from the carpal tunnel. An additional site that is sometimes responsible for recurrent carpal tunnel syndrome is the distal edge of the TCL, as adequate visualization at the distalmost extent of the carpal tunnel release can be challenging through the endoscope. The endoscopic technique avoids making a large incision in the palm, which results in less immediate incisional pain, but displays long-term outcomes equivalent to the open technique [24].

Ulnar Nerve: Cubital Tunnel Syndrome

Ulnar nerve compression at the elbow, more commonly known as cubital tunnel syndrome, is the most common site for ulnar nerve compression and is the second most common compression neuropathy in the upper extremity. Cubital tunnel syndrome presents as numbness and tingling of the ring and small fingers; in severe cases, patients also present with wasting of the intrinsic hand muscles and weakness in grip strength.

Diagnosis can be confirmed on NCS with slowing of nerve conduction velocity across the elbow and prolonged sensory latency, as well as on EMG with denervation in the first dorsal interosseous muscle. MR neurography can show nerve hyperintensity, prominent fascicles, and space-occupying lesion in the tunnel if present.

The ulnar nerve travels on the medial aspect of the arm, between the brachialis and the medial head of the triceps. The ulnar nerve runs posterior to the medial intermuscular septum, which extends from the coracobrachialis to the medial epicondyle of the humerus. At 8 cm proximal to the medial epicondyle, the nerve runs beneath a band of the deep brachial fascia (arcade of Struthers) that connects to the medial intermuscular septum. Near the elbow, the ulnar nerve travels in a sulcus on the posterior surface of the medical epicondyle as it enters the cubital tunnel. The floor of the cubital tunnel is formed by the ulnar collateral ligament of the elbow; the roof of the tunnel is formed by the cubital tunnel retinaculum. As the nerve continues distally, it lies beneath Osborne's ligament, which spans from the medial epicondyle to the olecranon, and the flexor carpi ulnaris (FCU) aponeurosis, which envelops the humeral and ulnar heads of the FCU. The medial epicondyle and the olecranon form the two walls of the tunnel. Distal to the cubital tunnel, the ulnar nerve courses into the volar forearm beneath the deep flexor-pronator aponeurosis. Along the course of the ulnar nerve into and across the elbow, multiple potential compression sites exist. These include the arcade of Struthers, cubital tunnel retinaculum, Osborne's ligament, FCU aponeurosis, and the deep flexor-pronator aponeurosis.

Occasionally, anconeus epitrochlearis, an accessory muscle that extends from the olecranon to the medial epicondyle and is found in 11% of the population, can cause ulnar nerve compression [25, 26].

When the elbow is in full flexion, the distance between the medial epicondyle and the olecranon is greatest; consequently, the cubital tunnel becomes the tightest and the pressure within it becomes the highest. In addition, the ulnar nerve is under greatest tension when the elbow is in flexion, as evidenced by the subgroup of patients whose ulnar nerves "dislocate," or sublux, out of the cubital tunnel and over the medial epicondyle when they flex their elbows.

Mild cubital tunnel syndrome can be managed non-operatively by avoiding prolonged elbow flexion, especially during sleep, to minimize traction and compression of the ulnar nerve. When non-operative management fails, surgery is recommended to forestall intrinsic hand muscle wasting.

Surgery aims to decompress the ulnar nerve and relieve traction force on it. Decompression is achieved by releasing all potential compressive points as mentioned earlier (arcade of Struthers, Osborne ligament, FCU aponeurosis, and the deep flexor-pronator aponeurosis). Meta-analysis studies have demonstrated equivalent clinical outcomes for patients with ulnar nerve decompression alone ("in situ" release) compared to patients with ulnar nerve decompression plus anterior nerve transposition to also relieve nerve traction [27]. Currently, in situ decompression is the most common technique for treating cubital tunnel syndrome. Intraoperatively, after completion of ulnar nerve decompression, the elbow is ranged to determine if the ulnar nerve translocates over the medial epicondyle during full elbow flexion (or if the patient has ulnar nerve subluxation preoperatively), anterior transposition is added.

Complicating the surgical approach further, anterior transposition of the ulnar nerve is fraught with potential for iatrogenic nerve compression. Moving the ulnar nerve to a new, extra-anatomical location can introduce additional compressive anatomical structures along the course of the nerve. Therefore, it is important to release potential compression points at the fascia of the medial intermuscular septum and the flexor-pronator origin. Once the ulnar nerve has been transposed anteriorly, it can be left in the subcutaneous plane (subcutaneous transposition) or placed within a groove made through the flexor-pronator muscle (intramuscular transposition). A fascial sling is created from the flexor-pronator origin to hold the ulnar nerve loosely in place at its new location and prevent the nerve from falling back into its native position posterior to the medial epicondyle where it is susceptible to traction during elbow flexion. The fascial sling must not be too tight, and the transposed portion of the ulnar nerve should follow a smooth transitional curve without any kinking by adjacent anatomical structures. Otherwise, these can become more new sites of ulnar compression or tethering.

Radial Nerve: Radial Tunnel Syndrome

The radial nerve enters the forearm as it travels in the interval between the brachialis and the brachioradialis (BR) muscles. In the proximal forearm, the radial nerve splits into deep and superficial branches. The superficial branch of the radial

nerve (SBRN) travels beneath the BR and emerges to the subcutaneous plane in the distal third of the dorsal forearm to supply sensory innervation to the dorsoradial aspect of the wrist and hand. The deep branch of the radial nerve (DBRN) passes between the superficial and deep heads of the supinator muscle while giving off motor branches to innervate the supinator. Distal to supinator, the DBRN becomes the posterior interosseous nerve (PIN), which provides motor innervation to all extensor muscles to the wrist and digits. Although the DBRN and PIN contain mostly motor nerve fibers, they also carry some sensory fibers that carry proprioception and pain sensation from the extensor muscles and wrist joint [28, 29].

Compression of the DBRN in the proximal forearm is known as radial tunnel syndrome, which presents primarily with pain occurring 3–5 cm distal to the lateral epicondyle. Weakness or motor deficit from radial tunnel syndrome typically occurs secondary to pain. There are no specific changes on NCS/EMG, which makes diagnosis of this syndrome somewhat controversial due to the heavy reliance on physical exam findings. MR neurography can show radial nerve signal and caliber alterations, thickened supinator fascial edge, and denervation changes in the extensor muscles. Due to its proximity to the lateral epicondyle, radial tunnel syndrome can easily be confused with lateral epicondylitis and places additional demands on the examiner to achieve diagnostic accuracy.

The lateral wall of the radial tunnel is formed by the "mobile wad" constituted by the BR, extensor carpi radialis longus (ECRL), and extensor carpi radialis brevis (ECRB). The medial wall of the radial tunnel is formed by the biceps and the brachialis. From proximal to distal, the floor is formed by the radiocapitellar joint capsule and the deep head of the supinator. As the DBRN traverses the radial tunnel, potential compression points include fibrous bands superficial to the radiocapitellar joint, the radial recurrent artery with its vena comitans (leash of Henry), the proximal medial edge of ECRB, the proximal edge of the superficial head of the supinator (arcade of Frohse), and fibrous bands within the superficial head of the supinator.

Surgical decompression of the DBRN can be performed through several approaches which vary based on the relationship of the incision to the BR muscle. We prefer the modified posterior approach that utilizes the interval between the BR and ECRL [30]. Upon splitting the interval between these two muscles, the radial tunnel is opened, and the DBRN, SBRN, and the supinator are visualized. The DBRN, which is the target of decompression, is first seen where it passes beneath the proximal edge of the superficial head of the supinator. The leash of Henry, which runs over and across the path of the DBRN, is divided. The entire superficial head of the supinator is divided over the DBRN to ensure complete release of both the proximal fibrous edge (arcade of Frohse) and any intramuscular fibrous bands. The proximal medial portion of the ECRB, which is usually fibrous, is excised; this also theoretically addresses any incidental symptoms of lateral epicondylitis involving the ECRB origin.

Lower Extremity

Sciatic Nerve: Piriformis Syndrome

Piriformis syndrome occurs when the sciatic nerve is compressed as it exits the pelvis at the sciatic notch, where the nerve passes under or through the piriformis muscle. This compression is caused by tight fascial bands within the muscle resulting from anatomical variation or post-traumatic scar formation. Patients present with numbness and tingling that localizes to the sciatic nerve distribution and pain that occurs in the buttock and radiates down the leg. Symptoms are often exacerbated by prolonged sitting, walking, or activity. Because these symptoms are also commonly found with spinal pathology and hip joint disorders, patients with piriformis syndrome often undergo a circuitous diagnostic and treatment course.

Traditional teaching indicates that there are few, if any, objective measures to diagnose piriformis syndrome, which has led to substantial controversy in making a diagnosis. Electrodiagnostic studies can show dysfunction or denervation in the sciatic distribution, but these are also often present in spine cases. The H-reflex, an electrophysiologic correlate of the deep tendon reflex, can have position-dependent changes in sciatic nerve conduction as a result of piriformis syndrome [31, 32]. Imaging studies also aid diagnosis by demonstrating nerve and muscle changes at the site of compression [33, 34].

On physical examination, patients can have tenderness at the intersection of the sciatic nerve with the piriformis muscle and a positive straight leg raise sign. Other signs of sciatic neuropathy are a Tinel sign along the course of the nerve distal to the piriformis and a positive SCT at the piriformis. Neuropathic symptoms of piriformis syndrome can be reproduced by placing the patient passively into the hip flexion, adduction, and internal rotation (FAIR) position, which is tested with the patient lying decubitus on the unaffected side [32]. The FAIR position induces passive stretch of the piriformis structures over the sciatic nerve.

The sciatic nerve exits the pelvis by passing through the greater sciatic notch and beneath the fibrous/tendinous edge of the piriformis muscle. The piriformis originates on the sacrum and inserts on the greater femoral tuberosity. At this proximal level, the sciatic nerve already contains distinct tibial and peroneal fascicles, which will go on to bifurcate into the tibial and common peroneal nerves at the distal thigh. In some patients, the tibial and peroneal fascicles travel in different planes around or through the piriformis, and they can display differing degrees of compression [35].

Although injection of the piriformis muscle has a role in the diagnosis and treatment of piriformis syndrome, surgical decompression remains an important modality for the alleviation of symptoms [31, 32, 36, 37]. The approach is through an oblique buttock incision, splitting the fibers of the gluteus maximus in order to reach the piriformis muscle on its deep surface, where the piriformis crosses over the sciatic nerve as it exits the pelvis.

Once identified, the piriformis is dissected circumferentially, and all compressive structures overlying the sciatic nerve are divided with bipolar electrocautery while meticulously shielding the sciatic nerve from iatrogenic trauma, such as excessive traction or heat and current spread from the cautery. Care is taken to visualize all components of the sciatic nerve to avoid iatrogenic injury and to achieve complete decompression.

Common Peroneal Nerve: Peroneal Nerve Compression at the Fibular Neck

Common peroneal nerve (CPN) compression at the fibular neck is the most common compression neuropathy of the lower extremity [38, 39]. In such patients, the CPN is entrapped as it crosses the fibular neck, where it winds from the posterior thigh and popliteal fossa to the anterior and lateral compartments of the leg. CPN compression can occur as a result of trauma, prior surgery, or no identifiable cause. Patients with CPN compression complain of foot drop deformity due to tibial anterior weakness, and dorsal foot and first webspace numbness due to sensory dysfunction [40]. A diagnosis of CPN compression is largely clinical, relying heavily on history and physical examination. Provocative examination findings are limited to a positive Tinel sign and SCT findings at the fibular neck compression point, with possible additional distal compression sites of the deep peroneal nerve (dorsal foot and ankle) and the superficial peroneal nerve (lateral leg) reflecting a double-crush pathology [10].

Electrodiagnostic studies can aid diagnosis by showing conduction changes in the CPN across the fibular neck and muscle denervation changes in the anterior and lateral compartment muscles [41, 42]. MR neurography shows signal and caliber alterations in the CPN across the fibular neck and regional muscle denervation changes. Mass lesions, such as intra- and extraneural ganglion cysts, can also be identified.

As a discrete fascicle within the sciatic nerve, the CPN component is postulated to be more susceptible to stretch injury than the tibial nerve, due to its oblique and superficial course within the sciatic nerve and its weaker system of connective tissue support [43]. The CPN departs the sciatic nerve in the distal posterior thigh and crosses the fibular neck at the lateral aspect of the knee. It runs between the two heads of the peroneus longus muscle, where the nerve traverses overlying and underlying fascial bands that constitute its main compression point. The CPN then bifurcates into its deep peroneal and superficial peroneal branches that supply their respective anterior and lateral compartment muscle targets. The sensory components of these branches continue past the leg, terminating in the first webspace (deep peroneal) and central dorsum (superficial peroneal) of the foot.

Surgical decompression remains the only recognized treatment of CPN compression. An oblique curvilinear incision is made over the fibular neck. The CPN is

identified as it arises from the popliteal fossa and enters the crural fascia overlying the peroneus longus muscle. The fascia of the peroneus longus is opened along the course of the CPN to facilitate exposure of the nerve. Tight fibrous bands over and under the CPN are carefully divided. The underlying lateral border of the gastrocnemius muscle fascia can form a deep compressive band and is often divided. The CPN bifurcates into the deep and superficial peroneal nerves just at or distal to the fibular neck. Both branches are followed toward and into their respective muscular compartments to confirm complete release.

In patients presenting with common peroneal neuropathy in the absence of preceding trauma or surgery, special consideration is given to intraneural ganglion of the CPN as a possible etiology. Such patients often experience sudden tearing pain, followed by the loss of ankle dorsiflexion, resulting in foot drop deformity. A suspected diagnosis of intraneural ganglion should be investigated using MRI [44]. The anatomy, pathophysiology, and treatment of CPN intraneural ganglion was described in detail by Spinner's group [45, 46]. In these patients, CPN decompression is performed as described earlier, with the addition of unroofing the intraneural ganglion and dividing the origin of the ganglion at the articular branch to the proximal tibiofibular joint. Surgical obliteration of the proximal tibiofibular joint can also be warranted, requiring advance planning if undertaken during the CPN decompression procedure.

Tibial Nerve: Tarsal Tunnel Syndrome

Tibial nerve compression at the medial ankle, where the nerve passes through the tarsal tunnel distal to the medial malleolus, leads to sensory disturbance in the plantar foot. Symptoms include tingling, numbness, burning, and pain. Tarsal tunnel syndrome is increasingly recognized as a key morbidity in patients with diabetes, and it has been suggested as an etiologic factor in diabetic neuropathy presenting with numbness in the feet [47]. Diagnosis is supported by electrodiagnostic examination changes and physical provocative maneuvers such as a positive Tinel sign [48] and SCT.

After the sciatic nerve bifurcates into the CPN and tibial nerve in the distal posterior thigh, the tibial nerve travels with first the popliteal vessels and then the posterior tibial vessels as it courses into and down the deep posterior compartment of the leg. At the entry to the deep posterior compartment, the tibial nerve crosses the fibrous arch of the soleus muscle origin, which is a potential compression point also known as the "soleal sling" [49–51]. The tibial nerve and posterior tibial vessels enter the ankle medially and pass under the flexor retinaculum, or laciniate ligament, which is a distal continuation of the intermuscular septum of the leg and forms the roof of the tarsal tunnel. The flexor retinaculum is anchored on the medial malleolus anteriorly and the calcaneus posteriorly. Near the flexor retinaculum, the tibial nerve bifurcates into the medial and lateral plantar nerves that supply the

small muscles of the plantar foot and the sensation of the toes and plantar skin. Each of the medial and lateral plantar nerves is accompanied by a branch of the posterior tibial artery and travels through a discrete tunnel that must be decompressed, in addition to dividing the flexor retinaculum, to fully address compression neuropathy of the tibial nerve and its distal territories. A fascial septum between the medial and lateral plantar tunnels should be excised to maximize release of these terminal branches [47]. Of special note, the calcaneal branch of the tibial nerve arises either proximal to or within the flexor retinaculum or both, and it can contribute to heel pain either before or after surgical release. The calcaneal branch can travel via its own fibrous tunnel toward the calcaneus and is protected as a matter of routine during surgery and is released as needed.

Summary

Carpal and cubital tunnel release surgeries are frequently employed with extremely low rate of complications. Poor results after nerve decompression can be due to scar adherence from immobilization and failure to allow appropriate nerve gliding within the early postoperative period. Most nerve decompression patients can and should be allowed near maximal excursion as early as possible, whereas actual reconstructive nerve repairs are typically splinted for 2–3 weeks. Another cause of poor results is incorrect diagnosis of the patient's symptoms, which emphasizes the importance of a skilled clinician in diagnosing and treating compression neuropathy.

Actual failure of nerve decompression is usually caused by incomplete release and/or creating a new site of relative compression. For example, after anterior transposition of the ulnar nerve at the elbow, the surgeon must check the medial intermuscular septum as a new site of compression along the rerouted nerve; additionally, internal neurolysis and mobilization of FCU motor branches may be required to allow the nerve to transpose efficiently without tethering. These factors may account for the higher rate of revision after ulnar nerve transposition when compared to in situ release. Care is also taken to protect vasa nervorum and the surrounding vascular plexus to preserve perfusion of the ulnar nerve.

New symptoms early after nerve decompression are a sign of iatrogenic nerve injury and should prompt exploration. The third webspace fascicle is the most commonly injured nerve in carpal tunnel surgery.

When other therapy fails, neuromodulation via cervical spinal cord stimulation, dorsal root ganglion spinal stimulation, and peripheral nerve stimulation can achieve sustainable results. Varying levels of evidence exist to support the gate control theory mechanism of action in neuromodulation for control of neuropathic pain. The implantable devices and equipment are improving, with more validation studies needed. These procedures, which are performed by anesthesia pain specialists, neurosurgeons, and interventional radiologists, further illustrate the importance of a

Table 25.1 Treatment classification for peripheral nerve compression pain

Evidence-based treatment	Surgical decompression of peripheral nerve compression has high patient satisfaction Endoscopic and open carpal tunnel release provide equivalent long-term outcome [24] In situ ulnar nerve decompression equivalent to ulnar nerve transposition [27]
Emerging/Promising treatment	Scar neuroma surgery can provide relief for refractory chronic pain [18–20] Surgery can effectively attenuate CRPS2 when a clear anatomical cause is identified [52] Targeted Muscle Reinnervation (TMR) decreases phantom limb pain and improves prosthetic interface [21]
Accepted but unproven treatment	Cognitive behavior therapy improves patient-reported outcome measures Neuromodulation spinal stimulation
Disproven treatment	Opioid intake associated with greater pain intensity and decreased satisfaction with pain control [13]

multidisciplinary team approach to goal-directed nerve pain relief in a challenging, yet potentially rewarding, patient population. Table 25.1 summarizes a classification of treatments and their effectiveness for peripheral nerve compression pain.

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Chapter 26
The Surgical Management of Pain

Zachary D. Johnson, Megan Still, Steve Hong, Salah G. Aoun, and Mazin Al Tamimi

Deep Brain Stimulation/Motor Cortex Stimulation

Overview

Deep brain stimulation (DBS) of the thalamus and periventricular–periaqueductal gray (PVG/PAG) can be used to treat medically refractory pain. Stimulation of the ventral posteromedial (VPM) nucleus or ventral posterolateral (VPL) nucleus of the thalamus may improve deafferentation pain syndromes such as thalamic pain syndrome, anesthesia dolorosa, and spinal cord injury pain. In these cases, the contralateral VPM nucleus is the selected target for facial pain, while the contralateral VPL nucleus is the target for extremity pain. Stimulation of these nuclei generally produces a characteristic pleasant paresthesia in place of the painful sensation. On the other hand, nociceptive pain syndromes more frequently respond to stimulation of the PVG/PAG [3]. Finally, patients suffering from cluster headaches may benefit from stimulation at the posterior hypothalamus, although this is not a common practice at this time [2].

The motor cortex provides an additional intracranial target for neuromodulation. Motor cortex stimulation (MCS) has demonstrated promising results in the treatment

Z. D. Johnson · S. G. Aoun · M. Al Tamimi (✉)
Department of Neurological Surgery, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: Mazin.AlTamimi@UTSouthwestern.edu

M. Still
UT Southwestern Medical Center, Dallas, TX, USA

S. Hong
Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA

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of refractory trigeminal neuropathic pain, thalamic pain syndrome, and poststroke pain among others. It is important to consider the homuncular representation of the body on the motor cortex when placing the electrodes to maximize coverage of the affected body regions, with the lower extremities being the most difficult to cover [3].

Procedure

DBS and MCS therapy consist of a multistep process. Patients must first be evaluated by a neurosurgeon for suitability, psychological preparedness, and optimal target selection for those deemed candidates. In those undergoing DBS placement, a frame is placed on the patient's head on the day of surgery, and a thin-cut, stereotactic magnetic resonance imaging (MRI) or computed tomography (CT) scan is obtained to determine the stereotactic coordinates. These coordinates are then used intraoperatively to guide the electrodes to the preselected target. The operation is generally performed with an awake patient undergoing neurological monitoring to minimize the risk of potentially dangerous side effects related to malpositioning. For MCS, the placement of the electrodes into the motor cortex is often performed with a small craniotomy using neuronavigation and results from a previously obtained fMRI to properly localize the motor cortex. In either case, the electrodes are then externalized, and the patient undergoes up to a week of trial simulation. If the trial period is successful, stage 2 of the operation is performed under general anesthesia by placing the permanent implanted pulse generator (IPG) into a subcutaneous pocket and connecting the generator to the tunneled electrodes [4].

Outcomes

Successful outcomes for DBS are tied directly to the type of pain the patient suffers from (nociceptive vs. neuropathic) and the selected target (VPM/VPL vs. PVG/PAG). In a 2010 meta-analysis review, 1114 patients undergoing deep brain stimulation for chronic pain were reviewed, with 561 (50%) experiencing long-term pain relief with DBS. Of patients with neuropathic pain, 42% (296/711) experienced long-term pain relief. When comparing stimulation targets of these patients, 56% demonstrated favorable long-term outcome with stimulation of the VPL/VPM of the thalamus compared to 23% treated with stimulation of the PAG/PVG. For those patients with nociceptive pain, 61% (272/443) demonstrated long-term pain improvement with DBS of all targets. Targeting the PVG/PAG for the treatment of nociceptive pain achieved a 59% long-term success rate, while no patients (0/51) with neuropathic pain experienced long-term pain relief. This provides the basis of targeting the thalamus for neuropathic pain and the PVG/PAG for nociceptive pain [3]. Studies regarding motor cortex stimulation have demonstrated greater than 50%

pain reduction in approximately 75% of patients with neuropathic facial pain and nearly two-thirds of patients with poststroke pain [3].

Multicenter randomized trials are still lacking and current data demonstrate mixed results. This may be due in part to the patient population of published studies, which have largely only included patients who have failed other treatment modalities, including spinal cord stimulation, and are the most challenging to treat. Additionally, at least 50% reduction of pain is a common threshold for defining success for these trials, and this may be more than what is required to improve the quality of life in these patients [6]. Although additional studies are needed to identify the optimal patient population, intracranial neuromodulation is a promising approach to pain management in patients with pain that has been shown to be refractory to other modalities, especially given its relatively low-risk profile and the option to remove the implant if no longer desired. Choosing a proper stimulation target as well as patient selection are the most important factors identified for successful pain relief.

Complications

Complications of device placement are uncommon, but include surgical site infection/wound breakdown, electrode fracture, intracranial hemorrhage, and meningitis, as seen with DBS device placement for other indications [4]. Side effects of stimulation vary based on the location and the frequency of stimulation. Stimulation of the PVG/PAG may cause a feeling of warmth, dizziness, or floating at low intensities or anxiety at high intensities. A patient can experience visual disturbances if the stimulation spreads below the commissural line and paresthesias on the contralateral side of the body due to a more posterior spread. Stimulation of the lateral thalamus can be painful at suprathreshold levels and may cause dystonic movements due to the spread to the internal capsule [5]. These side effects can be minimized by testing an awake patient during the electrode insertion phase to optimize the final electrode location, thereby maximizing pain relief benefits while minimizing unwanted side effects. With MCS, stimulation does not typically lead to the sensory changes seen with stimulation of the other targets. However, seizures are seen more frequently with MCS, with the subsequent development of epilepsy being rare.

Spinal Cord Stimulation

Overview

Direct spinal cord stimulation (SCS) by paddle or percutaneous lead electrodes may be used to treat a wide range of pain syndromes including complex regional pain syndrome (CRPS), failed back surgery syndrome (lumbar postlaminectomy

syndrome), multiple sclerosis, diabetic neuropathy, postherpetic neuralgia, refractory angina pectoris, painful limb ischemia, spastic hemiparesis, and dystonia. The best response is seen with neuropathic pain caused by the altered function or damage of a nerve. While the mechanism of action is incompletely understood, it is thought to be a combination of the release of endorphins, the increase in GABA and serotonin levels, and the physical stimulation of the spinal pain gates and supraspinal centers.

For effective pain reduction, patient selection and appropriate choice of the treatment modality are critical. Conventional SCS involves stimulation at the dorsal columns at a rate of approximately 40–60 Hz. This method is generally cited to be about 40–50% effective, but has several drawbacks including dependence on the induction of paresthesia over the area of stimulation, a high rate of nonresponders, a limited number of indications, and tolerance over time [20]. Modern attempts are aimed at preferentially stimulating the ventral columns to minimize paresthesia as a side effect. A high frequency (10 kHz), low amplitude paradigm has been introduced with promising results of paresthesia-free pain reduction with improved long-term efficacy [20–22]. Burst stimulation has also shown promise with largely paresthesia-free, long-term pain relief in patients with chronic neuropathic pain [9]. Additionally, new targets such as the dorsal root ganglion have been attempted with promising success seen, particularly for patients with distal neuropathic pain [23].

Patient Selection

Spinal cord stimulation appears to significantly improve pain for a great number of patients, allowing them to regain functionality and improve their quality of life, although the effects may wane over time. This method is less likely to be effective in patients with direct spinal cord injury, those with lesions proximal to the ganglion, those with failed back surgery syndrome who have undergone multiple prior surgeries, and those with significant psychological factors impacting their pain experience [19]. Additionally, spinal cord stimulation is not recommended for patients with pain due to malignant spread or those with a limited life expectancy.

Eligibility for permanent spinal cord stimulator placement is based on a successful trial period with an external generator. Electrodes are placed into the epidural space in one of two ways: (1) via a laminotomy to place a paddle-style electrode or (2) percutaneously using a Tuohy needle to insert wire electrodes with fluoroscopic guidance. Efficacy of the spinal cord stimulation is then tested over the subsequent week following surgery, and a permanent pulse generator is implanted subcutaneously if the patient experiences a greater than 50% reduction in pain [1, 24].

Outcome

Spinal cord stimulation has been employed in a variety of pain syndromes with promising results, not only with improved pain control but also with improvement in functionality. In a single institution review of 171 consecutive patients who received a permanent SCS implant for any cause of pain, 52% experienced at least a 50% improvement in their pain at a 7-year mean follow-up [7]. Results have continued to improve with a combination of advancements in neuromodulation and a better understanding of proper patient selection.

Many patients with CRPS have been shown to have reduced pain and allodynia in addition to improved limb function and quality of life scores after implantation of their stimulator [8, 9]. Earlier, more aggressive stimulation may produce better long-term outcomes. Some studies suggest pursuing more invasive interventions, including SCS, as early as 12–16 weeks after the diagnosis of CRPS is made in patients with persistent symptoms in attempt to prevent a plateau of progress during the rehabilitation phase [10, 11]. However, long-term pain control may still be challenging, and while many may find relief in the first few years after stimulator placement, there are some data suggesting that these effects may wane over time [8].

For patients with failed back surgery syndrome, spinal cord stimulation often improves pain control over physical therapy or medical management alone. Patients who have undergone less than three back surgeries and had less than 12 months of pain are more likely to benefit [9, 14, 15]. Furthermore, stimulation has been shown to be as effective as or better than reoperation on the lumbosacral spine for persistent or recurrent radiculopathy at 24 months, with no statistically significant difference in work status, cost effectiveness, or activities of daily living [12, 13]. It is important to note, however, there are some cases where reoperation on the lumbosacral spine is required, including cases of progressive neurologic dysfunction such as new weakness or loss of bowel/bladder dysfunction.

Spinal cord stimulation for angina pectoris has been found to be as effective as a CABG in controlling refractory pain and protecting against additional myocardial infarctions. This may be due in part to an increase in exercise capacity with reduced pain burden [16, 17]. In one study, those who underwent spinal cord stimulator placement were found to have fewer angina attacks, a significant decrease in nitrate use, and improved Canadian Cardiovascular Society grading score after 1 year [18].

Complications

Potential complications include surgical site infection, electrode migration with subsequent decreased efficacy, lead breakage, epidural fibrosis formation with spinal cord compression, and intermittent interference with other implanted devices such as pacemakers.

Direct Drug Administration into CNS

Overview

CNS administration of anesthetic and narcotic medications may be achieved by direct introduction into the epidural, subarachnoid, or intraventricular spaces. Efficacy is significantly increased by bypassing both the blood–brain barrier (increasing the CNS bioavailability) and the liver (the primary site of opioid metabolism). Furthermore, systemic side effects are significantly reduced, resulting in less sedation, confusion, constipation, and nausea compared to oral narcotics [25]. The administration of medications directly into the CNS is most commonly used as a one-time treatment for significant perioperative pain or during delivery in pregnancy, but it can also be used long term in patients who require chronic narcotic administration at higher doses, but do not tolerate their systemic side effects. In these cases, an epidural or intrathecal catheter can be connected to either a subcutaneous reservoir for intermittent administration or a pump mechanism for continuous infusion. Intrathecal pain catheters have shown up to 90% efficacy in cancer pain and 50% improvement in neuropathic pain [1]. Complications include migration of the catheter tip, fracture of the catheter, catheter granuloma formation, disconnection from the medication reservoir, and medication overdose or withdrawal.

Direct intraventricular injections of narcotic medications are usually reserved for patients with refractory pain secondary to cancer of the head and neck and a life expectancy of less than 6 months. Injections typically confer 24 hours of analgesia and thus must be repeated frequently through a subcutaneous reservoir connected to an intraventricular catheter. Patients have been found to have approximately 70% pain control at 2 months, but this response tends to decrease over time because of narcotic tolerance [1, 26]. Possible complications include those typically associated with other indwelling intraventricular catheters including intraventricular hemorrhage, bacterial colonization, frank meningitis, and catheter dislodgment.

Procedure

Prior to the placement of a permanent catheter and medication pump or reservoir, a trial injection should be performed to determine the efficacy and tolerance of the analgesic. If significant improvement in pain with acceptable side effects is achieved after a test dose, a permanent drug pump or reservoir can be implanted into a subcutaneous pocket and connected to the catheter. Intrathecal catheters can be implanted into the subarachnoid space percutaneously using a Tuohy needle or directly via a hemilaminectomy [1]. It is important that the catheter tip is placed as close as possible to the target receptors in the spinal segment from which the pain is originating to maximize benefit [27]. Ventricular catheters are usually placed into the lateral ventricle through a small burr hole, most commonly in the frontal region.

Medication Options

The choice of analgesic for intrathecal therapy is dependent on the indication for treatment and tolerance of the agent. According to the 2017 Polyanalgesic Consensus Conference (PACC), morphine is recommended as a first-line agent for patients in chronic intractable pain for whom systemic oral or IV narcotics are no longer efficient [27]. Improved efficacy may be seen with combination therapy of morphine and bupivacaine. Side effects are similar to those seen with oral opioids and include sedation, respiratory depression, nausea, pruritus, and cognitive changes. Zinconotide, a non-opioid medication, is another first-line option for those who are intolerant of intrathecal opioids. Side effects include cognitive and psychiatric effects, ataxia, nausea, and hypotension [28]. Fentanyl, hydromorphone, and clonidine may also be trialed as a single agent or in combination therapy. Clonidine may have an advantage over morphine because it does not cause respiratory depression, urinary retention, or gastrointestinal effects. However, it can result in cardiac depression and other cardiovascular effects, sedation, and peripheral edema. Combination therapy of the above-discussed medications is recommended prior to a trial of baclofen, a GABA receptor agonist, for neuropathic, but not nociceptive, pain. Baclofen may also be used as a first-line intrathecal therapy for intractable spasticity, commonly in patients with cerebral palsy or multiple sclerosis. Side effects include headache, delirium, and transient global amnesia, while malfunction or sudden discontinuation may lead to life-threatening withdrawal (high fever, increased spasticity, altered mental status, seizures, and hemodynamic instability) [2].

Spinal Ablative Procedures

The use of neuro-destructive procedures has generally declined with the improvement in neurostimulation (DBS, MCS, and SCS) and intrathecal medication administration, as these interventions are both titratable and reversible. However, a role for ablative procedures remains in patients who continue to have pain refractory to optimized medical management and neurostimulation. An excellent understanding of spinal cord anatomy is critical in obtaining good outcomes and minimizing complications in these irreversible procedures.

Anterolateral Cordotomy

Overview

An anterolateral cordotomy consists of the spinal lesioning of the anterolateral spinothalamic tract (STT). These tracts are responsible for carrying the ascending pain and temperature fibers from the contralateral side of the body. It is important

to note that loss of pain/temperature on the contralateral side will not begin until several segments below the lesioned level. It has been used for both malignant and nonmalignant pain, although noncancer patients tend to have only moderate improvement with short-lived pain relief and painful dysesthesias. This is in contrast to many series reporting excellent pain improvement (up to 95% initially) with long-lasting effects (up to 75% at the time of death) for cancer-related pain [29, 30]. In general, ideal candidates are patients with medically refractory, cancer-related pain isolated to the lower trunk, pelvis, hip, or a single extremity. However, patients with bilateral pain can be considered for a bilateral anterolateral cordotomy [31, 32, 34, 35].

Percutaneous Versus Open Surgery

Both percutaneous and open techniques have been used to perform the operation. The percutaneous approach is generally performed at the C1/2 interspace under fluoroscopic or CT guidance. Test stimulation must be performed with the cooperation of an awake patient to confirm location of the STT and to minimize potential side effects from the ablation. Unilateral procedures are generally well tolerated. Bilateral procedures carry an additional, potentially fatal risk of respiratory compromise, given the neighboring neurons responsible for maintaining respiratory drive [32–34].

The open approach is generally performed with general anesthesia in prone positioning. Direct visualization of the spinal cord is obtained with a laminectomy and dural opening. Although it is associated with higher operative morbidity, the open approach allows for the surgeon to tailor the location of the lesioning to the patient's clinical picture since it is not confined to the C1/2 interspace. Similar to the percutaneous approach, the patient is awakened prior to the ablation to confirm the proper location of the STT [31, 35].

Complications

The operation is generally well tolerated with an approximate risk of major adverse event of less than 5% in the hands of an experienced operator [32]. The most common side effect of the operation is urinary retention, seen in 11–33% of patients postoperatively. Transient (~10%) and permanent (1–2%) weakness can occur due to damage of the lateral corticospinal tracts. Mirror-image pain may be experienced postoperatively and has been reported to occur in 9–63% of cases. Other side effects include ataxia due to damage of the spinocerebellar tract and painful dysesthesias in 5–15% [31–35]. The open approach carries with it the additional risks of spinal instability and CSF leak [31, 35].

Dorsal Root Entry Zone (DREZ) Lesioning

Ablation of nociceptive pain transmission at the dorsal root entry zone is the target of the DREZ procedure. Radiofrequency Dorsal Root Entry Zone lesioning consists of two main subtypes: Spinal DREZ lesioning and, more recently, Nucleus Caudalis DREZ lesioning [36].

Spinal DREZ

The spinal dorsal root entry zone consists of the dorsal rootlets, dorsal horn, and Lissaeur tract, all of which are important in the transmission of nociceptive information. Candidates for lesioning of the spinal DREZ are patients with deafferentation pain conditions including brachial plexus avulsion, spinal cord injury (particularly those with "end-zone pain"), postherpetic neuralgia, and phantom limb pain [30, 32, 36]. Spinal cord injury end-zone pain refers to girdle-like pain at the transition zone between normal sensation and complete analgesia. Although the spinal DREZ is typically considered a treatment for pain isolated to a single limb, bilateral procedures have been attempted in select patients [36]. An open approach is performed with a wide laminectomy and dural opening to adequately visualize the dorsal root entry zone. Radiofrequency thermocoagulation is used to create the ablation [32, 36]. The electrode is typically inserted to a depth of 2 mm at the lateral edge of the spinal rootlet as it enters the cord. Lesioning should encompass two levels above and below the involved segments due to travel of the nociceptive fibers rostrally and caudally in Lissaeur's tract [32].

Excellent success of pain improvement of patients with a brachial plexus avulsion injury has been reported, with 54–91% of patients in the literature experiencing good or excellent outcomes, and 50% of patients continuing to have good outcomes at 5-year follow-up [30, 32, 36]. The DREZ procedure has also been shown to be effective for spinal cord injury end-zone pain, but poor outcomes are generally seen in diffuse spinal cord injury pain [32, 36]. The DREZ procedure has been utilized in the treatment of postherpetic neuralgia with poor results historically, although a recent case series by Moosy et al. reported 3 out of 5 patients with cervical postherpetic neuralgia and 9 out of 11 patients with thoracic postherpetic neuralgia experienced excellent pain improvement postoperatively with an average time to relapse of 4.2 years [36]. The primary complications are ipsilateral weakness/paralysis below the level of the ablation, usually due to injury to the lateral corticospinal tract (lesioning too far laterally), and ipsilateral loss of proprioception, fine touch, and vibratory sensation due to damage of the dorsal columns more medially. Although sensory deficits (2–70% reported incidence) are reported to occur more commonly than weakness/paralysis (3–14% reported incidence), they are generally better tolerated [32, 36].

Nucleus Caudalis DREZ

The Nucleus Caudalis DREZ targets the spinal trigeminal nucleus pars caudalis at the level of the cervicomedullary junction. It is utilized in the management of medically intractable facial pain including atypical facial pain, postherpetic neuralgia, trigeminal deafferentation pain, and neuralgias of the trigeminal, glossopharyngeal, and occipital nerves. An open approach and lesioning similar to the spinal DREZ are performed. Reported outcomes include excellent immediate improvement in pain in 60–97% of patients with 58–67% of patients experiencing continued pain relief at 1 year. Ataxia has been the most commonly reported complication [36].

Punctate Midline Myelotomy

Although myelotomy procedures were initially targeted at disrupting commissural fibers of the spinothalamic tracts, recent evidence has demonstrated an ascending nociceptive pathway near the midline of the dorsal columns that appears to play a greater role of transmitting visceral nociceptive information than the anterolateral system [37–40]. This pathway is the target of the punctate midline myelotomy. This procedure has been shown to be effective in the treatment of severe, refractory visceral pain secondary to abdominal or pelvic malignancies [38–40]. Three techniques have been used for the approach: open limited myelotomy with a laminectomy, percutaneous radiofrequency myelotomy, and percutaneous mechanical myelotomy. The surgical level should be tailored to the patient's clinical picture. Important anatomical considerations include the well-known fact that the thoracic spinal cord segment is usually several segments above the corresponding vertebral body level. Furthermore, the segment that is ablated should be several segments above the innervating segment of the spinal cord [39]. The T3–4 level is commonly used for upper abdominal pain, while the T6–7 level is commonly used for perineal pain [40]. A 16-gauge needle is typically inserted directly at the midline to a depth of 5 mm to complete the ablation [38–40].

Outcomes are generally favorable with significant immediate improvement of pain. Although pain recurrence is common, the severity is typically less than the preoperative baseline. Pain in new locations secondary to progression of the primary disease can also occur [38, 39]. Viswanathan et al. reported greater pain improvement with the open approach compared to percutaneous approaches in their study of eight patients. In their retrospective review, all four patients undergoing open limited myelotomy experienced excellent pain outcomes compared to zero undergoing percutaneous approaches (one good outcome, one fair outcome, and two poor outcomes). Of the one patient undergoing percutaneous mechanical lesioning, a good outcome was reported [40]. However, one must also consider the potential tolerance of a patient with often-advanced cancer in undergoing an open laminectomy required to create the lesion. Long-term results are limited, as the majority of patients have a life expectancy of less than a year at the time of presentation. Given the limited ablation needed to produce the desired result, complications are uncommon, but are

usually related to the dysfunction of the dorsal columns resulting in sensory changes or paresthesias of the trunk and lower extremities [38–40].

Intracranial Ablative Procedures

Similar to spinal ablative procedures, the use of intracranial ablative procedures has decreased in modern years with the improvement in the medical management of chronic pain and the further development of neuromodulation. However, despite these advancements, a subset of patients, particularly terminal cancer patients, who have pain refractory to these management options in certain distributions, may benefit from targeted ablation of specific intracranial pathways associated with pain.

Bilateral Anterior Cingulotomy

A cingulotomy for the treatment of chronic intractable pain is based on the premise that pain has three dimensions: a sensory component involved in pain intensity, an affective component involved in pain unpleasantness, and a cognitive component involved in the awareness of pain [41]. The anterior cingulate gyrus, part of the limbic system, has been linked to involvement in the affective component of pain, leading to an experience of pain as being unpleasant. Therefore, the role of a cingulotomy in the treatment of chronic pain is not to modulate the sensation of pain intensity, but rather to alter the patient's emotional reaction to the pain experienced [41–43]. Some studies suggest that patients suffering from chronic pain with associated depression and/or anxiety are those who most benefit from a cingulotomy [43].

Cingulotomies have been used for decades in the treatment of chronic, medically refractory pain, as well as in other disorders including obsessive-compulsive disorder, depression, and severe anxiety. A bilateral lesion is required to produce the desired effects. Modern techniques involve CT- or MRI-guided stereotactic ablation of the bilateral anterior cingulate gyri [42, 43]. A systematic review of the literature of anterior cingulotomy for the treatment of chronic pain by Sharim and Pouratian reports that 67% (149/224) of patients experienced significant pain relief immediately postoperatively and 65% (53/82) at 1 year, with similar findings in both neoplastic and non-neoplastic sources [41].

The operation has been generally well tolerated with common adverse events including transient confusion, urinary incontinence, headaches, and fever. More serious complications are rare and include hemiparesis, seizures, and hemorrhage. These complications were exceedingly rare in studies involving MRI guidance [43]. Neuropsychological adverse effects are, however, common, including deficits in executive function, attention, and response production similar to patients with frontal lobe dysfunction [41]. However, there has been no evidence of change in cognition, and some patients may even have improvement in executive function and attention, given the improvement in pain control [42, 43].

Medial Thalamotomy

Most recent studies of a thalamotomy for the treatment of refractory pain have been performed using gamma knife radiosurgery. The target is the medial thalamic nuclei complex, namely the centromedian and parafascicularis nuclei, given their role in the transmission of pain. Radiation doses of 140–180 Gy are commonly administered with reports of excellent or good pain improvement ranging between 43.3% and 66.7% in reported studies. Despite these marginal results, it is important to consider that this particular procedure is reserved only for the most refractory cases of chronic pain, so there remains a potential benefit with low side effects in patients that have failed numerous nonsurgical and surgical treatments. There have been limited side effects reported in recent studies, although radiation necrosis and damage to adjacent thalamic nuclei remain potential complications, particularly with the high radiation doses required to create a lesion [44].

Stereotactic Mesencephalic Tractotomy

Mesencephalic tractotomy is typically reserved for patients with an expected life expectancy of less than 1 year who suffer from severe and intractable cancer-related pain of the face and/or neck [45]. The operation involves MRI-guided stereotactic targeted ablation of the spinothalamic, trigeminothalamic, and spinoreticular tracts at the level of the midbrain. The spinothalamic and trigeminothalamic tracts carry nociceptive pain information from the body and the face respectively, while the spinoreticular tract is involved in the emotional response to pain. Lesioning of these tracts therefore leads to not only pain relief, but also improvement of pain-associated anxiety similar to that of a bilateral cingulotomy [45, 46]. Complication rates have improved with stereotactic techniques. A range of complications have been reported in the literature, including dysphagia, dysarthria, upward gaze paralysis, ocular convergence defects, skew deviation, miotic pupils, weakness/paralysis, painful dysesthesias, and altered mental status [45, 46].

Surgical Management of Trigeminal Neuralgia

Overview

Trigeminal neuralgia is an often-debilitating disease characterized by unilateral, paroxysmal, shock-like, or stabbing pain in the distribution of one or more of the divisions of the trigeminal nerve. The neurologic exam is usually benign other than

occasional sensory changes of the face. The most recent classification of trigeminal neuralgia involves three categories: classic trigeminal neuralgia, secondary trigeminal neuralgia, and trigeminal neuralgia of unknown etiology or idiopathic trigeminal neuralgia. Classic trigeminal neuralgia is secondary to an aberrant vessel loop, commonly the superior cerebellar artery, contacting the dorsal root entry zone of the trigeminal nerve, while secondary trigeminal neuralgia is due to an identifiable neurologic cause of trigeminal neuralgia such as multiple sclerosis, a tumor, or a vascular malformation [47]. Obtaining an MRI of brain with and without contrast is essential to rule out a secondary cause of trigeminal neuralgia in the initial workup [47, 48].

There are a variety of medications available for the treatment of trigeminal neuralgia. First-line treatment consists of carbamazepine or oxcarbazepine. Baclofen and lamotrigine are considered second-line therapy, and a number of newer AEDs have been given for refractory cases with varying successes [48]. Surgical management is an excellent option in medically refractory cases and consists of microvascular decompression, percutaneous treatments, and stereotactic radiosurgery.

Microvascular Decompression

Microvascular decompression is considered the gold standard surgical treatment for classic trigeminal neuralgia. However, it is also the most invasive surgical treatment and is associated with the highest morbidity. A retrosigmoid suboccipital craniotomy is used for approach to the lateral brainstem. The trigeminal nerve is then identified and explored. Once the aberrant loop of vessel is identified along the root entry zone of the trigeminal nerve, it is carefully dissected and mobilized. Telfa or teflon pledgets are then placed between the vessel and nerve to prevent migration of the vessel back to its previous location and subsequent recurrence. Patients are admitted to the hospital postoperatively for neurologic monitoring and routine care [49].

Microvascular decompression is considered the most effective and durable surgical treatment of trigeminal neuralgia. Studies have reported an immediate pain improvement in 80–96% with continued favorable outcomes of 72–85% at 5 years and 70–75% at 10 and 15 years. Repeat operations can be considered for those who responded well initially before recurrence, or for those who failed percutaneous treatments [49].

Despite being the most invasive option, the operation is generally well tolerated with a risk of serious adverse event of less than 5%. More common complications include facial numbness (6–22%), facial weakness (0.6–10.6%), hearing loss (1.2–6.8%), anesthesia dolorosa (0–4%), and aseptic meningitis (2%), while major adverse events including postoperative CSF leak, meningitis, stroke, and intracranial hematoma are less common (4%) [49].

Percutaneous Treatments

Percutaneous treatments remain an excellent option for patients who are not deemed surgical candidates for a craniotomy, who have had poor results following MVD or SRS, or who wish to pursue a less invasive option. Three techniques are generally used: balloon compression (BC), glycerol rhizotomy (GR), and radiofrequency thermocoagulation (RFT). The goal is selective destruction of the pain fibers, while preserving the fine touch fibers of the trigeminal nerve. Benefits of percutaneous treatments include immediate pain relief, short operative time/low anesthesia risk, and discharge commonly the same or next day. Furthermore, RFT offers the additional benefit of immediate patient feedback, as a portion of the operation is typically done awake [50, 51].

Access to Meckel's cave through the foramen ovale is performed in a similar manner in all three operations. Transcutaneous pacemakers should be placed prior to the case, given the risk of stimulation of the trigeminal depressor response leading to transient but often-profound bradycardia or asystole [50, 51]. The patient is positioned supine with the neck extended 15 degrees using a neck roll [50, 51]. A stab incision is generally made 2.5 cm to the corner of the mouth on the ipsilateral side of the patient's symptoms. The desired needle is directed at a trajectory toward a point in line with the ipsilateral pupil and 3 cm anterior to the external auditory canal (Hartel's landmarks) under fluoroscopic guidance [50, 51]. Once the foramen is accessed, the characteristic depressor response occurs. The remaining steps are specific to the particular percutaneous technique selected [50, 51]. Neurovascular injuries from puncture of the nearby internal carotid artery or cannulation of the jugular foramen are rare, but potentially serious complications that can occur during this stage of the operation [51].

For balloon compression, once the foramen ovale is accessed with a Tuohy needle, the stylet is removed, and a Fogarty catheter is inserted through the foramen ovale into Meckel's cave and inflated with contrasted fluid. This causes a characteristic pear shape under fluoroscopy once fully inflated. The depressor response commonly occurs again once the balloon is inflated, and the anesthesia provider should be warned about the potential for severe bradycardia and hypotension that is always transient. The balloon is typically inflated for 60–90 seconds followed by deflation and removal of the catheter and needle [50, 51]. Benefits of balloon compression include the selective injury of large and medium myelinated pain fibers with the relative sparing of smaller fibers involved in the corneal reflex. Furthermore, unlike RFT, balloon compression can be performed under general anesthesia since cooperation of an awake patient is not required. Immediate outcomes are excellent following balloon compression. Recent studies have reported immediate pain improvement in up to 94%, with long-term rates of 91% at 3 months and 69% at 3 years [50]. Other similar studies have reported immediate pain improvement in up to 85–100% of patients with highly variable recurrence rates [51]. Dysesthesias and significant numbness are the most common complications following balloon compression, with a 10–20% reported incidence. Less common complications include

masseter weakness, meningitis, cranial nerve deficits, anesthesia dolorosa, and stroke [50].

During glycerol rhizotomy, a 20-gauge spinal needle is used to enter the foramen ovale as previously described. Once the needle is inserted into the foramen, the head of the bed is elevated to 60 degrees on the operating table. The volume of the trigeminal cistern is then assessed with a contrast cisternogram using contrasted fluid. The desired volume of glycerol is then determined using the results of the contrast cisternogram and injected, followed by needle removal. Postoperatively, the patient is maintained in the sitting position for 2 hours to prevent glycerol leakage into the posterior fossa [50, 51]. Similar outcomes to balloon compression have been reported. Most studies demonstrate >90% immediate pain relief with long-term rates of 78–88% at 6 months and 53–54% at 3 years. Common complications of glycerol rhizotomy include dysesthesias, corneal numbness, masseter weakness, and herpes labialis [50].

Finally, radiofrequency thermocoagulation requires an awake and cooperative patient during the critical portion of the operation [50, 51]. Once the foramen is accessed, an electrode is introduced and the patient is awakened. The stimulating electrode is used to create a detailed mapping of optimal locations to lesion in order to maximize pain relief and minimize deficit. Following the mapping, the electrode is replaced with the thermocouple and lesions are made at the mapped locations. Benefits of RF compared to the other percutaneous treatments include immediate feedback from the patient and the ability to be more selective in the roots treated [50, 51]. Rates of initial pain relief are excellent, with lower rates of recurrence seen compared to balloon compression and glycerol rhizotomy. In a study of 1561 patients, Kanpolat et al. reported that 97.6% of patients experienced immediate pain relief with long-term rates of complete pain relief of 57.7% at 5 years and 42.2% at 15 years. This increased to >90% at 5 and 15 years in patients treated multiple times with RF [50]. However, RF is associated with a higher frequency and severity of side effects compared to other techniques. Reports of masseter weakness have been up to 29%, dysesthesia in the range of 1–11%, and corneal numbness between 3% and 20% [50].

Stereotactic Radiosurgery

For those not interested in undergoing invasive surgical procedures or for those with medical comorbidities precluding surgery, stereotactic radiosurgery has been shown to be an effective treatment option for trigeminal neuralgia. Typically, a dose of 60–90 Gy is administered to the affected trigeminal nerve, usually excluding the brainstem, under the guide of a neurosurgeon, radiation oncologist, and medical physicist. It is important to note that unlike microvascular decompression and percutaneous rhizotomies, immediate pain relief is not expected with radiosurgery [52].

Nuranjan and Lunsford reported a prospective series of 503 patients undergoing GKS at the University of Pittsburgh for trigeminal neuralgia in which 89% of patients

responded successfully to the treatment at a median latency of 1 month. Major pain relief was achieved in 73% patients at 1 year, 65% at 2 years, and 41% at 5 years. Other series have demonstrated similar results. For patients who respond initially but develop recurrent symptoms, repeat radiosurgery can be offered [52]. Of note, there is some evidence that patients who have not been treated with previous surgery have improved and longer-lasting outcomes [49, 52]. Complications include dysesthesias, corneal numbness, facial numbness, and rarely, anesthesia dolorosa [49].

Surgical Management of Occipital Neuralgia

Occipital neuralgia is an often-debilitating pain syndrome characterized by occipital headaches radiating from the base of the skull and up to the head, typically in the distribution of the greater occipital nerve (90%) or lesser occipital nerve (10%). It is commonly associated with a trigger point along the superior nuchal line. Diagnostic workup may include an occipital nerve block leading to temporary resolution of the headaches. The etiology is often idiopathic, but other causes include trauma/whiplash and entrapment. Occipital neuralgia has a relatively low incidence, limiting studies to small sample sizes. Medical management includes NSAIDs, corticosteroids, carbamazepine, gabapentin, tricyclic antidepressants, and analgesics. Noninvasive management options include heat treatment, temporary immobilization, physical therapy, transcutaneous electrical neurostimulation (TENS), occipital nerve block, botulinum toxin injections, and acupuncture [53]. In cases of severe, disabling pain poorly responsive to nonsurgical treatments, surgical management should be considered. Many surgical options have been attempted with varying success rates including occipital nerve decompression, neurolysis, radiofrequency ablation, ganglionectomy, cervical fusion, and occipital nerve stimulation. A few of the more common surgical options are discussed below [53–55].

Occipital Nerve Decompression

Greater occipital nerve compression is a well-established potential cause of occipital neuralgia. There are five potential sites of compression of the greater occipital nerve: (1) C2 root compression in the cervical spine, (2) within the inferior oblique muscles, (3) within the semispinalis capitis, (4) within the trapezial tunnel, and (5) by angiolymphatics crossing the nerve during its course. Occipital nerve decompression operations are typically targeted at decompressing the two most common sites of compression, namely the semispinalis and trapezius muscles. Some advocate division of the inferior oblique muscles as well, if certain neck movements trigger the characteristic pain [53, 54].

In a series of 11 patients undergoing greater occipital nerve decompression for occipital neuralgia, Roychoudhury et al. reported that 3 patients experienced elimination, 6 patients demonstrated improvement, and 2 patients had no improvement in their symptoms postoperatively. Patients undergoing nerve decompression are at particular risk of recurrence of symptoms due to resultant compression from scar formation, although patients are unlikely to suffer recurrence if they have not done so by the 2-year mark [53, 54].

Occipital Nerve Stimulation

In contrast to the ablative interventions, occipital nerve stimulation carries the benefit of being reversible and nondestructive. Prior to consideration of a permanent stimulator placement, patients commonly undergo an occipital nerve stimulator trial. Those who experience improvement in their pain during the trial period are considered candidates for a permanent stimulator placement. The operation is usually done with an open cervical incision. A Tuohy needle is inserted through the incision toward the mastoid process under fluoroscopic guidance. Once in appropriate position, the stylet is removed and the electrode is inserted through the Tuohy needle. Once the needle is subsequently removed, the electrode is secured to the fascia and tunneled to the site determined for the internal pulse generator and connected [53, 55].

In a case series of 20 patients undergoing occipital nerve stimulator placement, Boulis et al. reported a >50% reduction in pain in 85% of their patients, with an overall reduction in average pain score from 7.4 to 2.9. Complications occurred at a rate of 20% in their study including infection, loss of effect, lead migration, and erosion at the site of the hardware [53, 55].

Conclusions

The management of chronic pain that is refractory to nonsurgical management remains one of the most common, complex, and difficult problems that medical professionals face. In these cases, it is important to keep in consideration the potential surgical options that may be available. Advancements of neuromodulation as well as improvements in medication optimization and delivery have largely replaced neuroablative procedures. However, there remain specific indications and clinical scenarios when even these destructive procedures may be of significant clinical benefit. Knowledge of the options and indications are important to be familiar with to identify which patients may benefit from referral to a neurosurgical provider for further evaluation.

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Part VI
Pain in Early and Late Life

Chapter 27
Pediatric Pain Management

Yuan-Chi Lin and Susan Sager

Introduction

Pain sensation is a common protective mechanism and it is essential for survival for adults as well as children. Too much pain causes suffering in children and can prevent kids' participation in regular activities. Infants and children can feel pain like what occurs in adults. Acute pain is common, occurring as a result of tissue trauma, surgical procedures, and disease progression. It can be associated with increased anxiety and distress among pediatric patients and their families. If pain persists, it can result in changes in the CNS pain processing pathways, and the development of chronic pain.

Historically, children often receive inadequate treatment for pain. Pain and stress can induce significant physiological and behavioral responses, even in infants. Inadequate knowledge among health-care providers and insufficient medical evidence can contribute to ineffective pediatric pain management. An understanding of the developmental, physiological, and psychological factors relevant to pain is necessary to provide optimal care for children. Adequate psychological preparation and age-appropriate descriptions of options to relieve pain and suffering are essential to effective pediatric pain management. In recent years, there have been remarkable advances in pain management for the pediatric population.

Many hospitalized children experience pain during their stay. Procedures and treatment interventions were the most commonly reported and worst causes of pain in a 24-h period [1]. The prevalence of pain in hospitalized children was studied over a single day at a Canadian tertiary pediatric hospital. While 27% patients

Y.-C. Lin (✉) · S. Sager
Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Boston, USA

Department of Anaesthesia, Harvard Medical School, Boston, MA, USA
e-mail: Yuan-Chi.Lin@childrens.harvard.edu

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experienced pain prior to admission, 77% reported pain while hospitalized. Pain occurred across all age groups and services, though it was infrequently assessed or documented in the medical record, despite the fact that 90% of patients who received single agent analgesics found these helpful [2]. Another hospital-wide study noted that pain was twice as prevalent when reported by parents and children as when documented by nurses. Across all age groups, pain in infants was recognized and treated at significantly lower rates than older age groups. Compared to adults, children are provided inadequate and lower quality pain management [3]. In the pediatric surgical patient, pain may persist beyond the expected period of recovery. Children at risk for prolonged postoperative pain benefit from coordinated preoperative planning among anesthesiologists, pain physicians, and surgeons. Effective and safe perioperative pain management requires the selection of proper analgesic techniques and medications, the administration of appropriate doses to selected patients, and application in a suitable environment [4]. Pain management is most challenging after same-day surgery where parents are responsible for managing their child's pain at home. A study of 100 parents of children undergoing same-day surgery found that parents were able to manage their child's pain at home if provided with information and suitable analgesia on discharge [5].

New discoveries and emerging research in pediatric pain are helping us develop better tools for the treatment of pain in infants and children. Evidence-based randomized controlled trials for treatment of pediatric pain are lacking, and treatment recommendations are commonly based on clinical experience or extrapolated from adult studies. Using a critical analysis of the peer-reviewed literature, this chapter will present an evidence-based approach to pediatric pain management.

Developmental Pain

Afferent nociceptive sensory neurons are present at birth, though spinal cord sensory processing has yet to fully develop. At birth, there is a relative excess of excitatory signaling due to immature, less-developed spinal inhibitory pathways. Studies in newborns have demonstrated lower spinal reflex thresholds, with more sustained and synchronized reflex muscle contractions; induced hyperexcitability with repeated skin stimulation; and increasing reflex thresholds with post conceptual age [6–8]. Absence of adequate spinal and central inhibitory mechanisms at birth may lead to exaggerated and generalized neuronal responses, potentially amplifying the central effects of painful experiences in infancy.

Pain pathways undergo major reorganization after birth due to neuroplasticity and in response to intense or repetitive sensory stimulation. Newborns who have sustained tissue injury have been shown to have increased pain in the affected region later in life. Peripheral nerve sprouting, increased transmission of afferent impulses, and changes in modulation at the dorsal horn explain the development of central sensitization and hyperalgesia [9]. The plasticity of both peripheral and central sensory connections in the neonatal period can lead to structural and functional alternations in pain pathways that can last into adult life [6].

Although neonates undergo considerable maturation of peripheral, spinal, and supraspinal pathways over the early postnatal period, they respond to tissue injury with pain behaviors, accompanied with autonomic, hormonal, and metabolic signs of stress and distress. Understanding the developmental aspects of pain neurotransmission informs the approach to the pharmacological treatment of neonatal pain.10 It is observed that repeated exposure to morphine in infancy can cause hypersensitivity in the postnatal period. Changes in the structure and function of primary afferent synapses, neurotransmitter receptor expression and function, and neuronal modulation from higher brain centers may be part of a general reorganization that takes place in infancy [11].

Pain Measurement

Regular assessment of the existence and severity of pain and the child's response to treatment are essential for pediatric pain management [12]. Pain can be assessed by self-report, physiological measures, or behavioral observation, depending on the age of the child and ability to communicate. The child's perception of pain and psychological and developmental factors must be taken into consideration for accurate pain assessment. Accurate pain assessment can be challenging in patients with cognitive or motor impairments. Both subjective and objective tools may be utilized, depending on the patient's age and clinical status.

Pain is a subjective experience; therefore, individual self-report is often preferred. Children between the ages of 3 and 7 years are competent to provide information regarding the location, quality, intensity, and tolerability of pain. Observation of behavior should be used to complement self-report and can be an acceptable alternative when valid self-report is not available. The pain assessment tool should be introduced before the surgery or before the pain occurs. Each institution needs to adapt a uniform tool for pain assessment for pediatric patients.

The six-face Faces Pain Scale-Revised is useful in the assessment of acute pain intensity in children who have reached the developmental age of 4 years or greater. The FACES-R scale correlates well with the metric scoring system (0–10) and the linear interval scale [13]. In a study of 276 children, Baxt et al. demonstrated the feasibility of assessing pain following pediatric injury using two validated scales, that is, Bieri Faces Pain Scale and Color Analogue Scale. They also established the worth of parental report of pain when the child is not able to provide self-report [14].

Pain assessment is an especially difficult task for parents at home following children's surgery. The Parents' Postoperative Pain Measure (PPPM) was found to be a reliable and valid measure of postoperative pain among children aged 2–12 years [15]. Pain assessment can be challenging for patients with cognitive or motor impairments. This vulnerable population often receives less opioids in the perioperative period than children without cognitive impairment [16]. For patients who cannot reliably self-report, behavioral observations and individualized numeric rating scales are reliable and validated pain measures. The FLACC (Faces, Legs, Activity, Cry, Consolability) and FLACC-R (Revised) scales are known for interob-

server reliability and ease of use [17]. The I-NRS (Individualized Numeric Rating Scale) is individualized by parents with their child's pain behaviors [18]. Adult pain fear avoidance models have been applied to pediatric pain management, which demonstrates that cognitive–affective processes can be used in the pediatric population [19]. Parents and family factors can influence the behavior of pediatric pain. Parent Fear of Pain Questionnaire assesses parents' fears and avoidance behaviors related to their child's pain [20]. There are potential gender biases toward adult observer ratings of pediatric pain [21].

Pain Therapies

Acetaminophen and Nonsteroidal Antiinflammatory (NSAIDs)

Acetaminophen and ibuprofen are the most widely available over-the-counter drugs on the market for relief of pain. They are commonly used for mild-to-moderate postoperative pain. A single dose of ibuprofen (4–10 mg/kg) or acetaminophen (7–15 mg/kg) has similar efficacy for relieving moderate to severe pain, and similar safety as analgesics or antipyretics. Ibuprofen (5–10 mg/kg) is a more effective antipyretic than acetaminophen (10–15 mg/kg) at 2, 4, and 6 h post treatment [22]. Rectal suppository acetaminophen can be a useful analgesic in neonates or preterm infants [23]. However, absorption can be variable due to first pass metabolism. Intravenous acetaminophen has more predictable bioavailability and it can be used for neonates and infants [24]. Adverse effects of NSAIDs include gastritis, potential gastrointestinal bleeding, platelet, and renal function impairment. The mechanism of action of NSAIDs is inhibition of prostaglandin synthesis by inhibition of cyclooxygenase. Aspirin is not recommended for pediatric patients because of its association with Reye's syndrome. COXII selective inhibitors, such as celecoxib, can also be administered to children.

Ketorolac is a parenteral NSAID and is frequently administered as an adjuvant for acute pediatric pain management [25]. Intravenous ketorolac (0.3–0.5 mg/kg) is recommended for children. Parenteral ketorolac (0.5 mg/kg 4–6 hourly for 5 days or less) is generally well tolerated and has opioid-sparring effects in children [26]. The maintenance dose requirements of ketorolac are similar in children, adolescents, and adults [27]. Pharmacodynamics and pharmacokinetics are similar to adult values after the neonatal period.

Systemic Opioid Analgesia

Opioids can be used effectively and are commonly administered for pediatric postoperative pain treatment. Morphine is the most commonly used opioid analgesic and its pharmacology is well studied in pediatric patients. Pharmacokinetic and

pharmacodynamic developmental differences include reduced plasma clearance, smaller volume of distribution, and slower elimination compared to adults. Studied ventilated preterm neonates revealed that morphine clearance was 50% that of the mature value at 54.2 weeks postmenstrual age. The volume of distribution in preterm neonates did not change with age [28]. Renal clearance is reduced in the neonatal kidney. Hepatic metabolism is less in neonates. Researches in the pharmacokinetics and metabolism of morphine and its morphine-3-glucuronide and morphine-6-glucuronide metabolites revealed that the total body morphine clearance is 80% that of adult values by 6 months [29]. During the neonatal period, the volume of distribution appears to be smaller in neonates than in adults, but adult values are reached soon thereafter. For all the opioids studied, elimination is slower in neonates than in adults. The rate of elimination generally reaches and even exceeds adult values within the first year of life. Opioid-induced respiratory depression may be more pounced in neonates [4]. Intravenous opioid can be used during the perioperative period in the pediatric population. Intravenous infusion, nurse-controlled analgesia, patient-controlled analgesia, or oral formulations are vital for pediatric postoperative pain management. In addition to adjusting the opioid dose, the pain clinicians should collaborate with the child, family, and all teams involved. Hospital staff and family need to be aware of the challenges and be educated before surgery about strategies for postoperative management and discharge planning [30]. Codeine and tramadol are metabolized in the liver to active compounds via the cytochrome P450 2D6 enzyme. Across the population, there is considerable genetic variability in activity of the P450 2D6 enzyme, which in turn affects the rates of metabolism of these drugs to their active metabolites. Patients who are rapid metabolizers produce increased amounts of the active metabolites, which can cause oversedation, respiratory depression, and death. Conversely, in slow metabolizers, their pain is inadequately treated with standard dosing. The U.S. Food and Drug Administration posted warnings regarding codeine and tramadol use in the pediatric population [31].

Patient-controlled analgesia (PCA) can be safely used for children older than 6 years. Morphine, hydromorphone, and fentanyl are all equally effective. Nurse-controlled analgesia can allow greater flexibility and is commonly employed for those too young to use PCA. The PCA bolus plus basal rate continuous/infusion mode can improve nighttime sleep for children. Loading doses may be needed in some patients to establish analgesia. The lock-out time can be 5–12 min.

	Loading dose	Basal rate	PCA demand	1 h limits
Morphine (1 or 5 mg/ml)	0.03 mg/kg (MAX 2 mg)	0.015 mg/kg/h (MAX 1 mg/h)	0.025 mg/kg (MAX 1.8 mg)	0.1 mg/kg
Hydromorphone (100 mcg/ml)	5 mcg/kg (MAX 0.4 mg)	1 mcg/kg/hr. (MAX 0.2 mg/hr)	2 mcg/kg/h (MAX 0.3 mg)	20 mcg/h
Fentanyl (50 mcg/ml)	0.3 mcg/kg (MAX 20 mcg)	0.1 mcg/kg/h (MAX 10 mcg/h)	0.25 mcg/kg/h (MAX 18 mcg)	1 mcg/h

For patients in whom PCA is not appropriate, bolus and continuous infusion nurse-controlled analgesia can be utilized. Morphine infusion (10–30 mcg/kg/h) results in serum concentration of 10–22 ng/ml and adequate analgesia [32]. If patients can tolerate oral medications, it is the preferred route of administration. Adjustments to account for oral bioavailability of drugs are required. Medication should be titrated to appropriate analgesic effect. Oral opioid preparations (oxycodone, morphine) and combinations of opioid/NSAID are widely and effectively administered for acute postoperative pain management in children.

Regional Anesthesia

Multiple studies have shown that regional anesthesia could successfully be used to treat acute pain, reduce opioid consumption, and prevent unanticipated hospital admissions in pediatric patients with acute extremity injuries [33, 34]. Nineteen studies were found investigating regional anesthesia procedures in pediatric children with acute orthopedic injuries. Forearm blocks of the ulnar, median, and radial nerves can be performed in the emergency room to decrease pain and minimize opioid use [35]. Bier blocks with low-dose lidocaine are safe and effective at reducing upper extremity fractures but do require an intravenous catheter in the injured arm [36]. In children undergoing forearm fracture reduction, no significant difference in procedural distress, patient satisfaction, and parental satisfaction have been noted between children who receive an axillary block and children who receive deep sedation with midazolam and ketamine [37]. Intraarticular injection of bupivacaine reduced opioid consumption postoperatively when compared with intraarticular injection of saline [38]. No significant difference in pain reduction was noted between femoral nerve blocks and fascia iliac nerve blocks for ACL repair but pain may still be present postoperatively from harvesting the gracilis and semitendinosus tendons [39] Fascia iliaca blocks had higher success rates than three-in-one femoral blocks for children [40] Local anesthetics infused via catheters inserted under the fascia layer of the incision have been found to reduce postoperative opioid use compared to catheters filled with placebo but pain scores were only significantly reduced after postoperative hour four [41]. Outpatient peripheral nerve block catheters can provide efficient analgesia and shorten hospital stay for children with suitable family environments [42]. Multiple studies have demonstrated the lack of delayed diagnosis of compartment syndrome if frequent clinical evaluation is performed for breakthrough pain despite a functional nerve block [43–45]. The Pediatric Regional Anesthesia Network obtained valuable data on practice patterns and complications and to facilitate collaborative research in regional anesthetic techniques in infants and children. The neuraxial as well as peripheral block regional anesthesia complications in children as commonly performed in the United States is very low [46]. Ultrasound is commonly being utilized for peripheral nerve blocks.

Neuraxial Block

Caudal epidural block is one of the most common regional anesthetic techniques for pediatric ambulatory surgical procedures below the umbilicus. It is used for procedures involving the lower thorax, hip, pelvis, urogenital/perianal regions, and lower extremity. It also provides effective analgesia after bone marrow harvest.

Caudal blocks are easy to perform. A single injection achieves long-lasting postoperative analgesia in pediatric ambulatory patients. Alternatively, an epidural catheter can be placed through a standard IV cannula (e.g., Angiocath) to deliver prolonged postoperative analgesia. Conroy et al. compared the effectiveness of caudal epidural block to surgical wound infiltration in providing postoperative analgesia after inguinal herniorrhaphy in 35 children. Patients who have received caudal epidural block had shorter emergence times, less pain-related behavior, and lesser opiate requirements postoperatively [47]. General contraindications include uncorrected coagulopathy and localized infection at the injection site. Specific contraindications include spinal deformities such as myelomeningocele and abnormalities in the sacral anatomy.

In general, caudal epidural block is safe. Rare complications include subcutaneous injection, dural puncture, subarachnoid injection, intravascular injection, intraosseous injection, hematoma, infection, and urinary retention. Broadman et al. reported that in 1154 consecutive pediatric cases, no serious complications occurred. One dural puncture occurred and was detected by aspiration prior to injection of local anesthetics [48]. Fisher et al. demonstrated that the time to postoperative micturition in 82 children undergoing herniorrhaphy and orchiopexy was independent of whether caudal epidural block or ilioinguinal nerve block was utilized [49]. Caudal anesthesia seems to be an inexpensive, simple, and effective technique not only as a supplement for postoperative analgesia, but also as the sole method of anesthesia [50]. An observational study using the Pediatric Regional Anesthesia Network database included 18,650 children who received a caudal block. The estimated complications rate after caudal blocks was 1.9%. The complications include block failure, blood aspiration, and intravascular injection [51]. Caudal blocks are safe in pediatric populations.

Lumbar epidural block is utilized for surgical procedures on the hip, pelvis, and lower extremity. For patients with previous surgery involving the rectal and sacral areas or with anatomical abnormalities in the sacral area, lumbar epidural block is a practical alternative to caudal epidural block. Epidural anesthesia decreases the requirement for general anesthesia and alleviates postoperative pain [52]. Most pediatric patients require sedation or general anesthesia prior to epidural placement. The depth of the lumbar epidural space from skin to the epidural space is $15 + 1.5 \times \text{Age (mm)}$. Prior to the injection of local anesthetics, aspiration for blood and CSF must be negative. Epidural anesthesia is accomplished through single injection or continuous infusion of local anesthetics via an epidural catheter. Complications include accidental dural puncture, direct trauma to spinal cord, embolism from air introduced during epidural needle placement, and seizures in patients receiving continuous bupivacaine infusion.

Epidural analgesia is effective in alleviating intense localized pain, somatic pain, and visceral pain. Analgesia can be provided by local anesthetic bolus or continuous infusion. They provide greater pain relief at lesser doses and with less sedation than parenteral narcotics. Epidural techniques in children are associated with cardiovascular safety and analgesic efficacy [53], reduction of the stress response to abdominal surgery in infants [54], and improved outcome after patent ductus arteriosus ligation [55].

The most common insertion site for epidural analgesia include: (a) caudal route for patients under 12 months old; (b) lumbar approach for patients over 12 months old; (c) thoracic route for patients with specific indications, such as thoracic or upper abdominal surgeries. In addition, single-shot caudal blockade is very useful for minor procedures. It is best to avoid using air-filled syringe for loss of resistance for locating the epidural space. This will cause air embolism in some pediatric patients. Epidural catheter placement using electrical stimulation guidance is an alternative approach for positioning the catheter into the thoracic region via the caudal space. This easily performed clinical assessment provides optimization of catheter tip positioning for achieving effective pain control [56].

For small infants, an epidural solution of 0.1% ropivacaine with 3–10 mcg/ml hydromorphone can be administered at 0.2–0.4 ml/kg/h. In neonates, the recommended rate for continuous epidural infusion of ropivacaine is 0.2–0.3 mg/kg/h [57, 58]. Continuous thoracic epidural infusions for postoperative analgesia are effective after pectus deformity repair, and decrease the requirement for intravenous opioid, and, in one study, was associated with no catheter-related complications [59]. Continuous regional techniques, including epidural infusions, in pediatric patients are effective. Because of their potential complications, these blocks should be performed, monitored, and cared for by staff experienced with and trained in them [60].

Pain relief from patient-controlled epidural nerve catheters can be augmented with dexmedetomidine, fentanyl, morphine, hydromorphone, or epinephrine; the former option is associated with fewer bolus doses immediately postoperatively and no significant delay in emergence from anesthesia or recovery room stay [61]. Epidural solutions augmented with fentanyl demonstrate superior analgesia compared to epidural solutions without fentanyl but leads to significantly more postoperative nausea and vomiting [62]. Epidural blocks augmented with low-dose morphine can provide adequate postoperative pain relief for over 12 h but may be associated with a high incidence of postoperative vomiting [63]. Patients receiving epidural solutions with hydromorphone reported fewer rates of respiratory depression, nausea, vomiting, and somnolence compared to patients receiving epidural solutions with morphine [64]. Epidural solutions with fentanyl and epinephrine can provide effective pain relief but mild side effects include pruritus and nausea [65]. Epidural morphine, when compared to PCA morphine, is associated with less drowsiness but higher rates of pruritus and urinary retention [66].

Interscalene Block

The interscalene block is indicated for procedures on the clavicle, shoulder, and upper arm. The patient is placed in the supine position. By having the patient voluntarily lift his head off the operating table, the interscalene groove is accentuated and marked prior to induction of general anesthesia. Since patient cooperation is necessary, this block may not be feasible in younger patients. At the level of the cricoid cartilage, a 22- to 25-gauge needle is inserted into the interscalene groove and directed medially, caudally, and posteriorly toward the C6 transverse process. Nerve stimulation can assist in confirming correct needle placement. A mixture of 1% lidocaine 0.5 ml/kg and 0.1% tetracaine or 0.5 ml/kg of 0.25–0.5% bupivacaine can be used for the interscalene block. A continuous catheter technique can also be used [67]. Complications include intravascular injection, hematoma, and infection. Phrenic nerve block with unilateral diaphragmatic paralysis, subarachnoid injection with total spinal anesthesia, and basilar artery injection has also been reported.

Femoral Nerve Block and Adductor Canal Block

The femoral nerve block and the 3-in-1 block are indicated for femoral osteotomy, quadriceps, and vastus lateralis muscle biopsy, and the donor skin harvesting from the anterior thigh. Both blocks relieve muscle spasm in femoral shaft fractures. The femoral artery lies medial to the femoral nerve and serves as the anatomic landmark. At the level of the inguinal ligament, a short-beveled needle is inserted perpendicular to the skin and lateral to the femoral artery pulsation. Paresthesia is not necessary. Ultrasound and a nerve stimulator aid in localizing the nerve. After a negative test aspiration, local anesthetics are injected in a fan-like manner lateral to and deep into the femoral artery to anesthetize the lateral femoral cutaneous nerve. The 3-in-1 block (inguinal perivascular technique) is performed in a manner like that for the femoral nerve block. The needle is inserted pointed rostrally at a 30-degree angle from the anterior thigh. Local anesthetics are injected with compression of the femoral canal distal to the needle. For femoral nerve block, 0.2–0.3 ml/kg of 0.25–0.5% bupivacaine is recommended. For the 3-in-1 block, 0.5–0.7 ml/kg of 0.25–0.5% bupivacaine is recommended (maximum dose: 2.5 mg/kg). The duration of analgesia is about 3–6 h. Complications include sympathetic nerve block, injury to adjacent blood vessels, and hematoma. Sympathetic nerve block is transient and improves peripheral circulation to the lower extremity [68–70]. The fascia iliaca block provided more effective pain relief and longer duration of pain relief compared to intravenous morphine in children with femur fractures [71]. Comparing intravenous opioids with femoral nerve blocks and lateral femoral cutaneous nerve blocks showed no difference in intraoperative anesthetic requirements, postoperative opioid requirements, and time to first opioid administration [72].

Adductor canal blocks with dexmedetomidine can provide low postoperative pain levels without reducing quadriceps muscle strength as do femoral nerve blocks [73].

Pediatric and adolescent patients undergoing anterior cruciate ligament (ACL) reconstruction surgery treated with femoral nerve block for postoperative analgesia had significant isokinetic deficits in knee extension and flexion strength at 6 months when compared with patients who did not receive a nerve block [74]. Adductor canal block theoretically causing less quadriceps weakness during the immediate postoperative period can be an alternative method to femoral nerve block for postoperative analgesia for the anterior cruciate ligament. A randomized controlled trial of 102 patients undergoing primary ACL reconstruction using a variety of graft types indicated that there was no statistically or clinically significant difference in quadriceps strength at 3 and 6 months postoperatively in patients who received adductor canal block or femoral nerve block for ACL reconstruction.75

Lateral Femoral Cutaneous Nerve Block

The lateral femoral cutaneous nerve block is indicated for muscle biopsy at the thigh, skin graft harvesting, and lateral thigh incision [76]. The lateral femoral cutaneous nerve has no motor component, and the block does not interfere with lower extremity motor function. The lateral femoral cutaneous nerve (L2–L3) passes under the fascia iliaca and enters the thigh deep into the inguinal ligament and medial to the anterior superior iliac spine. At the level of the inguinal ligament, a 22-gauge, short-beveled needle is inserted 1–2 patient's finger breadth medial to the anterior superior iliac spine. Resistance is felt as the needle penetrates, in turn, the external oblique aponeurosis, the internal oblique muscle, and the fascia iliacus.

Fascia Iliaca Compartment Block

Fascia iliaca compartment block is used for femoral osteotomies, femur fracture repair, hip surgery, knee arthroscopy, and muscle biopsy. The patient is placed in the supine position. Landmarks consist of the anterior superior iliac spine, the pubic tubercle, and the inguinal ligament. At 0.5 cm caudal to the junction of the lateral third and the medial two-thirds of the inguinal ligament, the needle is inserted perpendicular to the skin. Distinctive losses of resistance occur when the needle punctures the fascia lata and the fascia iliaca. Then, local anesthetics are injected with firm pressure applied caudal to the needle. This technique favors cephalad spread of local anesthetics in the fascia iliaca compartment. Dalens compared 60 children who received a fascia iliaca compartment block with 60 children who received a 3-in-1 block. Ninety percent of patients who received a fascia iliaca compartment block had adequate analgesia compared with 20% of patients who received a 3-in-1 block.40 One effective local anesthetic combination is a 50:50 mixture of 1% lidocaine and 0.5% bupivacaine with 1:200,000 epinephrine. The volume is based on patient weight: 0.7 ml/kg for fewer than 20 kg, 15 ml for 20–30 kg, 20 ml for 30–40 kg, 25 ml for 40–50 kg, and 27.5 ml for over 50 kg. The fascia iliaca compartment block lasts from 12 to 15 h.

Popliteal Fossa Nerve Block

The popliteal fossa nerve block anesthetizes the sciatic nerve and its two branches, the tibial and peroneal nerves. The block is indicated for procedures below the knee such as hallux valgus surgery, tendon surgery, synovectomy of the metatarsal joint, toe amputation, foreign body removal, and tumor excision. The popliteal fossa is a diamond-shaped area bound superiorly by the biceps femoris muscle, the semitendinosus muscle, and the semimembranosus muscle, and inferiorly by the medical and lateral heads of the gastrocnemius muscle. The sciatic nerve bifurcates at the apex of the popliteal fossa into the tibial nerve, which runs medially, and the common peroneal nerve, which runs laterally. A nerve stimulator assists in accurate localization [77]. The patient is placed in the prone position with the knee slightly flexed, allowing the upper borders of the popliteal fossa to become more palpable. When the patient is in the prone position, the needle is introduced at the apex of the popliteal fossa; the sciatic nerve is blocked, resulting in complete anesthesia of the foreleg and the foot, except for the skin around the medial malleolus. Individual blocks of the tibial nerve and the common peroneal nerve are easily performed. When the fascia covering the popliteal fossa is penetrated, loss of resistance is felt. Subsequently, the needle is advanced an additional 5 mm. This technique is a safe and reliable alternative to more common forms of anesthesia for surgery below the knee [78]. Continuous popliteal sciatic nerve blocks were associated with lower risks of urinary retention, nausea, and vomiting compared to continuous epidural blocks [79]. Lumbar plexus blocks (also known as psoas compartment blocks) can also reduce postoperative pain scores and have the added benefit of only affecting one side [80].

Penile Nerve Block

The penis receives innervation from the dorsal penile nerves, the genitofemoral nerve, and the iliohypogastric nerve. The distal two-thirds of the penis are innervated by the paired dorsal penile nerves, which emerge caudal to the symphysis pubis and run down the penile shaft beneath Buck's fascia at one and eleven o'clock. The penile nerve block is indicated for patients undergoing circumcision or distal hypospadias repair. A comparison of the penile block versus the caudal block for circumcision revealed that the penile block is equally effective without associated motor blockade. Three approaches to the penile nerve block have been described. First, a 22-gauge short-beveled needle is inserted perpendicular to the midline at the inferior edge of the symphysis pubis and advanced until loss of resistance indicates penetration of Buck's fascia. After negative test aspiration, local anesthetics are injected. Second, sites at one and eleven o'clock deep into Buck's fascia are injected with local anesthetics. The third method is the subcutaneous infiltration ring block at the penile base. The most successful technique combines injection of the dorsal penile nerves at one and eleven o'clock with subcutaneous infiltration at the penile

base dorsally from three to nine o'clock [81]. Epinephrine-containing solution is never utilized. Complications include intravascular injection, hematoma, infection, and ischemia.

Ilioinguinal and Iliohypogastric Nerve Blocks

Ilioinguinal and iliohypogastric nerve blocks are commonly performed for inguinal hernia repair and orchiopexy. The blocks provide effective operative and postoperative analgesia. Cross and Barrett compared the use of iliohypogastric and ilioinguinal nerve blocks with 0.25% bupivacaine and 1:200,000 epinephrine versus caudal anesthesia with 0.25% bupivacaine in children undergoing herniorrhaphy and orchiopexy.82 The two techniques did not differ in the duration and the quality of analgesia, incidences of vomiting, or time to first micturition. The principal anatomic landmark is the anterior superior iliac spine. At one patient's finger breadth medial to the anterior superior iliac spine, a 22- to 25-gauge, short-beveled needle is inserted perpendicular to the skin. A subtle loss of resistance occurs as the needle penetrates the external oblique aponeurosis and the internal oblique muscle fascia. After a negative test aspiration, local anesthetics are injected. Using a single injection technique, ilioinguinal and iliohypogastric nerve block provides adequate analgesia for children undergoing hernia repair.83

Side Effects of Treatment and Postoperative Monitoring

Standardized order sets for dosing, and routine monitoring during continuous infusions of opiates or local anesthetics can be helpful for managing acute pain and provide an added layer of safety. The use of pulse oximetry is recommended for the first 24 h after beginning an infusion or after increasing the rate. Newborns should be continuously monitored for respiratory depression. Nausea/vomiting can be treated with ondansetron 0.1 mg/kg/dose (maximum 2 mg) IV 4–8 hourly PRN. Pruritus can be treated with nalbuphine 0.01–0.02 mg/kg/dose (maximum 1.5 mg) IV 6 hourly PRN, or diphenhydramine 0.25–0.5 mg/kg/dose (maximum 25 mg) IV 6 hourly PRN. Respiratory depression should be treated immediately. The dosage for naloxone is 0.1 mg/kg (maximum 80 mg) IV PRN.

Epidural infection is rare in pediatric patients who receive short-term catheterization postoperatively [84]. Kost-Byery et al. studied bacterial colonization and the infection rate of continuous epidural catheters in children. They reported that in patients treated with caudal epidural catheters, children aged 3 years and older were less likely to have colonized epidural catheters than younger children. Age did not affect the probability of developing cellulitis at the insertion site. Despite bacterial colonization of caudal and lumbar epidural catheters, it was observed that serious systemic and local infection after short-term epidural analgesia did not occur [85]. Seth et al. studied postoperative epidural analgesia in 100 consecutive children

aged 1 day to 15 years. They revealed that minor local signs of inflammation and infection are common in pediatric patients during continuous epidural infusion. Epidural catheter tips are also frequently culture positive in patients with and without local signs and who may not go on to develop further signs or symptoms of infections [86].

Other Pain Treatment Approaches

Intraoperative neural blockade or local infiltration for postoperative analgesia in children should be considered whenever possible. Nonpharmacologic treatments are also helpful adjuvants, for example, hypnosis, relaxation, biofeedback, TENS, art therapy, and acupuncture may offer pain relief for children and adolescents [87]. Children and adolescents will benefit from coordinated efforts to manage acute pain. Anesthesiologists who manage perioperative pain in pediatric patients should be familiar with the special characteristics of this population and utilize the appropriate pharmacologic and nonpharmacologic strategies.

Postoperative Pediatric Pain Management Service

Many hospitalized patients followed by the Pain Service are patients who have undergone surgery. Ideally, the Pediatric Pain Management Service is a multidisciplinary team of pediatric physicians, nurses, physical therapists, and psychologists. Close communication with the Pediatric Surgical and Medical specialists helps assure coordination of care in anticipation of discharge [88]. The American Society of Anesthesiologists has published practice guidelines for acute pain management in the perioperative setting. Standard protocols for acute pediatric pain management have been established for the purposes of patient care, as well as ongoing education and training to ensure that hospital personnel are knowledgeable and skilled regarding the effective and safe use of the available treatment options in the hospital. Optimal pain management for pediatric patients requires reliable assessment tools and aggressive management of the pain symptoms and side effects with consideration of the emotional as well as social factors contributing to the pain.

Although methods for the safe and effective management of pain in children are now known, this knowledge has not been widely used in routine clinical practice. Pain in early life may lead to long-term behavioral consequences. The timing, degree of injury, and administration and nature of analgesics may be important determinants of the long-term outcome of children and infants who experience pain perioperatively. The assessment and management of this pain and understanding its functional consequences present considerable and important challenges to those who care for children who require surgery [89].

Chronic Pediatric Pain

Children frequently experience a variety of recurring or chronic pains, such as headache or abdominal pain, that are typically not associated with an underlying organic disease. Sometimes, these recurring pains can induce changes in the CNS and alter pain processing, resulting in chronic neuropathic pain. Some painful conditions such as rheumatoid arthritis, malignancies, and sickle cell disease can be associated with both acute painful events as well as chronic neuropathic pain. Like the adult experience, pediatric patients with chronic pain often face diagnostic uncertainty. For some, the belief that serious pathology is being overlooked leads to extensive evaluations and often unhelpful interventions. A meta-analysis of psychological intervention studies for children and adolescents with functional unexplained somatic symptoms indicates that psychological interventions reduce symptom load, disability, and school absence [90]. Pain neuroscience education, designed to increase understanding of parents and children to the diagnosis of chronic pain, will more directly influence in pediatric pain management [91].

Headaches

Recurrent headaches are an exceedingly common form of recurrent pain in pediatric patients. The most common types of headaches children experience include migraine, tension headache, and combined migraine–tension headache. The prevalence of nonmigraine headaches in childhood and adolescence is 10–25%, of which the highest is with increasing age and in females [92, 93]. Migraine headaches are more commonly experienced by boys than girls in early childhood but become more common in girls at puberty. There is usually a strong family history of migraine headaches. Children typically report an abrupt onset of unilateral or bilateral severe, throbbing headache pain, which is often associated with nausea and vomiting. Although some children experience classic visual or auditory auras of migraine, many experience more subtle premonitory signs such as pallor, irritability, and fatigue [94]. Patients typically experience relief after sleep. Tension-type headaches are most common among adolescents. These headaches are usually described as a squeezing pain located circumferentially around the head. It is not uncommon for patients with tension headaches to experience them daily.

Children with combined headaches experience both chronic tension headaches and superimposed episodic migraines with their associated abdominal pain, nausea, and vomiting. Children with mixed headaches have a higher incidence of learning disability compared to those with migraine alone [95]. The diagnosis of chronic daily headache is made when headaches have been present for more than 15 days per month, with a duration of 3 months or longer.

Most headaches in children are not associated with serious underlying intracranial pathology or organic disease. A thorough history and physical examination are

essential and should include a careful neurologic and funduscopic examination. A psychosocial history is also beneficial in helping to determine whether family stressors or maladaptive behaviors might play a causative role in reinforcing pain behaviors. The routine use of diagnostic studies is not indicated when the clinical history reveals no associated risk factors and the child's examination is normal [96]. A history of personality changes, visual disturbances, fever, or headaches associated with neurologic deficits are signs that neuroimaging is indicated. Chronic progressive headache is most likely the result of a secondary etiology, such as changes in intracranial pressure, infection, or neoplasms, and warrants neuroimaging to investigate for structural abnormalities or malignancies [97].

Treatment for headaches in children includes the use of both pharmacologic and nonpharmacologic therapies. Education should be provided to patients and families, along with reassurance that the most worrisome cause of headaches is unlikely, and that reevaluation will be ongoing. Often a diary will be kept by the patient for documenting the characteristics of the headaches, medications tried, diet, and stress level at the time of onset to identify aggravating factors. Lifestyle modifications to improve school attendance, sleep, physical activity, and mood can be important interventions for treating daily headaches. In addition, cognitive–behavioral interventions can alleviate headache pain and promote functional and adaptive behavior. Combinations of analgesics, antiemetics, and 5-HT serotonin agonists are commonly used abortive migraine therapies for children. Nonsteroidal antiinflammatory drugs (NSAIDs) are often first-line agents for migraines, tension headaches, and combined headaches [98]. Patients should be instructed about proper dosing, as excessive use of NSAIDs, acetaminophen, and combination drugs such as Fioricet (butalbital, acetaminophen, and caffeine) can cause rebound headaches [99].

Systematic reviews of NSAIDs among adult patients report little difference in their clinical effectiveness. However, parenteral NSAIDs such as ketorolac are often used in patients with persistent vomiting, who cannot tolerate oral intake. In a randomized crossover study, ibuprofen was found to be more effective than acetaminophen for interruptive therapy [99]. Ibuprofen in suspension form is commonly used for abortive headache therapy in children who are unable to swallow pills. The recommended pediatric doses are between 6 and 10 mg/kg, taken orally. Chronic opioid use is generally not recommended for the treatment of recurrent or chronic headaches [100].

The 5-HT serotonin agonists, such as sumatriptan, zolmitriptan, and rizatriptan, have been shown to be effective abortive therapies in patients with severe migraines [101–103]. Antidepressants, anticonvulsants, and beta-blockers are frequently used for prophylactic migraine therapy. Low-dose tricyclic antidepressants, such as amitriptyline or nortriptyline, may provide effective migraine prophylaxis. Typical starting dose for tricyclic antidepressants in children is 0.2 mg/kg, administered at bedtime, to promote improved sleep. The doses are titrated, based on the clinical response and any side effects the patient may experience. Gabapentin 5–10 mg/kg/day, with maximum dose of 2400–3600 mg, is commonly prescribed for patients with chronic headache. Several studies have shown positive clinical results from treatment with calcium channel blockers. Propranolol is often used in doses of

1–2 mg/kg daily; however, controlled studies in pediatric headache management have shown equivocal results [104, 105]. Coenzyme Q10 supplement 25–300 mg/day can be effective in the prevention of migraine [106]. Occipital nerve blocks and botulinum toxin injection can control some intractable headaches [107].

Nonpharmacological therapies and treatments for chronic headache in children include cognitive–behavioral therapy, biofeedback, relaxation, guided imagery, self-hypnosis, family therapy, and acupuncture. Evidence supports the effectiveness of biobehavioral headache management, when compared to pharmacologic agents, for certain types of headaches in children [108]. Through biofeedback, guided imagery, and progressive muscle relaxation, patients learn to shift their cognitive focus away from the pain, thereby decreasing their experience of pain. These skills reduce stress and anxiety, which are precipitating factors in many children with headaches. Cognitive–behavioral strategies help patients to improve coping skills, return to school, recognize maladaptive behaviors, and reinforce more functional lifestyles. Acupuncture may be a valuable tool for patients with frequent, episodic, or chronic tension-type headaches [109]. Available studies suggest that acupuncture is at least as effective as, or possibly more effective than, prophylactic drug treatment and has fewer adverse effects [110].

Chest Pain

Chest pain in children and adolescents is a common presenting symptom in emergency rooms, general pediatric practices, and pediatric pain clinics. Because chest pain is often an ominous symptom among adults, it causes much distress to children and their parents. It is, however, not commonly associated with heart disease in children. Of 67 patients referred to a pediatric cardiology clinic with chest pain, only 6% were found to have underlying cardiac disease [111]. The most common reasons of chest pain in children include costochondritis, idiopathic causes, muscle pain from coughing, and other musculoskeletal causes [112, 113]. Additional causes of chest pain in children include slipping rib syndrome and abdominal and gastroesophageal disease [114]. A thorough medical history and physical examination help to identify cardiac symptoms. Selbst and colleagues found that organic causes of chest pain in children were more common when associated with abnormal findings on physical examination or symptoms were present in a younger child [112]. A history of syncope, presyncope episodes, or history of palpitations warrants further evaluation. Gastroesophageal reflux or esophageal spasm may cause referred pain in the chest. In the absence of worrisome findings on history or physical examination, education and reassurance that heart disease is not a likely cause for the pain are helpful in resolving the symptoms long term [111, 115]. A trial of NSAIDs may be helpful for patients with musculoskeletal causes such as costochondritis. Nonpharmacological therapies such as physical therapy, transcutaneous electrical nerve stimulation, heat, and relaxation therapies are helpful for many pediatric patients experiencing chest pain.

Abdominal Pain

Abdominal pain is a common painful condition in infants, children, and adolescents. Functional abdominal pain (FAP) is recurrent episodic pain with no evidence of structural or inflammatory origin [116–120]. It is a common condition among school-aged children. A cross-sectional study was conducted in which US mothers ($n = 1255$) of children aged 0–18 years old were asked to complete an online survey about their child's GI symptoms, quality of life, and other health conditions. Infants and toddlers aged 0–3 years and children as well as adolescents aged 4–18 years who fulfilled symptom-based criteria for a functional GI disorder are 24% and 25%, respectively. Children were more likely to have a functional GI disorder if their parent qualified for a functional GI disorder of all ages groups with functional abdominal disorders are associated with decreased quality of life [121]. FAP disorders occur significantly more in girls than in boys. It may associate with the presence of anxiety and depressive disorders, stress, and traumatic life events [122].

A few clinical characteristics distinguish benign FAP from other types of childhood abdominal pain. In general, children with FAP are between 4 and 16 years of age, experience episodic abdominal pain interspersed with pain-free periods, and are otherwise thriving and medically well. Children with FAP frequently describe diffuse poorly localized periumbilical pain. It rarely radiates to the back or the chest. Pain is often worse at night but rarely awakens the child from sleep. Many children experience other chronic symptoms, such as headaches, nausea, and dizziness. In most cases, it lacks an identifiable biochemical, structural, or other organic cause. A subgroup of patients will have a recognizable underlying disease, such as lactose intolerance, constipation, ureteropelvic junction obstruction, inflammatory bowel disease, or endometriosis [123–127]. For many children, however, an underlying etiology is not diagnosed. Some studies suggest that FAP may be a precursor to irritable bowel syndrome, and that some children and adolescents may progress to meet the standardized criteria for IBS as adults [128, 129].

The diagnosis of FAP should be based on thorough history and physical examination. FAP disorders can be subdivided into four subgroups which include functional dyspepsia, irritable bowel syndrome, abdominal migraine, and FAP not otherwise specified. Significant degrees of overlapping among these conditions exist [130]. A psychosocial history is essential to learn how the child and family cope with pain and to identify issues, such as school avoidance and reinforcers of pain. A history of fever, weight loss, growth failure, rash, or other symptoms of systemic illness should prompt further investigation of organic causes [131]. Occurrence of persistent pain or recurrent abdominal pain in children younger than 4 years of age is also of concern. Physical examination should include a rectal examination with stool guaiac, evaluation for undescended testes, hernias, and abdominal masses. Findings on history and physical examination suggesting a possible underlying organic disorder should serve as a guide to laboratory and diagnostic testing. In general, extensive routine screening tests such as endoscopies, barium studies, and other radiographic studies are of low yield, particularly

when there are no specific clinical suspicions from history or physical examination. In addition to careful history and physical examination, baseline complete blood count, sedimentation rate, and urinalysis are reasonable screening tests to help rule out occult organic disease. A family history of inflammatory bowel disease in a child with chronic abdominal pain warrants further laboratory and possibly diagnostic testing. In children who experience chronic persistent abdominal pain, rather than the more characteristic episodic pain of FAP, laparoscopy identifies treatable conditions in a high percentage of cases [132, 133]. In a study of 104 children with FAP, parents were randomly assigned and trained to interact with their children according to one of three conditions: attention, distraction, or no instruction. Parents of the pain patients rated distraction as having a greater negative impact on their children than attention [134]. A significant component of treatment is education and reassurance that no serious organic illness is likely. It should be emphasized that the child's pain is genuine and that clinical reassessments will be ongoing.

Treatment is based on improving function and reducing maladaptive pain behaviors through emphasis on cognitive–behavioral therapies [135–138]. Underlying anxiety or depression should also be addressed. A return to school and participation in normal family and social activities is essential. Extensive diagnostic testing and referrals to multiple subspecialists may heighten patient and parental anxiety and reinforce a patient's "sick role."

In a study of 200 children with recurrent abdominal pain, somatic causes were found in 26%. Laxative therapy was successful in 46%, which resulted in nearly all patients with FAP becoming pain-free. Eventually, 99% became pain-free using a therapeutic intervention protocol [139]. Although the study indicated no significant difference between amitriptyline and placebo after 4 weeks of treatment [140], tricyclic antidepressants are commonly used. A recent report indicates that the evidence of the efficacy of antidepressants in the management of pediatric FAP is inconclusive [141]. Antispasmodics are sometimes used; however, there are limited data on the efficacy of drug therapy. The routine use of pain pharmacological therapy should be avoided. As a high placebo response, nearly 41% of children with abdominal pain related FAP disorders improve on placebo [142].

Hypnotherapy can be used for children with FAP disorder [143]. Longitudinal studies show that only 30% of children have resolution of pain within 5 years and 25–50% continue to experience symptoms as adults. Walker and colleagues found that in a 5-year follow-up only 1 in 31 children with FAP were eventually diagnosed with a definable "organic" disease [144]. A randomized controlled study of 200 children with persistent FAP indicates that children in the cognitive–behavioral condition showed greater baseline to follow-up decreases in pain and gastrointestinal symptom severity than children in the comparison condition [145]. A meta-analysis of 10 controlled studies regarding the effectiveness of psychological therapies for pain reduction in children with recurrent abdominal pain showed that psychological therapies are effective in treating children with chronic abdominal pain [146].

Chronic Pelvic Pain

Chronic pelvic pain is defined as lower abdominal pain lasting for at least 3 months. Chronic pelvic pain can lead to school absence and missed activities, decreased functioning, and decreased quality of life in the adolescent [147]. It is estimated that chronic pelvic pain affects 45–70% of adolescents [148]. The most common pelvic pain in females is dysmenorrhea and constipation. Dysmenorrhea is a syndrome characterized by recurrent, crampy, lower abdominal pain during menstruation, and greater sensitivity to pain [149]. Pain is often accompanied by nausea, vomiting, diarrhea, headaches, and muscular cramps, and frequently co-occurs with other chronic pain conditions, including migraine [150], IBS, and fibromyalgia [151]. Dysmenorrhea affects up to 30–90% of postmenarche adolescents, with 14–33% of adolescent females aged 15–22 years reporting pain as severe or affecting daily function. Dysmenorrhea is also associated with depression and anxiety in adolescents [152, 153]. Although dysmenorrhea is the leading reason for missed school days and work in adolescent girls, dysmenorrhea is rarely reported by adolescents. A menstrual history is frequently omitted by clinicians. The resulting paradox creates a knowledge gap in the diagnostic process, and pelvic pathology as a cause of chronic pain can be missed and remain untreated for years.

As with many repetitive painful events, dysmenorrhea can lead to central sensitization of pain pathways [154]. It also has changes in metabolic, morphologic, and functional connectivity between pain-related regions of the brain are present in women with dysmenorrhea [155, 156]. Dysmenorrhea is initially treated with nonsteroidal antiinflammatory drugs (NSAIDs). If pain persists, then cyclic hormonal therapy is used to lighten periods and decrease pain. If pain resolves with the use of NSAIDs and cyclic hormonal therapy, then no further evaluation is usually needed. Therapy needs to be individualized. If the pain persists, a specialist needs to be consulted for further care on treatment options [157].

Endometriosis is a painful chronic inflammatory condition which is defined as the presence of uterine tissue outside the uterus; it is the most common cause of secondary dysmenorrhea in adolescents. Endometriosis affects women of reproductive age, but adolescent girls can experience pain from endometriosis prior to onset of menses. A thorough history including sexual activities needs to be obtained. Chronic pelvic pain is multifactorial which involves components of myofascial pain syndrome and central sensitization [158]. Endometriosis symptoms can be cyclical, but more often pain is present throughout the menstrual cycle and associated with a preponderance of gastrointestinal symptoms due to CNS sensitization and development of visceral hyperalgesia. In adolescents, endometriosis pain can worsen with bowel movement or urination, and can be associated with painful tampon insertion or dyspareunia in sexually active adolescents [153] A variety of other medical conditions such as painful musculoskeletal disorders, constipation, urologic conditions, and irritable bowel syndrome may present as chronic pelvic or abdominal pain. Many adolescent patients with endometriosis report both cyclic and acyclic pelvic pain. Some patients experience more severe pain at midcycle and with menstrua-

tion, but many will experience pain throughout the month. There is evidence to suggest that the severity of endometriosis seen on laparoscopy does not necessarily correlate with the severity of pain [159].

Chronic pelvic pain treatment is a multidisciplinary endeavor, and communication among clinicians across disciplines is essential for good pain management outcomes. Acute exacerbations in endometriosis pain may be surgical or nonsurgical and an effort should be made to identify the cause of an acute increase in pain. Suspected surgical conditions include ovarian torsion, tubal, or ovarian cysts, and adhesions. Nonsurgical causes include missed or delayed oral contraceptive pills, change in absorption of oral contraceptive pills therapy due to medications, and switch in hormonal therapy. Close communication with the patient's gynecologist is important to understanding the etiology of episodic pain flares, and to advise further treatments.

Medications targeting neuropathic pain, including anticonvulsants such as gabapentin or pregabalin, and antidepressants such as amitriptyline, can be considered although there are no studies in adolescents to provide evidence for their usage in chronic pelvic pain. NSAIDs can be used short term for acute pain, for example, breakthrough bleeding or menstruation.

Pelvic floor physical therapy can be one of the effective treatment modalities for chronic pelvic pain. In a study of 9- to 20-year olds with unexplained chronic pelvic pain, 80% had improvement of pain with physical therapy [160]. Pelvic floor relaxation therapy, trigger point release, and biofeedback can reduce pain and medication use, and improve quality of life in adolescents with chronic pelvic pain and pelvic floor myalgias [161]. Cognitive–behavioral therapy, including guided imagery and biofeedback, has been shown to be beneficial with increasing evidence for chronic pelvic pain [162]. Acupuncture may be an effective, safe, and well-tolerated adjunct therapy for endometriosis related pelvic pain in adolescents [163].

Neuropathic Pain

Neuropathic pain conditions in children often result from postsurgical nerve injury, extremity trauma, malignancies, complex regional pain syndromes, and traumatic amputation. Diabetic peripheral neuropathy and trigeminal neuralgia seen in adult patients are rarely seen in children. Clinical features of neuropathic pain in children include allodynia, hyperpathia, and hyperalgesia to noxious, mechanical, and thermal stimuli. Some children will also experience autonomic dysregulation and motor weakness. Children frequently have difficulty describing neuropathic pain, and report pain that is "odd" or "strange." A detailed history and physical examination, including neurologic examination, are essential in evaluating a child with neuropathic pain. A broad-based evaluation may provide clues to fewer common causes of neuropathic pain such as underlying cancer, neurodegenerative disorders, and metabolic diseases. Nerve conduction studies are insensitive to abnormalities of C fibers and Aδ fibers, and therefore may be normal in patients with certain neuro-

pathic pain conditions. Quantitative sensory testing (QST), which assesses thermal and vibratory thresholds, may be especially useful in evaluating pediatric patients because it is painless and does not require the use of sedation [164].

The use of medications in the treatment of neuropathic pain in children is based on data extrapolated from adult studies. Randomized controlled studies of tricyclic antidepressants have shown effectiveness in treating neuropathic pain conditions in adults, including diabetic neuropathy and postherpetic neuralgia [165–167]. Nortriptyline and amitriptyline are antidepressants most commonly used in children, although desipramine is sometimes a useful alternative if excessive sedation is experienced. Due to rare case reports of sudden death attributed to cardiac dysrhythmia in children treated with tricyclics, a thorough cardiac history, physical examination, and baseline electrocardiogram is recommended prior to initiation of therapy [168]. Antidepressants such as selective serotonin reuptake inhibitors (SSRIs) are occasionally used in the treatment of neuropathic pain; however, additional studies are needed to determine efficacy. SSRIs can be useful for patients who have neuropathic pain associated with depressed mood or anxiety. Adult clinical trials have shown effectiveness of anticonvulsants such as carbamazepine, phenytoin, valproic acid, and gabapentin for the treatment of various neuropathic pain conditions [169–171]. Gabapentin has a lower side effect profile and fewer severe adverse effects than other anticonvulsants; and monitoring of serum levels is not necessary. The most frequent side effects include dizziness and somnolence. Gabapentin may also be effective in the treatment of mood disorders.

The 5% lidocaine transdermal (Lidoderm) patch is safe for neuropathic pain. It penetrates the skin to act locally on dysfunctional nerve fibers. The patch measures 10 × 14 cm and contains 700 mg of lidocaine mixture with a nonwoven polyethylene backing. The patch can be cut to the desired size. A 12-h-on and 12-h-off schedule is recommended with a maximum of three patches at a time applied to intact skin at or beside the area of the neuropathic pain [172].Most patients who are responsive to the Lidoderm patch experience relief within a few days of application. A trial of 2 weeks is recommended. Opioids' use in the treatment of neuropathic pain remains controversial.

Complex regional pain syndrome type 1 (CRPS 1), formally known as Reflex Sympathetic Dystrophy, is a neuropathic pain condition characterized by persistent limb pain with cyanosis, coldness, swelling, atrophy, or other signs of neurovascular abnormalities without an associated nerve injury. Complex regional pain syndrome type 2 (CRPS 2) refers to this clinical syndrome with a definable nerve injury. Functional MRI study in adolescents with CRPS indicates maladaptive neuroplasticity. With the disease progression, it showed decreased and reorganized somatosensory cortices correlating with the affected limb/region. Ongoing inflammation, psychological stressors, and genetic predispositions may also play a role [173]. The clinical presentation of CRPS in children differs from that in adults. Most children with CRPS are female with a lower limb affected. In adult presentation, gender differences are not significant, and upper and lower extremities are equally affected. CRPS in children occurs most frequently at 10–12 years of age, and rarely before the age of 6 years [174]. Many patients experienced eating disorders and

were involved in highly competitive sports, such as ballet and gymnastics. Compared to adults, children with CRPS are more likely to have spontaneous resolution of symptoms and show a greater response to early noninvasive treatment. Majority of pediatric CRPS patients had no or minimal residual pain following instruction of a self-administered mobilization program with massage and no medications [175].

Conservative treatment with aggressive physical therapy and cognitive–behavioral therapy results in marked improvement of symptoms in children with CRPS [176]. A prospective, randomized, controlled trial by Lee and colleagues showed that most children had clinical improvement with a regimen that emphasized physical therapy and cognitive–behavioral therapy [177]. Physical therapy is based on a rehabilitative approach involving desensitization techniques, weight-bearing exercises, and a gradual return to function. Cognitive–behavioral interventions typically include biofeedback training, relaxation techniques, and family and individual counseling. Education of both patients and parents is essential regarding the nonproductive nature of pain with CRPS, and that movement of the affected limb will ultimately diminish pain and dysfunction. Regular school attendance and participation in family and peer activities is emphasized. Often, a home diary that records pain scores and measures of function helps track response to therapy. Commonly used medications in the treatment of CRPS in children include antidepressants, anticonvulsants, and local anesthetic-like drugs. There is significant individual variation in response to medication trials. Sympathetic blockade is reserved for patients who do not improve with outpatient therapy and who continue to experience significant pain and limitations of limb mobility. Multidisciplinary and interdisciplinary pediatric pain management centers are popular as what is believed to be a more comprehensive approach to CRPS, both in the inpatient and outpatient settings [178].

Pain in Sickle Disease

Sickle cell pain ranges from acute vaso-occlusive episodes to chronic, daily pain. Acute painful episodes are characterized by an abrupt and usually unpredictable onset of severe ischemic pain. Vaso-occlusive episodes typically produce pain in the extremities, chest, lower back, and abdomen, and may be caused by a variety of factors such as infection, dehydration, hypoxia, and acidosis. Vaso-occlusive crises are the primary cause of hospitalization in patients with sickle cell disease.

Acute episodes of pain account for most hospitalizations and emergency room visits. In a prospective study, Platt and colleagues reported that 5% of patients with sickle cell hemoglobinopathy experienced over 30% of all painful episodes, and that the patients with the highest rates of painful episodes tended to die earlier than patients with lower rates of painful episodes [179].

Chronic pain may develop as episodic pain, become more frequent and severe, ultimately resulting in persistent daily pain. Bone infarction or necrosis may result in debilitating chronic pain conditions such as aseptic necrosis of the hip, vertebral compression fractures, and chronic low back pain. For home management of vaso-

occlusive episodes the use of NSAIDs is encouraged. Due to atypical cytochrome P450 2D6 (*CYP2D6*), pharmacogenetics would cause poor analgesic response. Though CDC has recommended not using codeine for pediatric patients less than 12 years old, in a study of 830 patients with sickle cell disease, 7.1% were ultra-rapid or possible ultra-rapid metabolizers and 1.4% were poor metabolizers. Codeine is not recommended for patients with a high-risk CYP2D6 status. By means of genetic profile to tailor analgesic prescribing retained an important therapeutic option [180].

Day treatment programs may provide effective alternatives to hospitalization or emergency room visits for some patients [181]. Hospitalization is necessary for patients who are unable to tolerate oral opioids due to vomiting or for patients with severe, escalating pain requiring rapid control with intravenous analgesics. Patient-controlled analgesia enables patients to rapidly titrate opioids according to the wide fluctuations in pain intensity common in vaso-occlusive episodes. A low-dose basal opioid infusion, in addition to on-demand doses, may provide effective analgesia, particularly during severe episodes of pain. However, there is some evidence that this regimen may increase the risk of hypoxemia at night [182]. Continuous epidural analgesia can provide effective analgesia and maintenance of respiratory drive in patients with acute chest syndrome [183]. It has not been established how frequently epidural analgesia should be chosen for patients with frequent, painful episodes. Self-report pain scales should be used as much as possible for pain assessment. Close nursing observation and monitoring is necessary, especially for patients at risk for opioid-induced respiratory depression and hypoxemia.

A multidisciplinary approach to sickle cell pain integrates pharmacologic therapy and cognitive–behavioral techniques to provide effective pain control, maintenance of normal functioning, and optimal quality of life. There is often excessive concern among health care providers and families about addiction to opioids, which has led to inadequate analgesia in some cases. Education is necessary regarding the use of opioids, home management strategies, and avoidance of precipitating factors of painful episodes. Cognitive–behavioral treatment such as biofeedback, hypnosis, guided imagery, and family therapy can improve coping mechanisms and prevent maladaptive behaviors [184].

Complementary Medical Therapies

With the growing opioid crisis in the United States, both clinicians and patients are trying to find nonopioid solutions for pediatric chronic pain by looking into complementary and alternative medicine. The National Center for Complementary and Integrative Health, previously known as the National Center for Complementary and Alternative Medicine, changed its name to include integrative health, which emphasizes the incorporation of complementary approaches into mainstream health care [185]. Most of the available evidence on complementary and integrative medicine has been extracted from clinical trials involving adult patients. Approximately

8.7 million children and adolescents in the United States utilize complementary and alternative medicine therapies for acute and chronic medical conditions [186].

The 2007 and 2012 National Health Interview Survey found that roughly 12% of children in the United States use complementary medicine [187]. Approximately 8.7 million children and adolescents in the United States utilize complementary and alternative medicine therapies for acute and chronic medical conditions [186]. The 2007 and 2012 National Health Interview Survey found that roughly 12% of children in the United States use complementary medicine, most often in the form of nonvitamin natural products and chiropractic or osteopathic manipulation [187]. Mind–body medicine employs a variety of methods of enhancing the mind's capacity to affect the body's functions. These include biofeedback, cognitive–behavioral therapy, guided imagery, hypnosis, relaxation therapy, meditation, mental healing, music therapy, yoga, tai chi, and patient support groups [188]. Behavioral medical therapies and complementary medical therapies play a major role in pediatric pain management.

Conclusions

A central component of the treatment of pain and distress in children is an in-depth understanding of pediatric diseases and the psychological and social dynamics involved in treatment of chronic pain conditions. Analgesics and specialized techniques should be combined with lifestyle changes and nonpharmacological approaches to provide optimal care. Additional prospective clinical trials are necessary in the understanding and treatment of chronic pain conditions in children. The multidisciplinary pediatric pain service would allow pediatric patients and family to be seen in a single visit by several pain specialists including the pain physician, child psychologist, physical therapist, and complementary medical therapy providers. This comprehensive approach for pediatric pain management would allow pediatric pain patients to obtain optimal care with least disruption for patients and their families.

An ideal model of pediatric care needs to be a patient-centered and family-oriented approach. Over the past few decades, significant understanding and progress has been made in acute, recurrent, and chronic persistent pediatric pain management. Pain assessment and treatment plans should be tiered to age and also be development-specific. Establishing multicenter clinical pediatric acute and chronic pain care research trials would be an important task.

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Chapter 28
Pain in the Elderly

Lisa To

Physiology

There are age-related changes in the structure and chemistry of the brain. It is difficult to truly assess how structural changes clearly change the function of a human brain, because there is a highly complex pain-processing pathway. However, literature suggests that unmyelinated and myelinated peripheral nerves are impacted, and there may be some degeneration of sensory fibers [4]. There are also studies that show that pain neurotransmitters occur at lower levels with increased age [5]. Despite these changes seen in animal and human models, there is no change in the pain stimulus–response curve [6]. Additionally, there is no consensus among studies regarding any changes in pain intensity, increased pain threshold, or pain duration. With these factors in mind, it can still be concluded that older adults can still be impacted greatly by the effects of chronic pain.

Assessing Pain in the Elderly

Pain is defined as an unpleasant sensory and emotional experience, associated with actual or potential tissue damage. Pain perception is a subjective experience that can be influenced by sensory stimuli, individual memory, and emotions [7]. As a result, this definition of pain can be unhelpful to the clinician as an operational definition. Unfortunately, since the perception of pain is a complex phenomenon, there is no biologic marker or other objective indicator of pain. Treatment should focus on

L. To (✉)
Department of Anesthesiology, UT Southwestern Medical Center, Dallas Veterans Hospital, Dallas, TX, USA
e-mail: Lisa.To@va.gov

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improving the patient's functional status rather than reducing pain. Thus, the ability to classify chronic pain may help the clinician begin to identify the pain generator, determine a prognosis, and select an appropriate therapy that is meaningful to the patient.

The effective assessment of pain in the elderly can prove to be quite challenging. A comprehensive assessment should first include a thorough review of history and review of systems with the patient and available family members, which will look for important medical, psychological, or social factors that contribute to the pain complaints. The basic elements of pain can be assessed by asking about location, duration, intensity, descriptive qualities, and aggravating or alleviating factors. A physical exam then allows the clinician to assess vital signs, cognition, strength, range of motion, mobility, and any potential fall risks. In some older patients, communication and cognitive changes can be significant obstacles to proper assessment [8]. In these patients, it is important to observe affect, cognition changes, pain vocalization, or other nonverbal pain behavior [9]. Imaging studies typically will show expected degenerative changes consistent with the aging process; but evaluation is important since imaging may also reveal any disease pathology that may necessitate specialized intervention.

A quantitative assessment of pain should be recorded by using a standard pain scale. For most elderly patients, they can verbally assess their pain intensity on a 0–10 scale. However, those with cognitive deficits, vision loss, hearing loss, or dementia can have difficulty with this commonly used pain assessment modality. There has been ample evidence that shows the reliability and validity of alternative pain scales with older patients, such as the visual analog scale or pain faces scale [10–12]. Another complementary assessment is using a pain diagram, which can help the patient mark the painful location on a body diagram [13]. Following this initial assessment of pain and initiation of therapy, the patient and their family should be encouraged to keep a record or log of their pain daily, which can allow for regular reassessment and further modification of these therapies [14].

Figure 28.1 shows a useful template for assessment of pain in nursing home patients.

Figure 28.2 shows common pain scales used for assessment in geriatric patients.

Figure 28.3 shows an example of a pain drawing used to assess pain location in a geriatric patient.

Figure 28.4 is an example of a pain log or diary.

Treatment of Pain

The goals of treatment should be focused on improving function and quality of life, while limiting adverse side effects. Education is integral, and it must be emphasized that although improvement of chronic pain can be expected, it may not be curable. There is a paucity of evidence-based literature on the assessment, treatment, and management of chronic pain in elderly patients. There are few randomized clinical

GERIATRIC PAIN ASSESSMENT

Date: _____ Medical Record Number _____

Patient's Name _____

Problem List: Medications:

_____ _____
_____ _____
_____ _____
_____ _____
_____ _____

Pain Description:

Pattern: Constant Intermittant
Duration: _____
Location: _____
Character:
Lancinating Burning Stinging
Radiating Shooting Tingling

Pain Intensity:
0 1 2 3 4 5 6 7 8 9 10
None Moderate Severe

Worst Pain in Last 24 hours:
0 1 2 3 4 5 6 7 8 9 10
None Moderate Severe

Other Descriptors:
_____
_____
_____
_____

Mood: _____

Depression Screening Score: _____

Gait and Balance Score: _____

Exacerbating Factors: Impaired Activities:
_____ _____
_____ _____

Relieving Factors: Sleep Quality: _____
Bowel Habits _____
_____ _____
_____

Other Assessments or Comments: _____
_____
_____

Most Likely Cause of Pain: _____

Plans: _____
_____
_____
_____

Fig. 28.1 Geriatric assessment of pain [25]

trials and meta-analyses in existing literature. Oftentimes, the studies on a younger population have been extrapolated to apply to an older patient population. The American Geriatrics Society and American Medical Directors Association have published guidelines for the assessment, treatment, and monitoring of chronic pain

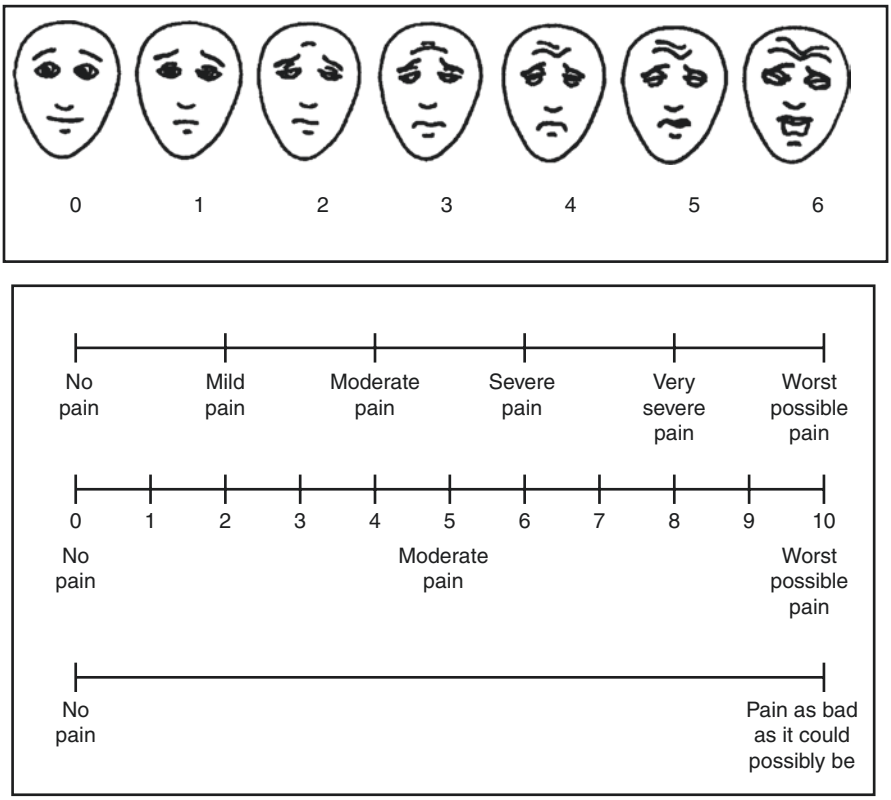

Fig. 28.2 Examples of pain intensity scales for use with older patients. (1) A faces scale [10]. (2) Visual analogue scales [26]

in older patients, advocating individualized pain management, which is vital to patients with multiple underlying chronic diseases. [15, 16]

Although adverse drug reactions in the elderly pose a significant risk, pharmacologic agents are a large component of pain therapy in the elderly population. The clinician must consider age-related pharmacokinetic changes, pharmacodynamic changes, and drug polypharmacy. Since the elderly population is incredibly diverse, there is no way to accurately predict optimal medication dosing or side effects. There are no recommendations for age-adjusted dosing for common analgesics; therefore, dosing should involve careful and slow titration, with frequent assessment and dosage adjustments to address pain symptoms while minimizing adverse drug reactions. Although it is recognized that polypharmacy can be major problem in this patient population, often times, it is necessary. By combining smaller effective doses of different analgesic medications, one can achieve the intended effect of pain relief, while minimizing the side effects seen with a higher dose of a single medication.

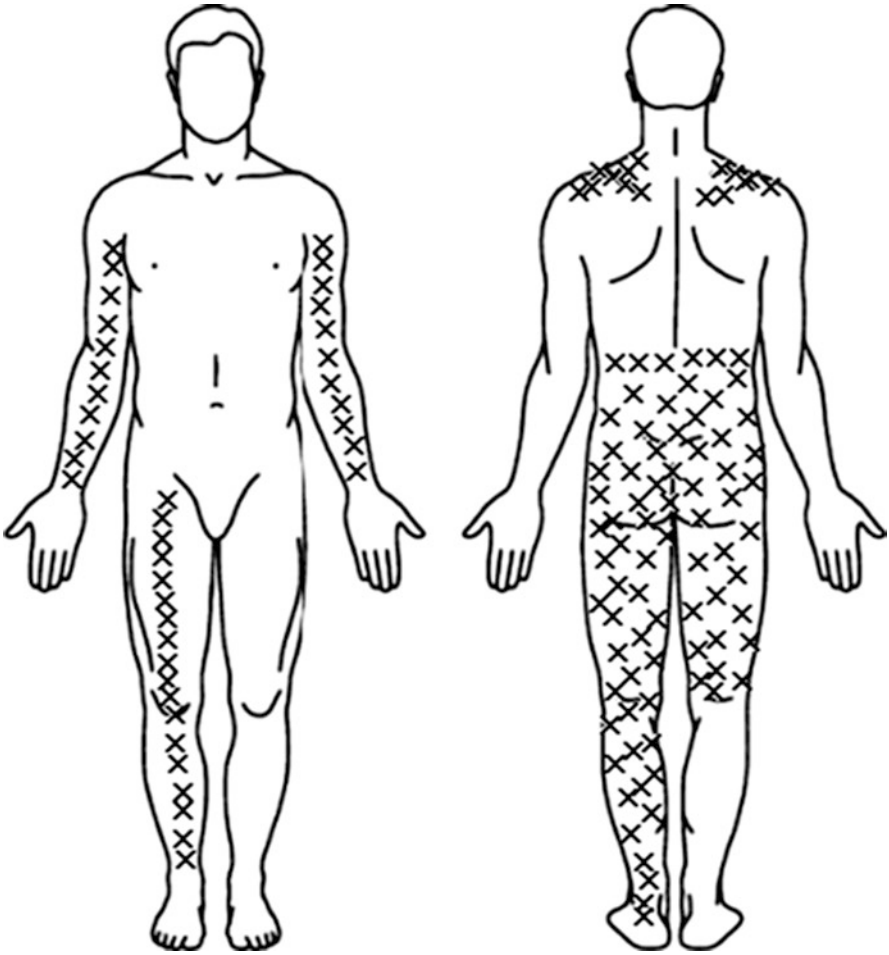

Fig. 28.3 Example of pain area drawn by a patient on a body diagram [27]

Acetaminophen

In the aging population, regular or scheduled use of acetaminophen provides adequate relief for mild-to-moderate musculoskeletal pain. This medication is well tolerated, with minimal side effects in the setting of intact renal and hepatic function, and should be considered as the first-line treatment of chronic pain [17]. Patients and their family should be educated on the maximum safe dose; less than 3 g in 24 h would be a good initial instruction. The American Geriatric Society guidelines consider <4 g in 24 h from all sources acceptable. It is prudent to ask these patients to bring in all their medications, including any over-the-counter products, to appropriately determine the total dosing of acetaminophen from all sources.

CHRONIC PAIN RECORD

Date: _____ Medical Record Number _____

Patient's Name: _____

Pain Medications and Directions:

_____

_____

_____

Pain Scale Used* _____

Date	Time	Pain Intensity*	Activity	Action	Results

*Choose an appropriate scale, indicate which scale is being used, and use the same scale for each assessment.

Fig. 28.4 Pain log [14]

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Although NSAIDs have a role in musculoskeletal pain as well, its association with gastrointestinal bleeding, peptic ulcer, cardiovascular disease, and/or renal dysfunction must be carefully examined prior to prescription to this patient population [18, 19]. They can be used for a short duration for episodes of acute pain. Low doses should be initiated and the choice of drug should be modified in the setting of any gastrointestinal disease or cardiovascular disease.

Anticonvulsants

Non-opioid adjuvants such as anticonvulsants can optimize analgesia. Gabapentin and pregabalin are useful in the treatment of chronic neuropathic pain. It is wise to use the lowest effective dose, which can optimize benefit and minimize the incidence of adverse side effects [20]. The clinical endpoint should focus, not only on decreased pain, but also on improved function, decreased disability, and improved mood and sleep.

Antidepressants

Tricyclic antidepressants, selective serotonin reuptake inhibitors, and selective noradrenalin reuptake inhibitors can all be used in the treatment of chronic neuropathic pain. However, these medications have significant risks of serotonergic, noradrenergic, and anticholinergic effects that can limit their safety profile and use in the elderly patients [20].

Muscle Relaxants

Baclofen, cyclobenzaprine, methocarbamol, and tizanidine can all be used for chronic myofascial pain; however, there are significant limitations with this class of medication due to sedation, dizziness, and anticholinergic effects [21].

Opioids

The use of opioids for nonmalignant pain is controversial, but it can be a tool for pain management in the elderly patient. The doses of opioids, if used, for chronic non cancer-related pain should be started low and slowly titrated, with careful monitoring

of adverse effects such as sedation, concentration, cognition, respiratory depression, and hypoxia. Nonopioid adjuvants such as anticonvulsants, steroids, local anesthetics, and antidepressants are other agents that should still be utilized since that can optimize analgesia. The clinical endpoint should focus not only on decreased pain, but also on improved function, decreased disability, improved mood, and sleep.

Nonpharmacologic Therapy

Nonpharmacologic strategies should be an integral part of pain management therapy. These strategies employ an extensive range of treatment modalities, such as relaxation, meditation, biofeedback, exercise programs, education programs, chiropractic, massage, and acupuncture therapy [22]. Interventional pain procedures have also added benefit and should be considered, when used in conjunction with drug therapy. However, patient education is substantial when treating pain in the elderly patient population. Studies have shown that patient pain education programs do have an overall impact on pain management and pain perception [23]. These education programs typically will educate the patient and patient caregiver regarding the nature of pain, pain assessment tools, medications, and nonpharmacologic strategies. For this patient population, behavioral techniques and relaxation can significantly improve quality of life, and should be utilized when applicable [24].

Conclusions

Treatment should address the cause of pain while considering comorbid conditions and medications, often associated with increased age. The patient and family should be involved in setting an achievable and appropriate endpoint—decreased pain, but improved function, decreased disability, and improved quality of life. Drug therapy should always be combined with nonpharmacologic strategies when applicable to optimize pain management therapy.

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Chapter 29
Pain Management in Serious Illness: The Palliative Medicine Approach

Alexis Barina, Kelley Newcomer, Padmaja Reddy, Caitlin Siropaides, Stephanie Terauchi, Kate Tindall, and Winnie Wang

The Concept of "Total Pain"

Dame Cicely Saunders, one of the founders of the hospice movement in the 1950s–1960s, coined the term "total pain" to describe the complex and multifaceted nature of pain in the context of serious illness. This chapter largely focuses on the ways in which palliative medicine providers address physical pain. That said, suffering is rarely solely physical. Most patients with serious illness also experience emotional, psychosocial, and spiritual distress that affect the perception of and ability to cope with physical pain. To ensure a patient's well-being, one must address all aspects of suffering in an interdisciplinary manner; treatment of one aspect of suffering requires treatment of the others. A clinician might screen for depression or anxiety, screen for adequate coping mechanisms, and consider referral to a psychologist for counseling. A chaplain might inquire about whether the patient's relationship with their faith has changed. A clinical social worker might provide insight into financial stressors, family dynamics, etc.

Any stressor can contribute to enhanced feelings of physical pain or other distressing symptoms. Nonphysical pain must be accurately assessed and treated to avoid exposing the patient to unnecessary medications, dose escalations, and side effects. When patients with a serious illness experience pain or other symptoms that seem out of proportion with their disease burden, consider consultation with an interdisciplinary palliative medicine team.

A. Barina · K. Newcomer · P. Reddy · C. Siropaides · S. Terauchi (✉) · W. Wang
Department of Internal Medicine, Section of Palliative Medicine,
University of Texas Southwestern Medical Center, Dallas, TX, USA
e-mail: alexis.barina@utsouthwestern.edu; kelley.newcomer@utsouthwestern.edu; padmaja.reddy@utsouthwestern.edu; caitlin.siropaides@utsouthwestern.edu; stephanie.terauchi@utsouthwestern.edu; winnie.wang@utsouthwestern.edu

K. Tindall
Austin Palliative Care, Austin, TX, USA
e-mail: ktindall@austinpalliativecare.org

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Pain Assessment

Physical pain associated with cancer or other serious illnesses should be assessed just as it would be in other contexts; with full history, instrument scale (numeric or Wong-Baker FACES Rating Scale), and evaluation of nonverbal indications of pain such as grimacing, restlessness, wincing, and moaning. Determination of the primary etiologies or mechanisms of the pain is essential so that the most effective and efficient medications are chosen.

Management Considerations in Palliative Medicine

Historically, the World Health Organization (WHO) advocated for a stepwise approach to treatment of cancer-related pain (Fig. 29.1) [1]. More specifically, cancer-related pain was to be treated initially with nonopioid analgesics (acetaminophen and nonsteroidal anti-inflammatory drugs [NSAIDs]) with or without adjuvants. A "weak opioid" (e.g., hydrocodone, codeine, or tramadol) and additional adjuvants could be added for persistent, mild to moderate pain. If pain is uncontrolled despite these interventions, one could consider transitioning to a "strong" opioid (e.g., morphine, hydromorphone, oxycodone, fentanyl, or methadone) along with more adjuvants. The philosophy was to start conservatively and to escalate analgesics slowly until adequate pain control was achieved.

In reality, the levels of pain encountered in metastatic cancer and in patients with short prognoses due to other illnesses often call for early initiation of opiates in addition to aggressive utilization of multiple adjuvant therapies. Palliative medicine patients often do not have the luxury of time and cannot wait for a regimen of adjuvants to be titrated to goal over a period of months, as might be done in other patient populations [2]. Often, aggressive symptom management is required for patients to tolerate treatment of the underlying serious illness. Examples include patients who are unable to tolerate lying flat for radiation therapy due to uncontrolled pain or who frequently miss chemotherapy due to recurrent hospital admissions for uncontrolled pain.

For the reasons described above, opioids are the principal mode of treatment for patients with cancer-related pain. Since the 3-step analgesic ladder was introduced by the WHO in 1986, research, clinical practice, and medications have evolved. Data have shown that initiation of "weak" opioids does not improve analgesia; use of "strong" opioids as first-line treatment for cancer-related pain is safe, well-tolerated, and more effective; interventional pain procedures should be integrated with pharmacotherapy; and coformulations of opioid and nonopioid analgesics such as hydrocodone-acetaminophen should be avoided [3, 4]. Updated WHO guidelines for treatment of cancer-related pain recommend against using coformulations of opioid and nonopioid analgesics due to the inability to titrate each analgesic independently and due to increased risk of toxicity from high doses of ibuprofen or

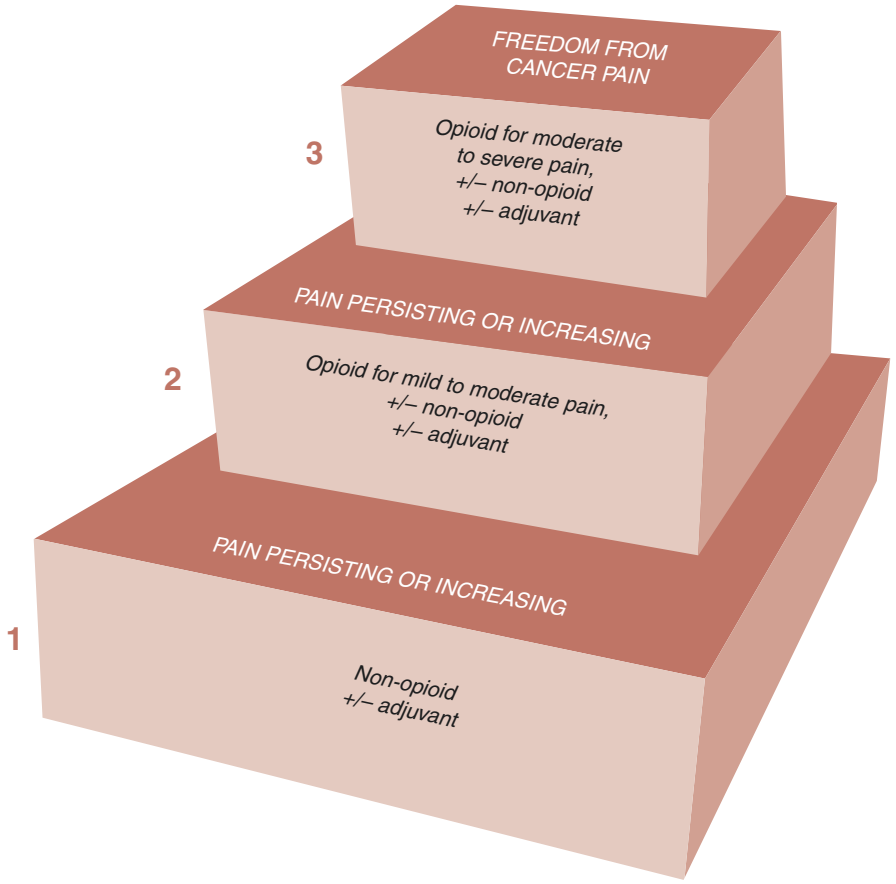

Fig. 29.1 3-step WHO analgesic ladder

acetaminophen [1]. The new guidelines also support individualized treatment plans, with choice of initial analgesic agent based on the type and severity of pain being treated [1].

The WHO ladder can still be a helpful tool in the creation of an individualized treatment plan. Mild cancer pain may respond to step 1 of the WHO ladder, but if pain progresses or is moderate to severe at the time of presentation, one can consider skipping step 2 and starting a "strong" opioid [4]. Initial opioid dose and type should be individualized based on a patient's degree of opioid tolerance, liver and renal function, and age [2]. Opioid-tolerant patients (defined by the Food and Drug Administration (FDA) as using greater than or equal to 60 mg of oral morphine equivalents per day for 7 days or longer) with uncontrolled pain will need escalation in their current opioid regimen while opioid-naïve patients should be started on the opioid-naïve doses [5]. In elderly patients, physiologic decline in organ function with age and increased volume of distribution secondary to increase in body fat

Table 29.1 Factors to consider when starting a patient on an opioid regimen

Opioid tolerant (using ≥ 60 mg of oral morphine equivalents per day for at least 7 days) vs. naive
Past issues with pain medications: tolerability, efficacy, side effects, allergies
Renal and liver function
Age
Available routes of administration
Available strength
Cost and coverage by insurance
Pharmacy availability
Strategies for prevention of side effects
Accessibility to necessary medical follow-up

content impact not only the time to onset of action of opioids but also their rates of elimination. For these patients, it is therefore necessary to start opioids at low doses and increase slowly. In patients with renal dysfunction, morphine should be avoided as its metabolites can accumulate and cause significant adverse effects. Opioid metabolism is also impaired in the setting of severe liver disease, so they should be used with caution in this context as well. Methadone and fentanyl are the two opioids with the fewest active metabolites and are thus considered to be safer than other opioids for patients with liver and renal dysfunction. However, because of its prolonged half-life, interactions with other medications, and associated side-effects, methadone is rarely prescribed by generalists. Consider consultation with a palliative medicine or pain expert prior to initiation or adjustment of methadone.

In addition to the clinical considerations above, one must factor in several practical matters when choosing an opioid, including available route of administration, available strength, cost, availability at local pharmacies, and strategies for the prevention of associated toxicities (e.g., opioid-induced constipation) [2]. There are many new opioids on the market with several different routes of administration. Although most often administered by mouth, opioids are available in many alternate formulations (intravenous, subcutaneous, transdermal, transmucosal, rectal, intranasal, and intramuscular, though the latter is generally avoided as it can cause significant discomfort) [1]. Table 29.1 summarizes factors to consider when starting a patient on an opioid regimen.

Titration of Opioids for Chronic Cancer-Related Pain

After a patient is started on an opioid regimen, it is vitally important that the physician keep an accurate record of a patient's opioid usage, both to ensure safe usage and to inform decisions about titration. Usually, opioid-naïve patients are started on only breakthrough (or rescue) short-acting opioids. If a patient is using more than three breakthrough doses in a typical day, it is reasonable to consider increasing the opioid regimen [2]. This is also a good time to consider consultation with a pallia-

tive medicine specialist, who can not only help adjust increasingly complex opioid regimens but also assume responsibility for opioid prescribing and monitoring in the outpatient setting.

When considering an increase in an opioid regimen, start by adding together the total daily dose for all opioids in the prior 24-h period. If the patient's pain is well controlled with breakthrough medications, divide the total opioid dose into a scheduled short-acting opioid with a breakthrough short-acting opioid or a scheduled long-acting opioid with a breakthrough short-acting opioid. If a patient's pain is not controlled on the current regimen despite appropriate use of breakthrough medication, consider a 25–50% increase in total daily dose for mild to moderate pain or a 50–100% increase in total daily dose for moderate to severe pain [2]. A general rule is to recalculate the breakthrough dose to be 10–25% of the total daily opioid dose [2].

For a patient with accelerated malignant pain in the hospital, one can consider scheduling a short-acting opioid with a breakthrough medication rather than jumping to a scheduled long-acting agent. As with any medication, long-acting opioids reach steady state in 4–5 half-lives and should not be increased prior to reaching steady state. By contrast, a scheduled short-acting agent can be adjusted multiple times in a single day if needed, leading to faster achievement of adequate analgesia.

Case Example

A patient presents to the hospital with fevers and shortness of breath. She is hypoxic, with chest x-ray findings concerning for pneumonia. She is admitted to the hospital, placed on 4 L nasal cannula for hypoxia, and started on IV antibiotics. She is expected to have at least a 1–2-day hospital stay. She also has increased malignant pelvic pain from progression of her ovarian cancer noted on imaging.

Option 1: Start scheduled short-acting opioid with breakthrough.

Day 1: At home, the patient was using morphine immediate release (IR) 15 mg tablets six times a day with suboptimal control of her pain.

- Calculate 24-hour total daily dose: 15 mg morphine IR × 6 = 90 OME (oral morphine equivalents).
- Schedule a short-acting agent: 90 OME/6 = 15 OME. Start morphine IR 15 mg every 4 h scheduled.
- Calculate breakthrough dose: This should be 10–25% of the total daily dose. Ten percent of 90 OME = 9 OME. Morphine IR is available in 15 mg tabs, so one can order morphine IR 15 mg as needed for breakthrough pain.

Day 2: Patient used all her scheduled morphine IR + 5 breakthrough doses of morphine IR. She has good pain control with no noted side effects. She is still hypoxic and requires 2 L nasal cannula.

- Last 24-h total daily dose: scheduled + breakthrough morphine IR = 165 OME.

- Adjust scheduled short acting to reflect the frequent use of breakthrough doses: 165 OME/6 = 27.5 OME. Increase scheduled morphine IR to 30 mg every 4 h scheduled.
- Calculate a new breakthrough dose: 10% of 165 OME = 16.5. The smallest dose of morphine tablet is 15 mg. One can keep morphine 15 mg as needed for breakthrough pain

Day 3: Patient used all her scheduled morphine + a single breakthrough dose. Pain is controlled with no noted side effects. The patient now has normal oxygen saturation on room air and wants to go home today. Readjust her opioid regimen for discharge.

- Last 24-h total daily dose: 195 OME
- Start long-acting opioid: 195 OME/2 = 97.5. Start long-acting morphine 100 mg every 12 h
- Calculate breakthrough: 10% of 195 OME = 19.5. The smallest dose of morphine tablet is 15 mg. Keep morphine 15 mg as needed for breakthrough pain.

Option 2: Start scheduled long-acting opioid with breakthrough.

Day 1: At home patient was using morphine IR 15 mg tablets six times a day with suboptimal control of her pain.

- Last 24-h total daily dose: 15 mg morphine IR × 6 = 90 OME (oral morphine equivalent)
- Schedule a long-acting agent: Start morphine extended release (ER) 45 mg every 12 h scheduled.
- Calculate a breakthrough dose: 10% of 90 OME = 9 OME. Morphine IR is available in 15 mg tabs, so one can order morphine IR 15 mg as needed for breakthrough pain.

Day 2: Patient used all her scheduled long-acting morphine (received 2 doses) + 5 breakthroughs. She has suboptimal pain control with no noted side effects. She is still hypoxic and requires 2 L nasal cannula. *She has only received 2 doses of her long-acting morphine, which has not yet reached steady state. Even though her pain is uncontrolled, it is not advisable to increase her long-acting morphine at this time because she can become oversedated. You can consider increasing her short-acting breakthrough agent.*

- Leave the scheduled long-acting agent alone: Continue morphine ER 45 mg every 12 h scheduled.
- Increase breakthrough dosage: Increase morphine IR to 30 mg as needed for breakthrough pain.

Day 3: Patient used all her scheduled morphine ER + 4 breakthrough doses of morphine IR. Pain is controlled with no noted side effects. The patient now has normal oxygen saturation on room air and wants to go home today. You readjust her opioid regimen for discharge.

- Last 24-h total daily dose: 210 OME
- Adjust long-acting opioid (can be safely done now that this morphine ER has reached steady state): 210 OME/2 = 105 OME. Start long-acting morphine 100 mg every 12 h

– Calculate breakthrough: 10% of 210 OME = 21. The smallest dose of morphine tablet is 15 mg. Keep morphine 15 mg as needed for breakthrough pain.

As you can see with option 1, one can obtain faster control of pain with rapid adjustment of short-acting opioids rather than immediately jumping to adjusting long-acting opioids. This is particularly true for long-acting opioids that take an even longer time to reach steady state (e.g. fentanyl patches and methadone).

Transdermal fentanyl provides long-lasting opioid therapy for stable chronic pain and should only be started in opioid-tolerant patients. Time to approach maximum concentration is about 36 h, and because transdermal fentanyl takes 3–6 days to reach steady state, it should not be titrated during acute management of uncontrolled chronic pain [6, 7]. This is the same for methadone, which has a very long and variable elimination half-life, ranging from 5 to 130 h with a mean of 20–35 h. Methadone can take 4–10 days to reach steady state and should not be titrated more frequently than every 5 days [8].

If a patient has uncontrolled cancer-related pain despite exceedingly high doses of opioids or if there is a significant neuropathic component, one can consider referral to a palliative medicine or pain specialist for initiation of methadone. Methadone is an opioid agonist, an *N*-methyl-D-aspartate (NMDA) antagonist, and an serotonin norepinephrine reuptake inhibitor (SNRI) [8]. NMDA receptors cause spinal neuron sensitization and are implicated in the development of neuropathic pain and opioid-induced hyperalgesia, a phenomenon in which use of opioids paradoxically increases pain. Methadone can decrease opioid tolerance and is efficacious for treatment of both neuropathic pain and opioid-induced hyperalgesia. Its many benefits include low cost, long half-life, and acceptable safety profile in patients with renal failure or morphine allergy. That said, it is not usually used as first-line therapy for cancer-related pain due to its complex pharmacokinetics and pharmacodynamics. More specifically, methadone interacts with multiple commonly used medications (Table 29.2), its half-life is long and somewhat unpredictable, and dose-conversion ratios with other medications are nonlinear.

In addition to methadone, treatment options for opioid-induced hyperalgesia also include ketamine and intravenous lidocaine. As with methadone, these medications are rarely prescribed by generalists, and their consideration should prompt consultation with a palliative medicine or pain specialist.

Table 29.2 Common drugs that interact with methadone

Increase methadone levels	Decrease methadone levels
Antifungals: azoles	Antiretroviral medications
Antibiotics: macrolides, fluoroquinolones	Spironolactone
SSRs	St. John's Wort
TCAs	Anticonvulsants: phenobarbital, phenytoin
	TB treatment: rifampin, rifampicin, rifabutin

Utilization of Nonopioid Adjuvant Analgesics for Nociceptive and Neuropathic Pain in Palliative Medicine

Many of the pain syndromes commonly treated in palliative medicine are caused by an overlap of nociceptive, neuropathic, and central mechanisms (mixed pain). We will address all nonopiates in this section, so as to highlight primary indications based on the etiology, discuss the benefits and barriers to their use, as well as consider the treatment choices based on symptom clusters. Palliative medicine–specific commentary is provided for each therapeutic class. This section is not a comprehensive review of all dosing, side effects, and monitoring recommendations.

As stated earlier in this chapter, clinicians must recognize the importance of time to effective pain control when considering the role for adjuvant analgesics in patients with serious illness. Many adjuvant therapies can take weeks to titrate to effective doses or to see full benefit of initial doses. Such a timeline can be inappropriate, for example, in a patient with a prognosis of 2–3 months. One must also consider the ways in which increased pill burden can become onerous for patients, as "symptom clusters" (i.e., pain, nausea, and constipation) may require a multitude of medications to optimize the quality of life. A previously healthy person could easily go from no medications to requiring 15 pills a day for symptom management alone.

Nonsteroidal Anti-Inflammatory Drugs and Acetaminophen

Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen (or paracetamol) are low cost, widely available, and are recommended as first-line therapy for mild pain in serious illness. They are most effective for nociceptive pain, and benefits can be seen within the first hours to days of therapy. NSAIDs include salicylates, propionic acids (i.e., ibuprofen, ketoprofen, naproxen sodium), acetic acids (i.e., ketorolac, diclofenac), enolic acids (i.e., meloxicam), and selective COX-2-inhibitor (celecoxib) [9].

Guidelines from the National Comprehensive Cancer Network suggest the NSAID therapy should start with ibuprofen dosed at 400 mg three times a day and should not exceed a maximum of 3200 mg per day. NSAIDs and acetaminophen can be scheduled with additional doses taken as needed so long as caution is taken not to exceed maximum daily dosing. NSAIDs are most commonly utilized when inflammation is suspected to be an underlying mechanism of pain, as with bone metastases and soft tissue or skeletal masses [10].

Many patients with advance illness are at high risk for complications, including, but not limited to, the following: acute kidney injury, gastrointestinal bleeding, cardiac toxicities, thrombocytopenia or anemia related to bone marrow infiltration, medication effects (e.g., hematopoietic suppression after chemotherapy), and underlying organ failure (e.g., significant renal or liver dysfunction). NSAIDs should therefore be used cautiously and monitored closely. Due to the potential for

rapid decompensation, patients with serious illness should have more frequent monitoring of renal function, liver function, and blood counts. Toxicities differ amongst NSAIDs, and one should consider side effect profiles and patient-specific comorbidities when choosing a drug. Use of COX-2 inhibitors, for example, is associated with increased risk of heart attack, stroke, and death and should be avoided in patients with significant cardiovascular risk factors [9]. Combining NSAIDs and steroids does not produce added anti-inflammatory effect and is not advised due to increased risk of upper gastrointestinal bleeding [11].

Corticosteroids

Corticosteroids are effective for the treatment of pain and other symptoms that are common in the setting of serious illness, including nausea/vomiting and malignant bowel obstruction [12]. Evidence and guidelines support the use of steroids when pain is thought to be related to mass effect or inflammation, as with brain tumors, spinal cord compression, and painful bone metastases [11]. Steroids are occasionally used in other pain syndromes (e.g., hepatic capsular stretch in the setting of enlarging liver metastases or involution of a necrotic metastatic mass), but there is less evidence to support their use in these situations [13]. On occasion, steroids are prescribed for management of anorexia, nausea, or fatigue.

Dexamethasone is the most frequently prescribed steroid, as it has less mineralocorticoid effect and therefore causes less fluid retention. It has a relatively long half-life and can thus be dosed once a day. Dosing is specific to each patient, but can range from 2 to 16 mg daily in 1 to 3 divided doses [11] Side effects include anxiety and insomnia, so evening doses are usually avoided. Corticosteroids are often used as a short-term bridge to other treatment modalities such as radiation or chemotherapy or until opioid and adjuvant therapies can be optimized. In general, corticosteroids should not be used for longer than 3 weeks in order to avoid complications of long-term use (e.g., Cushing's habitus, proximal myopathy, osteoporosis, etc.). In select cases, a longer course may be appropriate once one factors in prognosis, impact on quality of life, options for alternate therapy, and patient or family values [13]. In patients at the end of life with refractory pain or other symptoms, steroids may be continued longer than standard practice for optimization of quality of life, accepting that long-term consequences are unlikely to be encountered.

Neuropathic Pain

Neuropathic pain is commonly encountered in palliative medicine and may present in isolation or mixed with pain from other underlying mechanisms. Palliative medicine patients may experience focal insults affecting the peripheral nervous system as in nerve entrapment due to mass or extremity lymphedema, soft tissue

lesions in calciphylaxis or metastatic dermal infiltration, plexopathy from malignancy or radiation, or post-traumatic neuralgia after thoracotomy or chest tube placement. Generalized polyneuropathies are common, usually as a result of HIV/AIDS, certain types of chemotherapy, or carcinomatosis. Central nervous system lesions, as in spinal cord injury or malignancy, stroke, or primary or metastatic brain tumors, are also common [14, 15].

Neuropathic and mixed pain are particularly prominent in setting of head and neck cancers, pancreatic cancer, rectal and vulvovaginal cancers, peritoneal carcinomatosis, and hepatic metastases with capsular irritation. Neuropathic and mixed pain are also commonly present when a patient has cutaneous wounds, as can be the case with dermal infiltration of metastatic cancer, calciphylaxis, or ulceration due to pressure, venous stasis, vasculitis, or hypoperfusion.

Primary brain tumors and brain metastases are generally not painful unless causing increased cerebral pressure, which can in turn cause headaches. Patients with head and neck cancer can sometimes experience pain that seems out of proportion with tumor burden due to neural infiltration. This pain is commonly exacerbated during and after prolonged courses of radiation therapy, and patients can require rapid and aggressive titration of opioids and adjuvants to achieve adequate pain control. Vertebral or spinal cord metastases usually cause a combination of nociceptive and neuropathic pain. The prominence of each type of pain depends upon the affected location, the extent of bony destruction, and the degree to which a lesion impinges on nerve roots or the spinal cord.

Pain related to pancreatic cancer can vary in intensity and location. Depending upon the location of the mass, pain may be nociceptive and/or neuropathic and may be referred elsewhere. Pain is often described as aching, gnawing, or band-like, and these patients can respond to neuropathic-targeting pharmacologic therapies with or without opiates, likely due to the impact on the neural plexus in this area.

Peritoneal carcinomatosis is usually the result of metastatic spread of a primary abdominopelvic malignancy. Chronic abdominal pain due to peritoneal carcinomatosis has a strong neuropathic component. At the end stage, patients with peritoneal carcinomatosis can develop focal or diffuse malignant bowel obstruction, which often presents as a constellation of paralytic ileus, severe pain, nausea, and vomiting. Initially, conservative management includes bowel rest and nasogastric tube decompression, which often provides some relief from pain. While evidence is mixed, common clinical practice also includes corticosteroids to decrease bowel wall inflammation and edema, octreotide to decrease gastrointestinal secretions, and opiates for pain [12, 14].

Combination therapy is often required for adequate control of neuropathic pain in the setting of serious illness. Studies have shown that less than half of patients with neuropathic pain are well-controlled on monotherapy and may require two to three medications with additive or synergistic effects to achieve adequate analgesia. First- and second-line therapy for both peripheral and central neuropathic pain include tricyclic antidepressants, gabapentin or pregabalin, serotonin and norepinephrine reuptake inhibitors, and topical lidocaine for localized neuropathy. Opiates are considered as third-line therapy and should be used as combination therapy rather

than monotherapy [14]. Both tricyclic antidepressants and serotonin and norepinephrine reuptake inhibitors have excellent multimodal properties for symptom clusters such as neuropathic or central pain, anxiety/depression, and insomnia. The most prominent symptom in a cluster should determine initial treatment choice [16].

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are more effective for neuropathic pain and less costly than serotonin norepinephrine reuptake inhibitors. Secondary amine TCAs (nortriptyline and desipramine) are usually better tolerated with fewer side effects than tertiary amine TCAs (i.e., amitriptyline). While effective, they are not often chosen in the setting of serious illness due to concerns about anticholinergic side effects, sedation, and increased risk of cardiac arrhythmias. That said, if pain or anxiety results in insomnia, one can take advantage of the TCA side effect profile by prescribing this medication at bedtime for both pain and insomnia [14].

A baseline EKG should be obtained when therapy is initiated and periodically thereafter, as many of the medications prescribed for symptom management in the setting of serious illness (e.g., citalopram, amitriptyline, methadone, ondansetron) cumulatively increase risk for cardiac arrhythmias.

Serotonin Norepinephrine Reuptake Inhibitors

Comorbid complaints such as anxiety and depression are common in patients with serious illness. Serotonin norepinephrine reuptake inhibitors (SNRIs) are more effective and better tolerated than TCAs for anxiety and depression, and thus are commonly prescribed as adjuvants for patients that have pain with a neuropathic component [16]. Most commonly prescribed are duloxetine and venlafaxine, with starting doses at 30 mg and 75 mg, respectively. They can be uptitrated weekly as needed and tolerated to the effective dose. An adequate trial is 4–6 weeks. Both come in extended release formulations, which are generally preferred by patients to minimize pill burden.

Venlafaxine is considered to be more activating than duloxetine and may be preferable for patients who have depression with prominent features of fatigue and dysthymia. Venlafaxine may exacerbate preexisting anxiety [17].

Duloxetine can be slightly sedating and can be useful for patients with depression or anxiety in addition to insomnia.

Anticonvulsants

The anticonvulsants gabapentin and pregabalin (calcium channel α_2-δ ligands) are also commonly used for the treatment of neuropathic pain. Gabapentin is usually initiated at 100–300 mg, one to three times per day. This can be increased by

100–300 mg every 3–7 days to a maximal total daily dose of 3600 mg. Due to dosing frequency, associated increase in pill burden, and sedating side effects, many patients struggle to maintain adherence with this medication. Pregabalin is less sedating and is dosed less frequently. However, this medication is more expensive than gabapentin, and insurance companies often require documentation of failure of one to two alternate therapies before pregabalin is covered. An adequate trial of either medication is approximately 4 weeks. Both medications are renally excreted, and thus close monitoring is necessary for patients at increased risk for rapid changes in their renal function [14, 16, 18]. Both medications have anxiolytic properties and may be used as adjuvant therapy for anxiety, but this should not be the primary indication for use [19].

Topicals

Topical treatments for neuropathic pain, such as lidocaine (patch or gel), have a particularly important role in palliative care, specifically for focal neuropathies, mucositis, or painful cutaneous wounds. A lidocaine patch may be applied to an area of referred pain or near a chest tube site in the setting of post-procedural pain due to subcostal neuralgia. Compounds to treat symptoms of mucositis often include lidocaine or diphenhydramine, and specialists may consider the addition of opioid or ketamine solutions [20]. Pain associated with pressure ulcers, malignant wounds, or calciphylaxis may improve with compounded topical agents such as lidocaine, ketamine, tricyclic antidepressants, and opioids. Consider consultation with a palliative medicine or pain specialist if these interventions are being considered.

Bone Metastases: A Special Challenge

Bone metastases are a common source of pain in advanced malignancy. Up to 40% of patients with advanced cancers will develop bone metastases. This percentage gets significantly higher in certain types of cancers: breast, lung, prostate, renal, and multiple myeloma [21]. Studies show that 70–90% of patients with prostate and breast cancer have some form of skeletal metastasis postmortem [22, 23]. Bone metastases can lead to significant morbidity, so interventions focus not only on improving pain and function in the moment but also on reducing or delaying future risk of skeletal-related events (need for surgery or radiation to the bone, pathologic fractures, hypercalcemia, and spinal cord compression).

Management of bone metastases is driven by the underlying pathophysiology. Although the mechanism is not fully understood, the current consensus is that bone metastases are the result of disruption of normal bone remodeling and the balance between osteoclastic and osteoblastic activity. Osteolytic lesions are more likely to destabilize the bone, leading to pathologic fractures.

Bone metastases are usually detected in one of three ways: (1) suggestive abnormalities (i.e., elevated calcium and alkaline phosphatase) are noted in bloodwork and prompt further workup, (2) incidental lesions are seen on staging scans, or (3) workup is initiated in response to new symptoms. For those who are symptomatic, pain is the most common presenting symptom and is variably characterized. Isolated bone lesions may largely cause somatic pain that is dull or aching and may be constant or incidental. If a bone metastasis is causing compression of surrounding nerves, such as vertebral metastases, which compress either the spinal cord or exiting nerve roots, there may be a significant neuropathic component. Pain with acute onset may be due to pathologic fractures.

Palliative care providers use a multimodal approach to treat pain related to bone metastases. Often, both adjuvants and opioids are necessary. NSAIDs and steroids are the adjuvants most often used for bone pain. As discussed in other sections, careful consideration must be given to the risks and potential side effects of these medications. Steroids and NSAIDs are not generally given concurrently, given the increased cumulative risk of gastrointestinal side effects.

Steroids are thought to treat pain related to bone metastases by decreasing peritumoral edema and by inhibiting prostaglandin and leukotriene synthesis. Oftentimes, steroids are used as a short-term bridge while more sustained interventions are being implemented. However, if the patient is approaching end of life, a clinician may choose to extend the course of steroids indefinitely after considering the risks, benefits, and alternatives.

When adjuvants alone are insufficient, opioids are added to the pain regimen. In many cases, opioids can be weaned and even discontinued if patients have a significant response to radiation therapy or the other interventions detailed below.

Osteoclast Inhibitors and Bone Pain

Bone resorption is a primary process that leads to pain and bone instability in the setting of bone metastases. Bisphosphonates that lack a nitrogenous component (pamidronate and zolendronate) are ingested by osteoclasts, leading to osteoclast apoptosis and death. In addition to opioid and nonopioid analgesics, bisphosphonates are often given to patients with bone metastases, although not with the primary intention of producing analgesia. A Cochrane meta-analysis suggested that bisphosphonate use correlates with opioid-sparing effects, improved pain scores, and improved quality of life scores [24]. Bisphosphonates are also used to reduce the risk of future skeletal-related events. Adverse effects of these medications include osteonecrosis of the jaw, esophageal irritation, and fractures [25]. Currently, there are no oral bisphosphonates approved in the United States for use in the setting of cancer.

Desosumab is a human monoclonal IGF2 antibody that acts by binding to soluble and membrane-bound RANKL. This binding prevents contact that stimulates osteoclastic actively and therefore inhibits bone resorption.

Denosumab has been shown to prevent pain, lessen hypercalcemia, and prolong time to a skeletal-related event by 3.6 months when compared to zoledronic acid [26].

Interventional Approaches to Bone Pain

In patients with solitary or oligometastatic disease, use of radiation to treat bone metastases is both common and effective. Radiation treatments can lessen pain over 2–6 weeks of treatment. More recently, radiation oncologists are adapting palliative radiation treatments to target bone metastases with a single fraction. In one study, a single 8 Gy fraction was used to treat metastases to the bone from primary breast, prostate, renal, and lung cancers. Results showed that there was an average pain score reduction from 8.15 to 4.68 immediately post treatment. Three months post treatment, 23% of patients had complete response, 38% had partial response, 26% had stable disease, and 12% had progression of disease [27].

Radioisotopes also play a role in treating bone metastases. Generally, radioisotopes are used in the setting of multifocal, osteoblastic, or mixed lesions that are causing significant pain [28]. While radioisotopes have long been shown to improve pain scores, a newer radioisotope, radium −223, has also been shown to prolong time to skeletal-related events by 5.8 months and increase overall survival by 3.6 months [29].

In the setting of spinal metastases, minimally invasive techniques, such as vertebroplasty and kyphoplasty, are often used to control pain and stabilize the vertebrae. Decompressive laminectomy and fixation are occasionally pursued, although surgery is generally not considered first-line therapy.

Opioid Misuse in the Context of Serious Illness

In recent years, opioid misuse has drawn increasingly heavy scrutiny. Opioid misuse is a multifactorial problem, and in recent years, more and more clinicians have shied away from prescribing opioids altogether, regardless of the indication for the medication. Although some have argued for blanket policies that decrease total opioid use, pain management specialists from different fields have come together to argue instead for a more nuanced approach to prescribing that incorporates evidence-based strategies for opioid stewardship and recognition of the consequences of long-term opioid use. In the field of palliative medicine, this is a challenging and paradoxical issue. While clinicians clearly prescribe large quantities of opioids in the context of serious illness, there is also clear evidence of undertreatment of malignant pain [30]. Many worry that legitimate fears and concerns surrounding the opioid epidemic have directly contributed to the undertreatment of malignant pain.

People generally consider malignant pain as a separate entity from other forms of chronic pain. However, palliative medicine specialists and others who prescribe for malignant pain are not immune to concerns regarding substance abuse or diversion. Palliative medicine specialists, pain management specialists, oncologists, and others who treat malignant pain must be aware of how to safely prescribe these medications, both for the well-being of the individual patient and the well-being of the community as a whole.

In the setting of palliative medicine, there is a spectrum of inappropriate use of opioids. At one end of the spectrum are patients that self-adjust medications, take old prescriptions, or combine medications in ways that can lead to adverse outcomes. Patients are often unaware of how unsafe these practices can be and of the potential consequences. In these circumstances, there is a need for ongoing education, agreements regarding safe behaviors, and access to the appropriate resources for patients to safely get pain under control in a timely manner.

Further along on the spectrum are patients who are chemically coping. Fear surrounding a serious illness and comorbid diagnoses like depression or anxiety can impact how a patient perceives and copes with pain. It is not uncommon for patients to associate new or worsening pain with progression of disease. This perception can lead to a highly emotional reaction to changes in pain. Often, patients who chemically cope are unaware that they are relying on opioids to provide relief for emotional pain. Identifying these behaviors can be challenging and requires careful assessment of a patient's pain and response to pain medications, usually by a palliative medicine specialist.

Pseudo-addiction is a term used to describe patients who are using opioids appropriately, but whose behaviors are flagged as concerning for opioid misuse. A patient who frequently visits the ER complaining of uncontrolled pain, for example, may be perceived as exhibiting inappropriate opioid-seeking behavior, when they are in fact experiencing a failure of home medications in the setting of progression of disease. Similarly, an opioid-tolerant patient with severe pain may ask for more potent medications or higher doses of medication. In this situation, legitimate attempt to gain control of complex pain may again be interpreted as inappropriate opioid-seeking behavior.

The other end of the spectrum of misuse includes patients that have a history of active substance abuse or are intentionally diverting opioid medications. Patients who have cancer or other serious illnesses are not immune to the effects of potentially addictive medications like opioids on brain chemistry.

Diversion in the setting of serious illness is poorly studied. The scope of the problem is largely unknown, but several scenarios are common. Given the prevalence of opioid dependence in the community, it is not uncommon for patients to involve friends or relatives with a history of substance abuse in their care. These friends or relatives may take medication for personal use. Additionally, diverted medications may have significant street value, and patients or friends and relatives may use the money made by selling prescription opioids to pay for basic needs in the face of crippling medical bills. Regardless of the intentions underlying medication diversion, this behavior clearly fuels the opioid epidemic.

Palliative medicine patients are carefully screened for past and present recreational or prescription drug misuse. In addition, many palliative medicine providers use tools to identify those who may be at higher risk for developing substance use disorders. Of note, no tool has been validated for use in patients with malignant pain. Common screening tools include the ORT (Opioid Risk Tool) and the SOAPP (Screener and Opioid Assessment for Patients with Pain). It is important to remember that these are simply intended as screening tools; they are not used to diagnose substance use disorders.

If no active substance use disorder is identified, opioids may be prescribed. Often, providers will ensure that an opioid agreement is in place in advance and will start with short courses of medication (1–2 weeks) with intermittent urine toxicology screening. Training in the use of rescue naloxone therapy may be considered for some high-risk patients.

If a patient receiving chronic opioid therapy is found to be abusing illicit or prescription drugs, prescription opioids are rapidly tapered and discontinued. The patient should be provided with resources for treatment with an addiction specialist. Palliative care providers continue to provide support and manage pain with nonopioid medications. They maintain a therapeutic relationship and ensure nonabandonment, effectively "fir[ing] the opioid, not the patient" [31].

If a patient is on maintenance therapy for opioid addiction, care should be provided in collaboration with an addiction specialist. In certain circumstances, methadone or buprenorphine can be considered for dual purposes, both for pain and as maintenance therapy for opioid dependence.

In short, any clinician attempting to treat cancer-related pain must balance the obligation to protect individual patients and the community at large from potential adverse effects of opioid misuse with concerns about placing undue burden onto patients and families already struggling to cope with a serious illness. Ideally, these patients should have the benefit of a multidisciplinary team comprised of a palliative medicine specialist, a clinical social worker, and a psychologist or psychiatrist with specialized training in addiction medicine.

Strategies for Management of Psychiatric Comorbidities

As stated earlier in this chapter, emotional pain can heighten perception of physical pain and other distressing symptoms. For this reason, management of pain in the context of serious illness must occur in tandem with management of psychiatric comorbidities. Depression and anxiety are much more common in the palliative medicine population than in the general population. Exact prevalence has proven difficult to measure, but studies have found rates of Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) in the palliative medicine population ranging from 16% to 47% [32–35]. Practitioners can struggle to separate normal grief and worry from pathological depression and anxiety, and patients are often reluctant to raise concerns about mood when treatment of the underlying

disease process seems more urgent or important. For these reasons, psychiatric illness is underdiagnosed and undertreated in the palliative care population [36].

Psychiatric illnesses are diagnosed based on criteria found in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5). Below, the diagnostic criteria for MDD and GAD from the DSM-5 are listed:

To meet DSM-5 criteria for Major Depressive Disorder, in a 2-week period a person must experience at least five of the following and one of the symptoms must be depressed mood or anhedonia:

1. Depressed mood
2. Anhedonia
3. Appetite or weight changes
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue
7. Inability to think or concentrate
8. Feelings of guilt or worthlessness
9. Thoughts of death, suicidal ideation, suicide attempt [37]

To meet DSM-5 criteria for Generalized Anxiety Disorder, a person must experience excessive worry about a variety of topics. Worry occurs more often than not for at least 6 months and is excessive and challenging to control. In addition, anxiety and worry are accompanied by at least three of the following:

1. Edginess or restlessness
2. Increased fatigue
3. Impaired concentration
4. Irritability
5. Increased muscle aches and soreness
6. Difficulty sleeping [37]

Important principles to keep in mind when making a psychiatric diagnosis are that the symptoms must cause significant distress or dysfunction in order to be labeled a disorder and that the symptoms cannot be caused by other medical conditions [37]. In the palliative care population, somatic symptoms associated with mood disorders (weight loss, sleep disturbances, slowed mentation and physical responses, fatigue) are often directly caused by the disease process or treatments and so cannot be automatically assumed to be caused by a mood disorder [38]. There is evidence that relying more on cognitive symptoms such as tearfulness, social withdrawal, sense of failure, hopelessness, pessimism, and despair better predicts MDD in this population [38–41]. In contrast, normal grief is defined by the patient's ability to retain the capacity for pleasure and to look forward to the future [42].

MDD is not only distressing to patients and families; there is evidence that it is independently associated with increased mortality in cancer patients [43]. A cornerstone of the treatment of MDD in palliative care is aggressively addressing any distressing physical symptoms such as pain and dyspnea. Clinicians often also need

to reassure patients that their underlying medical condition will continue to be treated no matter what psychiatric diagnosis is reached.

If MDD is diagnosed, the gold standard treatment is a combination of supportive psychotherapy and antidepressant medication [44]. Options for psychotherapy include cognitive behavioral therapy (CBT) and dignity therapy. CBT requires significant concentration and multiple sessions with a provider and so is not generally suitable for patients with a short prognosis. Dignity therapy, in which patients focus on their achievements and the legacy they will leave, is more suitable for patients with a short prognosis.

Pharmacologic treatments for MDD include SSRIs, SNRIs, tricyclic antidepressants (TCAs), psychostimulants, bupropion, and mirtazapine. SSRIs and SNRIs take 6–8 weeks to determine therapeutic efficacy and so are best suited for patients with a prognosis of at least 3–4 months. SSRIs, SNRIs, psychostimulants, bupropion, and mirtazapine are generally well tolerated, while TCAs are considered second-line therapy for MDD because of significant anticholinergic side effects. Considerations when choosing an SSRI or SNRI include drug interactions and desire for more sedating (mirtazapine, paroxetine) versus more activating (fluoxetine, bupropion, venlafaxine) effects, although it is worth noting that the latter can exacerbate anxiety. Other considerations include the need to treat comorbid neuropathic pain (TCAs and SNRIs) or poor appetite (mirtazapine). For patients with a prognosis of days to weeks and up to a few months, a psychostimulant (methylphenidate, dextroamphetamine) can be used either as monotherapy or in addition to the above medications. Psychostimulants should be used with caution in patients with a history of arrhythmia or heart failure and delirium; they can also cause insomnia and anorexia. In MDD, which is refractory to initial therapy, a second medication can be substituted or added; if treatment is still not effective, the patient should be referred to a psychiatrist.

In GAD, as in MDD, patients may not directly express their mood concerns. However, patients' use of words such as "concerned," scared," "worried," and "nervous" should prompt clinicians to evaluate more closely for GAD [45]. Like MDD, GAD also is best treated with a combination of nonpharmacological and pharmacological therapies [42].

Nonpharmacological therapies for GAD include psychotherapy (supportive psychotherapy, cognitive-behavioral therapy, dignity therapy), complementary therapies, and behavioral interventions. Complementary therapies include some that are better suited for people with more energy and longer prognosis (art therapy, relaxation therapy with guided imagery, acupuncture) as well as some that can benefit even patients who are very weak and fatigued (music therapy, aromatherapy, mindfulness meditation) [46–49]. Behavioral therapies include physical exercise, which can be beneficial in the early or late stages of the disease process; even passive range of motion exercises have shown benefit [50]. Other behavioral therapies include assessment of caffeine and alcohol intake as well as sleep hygiene protocols.

The pharmacological treatments of choice for GAD are SSRIs and SNRIs. As in the context of MDD, these medications are generally well tolerated but take

6–8 weeks to reach therapeutic effect. If a more immediate result is needed, benzodiazepines such as clonazepam and lorazepam can be used, though caution should be taken in using benzodiazepines in elderly patients, those with delirium, those taking opiate pain medications, and those who have confusion or impaired memory. Another option for rapid treatment of anxiety is the atypical antipsychotic olanzapine; low-dose treatment at bedtime can help with anxiety as well as nausea, appetite, and delirium.

Pain Management in Hospice

Hospice incorporates a holistic, patient-centered, interdisciplinary approach to pain management. A typical hospice team consists of doctors, nurses, nurse aids, social workers, chaplains, and volunteers, all focused on the relief of suffering and total pain. It is beyond the scope of this chapter to describe all pain management strategies used in the hospice context. Rather, this section will focus on the pharmacologic treatment of pain in patients at end of life.

When to Refer to Hospice: The Surprise Question

The only definitive criteria that must be met for Medicare to provide hospice services to a beneficiary is that two physicians must agree that the patient has a life expectancy of 6 months or less if the patient's illness runs its expected course. If a clinician would be surprised if a patient were still alive in 12 months, a referral to hospice should be considered. The hospice team of experts can then determine if the patient meets criteria for hospice and if it is the right time to enroll.

Opiates in Hospice

The threshold for the use of opiates is much lower in the hospice setting. Many patients coming to hospice have battled severe cancer-related pain for years. Even noncancer pain in a patient with a life expectancy of 6 months or less can be managed with opiates if nonopiates have failed to provide relief, as development of addiction and tolerance are less likely in this timeframe.

As a disease progresses, a patient's pain may worsen, requiring higher and higher doses of opiates. Rapidly absorbed, sublingual opiate concentrates are often employed in the home setting in order to avoid the need for IV/SQ pumps. These can be especially important in patients who are no longer able to swallow. Table 29.3 summarizes common sublingual liquid opioid preparations.

Table 29.3 Common hospice opiate sublingual concentrates

Opiate medication	Usual concentration (mg/ml)	Dosage
Liquid morphine (Roxanol)	20	5–20 mg q 1–2 h (0.25–1.0 ml)
Liquid oxycodone (Oxyfast)	20	5–20 mg po/sl q 1–2 h (0.25–1.0 ml)
Liquid hydromorphone[a]	1	1–4 mg po/sl q 1–2 h (1–4 mls)[a]

[a]Hydromorphone is often compounded to 4 mg/ml for dosing 0.25–1.0 ml q 1–2 h to avoid confusion when changing from morphine or oxycodone liquid, but this concentration is not commercially available without compounding

Sometimes adequate doses can only be achieved with patient-controlled IV or SQ pumps. The ability to place a nurse at the bedside during pain crises can allow for rapid titration of opiates to control pain at home. The average cost of a PCA is much less if one is using morphine rather than hydromorphone or fentanyl.

Methadone and Ketamine in Hospice

Tolerance to high doses of opiates can pose quite a problem. If intravenous, subcutaneous, or sublingual formulations of traditional opiates fail to control pain in highly tolerant patients, or if harmful side effects (e.g., neuroexcitability or opioid-induced hyperalgesia) limit the ability to escalate to the necessary dose, the addition of methadone or ketamine should be considered. These medications produce analgesia by antagonizing *N*-methyl-D-aspartate (NMDA) receptors.

Caution should be used when starting or adjusting methadone as detailed elsewhere in this chapter due to its long half and its nonlinear and unpredictable kinetics. In general, methadone is increased by no more than 30% every 5–7 days in the hospice setting. A hospice RN case manager usually makes frequent home visits after methadone dosing is adjusted.

Ketamine can also be very useful for opioid-tolerant patients. Although oral bioavailability is low, IV ketamine can be compounded into an oral concentrate that results in adequate serum concentration for analgesia. One common regimen uses an IV formulation of 50 mg/ml and can be dosed as an oral concentrate starting at 10 mg (0.1 mL) by mouth 2–3 times per day. A 10 mL vial will yield a 30-day supply, making ketamine a cost-effective intervention in hospice patients. As with methadone, ketamine has a biphasic metabolism, and doses should be increased only every 4–5 days with close supervision and teaching from the hospice RN case manager. As ketamine is uptitrated and analgesia is achieved, traditional opiates can usually be reduced. Side effects can include hallucinations, dissociation, depersonalization, anxiety attacks, nausea and vomiting, and hypertension. However, these side effects are rare at the low doses most often utilized in hospice care and rapidly resolve with cessation of the medication [51].

Palliative Sedation

Palliative sedation is used to decrease awareness (either partially or fully) of refractory pain. If all forms of pharmacologic pain interventions have been exhausted and distressing physical symptoms persist, palliative sedation is an option, albeit one that is rarely employed. The level of sedation should be proportionate to the patient's level of distress and awareness preserved to whatever extent possible. Complete sedation to unconsciousness is only employed for intractable suffering at the very end of life, and only after careful discussion of risks and alternatives with the patient (if possible) and the patient's family. It is recommended that palliative sedation only be performed by an experienced hospice medical director with the permission of the patient's referring physician. The patient should be on continuous care with a nurse at the bedside. Palliative sedation protocols exist for use of intravenous or subcutaneous midazolam, lorazepam, haloperidol, phenobarbital, and ketamine. Regardless of which medication is chosen, one would start with the lowest possible dose and escalate for comfort [52].

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Part VII
Special Topics

Chapter 30
Quality and Safety in Acute Pain Management

Oren Guttman, Max Shilling, Archana Murali, and Andrew M. Mendelson

Conceptualization of Quality

The World Health Organization's (WHO) definition of quality of care is "the extent to which health care services provided to individuals and patient populations improve desired health outcomes [1]. In order to achieve this, health care must be safe, effective, timely, efficient, equitable, and people-centered." The term "safe" is further defined as "delivering health care that minimizes risks and harm to service users, including avoiding preventable injuries and reducing medical errors." The Institute of Medicine (IOM) in 1999 identified several quality domains, such as effectiveness, patient centeredness, and safety, within its definition of health care quality, defining it as "the degree to which healthcare services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge." [2]. The Donabedian model is a conceptual model that provides a framework for examining health services and evaluating quality in health care [3]. According to this model, structure of care, clinical processes, and patient outcome are all interrelated – improvement in structure of care should lead to improvements in clinical processes, and this should then improve patient outcome.

O. Guttman (✉)
Jefferson Health System, Sidney Kimmel Medical College, Philadelphia, PA, USA

M. Shilling · A. Murali · A. M. Mendelson
Department of Anesthesiology, Thomas Jefferson University Hospital, Philadelphia, PA, USA

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Definition and Measurement of the Quality of Pain Management

Barriers to effective pain management include inadequate knowledge among health care professionals, lack of knowledge regarding regulatory concerns, and limited opportunities for interdisciplinary care [4]. Additionally, the nature of pain being something that is often complex, multidimensional, and subjective adds to the challenge in both assessment of intensity and severity and in terms of relief as a response to treatment [5]. How quality of pain management is both defined and measured is difficult, but pain management standards are applicable to all Joint Commission–accredited hospitals [6]. These standards require hospitals to conduct pain assessment and pain management, collect and compile data, assess and manage patients' pain, and minimize the risks associated with treatment. Additionally, with pay-for-performance reimbursement structures based on Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS), patient satisfaction scores for pain continue to drive health care organizations to improve pain control [7]. Pain-related patient-reported outcomes include factors such as pain intensity, pain interference, pain relief, anxiety, depression, anger, sleep, and pain fear and avoidance, in addition to satisfaction with pain care [7]. Ultimately, high-quality pain management requires appropriate ongoing assessment, interdisciplinary and collaborative planning, appropriate treatment that is efficacious and culturally appropriate, and involves access to specialty care as needed [8]. A brief discussion of some commonly used tools and techniques for the evaluation of pain is worth discussing, including an evaluation of their efficacy and accuracy.

Visual Analogue Scale for Pain

The pain visual analogue scale (VAS) has been widely used for almost a century, dating back to use by Hayes and Patterson in 1921 and in psychology by Freud in 1924 [9]. Its acceptability as a generic pain measure was demonstrated in the early 1970s [10]. It consists of a straight horizontal or vertical line that is generally 10 cm in length. One end denotes "no pain at all," and the opposite end denotes "Pain as bad as it could be." Or "worst pain imaginable." [11], [12]. The patient is asked to mark his or her pain level somewhere on the line between the two descriptors. The distance between "no pain" and the patient's mark defines the subject's pain. Occasionally, descriptive terms are added to the 10 cm line – when this is the case, it is known as a graphic rating scale (GRS). Usual terms include "mild," "moderate," or severe. Alternatively, numbers from 0 to 10 are also added to the 10 cm line, forming the numerical rating scale (NRS). The pain VAS requires little training to administer and score.

Interpretation of data from the VAS has been assessed by several investigators. The VAS and GRS have been demonstrated to be sensitive to treatment effects and

were found to correlate positively with other self-reporting measures of pain intensity [11]. Bird and Dickinson tested whether the change in VAS associated with a clinically significant change in pain is related to the initial VAS score [13]. They concluded that patients with greater pain require a greater change in VAS score, to achieve clinically significant pain relief. In the setting of chronic back pain, a change of about 20% is regarded to be clinically significant. This is slightly greater than a change of 12% to reach clinical significance for acute pain [11]. In a population of those with rotator cuff disease, a minimum clinically important difference of 1.37 cm was demonstrated for a standard 10 cm pain VAS [14]. Intertest reliability was shown to be good overall, but higher among literate than illiterate patients in a rheumatoid arthritis population [10]. A study by Bodian et al. suggests that absolute values of VAS measurements are more clinically relevant than change in VAS scored. They also investigated whether patients should be provided with a new form, or the previous form, when evaluating for changes in pain. Their findings agree with a study by Joyce et al., which found little difference in the values of the VAS scores between patients who used a new form and those who kept using the same one [12, 15]. A transition from paper-based to electronic medical records may require pain assessment to be performed via electronic methods. In a study of 98 subjects, there was no clinically relevant difference between a traditional paper-based VAS assessment and VAS scores obtained from laptop-, computer-, and mobile phone–based platforms [9]. When evaluating overall quality of the VAS in measuring a patient's pain, it is critical to consider that the VAS, and related GRS and NRS, only evaluate one component of the patient's pain experience – pain intensity. The entire breadth of the patient's pain experience is not evaluated.

McGill Pain Questionnaire

The McGill Pain Questionnaire (MPQ) was developed by Dr. Melzack at McGill University in Montreal, Canada, in 1971 and published in 1975 [16]. It is a pain questionnaire that consists of three major measures. The questionnaire's pain-rating index assesses four dimensions, including the sensory, affective, and evaluative aspects of pain, and pain intensity in adults with chronic pain [10]. It also measures a 5-point pain intensity scale. The pain rating index contains 78 pain descriptor items categorized into 20 sub-classes, and each of these contain two to six words that fall into one of the four dimensions. The questionnaire is administered by an interviewer, who must read instructions to the patient. The patient is instructed to select one word within each sub-class that fits their present pain, and if none of the words describe their pain, then no word is selected. A higher score on the questionnaire indicates worse pain. One limitation to the questionnaire is the completion time, which can take up to 20 minutes [10]. Additionally, the varied descriptors used in the questionnaire can prove as a limitation to patients with a limited vocabulary, but the interviewer can facilitate the MPQ completion by providing respondents with clear definitions of words during administration. Papageorgiou and Bradley demonstrated

that the number of MPQ words selected was positively correlated with VAS scores of pain severity at rest and on movement, in patients with arthritis [17]. Additionally, they demonstrated that over one-third of patients offered affective words not included in the MPQ, suggesting that the questionnaire may neglect differences in the pain experience. In a cohort of cancer patients, the MPQ was demonstrated to be a valid, reliable, and sensitive multidimensional measure of cancer pain [18].

A short form of the MPQ (SF-MPQ) was developed by Melzack and published in 1987 [19]. The main component of the SF-MPQ consists of 15 descriptors (11 sensory, 4 affective), which are rated on an intensity scale of 0 = none, 1 = mild, 2 = moderate, or 3 = severe. Summing the intensity rank values allows for the calculation of pain scores. The SF-MPQ also includes the present pain intensity (PPI) index of the standard MPQ and a visual analogue scale. It was developed through a selection of a small representative set of words from the sensory and affective categories of the standard MPQ, through evaluation of the most commonly used terms. It was shown to correlate very highly with the major indices of the original MPQ. The SF-MPQ takes approximately 2–5 min to complete [10]. In 2009, the short form was revised for use in neuropathic and non-neuropathic pain conditions and is known as the SF-MPQ-2. Dworkin et al. revised the SF-MPQ by adding symptoms relevant to neuropathic pain and by modifying the response format to a 0–10 numerical rating scale [20]. The SF-MPQ-2 has excellent reliability and validity, based on a randomized clinical trial involving 882 individuals with diverse chronic pain syndromes and 226 patients with painful diabetic peripheral neuropathy [20]. Dworkin later published results demonstrating the utility, reliability, validity, and responsiveness of the SF-MPQ-2 in acute pain [21].

Pictorial Pain Scales

The faces pain scale (FPS) and the Wong-Baker Faces Pain Scale were initially developed for use with children but have demonstrated increasing utility in adults, especially elderly patients [22]. The scales display a series of progressively distressed facial expressions, and the patient chooses the face that represents the severity or intensity of their current pain. Herr et al. conducted a study of 168 patients aged 65 or older using the FPS and demonstrated support for the construct validity and strong test-retest reliability of the FPS [23]. These results have been reproduced by further studies in adult patients [24, 25, 26].

Quality Improvement in Acute and Cancer Pain

Implementation of the 1995 American Pain Society (APS) Quality Improvement Guidelines for the Treatment of Acute Pain and Cancer Pain produced improvements in both pain assessment and prescribing practices, while having less effect on

patient outcomes [4]. Initially developed and written in 1988, the 1995 guidelines were developed to improve treatment outcomes for patients with acute pain and cancer pain, in response to the widespread failure to recognize the presence of pain [27]. The guidelines are intended for settings in which conventional analgesic methods are used exclusively. The guidelines were revised in 2005, expanding their recommendations based on a review of available literature. The five recommendations made by the APS in 1995 include to recognize and treat pain promptly, involve patients and families in pain management plan, improve treatment patterns, reassess and adjust pain management plan as needed, and to monitor processes and outcomes of pain management. These recommendations were updated and expanded in 2005, with further emphasis on comprehensive assessment and preventive and prompt treatment, customization of care and participation of patient in treatment plans, providing multimodal therapy, and new standardized QI indicators [4]. New recommended quality indicators and suggested measures were also added in this update. These indicators were added based on a systematic review of 20 QI studies of pain that utilized the 1995 APS patient outcome questionnaire (APS-POQ) in inpatient settings. Six core quality indicators were recommended to improve processes and outcomes of hospital-based pain management. These included the following categories, which are focused on within the revised APS questionnaire (APS-POQ-R) [28]:

1. Use of numeric or descriptive rating scales for pain assessment
2. Documentation of pain intensity at frequent intervals
3. Treatment of pain by a route other than intramuscular
4. Administration of analgesics on a regular schedule, and when possible, use of a multimodal treatment regimen
5. Prevention and control of pain to a degree that facilitates function and quality of life
6. Provision of Adequate Information, so that Patients Are Knowledgeable about Pain Management

An evaluation of the psychometric properties of the revised APS guidelines was performed in a Danish population by Schultz et al. The authors reached the conclusion that the modified APS questionnaire demonstrated adequate psychometric properties for the subscales of pain severity, perception of care (satisfaction), pain interference with function (activity), emotions, and side effects of treatment (safety) [29].

Opioid Use, Storage, and Disposal

It is worth discussing the patterns of opioid use and storage in the outpatient population as well, given the continued rise of prescription drug abuse and death. Between 1997 to 2007, opioid sales in the United States increased by 400% [30], and overprescription of narcotics remains common. In 2017, retail pharmacies dispensed

more than 191 million opioid prescriptions to almost 60 million patients in the United States. During that same year, 47,600 people died from an overdose involving opioids [31]. Because patients are not being educated regarding the proper storage of opioids at home, there is a continuing and readily available source of opioids for diversion and for abuse. It has been estimated that 70% of those who abuse prescription opioids in the United States obtain those drugs from friends or relatives [30]. In a cancer outpatient population, 223 of 300 patients surveyed were unaware of proper opioid disposal methods and 138 had unused opioids at home [30]. Further analysis demonstrated that only 9% of these patients stored their opioids under lock and key and that 26% reported unsafe use by sharing or losing their opioids. Perhaps even more striking is that 39% of these patients were unaware of the risk of fatality when taken by others.

The over-prescription of narcotics is a well-known phenomenon within the United States today [32, 33, 34]. Bates et al. report the results of a survey performed 2 and 4 weeks post-operatively, revealing that 67% of 586 surveyed patients had surplus medication from their initial post-operative prescription, and that 92% had received no disposal instructions for their surplus medication. Ninety-one percent kept the leftover medication at home, while 1% returned it to a pharmacy [32]. Among a population of patients attending palliative care clinics, patients who received educational material on safe opioid use, storage, and disposal were more aware of the proper opioid disposal methods and were less likely to share their opioids with someone else. These patients were also less likely to have unused medication at home and more likely to keep their medications in a safe place [33]. In a large review of prescribing data from an orthopaedic surgical population, participants reported unused opioid medication in 61% of cases and only 41% of patients reported appropriate disposal of unused opioid pills.

In response to this growing problem, the DEA organized its first nationwide prescription drug take-back day in the August of 2010, and the event has occurred twice a year since then, with more than 912,305 pounds of prescription drugs returned for disposal at more than 5300 collection sites in 2017 [34]. In April 2019, the US Food and Drug Administration (FDA) announced the launch of a new educational campaign to help the US population understand the role that they play in removing and properly disposing unused prescription opioids from their homes. This new campaign specifically targets women aged 35–64, who are most likely to oversee household health care decisions and the dispensing of prescription medications in the home. As part of this campaign, named "Remove the Risk," the FDA launched a new toolkit of materials which includes fact sheets, social media posts, and website badges, helping to spread information and improve awareness of bring-back programs for opioids as well as safe disposal centers.

Identification and evaluation of incentives to promote safe medication disposal is key to curbing this problem, and some key information on patient attitudes towards opioid disposal is drawn out by Buffington et al. In a survey conducted by Buffington et al. [35], 82.9% of patients reported that they would be more likely to use a medication disposal kiosk or mail-in program if a small incentive was offered, with the preferred type of incentive being cash. Nearly 85% of patients indicated they would

be likely to use a drug disposal kiosk if placed in a location they visited frequently. Approximately half of the respondents indicated that they would be likely to use a licensed mail-in program that provided a prepaid envelope. The survey also identified the possibility of patients requesting only a partial fill of an opioid prescription. 51% of respondents indicated that they would be very likely or likely to select this option, with the most significant barrier being concern that they would not have the medication if needed, and the inconvenience of returning to the pharmacy to fill the remaining quantity [35].

Conclusion

With pain management standards becoming applicable to all Joint Commission–accredited hospitals, it is critical that the measurement of pain continues to be improved upon. After an evaluation of several tools used to measure pain, such as the VAS, MPQ, and MF-MPQ, it is clear that pain, and its many components, continues to be difficult to accurately measure. Continued improvement in the quality of pain measurement is described through the modified APS guidelines. This quality improvement in pain detection, measurement, and management will play a vital role in the opioid crisis that faces the United States.

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Chapter 31
Regulatory and Legal Issues in the Use of Controlled Substances in the Treatment of Chronic Pain

Vernon L. Krueger

Overview There are numerous approaches one can take when attempting to discuss the regulatory and legal issues in the treatment of pain. Just as it is when evaluating a patient and preparing a treatment plan, there are usually several potential options available. So it is when discussing regulatory and legal issues. The issues can range from federal guidelines and policies to state licensing board rules and policies up to civil and criminal allegations. This chapter focuses primarily on administrative (state medical board) policies and guidelines with a brief overview of the litigation process.

State Regulations

States have the primary responsibility to regulate and enforce prescription drug practice. Each state has laws that govern the prescribing of controlled substances, and each practitioner who prescribes pain medication is required to know and abide by these rules and regulations. Most states have enacted numerous regulations and requirements on most, if not all, aspects of prescribing and dispensing controlled substances. These include, but are not limited to, such things as prescription drug

V. L. Krueger (✉)
Krueger Law Group, LLP, Dallas, TX, USA
e-mail: vernon@kbbllp.com

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time and dosage limit,[1] prescription drug and physical drug examination requirements,[2] prescription drug monitoring programs (PDMP)[3] and monitoring patient compliance. At the present time, every state but Missouri has its own prescription drug monitoring program. These regulations may be created by the states' legislative body or its state medical board or both.

Role of State Medical Boards

A state's board of medicine oversees and to a large extent regulates the professional conduct of physicians within the scope of practicing medicine. A medical board may review the acts of a physician to determine whether or not the care and treatment provided to a patient meet the standard of care. Most, if not all, states apply the same or similar guidelines adopted by the Federation of State Medical Boards in its Model Policy for the use of Controlled Substances for the Treatment of Pain.[4]

The Model Policy is not intended to establish clinical practice guidelines nor is it intended to be inconsistent with controlled substance laws and regulations. The policy does set forth seven key areas that each prescriber should adhere to. The seven key areas are:

1. Patient evaluation
2. Treatment plan
3. Informed consent and agreement for treatment
4. Periodic review
5. Referral and patient management
6. Documentation
7. Compliance with controlled substance laws and regulations

In April 2017, the Federation of State Medical Boards adopted the Guidelines for the Chronic Use of Opioid Analgesics. "This policy is intended as a resource providing overall guidance to state medical and osteopathic boards in assessing physicians'

[1] Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Florida, Georgia, Hawaii, Idaho, Illinois, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin, and Wyoming

[2] Forty-one states and the District of Columbia have one or more laws that require a prescriber or dispenser to ensure that prescriptions for medications are based on an examination of the patient. (Centers for Disease Control and Prevention; Office of State, Tribal, Local and Territorial Support "Prescription Drug Physical Examination Requirements")

[3] A prescription drug monitoring program is an electronic database that tracks controlled substance prescriptions in a state.

[4] The Federation of State Medical Boards adopted the Model Guidelines for the use of Controlled Substances for the Treatment of Pain in 1998. The title was changed from Model Guidelines to Model Policy in 2004 to better reflect the use of the document.

management of pain in their patients and whether opioid analgesics are used in a medically appropriate manner."[5]

> These guidelines do not create any specific standard of care, the guidelines...[A]re not intended for the treatment of acute pain, acute pain management in the perioperative setting, emergency care, cancer-related pain, palliative care or end-of-life care. These Guidelines may apply most directly to the treatment of chronic pain lasting more than three months in duration or past the time of normal tissue healing however, many of the strategies mentioned here are also relevant to responsible prescribing and the mitigation of risks associated with other controlled substances in the treatment plan[6]

State medical may, and many have, adopted these guidelines for use in evaluating a practitioner's management of a patient with pain, including the practitioner's prescribing of opioid analgesics. The criteria for evaluation per these guidelines include:

1. Patient evaluation and risk stratification
2. Development of a treatment plan and goals
3. Informed consent and treatment agreement
4. Initiating an opioid trial
5. Ongoing monitoring and adapting the treatment plan
6. Periodic and unannounced drug testing
7. Adapting treatment
8. Consultation and referral
9. Discontinuing opioid therapy
10. Medical records
11. Compliance with controlled substance laws and regulations

How to Comply with these Guidelines

Even though there are a few differences between the Model Policy for the use of Controlled Substances for Use of Pain Management and the Guidelines for the Chronic Use of Opioid Analgesics, they are quite similar in their criteria.

1. Patient evaluation

> A medical history and physical examination must be obtained, evaluated, and documented in the medical record. The medical record should document the nature and intensity of the pain, current and past treatments for pain, underlying or co-existing diseases or conditions, the effect of the pain on physical and psychological function, and history of substance abuse. The medical record also should document the presence of one or more recognized medical indication for the use of a controlled substance.[7]

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[5] Federation of State Medical Boards Guidelines for the Chronic use of Opioid Analgesics, adopted April 2017; p.1.

[6] Id at p.2.

[7] Federation of State Medical Boards Model Policy

2. The Guidelines for Chronic Use of Opioid Analgesics states:

> The medical record should document the presence of one or more recognized medical indications and absence of psychosocial contraindications for prescribing an opioid analgesic and reflect an appropriate detailed patient evaluation.[8]

Additionally, the evaluation and initial patient assessment should include a systems review and relevant physical examination. Some areas to be included in the comprehensive evaluation and history might include the location of the pain, a description or character of the pain (i.e., continuous or intermittent, burning, shooting or stinging, worse in morning or at night), location of the pain and level of pain on 0 to 10 scale. An assessment of the patient's personal and family history of alcohol or drug abuse and relative risk for substance use disorder should also be a part of the initial evaluation.

When deciding to prescribe opioid analgesics it is strongly recommended that the state Prescription Drug Monitoring Program (PDMP) be consulted to determine if the patient is receiving prescriptions from any other providers. The results obtained from the PDMP should be reviewed. There is no specific reference as to whether or not the results obtained from the PDMP should be entered into or made a part of the patient's record.

Treatment Plan and Goals

The treatment plan and goals should be established as early as possible in the treatment process. The treatment plan should be written and the criteria or objectives stated to be used to determine treatment success. The treatment plan should be adjusted to the individual needs of the patient. There should be documentation of any additional diagnostic evaluations, referrals or consultations or additional therapies. The key here is adequate and clear documentation, which will allow an outside reviewer such as the state medical board to logically follow the decision-making process of the practitioner. The lack of an organized written treatment can be, and often is, a major issue when faced with a complaint to or an investigation by a medical board.

Informed Consent

The practitioner must discuss the risks and benefits of the proposed treatment with the patient. Many, if not most, states may require that that practitioner obtain a written informed consent that should include the potential risks and benefits of the proposed therapy, the potential side effects of the proposed therapy and risks including drug interactions and over-sedation.

[8] Guidelines for Chronic Use of Opioid Analgesics

If unexpected or adverse outcomes do occur, the practitioner may become the focus of a medical board complaint or a lawsuit. A patient who does not fully understand the potential risks of a treatment or procedure is not fully informed. Even though a patient may sign the "informed consent" document, it is imperative that the practitioner clearly communicate the risks and benefits to the patient. It is highly recommended that the practitioner document that he/she has discussed the risks and benefits of any proposed treatment or procedure with the patient. The failure to properly communicate the risks and document these steps can have serious consequences for the practitioner.

Treatment Agreement

Treatment agreements should be in writing. The agreement should include the major areas that have been agreed upon. Many state medical boards require a written treatment agreement. The agreement should contain items such as the treatment goals, the patient's responsibility for safe medication use, secure storage of medications, the patient's responsibility to obtain prescribed substances from only one practitioner or practice, the patient's responsibility for getting the prescription filled at only one pharmacy, the patient's agreement to periodic drug testing and the availability of the practitioner or have coverage available, to care for unforeseen problems.[9]

Many agreements also include a statement of the time frame during which the agreement is in effect; Administrative policies and expectations (follow-up, missed appointments and how emergencies will be handled).[10] It is worth knowing that from a legal standpoint, any written or oral agreement between a physician and a patient may be considered a "contract." This carries with it the duty and obligation of each party to fulfill the obligations contained in the "contract." The failure on the part of either party of the contract to meet their obligations can have significant ramifications. For the practitioner this would mean a state medical board complaint, a civil lawsuit or, in some circumstances, a criminal action.

Another very important issue for the practitioner and the patient to discuss during the treatment planning stage is the issue of a therapeutic trial when considering opioid analgesic therapy. The Federation of State Medical Boards' Guidelines for Chronic Use of Opioid Analgesics contains a provision that when a decision is made to initiate opioid therapy, it should be presented to the patient as a therapeutic trial or test for a defined period of time (usually no more than 30 days) and with specified evaluation points, including improvement in pain and function. It would be reasonable to include this type of language in either or both the consent forms and a treatment agreement. This type of documentation can be beneficial to both parties at the outset of what might become a long-term agreement. More importantly, perhaps, is

[9] Id at p.9

[10] Fishman, Scott M., Responsible Opioid Prescribing 2007

the potential that this trial period will allow the practitioner to carefully monitor both the benefits as well as identify any adverse events to the patients.

Some states and the Center for Disease Control (CDC) are now reamending specific dosage guidelines for opioids. Each practitioner needs to know the dosing guidelines for his or her state. If a dosage above those recommended by the CDC or state is prescribed and the patient has an adverse event, the knowledge of the dosage guidelines and a documented reason for exceeding those guidelines may play a significant role in changing the medication or stopping the treatment. There are many factors that each practitioner must take into consideration when making the decisions. Irrespective of the ultimate treatment choice, a clear and unambiguous record of the evaluation, progress and future treatment, if any, is mandatory when and if the practitioner's decision is called into question.

When treating a patient with opioid analgesics the practitioner should consider patient evaluations for adherence to the agreed-upon treatment plan. In addition to clinical evaluations, a practitioner may consider other methods, including unannounced drug testing. As previously discussed, the use of periodic and unannounced drug tests should be included in the agreement for treatment, clearly and completely discussed with the patient with appropriate documentation in the patient's record. If testing is used, test results should be discussed with the patient. The test results and any discussion with the patient should be documented in the patient's record. When a drug test shows the presence of drugs not prescribed by the practitioner, or illicit drugs, the practitioner must take some action. One such action would be to consult the state prescription drug monitoring program to determine if the patient is receiving prescriptions from other practitioners.

Referral and Consultation

A practitioner should consider referral of the patient as indicated for additional evaluation and treatment in order to achieve treatment objectives. Consideration should be given to an intradisciplinary pain management program. Such referrals may include areas such as physical rehabilitation, mental health, interventional pain management and possibly addiction.

As part of the practitioner's ongoing evaluation and monitoring, he or she should plan in advance and have potential referral sources available when and if such referrals are needed. Valuable time can be lost if there is a delay in referral or even longer delay in evaluation and management by the subsequent practitioner. This may result in worsening of the patient's condition and harm to the patient or others.

Documentation and Record Keeping

Proper and thorough documentation is essential in the management of any patient, but perhaps more so when controlled substances or opioids are used for pain management. A written record is the best and, perhaps, the only way of documenting the

treatment, remembering the details and properly managing a patient's treatment. To this end, every practitioner who treats chronic pain must maintain accurate and complete medical records. If, in responding to a medical board complaint or dealing with a civil or criminal lawsuit as a result of a patient having an adverse event, proper documentation is paramount. If there is no documentation as to why the practitioner decided to exceed the state and federal guidelines, this is a potential for catastrophic results to the practitioner. For the protection of all parties the clinician should clearly document in the medical record the rationale for using higher dosages than the recommended guidelines.

The records should contain the following:

- Copies of the signed informed consent and treatment agreement, including documentation of all discussions of the risks and benefits of the proposed treatment.
- The patient's medical history.
- Results of the physical examination and all laboratory therapeutic and diagnostic tests.
- Results of the risk assessment for opioid management, including results of any screening instruments used.
- A description of the treatments provided, including all medications prescribed or administered (including the date, type, dose and quantity).
- Results of ongoing monitoring of the patient's progress (or lack of progress), including levels of functioning, quality of life and pain intensity levels.
- Subjective complaints of the patient.
- Objective findings by the practitioner.
- Instructions to the patient.
- Referrals to any consultants (Should include the name of the consultant and the date the referral was made. If written correspondence is sent to the consultant, maintain a copy of the referral correspondence.)
- Correspondence, test results and treatment recommended or provided by the consultant.
- Results of inquiries made to the state prescription drug monitoring program.

Periodic and Ongoing Monitoring

Each practitioner should periodically review the course of pain treatment and any new etiology of the pain or the patient's state of health.[11] Objective evidence of the patient's response to treatment should be clearly documented in the patient's record. Such documentation provides support for the practitioner's decision to continue the current treatment and modify the current treatment by changing dosages of medications.

Any other information used to support the initiation, continuation, revision or termination of treatment and the steps taken in response to any aberrant medication

[11] FSMB Model Policy

use behaviors should be documented. These may include actual copies of, or references to, medical records of past hospitalizations or treatment by other providers. [12]

The medical record must include all prescription orders for opioid analgesics and other controlled substances whether written or telephoned. Written instructions for the use of all medications should be given to the patient and documented in the record. Whether facing a state medical board complaint or a matter in litigation, the practitioner's medical record will be one of, if not the most, the important aspects of any review or inquiry.

In a state medical board matter the medical board will thoroughly scrutinize the practitioner's record as part of its evaluation to determine if the care and treatment provided was within or outside of the standards of care. Much of this determination will depend on the written record. By reviewing the record, the reviewers will assess the practitioner's evaluation, treatment planning, management and monitoring of a patient. The review will assess the practitioner's judgment and rationale for treatment decisions. The record will be the primary focus of any such inquiry.

Drug Enforcement Administration Requirements

Federal law also governs the appropriate prescribing of controlled substances, and practitioners are required to know and adhere to these regulations. The Drug Enforcement Administration (DEA) requires a number of specific requirements a practitioner must follow to document the use of controlled substances. These requirements may, or may not, correspond with state specific requirements. A practitioner must know, understand and adhere to state rules as well as DEA requirements.

Conclusion

The appropriate application of up-to-date knowledge and treatment modalities can serve to improve the quality of life for those patients who suffer from pain as well as reduce the morbidity and costs associated with untreated or inappropriately treated pain. The diagnosis and treatment of pain is integral to the practice of medicine. All physicians should become knowledgeable about assessing a patient's pain and the effective methods of pain treatment, as well as statutory requirements for prescribing controlled substances. Inappropriate pain treatment may result from the physicians' lack of knowledge about pain management. Fears of investigation or sanction by federal, state and local agencies may also result in inappropriate treatment of pain. Appropriate pain management is the treating phy-

[12] NFMB Guidelines for Chronic Use of Opioid Analgesics

sician's responsibility. The inappropriate treatment of pain may be considered to be a departure from standards of practice and may result in investigations to any such allegations.

The medical management of pain should consider current clinical knowledge and scientific research and the use of pharmacologic and nonpharmacologic modalities according to the judgment of the physician.

Physicians should not fear disciplinary or legal action for ordering, prescribing, dispensing or administering controlled substances, including opioid analgesics, for a legitimate medical purpose and in the course of professional practice. However, physicians are expected to incorporate safeguards into their practices to minimize the potential for the abuse and diversion of controlled substances.

To be within the usual course of professional practice, a physician–patient relationship must exist and the prescribing should be based on a diagnosis and documentation of unrelieved pain.

Suggested Readings

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Chapter 32
Pain Prevention

Syed S. Jaffery, Coby Tran, Robert S. Ackerman, Nathaniel Loo, and Dawood Nasir

Introduction

The incidence of chronic pain is remarkably high. A meta-analysis of 68 articles relating the burden of chronic pain in several low- and middle-income nations reported chronic pain to be present in 34% of the general adult population [1]. Twenty-five percent have musculoskeletal pain, 42% headaches, 21% low back pain, and 14% have joint pain. Additionally, 35% have temporomandibular pain, 17% abdominal pain, 7% widespread pain, 12% migraine, 4% pelvic pain, and 6% have fibromyalgia. Chronic low back pain and musculoskeletal pain were found significantly more likely in the working population compared to the general adult population. In addition, musculoskeletal pain, joint pain, and other unspecified pains were more prevalent in the elderly population [1]. With such a high prevalence of chronic pain syndromes, primary prevention and avoidance of many of the triggers and inciting injuries is a key component of modern pain management practices.

General Injuries

The US Consumer Product Safety Commission (CPSC) publishes a report via the National Electronic Injury Surveillance System (NEISS) of the many injuries associated with consumer products as seen in emergency departments. A selection of product groupings and estimated number of injuries is shown in Table 32.1 [2].

S. S. Jaffery · C. Tran · R. S. Ackerman · N. Loo · D. Nasir (✉)
Department of Anesthesiology and Pain Management, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: Nathaniel.Loo@UTSouthwestern.edu; Dawood.Nasir@UTSouthwestern.edu

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Table 32.1 US injuries from consumer products in 2017 [2]

All toys	251,366
Sports and recreational equipment	
ATVs, mopeds, minibikes, etc.	214,761
Baseball, softball	187,447
Basketball	500,085
Bicycles and accessories	457,266
Exercise, exercise equipment	526,350
Football	341,150
Playground equipment	242,359
Soccer	218,926
Swimming, pools, equipment	199,246
Trampolines	145,207
Personal and home items	
Clothing	417,306
Cans, other containers	304,718
Home workshop manual tools	138,854
Home furnishings and fixtures	
Bathroom structures and fixtures	552,500
Beds, mattresses, pillows	898,485
Carpets, rugs	202,806
Chairs, sofas, sofa beds	669,992
Desks, cabinets, shelves, racks	304,169
Ladders, stools	268,695
Misc. furniture and accessories	113,585
Tables	355,821
Home structures	
Fences	113,650
Glass doors, windows, panels	139,313
Nonglass doors, panels	319,830
Stairs, ramps, landings, floors	3,134,957

In terms of sports injuries, an average of 8.6 million sports- and recreation-related injury episodes occurred per year from 2011 through 2014. Sixty-five percent of those involved kids, teenagers, and young adults, aged 5−24 years [3]. Males accounted for 61% of the injury episodes. One-half of the injuries resulted in a health clinic visit without an emergency department visit, whereas just over one-third yielded an emergency department visit, but no hospitalization. Those that required a full hospital admission and further care accounted for 2.7%. Most of the injury diagnoses included sprains (41%), fractures (20%), and superficial injuries/contusions (19%). Sports-related traumatic brain injuries accounted for 4.5% of the total diagnoses [3].

The Centers for Disease Control and Prevention (CDC) reports several health-related statistics, including those for accidents or unintentional injuries [4]. This

subtype of injury has resulted in 29.2 million emergency room visits in 2016 with 161,374 deaths, ranked third in the cause of death rank behind heart disease and cancer. The annual total per 100,000 people is increasing annually; in 2016, there were 49.9 deaths per 100,000 people, the highest value in the previous 18 years. In 1999, there were 35.1 deaths per 100,000 people attributed to accidents or unintentional injuries [4].

Guns

Per 2012 data reported in the *Washington Post*, "the United States has the highest gun ownership rate in the world and the highest per capita rate of firearm-related murders of all developed countries." [5] There are 88.8 guns per 100 people with 270 million total civilian guns. There are 9960 annual homicides by gun, roughly 67.5% of total homicides. By comparison, Switzerland has 45.7 guns per 100 people and 57 annual homicides by gun. Finland has 45.3 guns per 100 people and 24 annual homicides by gun. Japan has 0.6 guns per 100 people and 11 annual homicides by gun [5]. There are several political arguments related to gun ownership rights; in terms of pain and general medicine, gun safety is deemed a public health concern.

The National Rifle Association publishes several rules and guidelines for fundamental gun safety. These include never using alcohol, over-the-counter drugs, or prescription drugs before or while shooting; storing guns so they are not accessible to unauthorized persons; storing guns unloaded and in locked safes or other secure places; and keeping guns separated from ammunition [6].

Cars

The Insurance Institute for Highway Safety is a nonprofit research and education organization that tests cars and lists top safety picks in several categories. They examine the common kinds of crashes such as front, side, rollover, and rear. Their annual findings are published by car category and size [7].

General safe driving practices include using seat belts and head rests. Avoid driving while sleep deprived or while taking opioids or other sedating drugs. Additionally, strict adherence to speed limit regulations is encouraged.

Driving while distracted, particularly under the influence of electronics, can pose additional safety concerns. The phenomenon of "inattention blindness" occurs when a driver is texting or talking on their cell phone and misses as much as half of the driving environment [8]. A texting driver has his or her eyes on the phone and away from the road for 4–5 s on average. On the other hand, some new technological advances are trying to protect drivers from themselves, blocking incoming calls

while the person is driving, utilizing dashboard displays, in addition to new warning systems [8].

Motorcycles also pose a potential safety concern as 5286 motorcyclists were killed in motor vehicle crashes in 2016, 5% more than in 2015 [9]. These account for 14% of all traffic fatalities per data from the US National Highway Traffic Safety Administration. In addition, motorcycle riders involved in crashes had the highest percentage of alcohol-impaired drives (25%) compared to other vehicle derivers (21% passenger cars, 20% light trucks) [9]. Feet and legs are the most common site of injuries in motorcycle crashes. Denim jeans are inadequate protection; they are tested to protect skin for half a second, which is inadequate [10]. Minimum abrasion times in Europe are 4 s. Second most common are head and neck injuries, roughly 22% in total, with chest, back, and shoulder injuries third most common. Helmets are deemed mandatory in most places around the world, but mandatory boots and gloves are more often contested [10]

Winter Sports

Three out of every 1000 skiers and snowboarders get injured daily while out on the slopes, three times as likely in teenagers or younger. Women are more likely to get an injury, though men are more likely to have a serious injury [11]. Knee ligament injuries account for roughly one-third of all skiing injuries. Sharp turns and twists are often associated with these injuries; knee braces are sometimes useful to minimize risk. "Snowboarder's ankle" is a talus fracture that can be tough to diagnose on plain film; improved balance techniques and an ankle brace may be preventative [11]. "Skier's thumb" is a hyperextension injury and involves the ulnar collateral ligament, best prevented by avoiding placing hands into the ski pole loops unless necessary. Scaphoid and Colles fractures of the wrist are also common, the chance of which reduced when wearing wrist guards. Lastly, head and spinal injuries are rare, but can occur after collisions into rocks, trees, lift towers, etc. Helmets have been proposed, but research conclusions have been mixed [11].

Horses

Horseback riding injuries, although not terribly common, require unique practices to prevent the injury or decrease its severity [12]. The most common horse-related injury involves the upper extremity, followed by the lower extremity, with soft tissue injuries more common than fractures. Head and chest injuries caused most deaths. No horse is a safe horse, but precautions may be taken using knowledge obtained from studying horses [13]. Proper attire should include horseback riding helmets, sturdy boots, and clothing that is not loose. Saddles should always be kept

in good condition. Ride supervised during beginning stages and be alert. Never ride a horse when tired or under the influence of medications, alcohol, or other drugs [12].

Other Accidents and Injuries

While it is impossible to prevent many injuries, prevention may help limit chronic pain and its sequelae. In general, wear protective equipment such as gloves and goggles when appropriate [14]. Operate machinery or appliances after necessary training, keep walkways clear from tripping or falls. Do not work on electrical systems without turning off the electricity; additionally, be caution of hot cookware and knives as they can cause burn injuries. Avoid heavy lifting when possible and lift by bending the knees rather than the back [14].

A meta-analysis in *JAMA Internal Medicine* of 23 publications including 30,000+ patients with low back pain describes that exercise alone or exercise in combination with education strategies is best for preventing low back pain [15]. Shoe insoles, back belts, and education alone were not found to be effective. It is not known whether education, training, or other adjustments prevent sick leave related to low back pain episodes as the quality of evidence is low [15].

Preventative strategies for low back and neck pain include physical activity and weight loss [16]. To prevent falls, a home hazard assessment is recommended in addition to strength and balance training and other coordinated activities such as dancing and tai chi. Osteoarthritis is best prevented when incorporating regular activity and exercise and overall aerobic fitness, as well as other weight-loss strategies [16].

A report from the NIESS published from the CPSC describes the prevalence of several home- and sports-related injuries which resulted in emergency department visits. Those that exceeded 100,00 estimated injuries are shown in Table 32.1.

Acute Pain Transition to Chronic Pain

Chronic pain is a prevalent issue to society and the health care system. It is associated with leading causes of disability in both the USA and the world. Back and neck pain rank number 1 and 4, respectively. Migraine is number 5 on the list and musculoskeletal pain is number 10 [17]. Often, chronic pain originates from an episode of acute pain. While the mechanism is unclear, it is thought that the transition may be due to abnormal peripheral sensitization, central sensitization, and descending modulation over time [18].

In addition to timely treatment of the source of pain, it is important to address all physical and psychosocial aspects that can contribute to pain. A study that evaluated

the progression of acute to chronic pain found that more traumatic life events, greater depression in the early stage of an acute pain episode, and belief that the inflicted pain may be permanent contributed significantly to the duration of pain and disability [19].

The Work Wellness and Disability Prevention Institute endorses several chronic pain prevention measures, including not ignoring acute pain, maintaining a healthy lifestyle, maintaining strong social supports, getting enough sleep, reducing stress, ensuring an ergonomically safe work station, using headrests in cars, and avoiding high-risk sports and hazardous activities [20].

Sleep hygiene is very important for patients with pain. Patients with chronic pain have a sleep deficit of 42 min, and only 37% have good or very good sleep patterns [21]. Sleep hygiene includes going to bed at consistent times while allowing for 8 h of sleep. Maintaining a quiet, dark, relaxing bedroom at a comfortable temperature is important. Avoid using electronic devices in the bedroom, including television, smart phones, and computers. Eating, caffeine, and alcohol should be avoided before bedtime. Exercise during the day may help sleep quality [22].

Stress management is also important. Twenty-three percent of chronic pain patients report higher stress levels compared to 7% of pain-free people. After a stressful event, it is helpful to spend time with loved ones to support each other. Avoiding alcohol, nicotine, and other drugs is helpful to prevent relapsing or dependence. Seeking support from a friend, councilor, clergyperson, or doctor is useful. Staying socially connected is important to prevent isolation and loneliness. A healthy diet, exercise, sleep, massage, and pleasant activity can all be helpful. [23]

Obesity

Obesity and chronic pain are often comorbid. There is an observed linear correlation with pain as BMI increases. People with a body mass index (BMI) of 25–29 have 20% more pain than normal weight people, people with a BMI of 30–34 have 68% more, people with a BMI of 35–39 have 136% more, and people with a BMI over 40 have 254% more pain [24].

Obesity has several mechanisms in which it can exacerbate pain syndromes. As BMI increases, larger mechanical stress is exerted on the obese patient's joints and spine. Degenerative disk disease was found to be more common in the obese population, and as BMI increased, the severity of the degenerative disk disease also increased. In addition, a study found that for every pound of weight lost, there is a 4-pound stress reduction off of the knees [25].

Long-term mechanical stress creates more limitations for patient activity leading to increased physical deconditioning, which itself is another risk factor for both further obesity and chronic pain. This leads to an unfortunate feedback loop which becomes more difficult to break as the duration increases [26].

Comorbid with obesity are other lifestyle detriments that have been shown to be associated with exacerbated pain or can exacerbate pain. For example, sleep disorders are very prevalent among chronic pain and obese patients. For obese patients, this is largely related to higher risk for obstructive sleep apnea. Proper sleep hygiene remains an important lifestyle modification in patients. There is also some evidence to suggest that treatment of obstructive sleep apnea (OSA) with continuous positive airway pressure (CPAP) may improve pain tolerance in chronic pain patients [26].

Diet

In general, a proper diet with whole grains, fruits, and vegetables has been associated with significant health benefits [27]. There is a growing body of evidence to suggest that diet plays an important role in the development and maintenance of chronic pain. Though the extent to which diet contributes to different chronic pain syndromes is unclear, there are demonstrable effects of proper diet on chronic pain.

Rheumatoid arthritis is a chronic inflammatory condition of the joints. Historically, fasting with water only and fruit juice-based fasts have been shown to be an effective treatment for rheumatoid arthritis symptoms. However, these patients would relapse once the fasting period ended and a regular diet was reintroduced. When patients were started on vegetarian diets after the fasting period, patients showed significant improvement of all symptoms and disease markers compared to controls. These results may be explained by both weight control as well as avoidance of specific antigens found in many fatty or animal meat products that cause inflammation [28].

Vitamin D deficiency is noted to be prevalent in the chronic pain population, with studies estimating from 26% to 90%. Vitamin D is necessary in the body to promote proper bone and muscle health and acts as an anti-inflammatory mediator. Calcium and vitamin D deficiencies are associated with vertebral compression fractures and other stress fractures. Therefore, proper dietary supplementation with vitamin D is likely to promote less development of chronic pain by helping maintain the structural integrity of the patient's bony structures.

Proper use of supplements may help reduce other sources of pain as well. For example, knee osteoarthritis may be reduced by increasing dietary fiber [29]. In addition, preventative saffron supplementation for 10 days may help prevent delayed onset muscle soreness [30].

Back Pain

The lifetime incidence of low back pain is upwards of 80%. While structural sources of pain exist like compression fractures and radiculopathies, the most common type of low back pain is a nonspecific low back pain, meaning that the etiology is unclear

or cannot be readily diagnosed. While most episodes of nonspecific low back pain resolve by themselves with conservative interventions, acute episodes can persist and become chronic when lasting more than 3 months [31].

The risk factors for low back pain are wide and include heavy work, physical inactivity, obesity, arthritis or osteoporosis, pregnancy, age >30, bad posture, stress or depression, and smoking [31].

Low back pain presents a significant strain on society, with 20% of patients with chronic low back pain reporting significant limitations in their activity. Therefore, it becomes important to prevent the progression from acute to chronic low back pain as well as shorten the duration of chronic low back pain. The approach to prevention of chronic back pain must consider the wide variety of risk factors. Current studies have shown that low back pain can be prevented in high-risk patients through early intervention and a multidisciplinary program [32, 33].

Currently, regular exercise has most consistently been shown to prevent low back pain. While the mechanisms are unclear, it is believed to give additional musculoskeletal support in the form of flexibility and strength. A 9-month web-based education and exercise program was effective in improving quality of life and reducing chronic pain in patients with subacute nonspecific low back pain [34]. Based on current studies, no one exercise modality has been shown to be greater than another. The choice can be based on patient preference and fitness level.

Smoking is associated with back pain, spinal stenosis, osteoporosis, and spine fusion failure. To date, while quitting smoking has not been specifically shown to prevent low back pain, it is otherwise beneficial for the patient's overall health.

Everyday footwear that is comfortable and appropriate for the anticipated activity is important to avoid aggravating foot pain, which may contribute to chronic back pain.

The psychosocial aspects of chronic low back pain must be addressed as well. A cognitive behavioral therapy intervention prevented disability in people with a history of back pain who were not engaged as patients. Long-term sick leave in these patients was reduced threefold, showing strong potential in helping to prevent the societal consequences of back pain [35].

There is no one psychosocial treatment currently recommended above the others. The Örebro Musculoskeletal Pain Screening Questionnaire has been used to identify patients with different risk profiles, including a primarily risk avoidant profile, a primarily depressed profile, and a mixed profile. A study of tailoring interventions to match these three profiles was conducted to compare results with unmatched control treatment. All the groups improved with the treatments, and no effect was found by matching profiles to different psychological treatments. In addition, studies suggest that progressive muscle relaxation and music therapy may improve the quality of life and pain severity in pregnant women with low back pain [36].

It should be noted that educational interventions, worksite prevention programs, and mechanical supports are not proven to be effective at preventing back pain.

Orthotics

Orthotics are adjunct external support measures for supporting joints typically at the hip, knee, ankle, or foot. While some orthotics may be bought over the counter, many are customized or prescribed by a professional, such as a doctor or physical therapist. The goal of these external supports is to relieve pain by absorbing forces of impact on joints due to suboptimal body movement or positioning.

While a consensus has not been reached yet, some studies have shown benefits in the use of orthotics for pain. In one study, knee orthoses were helpful in preventing the progression of knee osteoarthritis [37]. The use of shoe orthotics may also be helpful in alleviating lower back pain [38].

Temporomandibular Dysfunction

The temporomandibular joint acts as a hinge with sliding capabilities, allowing for normal motion of the jaw. Disorders arise with improper alignment of the joint in relation to the disc or damage to any of the anatomical structures. This causes pain and discomfort around the jaw, the temporomandibular joints, and ear, which may be exacerbated by chewing. Temporomandibular dysfunction is classified as a secondary-type headache.

Temporomandibular disorders are common and have a strong societal impact. Temporomandibular disorders account for 17.8 million lost work days a year for every 100 million workers [39]. While a structural component exists and is the strongest contributor of symptoms, other environmental and psychosocial factors play a role in the development of symptoms.

Management and prevention are aimed at lifestyle modifications and correcting anatomical abnormalities. Initial lifestyle modifications include proper posture of the head and neck during the day and while sleeping at night. Psychosocial aspects of patients' lives should also be addressed when dealing with chronic temporomandibular dysfunction.

Splints are a common adjunct of conservative therapy for temporomandibular disorders. There are two main types of splints: occluding and nonoccluding. Occluding splints generally improve upper and lower alignment. Nonoccluding splints will open the jaw, release muscle tension, and prevent teeth clenching. For temporomandibular disorders, occluding splints are generally used. The goal of therapy is to not only relieve the pain caused by the disorder but also to protect the joint from long-term erosion. Despite the common use of splint therapy, a randomized control trial suggested that use of splints is not superior to routine self-care [40].

Pharmacological therapy consists initially of short-term nonsteroidal anti-inflammatory drugs (NSAIDs). Muscle relaxant drugs can also be used for patients with pain to palpation of the joint.

Most individuals with TMD respond to treatment; however, a small group of patients develop chronic TMD. The risk factors for the development of persistent

TMD are currently not well defined. In these cases, surgical procedures may be considered, including arthroscopy, arthrocentesis, arthrotomy, or other reconstructive procedures.

Tension-Type Headache

Tension-type headaches are the most common of the primary-type headaches. Classically, tension-type headaches present in a bilateral, band-like distribution, with a throbbing quality of pain. Tension-type headaches can be further classified by frequency of occurrence. This ranges from infrequent episodic attacks of less than 1 day per month, to attacks 1 to 14 days a month, to chronic tension-type headaches, which occur more than 15 days a month.

The etiology of tension-type headaches is unclear and likely multifactorial. It is thought that peripheral activation and sensitization of myofascial nociceptors contribute to the transition from episodic to chronic headaches.

While generally considered milder to moderate in intensity, when occurring chronically at higher frequencies, they contribute to personal and society stress. In a population study, patients identified with chronic tension-type headaches reported on average a loss of 27 days of work per year and 20 reduced-effectiveness days [41].

Due to the multifactorial nature of tension-type headaches, treatment and prevention is multidimensional, including cognitive-behavior therapy, biofeedback, and pharmacologic interventions. Modifications like limiting stress, planning ahead, staying organized, massage and meditation, exercise, and stretching around the neck, shoulder, and jaw all may help prevent tension-type headaches.

Pharmacologically, amitriptyline is recommended as the first-line drug for prophylaxis. For patients with higher frequency headaches that are not responsive to lifestyle modifications or amitriptyline, acupuncture or physical therapy may offer some degree of pain relief [42].

Postdural Puncture Headache

Postdural puncture headache (PDPH) is a well-known complication that can occur after a breach in the dural wall. This includes intentional puncture with spinal anesthesia or lumbar sampling or can occur with inadvertent puncture of the dural wall during placement of epidural anesthesia.

The exact cause of why headaches develop in postdural puncture patients is unclear. It is currently believed to be related to the amount of cerebrospinal fluid (CSF) leak that occurs post puncture. The loss of CSF is believed to create traction on nervous system structures, thus causing a headache. In addition, another possible cause is that intracranial vasodilation occurs in response to the CSF drop in order to maintain a constant intracranial volume.

The classic symptoms of a PDPH is a positional headache, worse with sitting up or standing, and improved with lying flat. There is associated nausea, photophobia, and neck stiffness. These symptoms represent a significant source of morbidity due to their duration and severity. Postdural puncture headaches are a common reason obstetrical patients sue after epidural analgesia for delivery [43].

Both patient and equipment used affect the risk of dural puncture headache. Patient risk factors include young age, female sex, and pregnancy. The equipment used is also important as larger-sized punctures are associated with a higher incidence of headaches. Blunt (Gertie Marx) needles have been shown to be associated with fewer headaches after lumbar puncture compared to sharp (Quinke) needles, 4.48% versus 11.32%. Of note, the lumbar puncture failure rate was higher in the blunt needle group, 26.3–9.4% [44]. In addition, several studies have shown that with increased size of needle, there is an increase in incidence and severity of PDPH. It is estimated that inadvertent puncture with an epidural Touhy needle has a rate of 1.5% and that PDPH occurs in about 50% of these patients.

After inadvertent dural puncture occurs, there are several conservative and invasive options for PDPH prophylaxis. Epidural morphine has been shown to be effective in preventing PDPH when given as two epidural injections of 3 mg, 24 h apart from each other [45]. Intravenous cosyntropin has also been shown to be effective in prevention. After dural puncture, 1 mg IV cosyntropin was administered, which halved the number of patients who developed PDPH. While the mechanism is unclear, it is suggested that the cosyntropin stimulates aldosterone, which increases total blood volume. The increase in volume creates mild dural edema, which closes the puncture site [46]. Caffeine has also been used to prevent and treat dural puncture headaches. The proposed mechanism of its efficacy is by cerebral vasocontraction augmented CSF production. However, supporting evidence is not yet adequate to support its efficacy [47].

A prophylactic epidural blood patch is another option. This is done by a reinsertion of the epidural needle at a different level after dural puncture. Autologous blood is then injected into the new space. The blood is believed to seal off the puncture site. While the epidural blood patch is a very efficacious means of treating PDPH, the evidence behind its use for prevention of headaches is not as strong [48].

Postherpetic Neuralgia

Varicella and herpes zoster are two distinct disease processes that are caused by the varicella zoster virus. Varicella is typically seen in children and is the primary infection that occurs with patients. After the initial infection, the virus remains dormant in the dorsal root ganglia of the cranial or spinal nerves. With aging or immunosuppression, the virus can reactivate, causing an acute and painful neuritis. This acute phase typically lasts for 30 days. Afterwards, a persistent pain syndrome known as postherpetic neuralgia can occur when the pain continues for more than 4 months

after the rash emergence. The pain in any phase is characterized as sharp, burning, or stabbing and is highly associated with allodynia.

Not all patients who get herpes zoster get postherpetic neuralgia. The major risk factors for development of postherpetic neuralgia include advancing age, more intense pain during the acute phase, and rash severity. In patients 60–69 years old, postherpetic neuralgia occurred in 6.9 percent. However, in patients greater than 70 years old, postherpetic neuralgia occurred in 18.5%.

Prevention of postherpetic neuralgia involves vaccination and prompt treatment of the acute herpes zoster attack. The new vaccine, Shingrix, reduces the incidence of shingles approximately 90% [49]. Healthy adults 50 years and older should get two doses of Shingrix, separated by 2–6 months. Patients should get Shingrix even if shingles has occurred or received Zostavax or history of chickenpox is unclear. Interestingly, the incidence of herpes zoster has increased as the varicella vaccine rate has increased in children [50–52].

In patients who receive the vaccine and develop herpes zoster, postherpetic neuralgia is reduced by 70–90% [53]. Pharmacologically, oral famciclovir 500 mg three times daily or oral acyclovir 800 mg five times daily for 7 days are similarly effective at shortening the duration of shingles and reducing postherpetic neuralgia [54]. Famciclovir is usually preferred due to an easier dosing regimen. Prednisone 60 mg/day for the first 7 days, 30 mg/day for days 8–14, and 15 mg/day for days 15–21 shortens the duration of herpes zoster [55]. Amitriptyline 25 mg per day reduces the prevalence of postherpetic neuralgia 50% in elderly patients [56].

Ischemic Pain

Sickle cell disease is a genetic disorder that involves a homozygous genotype for the hemoglobin protein hemoglobin S. Patients affected have red blood cells that are predisposed to sickling during periods of hypoxia. The sickling produces painful vaso-occlusive episodes in which there is microvascular occlusion to organ systems. Chronic pain is highly prevalent in these patients, with an estimated 29% experiencing daily pain. Due to the large amount of pain medications prescribed to control their symptoms, pain management at home and in the hospital setting can be difficult.

A randomized control trial comparing an individualized patient-based pain regimen to a standardized protocol demonstrated that the patient's pain responds better to opioid doses based on outpatient opioid doses rather than standard weight-based doses. Appropriate first doses of pain medications resulted in higher initial opioid doses and improved pain scores [57].

An appropriate hydroxyurea is important in reducing the number of vaso-occlusive episodes experienced by patients. Hydroxyurea works primarily by increasing the percentage of fetal hemoglobin, which reduces the hemoglobin S polymerization. The current recommended indication for hydroxyurea is for patients who experience more than three severe painful episodes in a year. L-glutamine is

also recommended as a separate therapy that can work to decrease the number of vaso-occlusive events. Due to working through an independent mechanism of hydroxyurea, it can be prescribed in conjunction with hydroxyurea therapy. In addition, for refractory painful episodes, a short period of regular transfusions can be useful in controlling the amount of painful episodes experienced by the patient. It is thought to work by decreasing the percentage of hemoglobin S, which helps prevent vaso-occlusion. Lastly, as with other chronic pain conditions, addressing and treating concomitant psychiatric and social dysfunction remains important in sickle cell patients.

Ischemic pain can also come from acute coronary syndromes and peripheral vascular disease. Prevention in these cases is directed towards ensuring proper vascular flow to the affected areas. For example, in patients who had a myocardial infarction and underwent angioplasty, a preventative angioplasty was performed on coronary arteries that were diseased but not involved with the infarction. Those who underwent preventative angioplasty had less adverse cardiovascular events [58].

Prevention of Acute Pain after Surgery

Preemptive analgesia became an exciting concept after reports of phantom limb pain elimination following epidural analgesia [59]. Unfortunately, preemptive analgesia has been difficult to reliably reproduce. The Danish surgeon Henrik Kehlet pioneered what is now Enhanced Recovery After Surgery (ERAS). His remarkable surgical skill allowed him to abandon dogmas such as routine nasogastric tubes after colon resection, listening for bowel sounds before initiating postoperative feedings, extended bed rest, prolonged length of stay, etc. His group reported profound analgesia after open cholecystectomy with epidural analgesia, incisional local anesthetic, and NSAIDs [60]. This line of research has taken us from simply "pain management" to "functional restoration" after major surgery.

Preoperative assessment and treatment planning are critical in order to improve pain management and reduce opioid side effects and risks. Patient education and nonpharmacological treatments should be optimized in order to reduce an overreliance on drugs. Opioid-tolerant patients have difficulty with acute postoperative pain control, often requiring increased doses of opioids, and may benefit from alternative analgesic techniques. Opioid-naïve patients may develop hyperalgesia from short-acting opioids such as remifentanil. Prescribing opioids to facilitate early hospital discharge may lead to prolonged opioid use and dependence, while unused opioids create diversion risk [61].

Acute pain severity after surgery is quite variable among patients having the same surgery. In a study by Gerbershagen et al. comparing 179 surgical procedures, the most painful operations had a median worst pain score of 7 [62]. However, each of these operations was associated with some patients reporting mild pain and some patients reporting very severe pain. Attempting to standardize doses of opioids with this much variation is likely to overdose some patients and underdose others.

Many of the most painful operations are spine surgeries and orthopedic surgeries. Other operations with the most severe pain include: open reduction of calcaneal fracture, spine fusion, open myomectomy, proctocolectomy, spine reconstruction, foot arthrodesis, hand arthrodesis, caesarian section, open reduction acetabulum and femoral head, hand resection arthroplasty, shoulder replacement, ankle arthrodesis, pancreatectomy, open knee refixation and reconstruction, open reduction tibial shaft, open reduction patella, open reduction proximal tibia, open reconstruction shoulder joint ligaments, partial shoulder replacement, hemorrhoids, tonsillectomy, open cholecystectomy kidney transplantation, and hysterectomy.

Interestingly, operations done laparoscopically were associated with less pain, but the median pain level was only 1 point less on a scale of 0 to 10. Some operations done with scopes were associated with more pain than the open procedure. In a separate study by Gerbershagen looking at 30 surgical procedures with greater than 20,000 patients, consistent risk factors for postoperative pain were found to be younger age, preoperative pain, and female gender [63].

Risk factors for prolonged opioid use after surgery include painful surgery, high doses of opioids, and longer duration of discharge prescription. Patient risk factors for prolonged opioid use include age over 50, male gender, lower income, diabetes, heart failure, pulmonary disease, depression, preoperative opioid treatment, benzodiazepine and antidepressant use, ACE inhibitors, illicit drug use, tobacco use, and preoperative pain [61].

Opioids are commonly used as first- and second-line drugs for postoperative pain. Acute opioid administration produces analgesia, but also may produce nausea, respiratory depression, constipation, psychological reward, rapid tolerance, and opioid-induced hyperalgesia [61]. Also, opioids as a monotherapy may be inadequate.

Lidocaine and other local anesthetics are used for topical application, wound infiltration, peripheral and plexus nerve blocks, as well as neuraxial blocks for anesthesia and analgesia. They can serve as adjunct or alternative modality to opioids for pain control. Local anesthetic epidural blocks have served as the most effective analgesic technique to prevent labor pain and can also prevent chronic pain after surgery [64]. Intravenous lidocaine infusions and paravertebral blocks reduce the incidence and severity of pain in patients with postmastectomy syndrome. Thoracic epidural analgesia prevents chronic postthoracotomy pain [65]. Intercostal nerve block followed by local anesthetic infusion of three subchondral spaces was effective for postoperative pain [66].

However, rebound pain can occur after peripheral nerve blocks dissipate. A study by Williams et al. quantified the duration of prolongation needed to block rebound pain. Approximately 33 h of additional nerve block duration were required to reduce rebound pain scores by one unit. This rebound pain can be blunted by prolonging the block by a continuous infusion of local anesthetic. However, each hour of additional infusion is predicted to reduce rebound pain by only 0.03 on a visual analogue scale [67]. Rebound pain may be less common with liposomal bupivacaine used for wound infiltration.

Acetaminophen is more effective if given preoperatively compared to after surgical incision. Preoperative acetaminophen reduces pain, opioid consumption, and

vomiting compared to acetaminophen given post incision [68]. Parecoxib given before and after discectomy is more effective than parecoxib given either before or after surgery [69, 70]. However, tramadol given before surgery is not superior to tramadol administration later [71]. Studies of opioids as preventive analgesics are inconclusive [72].

The goals of multimodal analgesia are to restore quality of life and function after surgery by maximizing analgesia and minimizing the risks of opioid treatment not only for chronic pain but for acute pain as well. Multiple medications and analgesic combinations are used without specific limits on the number of multimodal interventions to use. However, the reported adverse effects of combination multimodal analgesia are sparse in the literature. Drug combinations may produce sedation or potentiate respiratory depression from opioids. Preoperative opioid dose is a major source of heterogeneity between studies of opioid-sparing effects of different multimodal analgesic treatments [73].

Acetaminophen, gabapentin, and NSAIDs are estimated to be the most effective opioid-sparing drugs, followed by pregabalin, tramadol, magnesium, lidocaine, ketamine dexamethasone, and nefopam. Peripheral sensitization can be blunted by nonsteroidal anti-inflammatory agents [74]. Corticosteroids have some potential benefit reducing peripheral sensitization as well.

Given alone, acetaminophen reduces morphine doses by 6.3 mg during the first 24 h after surgery. This compares to 10.2 mg with NSAIDs, 10.9 mg with COX −2 antagonists, and >13 mg with gabapentin [75]. Multimodal analgesia can be effective with acetaminophen and nonsteroidal anti-inflammatory agents. Acetaminophen acts through endogenous cannabinoid systems [76]. Combined with NSAID, acetaminophen has a significant additive effect [77]. The combination of the two drug classes may even be synergistic [78].

Information about combination drug treatment is limited, but a review by Dahl et al. found after dental surgery, the combination of acetaminophen 1 g and ibuprofen 400 mg has a number needed to treat (NNT) of 5.4 compared to ibuprofen 400 mg alone. The same combination has an NNT of 1.5 versus placebo. A lower dose of acetaminophen 500 mg and ibuprofen 200 mg has an NNT of 1.6 versus placebo [79].

Combined with ketamine, dexketoprofen before incision reduced morphine consumption and pain compared to postincision dosing [80]. Preoperative diclofenac reduces postcraniotomy headache and postoperative analgesic requirements through 5 postoperative days [81]. Two grams vitamin C preoperatively has a significant opioid-sparing effect. One gram for 50 days perioperatively reduces CRPS risk [82].

Intravenous magnesium 15 mg/kg/hr. started 15 min before anesthetic induction had a significant analgesic and opioid-sparing effect after abdominal hysterectomy. Reduced serum beta-endorphin concentration was also reported [83]. Applying low-level laser therapy to surgical wounds reduced biochemical markers and temperature consistent with anti-inflammatory effects. Pain and seroma were reduced [84].

Central sensitization can be blunted by ketamine. Gabapentinoids and dexmedetomidine may also be useful drugs for multimodal analgesia. Optimal multimodal analgesia

may consist of preoperative acetaminophen and NSAID plus some form of local anesthetic block, either wound infiltration or regional anesthetic. Gabapentin may be an alternative to NSAIDs when NSAIDs are contraindicated. Ketamine may be a drug to use for chronic pain prevention. Gabapentinoids treat neuropathic pain by blocking presynaptic calcium channels. Ketamine and magnesium treat neuropathic pain by blocking N-methyl-D-aspartate receptors (NMDA receptors). Intraoperative ketamine reduced opioid consumption by 1/3 in patients after spine surgery with coexisting opioid dependence [85]. After 6 months, pain, opioid use, and disability remained less in the ketamine group.

Another option to consider is the partial opioid receptor agonist-antagonist buprenorphine. A study by Dahan et al. found buprenorphine to have a ceiling effect for respiratory depression compared to full opioid agonists that do not. A ceiling effect for analgesia, on the other hand, was not observed [86]. Perhaps, buprenorphine should be a first-line opioid for acute postoperative pain in opioid-naïve patients. If patients develop substance use disorder after surgery, converting to a buprenorphine preparation for addiction would be easier than transitioning from a full agonist to buprenorphine/naloxone.

The differential diagnosis of inadequate analgesia after surgery includes inadequate analgesic treatment but also opioid-induced hyperalgesia, tolerance, acute neuropathic pain, and acute opioid withdrawal. Reducing opioid doses may improve hyperalgesia. Ketamine may reduce hyperalgesia by NMDA receptor blocking effects. Tolerance may be treated by increasing opioid doses, opioid rotation, and adding adjuvant analgesics. Acute neuropathic pain may be treated with gabapentinoids and topical lidocaine. Acute opioid withdrawal should be treated by avoiding abrupt opioid dose reductions and treating associated symptoms such as nausea, anxiety, and diarrhea.

The number of opioid doses prescribed for postoperative pain after discharge has become a target for reducing long-term opioid use. Between 2004 and 2012, the percentage of patients being prescribed opioids and the doses prescribed increased after surgery for carpal tunnel syndrome, laparoscopic cholecystectomy, and inguinal hernia repair and knee arthroscopy.

Recommendations for number of doses of oxycodone 5 mg or hydromorphone 2 mg have been made. Five doses are recommended for patients after thyroidectomy, breast biopsy, or lumpectomy or lymph node biopsy. Ten doses are recommended for laparoscopic cholecystectomy, laparoscopic appendectomy, inguinal or femoral hernia repair, and incisional hernia repair. Fifteen doses are recommended for ileostomy or colostomy creation, resiting or closure, open or laparoscopic colectomy, vaginal hysterectomy, laparoscopic or robotic hysterectomy, and abdominal hysterectomy. Twenty doses are recommended for open bowel resection, simple mastectomy, and wide local excision with or without node biopsy [87].

The physicians for responsible opioid prescribing petitioned the Food and Drug Administration (FDA) in 2012:

1. To strike the term “moderate” from the indication for noncancer pain
2. To add a maximum daily dose, equivalent to 100 milligrams of morphine for noncancer pain
3. To add a maximum duration of 90 days for continuous (daily) use for noncancer pain

Chronic Pain after Surgery

Iatrogenic neuropathic pain is a significant source of chronic postoperative pain [88]. However, surgery is often used as a treatment for pain, and patients tend to associate pain with surgery even though they had the same pain or pain in the same location before surgery.

Chronic pain after common surgeries:

- Limb amputation 30–85%
- Knee arthroplasty 13–44%
- Caesarian section 6–55%
- Cholecystectomy 3–50%
- Craniotomy 0–65%
- Hip replacement 27%
- Inguinal hernia repair 5–63%
- Laminectomy and spinal fusion 10–40%
- Mastectomy 11–57%
- Coronary bypass surgery 30–50%
- Thoracotomy 5–65%

Risk factors for chronic postoperative pain include younger age, less education, financial secondary gain, smoking, medical comorbidity, preexisting disability, longer surgery, surgical complications, preoperative pain, intense postoperative pain and postoperative pain greater than 5 days, anxiety, depression, pain catastrophizing, and pain interference. Other factors are female gender, living alone, unemployment, higher body mass index, nerve injury, and no regional anesthesia [89].

Preoperative chronic pain, history of opioid analgesic use, anxiety, depression, pain catastrophizing, and surgery associated with neuropathic pain, such as thoracotomy and amputation, have also been identified as risk factors for chronic postoperative pain [90]. A history of poor pain control in the hospital may be another risk factor.

Primary prevention of chronic pain is possible by avoiding surgery or minimizing surgery with smaller incisions and nerve-sparing techniques. Avoiding surgery altogether may be a good strategy if surgery is elective and the patient is at high risk for chronic pain after surgery [90].

It was found in a study by Kalso et al., postmastectomy syndrome is less common in high-volume practices compared to lower-volume practices. This can be attributed to the intercostobrachial nerve being sparred in 42% of the cases in high volume practices and only 10% in low volume practices. Phantom breast sensations occurred in 26% of cases at high volume centers versus 66% at low volume centers [91]. While another study by Petersen et al. identified more than three times as many patients have severe pain after a second knee replacement compared to initial arthroplasty [92].

Prehabilitation prior to surgery may improve outcomes including pain. Secondary prevention can be achieved with aggressive treatment of inflammatory pain and

nerve injury pain postoperatively. Tertiary prevention can be targeted by treating chronic pain with both pharmacological and nonpharmacological therapies [93, 94].

Failed back surgery syndrome occurs in as many as 20.6% of patients [95]. The incidence of chronic pain in liver donors was 31% 6 months after surgery and 27% 12 months afterwards. Seventeen percent of patients had chronic pain after laparoscopic colorectal surgery, and 21% had chronic pain after emergency laparotomy. After breast reconstruction, 23% had pain after 12 months. The incidence of postmastectomy pain is 30–60%. Forty-three percent of patients have pain 3 months after cardiac surgery. After laparoscopic or vaginal hysterectomy, 26% have pain 6 months after surgery. Inguinal hernia surgery is associated with chronic pain in 43% for patients between the ages of 18–40 years after 1 year, 29% for 40–60-year olds and 19% for patients over 60 years of age. After total knee arthroplasty, 58% have pain. Twenty-two percent have moderate to severe pain and 11% have neuropathic pain. Postthoracotomy pain occurs in 57% at 3 months, 39–56% at 6 months, and 50% after 1 year. Thirty-seven percent of patients have pain after robot-assisted thyroidectomy after 3 months [96]. Another study found that neuropathic pain after thoracotomy occurs in 66% of patients and 68% after breast surgery. Thirty-one percent after inguinal hernia surgery, 31% after hip arthroplasty and 6% after knee replacement [97].

To combat neuropathic pain, agents such as venlafaxine and duloxetine have shown positive outcomes. Venlafaxine 37.5 mg reduced the incidence of postmastectomy at 6 months. Gabapentin helped with the burning component [98]. Duloxetine reduced pain after total knee replacement surgery [99].

In one study, 3 months after surgery, 6 out of 22 patients in the placebo group had pain versus 2 out of 21 in the duloxetine, but this was not significant. Another study observed an opioid-sparing effect with duloxetine through 3 months postoperatively [100]. Gabapentin is more effective than ketamine in preventing chronic pain after hysterectomy, but both have an opioid-sparing effect with acute postoperative pain [101]. Postthoracotomy pain was not reduced by ketamine [102]. However, pregabalin is effective at reducing postthoracotomy pain [103]. Studies of intravenous lidocaine, to prevent chronic pain, are inconclusive according to a recent Cochrane review [104]. Regional anesthesia has been associated with long-term analgesic benefit following laparotomy, caesarian section, and cardiac surgery [105, 106]. However, in other studies, regional anesthesia in patients undergoing gynecologic surgery and inguinal herniorrhaphy had no long-term analgesic effects observed [107, 108].

Wound infiltration and intercostal nerve block have not had a preventative effect in patients having surgery for breast cancer [109]. However, paravertebral blocks have shown a preventive effect in two trials. A study of paravertebral block before breast surgery showed a reduction of postmastectomy pain 12 months after surgery [110]. And another study of paravertebral blocks shows a reduction in the incidence of postmastectomy pain 4–5 months after surgery [111].

Epidural analgesia preoperatively reduces postthoracotomy pain 6 months after surgery more than epidural analgesia initiated after surgery. Both techniques were more effective compared to intravenous patient controlled analgesia (PCA) [112]. Epidural analgesia is more effective than cryoanalgesia 12 months after thoracot-

omy for allodynia, moderate to severe pain and interference with daily activity in thoracotomy patients [113]. Epidural anesthesia and paravertebral block may prevent persistent postoperative pain after thoracotomy and breast cancer surgery, respectively, in about one out of every four to five patients treated [114]. Epidural injection of 100 IU calcitonin reduced phantom pain, allodynia, and hyperalgesia through 1 year after lower limb amputation [115]. Preventive nefopam reduced chronic pain 3 months after breast cancer surgery [116].

A comprehensive evaluation and management approach has been advocated for chronic postoperative pain [117]. However, long-term pain relief is possible with simple acute interventions, such as timing analgesic doses to coordinate with physical therapy, focusing on ambulating 8 steps as rapidly as possible, and treating constipation, delirium, and nausea and sedation aggressively [118]. Additionally, multimodal combinations need to be studied to determine which combinations are optimal and which combinations have the optimal risk benefit ration and which combinations are cost-effective [119].

Preventing Chronic Pain Secondary to Opioid-Induced Hyperalgesia

Opioids may inhibit their own analgesic effect by tolerance and hyperalgesia. Metabolites may antagonize analgesic effects. Analgesia can reduce the stimulatory effect pain has on respiration. These effects may drive addictive behavior and overdose risk [120].

Opioid treatment may cause or aggravate other disease states, including hyperalgesia, respiratory failure, substance use disorder, depression, and chronic pain. Long-term opioid use has a drug-opposite response such that the initial euphoria associated with acute opioid use results in a negative mood response [121].

In patients with narcotic bowel syndrome, detoxification was associated with pain reduction. Continued opioid abstinence was associated with additional pain reduction, while opioid relapse was associated with increasing pain [122]. This paradoxical pattern may illustrate opioid-induced hyperalgesia and pain related to constipation. Avoiding opioids for chronic pain may be the most effective method to avoid opioid-induced hyperalgesia.

The Harvard health website endorses multiple nonopioid treatments for pain [123]:

- Cold and heat
- Exercise
- Weight loss
- Physical therapy (PT)
- Occupational therapy
- Transcutaneous electrical nerve stimulation (TENS)
- Iontophoresis
- Ultrasound

- Cold laser therapy
- Therapeutic massage
- Chiropractic
- Acupuncture
- Psychotherapy
- Topical pain relievers
- Over-the-counter medications
- Herbal or nutritional pain relievers
- Nonopioid prescription drugs
- Corticosteroid injections
- Yoga and Tai Chi
- Mind body techniques:
  - Meditation
  - Mindfulness
  - Progressive muscle relaxation
  - Breathing exercises
  - Hypnosis therapy
  - Biofeedback
- Pain-relieving devices:
  - Splints
  - Braces
  - Canes
  - Crutches
  - Walkers
  - Shoe orthotics

Measures to reduce opioids and the other adverse consequences of opioids are gaining in popularity. In a study by Nguyen et al., reducing opioids before total joint arthroplasty is associated with improved outcomes 6–12 months postoperatively [124]. Opioid tapering, in the hospital after surgery, as a part of an interdisciplinary pain program, has been effective as well [125]. In a randomized trial in patients with chronic pain, a taper support program using cognitive behavioral therapy, opioid doses were reduced without increasing pain [126]. Pain, function, length of stay, and quality of life were improved with this approach.

Summary

- A healthy lifestyle can reduce the incidence and severity of pain. Maintaining a healthy body mass index and eating whole grains, fruits, and vegetables have multiple health benefits, including possible pain prevention.
- Moderate exercise prevents pain.

- Safety measures such as wearing helmets while cycling and skiing and seatbelts while driving have become law in many countries. It is unknown if self-driving cars or driver-assisting technology will improve safety.
- Pain-prevention treatments can prevent chronic pain after trauma and surgery. Patient education about pain prevention and changing clinical practice to incorporate evidence-based pain prevention strategies into routine care should have a significant impact on the incidence and severity of acute and chronic pain.

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Chapter 33
Chronic Pain within the Refugee Population: Evaluation and Treatment

Peter B. Polatin

…..being a refugee is just being cast by life- being thrown out of your home, and looking for a home now. And it can take ages. You can spend your whole life moving around…..Refugee is (a term) for the people that were thrown out by war and who have been uprooted from their countries….But a refugee is a person just looking for home and safety.
ASAM HUSSEIN, 22, SOMALI, Born in Dadash refugee camp, Kenya; arrived
U.S. 2018 to study at Princeton University

Refugee and immigrant are very different. A refugee is someone ejected from his or her past, who has no future, whose present is totally empty of meaning. In a refugee camp, you live outside of time—you don't know when you're going to eat, let alone when you're going to get out of there. And you're also outside of space because the camp is no man's land. To be a human being you have to be part of something…….

KIM THUY, Refugee and Writer (titles: Ru, Man, Vi).

Introduction

A refugee (or "forced migrant") is an "externally displaced" individual. This is defined as "someone who has been forced to flee his or her country because of persecution, war, or violence" [1]. In 2017, there were 68.5 million refugees in the world, of whom over 50% were under the age of 18 [2]. In 2016, almost 85,000

P. B. Polatin (✉)
International Rescue Committee, Dallas, TX, USA

Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA

Harvard Program in Refugee Trauma, Cambridge, MA, USA

Global Mental Health, Department of Psychiatry, George Washington University, Washington, DC, USA

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persons were admitted as refugees to the United States, and 48% of them were under the age of 21 years [3].

There is an enormous difference between immigrants and refugees. Immigrants electively choose to move to a new place for a better life, although frequently under duress, and may carry substantial resources with them. Refugees have no choice but to move, and have very little if any resources. The suffering documented in this group of individuals is very high, and includes experiences of physical violence, sexual violation, emotional traumatization, and overwhelming losses [4].

The first phase of suffering takes place in their country of origin, where they endure and then flee from war, genocide, persecution, and lack of humanitarian protective safeguards. The second phase occurs during their flight, which can include journeys of great danger and hardship, and then prolonged periods of time in refugee camps with extremely poor living conditions and the potential for additional physical harm. Suffering continues into the third phase, upon arrival at their asylum destination, where they face the challenges adapting to new customs, learning a new language, and finding and sustaining support for themselves and their families, many of whom may not yet have made the journey and require survival assistance from those that have. Additionally, as the numbers of refugees have increased, countries that were previously friendly destinations have become more restrictive, and refugees are frequently greeted with hostility, discrimination, and exclusion [5, 6].

Resettled refugee youth and their families face a host of substantial adversities [7]. A recent review [8] indicates that as many as half have had diagnoses of PTSD and a third have depression or anxiety. Emotional and behavioral problems without diagnoses are reported in as many as a third. There is a well-documented comorbidity between PTSD, depression, and chronic pain within the refugee population [9–11].

Cultural Competence in Treating Refugees

Treating a refugee or any other patient from a different culture requires "cultural competence," a term that refers to *"the ongoing process in which the health care provider continuously strives to achieve the ability to effectively work within the cultural context of the client (individual, family, community)"* [12]. Issues of health-care quality and satisfaction are particularly relevant for patients with long-term conditions such as chronic nonmalignant pain, who seek out and are compliant with care only if they feel comfortable with their health-care providers [13].

In treating patients from another culture, the clinician faces multiple challenges [14], particularly inadequate communication and understanding. There may be culturally determined differences regarding such things as eye contact and vocal intonation. A perceived uncomfortable power differential between the patient and the provider may block open communication. There may be certain taboos, particularly around gender issues (such as touching, examining, or even shaking

hands with a patient of the opposite sex). These patients can be, from past experience, particularly sensitive about perceived discrimination. There may be a lack of understanding of such conventions as confidentiality (particularly within family dynamics). Prior adverse and sometimes abusive experiences with health-care providers may have resulted in lack of trust. In some cultures, patients are accustomed to receiving a pill or an injection, and judge their care as inadequate if they do not. Clinicians must also be aware of the impact of such practices as religious fasting and traditional medicines being used but not disclosed, and how this might interact with prescribed remedies. Ethno-pharmacology, that is, ethnic differences in drug tolerance and response [15], must be kept in mind when medications are prescribed. For example, many Asian patients have a potential hypersensitivity to selective serotonin reuptake inhibitors (SSRIs) and need to be started on very low doses [16]. Additionally, patients may be communicating with family and other community figures such as traditional healers and spiritual leaders, both locally and back in their country of origin, and if so it is important to find out what they are being told.

To understand the expression of symptoms associated with chronic pain among refugees from different cultures, the clinician will require an enlarged cultural perspective, either through independent study or, more optimally, by utilization of a "culture broker," a resource person who can help to interpret the cultural meaning of illness behavior and healing, over and above linguistic interpretation [17]. Unfortunately, culture brokers are not commonly available within Western health-care settings, although standards have been proposed to provide "effective, equitable, understandable, and respectful quality care and services that are responsive to diverse cultural health beliefs and practices, preferred languages, health literacy, and other communication needs" [18, 19].

Understanding the Etiology of Chronic Nonmalignant Pain in Refugees

It is important for the clinician to be aware of the high rates of physical and emotional traumatization among refugees. Almost 50% of adult refugees entering the US have experienced or have an immediate family member who has experienced severe forms of persecution, including incarceration and physical punishment, with the clear result of poorer health status in general [20]. Over and above the increased incidence of chronic pain in association with emotional distress [21], many of them have been physically brutalized in different ways, including torture; cruel, inhuman, or degrading treatment (CIDT); collective or organized violence; rape; and stigmatization with social isolation. In a recent systemic review of the literature, Sigvardsdotter found that the experience of torture ranged up to 76% (median 27%) [22]. As many as 87% of torture survivors have residual chronic pain as a result of being tortured [23, 24].

If there are findings on the physical examination, the clinician's ability to diagnose the etiology of a pain complaint may be relatively unimpeded. However, certain cultures may or may not acknowledge emotional distress as a health issue because of stigmatization of mental illness, or alternative idioms of distress which are culturally specific [25]. Some patients may be "culturally alexithymic" [26] and express emotional distress as somatic symptoms, most frequently pain. This is commonly seen in some Asian, African, and Latin American cultures [27, 28].

However, it would be wrong for the clinician to dismiss a refugee patient's presentation as "somatic" without exploring the history in full detail. This includes "digging" for information about both physical and emotional traumatization. Typically, except in the case of asylum seekers who understand the importance of documenting torture, most refugees who have suffered from emotional and/or physical traumatization are not comfortable discussing their experiences unless they feel safe and secure, and have developed a trust in the health-care provider [29, 30]. Unless this kind of relationship exists with at least one person on the treatment team, telling and retelling the "trauma story" can be an extremely disturbing experience for the patient [31].

Common Presentations of Pain Aamong Refugee Patients Who Have Been Tortured

Torture and the ways in which violence may be inflicted will determine the location and type of chronic nonmalignant pain among refugees. A comprehensive review is offered by Quiroga and Jaranson [32], who cite the residual chronic pain as presenting as nociceptive regional syndromes, neuropathic presentations as a result of injuries to the brain or peripheral nervous system, or psychosomatic patterns of pain. Among the regional syndromes, they mention trauma to the ears or nose resulting in residual tinnitus, hearing loss, dizziness, or blocked nasal passages (from "telephono," a torture technique in which the victim sustains a hard slap to one or both ears, rapidly increasing the pressure in the ear canal and rupturing the tympanic membrane). Acute rhabdomyolysis from massive tissue trauma may present as a compartment syndrome. Others have documented the physical sequelae of torture. Amris [33], in a study of 48 survivors of torture (SOTs) from the Middle East, classified their residual pain by body region frequency (as shown in Table 33.1).

Goldfield et al. [34] described the frequency of torture methods in a sample of 319 SOTs (Table 33.2).

If we review these two tables side by side, it is fairly easy to imagine and clinically search for the pain syndromes that might result from a particular torture experience. For example, falanga (also known as "foot whipping" or "bastinado") consists of the beating on the bare soles of the feet with a light cane, knotted cord,

Table 33.1 Residual pain in survivors of torture by body region frequency

Body region	Percentage (%)
Feet	53
Lower extremities	71
Lower back	87
Neck and shoulder girdle	93
Thorax, including spine	38
Upper extremities	54
Headaches	93
Three or more regions	63

Table 33.2 Torture methods used and their frequency

Method of torture	Frequency in samples of SOVs (%)
Medicine administration	3.8
Throwing urine or feces on victims	5
Lifting by hair	2.5
Forced standing	5.9
Telephono	7.2
Rope bondage	9.4
Falanga	9.7
Burning	13.7
Sexual torture	13.8
Hanging	14.1
Sleep deprivation	15.4
Starvation	15.7
Isolation	15.7
Water asphyxiation	16.9
Mock execution	27.9
Blindfolding	32.9
Electric torture	46.7
Threats	77.1
Beating	100

or lash. It has a long history, was commonly practiced in Europe up through the 1950s, and is used today in the Middle and Far East. It results in chronic pain in the feet and lower legs and a compensated gait pattern, with severe pain when walking. These patients also have reduced light touch and thermal sensation, tactile dysesthesia, allodynia, and tenderness to palpation [35]. Another torture technique is called "strappado" (or "corda," "Palestinian hanging," or "reverse hanging"), in which the victim's hands are tied behind his back after which he is suspended by a rope attached to the bound wrists, typically resulting in dislocated shoulders and if he survives severe residual shoulder, neck, and upper body pain. Pollanen describes a case of fatal rhabdomyolysis after Palestinian hanging [36].

The Istanbul Protocol [37] is a detailed manual on the effective investigation and documentation of torture and other cruel, inhuman, or degrading treatment or punishment, providing detailed instructions on the physical and psychological evaluation of a SOT, and a chronicled list of possible findings. It is the accepted reference for the medical documentation of torture for purposes of defining human rights abuses and the need for asylum, but is also an excellent and comprehensive guide to a thorough evaluation by a health-care provider to understand the impact of torture in an individual case.

Understanding Somatization as a Reflection of Emotional Distress

Rohlof et al. [25] conclude that the well-documented high incidence of somatization among refugee populations is a reflection of general psychopathology, specifically the impact of traumatization and torture, in addition to the stigmatization of psychiatric care. Non-Western patients who present with somatic symptoms are not looking for psychiatric treatment, and without time spent on psychoeducation will reject it when it is offered. Among the most common somatic complaints seen in primary care refugee patients are pain syndromes, such as headaches, stomachaches, low back pain, muscle, joint and bone pain, total body pain, heart complaints, insomnia, weakness, and pelvic pain [38–44]. When the clinician is faced with what appears to be somatization complaints, there are certain differential diagnostic hypotheses that should be entertained: traumatization (both physical and emotional), adverse life events, psychopathology (depression, PTSD, and generalized anxiety disorder), and specific culturally determined "idioms of distress" [45, 46]. Proceeding with a physical intervention for a stated pain problem whose etiology is somatic will almost always have a poor outcome, unless mental health and educational issues are addressed [47].

Traumatic Brain Injury in Refugees

A high incidence of traumatic brain injury (TBI) has been consistently reported among refugees who have experienced torture, war trauma, or mass violence [48–53]. TBI in this patient group has been found to be associated with a higher number of somatic complaints and greater severity of PTSD symptoms [54]. Additionally, depending upon the severity of the resulting cognitive deficit, TBI may require modifications in the treatment approach for chronic pain, particularly around psycho-education and cognitive behavioral therapy. Problems with memory, emotional lability, and functional potential must be factored into treatment planning.

"Metabolic Syndrome" as an Outcome of Traumatization

Metabolic Syndrome (MetS) is defined as a constellation of risk factors, including abdominal obesity, hypertriglyceridemia, low HDL-C, elevated fasting glucose, and hypertension. These factors are seen together frequently in victims of severe emotional and physical traumatization [55, 56], particularly torture [32], and place the patient at an increased risk for diabetes and cardiovascular disease [57]. Refugees constitute a high-risk group for MetS, particularly if their experiences of high levels of stress are not adequately addressed, along with education about dietary and life style factors. If this syndrome develops, it can only exacerbate pre-existing pain complaints, and add additional risk for obesity-associated low back and hip pain, neuropathic pain secondary to diabetes, and the potential for angina as hypertension and cardiac insufficiency develop.

Retraumatizing "Triggers" for Refugees within Primary Care and Pain Management

Refugees may have had prior disturbing experiences with health care, institutional settings with small rooms, and high levels of noise and activity typical of an emergency room setting or a busy medical practice. The processes of being questioned by a health-care provider, undergoing a physical examination, having diagnostic procedures such as phlebotomy or X-rays, receiving injections or electrodiagnostic interventions, being tightly enclosed for MRI or CT imaging, being in an examination room in which medical equipment is displayed, all have the potential to increase the patient's level of anxiety. It is important for the provider to try to ensure as comfortable and quiet an environment as possible and to anticipate the possibility of a retraumatization experience that may be precipitated by something in the treatment milieu [58].

Clinical Case Reports

1. CS is a 49-year-old Congolese female, interviewed in Kiswahili with the help of a translator. She has been in the US for 18 months and has been given asylum. On initial evaluation, she complains of pelvic, low back, and abdominal pain, hypermenorrhea, insomnia, nightmares, flashbacks, panic attacks, depression, hypertension, and tachycardia. She was married and had five children. Her village was attacked by an army from a warring tribe, and she witnessed the murder of her husband and three of her children, and was raped multiple times. She escaped into the "bush" and fled to Tanzania under conditions of extreme hardship and danger. She spent 2 years in a refugee camp there, where

she received medical care for her pelvic lacerations and vaginal bleeding. She describes the conditions in the camp as difficult. The women who were unaccompanied slept in tents and had their own latrine, but many were afraid to go out at night to relieve themselves, for fear of being raped. Food was scarce and safety was a concern at all times. She came to the US 6 months ago, alone. Her two surviving children remain in Congo. She stays in touch with them, but is very worried about their safety. Because of her perceived health status, she has been taken in by a sympathetic couple who helps care for her. She refuses medication, prescribed by a general physician, gynecologist, and psychiatrist, but uses her own remedies (garlic, honey, and brandy). Her pain has diminished, but she still has some vaginal bleeding. She carries the diagnoses of pelvic pain, low back pain, depression, and PTSD. Although she refused much of the medical treatment offered to her, she was willing to engage in psychotherapy. She has subsequently completed a course of psychoeducation and trauma-focused cognitive behavioral therapy and has told and transcribed her trauma story. While she remains symptomatic with residual panic attacks and occasional nightmares, she is able to hold a job, and is looking forward to her children's arrival to join her. She refuses any further evaluation or treatment for pain mitigation.

2. HH is a 33-year-old Iranian male interviewed with a translator. He complains of chronic back pain and bilateral upper extremity pain, as well as auditory hallucinations. He arrived in the US 6 months ago, after escaping from Iran and spending 3 years in a refugee camp in Turkey. In Iran, he was a political protester, organizing and participating in demonstrations against the government. He was imprisoned and tortured, including Palestinian hanging, frequent beatings, and blows to the head, with several periods of unconsciousness. While in Turkey, he was evaluated and treated by a psychiatrist, who prescribed an antipsychotic medication which reportedly improved his mental status. At the present time, he complains of limited use of his arms, with pain and crepitus in his shoulder, nonradiating low back pain, difficulty with memory and concentration, nightmares, flashbacks, panic attacks, and depression. He hears voices telling him to kill himself, and has attempted suicide several times with overdoses of over-the-counter medication. He has been hospitalized in a psychiatric unit twice, but says that the medication that is prescribed makes him ill, although it diminishes his psychotic ideation. He was referred for orthopedic evaluation, but refuses to go. He has also been referred for physical therapy, and did attend one session, but had a panic attack and had to leave. He is noncompliant with prescribed medication and there is a high level of concern that he may intentionally overdose again. He attends a community mental health center, but translation services are not consistently available and so he has stopped going.
3. JHM is a 31-year-old Iraqi male who worked with the US military. He and his family were threatened by the ISIS and were evacuated to the US. He lives with his wife and three children, ages 3, 5, and 9 years. While serving as a translator for the US military, he witnessed multiple incidents of engagement and violence. He, himself, was blown up by a roadside bomb while in a military vehicle, and sustained multiple bruises and lacerations, but was not unconscious. He is inter-

viewed with a translator but, in fact, speaks serviceable English. He complains of low back pain radiating to the left foot and neck pain, as well as insomnia and panic attacks. He is now trying to work as a stocker on the evening shift, but worries about security at the work place, as well as the safety of his family when he is away. He expresses disappointment at his life in the US, and feels alienated from other Iraqi immigrants, who regard him as a perpetrator of the war atrocities. He admits that he has struck his wife several times when she berates him for not having a better job. He has been drinking up to six beers a day, and smoking two packs a day. He has seen an orthopedist and had a lumbar MRI demonstrating a herniated disk to the left at L5-S1. After the experience of the first MRI, he refused the second one for his neck. He has been offered a lumbar epidural and physical therapy for his back pain, but has refused both. He has also refused an appointment with a psychologist. He carries the diagnoses of chronic lumbar radicular pain, chronic cervical pain, and probable PTSD. There is also concern about domestic violence and alcoholism.

What is illustrated in these cases is the following: (1) High levels of physical and emotional traumatization; (2) Difficulty engaging in treatment for a variety of reasons (distrust, alienation, and fear); (3) Psychiatric symptoms that interfere with a sense of safety and the development of a therapeutic relationship; (4) Problems accommodating refugee care and needs within the Western health-care system at the present time due to lack of cultural competence, available translation services, and lack of patient understanding of what health-care providers have to offer.

Refugees are best served when their needs are addressed from the "bottom up", that is, safety and security, a place to live, a means of support, a relationship of trust and empathic understanding, language and vocational training, family engagement, and health education which incorporates cultural competence and reassurance. Providers must reach out, either by personally becoming aware of cultural issues or by utilizing a "culture broker." The key tool to a seamless management of the health of refugees, including pain management, requires comprehensive case management, which embodies the "bottom-up approach." Too often, these services are not available, and refugees subsequently suffer at the bottom of the social ladder, receiving neither the integrative services required nor the health care that is necessary for their transition to productivity.

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Chapter 34
The Future of Pain Therapeutics

Candler Paige, Stephanie Shiers, and Theodore J. Price

Individualized Approaches

Chronic pain manifests itself differently in most patients. Since it is clear that the experiences and symptoms of pain patients are largely heterogeneous, personalized pain medicine that focuses on the individualized needs of each patient will likely become standard in the treatment of chronic pain. Technological advancement in diagnostic tools, such as next generation sequencing, will likely also transform our ability to recognize specific pain mechanisms in individuals. This will hopefully allow for tailoring of therapeutic regimes that have the best chance of achieving efficacy.

Diagnostic Tools

One challenging aspect of treating chronic pain is the lack of quantitative diagnostic tools. We are not aware of any currently existing lab tests that can be used to diagnose pain magnitude or specific molecular mechanism for any kind of chronic pain. A set of predictive and accurate diagnostic tools would be useful for both health care practitioners trying to diagnose and accurately treat a chronic pain state and for patients that have difficulty finding treatments for their pain.

C. Paige · S. Shiers · T. J. Price (✉)
School of Behavioral and Brain Sciences and Center for Advanced Pain Studies, University of Texas at Dallas, Richardson, TX, USA
e-mail: cap150130@utdallas.edu; sis150030@utdallas.edu; theodore.price@utdallas.edu

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Quantitative Sensory Testing

Quantitative sensory testing (QST) uses a set of well-defined psychophysical tests to assess the function of the peripheral (PNS) and central nervous systems (CNS) [1]. This battery of tests includes pin-prick testing, von Frey testing, both cold and hot thermal thresholds, vibration threshold, and pressure threshold testing [2]. While the goal of obtaining a phenotype-based sensory profile for chronic neuropathic pain patients has existed for decades [3], this approach has been difficult to apply in clinical practice because the phenotypic sensory profiles of chronic pain patients are quite heterogeneous. For instance, the QST manifestations of neuropathic pain, as well as fibromyalgia and various musculoskeletal pain conditions, are different among most patients [1]. In contrast, recent work has focused on using QST to determine the mechanism underlying chronic pain [4], and this approach is likely to be useful in determining the best treatment method for each individual patient. Along these lines, the German Neuropathic Pain Network has collected QST profiles of hundreds of neuropathic pain patients allowing them to create patient clusters organized by mechanism-based phenotypes. These phenotypes can then be used to stratify or enrich clinical trial cohorts to assess drug-efficacy in specific QST clusters [5]. As this line of work continues to progress, it is likely that QST profiles can be used to determine best courses of pharmacological treatment for individuals.

Skin Biopsies

Skin biopsies are 3 mm wide punches of tissue which can then be stained to identify epidermal nerve fibers that are then quantified [6]. This technique has been used routinely to diagnose patients with small fiber neuropathy (SFN) [7], but additional diagnostic applications have been limited. More recently, skin biopsy has been used to identify underlying pathology in diabetic neuropathy [8], transthyretin familial amyloid polyneuropathy [9] and chemotherapy-induced peripheral neuropathy [10]. There is also evidence that skin biopsy may be used to identify neuropathy that may underlie fibromyalgia [11]. While skin biopsy has shown promise as a diagnostic tool for detecting signs of neuropathy in several chronic pain conditions, it is important to note that the biopsies are only able to identify changes in the PNS that may not reflect pathology that can occur in the CNS [1]. While this technology has traditionally been used simply to stain for nerve fibers, or other types of skin cells, advancements in multiplexed antibody and RNA detection technologies make it possible that this very old technique might be used in the future to examine very specific molecular markers of disease mechanisms in peripheral nerve fibers.

fMRI Imaging

Functional magnetic resonance imaging (fMRI) in pain patients has been used as a research tool to understand the impact of pain on the brain. One example of the use of fMRI in pain research is the identification of many brain areas, sometimes

referred to as the "pain matrix" that are activated by noxious stimulation of peripheral tissues in volunteers and chronic pain patients [12]. While this systems level approach has provided vital information for how pain impacts brain function, it is still controversial whether this method can be used to identify a brain-based biomarker approach for measurement of pain intensity. There are, however, other approaches that demonstrate the utility of potentially using fMRI to diagnose and treat chronic pain patients. One promising possibility is the decrease in grey matter density found in many patients suffering from neuropathic pain and fibromyalgia [13–15]. Because these grey matter changes that are identified through fMRI imaging can be reversed following effective pain treatment, [16] they could potentially be used to assess treatment efficacy in certain patient populations. In addition to structural biomarkers identified through fMRI, other groups are currently using advanced network analyses to determine the brain regions responsible for individual pain experience. This approach may prove useful in determining pain mechanisms, pain intensity, and even treatment efficacy in the future [12].

Defining Pain Types in the Clinic Using these Technologies

The diagnostic tools described above can be used to gain insight into pain mechanisms and, potentially, treatment efficacy in individuals. As these tools are further developed and validated, we will begin to gain a clearer picture of their utility in the day-to-day practice of pain medicine. Advances in our understanding of how QST can be used to predict drug efficacy and underlying mechanisms of neuropathic pain are already fairly advanced and continuously progressing. Applying this basic knowledge to clinical practice is straightforward and likely to benefit most patients. Skin biopsy is an underutilized tool where advances in molecular diagnostics have simply not kept up. We propose that this is an area ripe for further development that can greatly augment our understanding of molecular mechanisms driving chronic pain in individuals. It will likely be particularly useful in patient populations where an "irritable nociceptor" phenotype can be identified by QST.

Brain imaging holds great promise as a diagnostic tool and as a method that can be used to determine treatment efficacy. While fMRI is still primarily used as a research tool, structural MRI is now widely applied in clinical settings. Identifying subtle brain structural changes in individuals has been a challenging area for clinical application, but informatic technologies combined with the proliferation of large normative datasets has the potential to change the way this technology can be applied in a personalized medicine approach to pain.

Genetics: DNA Sequencing

In the past two decades there has been a revolution in so-called next generation sequencing technologies. These technological advancements make it possible to cheaply and rapidly sequence genomes, placing sequencing technologies at the

forefront of discovery in clinical medicine. While developments in DNA sequencing technology have not yet revealed a single "pain gene" (and almost certainly will not ever reveal one), important genetic polymorphisms that have dramatic effects on pain phenotypes in people have been found [17]. Perhaps the best example is single nucleotide mutations in the SCN9A gene that encodes the voltage-gated sodium channel (VGSC) gene Nav1.7. Many gain-of-function mutations in the Nav1.7 channel have been discovered that cause a painful small fiber neuropathy [18]. In contrast, loss-of-function mutations in the SCN9A gene results in congenital insensitivity to pain [19]. Importantly, some recent studies have found that certain SCN9A mutations can cause increased likelihood of developing certain forms of neuropathic pain suggesting that point mutations in important pain genes can cause strong phenotypes in the absence of injury or disease but also enhance the probability of developing a chronic pain disorder with another disease state, like diabetes [20]. Genome-wide association studies (GWAS) have identified potential mutations underlying chronic pain states such as those with chronic low back pain [21]. As DNA sequencing becomes more common and more affordable, it is likely that this can be used as an additional tool to develop a personalized approach for diagnosing and treating chronic pain (Fig. 34.1).

Transcriptomics: RNA Sequencing

While DNA sequencing can be used to identify mutations that may lead to rare phenotypes (e.g., congenital insensitivity to pain), or genetic variants that may predispose to more severe pain in certain disease states (e.g., SCN9A mutations in diabetic neuropathy), this technology does not give insight into cell-type-specific changes that may promote pain disorders. The dramatic gains that have been made in DNA sequencing technologies have had a dramatic effect on our ability to also sequence RNA. This technology, now widely termed RNAseq, has great potential to be used to identify biomarkers of pain and/or pain mechanisms in patient populations (Fig. 34.1). The advantage of RNAseq is that it gives an unbiased and comprehensive picture of gene expression, often called the transcriptome, in individual cell types or tissues. Datasets that are based on human and animal model tissues are rapidly becoming widely available and include databases that focus on finding drug targets unique to different types of pain states [22, 23]. In addition to bulk RNA sequencing data sets, where different types of cells within a tissue are sequenced together, new RNAseq techniques are being continually created to examine single cell transcriptomes in normal and disease states [24]. Looking forward, RNAseq holds great promise because it can be used to gain insight, with astonishing clarity, into cellular changes that are likely the mechanistic drivers of many types of chronic pain. A challenge will be using this technology in the research setting on tissues where access is going to be limited in the clinical situation (e.g., the nervous system) to gain insight into how the technology can best be applied in individual patients. While there is much work needed in this area, it not unreasonable to assume

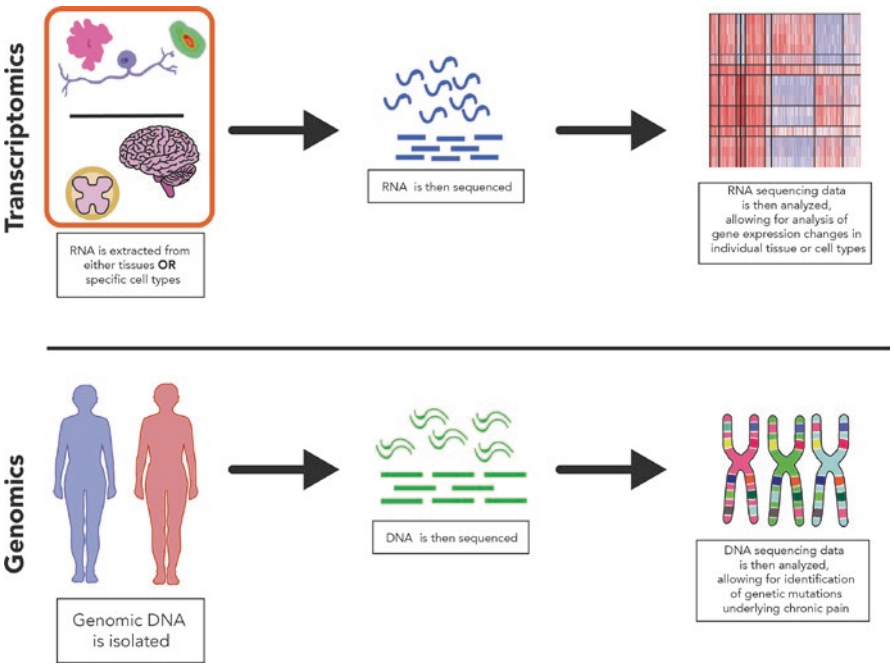

Fig. 34.1 The use of transcriptomics and genomics in the diagnosis of chronic pain. In transcriptomics, RNA is isolated from specific tissue or cell types, and then the sequencing data is analyzed to identify gene expression changes. For genomic analysis, DNA is isolated and sequenced allowing for analysis of heritable genetic changes or mutations resulting in chronic pain states

that RNAseq may be used on standard blood samples or skin punch biopsies to make accurate predictions of disease mechanism or treatment efficacy in the not-so-distant future.

Sex-Specific Therapeutics

While it has been standard practice to include male and female subjects in human research studies for decades, the National Institutes of Health (NIH) only recently mandated that preclinical studies consider sex as an important biological variable. Until this point, the vast majority of preclinical work (mostly rodents) in the neuroscience and pain area had been done in male subjects. Since the implementation of this change, a large number of studies have demonstrated robust differences in the molecular pathways underlying chronic pain in males and females. The most robust findings to date demonstrate that immune cells differentially contribute to chronic pain in males and females [25]. In males, there is now abundant evidence that inhibiting microglial activation and/or activity blocks hyperalgesia in several models of chronic pain, but this microglial inhibition has little to no effect in female

rodents [26–29]. Whether or not microglia play any role in chronic pain in female rodents has yet to be determined, but these studies have also highlighted that very little is known about how chronic pain is promoted in females. One potential mechanism responsible for promoting chronic pain in females is T-cell regulation of neuropathic pain [30]; however, other studies have suggested that T-cells may also play a key role in pain resolution [31, 32] so the complete picture of how T-cells regulate pain in either males or females has yet to be resolved. Importantly, none of these findings have been tested in any detail in humans, but some microglial-targeted approaches have failed in neuropathic pain clinical trials.

This area of research is progressing rapidly. In a relatively short period of time it has become very clear that there may be important differences in how chronic pain develops in male and females in preclinical models. Emerging lines of evidence, mostly relying on RNAseq, suggest that this may also occur in humans. If this holds up with further study, it will have profound implications for the development of chronic pain therapeutics and for the treatment of chronic pain. We posit that it is not unreasonable to assume that the chronic pain therapeutics of tomorrow will be sex specific [23].

New Drug Classes

Drug development has been slow in the chronic pain field, leading to a great deal of angst in relation to the utility of preclinical models. However, many new drug classes are currently in development with some promising early results [33]. Many new types of drugs are currently in clinical trials or are recently Food and Drug Administraton (FDA) approved for use in the clinic.

Biologics: Monoclonal Antibodies

Using monoclonal antibodies to sequester pain-promoting molecules has become a novel drug class to treat chronic pain. In 2018, several calcitonin gene-related peptide (CGRP) or CGRP receptor antibodies were in either late-stage clinical trials or approved for use in treatment of chronic migraine [34–37]. Additionally, nerve growth factor (NGF) antibodies are in clinical development for treating osteoarthritis [38, 39]. Several other monoclonal antibodies for use in the treatment of chronic pain are also in development, including a Nav1.7 channel antibody [40]. While NGF antibodies have shown some concerning safety issues in clinical trials, this new class of drugs has shown to be safe and efficacious in the majority of treated patients. Areas where NGF antibodies have shown efficacy include osteoarthritis, low back pain, and some types of cancer pain. It is possible that this form of biologic will be effective in many different types of chronic pain as preclinical data supports an important role of NGF in nociceptor sensitization across models. An additional advantage of these new types of drugs is that the half-life can be upwards

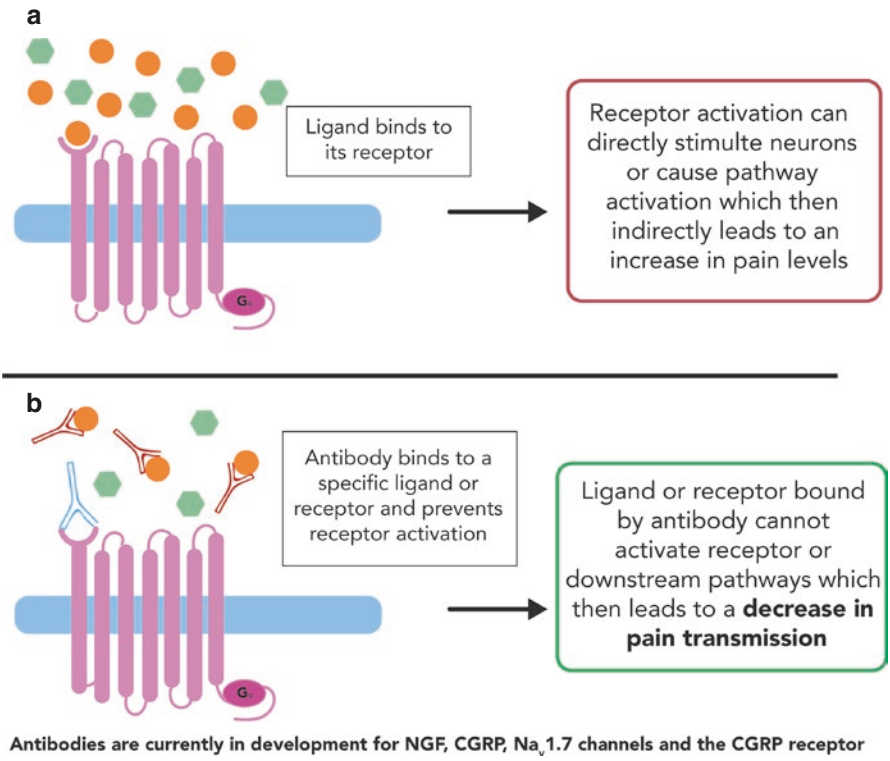

Fig. 34.2 Using antibodies for the treatment of chronic pain. Antibodies can bind to either a ligand or receptor preventing the activation of a pathway involved in pain transmission. Antibodies are being developed or are currently in use for NGF, CGRP, $Na_v1.7$ channels, and CGRP receptors and have been found to be highly efficacious and safe

of 30 days, meaning that dosing only needs to occur monthly. As clinical trials are completed for these drugs, it is likely that more monoclonal antibodies will be available for use as therapeutics in chronic pain patients (Fig. 34.2).

Small Molecules

Based on molecular mechanisms discovered in preclinical research, several new small molecules are in development for use in treating chronic pain. Sodium channels are popular targets for new small molecule antagonists. In a patient population, a Nav1.7 small molecule antagonist has been used to treat pain in inherited erythromyalgia patients [41]. This is a logical target since erythromyalgia is caused by a gain of function mutation in Nav1.7. In preclinical studies, $Na_v1.8$ antagonist have been demonstrated to have efficacy in vitro on human DRGs and in vivo in rat

models of chronic pain [42]. Currently, small molecules specific for $Na_v1.9$ are also being screened as human genetics also support a role of this VGSC in chronic pain.

In addition to VGSCs channels, reactive oxygen species (superoxide) and reactive nitrogen (peroxynitrite) species have both been demonstrated to have a significant involvement in the development of chronic pain [43], and a superoxide dismutase has demonstrated decreased pain levels in osteoarthritis patients that were given the drug [44]. Reactive Nitrogen Species (RNS)- and Reactive Oxygen Species (ROS)-modulating small molecules (sequestering and decomposing agents) are currently in development for use in treating chronic pain. Many other targets are constantly under development for the treatment of pain so it is likely that many additional targets with small molecule approaches to drugging the target will emerge. Unfortunately, there have been many recent failures in this specific area of therapeutic development, including TRPV1, NK1, FAAH, and CB1. It remains to be seen if this approach will be able to reach the success that have so clearly been observed in the biologics area.

New Types of Opioids

Opioids remain the most widely prescribed pharmaceuticals used to treat pain, even with the dangerous side effects that these drugs unquestionably possess. In order to address these well-known side effects, many researchers are searching for new classes of opioids. The first of these is peripherally restricted μ-opioid receptor agonists. Peripheral restriction would limit the ability of these drugs to cause respiratory depression and addiction, while still potentially treating a variety of pain conditions [45]. A limitation here is that this approach has yet to demonstrate the efficacy that is likely needed to produce adequate analgesia in patients. Another approach is to use so-called biased agonists of the mu-opioid receptor to induce analgesia without side effects such as reward or respiratory depression. While this approach held great promise in many basic studies, it has thus far not panned out in clinical studies where these biased agonists have caused analgesia but also reward and respiratory depression. It remains to be seen if this approach can be used in the clinic to induce mu-opioid analgesia without side effects.

The above approaches focus on the mu-opioid receptor. A recent focus has been on the kappa-opioid receptor. There are two approaches that are being proposed here, peripherally restricted kappa agonists and centrally penetrant kappa antagonists. The antagonist approach is based largely on some original studies showing that κ-opioid antagonists can have good analgesic efficacy in some animal pain models [46]. More recent studies have focused on how kappa-opioid receptor activation in the brain promotes negative affect with the idea that this is a major problem in many types of chronic pain. Kappa-opioid antagonists may prove to be a safe and effective way to reduce negative pain affect. Another approach is to target the kappa-opioid receptor with peripherally restricted kappa agonists. These drugs would inhibit peripheral nociceptors and potentially reduce pain and/or itch. While much development is still needed in this area, both approaches have shown promise

in preclinical models. Ultimately, until pain therapeutics are discovered, which treat pain as well as opioids, pain researchers will continue to attempt to modify molecules that target the opioid receptors to take advantage of their desirable effects while hopefully minimizing the risks associated with their administration.

Optogenetics

The engineering of light-sensitive proteins that can be used to control cell excitability has revolutionized genetics-based approaches to understanding the function of neuronal subpopulations. Optogenetics is a technology that relies on light-delivery systems to activate light-sensitive proteins *in vivo* and *in vitro* to achieve previously unprecedented temporal and spatial control over neuronal membrane potential. The major strengths of this technology are in its capacity to control very specific populations of cells simply by illumination and to observe and/or manipulate behavioral changes in freely moving animals. Our understanding of neuronal networks at the systems neuroscience level has advanced tremendously over the last 10 years due to employment of optogenetics in basic science research. Application of this technology in humans has only recently begun, but a large potential lies in its use for the treatment of pain and other neurological diseases (Fig. 34.3).

Opsins

Microbial rhodopsins are a family of light-sensitive proteins that originate from bacteria, algae, fungi, and archaea. The proteins have been engineered such that upon light exposure, these proteins undergo a conformational change that can generate membrane ion gradients within cells. Channelrhodopsin (ChR2), the most widely studied opsin, undergoes a conformational change upon exposure to blue light, allowing cations to enter and depolarize the cell. In contrast, neuronal silencing can also be achieved by using inhibitory opsins such as archaerhodopsin (Arch), a proton pump that drives an increase in intracellular chloride upon exposure to yellow light.

Delivery

Gene therapy via the use of viral expression systems offers a cell-specific approach to inserting opsins into target tissues. Viral vectors utilize a cell-type-specific promotor to achieve transcriptional control over opsin expression in a select cell population. The most commonly used viruses, the adeno associated virus (AAV) or the herpes simplex virus (HSV), yield high temporal, spatial, and stable transfections of host cells across species with very few side effects. The

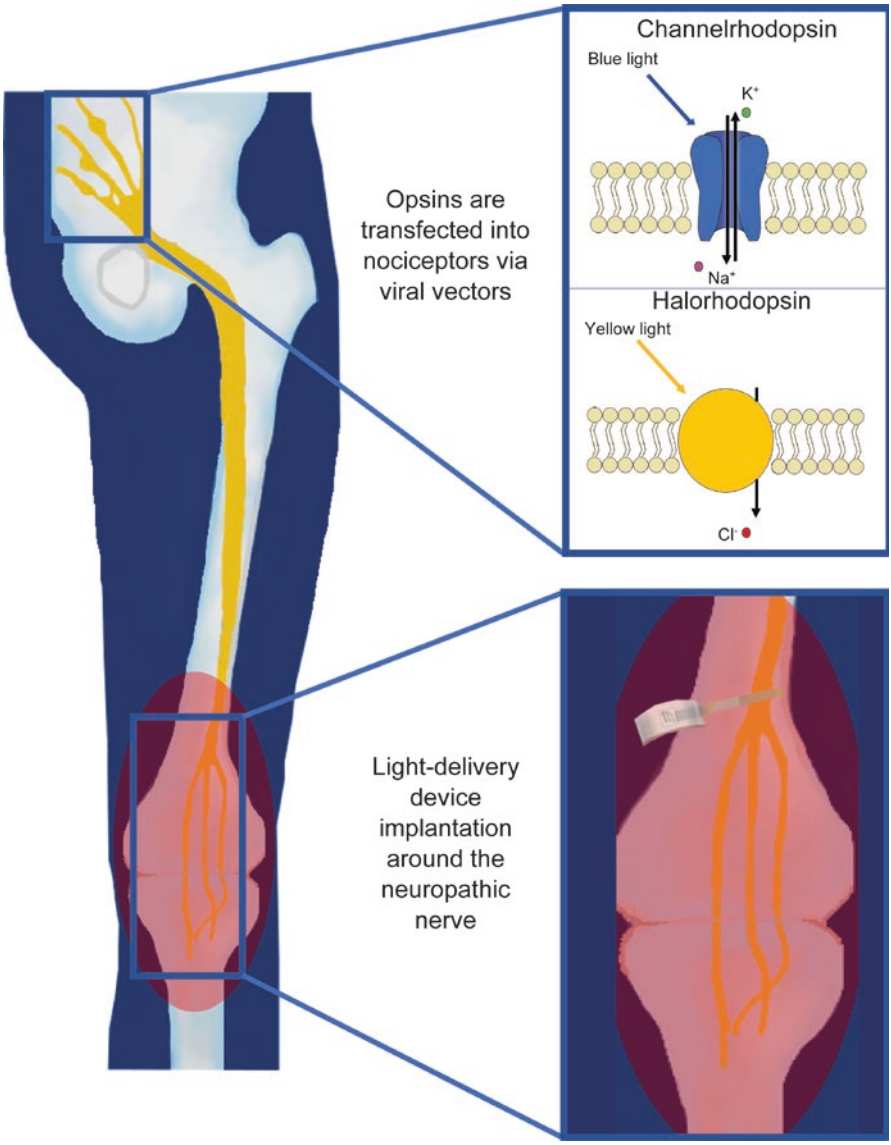

Fig. 34.3 Optogenetics as a future pain therapy. Opsins, a class of light-sensitive proteins, are transfected into the damaged nerve of a neuropathic pain patient using viral vectors. An implantable, wireless, light-delivery device is implanted around the neuropathic nerve, allowing for light activation of the opsin protein. Viral expression and light activation of halorhodopsin in the nociceptive fibers will lead to Cl- influx and inhibition of the nociceptors, reducing pain neurotransmission

most common adverse effects converge on the body's innate immunity to attack the foreign virus, reducing transfection efficiency. However, these effects are minor as AAV transfections in human tissues have been reported to last upwards of 10 years [47]. Differences between virus transfection efficiency usually

pertain to each virus's affinity for a neuronal subtype or route of delivery. While AAVs enter the cell via receptor-mediated endocytosis, HSVs can infect axons and be retrogradely transported to the soma. Therefore, HSVs have a potentially more therapeutic use in humans for the management of pain as they can invade sensory axons in the cutaneous or mucosal epithelium and be retrogradely transported to the soma of nociceptors in the dorsal root ganglia. Use of HSVs in this manner would require superficial injections, lowering the risk associated with injection at the level of the DRG or spinal cord.

Devices

To activate transfected opsins, a light-delivering device needs to be localized around the target tissue. Classic devices used in rodents are bulky with a significant portion being located external to the target tissue for fiberoptic cable connection. These types of arrangements bear the risk of tissue damage due to the increased weight, exposure to the environment, and cable connections that can easily be tangled. The tethering distance of the cable to device can also impede free-range movement. However, recent engineering advances in device construction have shown much promise for mitigating these constraints. Untethered, wireless devices that are powered remotely and miniaturized offer a safer alternative for device implantation and light delivery [48–51]. These devices are made of soft, flexible material that can be fully implanted into the spinal cord or peripheral nervous system for manipulation of pain circuitry [51]. However, these devices have not yet been tested in humans. An advantage of these devices is that they can also be engineered with recording capability so that optogenetic manipulation can be paired to endogenous signals. This approach has recently been applied to create a closed-loop system to correct bladder dysfunction in rodents with cystitis [52].

An alternative to device implantation is direct stimulation of sensory afferents in the skin via an external light source. Animal studies have shown that ChR2-expressing sensory fibers can be activated by light exposure of the skin [53–55], and a similar approach can be used to inhibit afferents in mice with neuropathic pain [56], suggesting that application of such measures in humans could provide an individualized approach to pain care.

Indications for Therapeutic Application

Optogenetic targeting of primary nociceptive afferents shows promise for the management of pain. In rodents, fiberoptic stimulation of ChR2-expressing nociceptive fibers in the hind paw leads to robust nociceptive behaviors in the absence of injury [54, 55], suggesting that optogenetic inhibition of the same pathways may have therapeutic

effects. Indeed, viral delivery of an inhibitory opsin into primary afferents reduces neuropathic pain behaviors in awake animals, [55] while direct manipulation of TRPV1-positive nociceptors in the DRG represses pain transmission [57].

Future use of optogenetics in humans could provide an individualized approach to pain management in which the patient could control their own pain by delivery of light directly to their own skin or remotely via the use of external electronics (phone application, computer, etc.) that could activate implanted light-delivery devices. While more work is needed to assure safety and efficacy over the long-term, advances in the engineering of inhibitory opsins demonstrate a clear path toward the ability to silence neuronal populations, such as hyperactive nociceptors in neuropathic pain patients, for extended periods of time with viral vector delivery of the inhibitory opsin and a device to deliver the appropriate light stimulus.

Chemogenetics

Chemogenetics is a powerful technology that can be used to control neuronal signaling in a cell-type-specific manner. Engineered receptors known as designer receptors exclusively activated by designer drugs (DREADDs) can be expressed in neuronal subpopulations via viral vectors using a cell-type-specific promotor. The uniqueness of this technology lies in the receptors' activation exclusively by exogenous compounds. Similar to optogenetics, neuronal activity can be carefully controlled with high spatial and cell-type specificity, and behavioral outcomes can be observed in freely moving animals. Employment of this technology in humans has not yet been utilized, but chemogenetic therapy could be a novel approach for the future of pain management (Fig. 34.4).

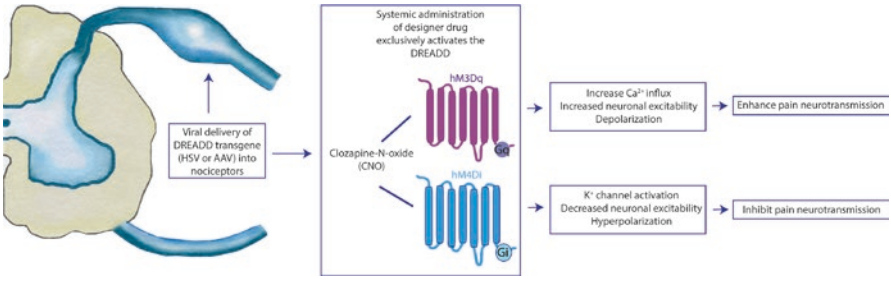

Fig. 34.4 Chemogenetics as a future pain therapy. Designer receptors exclusively activated by designer drugs (DREADDs) are a class of exogenous receptors that are activated by commercial compounds. Viral delivery of DREADDs into the neuropathic nerve is achieved using herpes simplex virus (HSV) or adeno-associated virus (AAV). System administration of the designer drug exclusively activates the DREADD and leads to changes in nociceptor activity. For example, clozapine-N-oxide (CNO) delivery and expression of hM4Di in nociceptors leads to K+ channel activation and inhibition of the nociceptor activity, reducing pain neurotransmission

DREADDs

As the name implies, DREADDs are a class of engineered receptors that are exclusively activated by designer drugs. The most widely used DREADDs are G-protein coupled receptors (GPCRs) that when activated by an exogenous ligand can either activate or inhibit the cell [58]. Similar to opsins, DREADDs are inserted into the target cells by viral vectors with a cell-type-specific promotor. Systemic delivery of the designer drug is required for DREADD activation. The drug used to activate DREADDs is clozapine-N-oxide (CNO); however, metabolites of this drug were shown to have biological actions in the nervous system. This has led to the proliferation of many similar approaches with drugs that are apparently more inert than CNO.

Chemogenetics Vs Optogenetics

Although chemogenetics and optogenetics offer similar means to controlling cellular activity in freely moving animals, chemogenetics does not offer the same temporal control as optogenetics. Instead, temporal authority over the cell's activity is limited to the pharmacodynamics and pharmacokinetics of each designer drug (e.g., CNO). Likewise, optogenetics approaches and its translation into human is progressing much faster as light delivery systems such as wireless LED devices offer a unique, individualized approach to pain management. However, the use of both technologies in humans is still impeded by the need for gene therapy, and modified viruses remain the strategy of choice. A more concentrated focus on human viral delivery systems may be the only obstacle between unlocking the boundless potential of these two technologies in the treatment of pain and other neurological disorders.

Harnessing Endogenous Pain Resolution Mechanisms

Endogenous mechanisms have long been recognized to have analgesic effects in patients with chronic pain, but they are rarely incorporated into routine chronic pain care. While the basic mechanisms underlying how these approaches may work have mostly not been clear, many research groups have recently demonstrated molecular mechanisms for their efficacy. As more patients are diagnosed with chronic pain diseases, this area of blossoming research is likely to enhance our understanding of how these approaches work with the idea that advances in the science of these approaches will increase knowledge and utilization.

Exercise for Pain Treatment

One of the most consistent findings in clinical pain research is that exercise is an effective treatment approach for chronic pain treatment. There is also abundant evidence that exercise can help to prevent the development of chronic pain. Until relatively recently, mechanisms underlying these effects were not known [59]. Some studies on rats with neuropathic pain have demonstrated that exercise can reduce neuropathic pain via upregulation of interleukin 10 (IL-10) and subsequent decrease in microglial activation [60]. While the microglial observations in that study may be sex specific, other studies have demonstrated that IL-10 can be an effective analgesic molecule in female rodents [31]. There are likely other mechanisms through which exercise can alleviate chronic pain.

Understandably, many chronic pain patients are hesitant to participate in strenuous physical activity because of fear of exacerbating their preexisting pain. In this regard, the use of transcutaneous electrical nerve stimulation (TENS) devices can significantly reduce pain levels following exercise [61]. The benefits of regular physical activity for the treatment of chronic pain are very consistently observed in clinical studies [59], and the use of TENS devices to treat additional pain that may result from increased activity may make patients able to use this endogenous mechanism to treat their pain.

Diet: Behavior to Immune Regulation

It has long been recognized that diets high in carbohydrates and fat lead to increased levels of inflammatory mediators accumulating in adipose tissues and other parts of the body [62]. Additionally, high fat diets lead to an increase in monocytes and neutrophils and an increase in mechanical and thermal sensitivity in animals [63, 64]. This suggests that diet-induced changes in the immune system can drive altered pain sensitivity, potentially making pain worse or increasing chronic pain susceptibility. When animals were switched from a high-fat diet to a low-fat diet the levels of monocytes and neutrophils returned to normal levels, normalizing pain thresholds [64]. While studies in humans examining the impact of diet on chronic pain states are sparse, there is evidence that various low fat, more nutrient-rich diets decrease levels of pain in patients [65, 66]. Balanced diets that limit fat and carbohydrate consumption induce endogenous anti-inflammatory mechanisms and may be useful in treating chronic pain.

Meditation

Meditation has long been used to modulate the pain experience. Recently, many studies have sought to quantify and examine the mechanism behind the effect of meditation on chronic pain [67]. For example, a study in long-term meditation prac-

titioners demonstrated they had decreased pain, unpleasantness scores, and an increase in activity in the anterior insula [68]. Recent studies have demonstrated that patient willingness to use meditation or other mindfulness activities to supplement their treatment regimen is increasing, with 27% of veterans being treated for chronic pain using at least one type of meditation practice with positive results [69]. One major obstacle for patients implementing complementary practices, like meditation, into their treatment regimen is the amount of coaching and support required to become proficient in self-management of their meditation techniques. As access to smart phones has become ubiquitous, free meditation apps developed specifically for patients with chronic pain are a promising tool that will allow for a widespread use of mindfulness techniques even in patients that do not have regular access to a support team [70]. While future research will determine the mechanisms underlying meditation-induced analgesia, mindfulness is a well-established method for combating chronic pain and can be quickly implemented in the treatment regimen of many patients.

Genome Editing

A new genome editing technology known as the CRISPR-Cas9 system offers an efficient and rapid means to alter DNA [71]. Preclinical applications of the CRISPR-Cas9 system have been used to better understand gene function, establish genetics-based disease models (i.e., mutations), and to correct genome damage for disease treatment. However, the technology is still far away from being safe to use in humans. Although the CRISPR-Cas9 system shows much promise in its potential to correct hereditary-associated pain diseases, a large gap lies in its feasibility for safe practice in humans [72, 73]. Gene editing can lead to unpredictable cellular, organ, and/or whole-body repercussions if each edited gene is not first thoroughly vetted in preclinical animal models. Nevertheless, the potential for curing not only chronic pain but many other diseases through editing of mutations that cause heredity-based disease, insertion of gain of function alterations to correct disease, or altering the genome of cancer cells is unprecedented.

CRISPR-Cas9

CRISPR refers to clustered regularly interspaced short palindromic repeats and was originally discovered as prokaryotic DNA that contain short repeats of base sequences that are derived from sequence fragments of invading viruses. These sequences serve as an antiviral defense system as transcription of the CRISPR sequence yields two non-coding RNAs that can base pair with viral DNA during a second viral invasion. Recruitment of CRISPR-associated 9 (Cas9) endonuclease to the CRISPR sequence leads to a double-stranded DNA break and removal of the

foreign DNA from the genome, preventing the viral DNA from altering the livelihood of the bacterium or archaea. After the double-stranded break, DNA repair is attempted by random insertion and/or deletion of base pairs at the edited site; or, in the presence of a homologous DNA donor template, cells can repair their DNA by homologous recombination resulting in a genomic knock in [74]. Engineering of this ancient system has made it viable for use in eukaryotic cells, and the technology can be applied in vivo in mammals. Viral delivery of the Cas9 gene, and a CRISPR guide RNA that is complementary to the targeted gene, can lead to genome editing in eukaryotic cells. The technology is now widely used to generate knockout and transgenic mice in a fraction of the time that was previously required, and many new technologies have been developed to use CRISPR-Cas9 in vivo [75].

CRISPR-Cas9 for Pain Management

One of the most exciting applications for CRISPR-Cas9 in pain management is in its prospect to treat hereditary-associated pain diseases. These diseases involve a loss or gain of function mutation in nociceptor-related genes, such as the voltage-gated sodium channels that cause an insensitivity to pain or extreme pain [76]. For example, autosomal-dominant gain-of-function mutations in the voltage-gated sodium channel, Nav1.7 causes a pain condition known as primary erythromelalgia that is characterized by a spontaneous burning sensation in the extremities and increased skin temperature. Viral delivery of the guide RNA that is complementary to the mutated gene along with the Cas9 endonuclease could lead to removal and repair of the mutated Nav1.7 gene, offering a new pain management treatment for patients with these severe pain diseases. Conversely, in situations where a loss of function mutation renders nociceptors unable to generate nociceptive signals, insertion of the fully functional gene could repair this situation and restore normal pain sensation [76]. As our ability to sequence patient populations increases, it is becoming clear that some mutations in sodium channel genes increase susceptibility to development of neuropathic pain [20]. Insofar as these chronic pain disorders may also be caused by these mutations, CRISPR-Cas9 may be used to treat these patients through genome editing. Much work is still needed to advance this technology towards the clinic [72, 73], but it holds significant promise for many heritable pain disorders.

Closing Remarks

The pain research area is rapidly evolving, aided by the emerging technologies discussed in this chapter. In the coming years, we think it is likely that major changes will come in diagnostic tools and therapeutic approaches. On the diagnostic front, it is likely that combination approaches (e.g., QST with RNAseq) will reveal new

ways to accurately diagnose underlying mechanisms, causing chronic pain in individual patients. This will unquestionably have a big impact on decision-making for therapeutic approaches and likely also on clinical trial design. On the therapeutic development front, there are exciting opportunities in many areas. We think that the most exciting of these are biologics and optogenetics. As we learn more about pain mechanisms driving chronic pain in defined subsets of patients, it is likely that biologics can eventually be rapidly deployed to treat what is promoting pain in these specific populations. Likewise, optogenetic technologies have developed with extraordinary speed and essentially only require viral vectors to deliver the channels to make the approach work in patients. This will likely completely transform the neuromodulation field and will undoubtedly have a strong influence on how chronic pain is treated. As we have proposed previously (Price and Gold 2018), the future is bright for the possibility of a series of cures for chronic pain conditions.

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