

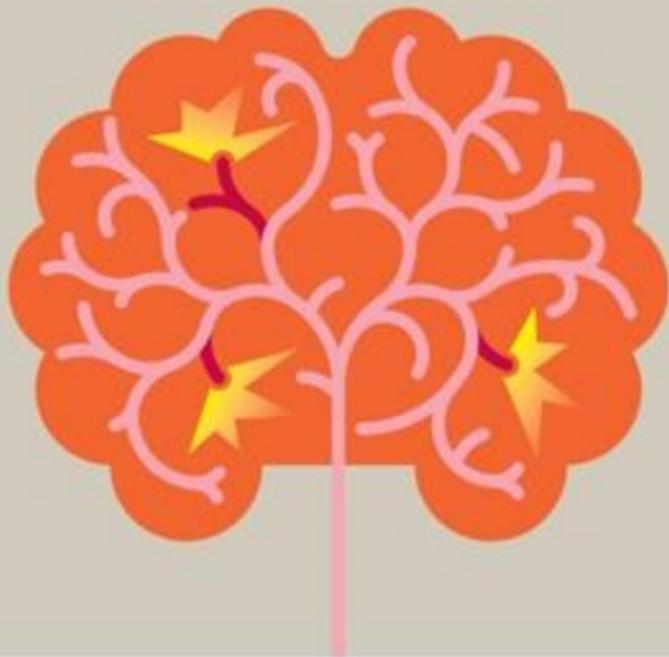
Continuum

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Pain Management in Neurology

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VOL. 30 NO. 5

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An Invisible Pandemic



Most of us read the clinical literature with an objective eye. Articles can draw our attention with an interesting finding, a new treatment, a catchy title, and especially content that is highly relevant to our clinical practice. If I see a lot of patients with meningoleukoencephalomyeloneuropathy, you can bet I'll read any article with that word in the title.

Oddly, many of us have a pain-shaped scotoma in our clinical vision. Pain is highly relevant to neurology practice, just as it is for every facet of medicine. More than 1 in 5 adults in the United States currently experience chronic pain.¹ In almost 1 in 10 adults, chronic pain has meaningful negative effects on life and work.¹ Many of us feel unprepared to help patients with pain, despite the fact, dear reader, that we ourselves are more likely to experience chronic pain than almost any other condition discussed in the pages of this journal. This fact adds subjective salience to the topic. The fact that all pain is neurologically mediated, if not generated, places pain squarely in our domain.

In this first issue of *Continuum* fully dedicated to the diagnosis and management of pain disorders, Dr Nathaniel Schuster has assembled an extraordinary cast of authors and topics. The full range of pain disorders encountered in neurologic practice is included (readers interested in a thorough review of headache can pick up a copy of our April 2024 issue dedicated to the topic). In the lead article, Dr Beth Hogans provides a practical framework for principles of pain management. Dr Vernon Williams takes the reader through a modern, science-based approach to the ubiquitous spine pain disorders. Peripheral neuropathic pain, a topic familiar to most neurologists, is thoroughly reviewed by Drs Victor Wang and Miroslav Baćkonja, complemented next by an expert discussion of central neuropathic pain by Dr Charles Argoff. Drs Meredith Barad and Marcela Romero-Reyes get to the root of orofacial pain, an entity that most of us encounter but is lightly covered in neurology

training. The widespread pain syndromes are demystified by Dr Narayan Kissoon, who provides the reader with the latest on the pathophysiology and treatment of these common disorders.

The balance of this issue pivots from categories of painful disorders to the practical management of pain. The complex and divergent trajectories of opioids and cannabinoids in modern clinical practice receive an excellent discussion from Dr Friedhelm Sandbrink and Dr Schuster in an editor-author capacity. Dr Prasad Shirvalkar's comprehensive article on neuromodulation offers an exciting window into current and future alternatives for pain management. Embracing pain management through the modern biopsychosocial construct, Dr Mirsad Serdarevic covers everything a neurologist needs to know about chronic pain psychology. Dr Alyssa Lebel and Dr Schuster round out the clinical reviews with a complete review of pediatric pain.

The clinical complexities of pain management are compounded by the arcane and evolving legal and regulatory framework that has developed to address the ongoing opioid crisis (an epidemic within a pandemic). To help neurologists navigate this territory, Dr Joseph Kass and Rachel Rose provide practical background and tips in this issue's Selected Topics in Neurology Practice article.

As always, after reading this issue, subscribers can obtain up to 20 *AMA PRA Category 1 Credits™* toward self-assessment CME or, for Canadian participants, a maximum of 20 hours toward the Self-Assessment Program [Section 3] of the Maintenance of Certification Program of the Royal College of

Physicians and Surgeons of Canada with our posttest, written for the issue by Drs Nuri Jacoby and James Owens.

Available to all listeners who want to learn more about pain management in neurology practice, *Continuum* Audio provides easily accessible podcast interviews with our guest editor and expert authors. CME for these interviews is available to American Academy of Neurology (AAN) members at [continpub.com/AudioCME](http://continpub.com/audiocme). *Continuum* subscribers have access to exclusive interviews not found on the podcast and CME accompanying those interviews. Verbatim audio recordings of each article from this issue are available to subscribers through our *Continuum Aloud* program, found at the article level at ContinuumJournal.com and in the AAN's Online

Learning Center at [continpub.com/Audio](http://continpub.com/audio), perfect for your commute to and from work.

There are many invisible epidemics (an internet search suggests my title to this preface is neither particularly creative nor specific to one condition). Our hope with this issue of *Continuum* is to help patients by helping our readers feel more comfortable in the management of pain. I am deeply grateful for Dr Schuster's leadership in bringing this issue to print and for shedding light on one of the most meaningful ways we can improve the lives of our patients.

—LYELL K. JONES JR, MD, FAAN
EDITOR-IN-CHIEF

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...we ourselves are more likely to experience chronic pain than almost any other condition discussed in the pages of this journal.

REFERENCE

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Principles of Pain Management

By Beth B. Hogans, MS (Biomath), MD, PhD

ABSTRACT

OBJECTIVE: This article introduces the general principles of assessing, diagnosing, and managing pain relevant to neurologic practice.

LATEST DEVELOPMENTS: Scientific understanding of and clinical practices related to pain and pain management are advancing. The field is remarkable for the diversity of health professions engaged in this effort, including physicians, scientists, psychologists, pharmacists, and many others. Pain classification is transforming with pending changes to the *International Classification of Diseases* diagnostic coding system, and pain assessment has moved toward consistent application of the biopsychosocial model. The diagnosis of pain has continued to become more sophisticated with the development of additional testing modalities, clearer classification systems, and diagnostic criteria. Pain management requires both pharmacologic and nonpharmacologic elements; systematic review evidence for both of these and interventional and surgical management are increasingly available. The context of treatment remains important given the impact of social determinants of health and limitations of access to diagnostic and treatment resources. Due to global and interprofessional collaborations as well as new research funding, the outlook is positive.

ESSENTIAL POINTS: Pain is a protean experience for humans; functional MRI (fMRI) and other research modalities show that pain perception is highly multifocal, and modulation occurs at many nervous system levels. Neurologists bring special skills to pain evaluation and management, are well equipped to appreciate both the focal and diffuse nature of pain, and can envision how pain attenuates sleep, cognitive function, mobility, motivation, and social connection. By operationalizing expert knowledge of the nervous system, implementing relevant therapies, and collaborating with diverse health professions to manage pain, neurologists can succeed at and find meaning in optimizing patient outcomes.

INTRODUCTION

Pain-associated conditions are highly prevalent in neurology and include headache and orofacial pain, spinal disorders such as cervicalgia and lumbar radiculopathy, neuropathic disorders such as diabetic peripheral neuropathy and postherpetic neuralgia, and pain syndromes that arise in the context of other neurologic conditions

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Dr Hogans discusses the use of several pain-active antidepressants and antiseizure medications, none of which are approved by the US Food and Drug Administration (FDA) for the management of pain.

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such as multiple sclerosis.¹ Arguably, all pain-associated conditions are of interest to neurologists as all pain is neurally mediated; however, the enrollment of neurologists in pain fellowship training programs remains sparse. This article addresses the general principles of pain assessment, diagnosis, and management and the context of treatment, highlighting some broad developments in pain science and clinical practice. The classification and basic terminology of pain-associated conditions continue to evolve, and several commonly used pain terms are highlighted in TABLE 1-1²⁻²¹ along with selected caveats and limitations.^{13,22,23}

PAIN CLASSIFICATION, TERMINOLOGY, AND APPROACH

The diagnostic classification of pain is best exemplified by the systematic classification of facial pain and headache disorders found in the International Classification of Headache Disorders (ICHD), which allows for relatively detailed diagnoses of these disorders in both inpatient and outpatient neurology settings that are consistent from one location to another.²⁴ The development of headache and facial pain diagnostic nosology reflects the efforts of Arnold Friedman and colleagues²⁵ who published an initial classification framework in 1962. The ICHD was first published in 1988 and subsequent editions have responded to advances in science and clinical practice.²⁵ The advantage of having a unified approach to headache and facial pain diagnosis is that, although there are many different types of headache and facial pains and all are principally subjective, there is a specific set of standards on which to base the diagnosis of each disorder. This approach to diagnosis and classification has further advanced pain research as specific mechanisms and disorder-specific treatments have been developed and tested.²⁶⁻²⁸ The ICHD can be viewed online without a subscription and is a useful resource for students, residents, and nonspecialists. The current version is harmonized with the version of the *International Classification of Diseases (ICD)* available at the time of publication.²⁹ Neurologic management of headache and facial pain shares features with the management of other forms of pain including a focus on attending to and acknowledging the patient's experience of pain and related symptoms, seeking diagnostic information through neurologic examination and diagnostic testing, and integrative management including pharmacologic and nonpharmacologic therapies, potentially incorporating lifestyle modifications using a "whole-health" approach and interprofessional collaboration.^{30,31}

Pain-associated spine disorders are highly prevalent in neurology practice.^{8,32,33} At present, disorders of the spine are not systematically diagnosed and classified in the same manner as headache disorders.³⁴⁻³⁷ There is no widely recognized and accepted universal classification scheme for spine disorders, and the most cited articles addressing low back pain support a reductionist approach, instructing generalists to classify most low back pain as nonspecific and screen for red flags (although a consensus on red flags does not exist) and to advise patients to remain active and take over-the-counter analgesics.^{34,38-41} Because neurologists have expertise in neurologic localization and diagnosis, spine pain guidelines intended for generalist practice will not be comprehensive and further diagnostic discernment is generally required.⁴² Neurologists can identify focal neurologic deficits and emergently manage both common and potentially catastrophic neurologic

KEY POINTS

- The systematic classification of facial pain and headache disorders in the International Classification of Headache Disorders allows for relatively detailed diagnoses of these disorders in both inpatient and outpatient neurology settings that are consistent from one location to another.
- The neurologic management of headache and facial pain includes acknowledging the patient's experience of pain and related symptoms; seeking diagnostic information through neurologic examination and diagnostic testing; and integrative management including pharmacologic and nonpharmacologic therapies, potentially incorporating lifestyle modifications using a "whole-health" approach and interprofessional collaboration.

disorders.⁴²⁻⁴⁵ This capability is consistent with neurologic training and scope of practice, and in many instances, neurologists will recognize specific syndromes and conditions relating to spinal pathology, as illustrated in **CASE 1-1.**^{35,44} The classification of pain in the setting of spinal cord injury is one example of how pain classification can both support patient care and advance broader understanding by carefully parsing the origins of pain in a manner that reflects both pain mechanisms and therapeutic needs.⁴⁶ Pathologic processes giving rise to spine pain can be biomechanical, musculoskeletal, neuropathic, nociceptive, central sensitization mediated, infectious, and immune mediated. In

TABLE 1-1**Frequently Referenced Definitions in Pain**

Term	Definition	Limitations and concerns
Pain	"An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." ²	The current definition may not acknowledge a patient's experience of pain feeling akin to "tissue damage" and may not sufficiently incorporate psychosocial factors ²
Nociceptive pain	"Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors." ³	This raises the question of whether pain experienced acutely from nerve damage is truly neuropathic or nociceptive
Neuropathic pain	"Neuropathic pain can be defined as a process occurring after a primary lesion or disease of the somatosensory nervous system." ⁴	The prior IASP definition included "dysfunction" as well as disease By excluding dysfunction and focusing on demonstrable lesions, molecular, microscopic, and "as yet to be defined" neuropathic changes are excluded ⁵
Inflammatory pain	"...associated with tissue injury and infections, results from the heightened sensitivity of the peripheral terminals of nociceptor sensory neurons in response to exposure to inflammatory mediators." ^{6,7}	By many measures, inflammatory pain accounts for the vast majority of pain globally; nonetheless, the IASP currently excludes this mechanism ^{8,9}
Nociplastic pain	"Altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain." ¹⁰	Newer term; not well validated; the definition of "actual or threatened tissue damage" is constrained by clinical resources and expertise ¹¹ ; potentially excludes overlap with other pain forms
Allodynia	"Pain due to a stimulus that does not normally provoke pain." ³ "Pain caused by a normally non-painful stimulus." ¹²	Note that this is a pain response not typical of normal nociceptive processing
Hyperalgesia	"Increased pain from a stimulus that normally provokes pain" ³ "A heightened experience of pain caused by a noxious stimulus." ¹²	Note that this is a pain response not typical of normal nociceptive processing

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general neurologic practice, which includes urgent and emergent hospital consultations, cases of spinal cord disorders presenting with prominent pain may lead to death, paralysis, or permanent disability, and focal neurologic findings can herald dire outcomes if the underlying syndromes (eg, infection, tumor, stroke of the spinal column) go unaddressed.⁴³ For example, Guillain-Barré syndrome, the most common sporadic form of paralysis, can present in urgent care settings with acutely developing diffuse low back pain and may initially manifest with only subtle decreases in muscle stretch reflexes and mild weakness, yet evolve to apnea within hours.⁴⁷

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Term	Definition	Limitations and concerns
Hypoalgesia	<p>"Diminished pain in response to a normally painful stimulus."³</p> <p>"A decreased perception of pain caused by a noxious stimulus."¹²</p>	Note that this is a pain response not typical of normal nociceptive processing
Chronic pain	<p>"Pain that persists or recurs for more than 3 months" or pain which persists beyond the time required for normal healing to occur.¹³</p>	The IASP definition excludes the possibility that normal healing time would exceed 3 months, which could be normal for some conditions (eg, complex spine surgery)
Breakthrough pain	<p>Most commonly used in the context of cancer pain management</p> <p>"A flare of pain that might happen even though you are taking pain medicine regularly for chronic pain" (lay definition)¹⁴</p> <p>"Episode of severe transient pain in patients with cancer"¹⁵</p>	The application of cancer pain management principles to the treatment of chronic noncancer pain has not been validated and may have contributed to the US opioid epidemic and ensuing corrections ¹⁶
Central sensitization	<p>"Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input."³</p> <p>"An amplification of neural signalling [sic] within the central nervous system that elicits pain hypersensitivity"¹⁷</p>	Incorporates multiple mechanisms (eg, long-term potentiation, glial activation, sprouting, phenotypic switching), none of which are currently confirmable using widely available clinical tests
Central sensitivity syndromes and chronic overlapping pain conditions	<p>Prevalent chronic pain conditions which may coexist in specific individuals; conditions include migraine; chronic tension-type headache, temporomandibular joint disorder, chronic low back pain, urological, pelvic, and gynecological pain disorders, irritable bowel syndrome, and fibromyalgia¹⁸</p>	<p>These conditions have increased risks for sleep disturbance including obstructive sleep apnea, fatigue, and selected psychological features^{19,20}</p> <p>There is considerable overlap between the set of conditions termed <i>central sensitivity syndromes</i> and those termed <i>chronic overlapping pain conditions</i></p>
Opioid-induced hyperalgesia	<p>"Nociceptive sensitization following acute or chronic exposure to opioids."²¹</p>	Note that multiple mechanisms are potentially included here including active opioid exposure, withdrawal, and persistent hyperalgesia following long-term cessation

CASE 1-1

A 47-year-old woman underwent right shoulder surgery, and upon awakening reported acute low back pain. A neurology consultation was requested, and the patient described mild dull pain at rest that became sharp with rolling over in bed, sit-to-stand, and attempts at ambulation. The patient pointed to the maximal pain area with one finger (left low back at the L5 disk level, 2 to 3 inches lateral of midline) but indicated that the pain radiated “all over” the buttock. She had no prior history, although she acknowledged years of intermittent mild-to-moderate axial low back pain following exertion such as lifting heavy objects. She noted that the current pain was so severe that she was nauseous and had an urge to defecate when standing. Having recently moved to the area, she felt unsure about managing her pain at home.

Examination revealed a body mass index of 28.4 and intact mental status, cranial nerves, sensation, and reflexes. Her upper extremity coordination and strength were normal except for limitations due to the recent surgery. A lower extremity motor examination showed full strength on the right with mild guarding upon hip testing; her left leg showed full strength except for antalgic guarding on hip testing. Palpation testing demonstrated tenderness without evident mass or swelling over the area of the left rostral sacroiliac joint. Straight leg testing showed an equivocal result with pain radiating to the buttock on the left and mild guarding on the right. Plain-film radiography of the lumbosacral spine demonstrated minimal spondylosis. Due to the absence of neurologic deficits, referral to a pain medicine specialist was contemplated; however, no immediate consultation was available and there was a 3-week wait for pain clinic appointments.

Sacroiliac joint dislocation resulting from asymmetrical loading was suspected based on the history and presentation and was confirmed by the examination. As the patient was still recovering from her surgery, a physical therapist was consulted to provide bedside manual manipulation. Cold packs were applied 3 times a day for pain relief.

COMMENT

This case exemplifies the importance of interdisciplinary collaboration in the diagnosis and treatment of neurologic pain. In addition, this case demonstrates that musculoskeletal conditions, which involve mechanisms of nociceptive and inflammatory pain, may present with radiating pain and be interpreted as neurologic by non-neurologists. Conditions like this are nonetheless profoundly impactful in terms of producing severe pain and motor dysfunction. The differential diagnosis included radiculopathy and other nerve injuries, and thus neurology was consulted; however, the neurologist suspected sacroiliac joint dislocation. Knowing the basic diagnosis and management of common conditions in the pain differential diagnosis can spare patients from unnecessary treatment delays.

Current pain categorization systems generally organize pain into one of four domains: nociceptive pain, neuropathic pain, inflammatory pain, and nociplastic pain. Nociceptive pain is caused by tissue injury or trauma. Neuropathic pain is caused by disease or dysfunction of the nervous system. Inflammatory pain is associated with phenotypic changes in afferent neurons mediated by inflammatory mediators, resulting in increased sensitivity to painful and nonpainful stimuli. Nociplastic pain is a relatively recent construct defined as pain reflecting central sensitization. The following sections describe neuropathic and nociplastic pain.

NEUROPATHIC PAIN

Neuropathic pain takes several forms but almost all relate to a disease or dysfunction of the nervous system.^{22,31,45,48-52} Although recent revisions to the International Association for the Study of Pain (IASP) definition of neuropathic pain have emphasized demonstrable lesions of the nervous system, this definition may have more utility in research settings than in clinical practice.⁵³ The IASP currently endorses that “[a] suspected diagnosis of neuropathic pain requires specific investigations to ascertain that the pain originates in the nervous system.”^{51,22} Whether such investigations involve only a systematic neurologic examination or necessitate “objective testing” depends on provider expertise, clinical circumstances, and the availability of specific resources.^{48,52} For example, the diagnosis of small fiber neuropathy has been constrained by limited access to expert clinicians and skin biopsy staining for epidermal nerve fibers or quantitative sensory testing.^{51,52} Clinically, neuropathic pain disorders are often most effectively classified in terms of etiology, as this will determine the treatment approach; however, at the time of first presentation, the etiology may not be established.^{45,46,48,51,52} Pattern recognition is an important tool for the assessment of a patient with any form of pain, as establishing the neuroanatomic distribution of positive and negative symptoms and signs is key to unlocking the differential diagnosis.

Common neuropathic pain patterns include a distal symmetrical gradient-type pattern, neuropathy affecting only small fibers (typically diffusely distributed), “named nerve” patterns which demonstrate clear delineation between normal and abnormal areas, radicular (dermatomal) patterns, and visceral involvement patterns.⁴²⁻⁴⁴ Other regional pain patterns that are important for the differential diagnosis but are not specifically neuropathic include the patterns associated with muscle injury, bone injury (ie, sclerotomes), ligamentous and tendinous strain, disk injury (ie, diskogenic pain), and multicentric patterns such as diffuse enthesopathy (related to vitamin D deficiency), osteogenic syndromes, and fibromyalgia.⁵⁴⁻⁵⁶ It is difficult to overemphasize the importance of pain patterns in the differential diagnosis of pain, and it is important to recognize that neuropathic and non-neuropathic pain syndromes have stereotypical and nontypical patterns of pain signs and symptoms.

CENTRAL SENSITIZATION, NOCIPLASTIC PAIN, AND SYNDROMES OF ABERRANT PAIN SIGNALING

There is debate over whether central sensitization represents a form of neuropathic pain. This is important conceptually as the underlying pathologic processes will ultimately determine the nature of the definitive treatments,

KEY POINTS

- Pathologic processes giving rise to spine pain can be biomechanical, musculoskeletal, neuropathic, nociplastic, central sensitization mediated, infectious, and immune mediated.
- Common neuropathic pain patterns include a distal symmetrical gradient-type pattern, neuropathy affecting only small fibers (typically diffusely distributed), “named nerve” patterns, radicular (dermatomal) patterns, and visceral involvement patterns.

which are yet to enter the clinical armamentarium. The debate arose from a decision by the IASP to redefine neuropathic pain to only include conditions that have a demonstrable lesion (ie, provable through imaging or neurophysiology) and exclude conditions that are traceable to a neurochemical, molecular, or microscopic cause. No well-established clinical tests are currently used to determine the presence of central sensitization, which can manifest from one or more underlying pathophysiologic processes, including long-term potentiation, phenotypic reorganization, central axonal sprouting, proliferation of microglia, and glial sensitization. This will be an area of evolving practice refinement in the next decade.^{17,57,58}

The initiative to apply the term *nociplastic* to certain forms of pain is a relatively new development that is not reflected in the current version of the *ICD* system and that continues to undergo definitional development. Several recognized syndromes may reflect processes related to central sensitization and may include the highly prevalent tension-type headache; chronic overlapping pain conditions, which include temporomandibular joint disorder, dysmenorrhea, and irritable bowel syndrome; complex regional pain syndrome types I and II; and widespread pain syndromes, which include fibromyalgia.^{59,60} For more information on several syndromes related to central sensitization, refer to the article “Chronic Widespread Pain” by Narayan R. Kissoon, MD,⁶¹ in this issue of *Continuum*.

Both clinical and basic science evidence suggests that the current scheme overlooks the effects of inflammation (eg, osteoarthritis) in inducing persistent phenotypic changes in somatosensory elements as a mechanism working in concert with neuropathic processing alterations.^{6,10,11,22,23,62,63} Some authors refer to this as inflammatory pain, whereas others incorporate this into the nociplastic category. Nociceptive pain is associated with acute injury or trauma, and some syndromes involve recurrent acute trauma at macroscopic or microscopic levels (eg, spondylolisthesis, sacroiliac joint dysfunction, other joint instability syndromes). Given the frequency with which patients with complex pain conditions are encountered in clinical practice, neurologists need to know that several pain mechanisms may be active at any phase of treatment. Rational pain therapy incorporating agents and therapies to address nociceptive, inflammatory, and neuropathic pain may necessitate the use of polypharmacy and multiple nonpharmacologic therapies to successfully manage complex pain conditions, especially spine-related pain conditions and other orthopedic conditions with compressive peripheral nerve involvement (ie, Ehlers-Danlos syndrome).

Other neurologic syndromes demonstrate high rates of pain. People with traumatic brain injury and multiple sclerosis are especially likely to experience persistent pain, whether from headache, cervical syndromes, or other pain processes.⁶⁴ People with Parkinson disease have increased rates of pain diagnoses and, although the association of pain with specific dementias is not well defined, the management of pain in the context of dementia is more complex. Conditions such as motor neuron disease and muscle diseases are often associated with pain. Polymyalgia rheumatica and giant cell arteritis are often associated with shoulder girdle and hip girdle pain as part of the syndrome.²⁴

The management of pain-associated conditions in neurologic practice may be iterative. Establishing a firm diagnosis may require testing; for this reason, it is

often necessary to initiate symptomatic treatment concurrently with the diagnostic workup so that patients do not continue to experience uncontrolled pain while awaiting test results. This is referred to as the *parallel path model*, which envisions assessment and symptomatic treatment occurring in a coordinated, concurrent manner.⁶⁵

Pain is a highly active area of research and related activity. Recent key developments include a revised IASP definition of pain and other aspects of pain including a definition of neuropathic pain, developed primarily as a research tool.^{12,13,22,23} The mandatory adoption of the tenth edition of the *ICD (ICD-10)* in late 2016 was followed by several revisions to the *ICD-10* codes available, and stakeholder work for the upcoming eleventh edition of the *ICD (ICD-11)* has been completed.⁶⁶ The new classification system will require a major revision to coding practices as practitioners will be expected to distinguish both pain mechanisms and underlying pathologies. With the *ICD-11* system, providers will be expected to distinguish chronic primary musculoskeletal pain from chronic secondary musculoskeletal pain, even though the distinction between these is unclear and subject to considerable controversy.²³ From a neurologic viewpoint, it is not clear what a chronic primary musculoskeletal pain condition would be as primary pain conditions are understood to arise directly from disease or dysfunction of the pain system itself, whereas the musculoskeletal system is principally a structural and locomotor system.¹⁰ Chronic neuropathic pain is not specified as a “secondary pain” but is shown consistently in diagrams colocated with other secondary pain diagnoses.^{22,66} There will also be codes for distinguishing “central” from “peripheral” neuropathic pain, a potentially false dichotomy that may exceed the bounds of clinical discernment, as peripheral nociceptive, inflammatory, and neuropathic processes can and will result in central sensitization.^{17,67}

Pain research will continue to improve practice and patient experience. In the realm of nociceptive pain, the enhanced postoperative recovery programs system of formalized quality improvements in perioperative care has resulted in dramatic reductions in pain during and following surgery as well as marked decreases in opioid dispensing in the context of operative management.^{68,69} Federal research and industry-sponsored studies continue to generate new therapeutic approaches as well as improved implementation and delivery of existing treatments.⁷⁰ Patient and caregiver engagement requires the readiness of health care professionals to use the frameworks of “whole health,” shared decision making, motivational interviewing, a therapeutic alliance, and other evolving frameworks that, taken together, will further improve pain-focused neurologic care.⁷¹

ASSESSMENT

Neurologic appraisal may be instrumental in attaining a clear diagnosis and treatment plan for many patients with pain. Neurologic history taking and examination typically focus on describing and delineating areas of neural function and dysfunction in both the central and peripheral nervous systems,⁴³ and almost universally, the process of history taking is essential to defining a pain-associated condition.^{72,73} Features of pain presentation of particular interest include symptom quality, region, severity, and timing, as well as identifying factors that alleviate and worsen symptoms (**TABLE 1-2**).⁷⁴

KEY POINTS

- There are no well-established clinical tests currently used to determine the presence of central sensitization.
- Given the frequency with which patients with complex pain conditions are encountered in clinical practice, neurologists need to know that several pain mechanisms may be active at any phase of treatment.
- It is often necessary to initiate symptomatic pain treatment concurrently with the diagnostic workup so that patients do not continue to experience uncontrolled pain while awaiting test results.
- New pain classification systems will require a major revision to coding practices as practitioners will be expected to distinguish both pain mechanisms and underlying pathologies.
- Features of pain presentation of particular interest include symptom quality, region, severity, and timing, as well as identifying factors that alleviate and worsen the symptoms.
- In the diagnosis of pain-associated conditions, there is a role for the assessment of musculoskeletal dysfunction.

Patients with chronic pain will often have multiple pain areas or diagnoses. Optimally, the clinician characterizes each of these, at least in part, to ascertain whether they represent separate processes or a single phenomenon such as a chronic widespread pain syndrome (a form of chronic primary pain in the *ICD-11* classification system).¹³

Neurologic examination is crucial to informing a pain diagnosis. In many cases, the sensory examination may take precedence, especially when neuropathic pain is suspected, with motor, cerebellar, and autonomic features taking on a confirmatory role.⁴⁴ In the diagnosis of pain-associated conditions, there is a role for the incorporation of musculoskeletal dysfunction assessment.⁷⁴ For example, appraising spine pain may require an assessment of range of motion and provocative tests, headache may require palpation of the head and neck as well as range of motion, and neuropathy testing may require an assessment of pulses and peripheral edema.^{47,75}

Clinical reasoning in the context of pain-associated conditions may prioritize findings and symptoms arising from the sensory system. This contrasts with other disorders where sensation is often viewed as confirmatory. In assessing and diagnosing patients with pain-associated conditions, the primary focus will be on the perceptions of pain and other sensory inputs, contrasting small fiber

TABLE 1-2

Features of a Pain-focused History and Physical

Quality of symptoms

- ◆ Includes descriptors such as burning or aching
- ◆ May guide the distinction between neuropathic and non-neuropathic pain

Region of symptoms and signs

- ◆ May include neurologic patterns (eg, radicular, dermatomal, hemisensory, radiating, diffuse)
- ◆ May also include non-neurologic patterns (eg, sclerotomal)

Severity

- ◆ Most often defined as relating to pain intensity
- ◆ Pain intensity communicated using a 0 to 10 (11-point) numerical rating scale
- ◆ Pain intensity shows high variability between individuals
- ◆ Pain intensity ratings are often highly reproducible for individuals in research settings
- ◆ Pain intensity ratings may worsen (ie, a mild stimulus will produce more pain) with chronic pain
- ◆ Pain intensity ratings may improve or worsen (ie, increase or decrease in response to a fixed stimulus) with psychosocial factors
- ◆ Pain intensity assessment with a numerical rating scale is exceptionally rapid and feasible for those with low literacy
- ◆ Pain interference is the extent to which pain interferes with activity (eg, sleep, enjoyment)
- ◆ Pain-related distress is the affective aspects of pain (eg, suffering)

CONTINUED ON PAGE 1327

functions of heat, cold, and pain sensation as well as itch and efferent small fiber functions (eg, focal erythema) with large fiber functions of proprioception and vibration which may or not be involved, depending on the etiology.^{48,51,76} It is important to recognize that pain may have impacts on motor, cerebellar, and cognitive function, but these will vary by etiology and, while presenting management issues, will be findings that are confirmatory in nature.

Patient characteristics have a modest impact on clinical pain reasoning, with some exceptions. Some conditions are far more prevalent in older adults than those typical of pediatric or middle-aged patients.^{1,56} While some conditions pertain to primary and secondary sex organs, male-female differences in pain prevalence are small. Populations facing socioeconomic and social disparities do demonstrate some variability in rates of pain conditions, but epidemiologically, access to care is a major barrier, and once care is accessed the focus should be on providing excellent quality care to each patient.⁷⁷ Pain can present in patients from any demographic group. Although there are groups with higher rates of specific pain-associated conditions, pain is so prevalent that because patients are evaluated as individuals in a clinical setting, it is typically not possible to exclude most pain diagnoses based on demographic features alone. For example, although studies based on clinic

CONTINUED FROM PAGE 1326

Timing

- ◆ Timing of pain and related symptoms is critically important to diagnosis
- ◆ Acute pain, especially with motor features, may necessitate emergent assessment
- ◆ Chronic pain: definition of *chronic* varies with underlying process
- ◆ Chronic pain is that exceeding “normal time for healing” (some use 3 months)
- ◆ Waxing and waning pattern of variation in pain may be informative
- ◆ With insidious pain, providers may need to revisit the initial diagnosis
- ◆ Breakthrough pain: often associated with cancer-related pain
- ◆ Breakthrough pain may also pertain to patients with stable, known chronic pain-associated conditions who experience concurrent development of a new condition
- ◆ Worsening pain may also reflect entering a progressive phase of chronic illness
- ◆ Timing is important for the management and selection of therapies

“Usually associated with”

- ◆ Association of pain with additional symptoms, such as rash, may illuminate diagnosis

“Very much better with”

- ◆ Alleviating factors can inform diagnosis
- ◆ Substantive relief with specific treatments or activity may guide treatment planning

“Worsened by”

- ◆ Aggravating factors are important for diagnosis and management
- ◆ Mitigation of aggravating factors may be important for sustaining vocational and avocational function

samples find that rates of fibromyalgia among female patients far exceed those in males, population-based symptom surveys indicate that sex differences are much smaller, suggesting that true prevalence differences may be smaller than commonly thought.^{60,78,79} Tension-type headache is an example of a condition with remarkably high population prevalence that is relatively rare in the clinical setting, as most patients will self-manage uncomplicated tension-type headache.⁸⁰ Among older adults, there is a slight female predominance for most pain diagnoses, with the exception that diabetic peripheral neuropathy has a slight male predominance.⁸¹

Health systems vary in terms of both the opportunities for interprofessional collaborative care for patients with chronic pain and the provision of a broad range of therapies.^{82,83} For patients with neuropathic pain, it is often appropriate to consider whether the neuropathic pain syndrome would benefit from the addition of physical or occupational therapies. Physical therapy can be especially important for older adults with length-dependent peripheral neuropathies where the risk for falls and ensuing orthopedic injuries is high.⁸⁴ For spinal disorders, there is consideration for collaborative care or referral to chiropractic, physical therapist, pain interventionist, or surgical evaluation depending on the clinical presentation and the patient's preferences.⁸⁵ Few health systems have truly integrated care for persons with chronic pain, as these services tend to be highly resource intensive. The Veterans Health Administration is an example of a health system that prioritizes the engagement of prosthetics and offers a wide range of treatments including whole-health modalities such as exercise, nutrition, and mind-body therapies like yoga and qigong, while also offering mental health comanagement and specific clinical psychological therapeutic approaches such as cognitive behavioral therapy and acceptance and commitment therapy.⁸⁶

Interprofessional collaboration is an important evolving approach for health care professionals who come to their work through separate professional training tracks. Long led by physicians, teams of health care workers are increasingly recognizing that team-oriented health care delivery can be more effective and satisfactory.^{87,88} Even when health care cannot be delivered within a single integrated health system, interprofessional collaboration and the principles of teamwork, communication, ethics, and values, and the responsibility and roles of other professions can deliver care that is patient centered and responsive to the community's needs.⁸⁹ Some exposure to these approaches is helpful as we bridge communication gaps between professions, acknowledging the professional expertise of pharmacists, physical therapists, clinical psychologists, nurses, nurse practitioners, physician assistants, chaplains, and others as members of the health care team.⁹⁰ Finally, the patient, caregivers, and even support animals are important parts of the health system and team when addressing pain.⁹¹ The use of motivational interviewing methods prepares neurologists and others to elicit patient values and priorities in the design of coordinated pain management plans (**FIGURE 1-1**).⁹²

DIAGNOSIS

Diagnostic approaches to pain-associated conditions are distinct from those for other neurologic and neurally mediated conditions in terms of the focus on the somatosensory system and associated processes. Nociceptive processing, like all somatosensory signals, involves (1) transduction, the process of translating

external energy (eg, heat, cold, pressure) into action potentials; (2) transmission, which carries information from the peripheral sensing structures to the spinal and supraspinal centers; (3) modulation, which tempers the flow of information; and (4) perception, which for pain is highly multicentric. The exceptional features of nociceptive processing are delineated with selected clinical implications.^{58,93,94}

The differential diagnosis is critically important to the evaluation process for patients with pain conditions, and the identification and localization of lesions of the nervous system are especially valuable in this regard. Often, non-neurologists may not be familiar with the innervation of a particular area and seemingly minor clues can yield important diagnostic information (eg, reflex asymmetry, focal weakness, autonomic aberrations).⁷⁶ The development of an appropriate differential diagnosis requires knowledge of the most relevant common conditions as well as those that are potentially catastrophic. When a condition presents that could be benign, problematic but self-resolving, or catastrophic, it is always important to weigh the potential harm to the patient of a missed catastrophic diagnosis. For example, new-onset midthoracic spine pain could be nonspecific “back” pain, ligamentous strain, shingles, a collapsed vertebra, or a spinal abscess; some of these are benign, while others present substantial peril. Through neurologic assessment and diagnostic reasoning, the neurologist’s role is to discern the likelihood of needing time-sensitive and resource-intensive testing.

Diagnostic testing is driven by the conditions identified in the differential diagnosis, with special attention to those entities likely to be present, progressive, and harmful. When central nervous system conditions such as myelitis, tumors, infectious masses, or multiple sclerosis are suspected, MRI is typically necessary. For peripheral neuropathy, nerve conduction studies and EMG are most helpful unless there is evidence of only small fiber involvement to the exclusion of large fibers, as evidenced by exam findings of hypersensitivity to repeated presentation of sharp stimuli (eg, sharp-stick tapping test) in the context of

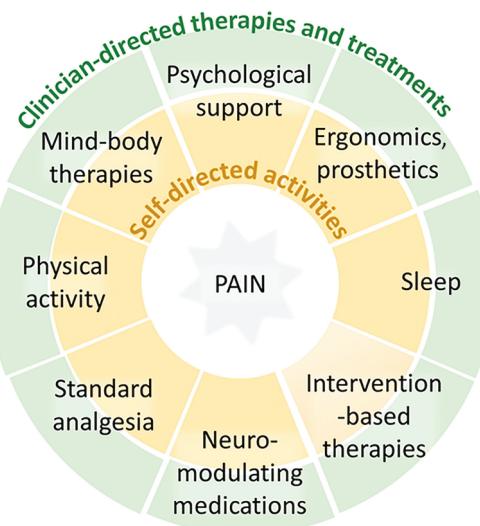


FIGURE 1-1

Coordination of pharmacologic and nonpharmacologic therapies in the management of pain. This model incorporates features of interprofessional collaboration and whole-health and rehabilitative approaches. The aim is to activate as many pain modulation mechanisms including endogenous pain modulation mechanisms (eg, endorphins and endocannabinoids) as feasible for patients with chronic pain, with the goal of restoring health through the modulation of pain in a patient-centered and practical manner. The pharmacologic and nonpharmacologic domains shown here can serve as a framework for a coordinated management plan. Motivational interviewing approaches are used to engage the patient in identifying self-directed health behaviors (yellow bands; eg, moderate physical activity) known to reduce pain and participation in clinician-directed therapies (green bands).

KEY POINTS

- Pain may impact motor, cerebellar, and cognitive function, but these effects will vary by etiology.
- Health systems vary in terms of both the opportunities for interprofessional collaborative care for patients with chronic pain and the provision of a broad range of therapies.
- Interprofessional collaboration and the principles of teamwork, communication, ethics and values, and the responsibility and roles of other professions can deliver pain care that is patient-centered and responsive to the community's needs.
- Normal nociceptive processing, like all somatosensory signals, involves (1) transduction, the process of translating external energy (eg, heat, cold, pressure) into action potentials; (2) transmission, which carries information from the peripheral sensing structures to the spinal and supraspinal centers; (3) modulation, which tempers the flow of information; and (4) perception, which for pain is highly multicentric.
- The development of an appropriate differential diagnosis requires knowledge of the most relevant common pain-associated conditions as well as those that are potentially catastrophic.

normal reflex, strength, vibratory, and proprioceptive findings. For small fiber neuropathy, skin biopsy testing for epidermal nerve fiber density is helpful, although some regional practice patterns favor quantitative sensory testing.⁹⁵ For these conditions, serologic, CSF, or other ancillary testing such as autonomic testing may be needed.

Spine pain-associated conditions may require various approaches to imaging depending on the duration, severity, and neurologic concomitants of the presentation. Plain x-rays (two or more views) can provide rapid information about conditions such as spinal fracture, dislocation (spondylolisthesis), spondylosis, and the general likelihood of disk degeneration; however, for more precise characterization of many persistent, neurologically involved, or progressive spine pain-associated conditions, MRI is needed to assess any compromised neural structures, and CT scan may be needed to further assess bony structures. For structural lesions, imaging is typically considered the definitive diagnostic test, although, in the context of suspected nerve or root compression, nerve conduction studies and EMG may be necessary to appraise functional impact. Plexopathies may require both nerve conduction studies and EMG and MRI to evaluate the plexus using MR neurography. Other testing may be required to either identify a lesion (eg, soft-tissue ultrasound) or evaluate elements included in the differential diagnosis (eg, vascular studies).

PSYCHOSOCIAL FACTORS

Psychosocial systems incorporating psychological, emotional, social, and sociological factors are especially important in pain. Psychosocial factors are often multiply present (eg, depression, trauma, and socioeconomic disadvantage occurring simultaneously). In addition, psychosocial factors have a profound impact on outcomes for patients with pain, so much so that over the last several years factors such as depression and a sedentary lifestyle have been strongly associated with several common pain syndromes, while persistent overexertion can also cause pain.⁹⁶ For many patients, one helpful approach is to invite the patient to identify the psychosocial factors that they believe are important to their current pain management. While this approach may not be appropriate for those with acute pain, when chronic pain is present, patients often have insightful perspectives on their own condition. One technique is to provide the patient with a list of common biological, psychological, and social factors observed in those with chronic pain and ask them to select those they believe are relevant. This both saves time and avoids unintended slights that may arise from asking about these items verbally.

In psychological terms, pain is a stressor that can result in decompensation in patients with both mild and serious mental illness. Substance use lapses and relapse behaviors may be exacerbated by trauma and posttraumatic stress disorder, and management may be complicated in the context of personality disorders.⁹⁷ Depression has a bidirectional relationship with pain in that pain increases the risk for depression and depression appears to increase the risk for chronic pain.⁹⁸ There is similarly a bidirectional relationship between anxiety and pain. Neurologists should be vigilant and diligent in screening for affective disorders and suicidality as the risk of suicide is increased for patients with chronic pain.⁹⁹ Substance use has a variable association with pain as nicotine and alcohol have limited impacts on pain diagnosis rates

(excluding headache); however, the prominent impact of opioids on pain processing and the profound reinforcement of opioids in terms of both pain relief and reward pathways means that in clinical practice opioid use disorder may have an outsized impact.¹⁰⁰⁻¹⁰² The relationships between pain, substance use, and affective disorders may be further complicated in the settings of trauma, polytrauma, sexual trauma, and posttraumatic stress disorder.^{103,104} Personality disorders and certain personality types may be overrepresented in the population of people with chronic pain. Taken together, the interplay between psychological and chronic pain disorders requires neurologists to be prepared to rapidly engage in psychiatric or psychological comanagement, as well as have a standard operating procedure to ensure the safety of themselves and staff. Neurologists should have a low threshold for requesting a chaperone for a visit and should have no tolerance for abuse by patients or those accompanying patients.

Sleep also has a bidirectional relationship with pain in that even modest amounts of pain may worsen sleep quality and limit sleep duration; at the same time, poor quality and limited duration of sleep will limit patients' self-modulatory pain mechanisms.¹⁰⁵ There are many reasons to consider referral to a sleep clinic for patients with actively managed pain.

Social systems have a profound impact on the experience of pain. Employment, education, and economic status impact pain rates at the population level. At the individual level, neurologists can have the greatest impact by proactively inquiring about barriers to pain management in the workplace and providing support to overcome those barriers. These can take the form of ordering prosthetics or ergonomic equipment, completing Family Medical Leave Act paperwork to allow for a modified work schedule, ordering a period of light duty, coaching the patient to request an ergonomic workstation assessment, or engaging with the patient's functional capacity assessment process. Social support, social isolation, and caregivers have a major impact on outcomes and quality of life for people living with pain. Neurologists should assess and document the patient's social status and follow up consistently where relevant. Stages of life and major life events (eg, military service, schooling, work, aging) can impact a patient's experience of pain.¹⁰⁶ Neurologists should determine and respond to the work and home-life factors that influence a patient's capacity to manage pain. Aging, family, and independence are often major factors for how older adults approach living with chronic pain; utilizing techniques of motivational interviewing and acceptance and commitment therapy, which focuses on pursuing activities that have the greatest personal meaning, can be very helpful for prioritizing activities and selecting therapies.⁹²

Disparities, stigma, and bias are central to the experience of pain; for example, patients with neuropathic foot pain often feel that people judge them because they have no physical signs of illness, but their feet hurt them terribly, destroying sleep quality and attenuating their confidence in ambulation. Social disparities and social stigma compound the suffering associated with pain. As noted above, sex has some impacts on pain diagnostic rates, but the experience of access to care or feeling believed and trusted as a patient can vary widely by sex and gender. Gender impacts pain processing, in terms of both psychosocial experience and in response to gender-affirming treatments.¹⁰⁷ Further study is needed to elucidate the mechanisms of these effects. Active and retired military

KEY POINTS

- For structural spine lesions, imaging is typically considered the definitive diagnostic test, although, in the context of suspected nerve or root compression, nerve conduction studies and EMG may be necessary to appraise functional impact.
- For many patients, a helpful approach is to invite the patient to identify the psychosocial factors that they believe are important to their current pain management.
- Neurologists should be vigilant and diligent in screening for affective disorders and suicidality as the risk for suicide is increased for patients with chronic pain.
- Even modest amounts of pain may worsen sleep quality and limit sleep duration; at the same time, poor quality and limited duration of sleep will limit patients' self-modulatory pain mechanisms.
- Motivational interviewing and acceptance and commitment therapy, which focuses on pursuing activities that have the greatest personal meaning, can be very helpful for prioritizing activities and selecting therapies for patients who have pain.

personnel and members of military families have high rates of direct and indirect experiences with pain.¹⁰⁸ Finally, access to health care and health care literacy have profound impacts on pain outcomes; persistent individual efforts, interprofessional collaboration, and community engagement may help to bridge these gaps.

Disability related to pain can be the most important aspect of a patient's experience of pain. For some patients, pain entails motor impairment, coordination, or autonomic dysregulation. It is critically important for the neurologist to assess the patient's mechanics to the extent possible within the scope of consultative or ongoing neurologic care. Ergonomics and prosthetics including adaptive work furnishings, braces, specialized footwear, and assistive devices may be crucial for continued vocational engagement. Neurologists can work with physical, occupational, and recreational therapists, as well as podiatrists, prosthetists, and social workers, among others. It is important to distinguish impairment (which physicians assess) from disability (which disability boards assess) and to help the patient distinguish being impaired in a specific life role (eg, school bus driver, spouse, caregiver) from complete and total disability. If it is not possible for the patient to continue to work in their chosen career, it may be necessary to have an open conversation about the patient's domains of preserved function and career interests and look for potential areas of fruitful overlap. This is not the first choice, but for some patients, permanent disability is not an inevitable outcome, and evidence indicates that vocational engagement has a long-term positive impact on chronic pain.^{109,110}

MANAGEMENT

The first key to managing pain is ensuring that pathologic factors are addressed to the extent necessary and possible. In many situations, pain serves an essential signaling function, indicative of pathology or a need for treatment. This fact is sometimes overlooked in the pain literature, which tends to focus on high-impact (high-utilization) chronic pain. With a differential diagnosis established and a workup in progress, it is also important to attend to symptomatic pain treatments from the first encounter.

Pharmacologic and nonpharmacologic management are both important to optimize pain control while minimizing problematic side effects. For some patients, oral medication may be sufficient to address a particular problem. For those patients for whom single-agent or dual-agent therapy is insufficient, or when side effects are problematic, it becomes more important to introduce the possibility of integrating pharmacologic and nonpharmacologic therapies. By the time a patient is referred to a neurologist, basic treatment approaches have often already failed to alleviate the patient's pain. For patients for whom pain interventional therapy is viewed as most appropriate, the primary care provider will often refer directly to a pain management specialist. A major reason to favor management that proactively incorporates nonpharmacologic approaches is that most pain medications can cause sedation and some degree of cognitive impairment; nonpharmacologic therapies may improve sleep quality, physical function, and quality of life while not having negative impacts on cognition.¹¹¹ In some settings, medication-based solutions continue to be the most common as patients have limited access to, limited capacity for, and financial barriers to nonpharmacologic therapies.¹¹²

The neurologist confronted with managing pain will want to employ an evidence-based approach to the greatest extent possible.¹¹³ Prescription medications used for the management of chronic and neuropathic pain include pain-active antidepressants and pain-active anticonvulsants (including gabapentinoids). All pain-active antidepressants carry a boxed warning for suicidality risks, and these should be explained to patients and instructions for how to respond in the event of suicidal ideation should be provided. In most cases, the neurologist will want to begin pain-active antidepressants at a low dose and titrate up the dose over several weeks. Pain-active anticonvulsants include gabapentin, which was originally developed to mimic γ -aminobutyric acid (GABA) but was found to not affect GABA receptors in vivo. However, it was released as an adjunctive anticonvulsant and later demonstrated to have benefit as a pain treatment, with strong evidence for efficacy in postherpetic neuralgia and painful diabetic peripheral neuropathy. The development of pregabalin offered another alternative in the same chemical class. Carbamazepine and oxcarbazepine are used as first-line treatment for trigeminal neuralgia, and other anticonvulsants may be used for specific neuropathic pain diagnoses.

Cannabinoids remain experimental and may carry specific health harms, including, as for many pain-active medications, a risk of driving impairment.^{114,115} The use of opioids and opioidlike agents for the management of chronic noncancer pain has decreased since the publication of the first set of Centers for Disease Control and Prevention (CDC) guidelines on opioid prescribing in 2016; an updated version of these guidelines was published in 2022.^{16,21,116} Neurologists may find it helpful to learn about topical options for the treatment of focal neuropathic pain; in many locales, over-the-counter and compounded topical preparations offer an additional therapeutic tool for patients.

Systematic reviews, recommendations, and guidelines for nonpharmacologic therapies for pain-associated conditions managed in neurology practice continue to accrue evidence of measurable benefits. Current meta-analyses primarily pertain to headache and musculoskeletal conditions, with more limited data for neuropathic conditions. An assessment of the utility of nonpharmacologic therapies for common pain-associated conditions was undertaken by Skelly and colleagues^{9,117} and published in 2017 and 2018. They focused on a specific set of common conditions, including: nonspecific low back pain; cervicalgia; knee, hip, and shoulder pain; tension-type headache; and fibromyalgia. Skelly and colleagues^{9,117} reviewed a massive body of literature to identify the effect size and quality of evidence for a variety of nonpharmacologic therapies for pain intensity and functional interference, including physical activity (many with active physical therapy direction), massage, mind-body therapies such as yoga and tai chi, clinical psychology treatment, manual therapy, and others. Their review demonstrated that for back pain and other common (non-neuropathic) pain conditions, many therapies have at least some benefits in the short and medium terms, with insufficient evidence to support sustained benefits. Chou and colleagues¹¹³ concurrently examined the evidence in support of medication-based therapy for chronic pain, including low back pain, and found very modest short-term and medium-term benefits and little substantive evidence of long-term benefits.

KEY POINTS

- Disability related to pain can be the most important aspect of a patient's experience of pain. For some patients, pain entails motor impairment, dyscoordination, or autonomic dysregulation.
- Pharmacologic and nonpharmacologic management are both important to optimize pain control while minimizing problematic side effects.
- All pain-active antidepressants carry a boxed warning for suicidality risks; these should be explained to patients and instructions for how to respond in the event of suicidal ideation should be provided.
- Nonpharmacologic therapies for pain-associated conditions managed in neurology practice continue to accrue evidence of measurable benefits.
- Physical activity is important for many reasons, including the upregulation of endogenous analgesic mechanisms and preservation of function, and psychological support is important to reduce pain-related interference with function, suffering, and pain intensity.
- Incorporating coordinated nonpharmacologic therapies can reduce pharmacologic focus and polypharmacy, which is associated with cognitive interference and increased falls in older adults and accidental injury, substance use disorders, and long-term dependency in passive pain relief strategies.

The coordination of treatment options is an important aspect of modern neurologic practice and is not unique to pain-focused care. Cognitive disorders, movement disorders, and other neurologic conditions benefit from “comprehensive” management that selectively incorporates evidence-based therapies. In pain management, there are specific therapeutic domains that are especially relevant. Physical activity is important for many reasons, including the upregulation of endogenous analgesic mechanisms and preservation of function, and psychological support is important to reduce pain-related interference with function, suffering, and pain intensity. Mind-body therapies including yoga and tai chi have demonstrable benefits for several forms of pain, as do specific types of meditation and healthful nutrition. Ergonomics and prosthetics are essential for many patients with pain-associated conditions and should be incorporated proactively into treatment plans. Sleep has a profound association with pain, and efforts to improve sleep can reduce pain impact and severity. Surgical and interventional approaches may be needed; neuromodulating medications should be rationally incorporated into the treatment plan, with evidence-based therapies being selected first, and over-the-counter oral medicines and other preparations may be useful. It is necessary to adapt the selections in these domains for each type of pain, as illustrated in **TABLE 1-3**.¹¹⁸⁻¹²² Incorporating coordinated nonpharmacologic therapies can reduce pharmacologic focus and polypharmacy, which is associated with cognitive interference and increased falls in older adults and accidental injury, substance use disorders, and long-term dependency in passive pain relief strategies.

Interprofessional collaboration is a model of care that aligns especially well with managing pain through the coordination of treatment options.⁸⁹ By working with collaborating providers (eg, physical therapists and clinical psychologists), patients will make important and helpful connections that foster a proactive dynamic toward pain, including increased pain self-efficacy.^{30,87,123} Physical therapists are especially effective in coaching patients to take charge of pain; clinical psychologists implement evidence-based methods of helping patients gain control over pain; and pharmacists, nurse practitioners and nurse educators, chaplains, nutritionists, and social workers all contribute professional perspectives and support patients in acquiring knowledge and skillfulness in pain self-management. Pain self-management alone may not be sufficient to control a severe pain problem, but pain medications alone may provide less robust and durable clinical benefits than desired, and coordinated management is essential for quality of life and function.

Approaches may vary according to patient characteristics, especially when pain is chronic and severe. For patients with busy work schedules or limited access to transportation, therapies that require attendance at multiple daytime sessions become less feasible. For patients with cognitive impairment, it may be necessary to sequence therapies rather than propose concurrent implementation of multiple therapies at once.

CONTEXT OF TREATMENT

Neurologists can function as consultative members of the pain team or as team leaders. There is evidence that pain rates are rising, and this is likely compounded by the aging population. The future of pain management may see more neurologic involvement in pain care. Neurologists bring a special skill set with advanced training in neurologic localization, familiarity with issues pertaining to

Examples of Coordinated Management of Common Pain-associated Conditions

TABLE 1-3

Therapeutic domain	Conditions		
	Low back pain	Lumbar radiculopathy	Distal symmetrical peripheral neuropathy (hyperglycemic)
Physical activity	Remain as active as possible, may need physical therapy (PT) for neuromuscular retraining ^{9,117}	Limit initially as activity may exacerbate nerve and disk pain; PT for palliation and rehabilitation	Remain active to help moderate blood sugar; avoid impact as this may worsen foot pain; consider PT for fall prevention
Psychological support	If self-limited: relaxation, guided imagery; if chronic: cognitive behavioral therapy (CBT) ^{9,116}	Situationaly dependent: eclectic, CBT, stress management, activity pacing	Acceptance and commitment therapy or CBT
Mind and body therapies including nutrition	Gentle yoga or tai chi, meditation, healthful nutrition to support weight reduction ^{9,117}	Yoga: modified and supervised (eg, chair yoga) as tolerated; tai chi as tolerated	Gentle yoga or tai chi, meditation, nutrition counseling to avoid concentrated sugars
Ergonomics and prosthetics	Lumbar support, improved footwear	Lumbar roll, leg bolster, footwear	Diabetic footwear as needed, podiatry
Sleep	Consider heating pad (on medium) for comfort, may need mattress topper	Use leg bolster to reduce spinal pressure; daytime recumbency breaks using bolster	Keep feet cool at night as warming increases pain signaling; time medication for bedtime pain relief
Rescue therapies	Some patients may be candidates for interventional treatments based on underlying pathophysiology ¹¹⁸	Lumbar steroid injection may yield modest short-term pain relief ¹¹⁹ ; if neurologic deficits are present or pain is unmanageable, consider surgical management ¹¹⁸	For poorly controlled neuropathic pain, consider addition of transcutaneous electrical nerve stimulation or spinal cord stimulation ^{120,121}
Neuromodulating medications (including pain-active antidepressants, gabapentinoids, and topical agents such as local anesthetics)	May be beneficial if pain is greater than mild and persistent	May be needed to manage pain; can be incorporated as part of a multimedication regimen to address neuropathic, nociceptive (disk tear if present), and inflammatory components of pain	May be needed to manage pain, as pain may be moderate-to-severe and is typically persistent; consider use of pain-active antidepressants or gabapentinoids; topical lidocaine for focal pain
Over-the-counter (OTC) and standard analgesia	OTC medications are typically recommended; avoid long-term use; avoid opioids; avoid oral steroids; consider OTC topicals ¹¹³	Likely that OTC medications are only minimally effective; avoid opioids; single-dose or short-course oral steroids may provide modest short-term benefit ¹²²	OTC analgesia is unlikely to be effective; due to expectation of longer pain persistence, opioids should be avoided

impairment and disability, and expert knowledge of several medications used for chronic pain.

The US population is facing major challenges in terms of population aging and the pervasive impacts of opioids and other substance use disorders. Most older adults have at least one pain-associated condition, and pain-associated conditions are associated with impairments in mobility and functional independence.

Virtually all older adults with opioid use disorder have at least one pain-associated condition and rates of substance use in older adults are rising, meaning that neurologists will be seeing more patients with general neurologic conditions complicated by concurrent pain and substance use disorders.¹⁰⁰ Coordinated pain management and interprofessional collaboration are essential for these patients (**FIGURE 1-1**).

The current state of pain management has developed over several decades of concerted efforts to improve the understanding and treatment of pain in all areas of health care. Pain was documented in some of the earliest extant human writings, and ancient systems of pain regulation—especially meditation, yoga, acupuncture, and qigong—have developed over millennia. Evidence suggests that access to pharmacologic anesthetics was sharply limited before the modern era. With the advent of microscopy, early scientists such as René Descartes and Robert Remak identified the neural structures, in particular C-fibers, that subsume pain transmission from the peripheral to the central nervous system.^{124,125}

The development of some anesthetics had a perilous early history, including the misuse of cocaine and heroin, which were initially described as “safe.”¹²⁶ The study of ballistic injuries experienced during the American Civil War led Silas Weir Mitchell¹²⁷ to describe causalgia (more recently termed complex regional pain syndrome) and related chronic neuropathic pain conditions. The lack of safety controls in patent medicine preparations, many consumed by those seeking pain relief, led to the creation of the US Food and Drug Administration (FDA) in the early 1900s. By the middle of the 20th century, Kenneth Keele¹²⁸ and others were systematically documenting patients’ pain reports using systematic methods. Scientifically, Alan Hodgkin and Andrew Huxley¹²⁹ elucidated the mechanisms of action potential propagation essential to nociceptive (and all) neural processing. In the latter half of the 20th century, Barbara Travell systematized the study of referred pain and muscular “knots” arising in patients with visceral ischemia, later publishing the landmark description of myofascial trigger points with David Simon.⁵⁴ John Bonica and colleagues²⁴ formed the IASP in 1975, catalyzing growth in basic, translational, and clinical pain research around the globe from that time onward. The systematic classification of headache disorders, starting with the first edition of the ICHD published in 1988, had a major role in advancing headache and facial pain clinical care and science, which arose from an earlier classification published in the 1960s. Peter Dyck and John Griffin¹²⁹⁻¹³¹ contributed to understanding the pathophysiology of peripheral neuropathy. The fall of multidisciplinary pain clinics due to insurance constraints and the resistance of medical schools to incorporating pain as part of the standard curriculum presented substantive and persistent systemic barriers to improvements in pain care.¹³²

Pain clinicians began to widely champion the use of the numerical rating scale for rapid clinical pain assessment in the mid-1990s; at the same time, pharmaceutical companies were strategizing to market opioid medications for

wider use against pain, breaking the long-standing taboo that limited opioids to use in those with terminal cancer pain.¹³³ The publication of a major report for the National Academy of Science, Engineering, and Medicine in 2011, “Relieving Pain in America,” was initially hailed but later met with criticism as some began to associate the dramatic increases in prescription opioid use with the well-intentioned efforts to assess and treat pain with knowledge and compassion, as mandated by the Joint Commission.^{134,135} Prescription opioids undoubtedly contributed to the deaths of many thousands of Americans.¹¹⁶ The CDC opioid guidelines published in 2016 led to a reduction in opioid prescriptions in the United States, and there is evidence that rapid opioid tapering carries increased risks for suicide and mental health deterioration.¹⁰³ Meanwhile, the global context of end-of-life pain management continues to be characterized by extremely limited access to prescription opioids.¹³⁶ The National Institutes of Health (NIH) is currently investing millions of dollars into pain research, promising improved pain care in the future. The efforts to advance pain science and clinical care have continued on many fronts and include innumerable studies, systematic reviews of pharmacologic and nonpharmacologic therapies, and a new era of patient and caregiver empowerment and access to resources to improve pain care.¹³⁷

KEY POINTS

- By working with collaborating providers (eg, physical therapists and clinical psychologists), patients will make important and helpful connections that foster a proactive dynamic toward pain, including increased pain self-efficacy.
- Neurologists bring a special skill set to pain management, with advanced training in neurologic localization, familiarity with issues pertaining to impairment and disability, and expert knowledge of several medications used for chronic pain.

CONCLUSION

Several decades of clinical program building and research, from basic science to meta-analysis studies, have established an integrated pain system with fascinating pathophysiologic features and protean impacts on clinical outcomes and society. A systematic approach to pain clinical care is highly effective and ideally incorporates knowledge, skills, and compassion. A degree of formal training in pain assessment, classification, diagnosis, and management, together with the ability to navigate limitations in health system capacities, the determination to maximize care through interprofessional collaboration, and meaningful responses to the need for advocacy for those affected by social determinants of health are all necessary to improve outcomes. Extensive evidence supports the use of comprehensive pain treatment strategies, which may include pain self-management, integrative, complementary, and whole-health approaches in coordination with pharmacologic and interventional strategies. Exceptional pain care relies on a strong therapeutic alliance between the patient, their caregivers and family members, and clinicians, among whom the neurologist may serve a vital role.

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Spine Pain

By Vernon B. Williams, MD, FAAN

ABSTRACT

OBJECTIVE: Spine pain is one of the most common presenting concerns in health care settings. This article reviews clinical strategies for evaluating and managing patients with spine pain.

LATEST DEVELOPMENTS: Minimally invasive interventional procedures, virtual reality, predictive analytics, neuromodulation, and other evolving technologies are significantly impacting the management of spine pain. Advances in modern pain science have also led to effective skills and treatment strategies, including patient interviews and queries for insight regarding pain, education, and cognitive restructuring, and adjusting the timing of examination (after reeducation) and examination techniques to encourage the experience of movement in the absence of assumed tissue damage. An evolving understanding of the influence of patient-centric thoughts, framing, emotional status, and cognitive restructuring's influence on the brain's response to perceived threat are important aspects of spine pain management.

ESSENTIAL POINTS: The correlation of clinical presentations with structural abnormalities is necessary but insufficient to evaluate and manage spine pain. Modern pain science acknowledges pain as a subjective experience but recognizes a critical distinction between tissue damage, nociception, and the experience of pain. What and how we communicate with patients, as well as evolving neuromodulation technologies, augment conventional approaches.

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Dr Williams discusses the use of antidepressants and antiseizure medications, none of which are approved by the US Food and Drug Administration (FDA) for the treatment of spinal pain.

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INTRODUCTION

Other than headache, perhaps no other pain is more commonly experienced than spine pain.¹ Low back pain remains the leading cause of years lived with disability globally, and it is projected that by 2050 more than 800 million people will have low back pain.² The lifetime prevalence of low back pain is approximately 70%, generating \$87 billion in US health care costs annually.³ It is critical to appreciate the subtle but important distinctions between abnormal imaging, tissue damage, nociception, and the experience of pain.⁴⁻⁵ Cognitive restructuring, neuroplasticity, and neuromodulation can play an effective role in the management of spine pain.⁶⁻⁸

Pain is, by definition, a subjective experience.⁹ Although the anatomic structures, nociceptive signals and pathways, descriptive terms, clinical syndromes, examination findings, diagnostic tests, and treatment options applied to spine pain can fill volumes, the objective of this article is more

focused. This article provides the reader with a fund of knowledge to effectively assist patients with spine pain by accurately understanding, framing, navigating, and overcoming their subjective experience. The goal of this article is to enable the reader to improve their abilities and success at serving patients living with spine pain.

Many general neurologists encounter patients with spine pain. Neurologists with subspecialties unrelated to the spine or pain will also have frequent occasion to evaluate this patient population. An increasing number of neurologists specialize in pain medicine, often with interventional practices.

The majority of patients with spine pain conceive of and frame their experience as the direct and sole result of physical stimuli (“pain signals”) resulting from tissue damage. Modern pain science recognizes the inadequacy of this simplistic concept.⁹ Most treating physicians have content-level knowledge of pain-related neuroanatomy. Physicians treating spine pain will also benefit from an updated awareness and understanding of pain-related neurophysiology and concepts related to neuroplasticity and neuromodulation.^{7,8,10} Most significantly, modern pain science establishes additional factors such as expectation, the brain’s processing and interpretation of sensory input, variations in nociceptive thresholds, and other factors that are critical to the pain experience. However, a significant gap exists, as many treating practitioners lack awareness of these concepts. This gap is particularly concerning (and represents a significant opportunity) given the influence of cognitive restructuring on the pain experience. Unknowingly, the very act of seeking treatment for spine pain may further contribute to nocebo and maladaptive pain-related neuroplasticity through naive (although often well-intentioned) body language, nonverbal messaging, language, and interpretation of test results. “The large disk herniation at L₅-S₁ is what’s causing your pain” may be a well-intentioned statement (or electronic health record message in response to the question “What did my MRI show?”), but it potentially fails to help the patient.

The clinical evaluation and management of patients with spine pain should begin with and continuously reinforce modern pain science while collecting patient history and performing and interpreting the physical examination, while planning and interpreting the results of diagnostic testing, when reviewing findings with patients, and when contemplating a menu of multidisciplinary treatment options.

With these concepts in mind, this article reviews principles related to clinical features associated with commonly encountered diagnoses and etiologies and presents treatment options with an emphasis on emerging developments such as minimally invasive procedures and neuromodulation-based strategies. Pearls, pitfalls, and communication styles are also discussed. Finally, the presence and impact of disparities affecting patient populations with spine pain are reviewed.

SPINE PAIN IN THE CONTEXT OF MODERN PAIN SCIENCE

Modern pain science and emerging theories related to the experience of pain involve far more complex physiologic activity than the ascending and descending pain nervous system pathways typically used to show nociceptive and modulating signals.^{11,12} Additional endocrine and immune system processes influence the body’s response to nociceptive electrical signals.¹¹ This complex physiologic activity is not only variable between individuals but can fluctuate within an individual based on personal history, context, predictions, and

KEY POINTS

- Many patients with spine pain conceive of and frame their experience as the direct and sole result of physical stimuli (“pain signals”) resulting from tissue damage. Modern pain science recognizes the inadequacy of this simplistic concept.
- Modern pain science establishes additional factors such as expectation, the brain’s processing and interpretation of sensory input, variations in nociceptive thresholds, and other factors that are critical to the pain experience.
- Modern pain science and emerging theories related to the experience of pain involve far more complex physiologic activity than the ascending and descending pain nervous system pathways typically used to show nociceptive and modulating signals.
- Pain is defined as an unpleasant sensory and emotional experience associated with or resembling that associated with actual or potential tissue damage.
- Communication with patients who have spine pain should reinforce concepts related to modern pain science. Without vigilant attention, actions and words can negatively impact patient insight, framing, and outcome.

internal models regarding threat and sensory inputs, as well as many other known and unknown factors.¹³ Emerging recognition of how both neuroplasticity (ie, the formation or reorganization of connections in response to injury, stimulation, or experience) and general bioplasticity (ie, similar abilities of the endocrine, immune, musculoskeletal, and other systems) change and evolve in response to nociception and the experience of pain contributes additional complexity.¹²

Clearly, pain is not synonymous with nociception¹⁴ and is defined as an unpleasant sensory and emotional experience associated with or resembling that associated with actual or potential tissue damage.⁹ Forthcoming sections will discuss how and why these foundational concepts are important in the clinical evaluation and management of a patient with spine pain. The basis of the “tissue damage, nociception, and pain are different” principle lies in both a rational consideration of clinical features of pain and basic scientific experimentation, including tissue damage, structural abnormalities on imaging, and the lack of a clear one-to-one relationship between nociceptors and pain.¹⁵

Internalizing principles of modern pain science will influence the treating practitioner’s patient assessment. A single-minded focus on a search for the often elusive structural pain generator via physical examination and diagnostic imaging should be balanced by additional assessments of psychological, emotional, and social factors that influence the expression of pain. The tenor, tone, and content of communication with patients should be informed and influenced by modern pain science. For instance, “I’m going to order an MRI to see what’s causing your pain” is a subtle reinforcement of the “tissue damage equals pain” misconception. Without vigilant attention, actions and words can negatively impact patient insight, framing, and outcome.

Understanding and internalizing concepts related to modern pain science should influence the management of spine pain. As with the assessment and communication-related implications, the management of chronic spine pain is even more significantly influenced than that of acute pain. While there are multiple opportunities to incorporate modern pain science principles into management strategies, perhaps the most critical are related to neuroplasticity and neuromodulation. When devising management strategies, the consideration of neuroplasticity will involve an expanded appreciation of biological factors (at the level of the spinal cord, within the brain, and distributed throughout the body) contributing to the pain experience and prevent inappropriate and sole focus on the simple treatment of a peripheral anatomic spine “pain generator.” Traditional approaches to neuromodulation (eg, radiofrequency ablation, cryoanalgesia, spinal and peripheral nerve stimulation) as well as what can be described as “broad net view” versions of neuromodulation (ie, the alteration of neurologic activity and function through the purposeful application of cognitive restructuring, autonomic quieting, optimization of sleep, and incorporation of movement and exercise) become integral aspects of a multidisciplinary, holistic, and rational approach to the management of spine pain.

CLINICAL EVALUATION OF SPINE PAIN

This section provides a reasonable approach to the evaluation of a patient with spine pain. These general principles and categories are not exhaustive but rather provide a framework for patient assessment.

Classification Strategies

There is a rich and complicated collection of structures in the spine capable of contributing to nociceptive signaling. One strategy for organizing candidate structures and potentially associated etiologies is to categorize the anatomic structures by elements in the axial plane (**FIGURE 2-1**¹⁶). Anterior compartment structures include vertebral bodies and disks. Compression fractures with wedge deformities, internal disk disruption, annular tears, disk herniations, and other pathologies may be present in this compartment. The neuraxial compartment structures include the epidural space and neural structures. External compression of neural structures (eg, disk herniations, stenosis, avulsion fractures) and compressive effects of intraspinal masses are examples of pathologies in this compartment. The posterior compartment includes muscles and joints. Pars fractures, facet arthropathy, and muscular sprains or contusions may be present in this compartment.

Compartmental classification strategies are often employed in conjunction with common pathologic conditions, which can be further classified (eg, musculoskeletal, degenerative, nerve related, systemic). Temporal classification as acute (present for less than 12 weeks) or chronic (present for 12 or more weeks) may aid the clinical evaluation of spine pain. Of course, many patients will experience both acute and chronic pain and intermittent flare-ups of chronic spine pain. This kind of classification strategy is most helpful when considering the effects of time on pain-related physiology. While acute pain is more consistently associated with clear and distinct location, character, distribution, and exacerbating and relieving factors that correlate with classic clinical presentations, these specificities are less consistent in the setting of chronic pain. Likely owing to the maladaptive effects of neuroplasticity with time, chronic pain becomes less specific relative to location. Patients may describe more diffuse pain areas rather than denoting a specific location in the neck, back, or extremities. As pain becomes more chronic, patients are more prone to fear avoidance, with subsequent effects on movement and range of motion. The importance and role of associated changes in mood and motivation begin to

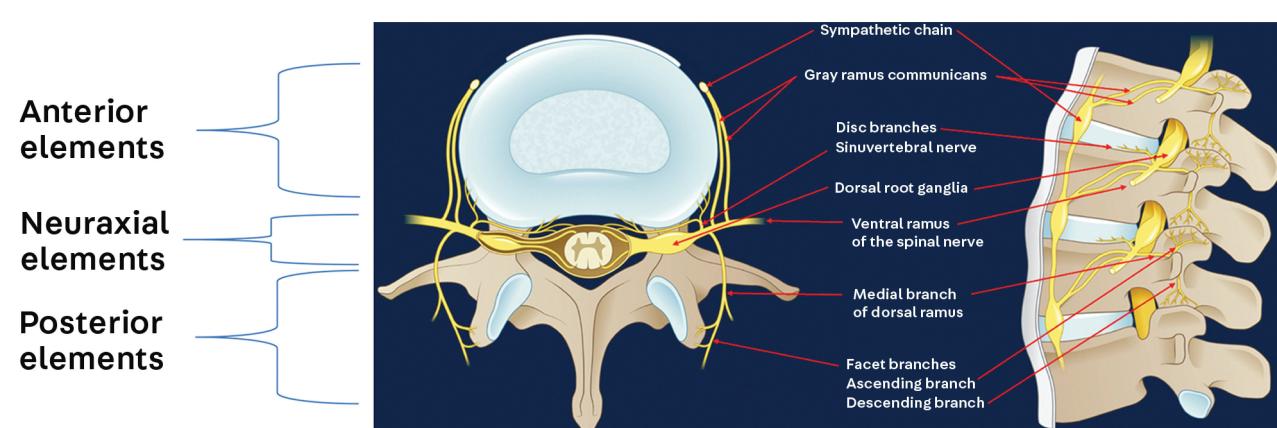


FIGURE 2-1

Spine neuroanatomy and the pain-signaling mechanisms in the anterior, neuraxial, and posterior elements.

Modified with permission from Ota Y, et al, Radiographics.¹⁶ © 2020 Radiological Society of North America.

surpass the role of traditional nociceptive encoding systems in a patient's presentation and pain experience (**CASE 2-1**).

Finally, evaluation and management may be aided by classification using special patient categories. For instance, adolescents with back pain can be classified as a special patient category in that they are susceptible to pars stress reactions and fractures. Individuals with spine pain after trauma are also at risk of fracture. Patients with a preexisting history of cancer represent a special category, given their increased risk of spinal malignancy. A special patient category may be considered for those with "red flags" such as associated fever, infection, IV drug use, or other increased risk of infection; bowel or bladder disturbance or other

CASE 2-1

A 45-year-old woman was injured while working as a flight attendant 6 months before presenting to the pain clinic. At the time, she had experienced sudden-onset, severe, axial lower spine pain without radiation into either leg. She reported ongoing pain rated at 10/10 in severity despite treatment with physical therapy, medications, and acupuncture. MRI revealed an annular tear of the L5-S1 disk, and she attributed her pain and functional limitations to this finding. She had undergone two lumbar epidural steroid injections with temporary partial relief.

Her examination was significant for marked pain behaviors, including grimacing with movement, frequently changing and readjusting her sitting position, and tearfulness during the interview. Her physical examination was significant for give-way weakness on motor testing and reduced lumbar range of motion, but was otherwise normal. There was tenderness with spasm and guarding of her lumbar paraspinal muscles. She described pain radiating from the lower back up to the neck and shoulders with palpation of the lumbar spine. Her gait was slow, guarded, and antalgic.

Based on her presentation, a 12-week, home-based, functional recovery program was recommended including a personal pain coach for education and cognitive restructuring to reframe the "tissue damage equals pain" concept, with accompanying access to an immersive virtual reality-assisted embodiment training program to reverse maladaptive pain-related changes, leverage neuroplasticity to facilitate motion, and decouple the "movement equals pain" experience to reduce fear avoidance. Significant and progressive improvement was noted in her level of insight, the recognition of contributors to her personal pain experience, and accessible mitigation strategies. Upon completing the 12-week program, she had significantly improved, including her visual analogue scale score and physical examination findings.

COMMENT

This case illustrates several important points related to chronic pain in general and spine pain specifically. Changing the patient's beliefs about the relevance of the MRI abnormalities and reframing her understanding of pain concepts changed the status and course of her condition for the better.

cord compression risks or cauda equina syndrome; progressive neurologic deficit; rapid deterioration; or those requiring urgent and aggressive intervention.

Patient History

Besides the traditional aspects of a pain history (eg, onset, duration, course, location, severity, character), historical features that assist in the evaluation and management of spine pain involve the collection of additional useful information. It is important to determine if the pain is axial or radicular, or comprises components of both. Axial pain without significant radiation into the legs (particularly below the knee) suggests vertebral body, diskogenic, facet, sacroiliac, or muscular conditions. Radicular or radiating pain from the spine into one arm or leg suggests nerve root compression, whereas pain radiating from the spine into both arms or both legs symmetrically suggests an intraspinal condition. Historical features related to exacerbating and relieving factors relative to position and activity can also be helpful (**TABLE 2-1**).

Patient Examination

The most important examination techniques for spine pain evaluation include musculoskeletal and neurologic components. A detailed motor, sensory, and muscle stretch reflex examination is necessary to evaluate specific spinal level, root, and dermatomal distributions that can be correlated with subjective symptoms, diagnostic imaging, and in some cases electrodiagnostic testing. Information on spinal root levels and correlated muscle innervation as well as dermatomal maps for sensory examination and referral patterns typical of pain distribution are widely available. Movement can be limited by changes in muscle tension and the production of a pain experience as a result of the brain's attempt to protect the body from tissue damage or worsening pain when a threat is perceived.

Range of motion should be documented and monitored with notation regarding pain-free range capabilities, as well as a detailed description of the language used to describe pain, evidence of fear avoidance, and comparison of reported limitation during formal examination compared with efforts and

Features to Consider in the Spine Pain History

TABLE 2-1

Exacerbating factor	Potential correlating considerations
Weight bearing (standing or walking)	Muscular, diskogenic, joint (facet, sacroiliac, or hip)
Prolonged sitting	Facet joint, sacroiliac joint, or both
Bending forward or flexion	Anterior compartment or muscles
Bending backward or extension	Canal or foraminal stenosis, facet joints
Turning or spinal rotation	Joint, muscle, or both
Valsalva maneuver	Diskogenic or neuraxial compartment
Worsens over the course of the day	Muscle fatigue or deconditioning
Only during the work week	Fatigue, job satisfaction

capabilities when distracted. For example, patients may successfully sit or arise from a chair in the waiting or examination room, yet exhibit a dramatic reduction in voluntary range of motion to flexion of the lumbar spine at the time of formal examination. Squinting, verbalizing, bracing, and other pain behaviors are often associated with fear avoidance. Patients may anticipate pain that never occurs (often to their surprise) with slow, guided encouragement. The range of motion assessment also provides an opportunity to use the examination as a tool to reinforce pain science, communicate with the goal of knowledge transfer, and positively contribute to cognitive restructuring. Many clinicians find value in overtly communicating differently with the patient before, during, and after range-of-motion assessments. Practitioners may find value in reassuring patients that, in the absence of red flags (based on the history already taken and aspects of the examination already performed), movement is safe (**TABLE 2-2**). Examining physicians may offer examples of how attempts at protection can result in the experience of pain in the absence of tissue damage or injury. Providing reassurance combined with examples of when the patient may have been observed to move, or reminding the patient of examples of having achieved movement even since the onset of symptoms without permanent worsening in their condition, can be helpful. Patients are often surprised that they possess the ability to move the head and neck or lower back without pain or significant worsening when they move slowly, are provided positive reinforcement, and are given a specific task with the intent of knowledge transfer in conjunction with physical assessment. If successful, this can be a powerful experience and an opportunity to demonstrate that even one pain-free “rep” is evidence that motion in and of itself is not

TABLE 2-2

Examples of Features to Consider Before Encouraging Movement in Patients With Spine Pain

Red flags: image before encouraging movement

- ◆ Loss of bowel or bladder control
- ◆ Acute-onset extremity weakness
- ◆ Severe or incapacitating pain
- ◆ Marked hyperreflexia or pathologic reflexes
- ◆ Symptom onset associated with trauma
- ◆ Structural deformity
- ◆ History of cancer

Yellow flags: consider imaging before encouraging movement

- ◆ Marked muscle spasm or guarding
- ◆ Severe pain with movement
- ◆ History of pathologic fractures
- ◆ Immunosuppression
- ◆ Prolonged duration of symptoms
- ◆ Progressively worsening symptoms
- ◆ Fever, weight loss

damaging. This kind of revelation can begin to reverse the process of negative reinforcement often inherent in the maladaptive neuroplasticity associated with chronic pain, subconscious neurologic predictions, and the contributions to the experience of pain made by attempted protection through limitation of motion. Finally, there are opportunities to further monitor a patient's range of motion as a means of evaluating the effects of treatment interventions and even to leverage predictive analytics in the setting of movement and range of motion as a treatment itself.

Provocative testing is a crucial aspect of the clinical evaluation of spine pain. For cervical spine pain, the Spurling test involves an evaluation of the cervical spine by extending, laterally flexing, and rotating the neck to one side. A positive test involves the reproduction of symptoms radiating into the arm on the affected side and suggests nerve root tension from compression or inflammatory irritation.

In addition to provocative maneuvers that reproduce or worsen symptoms, other examination techniques provide information by relieving symptoms with specific positioning or manipulation. Examples include cervical distraction, wherein the examiner places the patient in a neutral spine position (typically while lying supine, but also possibly in the sitting position). The head and neck are gently pulled upward (distracted) and the patient is queried about improvement in neck or arm pain. Relief or resolution of arm pain suggests cervical radiculopathy. The test may help distinguish between arm pain arising from the cervical spine versus that related to shoulder or plexus etiologies. Another maneuver involves having the patient raise the affected arm above shoulder level (as if raising the hand to ask a question) and then resting the arm on top of their head. Relief of radiating arm pain from this maneuver also suggests a cervical localization rather than a shoulder or plexus etiology for pain.

Axial pain in the cervical spine may also be assessed with provocation. The examiner placing a hand on the forehead and actively resisting attempted cervical flexion with resultant pain production suggests an increased risk of instability. In the lumbar spine, the straight leg raise test can be performed in both the sitting and supine positions. Positive testing, indicated by pain radiating down the leg, suggests nerve root tension, irritation, or compression. Bragard sign is positive if additional dorsiflexion of the patient's ankle further exacerbates pain after onset during the straight leg phase.

A positive crossed straight leg raise test involves radiating pain into one leg with straight leg testing on the opposite or unaffected side. There are also provocative tests that assist with the evaluation of axial (nonradicular) pain involving the lumbosacral region. While it is frequently taught that extension, rotation, and lateral bending "loads" the facet joints, with the reproduction or worsening of axial pain on the loaded side suggesting facet arthropathy as a contributing factor, attempts to validate this association have failed.¹⁷ In the supine position, **flexion, abduction, and external rotation of the hip (FABER test)** may reproduce pain emanating from the hip or sacroiliac joint.

Diagnostic Testing

Routine imaging for individuals with spine pain who have nonspecific symptoms, no red flags, and have not had appropriate trials of conservative treatments can be costly, ineffective, and may contribute negatively to patient outcomes.¹⁸ In the absence of red flags, imaging of the spine is not typically

KEY POINTS

- When devising spine pain management strategies, the consideration of neuroplasticity will involve an expanded appreciation of biological factors (at the level of the spinal cord, within the brain, and distributed throughout the body) contributing to the pain experience and prevent inappropriate and sole focus on the simple treatment of a peripheral anatomic spine "pain generator."
- Likely owing to the maladaptive effects of neuroplasticity with time, chronic pain becomes less specific relative to location.
- Axial pain without significant radiation into the legs (particularly below the knee) suggests vertebral body, diskogenic, facet, sacroiliac, or muscular conditions.
- Radicular or radiating pain from the spine into one arm or leg suggests nerve root compression, whereas pain radiating from the spine into both arms or both legs symmetrically suggests an intraspinal condition.
- Provocative testing is a crucial aspect of the clinical evaluation of spine pain.

warranted for spine pain with or without radicular symptoms when symptoms have been present for 6 weeks or less and there is no history of attempted treatment. However, patients with spine pain with or without radicular symptoms that have been present for 6 weeks or longer and who are potential candidates for interventional procedures may benefit from initial imaging.

MRI without contrast is the initial imaging modality of choice in most cases.¹⁹ In some circumstances, alternative imaging may be indicated. In patients with suspected spinal instability or adolescents with suspected pars fracture, radiography with flexion and extension views and oblique views, respectively, may be beneficial. A CT scan may be appropriate when a fracture is suspected or to evaluate suspected bony abnormalities.^{19,20} In patients with a history of lumbar spine surgery, MRI with IV contrast may provide additional benefit. Patients with metallic artifacts from prior surgery may benefit from a CT scan as well. MRI with and without IV contrast is indicated when infection or malignancy is suspected and in patients who are immunosuppressed.¹⁹

When interpreting imaging results and relaying information to patients (particularly those related to degenerative changes), it is critical to do so with appropriate respect for the power of nocebo effects and cognitive restructuring.²¹ *Nocebo* is defined as the expectation of sickness and the affective states associated with such expectation causing sickness in the expectant patient.²² As most patients equate imaging results with tissue damage and a linear relationship to pain, they are subject to the nocebo phenomenon. Most patients and treating practitioners are familiar with the concept of placebo.²³ There is far less familiarity with the concept of nocebo, which is equally influential in both its objective physiologic and subjective effects.^{21,22} In the setting of spine pain experienced by an individual with abnormalities on diagnostic imaging, the potential for nocebo effect exists when, for instance, the patient is told they have a disk herniation without additional explanation regarding whether the finding really represents a bulge, protrusion, or herniation; whether it is at a location that correlates with their symptoms and physical examination; or if they are informed that changes develop over time as part of the typical and expected evolution of the maturing spine, usually in the absence of pain or dysfunction (FIGURE 2-2). Similarly, degenerative disk disease, facet joint arthropathy, degenerative spondylolisthesis, and other imaging findings may be misinterpreted regarding

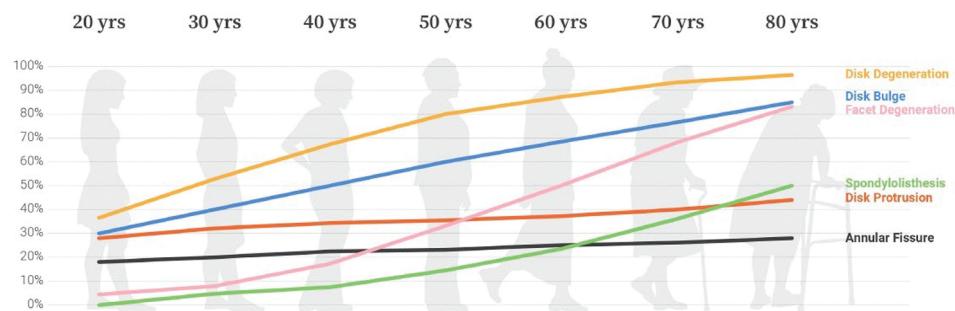


FIGURE 2-2

Prevalence of various common MRI abnormalities with age, even among healthy individuals without spine pain. This highlights and reinforces the lack of consistent correlation between structural changes, "tissue damage," and the clinical experience of pain.

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their relationship to tissue damage and being pain generators as opposed to normal and expected findings or findings that do not correlate with symptoms. This risk is of particular importance in the setting of electronic health records that, in the interest of providing full and immediate access to test results and other components of medical records, expose patients to the test results before they can be reviewed in context with the ordering provider.⁵

Diagnostic imaging in the evaluation of spine pain is not limited to x-ray, CT, and MRI. Despite some limitations relative to the depth of penetration, diagnostic ultrasound may assist in the evaluation of soft tissue structures (primarily myofascial) and assessment for inflammatory changes (such as those involving the sacroiliac joints and overlying iliosacral ligaments).²⁴ Additional testing may include electrodiagnostic and laboratory studies to evaluate for inflammatory, autoimmune, or other conditions associated with spine pain.

KEY POINT

- Routine imaging for individuals with spine pain who have nonspecific symptoms, no red flags, and have not had appropriate trials of conservative treatments can be costly, ineffective, and may contribute negatively to patient outcomes.

Nonspine Painful Conditions

It should be noted that part of spine pain evaluation involves awareness of and often specific testing to rule out conditions that may mimic a spinal condition. Shoulder and brachial plexus conditions may mimic a cervical spine condition. Retroperitoneal and abdominal structures with mass effect may drive a patient to seek care for what they believe is back pain of spinal origin. Hip pathology and piriformis syndrome can mimic lumbar radicular pain. Patients may have structural findings in multiple anatomic locations that could potentially contribute to subjective symptoms. A unifying hypothesis that respects Occam's razor (the philosophy that problem-solving principles recommend a search for the smallest possible set of elements or simplest explanation) is preferred. However, it is also possible that "epiphrenomena" associated with altered mechanics, motor weakness or asymmetries, and maladaptive compensation may result in multiple factors contributing to the patient's pain.

MANAGEMENT OF SPINE PAIN

There are general and specific approaches to the management of acute and chronic spine pain. Generally speaking, stratified care and shared medical decision-making principles employing evidence-based medicine strategies are most appropriate. The intensity of treatment relative to the level of invasiveness and risk of intervention should correlate with the duration and severity of the pain and the level of functional disability, with a progressive increase in intensity of intervention over time and as indicated. However, the presence of red flags, catastrophic or incapacitating pain, or a progressive neurologic deficit would justify immediate aggressive intervention.

Shared medical decision making recognizes the unique and individual characteristics of the patient experiencing pain and values patient preference in management options when multiple appropriate options are available. Cultural beliefs, past experiences, personal values, family or financial concerns, or other priorities may reasonably influence management decisions. As previously discussed, education and careful communication with the goal of meaningful knowledge transfer are paramount. Recommendations for treatment options should be grounded in evidence-based medicine. An exhaustive and comprehensive discussion of specific options in each management category is beyond the scope of this article. However, the following concepts should be considered.

Cognitive Restructuring

When considered in the context of spine pain management, careful communication and patient education aimed at meaningful knowledge transfer, particularly following the tenets and principles of modern pain science, usually represent a form of cognitive restructuring and a form of treatment intervention. It is a critical and effective component of management. When patients seek care for spine pain, there exists a tremendous opportunity to educate in ways that can undo maladaptive framing of their pain. Cognitive restructuring opportunities present themselves at multiple points in the evaluation and management, including the interpretation and discussion of patient symptoms, the physical examination, and the interpretation of diagnostic imaging and selection of other management interventions. One should be aware of what can be described as “nocebogenic” language or reinforcement of maladaptive framing.²⁵

Cognitive restructuring should be the foundation for communicating diagnoses, discussing treatment options, and answering these and other questions that arise that demonstrate inaccurate or maladaptive framing of the patient seeking care. Moreover, highlighting and reinforcing the benefits of movement and providing information that encourages optimism instead of any prior, pessimistic conception can help optimize the patient’s benefit from pain treatments.

Nonpharmacologic Interventions

Traditional options include physical and chiropractic therapies, home acupuncture, cognitive behavioral therapy, and judicious use of bracing. In the author’s experience, additional benefits can be seen with the formal prescription of additional strategies:

- ◆ Autonomic quieting through mindfulness meditation and purposeful breathing techniques. Framing these practices in the context of beneficial physiologic effects on stress response, heart rate variability, nerve sensitization, and muscle relaxation can improve patient acceptance and increase compliance.¹¹
- ◆ Purposeful increase in movement by walking (at speeds and for durations sufficient to result in moderate exertion), the elimination of prolonged sitting, and participation in a self-directed program of stretching and strengthening exercises.²⁶
- ◆ Prescribed and vigilant attention to optimal sleep hygiene focusing on regulating bedtime, sleep duration, wake time, and sleep efficiency.

Pharmacologic Interventions

General principles of pharmacologic intervention include the use of the minimal effective or necessary dose and the number of medications necessary to manage pain and optimize function. Acetaminophen, prescription analgesic medications in the nonsteroidal anti-inflammatory drug, corticosteroid, and muscle relaxant categories, and other adjunctive antidepressant and antiseizure medications (used off label) may have a role in the pharmacologic management of spine pain. Prescription opioid medications should generally be avoided except in selected circumstances (such as in the immediate postoperative period or limited supply of short duration for incapacitating acute pain), and then under close supervision with appropriate warnings, informed consent, and use agreements documented.²⁷ Every effort should be made to limit dosages to generally recognized as safe

morphine equivalent daily dosing and to avoid combinations of controlled prescription or over-the-counter substances that may synergistically depress nervous system function or respiratory drive and expose patients to a risk of catastrophic side effects or death.^{27,28} Alternative routes of administration and nontraditional forms of analgesics should be considered to minimize risk, minimize side effects, maximize safety profile, and optimize effect. For example, topical versions of local anesthetics and nonsteroidal anti-inflammatory drugs may augment, allow a reduction in the dose of, or replace systemic medications. Drug formulations with rapid onset of action, long-acting or gradual absorption, or those that do not require traditional gastrointestinal absorption (eg, intranasal, transmucosal, and transdermal versions of anti-inflammatories, partial agonist opioids) may be safer and more effective alternatives to consider in appropriate candidates.

Nonsurgical Interventional Procedures

Interventional procedures may be indicated in the evaluation and management of spine pain for diagnostic or therapeutic purposes. Generally speaking, diagnostic and therapeutic interventional spine procedures should be performed with image guidance (eg, ultrasound, fluoroscopy, CT, or, rarely, MRI) to reduce the risk of unintended needle placement (eg, intravascular, intrathecal, pneumothorax) and to document and confirm the intended placement and location and spread of injectate. Diagnostic injections are intended to confirm the source of a patient's pain, typically when considering radiofrequency ablation or surgical intervention. For example, a selective nerve root block in the cervical or lumbar spine may assist surgeons in selecting necessary spinal levels for surgical intervention. Diagnostic injections should be limited to local anesthetic and not include steroids, which can confound the interpretation of results. Injected steroids are subject to systemic uptake and can result in symptomatic improvement on that basis rather than the blockade of the specific and intended structure being tested.

Efforts should be made to collect objective responses to diagnostic injections that correlate with the expected duration of action of the local anesthetic used. Pain diaries or other strategies that allow for review of the patient's response as documented in real time may be more accurate than retrospective description, memory, or the misinterpretation of a temporary effect as ineffective. Therapeutic injections may include local anesthetics, steroids, onabotulinumtoxinA, or other substances, but the evidence for the use of regenerative injections in the spine is currently limited.^{29,30}

Differential diagnoses associated with spine pain based on combinations of subjective symptoms, physical examination, and diagnostic testing may result in potential targets, including but not limited to intramuscular trigger points, medial branches of the dorsal ramus (innervation of facet joints), facet joints, nerve roots, the epidural space, sacroiliac joints, iliosacral ligaments, cluneal nerves, lumbar rami communicantes, or sympathetic ganglia.³¹⁻³⁵ Generally speaking, axial pain results in the preliminary consideration of facet or medial branch targets, as well as lumbar rami communicantes structures. Radiating, radicular pain may result in the consideration of epidural steroid injections. Lower back pain with radiation into the buttock or groin raises suspicion for sacroiliac joint targets, whereas lower lumbar and gluteal pain may imply cluneal nerve targets. Again, due to the significant overlap and arborization of

KEY POINTS

- Cultural beliefs, past experiences, personal values, family or financial concerns, or other priorities may reasonably influence management decisions for patients with spine pain.
- Alternative routes of administration and nontraditional forms of analgesics should be considered to minimize risk, minimize side effects, maximize safety profile, and optimize effect in patients with spine pain.
- Drug formulations with rapid onset of action, long-acting or gradual absorption, or those that do not require traditional gastrointestinal absorption (eg, intranasal, transmucosal, and transdermal versions of anti-inflammatories, partial agonist opioids) may be safer and more effective alternatives to consider in appropriate candidates with spine pain.
- Diagnostic injections for spine pain should be limited to local anesthetic and not include steroids, which can confound the interpretation of results.
- Pain diaries or other strategies that allow for the review of the patient's response as documented in real time may be more accurate than retrospective description, memory, or the misinterpretation of a temporary effect as ineffective.

sensory fibers involving structures associated with the spine and surrounding tissues, pain location is only one factor to consider. Historical features related to onset, exacerbating and relieving factors, and physical examination findings in conjunction with diagnostic imaging are significant contributing factors.

Nonsurgical interventional procedures are not limited to injections. Together with growing experience and insight regarding neuroplasticity, neuromodulation strategies are increasingly employed in the treatment of spine pain. Moreover, the use of these strategies is no longer limited to a “last resort” or in the event of inadequate response to other intervention trials. Radiofrequency ablation and cryoanalgesia are effective strategies for facet joint–related pain and other pain with peripheral nerve targets involving sensory nerves (**CASE 2-2**).

CASE 2-2

An active 65-year-old man with a history of cervical spine surgery (anterior cervical discectomy and fusion at C4-C5) 8 months earlier presented with 8/10 axial neck pain and daily posterior and occipital headache that began 2 to 3 months after his surgery. He denied radiating arm pain (which he had experienced previously but that resolved after his surgery). The headaches had no migrainous features and were described as 6/10 to 7/10 in severity, “tight,” and “aching” with some radiation from posterior to anterior. He had tried oral medications without improvement. He was concerned that he needed “another surgery at the level above” and worried that he would lose function, ruining his quality of life. His examination was significant for a mildly positive Tinel sign with percussion over the greater occipital nerve on the right, and a negative Tinel sign on the left. There was reduced range of motion to cervical flexion and extension, with pain on extension. There was no significant tenderness to cervical palpation. Motor, sensory, reflex, and gait examination was normal.

Updated imaging of the cervical spine revealed levoscoliosis at the cervicothoracic junction, a degenerative disk with central disk protrusion and canal stenosis at C3-C4, an intact fusion at C4-C5 with residual foraminal narrowing, and multilevel facet arthropathy involving C2-C3 through C5-C6. Trials of oral medication, physical therapy, and occipital nerve blocks provided only partial benefit. Fluoroscopically guided diagnostic cervical medial branch blocks were performed with local anesthetic bilaterally at C2-C3 and C3-C4 on two occasions, each providing greater than 80% improvement in neck and headache pain consistent with local anesthetic effect (peak effect for 3 to 6 hours with gradual return of symptoms). Bilateral radiofrequency ablation was subsequently performed under fluoroscopic guidance at C2-C3 and C3-C4, resulting in a reduction in pain score from 8/10 to 1/10 to 2/10 in the neck and resolution of his posterior headache pain. Follow-up revealed a durable benefit in pain relief for approximately 4 to 5 months with a gradual increase and return of neck pain, but not headache. Repeating the procedure in combination with additional physical therapy, a regular exercise program, and cognitive restructuring effectively resolved the symptoms.

Perhaps the most significant recent developments in the neuromodulation of spine-related pain involve the growing evidence and experience in the application of spinal cord stimulation and peripheral nerve stimulation for chronic axial spine pain.³⁸⁻⁴⁰ While spinal cord stimulation involves an initial trial period of stimulation followed by permanent implantation of a system (which will eventually require additional procedures to change batteries and possibly address issues associated with lead migration or component failure), some peripheral nerve stimulation systems have demonstrated significant long-term benefit after temporary stimulation without requiring permanent implantation.^{39,41} For more information, refer to the article “Neuromodulation for Neuropathic Pain Syndromes” by Prasad Shirvalkar, MD, PhD,⁴² in this issue of *Continuum*.

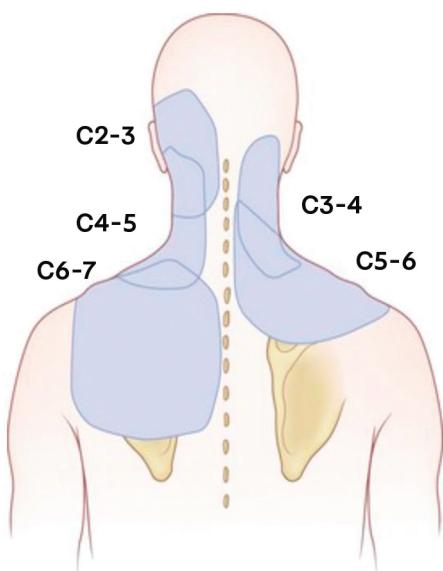


FIGURE 2-3
Pain referral patterns from the cervical facet joints in posterior orientation.
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This case demonstrates a common presentation of cervical facet syndrome with respect to axial pain without radiation; referral pattern, in this case into the occiput, which is consistent with upper cervical facet arthropathy (**FIGURE 2-3**³⁶); diagnostic imaging; history of evolution after cervical fusion; and positive response (at least 50% improvement) to diagnostic injections (which should always be limited to local anesthetic without steroids).³⁷

COMMENT

Although pain relief and symptomatic benefit may be limited to a 3-month to 4-month period, many patients will have a significantly longer duration of benefit, particularly with subsequent procedures and when combined with physical therapy, exercise, and cognitive restructuring.

Surgical Intervention

There are relatively few scenarios that would be classified as absolute indications for surgical intervention. Spinal cord compression with acute myelopathy, conus medullaris or cauda equina syndrome, rapidly progressing neurologic deficit, and incapacitating pain with clearly correlated structural explanations are examples, as is protection from the imminent or highly likely development of these conditions. Most surgical referrals will involve appropriate but relative indications for surgical intervention. Even in these cases, there should be a clear correlation between a structural abnormality and the patient's subjective symptoms and objective examination, an inability to manage the symptoms or prevent functional decline nonsurgically, an acceptable level of risk for medical and surgical complications, and appropriate expectations regarding surgical outcome.

It behooves the referring physician and surgeon to include a sober discussion with patients about the "risks, benefits, and alternatives" and the reality that the goal of surgical intervention may or may not be a return to normal. In many cases, the goal is to be better than the preoperative state or to prevent further deterioration, rather than "normal." As a long-time partner with orthopedic surgeons, it is the author's experience that surgery is rarely successful when performed because nothing else has helped or there is nothing else to do. Other general concepts to be aware of and discuss with patients are that, in general, chief symptoms of extremity pain are more successfully treated with surgery than axial pain. This is likely because there are many potential nociceptive structures contributing to axial pain, whereas radiating extremity pain is more successfully localized, providing more targeted surgical intervention. That said, surgery for back pain due to fracture, tumor, infection, or deformity tends to have better outcomes than surgery for back pain due to degenerative disease. Furthermore, with the extension and expansion of surgical levels comes an increasing risk of adverse events, complications, and persistent pain.

In general, larger surgeries are recommended and necessary for back pain than for leg pain. Multilevel anterior and posterior fusion with instrumentation has a different likelihood of success and risk of complication than single-level microdiscectomy. Surgical intervention in the spine can be categorized relative to the goal of decompression, fusion to reduce maladaptive motion, or disk replacement to facilitate motion. Decompressive technologies include minimally invasive procedures such as microdiscectomy and endoscopic procedures, which may be considered for disk herniations with nerve root compression as well as laminectomy for spinal stenosis. Minimally invasive implantation of spacers for spinal stenosis may be considered as well. Many spine surgeons will limit fusion for degenerative disease with criteria that may involve (but not be limited to) long-standing, chronic debilitating pain that does not respond to aggressive nonsurgical treatment including aerobic conditioning and trunk strengthening, the absence of reversible biological risk factors such as smoking, the absence of behavioral and psychological risk factors evaluated through psychological assessment and testing for outcome predictors,⁴³ and no evidence for alternative and competing etiologies for pain.

Social Determinants, Disparities, and Spine Pain

As previously discussed, pain (including spine pain) is best briefly described as a subjective experience. It does not exist without an individual experiencing the

effects of a complex interaction between biological, psychological, and social factors. Each component ingredient is itself complex and subject to variability affected by background, history, and context. As a result, health equity, health disparities, and social determinants of health must be recognized in light of the inevitable and inarguable effects on spine pain and addressed in all approaches to spine pain evaluation and management.⁴⁴ Health equity is the fair and just opportunity to be as healthy as possible. Health disparities involve the reality and existence of increased illness, increased burden of disease, decreased life expectancies, and increased health care costs observed in certain communities. There are known disparities in the rates of and outcomes from many conditions, including spine pain. There are multiple contributing factors and opportunities for improvement.

Disparities in spine pain have been seen in African American and Hispanic populations.⁴⁴⁻⁴⁷ There are also disparities in access to care due to insurance coverage, geographic limitations, and transportation issues⁴⁸; socioeconomic status, with limited access to specialty care, physical therapy, and nonsurgical treatments in lower socioeconomic groups⁴⁹; provider bias, including implicit bias, potentially affecting provider assessment of pain severity and treatment options⁴⁴; and sex and gender bias, with women more likely to report pain, but less likely to receive aggressive treatments.^{1,50,51}

Moreover, all clinicians should endeavor to improve potential disparities within the scope of their practice and influence, including those evaluating and treating patients seeking care for spine pain. The first step involves acknowledging that health inequity is a problem that eventually and in some way affects everyone (whether directly or indirectly). Additional steps involve using screening tools to discover inequities within and among practice patients, creating processes and protocols to improve health equity, earmarking resources for the purpose of improvement, and potentially partnering with outside organizations to better serve affected individuals.^{44,52,53}

KEY POINTS

- Increasingly, and in concert with increasing experience and insight regarding neuroplasticity, neuromodulation strategies are being successfully employed in the treatment of spine pain. Moreover, the use of these strategies is no longer limited to a “last resort” or in the event of inadequate response to other intervention trials.
- Surgical intervention in the spine can be categorized relative to the goal of decompression, fusion to reduce maladaptive motion, or disk replacement to facilitate motion.
- Health equity, health disparities, and social determinants of health must be recognized in light of the inevitable and inarguable effects on spine pain and addressed in all approaches to spine pain evaluation and management.

CONCLUSION

Spine pain is prevalent and leads to significant disability worldwide. It is one of the most common conditions for which an individual will seek medical care. Due to the complex nature of pain, its subjective nature, and complex physiology (which is widely distributed, involves multiple biological systems, and variable relationships between biological, psychological, and social factors), it is incumbent upon treating practitioners to resist the temptation to focus solely on potential anatomic structures as “pain generators” and narrowly focused treatment trials. Particularly in the case of chronic spine pain (but also with acute spine pain), successful evaluation and management must instead recognize and incorporate evaluation and management in a more holistic fashion.

Given the influence of prediction and protective neurologic activity on the experience of pain, it is critical to assist patients seeking care in developing an accurate model and framework for pain. Importantly, this involves reversing the common assumption that tissue damage, nociception, and pain are consistently, reliably, and inevitably connected. Patient education should indicate that nociception is not pain, and both nociception and pain can and do occur in the

absence of tissue damage. Knowledge of the musculoskeletal anatomy, candidate nociceptive structures, clinical presentations, diagnostic assessments, and effective interventions associated with evaluating spine pain is required but insufficient alone to successfully evaluate and manage spine pain.

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Peripheral Neuropathic Pain

REVIEW ARTICLE



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By Victor Wang, MD, PhD; Miroslav Baćkonja, MD

ABSTRACT

OBJECTIVE: This article synthesizes current knowledge on neuropathic pain, with a brief review of mechanisms, diagnostic approaches, and treatment strategies to help neurologists provide effective and individualized care for patients with this complex condition.

LATEST DEVELOPMENTS: The most promising developments in peripheral neuropathic pain are related to the molecular biology of the peripheral nervous system. Systematic molecular and genetic analyses of peripheral nerve terminals and dorsal root ganglia have advanced our understanding of the genetics of function and disease of peripheral nerves, as well as their physiology and clinical manifestations.

ESSENTIAL POINTS: Peripheral neuropathic pain, similar to central neuropathic pain, is primarily influenced by the biology and pathophysiology of the underlying structures, peripheral sensory nerves, and their central pathways. The clinical course is widely variable in sensory symptoms and intensities, natural history, and response to treatments.

INTRODUCTION

There are more than 100 different causes of peripheral neuropathy,¹ which can be overwhelming to a practicing neurologist. An efficient approach in differentiating categories of neuropathies is to start with identifying pain as a predominant component and then use the pain symptoms and the disease prevalence to establish the likelihood of a specific diagnosis.² Patients usually describe typical painful sensations such as tingling, pins and needles, burning, tingling, and stabbing, termed *paresthesia* and *dysesthesia*, as most bothersome. In addition to these pain symptoms, neuropathic pain frequently includes hyperalgesia (worsened pain from noxious stimuli) and allodynia (pain caused by innocuous stimuli).³ In the setting of many neuropathies, these symptoms typically involve the feet and sometimes the hands, although they can also affect other parts of the body. By the time the patient seeks medical help, the symptoms have usually become severe enough to interfere with activities of daily living. Severe cases of painful neuropathy can affect employment and relationships and cause significant anxiety and depression. Some patients may find it difficult to stand for any length of time, whereas others may find it more difficult to sit for long periods, both of which can make many tasks challenging.

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PRODUCTS/INVESTIGATIONAL
USE DISCLOSURE:**
Drs Wang and Baćkonja discuss
the use of divalproex sodium,
high-dose gabapentin, IV
ketamine, IV lidocaine,
lacosamide, α-lipoic acid,
peripheral nerve stimulation,
valproic acid, and venlafaxine,
none of which are approved by
the US Food and Drug
Administration (FDA) for the
treatment of peripheral
neuropathic pain.

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Peripheral sensory nervous system disorders are usually painless, regardless of underlying pathology.⁴ Most peripheral nerve pathologies result in the loss of function of the peripheral nerves across all types of nerve fibers. Because of their peripheral nature, these nerve fibers have a limited capacity for repair, resulting in chronic impairment and persistent pain. Disease-modifying therapy is generally limited to treatment of the underlying cause of the neuropathy when it can be identified. Despite these limitations, advances over the past 2 decades continue to lay the foundations for both the diagnosis and treatment of painful neuropathies.

Most peripheral neuropathic pain disorders are chronic, with variability in symptom manifestations and disease course. Postherpetic neuralgia, a chronic condition that can occur after herpes zoster from reactivation of a varicella-zoster infection, is an example of how acute pain can develop into a chronic neuropathic pain condition. The likelihood of chronic neuropathic pain in these patients, or postherpetic neuralgia, increases with age.^{5,6} Multiple investigators have demonstrated that peripheral neuropathic pain from different underlying etiologies share common clinical presentations and phenotypes.^{1,7} Underlying pathologies determine the course of the peripheral nerve disease, although the pain itself may follow an independent clinical trajectory.

Progress in the development of therapeutics for the treatment of pain in peripheral neuropathic pain has been slow. There is no curative therapy for peripheral neuropathic pain and, in all cases, the therapy and management are symptomatic, to relieve pain and improve function and quality of life. One area of progress has been the development of systematic approaches to the assessment of neuropathic pain, beginning with appropriate classifications of symptoms associated with neuropathic pain. These approaches include the recognition of sensory deficits and the positive sensory phenomena of ongoing pain, paresthesia, stimulus-evoked allodynia, hyperalgesia, and dysesthesia, which aid in the diagnosis of neuropathic pain.³ Based on these factors, several patient-reported outcome tools have been developed to quantify the signs and symptoms of peripheral neuropathic pain. Progress has also been made in using psychophysical and other approaches in treatment. Together, these tools have improved the systematic study of peripheral neuropathic pain. The most widely studied neuropathies are diabetic neuropathy, postherpetic neuralgia, traumatic neuropathies and neuralgias, and radiculopathies. More recent studies include other types of peripheral neuropathic pain, such as postsurgical neuralgias,⁸ which should improve our understanding of underlying mechanisms.

More recently, progress has been made in understanding molecular biology at the terminal and dorsal root ganglia level by identifying transduction mechanisms at the receptor level and other constituent elements of the nerve terminals and associated mechanisms. Some of this progress includes genetic factors, immune responses, and the influence of metabolic mechanisms that can lead to peripheral sensitization, which all contribute to the basis for the understanding of peripheral neuropathic pain.

PATHOPHYSIOLOGY

The traditional clinical approach to any potential disorder of neurologic origin starts with consideration of etiologies, with the goal of correcting the underlying cause of neurologic disease. However, for peripheral neuropathic pain, there is

no neuropathic pain–specific etiology or pathology; rather, a wide range of disorders present with peripheral nerve disease that may manifest with a component of neuropathic pain as a clinical feature (**TABLE 3-1**). In most patients with painful neuropathies there is impairment of other sensory functions, but the involvement of motor functions is less common. The etiologies of peripheral nerve disorders include, but are not limited to, metabolic, traumatic, toxic, infectious, paraneoplastic, inflammatory, autoimmune, and genetic neurodegenerative causes.

Several large clinical studies have demonstrated that painful neuropathies share distinct sensory pain phenotypes, pointing to shared pain pathophysiologic mechanisms regardless of pathology.⁹ **TABLE 3-1** lists several painful peripheral neuropathy disorders. These mechanisms are shared among various etiologies, which lead to the development of positive and negative sensory symptoms and signs.

The fact that the pathology and associated pathophysiology of the primary neuropathy process are frequently distinct from the pathophysiology of the associated pain makes treating peripheral neuropathic pain challenging. An extensively studied example of a primary peripheral nerve disease pathology with associated pain is diabetic neuropathy. The associated pain syndrome is frequently termed *painful diabetic neuropathy* or *neuropathic pain due to diabetic peripheral neuropathy*. Depending on the pain assessment approaches applied, the prevalence of pain in patients with diabetic neuropathy is reported to be in the range of 35% to 50%,^{10,11} demonstrating that most patients with diabetic neuropathy do not have pain. Pathologic mechanisms that lead to diabetic neuropathy include the metabolic burden of hyperglycemia together with dyslipidemia and altered insulin signaling, leading to several pathologic alterations in neurons, glial cells, and vascular cells. This cascade of metabolic abnormalities leads to failures of nerve function and ultimately neuropathy, which affects all elements of nerve structure and function, including DNA damage, endoplasmic reticulum stress, mitochondrial dysfunction, neurodegeneration, and loss of neurotrophic signaling; these can go on to trigger macrophage activation.¹² The importance of these pathways in the development of neuropathy varies with cell type, disease profile, and time course because distinct cell types are more or less susceptible to injury depending on the metabolic impairments,^{11,13} none of which have a primary role in the initiation and maintenance of neuropathic pain mechanisms that could be associated with neuropathy.

Although the primary pathology affects peripheral nerves in painful diabetic neuropathy, several pathologic changes in the peripheral and central nervous system neurons contribute to the pathophysiology of painful symptoms of diabetic neuropathy. Ion channels at the terminals of nociceptors can undergo glycation through the addition of methylglyoxal to form advanced glycation end products, which can contribute to the gain of function of these channels and neuronal hyperexcitability. Changes at the perikaryon include increased expression of voltage-gated sodium channels, such as Na_v1.8, which can lead to hyperexcitability.¹⁴ In myelinated axons, the expression of Shaker-type potassium channels is reduced, which can also contribute to hyperexcitability.¹⁵ Hyperexcitability of peripheral sensory neurons is termed *peripheral sensitization* and leads to increased stimulus responses and ectopic neuronal activity, leading to excessive nociceptive input to the spinal cord. In the spinal cord, microglia

KEY POINTS

- When discussing painful peripheral neuropathies, patients usually describe typical painful sensations such as tingling, pins and needles, burning, and stabbing, termed paresthesia and dysesthesia, as most bothersome.
- In addition to paresthesia and dysesthesia, neuropathic pain frequently includes components of hyperalgesia (worsened pain from noxious stimuli) and allodynia (pain caused by innocuous stimuli).
- Most peripheral neuropathic pain disorders are chronic, with variability in symptom manifestations and disease course.
- There is no curative therapy for peripheral neuropathic pain and, in all cases, the therapy and management are primarily symptomatic, to relieve pain and improve function and quality of life.
- A wide range of disorders may present with peripheral neuropathic pain as a clinical feature.
- Several large clinical studies have demonstrated that painful neuropathies share distinct sensory pain phenotypes regardless of etiologic pathology, pointing to shared pain pathophysiologic mechanisms.

become activated and further enhance excitability within the dorsal horn, all of which contribute to the chronicity and severity of pain in diabetic peripheral neuropathy through a process known as *central sensitization*.^{13,16,17} Central sensitization has been a focus of specific treatment approaches such as spinal cord stimulation, duloxetine, and nonpharmacologic treatments.

TABLE 3-1**Common Causes of Peripheral Neuropathic Pain****Diabetes****Chemotherapy-induced peripheral neuropathy****◆ Vinca alkaloids**

- ◆ Vincristine
- ◆ Vinorelbine
- ◆ Vinblastine

◆ Platinum chemotherapeutics

- ◆ Oxaliplatin
- ◆ Cisplatin

◆ Taxanes

- ◆ Paclitaxel
- ◆ Docetaxel

◆ Epothilones**Radiation therapy****Alcohol-use disorder****Shingles****◆ Postherpetic neuralgia****Nerve compression or injury****◆ Trauma****◆ Surgery****◆ Spinal root compression****◆ Tumor compression****Paraproteinemic peripheral neuropathies****Small fiber neuropathy****Cranial neuropathies****◆ Trigeminal neuralgia****Human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS)****Complex regional pain syndrome****Amputation****◆ Phantom limb pain****Paraneoplastic peripheral neuropathy****Hereditary peripheral neuropathies**

that likely provide pain and symptom relief by restoring the descending inhibition.¹⁸

Another example of a primary abnormality of peripheral nerve gain of function is the pathophysiology underlying erythromelalgia, in which peripheral sensitization is caused by small nerve fibers with abnormal physiologic function of the transient receptor potential cation channel subfamily V member 1 (TRPV1) receptors¹⁹ and Nav1.7 sodium channels.^{14,20,21} However, as in most painful disorders, sensory mechanisms in the periphery do not stop at the dorsal horn because, invariably, there is a component of central sensitization regardless of the peripheral mechanisms. The role of peripheral and central pain mechanisms is well demonstrated in painful diabetic neuropathy by the use of psychophysical (eg, controlled pain modulation), pharmacologic (eg, duloxetine), and stimulation (eg, spinal cord) interventions.

Traumatic nerve injury is known to cause pain; for example, in neuropathic pain due to brachial plexopathy from brachial plexus traumatic injury there is a sensory and motor deficit in addition to neuropathic pain, with both a peripheral and central component. Another painful disorder characterized by neuropathic pain is trigeminal neuralgia, usually caused by a compression of one of the branches of the trigeminal nerve by an adjacent tortuous blood vessel. The primary manifestation is the paroxysmal neuropathic pain evoked by stimulation of a circumscribed trigger zone over one of the trigeminal nerve branches on one side of the face, whereas other components of peripheral nerve functions are not affected.^{22,23}

To understand the dual peripheral and central nature of peripheral neuropathic pain pathophysiology, the diagnostic workup must account for peripheral nerve pathology and the sensory manifestations of peripheral and central sensitization. This can manifest in the form of allodynia and hyperalgesia and extend to a range of sensory modalities. Clinicians must assess for peripheral nerve pathology to account for sensory loss but also for positive sensory phenomena, which can be challenging.

ASSESSMENT AND DIAGNOSIS

It is important to translate an understanding of the complexity of the pathophysiology of peripheral neuropathic pain into clinical evaluation, assessment, and treatment planning. Initial assessment begins with taking a history of pain and its course and includes sensory and pain domains as well as psychological and social aspects, including the impact of pain on function and quality of life. Patients in acute pain may need more urgent workup. History taking for chronic pain is a source of information that should lead to appropriate peripheral nerve localization and identification of pain-associated clinical symptoms. The absence of gold standard diagnostic testing for pain other than descriptors identifying qualities of pain and localization of pain makes patient history of utmost importance. Many referrals to neurology are for pain of unknown etiology, making it challenging for neurologists to determine whether there is a clear neurologic cause for the pain after workup for other causes. The purpose of referral to neurology is often to exclude neuropathic pain.

The assessment and diagnostic process should identify critical elements to support the diagnosis of neuropathic pain. Because the nervous system functions as the transmission system for conveying sensory information, pain is often attributed to the neurologic messenger when the clear cause is not always

CASE 3-1

A 65-year-old man presented to the clinic with searing and itchy pain on his right forehead corresponding with a vesicular rash that lasted approximately 10 days. He had a history of hypertension. He was initially diagnosed with contact dermatitis and prescribed topical corticosteroids with instructions to keep the area clean. The pain increased, and the rash progressed to become clearly vesicular. The rash then cleared after another week, but the pain persisted. Three months after resolution of the rash, the patient sought neurologic evaluation because of persistent pain. He described the pain as a burning, itching, and aching pain, which he rated as 7/10 in severity. Over-the-counter pain relievers did not decrease the pain. On examination, a slight skin discoloration manifested with loss of pigment, and his forehead had no signs of lingering vesicular rash. Light touch exacerbated the pain over the right side of his forehead and to his right ear, and he did not wash the area often because any touch made his pain worse.

On further questioning, the patient remembered that he had a dozen painful vesicles the size of grains of rice; this was confirmed on a camera phone picture he took around the tragus of his right ear and in his forehead. He recalled that the pain and itching started a few days before the photo was taken. He was diagnosed with postherpetic neuralgia following V1 distribution herpes zoster and started on neuropathic pain treatment, including gabapentin and topical lidocaine.

COMMENT

This case stresses the importance of taking a thorough history to connect persistent symptoms with prior conditions that may have resolved. During acute varicella-zoster virus eruption in the V1 distribution, a primary concern is the possibility of eye involvement affecting the cornea, which can lead to keratitis, uveitis, and potential vision loss. For that reason, these patients should be referred to an ophthalmologist. Another important aspect regarding acute varicella-zoster virus infection is that the infection and pain should be treated aggressively with medications such as valacyclovir and gabapentin, respectively; early intervention leads to fewer complications related to both the infection and pain.^{24,25} Acute varicella-zoster virus can be misdiagnosed as other skin conditions that are similar in appearance, leading to delayed treatment and more severe postherpetic neuralgia. Postherpetic neuralgia is a known complication occurring after herpes zoster infection, and patients may not present with the typical dermatomal rash, which can manifest as only a small number of skin eruptions. For patients who do not benefit from gabapentin at recommended doses, pregabalin can be considered; although these two medications are pharmacologically related, many patients obtain analgesic benefits from this switch.

obvious or if a thorough workup has not been completed (**CASE 3-1**). Neuropathic pain is not exclusively caused by specific peripheral nerve damage and can be more clearly defined as a dysfunction of the nervous system. Neuropathic pain reflects activation of the nociceptive sensory nervous system, conveying nociceptive signals in the absence of specific sensory stimuli, such as in burning pain without thermal heat stimulation, as frequently reported by patients with fibromyalgia.

Peripheral neuropathic pain can be debilitating and interfere with activities of daily living. Neuropathic pain frequently causes emotional distress due to the chronicity and severity of the pain. This distress sometimes makes getting a clear history challenging, especially if the symptoms have been present for a long time. Patients can often be referred to a neurologist with an initial diagnosis, and it is important to consider a wide range of differential diagnoses.

Several patient-reported outcome tools have been developed over the past 2 decades; some help clinicians assess the severity of neuropathic pain symptoms, such as the Neuropathic Pain Symptom Inventory,²⁶ whereas others, in addition to assessing the severity of neuropathic pain symptoms, can assist in differentiating neuropathic pain from non-neuropathic pain (eg, Neuropathic Pain Questionnaire and painDETECT Questionnaire)²⁷⁻²⁹ and evaluating the effects of pain on patient life and quality of function (eg, Brief Pain Inventory).^{30,31} Otherwise, there is a complete library of patient-reported outcomes to assess pain and its interference and other aspects of neuropathic pain such as mood, anxiety and depression, catastrophizing, and sleep; these assessment tools can be found in the National Institutes of Health (NIH) Toolbox, called PROMIS (Patient-Reported Outcomes Measurement Information System).³²

Neuropathic pain is often described as burning, tingling, stabbing, or shooting sensations. The pain can be either constant or intermittent and usually affects the hands, feet, arms, and legs, but it can affect any part of the body. These qualities of pain can help differentiate neuropathic pain from non-neuropathic pain. To further support the possible diagnosis of peripheral neuropathic pain, colored pain drawings can be used to combine the description of pain with an anatomic distribution of pain on the body map.³³ This pattern of neurologic presentation in total is what distinguishes peripheral neuropathic pain from central neuropathic pain. In addition to distinguishing pain patterns, the presence of long tract signs, such as spasticity and hyperreflexia in the area of pain, are indicative of a possible central neuropathic pain process.

Specific elements, such as metabolic disorders, infections, or exposure to chemicals, including drugs from the patient's history, are used to determine the differential diagnoses. In addition to the patient history, a neurologic examination is important in localizing the lesion responsible for the neuropathy.

Depending on the backgrounds of the patient and provider, the term *pain* can take on many different meanings. However, many descriptors of pain are similar across patients. Nerve root dysfunction is often described as a shooting pain radiating down a specific dermatome in the upper or lower extremities but is sometimes described as an achy or tingling pain. Diabetic neuropathy is described by patients most often as tingling and numbness in a stocking-glove pattern. Early in the disease process, patients may report the symptoms starting in the soles of their feet. Diabetic neuropathy is one of many length-dependent

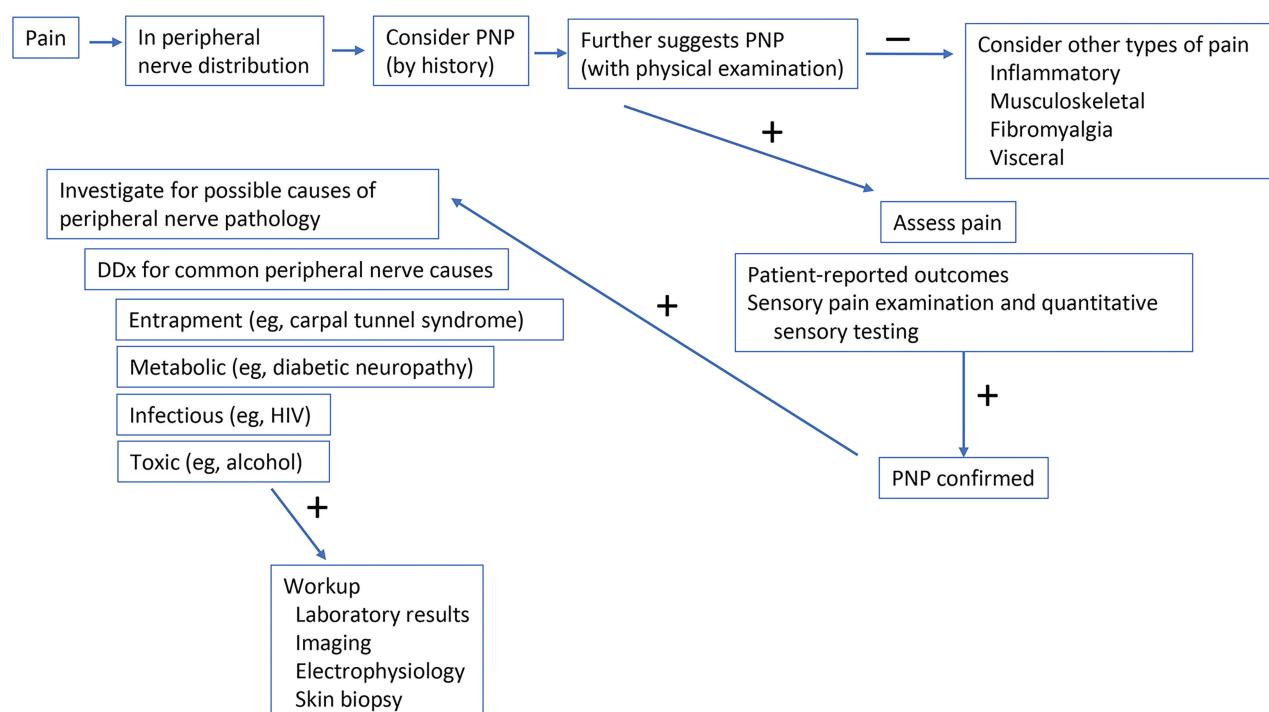
KEY POINTS

- To understand the dual peripheral and central nature of peripheral neuropathic pain pathophysiology, the diagnostic workup must account for peripheral nerve pathology and the sensory manifestations of peripheral and central sensitization.
- It is important to translate an understanding of the complexity of the pathophysiology of peripheral neuropathic pain into clinical evaluation, assessment, and treatment planning.
- Initial assessment of patients with neuropathic pain begins with taking a history of pain and its course, affected sensory and pain domains, and psychological and social aspects, including the impact of pain on function and quality of life.
- Several patient-reported outcome tools have been developed to help clinicians assess the severity of neuropathic pain symptoms and response to treatment.
- Negative sensory phenomena almost always conform to the peripheral nerve anatomy, following the nerve, plexus, or root distribution, whereas positive sensory phenomena are frequently detectable outside of the peripheral nerve distribution because of the central sensitization phenomenon.

peripheral neuropathies, and typically pain that starts in the toes and feet with time ascends to the lower legs and ultimately to the knees. When the symptoms reach the knees, patients usually begin to experience the same feelings in their fingertips because of the similar length of sensory nerves from the spinal nerve root entry zone to the knees and fingertips.

Once neuropathic pain is considered and the presence or absence of peripheral nerve pathology is determined, the physical examination is used to confirm sensory and potentially motor deficits, whereas the pain-related sensory examination findings are more positive for sensory phenomena such as paresthesia, dysesthesia, allodynia, and hyperalgesia (FIGURE 3-1). Negative sensory phenomena almost always conform to peripheral nerve anatomy, following the nerve, plexus, or root distribution, whereas positive sensory phenomena are frequently detectable outside of the peripheral nerve distribution because of the central sensitization phenomenon. Pain associated with weakness can facilitate localization with the additional possibility of injury to peripheral motor nerves, plexus, nerve roots, anterior horn, or spinal cord. Other causes such as myelopathy must be explored in the right context.

In addition to the clinical bedside evaluation, additional approaches to specifically evaluate neuropathic pain are available. These include quantitative sensory testing, a psychophysical method of quantitatively assessing neuropathic sensory abnormalities,^{34,35} and skin punch biopsy for evaluating intraepidermal nerve fiber count, which is the histologic assessment of the peripheral small nerve fiber status.³⁶ Nerve conduction studies and EMG may be performed

**FIGURE 3-1**

Diagnostic approach to the evaluation of patients with suspected peripheral neuropathic pain (PNP).

DDx = differential diagnosis; HIV = human immunodeficiency virus.

to assess peripheral nerve function; however, they do not serve as a replacement for the bedside sensory examination and quantitative sensory testing.³⁷ Initial blood screening tests include those used to evaluate for causes of neuropathy: complete blood cell count; thyroid, renal, and liver function tests; blood glucose, hemoglobin A_{1C}, and vitamin B₁₂ levels; and serum protein electrophoresis with immunofixation. If radiculopathy is suspected, MRI of the spine (lumbar, cervical, or thoracic) is usually ordered to examine for nerve root compression and other causes of radiculopathy.

Interventional pain procedures, such as nerve blocks, involve injecting local anesthetics near affected nerves to temporarily block transmission of action potentials in nociceptive small-diameter nerve fibers and are frequently used for diagnostic purposes to assess the possibility that a specific nerve is the sole source of pain. Nerve blocks can then be used for further diagnostic and therapeutic planning.

TREATMENT

There are no known curative therapies for peripheral neuropathic pain, and the main focus of neuropathic pain therapy is symptom control and improvement of function and quality of life. Neuropathic pain is best managed with a multimodal and multidisciplinary approach, which, in addition to pharmacotherapy, can include psychological support, training, and a comprehensive range of physical therapy modalities (**TABLE 3-2**; **CASE 3-2**). These optimally incorporate a tailored exercise program, ideally a patient-specific transdisciplinary care program, neurostimulation, and behavioral and functional restoration.

Pharmacologic Treatments

Pharmacologic treatments are more effective for positive phenomena, such as symptoms of neuropathic pain (eg, tingling, burning, stabbing, shooting, dysesthesia), than they are for negative symptoms (eg, hypoesthesia, numbness).

Several oral medication types are used for the symptomatic treatment of neuropathic pain. These include both antiseizure medications and antidepressants. US Food and Drug Administration (FDA)-approved medications for painful diabetic neuropathy include pregabalin, duloxetine, and tapentadol extended release. It should be noted that professional guidelines discourage the use of opioids, specifically for the treatment of pain in diabetic neuropathy; however, professional pain societies and guidelines recognize that some patients with severe neuropathic pain (other than painful diabetic neuropathy) still require treatment with opioids under close supervision by clinicians skilled in prescribing opioids.³⁸ Other medications widely used in the treatment of painful neuropathy include gabapentin, amitriptyline, dextromethorphan, venlafaxine extended release, divalproex sodium, lidocaine patch, and 8% capsaicin patch, based on trials conducted over the past 3 decades and summarized in various systematic reviews and professional society guidelines.³⁹ Topical capsaicin is another FDA-approved medication with a specific indication of treatment for neuropathic foot pain.

ANTISEIZURE MEDICATIONS. Antiseizure medications are usually the first-line treatment for painful neuropathies. Gabapentin is the most widely used medication, with studies showing doses of up to 1200 mg/d being tolerated by most patients with a reduction of pain, although FDA approval is up to

KEY POINTS

- There is no known curative therapy for peripheral neuropathic pain, and the main focus of neuropathic pain therapy is symptom control and improvement of function and quality of life.
- Neuropathic pain is best managed with a multimodal and multidisciplinary approach, which, in addition to pharmacotherapy, can include psychological support, training, and a comprehensive range of physical therapy modalities.
- Antiseizure medications are usually the first-line treatment for painful neuropathies.

1800 mg/d. Saturable active intestinal transport results in widely ranging serum concentrations of gabapentin across individual patients, so some studies have used up to 3600 mg/d in 3 divided doses, which has been a rationale for the off-label use of this medication to attempt to optimize relief. To overcome the issue of unpredictable absorption, gastroretentive preparations and strategies for improved absorption have been developed. Pregabalin is also considered first-line therapy and tolerated at levels up to 600 mg/d. Side effects of this medication class include somnolence, fatigue, dizziness, ataxia, weight gain, and swelling.

Carbamazepine was used as the first antiseizure medication to treat the neuropathic pain of trigeminal neuralgia; however, the utility of carbamazepine has been limited because of the monitoring required for side effects such as hyponatremia. Multiple drug-drug interactions with carbamazepine exist, including valproic acid, warfarin, phenytoin, antipsychotics, and birth control medications. A clinical trial has shown that oxcarbazepine, another pharmacologically related voltage-gated sodium channel blocker, specifically

TABLE 3-2

Peripheral Neuropathic Pain Treatments^a

Pharmacologic therapies

◆ Gabapentinoids

- ◇ Gabapentin^b
- ◇ Pregabalin^b

◆ Serotonin-norepinephrine reuptake inhibitors (SNRIs)

- ◇ Duloxetine^b
- ◇ Venlafaxine

◆ Tricyclic antidepressants

- ◇ Amitriptyline
- ◇ Nortriptyline

◆ Topical treatments

- ◇ Lidocaine^b
- ◇ Capsaicin^b

◆ Central-acting opioid agonist

- ◇ Tapentadol^b

Stimulation therapies

◆ Spinal cord stimulation^b

◆ Peripheral nerve stimulation

◆ Transcutaneous electrical nerve stimulation (TENS)

◆ Scrambler therapy

Psychological and behavioral therapies (part of multimodal integrative care)

^a This table contains currently used treatments, most of which have some evidence for analgesic efficacy based on results of clinical trials. Off-label use is discussed in the article.

^b US Food and Drug Administration (FDA)-approved therapies.

CASE 3-2

A 53-year-old woman presented to the neurology clinic with persistent tingling and numbness in her fingers and toes. Nine months ago, she was diagnosed with stage IIIB breast cancer and underwent surgery to remove the tumor and then underwent chemotherapy. Her chemotherapy regimen included doxorubicin and cyclophosphamide for four cycles followed by paclitaxel for another four cycles.

During her chemotherapy treatment, she experienced multiple side effects, including nausea, fatigue, and hair loss. She noticed tingling and numbness in her fingers and toes shortly after the beginning of treatment, making it difficult for her to button her clothes, hold utensils, and walk comfortably. She also noted that handling anything cold, such as taking bottles of beverages out of the refrigerator, was extremely painful, so she wore gloves to reduce the pain. Her physical examination revealed bilateral sensory deficits and diminished proprioception and vibration sense in her fingers and toes. Her Romberg test was positive. Nerve conduction studies and EMG demonstrated a length-dependent peripheral neuropathy.

The patient was diagnosed with chemotherapy-induced peripheral neuropathy-associated pain, and she was started on treatment with duloxetine at a dose of 60 mg/d, which caused nausea; the duloxetine was restarted at a lower dose of 20 mg/d with a slow titration to the therapeutic dose of 60 mg/d. She was referred for physical therapy and occupational therapy to help maintain fine motor skills and manage balance problems. The patient was evaluated by a health psychologist who diagnosed her with severe anxiety and insomnia and who initiated cognitive behavioral therapy to assist with developing better coping skills to address pain and anxiety. The paclitaxel was discontinued by the oncologist to prevent further neurotoxicity, and alternative chemotherapy regimens were discussed with the patient and her medical team.

This patient's symptoms align with the typical presentation of chemotherapy-induced peripheral neuropathy which is a potential complication of treatment with several chemotherapeutic agents such as paclitaxel. A thorough neurologic evaluation and extensive laboratory workup would assess for other contributing factors for the development of neuropathy, such as vitamin deficiencies or metabolic conditions that could coexist. The decision to alter the chemotherapy regimen is based on the effectiveness of ongoing cancer treatment and tolerance to side effects. Symptomatic treatment and supportive care can be instituted for the neuropathy. Early detection and interdisciplinary management of chemotherapy-induced peripheral neuropathy are critical to improving quality of life and ensuring continued cancer treatment with minimal interruptions.

COMMENT

relieves pain from irritable nociceptors demonstrated on quantitative sensory testing.^{40,41} A few smaller studies have also demonstrated the use of lacosamide, another voltage-gated sodium channel blocker, although its use would be considered off label.^{42,43}

Lack of response for FDA-approved drugs has led to the off-label use of antiseizure medications, with the rationale that many hyperexcitability mechanisms of epilepsy are also present in the generation and maintenance of neuropathic pain. One example has been the use of valproic acid, and its derivatives such as divalproex sodium, as alternative off-label treatment for neuropathic pain, although several studies failed to demonstrate the efficacy of this drug for neuropathic pain. Valproic acid is used more frequently and is FDA approved for the treatment of epilepsy, bipolar disorder, and migraine headaches. However, care must be exercised in the use of valproic acid because it holds several risks including teratogenic effects and pancreatitis. Valproic acid also has multiple drug-drug interactions with other frequently prescribed medications such as warfarin, aspirin, and oral contraceptives.

ANTIDEPRESSANTS. Duloxetine is the only FDA-approved antidepressant for use in painful diabetic neuropathy treatment, although several other antidepressants have been widely prescribed for painful neuropathy in general.^{18,44-46} Duloxetine is a serotonin-norepinephrine reuptake inhibitor (SNRI) that works through the modulation of both central and peripheral pain pathways. The approved duloxetine dose for the treatment of neuropathic pain is 60 mg/d to 120 mg/d. Tricyclic antidepressants, such as amitriptyline and nortriptyline, have demonstrated efficacy in relieving neuropathic pain in several trials⁴⁶⁻⁴⁸ across many neuropathic pain disorders but never underwent FDA approval after becoming generic. Tricyclic antidepressants have been used in low doses in the treatment of pain syndromes, including neuropathic pain.⁴⁶ It should be noted that the efficacy of nortriptyline is the same as amitriptyline, although nortriptyline has a significantly better and safer side effect profile. Because of this, both geriatric and primary care societies have identified amitriptyline as a medication that should not be prescribed for older adults.^{49,50} Venlafaxine, another SNRI, is also used off label for the treatment of neuropathic pain.⁵¹

TOPICAL THERAPIES. Capsaicin is the component in hot peppers that causes the classic heat sensation on ingestion; it works through the activation of the TRPV1 receptor on nociceptors by capsaicin, a TRPV1 agonist.^{52,53} On binding to the receptor, an influx of sodium and calcium depolarizes the nociceptor, causing the pain sensation. Theoretically, repeated applications of capsaicin desensitize the peripheral small sensory nociceptive fibers, thereby decreasing the neuropathic pain. An 8% capsaicin patch is FDA approved for both peripheral diabetic neuropathy and postherpetic neuralgia. Special precautions for both the patient and the provider are needed for the application of the patch, such as the use of gloves and minimizing exposure to other skin areas. These are the same precautions used in the culinary use of hot peppers (with special care when touching mucous membranes). The patch itself can also be painful on initial application, although the pain normally subsides after some time. Lower doses of capsaicin, such as that found in over-the-counter topicals (0.025%), have not been demonstrated to be as effective as the higher-concentration patch (8%) but are much better tolerated by patients.^{54,55} A lidocaine 5% patch has been FDA

approved for the treatment of postoperative neuralgia and other localized painful neuropathies. However, given the topical mode of delivery, lidocaine patch treatment is primarily used in focal or segmental neuropathies such as postherpetic neuralgia.^{56,57}

OTHER THERAPIES. Older therapies, such as IV infusions of lidocaine and ketamine, are still used off label for neuropathic pain. The utility of these treatments is primarily based on several positive small trials and studies.^{58–61} Because of the cost and reimbursement structure for relatively inexpensive therapies, these treatments are unlikely to be submitted for FDA approval, contributing to a lack of standardized guidelines for optimal and appropriate dosing. Published doses of IV lidocaine range from 3 mg/kg to 5 mg/kg administered over 30 to 60 minutes and result in widely ranging outcomes in terms of benefits. The frequency of dosing is yet another challenge. The patients who respond often have very dramatic improvement from treatment, but the benefits can last from 2 days to a few weeks, so repeated infusions are necessary and call into question the cost and benefits of therapy. IV ketamine infusions are also sometimes used off label to treat severe pain episodes (sometimes termed *pain crises*) in patients with neuropathic pain refractory to other therapies. Similar to IV lidocaine, dosing with ketamine is not well established, ranging from 0.2 mg/kg to 0.6 mg/kg infusions that vary widely in duration.^{60,61} IV ketamine carries the additional challenge of frequent side effects, particularly psychomimetic effects in some patients.

Finally, α-lipoic acid is another less conventional therapy available in IV and oral forms. α-lipoic acid has been used primarily in the treatment of painful diabetic neuropathy and has been found to have analgesic properties based on clinical trials.^{62,63} However, this therapy never garnered enough evidence to obtain FDA approval.

Stimulation Therapies

Several challenges to medication treatment of neuropathic pain include the possible addiction potential of opioids, systemic side effects that can affect function and the ability to preserve and maintain normal sensory processing, and the cost of novel analgesics. FDA-approved implantable devices have been more recently used for the treatment of neuropathic pain, although general acceptance has been slow because of the costs of a surgical procedure, and patient satisfaction is yet to be measured long term.

Spinal cord stimulation is becoming more common as a treatment modality for painful peripheral neuropathy. The stimulator consists of electrodes that are placed in the epidural space of the spine and connected to a rechargeable pulse generator surgically placed under the skin. The electrodes then emit electrical pulses to modulate the painful sensory spinal ascending transmission, which changes the painful sensations to tingling sensations or paresthesia. Different programming modalities can be adjusted wirelessly and optimized for patient comfort. Some newer technologies boast paresthesia-free settings using higher-frequency stimulation, so patients may experience decreased pain without paresthesia. MRI compatibility is another feature of newer stimulator models, with either MR-conditioned or MR-safe devices depending on the manufacturer. Spinal cord stimulation is currently FDA cleared specifically for several conditions including postlaminectomy syndrome, complex regional pain

KEY POINT

- Duloxetine is the only US Food and Drug Administration (FDA)-approved antidepressant for use in painful diabetic neuropathy treatment, although several other antidepressants have been widely prescribed for painful neuropathy.

syndrome, chronic painful neuropathy or plexopathy, postherpetic neuralgia, and intercostal neuralgia, and it was also recently FDA cleared for the treatment of painful diabetic neuropathy, with some promising results with newer stimulation patterns and technologies.⁶⁴

Peripheral stimulation, another use of the same technology of placing electrode leads next to sensory nerves, has also been used off label for the treatment of more focal conditions such as occipital neuralgia, pudendal nerve pain, intercostal nerve pain, and brachial or lumbar plexus neuropathy, among others. Examples of peripheral stimulation include transcutaneous electric nerve stimulation (TENS) and scrambler therapy.^{65,66} Both therapies have some evidence for the treatment of chronic neuropathic pain. TENS works through the placement of a conductive patch placed directly on the skin and connected by wires to a TENS unit, which generates electrical waveforms that can theoretically stimulate inhibitory A β fibers selectively, thereby inhibiting peripheral pain signals from C and A δ fibers. These waveforms can be adjusted by the patient and titrated to effect. Scrambler therapy is FDA approved for both neuropathic pain and chronic pain. Similar to TENS, scrambler therapy uses electrical stimulation, but instead, the output simulates non-noxious stimuli through the activation of C fibers in a specific dermatome to scramble the peripheral pain signal, thereby decreasing central sensitization. Unlike TENS, scrambler therapy comprises 16 specific waveforms that are sequenced by a proprietary algorithm. For more information, refer to the article “Neuromodulation for Neuropathic Pain Syndromes” by Prasad Shirvalkar, MD, PhD,⁶⁷ in this issue of *Continuum*.

Photobiomodulation therapy, or low-level red and infrared light therapy, is yet another mode of therapy being explored for the treatment of neuropathic pain.^{68,69} Some studies have found this form of therapy to be helpful, especially for chemotherapy-induced peripheral neuropathy, and possibly helpful for other forms of painful neuropathy.^{70,71} Its mechanisms are still unknown, but it is thought that the respiratory electron transport chain is involved because of the known absorption of light wavelengths in the red spectrum by cytochrome c oxidase, leading to an increase in ATP production.⁷²

Multimodal and Multidisciplinary Neuropathic Pain Management

Managing peripheral neuropathic pain requires a comprehensive and integrative approach that addresses the diverse aspects of the condition. This multidisciplinary and multimodal treatment involves combining various therapeutic strategies to improve pain relief, enhance function, and promote overall well-being.⁷³

Educational programs aim to enhance patients' understanding of their condition, treatment options, and active participation in their care.^{74,75} The effectiveness of treatment varies among individuals, and a personalized approach is crucial. A health care team, including neurologists, pain specialists, physical therapists, and mental health professionals, often collaborates to tailor a comprehensive treatment plan for each patient. Regular reassessment and adjustments to the treatment plan may be necessary to optimize pain management and improve the patient's quality of life.

Structured exercise programs tailored to individual needs can improve strength, flexibility, and coordination in patients with neuropathic pain.^{74,76} Low-impact exercises, such as swimming or tai chi, are often recommended to minimize stress on affected nerves. Massage, stretching, and joint mobilization

techniques provided by physical therapists can help alleviate muscle tension, improve range of motion, and reduce pain.⁷⁷ Engaging in regular physical activity can have positive effects on overall well-being and may contribute to pain management by improving circulation and reducing the inflammatory effects that contribute to pain.^{78,79}

Chronic pain often has negative effects on a patient's psychological well-being and coping ability. Mental health professionals can provide counseling and psychotherapy to help individuals cope with the emotional challenges associated with neuropathic pain. Cognitive behavioral therapy is an evidence-based therapeutic approach that addresses negative thought patterns and behaviors, improving coping skills and reducing the impact of pain on the daily life of patients with neuropathic pain.^{80,81}

KEY POINTS

- Managing peripheral neuropathic pain requires a comprehensive and integrative approach that addresses the diverse aspects of the condition. This multidisciplinary and multimodal approach involves combining various therapeutic strategies to improve pain relief, enhance function, and promote overall well-being.

- Structured exercise programs tailored to individual needs can improve strength, flexibility, and coordination in patients with neuropathic pain. Low-impact exercises, such as swimming or tai chi, are often recommended to minimize stress on affected nerves.

CONCLUSION

Peripheral neuropathic pain is mainly a clinical diagnosis, and the primary challenge to the clinician is to determine the underlying etiology of the symptoms while attending to the management of the pain. The clinician is advised to assess both the severity of pain and its impact on the patient. Treatment planning for neuropathy requires addressing the underlying pathophysiology and managing the pain and related symptoms by coordinating the use of medications and nonpharmacologic therapeutic modalities. These might include neurostimulation, physical therapy, and behavioral therapy.

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Central Neuropathic Pain

By Charles E. Argoff, MD

REVIEW ARTICLE



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ABSTRACT

OBJECTIVE: This article provides an approach to the assessment, diagnosis, and treatment of central neuropathic pain.

LATEST DEVELOPMENTS: Recent studies of the pathophysiology of central neuropathic pain, including evidence of changes in the expression of voltage-gated sodium channels and *N*-methyl-D-aspartate (NMDA) receptors, may provide the basis for new therapies. Other areas of current research include the role of cannabinoid-receptor activity and microglial cell activation in various animal models of central neuropathic pain. New observations regarding changes in primary afferent neuronal activity in central neuropathic pain and the preliminary observation that peripheral nerve blocks may relieve pain due to central neuropathic etiologies provide new insights into both the mechanism and treatment of central neuropathic pain.

ESSENTIAL POINTS: In the patient populations treated by neurologists, central neuropathic pain develops most frequently following spinal cord injury, multiple sclerosis, or stroke. A multimodal, individualized approach to the management of central neuropathic pain is necessary to optimize pain relief and may require multiple treatment trials to achieve the best outcome.

INTRODUCTION

The International Association for the Study of Pain has defined central neuropathic pain as “pain caused by a lesion or disease of the central somatosensory system.”¹ Central neuropathic pain can therefore be associated with a lesion involving the spinal cord, the brain, or both.

Commonly cited examples of central neuropathic pain include central pain associated with spinal cord injury, central pain associated with multiple sclerosis (MS), and central poststroke pain; however, it is important to recognize that these are not homogeneous conditions. For example, spinal cord injury has multiple etiologies and can be associated with tumors, injury, infarction, inflammation, syringomyelia, and trauma. The presentation of central pain associated with MS may vary considerably between people, and central poststroke pain occurs as the result of a variety of cerebrovascular events.² In addition, central neuropathic pain has been described as a consequence of brain trauma or brain tumors as well as in individuals with Parkinson disease. This article focuses on the assessment and treatment of central neuropathic pain associated with spinal cord injury, central poststroke pain, and MS since these are the most common conditions associated with central neuropathic pain. Three cases exemplifying these conditions highlight the complexity of managing a person with any of these conditions.

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RELATIONSHIP DISCLOSURE:

Dr Argoff has received personal compensation in the range of \$500 to \$4999 for serving as a consultant for Nevro Corp, Scilex Holding, and Vertex Pharmaceuticals Incorporated and on a speakers bureau and as an expert witness for Scilex Holding; in the range of \$5000 to \$9999 for serving as a consultant for Collegium Pharmaceutical and Xgene Pharmaceutical Group, on a scientific advisory or data safety monitoring board for Vertex Pharmaceuticals Incorporated, and on a speakers bureau for Lundbeck; and in the range of \$10,000 to \$49,999 for serving on a speakers bureau for AbbVie, Inc. Dr Argoff has received publishing royalties from a publication relating to health care. The institution of Dr Argoff has received research support from AbbVie, Inc, Lilly, Lundbeck, and Vertex Pharmaceuticals Incorporated.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:

Dr Argoff discusses several therapies, none of which are approved by the US Food and Drug Administration (FDA) for the treatment of central neuropathic pain.

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PATOPHYSIOLOGY

The pathophysiology of central neuropathic pain is incompletely understood; however, several proposed mechanisms have emerged. Denervation hypersensitivity of remaining spinothalamic neurons following central nervous system (CNS) injury is one of the mechanisms that may lead to neuronal hyperexcitability in the CNS. A consequence of this process is that the threshold for action potential generation and propagation is decreased and there may be increased spontaneous and postdischarge responses to both non-noxious and noxious stimuli.³ Abnormal spinothalamic tract function appears to be a nearly universal requirement in the emergence of central neuropathic pain. Since non-neuropathic pain conditions can develop in a person with a spinal cord injury, central poststroke pain, or MS, a person with a possible central neuropathic pain condition should be examined to determine if pain or temperature sensation is impaired in the affected limbs or body region. Noncentral neuropathic pain etiologies should be considered if pinprick and temperature sensation are normal.⁴

Changes in voltage-gated sodium channel expression patterns have been demonstrated in CNS neurons in rodent models of CNS injury. In a rodent model of spinal cord injury neuropathic pain, increased expression of $\text{Na}_V1.3$ was noted in the dorsal horn of the spinal cord and the thalamus, and increased expression of $\text{Na}_V1.5$ has been noted in MS demyelinating lesions.^{3,5-7} The up-regulation of N-methyl-D-aspartate (NMDA)-receptor expression has been demonstrated in both a model of spinal cord injury and a model of central poststroke pain, perhaps providing the basis for why ketamine, an NMDA-receptor antagonist, has been shown to reduce both continuous and evoked spinal cord injury-related pain.^{3,8} Several other classes of receptors have also been implicated in the pathophysiology of central neuropathic pain, including the calcium channel $\alpha_2\delta$ subunit in the dorsal horn of rats and the CB₁ and CB₂ cannabinoid receptors in models of spinal cord injury and cerebral ischemia.³ These findings have potential clinical relevance given the availability of pharmacologic agents directed toward sodium channels (local anesthetics and certain anticonvulsants), the availability of $\alpha_2\delta$ -subunit antagonists (gabapentin and pregabalin), and the demonstration that MS-related neuropathic pain may be responsive to cannabinoid-directed therapies.³

CNS inflammatory and immune mediators are also under active investigation for their role in the development of central neuropathic pain with microglial cell activation, with the overexpression of purinergic P2X receptors being demonstrated in various animal models.⁹⁻¹¹ Data has emerged suggesting that CNS injury can result in changes in the cell bodies of the dorsal root ganglia, primary afferent neurons, and the central and peripheral terminals of peripheral neurons. In central poststroke pain, complete but temporary pain relief was observed in 85% of patients with central poststroke pain who had been treated with an ultrasound-guided peripheral nerve block in the affected extremity. This observation is fascinating as it suggests that perhaps the central neuropathic pain associated with central poststroke pain is not completely caused by CNS activity but also requires input from primary afferents within the painful area. Although there is currently only one published case report to support the use of this modality, a separate published report describing the benefit of dorsal root ganglia stimulation in reducing central poststroke pain highlights an exciting observation and suggests the need for further study to better appreciate the respective roles of both peripheral and central mechanisms in central

neuropathic pain.^{12,13} Given the dearth of studies supporting a consistently effective approach to managing central neuropathic pain, the development of new safe and effective treatments would be most welcome.

DIAGNOSING CENTRAL NEUROPATHIC PAIN

This section describes approaches to diagnosing a central neuropathic pain condition. Distinguishing between central neuropathic pain states and non-neuropathic pain is important, especially when considering potential treatments.

Spinal Cord Injury Pain

Recent data suggests that the average patient age at the time of spinal cord injury has increased from approximately 29 years in the 1970s to 43 years in 2015. Motor vehicle accidents, falls, and injury due to violence or sports are the four most common causes of spinal cord injury, with motor vehicle accidents and falls totaling approximately 70% of cases.³ Not all spinal cord injury-related pain is neuropathic and multiple nociceptive pain conditions have been described following spinal cord injury. Neuropathic pain associated with spinal cord injury is spontaneous and associated with hyperalgesia, and descriptors used to describe this pain include squeezing, burning, and shooting, with a prevalence according to one meta-analysis of 53%.^{14,15} Non-neuropathic pain conditions experienced by patients following spinal cord injury include musculoskeletal pain, visceral pain, pain secondary to overuse, and pain associated with autonomic dysreflexia (including headache).¹⁶ Perhaps not surprisingly, it may be difficult to attribute a pain symptom to a specific pain type, and the pooled prevalence of all types of spinal cord injury-related pain is estimated to be 80%.¹⁷ Neuropathic pain occurring below the level of the spinal cord injury is classified as central; however, if neuropathic pain occurs at the level of the spinal cord injury it may be considered peripheral or central. For example, it is considered peripheral if the pain is caused by a lesion of the dorsal root and central if the pain is caused by a lesion of the dorsal horn. If pain is perceived within three levels below the injury, it is considered *at-level* pain, but if it is perceived greater than three levels below the lesion, it is considered *below-level* pain.¹⁶ These pain levels can certainly overlap. Below-level pain tends to occur later than at-level pain and it has been observed to be more resistant to treatment.¹⁷ Neuropathic pain associated with spinal cord injury does not generally improve over time; in fact, it is likely to worsen over time.¹⁸

Establishing the diagnosis of neuropathic pain, whether central or peripheral, is not always straightforward. Descriptions of symptoms may include terms such as tingling, burning, shocklike, pins and needles, tightness, squeezing, electric, cold, lancinating, and prickling. When evaluating a person with suspected neuropathic pain, the examiner may choose to use one of several validated diagnostic approaches. Multiple questionnaires have been developed to screen for neuropathic pain, including the Leeds Assessment of Neuropathic Symptoms and Signs, the painDETECT questionnaire, the Neuropathic Pain Questionnaire, and the Douleur Neuropathique 4.¹⁹⁻²² In addition to these questionnaires, certain clinical signs are observable in patients experiencing neuropathic pain, including allodynia and hyperalgesia. Allodynia refers to pain occurring following a stimulus that is normally not painful, and hyperalgesia is the term used to describe the experience of increased pain from a stimulus that is normally painful.³ The presence of these signs can be assessed during the neurologic

KEY POINTS

- The development of central neuropathic pain may occur following an injury of or in association with a disorder affecting the spinal cord or brain.
- Abnormal spinothalamic tract function is nearly always present in a person experiencing central neuropathic pain.
- Non-neuropathic pain may exist concurrently in a person experiencing central neuropathic pain.
- Mechanisms underlying central neuropathic pain include those involving both the peripheral and central nervous systems.
- Approximately 70% of spinal cord injuries are associated with a motor vehicle accident or a fall.
- Central neuropathic pain associated with spinal cord injury may occur concurrently with non-neuropathic pain associated with spinal cord injury, emphasizing the need for a formal neurologic assessment.

examination, emphasizing the importance of a formal assessment for these findings (**CASE 4-1**).

Central Poststroke Pain

Central poststroke pain is the most common form of central neuropathic pain.⁴ In general, pain after a stroke is highly prevalent and, in addition to central poststroke pain, can present as musculoskeletal symptoms, headache, or spasticity. An important risk factor for central poststroke pain is stroke location. Thalamic strokes (Dejerine-Roussy syndrome) and lateral medullary strokes (Wallenberg syndrome) are associated with the highest incidence of central poststroke pain. Thalamic strokes are associated with between 25% and 33% of instances of central poststroke pain. Within the thalamus, the risk of central poststroke pain is higher when the ventral posterior nucleus is involved and lower when the centromedian or median nuclei are affected.²³⁻²⁵ The development of central poststroke pain is associated with lesions involving the spinothalamic tracts terminating within the ventral posterolateral thalamus and lesions of the mesial lemniscal pathway and ventral posteromedial thalamus.²⁶ Lateral medullary strokes are associated with disturbed pain and temperature sensation on the ipsilateral face and contralateral body, facial numbness, ptosis, and contralateral spinothalamic sensory loss.²⁷ Strokes involving the

CASE 4-1

A 44-year-old man experienced a spinal cord injury 5 years ago following a ruptured arteriovenous malformation at the C3 level, resulting in spastic quadripareisis. Within the following year, he experienced severe dysesthesia in his lower extremities and burning pain in his trunk below his nipple line. These occurred independent of the pain associated with his spasticity and muscle spasms. In addition, he reported bilateral shoulder, hip, and low back pain. Multiple specialist evaluations included psychiatry, orthopedics, neurology, neurosurgery, and pain management. He was hospitalized multiple times for symptomatic treatment and inpatient rehabilitation.

On neurologic examination, manual muscle testing revealed symmetric 4-/5 weakness in the deltoid, biceps, triceps, wrist extensor, and intrinsic hand muscles. Hip flexors, quadriceps, hamstrings, and tibialis anterior muscles demonstrated symmetric 2/5 weakness. Muscle stretch reflex testing revealed hyperreflexia with sustained bilateral ankle clonus and bilateral extensor plantar responses. Sensory examination was inconsistent, with variable responses to light touch, pinprick, vibratory, and position sense testing. There was notable hyperalgesia and allodynia over the lower anterior chest wall and both upper extremities in a nondermatomal pattern.

Before his pain management evaluation, treatment included trials of oral baclofen 80 mg/day, tizanidine 24 mg/day, and onabotulinumtoxinA injections for his spasticity, with suboptimal responses. Additional treatments included gabapentin up to 3600 mg/day, pregabalin up to 600 mg/day, amitriptyline up to 100 mg/day, carbamazepine 500 mg/day, duloxetine 60 mg/day, lacosamide 400 mg/day, buprenorphine buccal

dorsal basal ganglia, posterior internal capsule, putamen, and parietal cortex may also result in central poststroke pain.^{28,29} The risk of central poststroke pain is similar whether the stroke is ischemic or hemorrhagic.⁴ Central poststroke pain usually occurs within 3 to 6 months of the stroke and is associated with altered temperature thresholds, allodynia, and hyperesthesia.²³ The neurologic examination of a person with suspected central poststroke pain must therefore include a general neurologic examination and a sensory examination that can assess for the findings noted above (**CASE 4-2**).

Multiple Sclerosis–related Pain

MS is an autoimmune disorder associated with demyelinating plaques within the brain and spinal cord. MS can be associated with multiple forms, including a progressive form and the more commonly experienced relapsing-remitting course with the onset of neurologic impairment followed by improvement and periods of stability. With either form, as the disease progresses, chronic pain may occur in as many as 80% of patients.³⁰ MS-associated trigeminal neuralgia is the presenting symptom of MS in 14% of patients.³¹ A characteristic sign associated with MS is the Lhermitte sign, in which neck flexion results in the sudden onset of an electrical shooting sensation traveling from the neck down to other areas of the spine and sometimes into the lower extremities. This sign has

film 1.5 mg/day, milnacipran 100 mg/day, mexiletine, IV lidocaine infusions up to a dose of 4 mg/kg/hour for 4 hours/session weekly for 4 weeks, and tramadol, without significant improvement. Routine laboratory testing including serum vitamin B₁₂ level was unremarkable.

The patient was advised of the potential for the use of intrathecal approaches to spasticity and pain management. After a successful test dose of intrathecal baclofen was completed, he underwent implantation of an intrathecal pump system and his spasticity control improved dramatically; however, his lower extremity dysesthesia and burning pain did not. He was offered multiple options, including retraling an oral medication he had used before the pump implantation or considering the addition of ziconotide to his pump. After a test dose of intrathecal ziconotide was successfully completed, he noted significant improvement in the lower extremity dysesthesia and burning pain, and he continued to receive a combination of intrathecal baclofen 600 µg/day and ziconotide 2.4 µg/day.

Below level of injury pain following spinal cord injury can occur years after the injury. This is considered a central neuropathic pain type and it can be challenging to treat. It is important to recognize that concurrent pain types that may be experienced by a person following spinal cord injury include chronic musculoskeletal pain, neuropathic pain unrelated to the spinal cord injury, peripheral neuropathic pain related to the spinal cord injury, and other nonspinal cord injury-related pain syndromes.

COMMENT

CASE 4-2

A 48-year-old man presented to the clinic for evaluation of facial and left upper and lower limb pain. His history was notable for a right lateral medullary ischemic infarction at age 33 years. Within several months following the stroke, he began to experience bilateral facial pain and burning pain over his left trunk and upper and lower extremities. His examination in the clinic demonstrated residual deficits from the stroke, including decreased sensation to light touch and pinprick and temperature sensation over the left trunk and upper and lower extremities. He was mildly unsteady and ambulated with a cane.

Prior trials of gabapentin, duloxetine, amitriptyline, and pregabalin were unsuccessful. He underwent trials of carbamazepine, oxcarbazepine, and lamotrigine, also without benefit. A trial of IV lidocaine infusions dampened the pain somewhat, but not to a clinically meaningful extent, so these were not continued. He was treated with physical therapy on multiple occasions and a trial of acupuncture was unsuccessful. He developed several other pain symptoms, including chronic migraine and chronic neck pain. He was found to have multilevel cervical facet arthropathy and he was treated successfully with topiramate and fremanezumab for his migraine. He was considered for cervical facet blocks and denervation, but he declined. Lacosamide was added to his regimen, followed by baclofen, with more success than with other pharmacologic approaches. The addition of extended-release oxycodone was also helpful. He was monitored regularly and settled into a pharmacologic analgesic regimen that included topiramate 100 mg/day, extended-release oxycodone 36 mg 2 times a day, lacosamide 200 mg 2 times a day, baclofen 20 mg each morning and 40 mg each evening, subcutaneous fremanezumab 225 mg/1.5 mL monthly, and ubrogepant 100 mg as needed at the onset of migraine. Although his pain was not completely controlled, he could function independently with a consistent 50% reduction in his central poststroke pain.

COMMENT

Although this patient experienced pain consistent with central poststroke pain, he also experienced other pain (eg, migraine, chronic neck pain) that may have had an onset after his stroke but would not be considered typical central poststroke pain. Furthermore, his migraine was responsive to acute and preventative pharmacotherapy. Few randomized controlled trials assessing the treatment of central poststroke pain have been completed, and there are no published multidrug studies of central poststroke pain. In addition, this patient was reluctant to undergo additional treatments that may have added to his pain relief. Therefore, the treatment of central poststroke pain in a practice setting is likely to be associated with multiple treatment trials and the use of a combination of pharmacologic and nonpharmacologic therapies.

been reported in 7% to 41% of patients with MS.³²⁻³⁴ Recent studies support that the Lhermitte sign is associated with abnormalities of posterior column function and not spinothalamic tract dysfunction.

Twelve to twenty-eight percent of patients with MS will experience central neuropathic pain during their lifetime. It often occurs more than 1 year after the onset of symptoms and can occur in more than one location at a time. This multifocality should not be surprising since demyelinating lesions occur in multiple locations.⁴ Central neuropathic pain associated with MS may occur in areas associated with spinothalamic tract sensory loss and is more common in patients with a progressive MS course, greater disability, longer MS duration, and older age.³⁵⁻³⁸ MS-related central neuropathic pain may occur in a patient with MS with spasticity; however, these may not always exist concurrently and therefore need to be considered separately (**CASE 4-3**).

Proposed Standardized Diagnostic Criteria

Diagnostic criteria for central neuropathic pain conditions were proposed in 2017 through the collaborative effort of the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks-American Pain Society Pain Taxonomy initiative.² **TABLE 4-1** lists the proposed diagnostic criteria for central neuropathic pain associated with spinal cord injury, central poststroke pain, and MS. For central neuropathic pain associated with spinal cord injury or central poststroke pain, it should be noted that the criterion that the pain onset is up to 1 year following the injury is in contrast to multiple reports of central neuropathic pain having an onset years after the injury.⁴

TREATING CENTRAL NEUROPATHIC PAIN

The management of central neuropathic pain is often challenging as there is a scarcity of large, high-quality randomized trials, and those that have been completed have often provided conflicting results. Staudt and colleagues³⁹ recently published the results of a prospective trial in the management of central neuropathic pain in which only 9.6% of patients achieved the primary outcome of 30% or greater reduction in pain intensity and a 1-point reduction on the Pain Interference Scale over a 12-month period. Pharmacologic therapies and to a lesser extent invasive pain management strategies comprise the majority of published evidence for the management of central neuropathic pain.

Antiseizure Medications

Gabapentin and pregabalin, sometimes referred to as gabapentinoids, are commonly prescribed for various neuropathic pain conditions such as painful diabetic neuropathy and postherpetic neuralgia. Although they share a common mechanism of action, their pharmacokinetics are different, with the bioavailability of pregabalin being much greater than that of gabapentin.³ Multiple randomized controlled trials have demonstrated the potential benefit of pregabalin in the management of spinal cord injury-related pain in doses up to 600 mg/day compared with placebo.⁴⁰⁻⁴² There are mixed data for gabapentin use in spinal cord injury-related neuropathic pain and virtually no evidence for its use in MS-related neuropathic pain.^{43,44} One observational study involving 84 patients with central poststroke pain following a thalamic stroke demonstrated that 59.5% of patients using gabapentin 600 mg/day for 1 month experienced clinically significant pain relief.⁴⁵ An open-label trial of pregabalin involving

KEY POINTS

- Central poststroke pain is the most common type of central neuropathic pain.
- Stroke location is an important risk factor for the development of central poststroke pain.
- Chronic pain occurs in the majority of patients diagnosed with multiple sclerosis (MS).
- Central neuropathic pain is one of several types of pain that a person with MS may experience, and formal assessment for each type of MS-related pain should be completed.
- MS-related central neuropathic pain is more likely to occur in patients with a progressive MS course, older age, greater disability, and longer MS duration.
- Formal diagnostic criteria for central neuropathic pain associated with spinal cord injury, MS, or central poststroke pain have been recently proposed.
- There is a scarcity of large, high-quality randomized trials for central neuropathic pain.

103 patients with any type of central neuropathic pain demonstrated that a dose range of 150 mg/day to 600 mg/day provided sustained benefit over 53 weeks.⁴⁶ A 2022 study involving patients from Japan, Korea, and Taiwan evaluated the role of mirogabalin, an $\alpha_2\delta$ agonist not currently available in the United States, for central neuropathic pain after spinal cord injury; responder rates for 30% or greater and 50% or greater pain intensity reduction were higher for treated patients compared with placebo at 14 weeks.⁴⁷

Additional antiseizure medications that have been evaluated for central neuropathic pain include lamotrigine, levetiracetam, lacosamide, valproic acid, phenytoin, and topiramate. A randomized controlled study evaluating lamotrigine in the management of central poststroke pain suggested that 200 mg/day may be effective, while an open-label study comparing lamotrigine to gabapentin in 30 patients with central poststroke pain demonstrated that 10 patients experienced more than 50% pain reduction when they were treated with lamotrigine.^{48,49} Patients with central neuropathic pain due to spinal cord injury were treated with lamotrigine in a randomized, crossover trial in which doses of up to 400 mg/day were used, without any difference seen during the different treatment periods.⁵⁰

CASE 4-3

A 66-year-old man had secondary progressive multiple sclerosis (MS), which he had managed for many years with an MS specialist. He had multiple pain symptoms, including spasms due to his lower and upper extremity spasticity, chronic bilateral shoulder pain, chronic low back pain, and left-sided trigeminal neuralgia. When he first presented to the pain management center for further treatment consideration, he was being treated with carbamazepine 600 mg 2 times daily, oral baclofen 20 mg 4 times daily, and lamotrigine 200 mg 2 times daily. This regimen provided him with some benefit, but he still experienced frequent paroxysms of burning, lancinating, and shocklike pain affecting the left V2 and V3 distributions. These paroxysms would last for days at a time, during which he was unable to eat, chew, brush his teeth, comb his hair, or have anything touch this part of his face without experiencing severe pain. He used a wheelchair and lived in a skilled nursing facility. Prior treatments for the trigeminal neuralgia had included gabapentin, nortriptyline, pregabalin, duloxetine, and as-needed use of either oxycodone or hydrocodone.

Brain MRI with and without contrast demonstrated sequelae of MS affecting both cerebral hemispheres and the brainstem. There was no evidence of new lesions, active enhancing demyelinating plaques, or vascular compression of the left trigeminal nerve. A neurosurgical consultation resulted in several recommendations, including a rhizotomy or gamma knife radiosurgery. A rhizotomy was performed but was not helpful, and the patient was ultimately not thought to be an appropriate candidate for gamma knife radiosurgery. His neurologic examination was most notable for severe allodynia and hyperesthesia over the left V2 and V3 distributions with multiple trigger zones in these regions including intraoral, as well as lower extremity spasticity, diffuse hyperreflexia, ankle clonus, and bilateral extensor plantar responses.

Based on randomized controlled trial results, there is no evidence for the use of levetiracetam for spinal cord injury or central poststroke pain and conflicting results for its use in MS-related central neuropathic pain.³ A single randomized controlled trial involving patients with spinal cord injury–related pain did not demonstrate any benefit of sodium valproate compared with placebo.⁵¹ One case report described the benefit of topiramate in a patient with MS-related pain, and while there is evidence for the use of lacosamide in peripheral neuropathic pain, there are no human studies demonstrating its benefit in central neuropathic pain.^{52,53} One study of the treatment of central poststroke pain with phenytoin showed that an equal number of patients experienced pain relief as did those who experienced increased pain with phenytoin use.⁵⁴

Antidepressants

Although antidepressants have been extensively studied in the management of neuropathic pain, there are few studies involving central neuropathic pain. Currently, available data suggest that amitriptyline may have benefit in certain patients with central neuropathic pain.⁵⁵ Although it is often considered a

The patient was presented with several treatment options. He derived no benefit from IV lidocaine or medical cannabis but responded favorably to subcutaneously administered injections of onabotulinumtoxinA into the skin overlying the left V2 and V3 regions. This off-label use of onabotulinumtoxinA helped him consistently for several years. He no longer used oral opioids or oral antiseizure medications, and the subcutaneously administered onabotulinumtoxinA injections did not result in facial muscle paralysis or asymmetry.

This patient's trigeminal neuralgia symptoms appeared to have been related to demyelinating plaque affecting the trigeminal nerve root entry zone, as evidenced by his MRI findings. His imaging did not suggest that he was an appropriate candidate for microvascular decompressive surgery, which is important to consider as a person with MS may develop trigeminal neuralgia as a consequence of vascular compression of the trigeminal nerve, similar to a person who develops trigeminal neuralgia without MS, suggesting in that instance that decompressive surgery might be helpful. In this case, the patient's trigeminal neuralgia is an example of an MS-related central neuropathic pain condition that developed as a consequence of demyelination. OnabotulinumtoxinA was used in this setting successfully and in an off-label manner, and there is evidence that onabotulinumtoxinA may be effective in reducing pain in other neuropathic pain states.

COMMENT

treatment for MS-related pain, there is very little evidence to support its use.⁵⁶ Two studies involving the use of duloxetine in central neuropathic pain have been published. In an open-label study of central poststroke pain, duloxetine 30 mg/day to 60 mg/day was associated with a 48% decrease in pain intensity using the Numeric Pain Rating Scale after 3 weeks.⁵⁷ In a randomized controlled study of patients with either spinal cord injury–related pain or central poststroke pain, duloxetine 60 mg/day to 120 mg/day did not significantly decrease mean pain intensity, but there was an improvement in dynamic evoked pain and cold allodynia in the treatment group.⁵⁸ In contrast, two randomized controlled trials showed that duloxetine 30 mg/day to 60 mg/day was associated with significant pain reduction compared with placebo in patients with MS-related neuropathic pain.^{59,60}

TABLE 4-1**AAPT Diagnostic Criteria for Central Neuropathic Pain Conditions^a****Spinal cord injury–associated pain**

- ◆ Diagnostic test confirming spinal cord injury
- ◆ Continuous or recurrent pain after a spinal cord injury with onset of pain at the time of or up to 1 year after the spinal cord injury
- ◆ Pain duration of at least 3 months
- ◆ Pain is located in the area of the body associated with the spinal cord injury
- ◆ Pain is associated with sensory changes in a neuroanatomically plausible distribution
- ◆ No other diagnosis more appropriately explains the pain

Central poststroke pain–associated pain

- ◆ Diagnostic test or history confirming or strongly suggestive of a stroke
- ◆ Continuous or ongoing pain after a stroke whose onset is at the time of the stroke or up to 1 year after stroke onset
- ◆ Pain duration of at least 3 months
- ◆ Pain is located within the body area affected by the stroke
- ◆ Pain is located within a neuroanatomically plausible distribution
- ◆ No other diagnosis more accurately explains the pain

MS-associated pain

- ◆ Established MS
- ◆ Continuous or recurrent pain after the established diagnosis of MS
- ◆ Pain duration of at least 3 months
- ◆ Pain is experienced within an area of the body that would be affected by MS lesions within the brain or spinal cord
- ◆ Pain is located within a neuroanatomically plausible distribution
- ◆ No other diagnosis to explain the pain

AAPT = Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks-American Pain Society Pain Taxonomy; MS = multiple sclerosis.

^a Data from Widerström-Noga E, et al, J Pain.²

Local Anesthetics

Local anesthetics block sodium channels and these agents have been used intravenously, orally, and topically. One randomized, double-blind, crossover trial studied IV lidocaine administered at a dose of 5 mg/kg over 30 minutes in 16 patients with spinal cord injury-related pain or central poststroke pain. Ten patients reported a greater than 50% reduction in spontaneous pain for up to 1 hour following the infusion. Twelve of the 16 patients were placed on oral mexiletine, an oral local anesthetic agent, with doses titrated to 400 mg/day to 800 mg/day, but the side effects resulted in no patient wanting to continue this medication, and only three patients noted significant relief.⁶¹ One crossover trial of patients with spinal cord injury-related pain and another trial of patients with MS-related pain demonstrated temporary improvement in pain intensity following IV lidocaine infusions.^{62,63} A 2022 systematic review of the role of IV lidocaine in the management of chronic neuropathic pain including patients with spinal cord injury-related pain concluded that larger randomized, double-blind, placebo-controlled trials are needed as there is insufficient evidence to make a recommendation regarding this modality for this population.⁶⁴

OnabotulinumtoxinA

Although the mechanism of action of onabotulinumtoxinA has been traditionally associated with the inhibition of acetylcholine release resulting in muscle relaxation, it has also been shown to inhibit the release of neurotransmitters and neuropeptides with “analgesic relevance,” such as calcitonin gene-related peptide, substance P, and glutamate, as well as reduce the expression of receptors (P2X3 and TRPV1) relevant to pain and inflammation. This mechanism may be relevant to both central and peripheral neuropathic pain, in part because onabotulinumtoxinA has been shown to reach the CNS via retrograde transport. OnabotulinumtoxinA has been successfully used in patients with poststroke and MS-related spasticity, and published case reports and randomized controlled trial results describe the benefit of onabotulinumtoxinA when injected subcutaneously at the site of the worst pain in patients with spinal cord injury-related pain.⁶⁵⁻⁷⁰

Cannabinoids

Cannabinoids act on multiple targets within the endocannabinoid system, and those that have been evaluated in neuropathic pain conditions include delta-9-tetrahydrocannabinol, dronabinol, nabilone, inhaled cannabis, and nabiximols (derived from plant extracts with various concentrations of delta-9-tetrahydrocannabinol and cannabidiol).⁷¹ The majority of studies regarding cannabinoids for central neuropathic pain have been in MS-related pain. A meta-analysis evaluating more than 3000 patients with MS concluded that there is a small therapeutic benefit for multiple MS-related symptoms including central neuropathic pain.⁷² In contrast, a different systematic review of three studies of cannabinoids in the treatment of MS-related neuropathic pain concluded that there is no meaningful evidence to support their use for analgesic purposes for patients with MS-related neuropathic pain.⁷¹

Opioids

Opioids are complicated medications to consider in any chronic pain setting. For central poststroke pain, a meta-analysis concluded that there is no clear evidence

KEY POINTS

- Multiple antiseizure medications have been evaluated for different central neuropathic pain states with mixed results.
- Based upon the results of two randomized controlled trials, duloxetine may be considered for MS-related neuropathic pain.
- Small studies suggest the potential role of IV lidocaine infusions for the treatment of central neuropathic pain.
- In addition to its role in the treatment of spasticity, onabotulinumtoxinA has been demonstrated to reduce pain in patients with spinal cord injury-related neuropathic pain when injected subcutaneously.
- Insufficient evidence is currently available regarding the effect of cannabinoids on central neuropathic pain.
- Insufficient evidence is available to broadly recommend chronic opioid therapy for the management of central neuropathic pain.

to support the efficacy of opioids in the management of poststroke pain.⁷³ Levorphanol was evaluated in 81 patients with resistant neuropathic pain, with five patients experiencing spinal cord injury-related pain and eight patients experiencing MS-related pain. Although both low-dose and high-dose levorphanol treatments resulted in pain reduction, 27% of patients did not complete the study due to side effects. In patients with spinal cord injury-related pain already being treated with antiseizure medications, the addition of oral oxycodone was associated with additional analgesic benefit.⁷⁴ Based on the available data, broad recommendations regarding the use of opioids for central neuropathic pain cannot be made.

Neuromodulation

A recent review of spinal stimulation for the treatment of peripheral or central neuropathic pain concluded that there is insufficient evidence to support its use in central neuropathic pain.⁷⁵ Intrathecal medications such as baclofen, morphine, or ziconotide have been used in the treatment of spasticity and chronic pain through an implanted catheter and pump. Intrathecal baclofen is used in the management of spasticity associated with stroke, cerebral palsy, MS, and spinal cord injury. Ziconotide is a conotoxin analog that blocks N-type voltage-gated calcium channels, and multiple randomized controlled trials have been published supporting its use for human immunodeficiency virus (HIV)-related pain, other noncancer-related pain, and cancer-related pain; however, no such study has been published for central neuropathic pain.³ A 2009 case series suggested that intrathecal treatment with baclofen combined with ziconotide may help reduce both refractory neuropathic pain and spasticity.⁷⁶ Managing patients with implanted pumps requires a significant commitment given the need for ongoing monitoring, dose adjustments, refills, and monitoring for side effects.

Other Treatments

Nonpharmacologic treatments for central poststroke pain were evaluated in a 2020 systematic review, which concluded that some improvement was demonstrated with a range of therapies including transcranial direct current stimulation, bee venom acupuncture point injection, and caloric vestibular stimulation.⁷⁷ Transcranial magnetic stimulation when used over the primary motor cortex has been shown to be helpful in central poststroke pain.⁷⁸ A single case report described a reduction in lower extremity pain in a patient with a thalamic stroke through the use of dorsal root ganglia stimulation.¹³ Of interest is that acupuncture, transcutaneous electrical nerve stimulation, cognitive behavioral therapy, and self-hypnosis were not shown to improve spinal cord injury-related neuropathic pain according to a Cochrane review.⁷⁹ The results of studies of either IV or oral ketamine in patients with central neuropathic pain due to either MS or spinal cord injury are mixed.³

Suggestions for first-line pharmacologic agents include tricyclic antidepressants, duloxetine, venlafaxine, pregabalin, and gabapentin.⁸⁰ While the evidence for their use for specific central neuropathic pain states is limited, the reader may benefit from viewing these as considerations as opposed to treatments with clearly established benefit.⁸⁰ While the focus of this article has been on central neuropathic pain, it is important to remember that other painful conditions, such as joint pain due to immobility or osteoarthritis or pain due to a

decubitus ulcer, may coexist in a person with central neuropathic pain and these need to be addressed and evaluated appropriately.

KEY POINTS

- Insufficient evidence is currently available to define the role of various neuromodulation approaches in the management of central neuropathic pain.
- Limited high-quality evidence exists for the treatment of central neuropathic pain, with the exception of pregabalin for spinal cord injury-related neuropathic pain. Commonly prescribed medications for central neuropathic pain do not have significant published evidence to support their use in general but may be considered on an individual basis.

CONCLUSION

The management of central neuropathic pain is challenging, in large part because safe and effective treatments have not been identified based upon currently completed clinical trials of patients with central poststroke pain, spinal cord injury, or MS. Nevertheless, multiple treatments are available for consideration for patients with central neuropathic pain according to the established principles of evidence-based medicine. While much attention has been given to the CNS, recent advances in the evaluation of the pathophysiology of central neuropathic pain and very preliminary published clinical data suggest that the peripheral nervous system may play a role both in the pathophysiology of central neuropathic pain and as a target for treatment. Such advances are exciting and will hopefully lead to medical and nonmedical treatments that are more helpful for people experiencing central neuropathic pain. Consistent with evidence-based medicine, clinicians treating patients with central neuropathic pain can approach each person in a multidisciplinary manner to integrate available treatments on an individualized basis in the best interest of that person according to the best available evidence. This approach truly epitomizes the art and science of clinical neurology.

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Orofacial Pain

REVIEW ARTICLE

By Meredith Barad, MD; Marcela Romero-Reyes, DDS, PhD



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ABSTRACT

OBJECTIVE: This article explores the multiple etiologies, diagnosis, and management of orofacial pain.

LATEST DEVELOPMENTS: Published in 2019, the International Classification of Orofacial Pain has become the internationally accepted classification system for primary and secondary facial pain. New discoveries in temporomandibular disorders have demonstrated that they are far more complex than the traditional dental mechanistic point of view. A 2020 consensus report released by the National Academies of Sciences, Engineering, and Medicine entitled “Temporomandibular Disorders: Priorities for Research and Care” highlighted this paradigm shift and its importance for patient care, education, and research.

ESSENTIAL POINTS: Orofacial pain comprises many disorders with different etiologies and pathophysiologies. The subjectivity of the pain experience and the interrelated anatomy and physiology of the craniofacial area add to the complexity of diagnosis when the source and etiology of pain are not clear. As orofacial pain straddles the expertise of multiple disciplines, a multidisciplinary approach combining medication, physical therapy, and procedural and psychological strategies is essential in treating patients with orofacial pain.

INTRODUCTION

Orofacial pain has traditionally signified pain in the mouth and jaw, while facial pain has been more commonly used to describe neurologic conditions including trigeminal neuralgia, other cranial neuralgias, postherpetic neuralgia, and trigeminal autonomic cephalgias. This distinction can be quite frustrating for patients who are often referred to multiple specialists before receiving a diagnosis. In truth, these patients need a multidisciplinary approach to their pain. In 2019, the Orofacial and Head Pain Special Interest Group of the International Association for the Study of Pain, the International Network for Orofacial Pain and Related Disorders Methodology, the American Academy of Orofacial Pain, and the International Headache Society developed an internationally accepted classification system for primary and secondary facial pain. Known as the International Classification of Orofacial Pain (ICOP),¹ this living document works in tandem with the International Classification of Headache Disorders, Third Edition (ICHD-3)² and focuses on diagnostic criteria of all facial pain. This article reviews the diagnoses and treatments of the most common types of facial pain with the goals of expanding the

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Dr Barad reports no disclosure.
Dr Romero-Reyes has received personal compensation in the range of \$500 to \$4999 for serving as an editor, associate editor, or editorial advisory board member for *Pain Medicine* and in the range of \$10,000 to \$49,999 for serving as a consultant for Pfizer Inc. The institution of Dr Romero-Reyes has received research support from Amgen Inc, the US Department of Defense (DoD), and the National Institutes of Health (NIH). The institution of an immediate family member of Dr Romero-Reyes has received research support from the DoD and NIH/National Institutes of Neurological Disorders and Stroke.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:

Drs Barad and Romero-Reyes discuss the use of multiple therapies for the treatment of burning mouth syndrome, persistent idiopathic facial pain, temporomandibular disorders, and trigeminal neuralgia, none of which are approved by the US Food and Drug Administration (FDA) except for carbamazepine for the management of trigeminal neuralgia.

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differential diagnosis toolkit available to neurologists and providing better patient care.

Both dental and nondental orofacial pain are prevalent and significantly affect quality of life.^{3,4} Chronic orofacial pain disorders induce substantial psychological distress and physical disability.^{5,6} Socioeconomic and demographic disparities exist in this patient population.^{3,4} Dental caries is the most common odontogenic disease among adults and children, with significant disparities between ethnic, racial, and socioeconomic groups, highlighting the need to strengthen preventive public health programs and facilitate access to care.⁷ More studies of diverse populations are needed to identify their unique needs regarding nonodontogenic facial pain. Unfortunately, it is not unusual for patients to visit several different dental and medical care providers with the hope of understanding their symptoms and alleviating their pain. The intrinsic subjectivity of the pain experience, the complexity of these disorders, and the underrecognition that these disorders require specialty care with a biopsychosocial lens add to the vulnerability of this patient population.^{5,8,9} Therefore, it is important that health care providers in dental and medical settings understand orofacial pain disorders and ideally have an orofacial pain specialist in their multidisciplinary care team to aid in diagnosis and management.

OROFACIAL PAIN ATTRIBUTED TO DISORDERS OF DENTOALVEOLAR AND ANATOMICALLY RELATED STRUCTURES

This review of painful conditions of the face begins with disorders of the mouth, which are perhaps the least familiar to neurologists.

Dentoalveolar Pain

Dentoalveolar or odontogenic pain is the most common acute pain in the orofacial region.^{1,10} ICOP defines dental pain as pain caused by lesions or disorders affecting one or more teeth, their direct surrounding, and supporting structures, such as the tooth pulp, gingivae, and periodontium, or both.¹ Dental pain is highly prevalent, with an estimated 12.2% of the US population experiencing a toothache in the last 6 months³ and an estimated 2.95 million emergency department visits for dental-related concerns in a 4-year period in the United States. Odontogenic pain is generally of nociceptive or inflammatory origin.¹¹ There are different dental and periodontal pathologies, but most odontogenic pain may be a symptom of pulp and periapical tissue pathology resulting in inflammation due to bacterial infection primarily related to caries (**FIGURE 5-1**).^{12,13} Odontogenic pain may also arise after traumatic injury such as tooth wear, abrasion, or fracture (**FIGURE 5-2**).^{11,14} Pain may be elicited by external stimuli such as cold, heat, sweet foods, or the application of pressure, and it may also appear spontaneously. The temporal pattern of pain may fluctuate and can be described as occasional, continuous, or recurrent.¹ Reported pain can range from mild discomfort to excruciating, disrupting daily life activities. Pain descriptors may depend on the source of pain (eg, dental, periodontium) and the subjectivity of the personal experience of the patient; therefore, they vary and may be described as throbbing, pulsating, sharp, shooting, zinging, or deep.^{11,15} It is important to note that pain arising from dentoalveolar and associated structures may refer to craniofacial structures including the ear, jaw, facial structures, and head as a form of secondary headache.¹⁵ The evaluation, diagnosis, and management of odontogenic pain is done in dentistry. Diagnosis requires clinical examination, dental history before

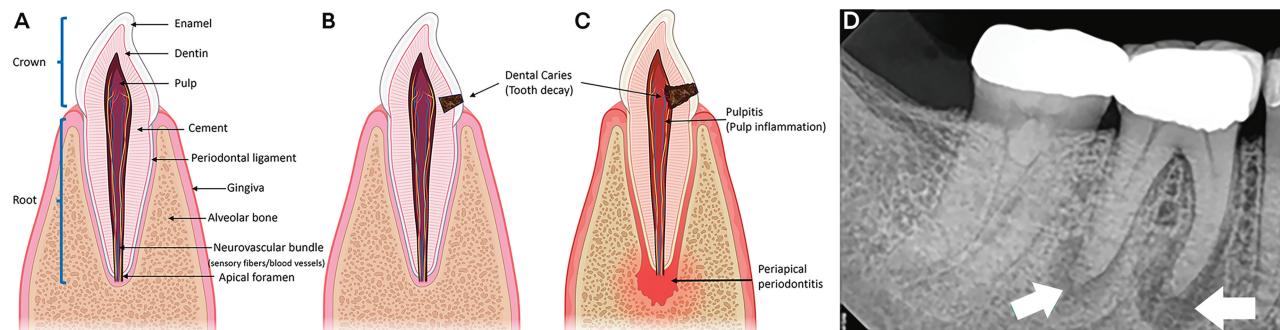


FIGURE 5-1

Dental pathology. **A**, Overview of tooth anatomy. **B**, Dental caries (cavity). **C**, Dental caries involving the pulp and peripapical periodontitis. When caries involves the dentin, painful symptomatology is present. The intensity of pain increases when the caries progresses to involve the pulp (pulpitis) and peripapical tissues (acute peripapical periodontitis). **D**, Periapical radiograph showing a lower first molar with peripapical radiolucencies (arrows) suggestive of peripapical periodontitis.

Panels A, B, and C created using BioRender. Panel D courtesy of Abdoul Koroni.

onset, and imaging evidence of a disease, lesion, or trauma known to cause dental pain.¹

Oral Lesion Pain

Some oral lesions in the oral mucosa can be painful. Lesions can arise from different etiologies, such as infection, inflammation, immune dysfunction, neoplasia, trauma, or idiopathic conditions.^{16,17} Common painful mucosal lesions include recurrent aphthous stomatitis; lesions induced by viral infection such as herpetic gingivostomatitis and herpes simplex labialis; lesions due to fungal infection such as erythematous (atrophic) candidiasis and pseudomembranous candidiasis (thrush), which may or may not be painful; and oral lichen planus, which is a common immune-mediated lesion with erosive or erythematous types that can be very painful due to inflammation and sensitization (FIGURE 5-3).^{16,18} The management of these lesions is directed at the underlying etiology and

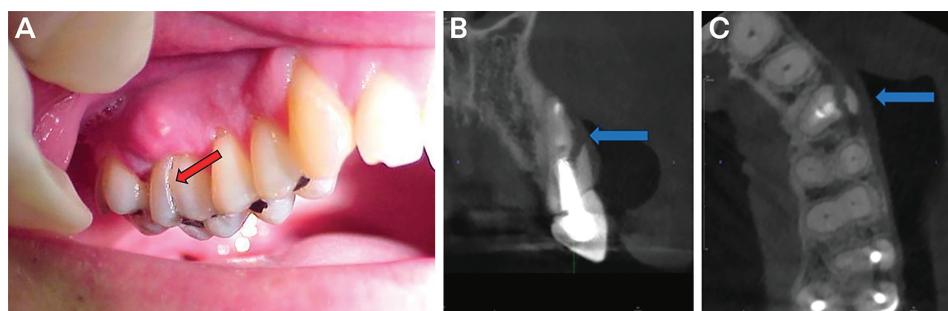


FIGURE 5-2

Fractured tooth. **A**, Crown fracture (arrow) in the right superior first molar and abscess. **B**, **C** Cone-beam computed tomography showing a fracture in the upper left canine (tooth #11, arrow) (**B**, cross-sectional view; **C**, axial view). Dental fractures are sometimes not as visible or obvious and a thorough clinical examination and cone-beam computed tomography imaging is necessary to localize the fracture.

Panel A courtesy of Anthony Schwarz. Panels B and C courtesy of Jeffery B. Price.

symptomatic relief and may include nutritional supplements, antiviral or antifungal medications, topical corticosteroids, and anesthetics.¹⁶

Cancer-related Pain

Orofacial pain may result from local and distant tumor effects in addition to being the sequelae of cancer treatment.¹⁹ Oral squamous cell carcinoma is the most common orofacial malignancy, accounting for approximately 90% of oral cancers.²⁰ Discomfort may be due to ulceration, perineural invasion and compression, and invasion of local anatomical structures. Hematologic cancers and metastatic cancers may spread to the oral region or refer pain to the orofacial region.²¹

Salivary Gland Pain

Pain arising from the salivary glands is usually due to a salivary duct obstruction or infection, but can also be caused by viral infections, autoimmune disorders, and tumors.²² Salivary gland pain is usually accompanied by inflammation or swelling (sialadenitis) of the affected salivary gland and can be exacerbated by applying pressure. Pain arising from an obstruction can be reported as acute and intermittent and is dependent on the extent of any infection.¹

Mandibular or Maxillary Bone Pain

Medications used for the management of osteoporosis or used in oncology such as bisphosphonate or antiangiogenic or antiresorptive agents may induce medication-related osteonecrosis of the jaw that is painful and sometimes accompanied by infection.^{1,23} The population taking these medications can be at risk for osteonecrosis after dental extraction and other bone-related dental procedures, so prevention protocols and management strategies should be implemented for these cases.^{24,25}

Temporomandibular Disorders

Temporomandibular disorders are a constellation of musculoskeletal disorders involving the temporomandibular joint (TMJ), the muscles of mastication, and their associated structures.^{17,26} After dental pain, temporomandibular disorders are the second most common source of orofacial pain and the second most common reason for patients to seek dental care.²⁷ When chronic, they are considered the most prevalent chronic orofacial pain.²⁸ It has been estimated that

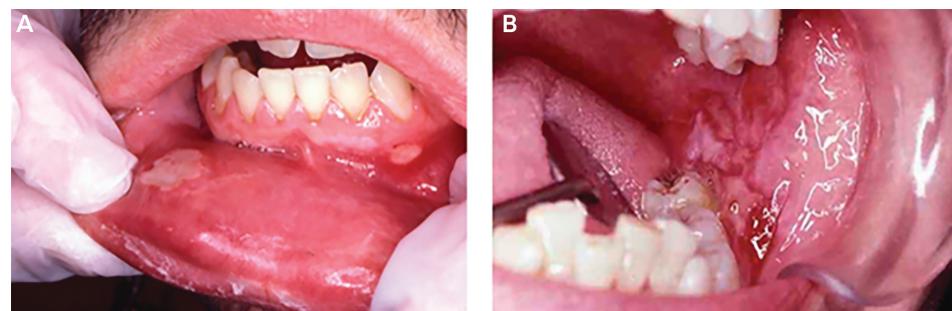


FIGURE 5-3

Oral painful lesions. **A**, Recurrent aphthous stomatitis. **B**, Erosive lichen planus.

Images courtesy of Francina Lozada Nur.

temporomandibular disorder symptomatology affects approximately 5% to 12% of the population,²⁹ with an annual incidence of first onset of symptoms of 3.9%,³⁰ and with female predominance.³¹ In children and adolescents, the prevalence varies between studies and populations but has been reported to be from 7.4% to 68%, to be more common in females, and to increase with age from childhood to adolescence.^{32,33} More comprehensive standardized protocols are being developed to improve assessment and diagnosis in this population.³⁴

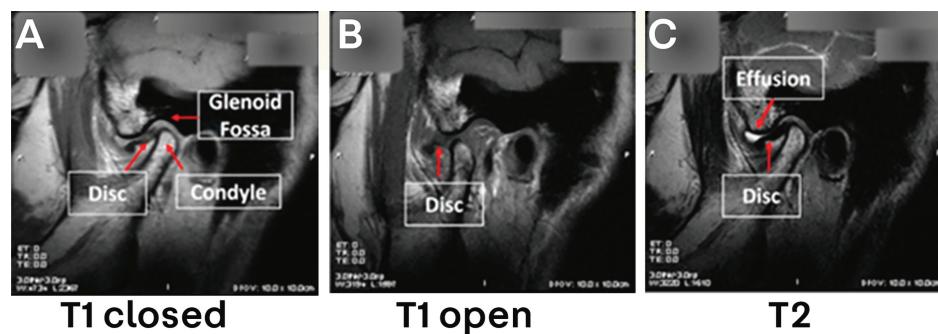
Patients may report a variety of symptoms of pain and dysfunction related to TMJ biomechanics and jaw movements that affect their daily routine. Symptoms include pain with chewing that limits mastication, that limits range of motion while opening the jaw wide on examination, and while talking or yawning. They may also report pain in the ear, face, or both and experience jaw pain as a source of secondary headache.^{2,17,35} Temporomandibular disorders are comorbid with several disorders including primary headache disorders (with migraine being the primary headache disorder with the highest prevalence in patients with temporomandibular disorders) and other chronic disorders such as fibromyalgia, chronic fatigue, sleep disorders, lower back pain, vulvodynia, irritable bowel syndrome, anxiety, and depression.³⁶ The Orofacial Pain Prospective Evaluation and Risk Assessment studies have contributed to our understanding of the complexity of temporomandibular disorder etiology and pathophysiology and support the notion of temporomandibular disorders as multifactorial disorders within a biopsychosocial scaffold that includes epigenetic and genetic factors, and that more research and education is needed to understand these conditions.^{30,37} This evidence-based paradigm shift has led to a move away from the gnathologic point of view, which focuses on dental occlusion and maxillomandibular relationships, that reigned in the dental field for several decades.^{37,38}

Temporomandibular disorders may be referred to as "TMJ"; however, this is not correct, as "TMJ" only refers to an anatomic structure (the temporomandibular joint) and not to a set of disorders or a diagnosis. The majority of temporomandibular disorders are characterized by painful symptomatology and dysfunction and may cause substantial psychosocial impairment.³⁹ The most common painful disorders according to the diagnostic criteria of temporomandibular disorders include myalgia, myofascial pain, arthralgia, and headache attributed to temporomandibular disorders.⁴⁰ However, not all temporomandibular disorders cause pain, and the most common intraarticular disorders may or may not cause pain and include disc displacement with reduction, disc displacement without reduction, degenerative joint disease, and subluxation.⁴⁰ In children and adolescents, the most commonly reported diagnoses are myofascial pain and anterior disc displacement with reduction.^{32,41} The presence of TMJ sounds during jaw movement such as popping, clicking, or grating is quite common and usually not painful, indicating a disc/condyle incoordination (ie, asymptomatic clicking sound when opening and sometimes closing the jaw, indicating a TMJ disc displacement with reduction) that generally does not require management.^{17,42} In cases of TMJ disc displacement without reduction, the disc is not recaptured or reduced so clicking is not present, and management is necessary since pain may be present and opening may be limited (**FIGURE 5-4**).

Bruxism is a group of parafunctional behaviors defined as repetitive activity of the muscles of mastication characterized by grinding or clenching of the

KEY POINTS

- Given the complexity and difficulty in diagnosis, a multidisciplinary approach is the best strategy for diagnosing and treating orofacial pain.
- Odontogenic pain is the most common acute source of orofacial pain and is usually the result of pulp or periapical tissue pathology.
- Odontogenic pain can be referred to adjacent craniofacial structures as a form of secondary headache.
- Other painful oral problems include oral mucosal lesions, cancer-related pain, salivary gland pain, or mandibular or maxillary bone pain.
- Temporomandibular disorders are a constellation of musculoskeletal disorders involving the temporomandibular joint, the muscles of mastication, and their associated structures.
- Temporomandibular disorders are the most prevalent chronic orofacial pain.
- Temporomandibular disorders are comorbid with depression, poor sleep, primary headaches, and other chronic pain problems.

**FIGURE 5-4**

MRI shows a temporomandibular joint disc displacement without reduction and superior joint space effusion. **A**, View of the anterior displaced position of the temporomandibular joint articular disc at closing. **B**, The disc is not recaptured during opening and remains displaced. **C**, High signal intensity showing inflammatory effusion in the superior joint space. Images courtesy of Gary Warburton.

teeth, bracing or thrusting of the mandible either during sleep or when awake, or both.⁴³ It is quite common to misattribute bruxism as a cause of temporomandibular disorders. This message from providers is reinforced by patients' beliefs^{44,45} and requests from both patients and providers for an oral appliance (eg, nightguard) for "management." There is no clear evidence that these parafunctional behaviors cause temporomandibular disorder symptomatology.^{17,46,47} However, it is important to highlight that, in some individuals, these behaviors may perpetuate, exacerbate, or even initiate temporomandibular disorder symptomatology, but more research is needed for clarification.^{46,48} Current knowledge about the etiology and pathophysiology of bruxism points toward a multifactorial explanation including contributions from central sensitization, genetic predisposition, and psychosocial domains.⁴⁷ Acute neurologic illnesses including traumatic brain injury, acute ischemic stroke, and encephalitis and several classes of medications including selective serotonin reuptake inhibitors (SSRIs) and phenethylamines, as well as alcohol, nicotine, and other addictive substances, may induce bruxism^{49,50} and need to be considered when taking the medical history. Temporomandibular disorders are multifactorial and management should be applied within a biopsychosocial framework, in which behavioral approaches complement conservative care protocols.²⁶ Therefore, a multidisciplinary approach is vital. The treatment program is tailored to a patient's needs based on diagnosis, symptomatology, source of pain, perpetuating and contributing factors, and comorbidities, with the goal of decreasing symptomatology and restoring function.¹⁷

EVALUATION. Following the diagnostic criteria of temporomandibular disorders and the fact that the ICOP distinguishes myofascial pain and TMJ pain as the two main diagnostic categories of temporomandibular disorders,^{1,40} it is important to emphasize that the main sources of pain may be from the TMJs, musculature (**CASE 5-1**), or both, but the most common temporomandibular disorders are myogenous, such as myofascial pain and myalgia.^{51,52}

Temporomandibular disorder evaluation includes an examination of the face, head, neck, and intraoral structures. Since pain in the orofacial region can be of different etiologies (eg, neuropathic, neurovascular, musculoskeletal), it is

important to recognize that the main goal of the examination is to replicate or detect a similar discomfort and symptomatology to what the patient is reporting as the primary symptom, and to detect associated dysfunction. This involves a detailed examination of the TMJs and muscles of mastication and may involve the cervical musculature since muscles of the cervical spine may refer to orofacial structures and may be associated with or be the source of the chief symptom. Briefly, it includes evaluation of the TMJs, their palpation and auscultation for TMJ noises during mandibular motions, and an evaluation and measurement of mandibular range of motion. A normal mouth opening range is 40 mm to 58 mm of interincisal distance and is influenced by craniofacial structure, age, and body size.⁵³ The assessment should also include imaging, and evaluation and palpation of the musculature, with special attention to detecting tightness, hypersensitive areas, and patterns of pain referral.^{54,55}

While palpating the TMJs and the main masticatory muscles such as the masseter and temporalis, it is important to ask if the elicited pain or symptomatology replicates or is similar to the reported pain. In addition, a brief questionnaire (**TABLE 5-1**⁵⁶) is useful to help recognize a possible temporomandibular disorder. When the evaluation and the patient's responses to the questionnaire point to the possibility of a temporomandibular disorder, some recommendations can be initiated in the medical setting while the patient is referred to an orofacial pain specialist for further evaluation and care. If the patient is reporting pain with TMJ biomechanics, a soft diet (ie, avoiding anything hard, crunchy, chewy, or that requires a long period of chewing) and cutting their food into small pieces to avoid discomfort while opening their mouth can be recommended. The application of moist heat in the area of muscular discomfort can be implemented and nonsteroidal anti-inflammatory drugs and muscle relaxants can be integrated into the preliminary plan.⁹

TREATMENT. For the majority of temporomandibular disorders, symptomatology is self-limited and transitory and patients report relief with noninvasive and conservative procedures.^{51,57} Thus, initial management should be noninvasive, conservative, reversible, and evidence based.⁵⁸ This includes patient education and a self-care program where the patient is informed about their condition and symptomatology. This support is critical to alleviate anxiety and improve patient outcomes. Depending on the diagnosis and examination findings, the self-care program should consist of focusing on resting the TMJ and masticatory musculature to facilitate healing, integrating a soft diet, limiting jaw movements, awareness of possible parafunctional habits, and the application of heat and cold therapy.⁵⁴ Pharmacotherapy may include nonsteroidal anti-inflammatory drugs, muscle relaxants, and trigger point injection therapy. Other pharmacologic classes may be used in refractory cases.

Oral appliances are commonly used for temporomandibular disorders. The primary use of a passive oral appliance, such as a stabilization appliance (which covers all maxillary or mandibular teeth), is to protect the teeth from wear due to excessive attrition. It is important to highlight that an oral appliance will not stop bruxism but may diminish the intensity, duration, and frequency of these parafunctional activities for variable amounts of time in some patients.⁵⁹ Moreover, studies have raised the question of the ability of stabilization appliances to aid in temporomandibular disorders, but other studies have shown

KEY POINT

- Bruxism may influence temporomandibular disorder symptomatology in some individuals, but more research is necessary to establish evidence of causality.

that they can help improve temporomandibular disorder symptomatology, either myogenous or arthrogenous in nature, as a part of a management plan.^{59,60} In addition to the use of oral appliances, behavioral therapy such as cognitive behavioral therapy and physical therapy (craniofacial and cervical therapeutics) are also included in the management protocol.^{9,17,54} When indicated, the plan may also integrate minimally invasive procedures such as TMJ injections and surgical interventions such as arthroscopic or arthrocentesis procedures.^{9,17} Patients may inquire about onabotulinumtoxinA injections as a way to manage temporomandibular disorders, and it is important to highlight that the use of onabotulinumtoxinA is neither considered first-line management for temporomandibular disorders nor approved by the US Food and Drug

CASE 5-1

A 31-year-old woman presented for a consultation regarding orofacial pain. The pain was localized in the left side of her face and jaw. She described the pain as a moderate steady dull aching pain that could be exacerbated while chewing her food or talking for long periods of time and while opening wide. She reported that she had this pain for the previous 3 months and that her teeth were “achy” and she had pain in her left ear, but odontogenic sources and ear pathology were cleared. She did not report any history or present symptomatology of temporomandibular joint (TMJ) noises or episodes of locking. During examination, she could open her mouth without pain to 40 mm. During muscle palpation, the left masseter muscle (superficial and deep belly) was severely tender to palpation and referred pain to her lower posterior teeth and left ear, replicating her chief symptom. She was diagnosed with myofascial pain with referral in the left masseter muscle.

COMMENT

This patient presented with pain with TMJ biomechanics, and the pain was replicated during examination (palpation) and the source was identified. In addition, the examination may include a trigger point injection of the masseter muscle (usually performed with 1% or 2% lidocaine without epinephrine) in the area of the hypersensitivity that elicited the referral (trigger point) to further clarify the source of pain. It is important to mention that the masseter, the temporalis, and anterior digastric muscles can refer to other craniofacial structures including the teeth, and sometimes this is the primary symptom related by the patient. The masseter muscle can refer to structures beyond its boundaries and, as in this patient, it can refer pain to teeth (lower and upper posterior teeth) and the ears, but also above the eye and along the face and jaw (**FIGURE 5-5**). It is important to mention that during examination, in addition to the TMJ evaluation, all muscles of mastication and cervical muscles are evaluated, and other muscles in addition to the TMJ often present some accompanying symptomatology. It would have also been important to investigate what happened to the patient 3 months ago to identify possible etiology, in addition to asking if the pain intensity changed during the day (worse in the morning or night) to detect any possible contribution of parafunctional behaviors.

Administration (FDA) for the treatment of temporomandibular disorders.⁹ Reductions of myogenous temporomandibular disorder symptomatology such as myofascial pain and sleep bruxism have been reported, but evidence still varies between studies.^{61,62} However, in cases when patients have been refractory to conventional therapy and in cases of severe bruxism, onabotulinumtoxinA may be a good option to explore with caution.^{63,64} Currently, there are no validated standardized protocols for its use in treating temporomandibular disorders and more randomized controlled trials and prospective studies are greatly needed to explore its long-term risks and benefits. Concerns of decreased bone density and muscle changes in response to onabotulinumtoxinA use need to be further investigated.

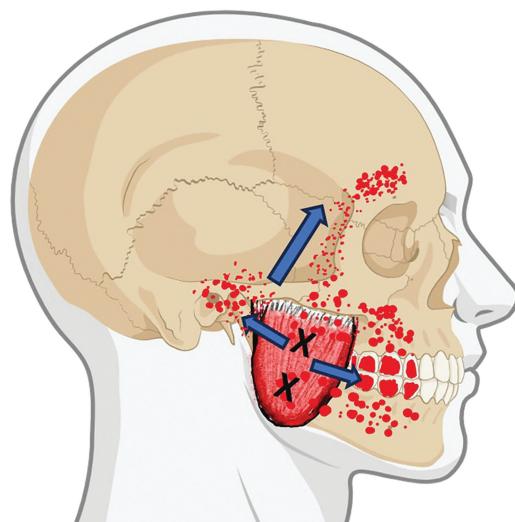


FIGURE 5-5
Muscular trigger points in the masseter muscle can spread along the muscle (myofascial pain) or refer to a distant site (myofascial pain with referral) along the mandible, malar area, ear, temple, above the eye and teeth as shown in this case.

Image created with BioRender.

NEURALGIC PAIN

Trigeminal neuralgia is the most well-known and often most severe facial neuralgia. The reported incidence of trigeminal neuralgia ranges from 4.3 to 27 new cases per 100,000 people per year.⁶⁵ The average age of onset is 53 years and incidence appears to increase with age.^{65,66} The lifetime prevalence of trigeminal neuralgia is higher in women and is estimated to be between 0.16% to 0.3%.^{65,66}

Diagnosis of Trigeminal Neuralgia

The diagnosis of trigeminal neuralgia relies predominantly on the history. The pain is described as severe, brief, and electrical or shocklike, occurring in one or more divisions of the trigeminal nerve, and can be precipitated by innocuous stimuli. **TABLE 5-2** lists the types of trigeminal neuralgia described by the ICHD-3 criteria.² For a thorough differential diagnosis, see **TABLE 5-3**. The chief clinical characteristics of trigeminal neuralgia that may help distinguish it from other facial neuralgias are location and severity. By definition, trigeminal neuralgia lies

TABLE 5-1

Temporomandibular Pain Disorder Screening Instrument^{a,b}

- 1 In the last 30 days, on average, how long did any pain in your jaw or temple area on either side last?**
 - a** No pain
 - b** From very brief to more than a week, but it does stop
 - c** Continuous

- 2 In the last 30 days, have you had pain or stiffness in your jaw on awakening?**
 - a** No
 - b** Yes

- 3 In the last 30 days, did the following activities change any pain (that is, make it better or make it worse) in your jaw or temple area on either side?**
 - A Chewing hard or tough food**
 - a** No
 - b** Yes

 - B Opening your mouth or moving your jaw forward or to the side**
 - a** No
 - b** Yes

 - C Jaw habits such as holding teeth together, clenching, grinding, or chewing gum**
 - a** No
 - b** Yes

 - D Other jaw activities such as talking, kissing, or yawning**
 - a** No
 - b** Yes

^a Reprinted with permission from Gonzalez YM, et al, J Am Dent Assoc.⁵⁶ © 2011 American Dental Association.

^b Items 1 through 3A constitute the short version of the screening instrument, and items 1 through 3D constitute the long version. An "a" response receives 0 points, a "b" response receives 1 point, and a "c" response receives 2 points. A positive score is 2 for the short version and 3 for the long version.

in the trigeminal distribution, most commonly in the maxillary division followed by the mandibular and then ophthalmic divisions ($V_2 > V_3 > V_1$), and the right side is affected more often than the left side.⁶⁶ The posterior one-third of the scalp, the outer ear except the tragus, and the angle of the mandible are not innervated by the trigeminal nerve, so pain experienced predominantly in these areas suggests an alternative diagnosis (FIGURE 5-6).⁶⁷ It appears that one-half of patients with trigeminal neuralgia experience concomitant continuous pain.⁶⁸ The continuous pain is often described as an aching, dull, or burning sensation, usually at a lower intensity.⁶⁹

Paroxysms of pain are typically severe and can limit a patient's ability to talk or cause them to wince and cover their face. Patients may experience several to one hundred such paroxysms a day, and they typically last from less than 1 second to 2 minutes, with most lasting a few seconds.⁶⁶ Simple activities of daily life are often triggers for the pain, including gently touching or washing the face, talking, and chewing.⁶⁷ The physical examination is important in that abnormal findings, other than allodynia, should suggest an alternative diagnosis. The examiner should not detect any facial asymmetry or significant hypoesthesia in patients with trigeminal neuralgia.⁶⁶ Advanced sensory testing may elicit subtle findings.⁷⁰ Importantly, loss of sensation or weakness and wasting in the masseter or temporalis may suggest a trigeminal neuropathy rather than trigeminal neuralgia. Attacks witnessed during examination are notable in that the patient will often contort and contract their facial musculature in response to the pain, a response known as *tic convulsif*.⁶⁷ After the attack, there is a refractory period where a new attack cannot be elicited, and this can present an additional examination finding. Autonomic symptoms, traditionally not thought to play a role in trigeminal neuralgia, are present in a large proportion of patients with trigeminal neuralgia.⁷¹

Classical trigeminal neuralgia is thought to be caused by neurovascular conflict with compression, meaning that there is a morphologic alteration of the

Types of Trigeminal Neuralgia^a

TABLE 5-2

Types of trigeminal neuralgia	Pathophysiology	Subtypes of trigeminal neuralgia
Classical trigeminal neuralgia	Neurovascular conflict	Trigeminal neuralgia with purely paroxysmal pain Trigeminal neuralgia with concomitant persistent pain
Secondary trigeminal neuralgia	Lesion in brainstem or nerve	Trigeminal neuralgia attributed to multiple sclerosis Trigeminal neuralgia attributed to space-occupying lesion Trigeminal neuralgia attributed to other cause
Idiopathic trigeminal neuralgia	Idiopathic; no detectable cause or etiology	Purely paroxysmal pain With concomitant persistent pain

^a Data from the Headache Classification Committee of the International Headache Society, Cephalalgia.²

trigeminal nerve by a vessel, most commonly an artery, in the prepontine cistern proximal to the Meckel cave. This morphologic change occurs in the root entry zone, the proximal 25% of the nerve as the myelin is transitioning from peripheral Schwann cells to central oligodendrocytes. In the root entry zone, the nerve is thought to be more vulnerable to pressure and compression from a blood vessel.⁷² The concomitant pain experience is thought to be due to either ectopic impulse generation, centrally mediated facilitation of nociceptive processing, or reduced descending inhibitory mechanisms.^{73,74} Importantly, the association of trigeminal neuralgia with neurovascular conflict is not sufficient to diagnose classic trigeminal neuralgia; in fact, 99.94% of neurovascular conflict seen on imaging in the general population was reported as asymptomatic.⁷⁵ It must be seen in combination with a history and physical examination suggestive of trigeminal neuralgia. It is also thought that there is a spectrum ranging from contact to compression, and current research aims to develop a grading system for neurovascular conflict and determine whether it correlates with microvascular decompression success.⁷⁶

Neurovascular compression is thought to be the main cause of classic trigeminal neuralgia, although a 2023 systematic review noted that neurovascular compression is seen in only 88.85% of patients with trigeminal neuralgia.⁷⁵ Alternative lesions can disrupt the trigeminal nerve, and this is commonly

TABLE 5-3**Differential Diagnosis of Trigeminal Neuralgia^a**

Feature of the pain experience	Disorder
Onset	
Recent rash related to herpes zoster infection	Painful trigeminal neuropathy attributed to acute herpes zoster (postherpetic neuralgia)
History of injury, trauma, or dental surgery or procedure	Painful posttraumatic trigeminal neuropathy
Location	
Pain in the jaw or teeth (intraoral)	Cracked tooth
Pain in the scalp or occipital region	Occipital neuralgia, primary stabbing headaches, or paroxysmal hemicrania
Pain in the back of the tongue, tonsil, or soft palate	Glossopharyngeal neuralgia
Pain deep in the ear	Nervus intermedius neuralgia or glossopharyngeal neuralgia
Duration	
Constant pain	Otitis, giant cell arteritis, osteomyelitis, burning mouth syndrome, trigeminal neuropathy, or persistent idiopathic facial pain
Associated symptoms	
Autonomic symptoms	Cluster headache, SUNA, SUNCT, or paroxysmal hemicrania

SUNA = short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms; SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

^a Modified with permission from Allam AK, et al, Neurol Clin.⁷¹ © 2023 Elsevier Inc.

referred to as *secondary trigeminal neuralgia*. About 15% of patients with trigeminal neuralgia attacks have secondary trigeminal neuralgia. Multiple sclerosis (MS) or benign tumors of the cerebellopontine angle are the most common causes of secondary trigeminal neuralgia. The prevalence of MS-related trigeminal neuralgia is 2% to 5% among patients with MS, and patients with MS have a 20-fold increased risk of developing trigeminal neuralgia. MS-associated secondary trigeminal neuralgia most commonly presents at a younger age and in the trigeminal distribution bilaterally.⁷⁷ Typically, trigeminal neuralgia symptoms will present approximately 12 years after the initial onset of MS.⁷¹ This type of trigeminal neuralgia is attributed to a demyelinating plaque along the fascicle of the trigeminal nerve as it passes through the ventral pons.⁶⁷ Surprisingly, one neuroimaging study demonstrated an association between neurovascular conflict and MS-related trigeminal neuralgia, suggesting that they may coexist and be additive.⁷⁸

Secondary trigeminal neuralgia can also be caused by mass effect in the cerebellopontine angle compressing the trigeminal nerve root. Lesions that can contribute to mass effect include acoustic neuromas, meningiomas, infiltrative malignant tumors, epidermoid cysts, and cholesteatomas.⁶⁷ Additional causes of secondary trigeminal neuralgia include skull-base bone deformity, connective tissue disease, arteriovenous malformation, dural arteriovenous fistula, and genetic causes of neuropathy or nerve hyperexcitability.²

Imaging is important in the evaluation of abnormalities in the nerve or brain leading to trigeminal neuralgia. A 3-T MRI is the imaging modality of choice because it can clearly delineate vascular compression and accurately identify secondary causes of trigeminal neuralgia.⁷³ In addition to the standard axial fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) sequences, constructive interference in steady state (CISS)/fast imaging employing steady state acquisition (FIESTA) sequences and three-dimensional time-of-flight MR angiography are also important for the evaluation of patients with trigeminal neuralgia. Imaging should also include postcontrast

KEY POINTS

- OnabotulinumtoxinA is not indicated as first-line management and is not US Food and Drug Administration (FDA) approved for the treatment of temporomandibular disorders, but it may be explored in refractory cases in consultation with an orofacial pain specialist.

- Trigeminal neuralgia is more common in women, appears to increase with age, and presents most frequently in the V2 distribution on the right side.

- One-half of patients with trigeminal neuralgia experience concomitant continuous pain.

- The examination in patients with classic trigeminal neuralgia is usually normal, and deficits in the distribution of the trigeminal nerve suggest trigeminal neuropathy.

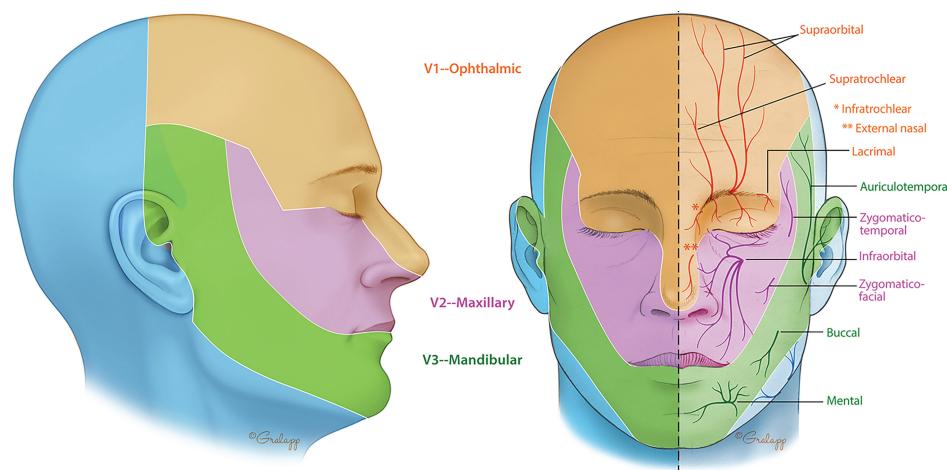


FIGURE 5-6

Trigeminal nerve divisions and terminal branches. The trigeminal nerve is the fifth cranial nerve. It has three major divisions and each division has multiple terminal branches.

Image designed by Chris Gralapp.

three-dimensional T1-weighted fast spoiled gradient recalled echo (GRE) imaging. The goal of these imaging techniques is to clearly see the trigeminal nerve and the surrounding vasculature in the brainstem.⁷⁹ Nerve deviation or distortion, groove formation, and atrophy can be clearly diagnosed using these sequences. Atrophic changes in the nerve should be noted as they may correlate with the severity of compression and may help to predict long-term prognosis after vascular decompression⁷⁹ (**CASE 5-2**).

Treatment

Pharmacologic management is the recommended first-line therapy for all types of trigeminal neuralgia (**TABLE 5-4**). The 2019 European Academy of Neurology Guideline on Trigeminal Neuralgia provides a comprehensive consensus statement. For acute exacerbations, in-hospital treatment may be offered for titration of preventive medication, rehydration, and IV infusion of fosphenytoin or lidocaine. For long-term treatment, carbamazepine (200 mg/day to 1200 mg/day) or oxcarbazepine (300 mg/day to 1800 mg/day) have the best evidence for effectiveness. If these drugs become ineffective or are poorly tolerated, other drugs to consider include lamotrigine, gabapentin, onabotulinumtoxinA, pregabalin, baclofen, and phenytoin. Overall, there is low to very low quality of evidence for these secondary medications either alone or combined with carbamazepine or oxcarbazepine when first-line drugs fail.⁸⁰ Observational and small open-label studies have shown pain reduction in trigeminal neuralgia with the use of topiramate,⁸¹ levetiracetam,^{82,83} and pregabalin.⁸⁴

The primary surgical treatment for classic trigeminal neuralgia refractory to medical management is microvascular decompression. The goal of microvascular decompression surgery is to separate the trigeminal nerve root from the blood vessels that are in contact with the nerve root. The surgery is performed through a retrosigmoid craniotomy. Although it is the most invasive option for trigeminal neuralgia treatment, it has been shown to provide both high patient satisfaction and low recurrence. In a summary of single-outcome intervention trials, over 73% of patients maintained pain relief 5 years after the procedure.⁸⁰ It was also noted that 62% to 89% of patients with classic trigeminal neuralgia were pain free throughout the follow-up period (3 to 11 years). After microvascular decompression, the generally cited average recurrent rate of trigeminal neuralgia is 4% per year.⁸⁰ Complications from microvascular decompression are rare, and morbidity ranges from 0.3% to 3% and mortality from 0.2% to 0.5%.⁸⁰

While microvascular decompression has demonstrated a longer period of pain relief and lower rates of recurrence, stereotactic radiosurgery remains an option for patients who are ineligible for microvascular decompression. Pooled analysis demonstrates that 30% to 66% of patients remained pain free 4 to 11 years after radiosurgery.⁸⁰ The pain relief is typically delayed by 1 month on average, but some studies have shown that pain relief can continue to increase for up to 24 months after stereotactic radiosurgery.⁷¹

For secondary trigeminal neuralgia refractory to medical management and idiopathic trigeminal neuralgia, neuroablative procedures of the trigeminal (gasserian) ganglion or stereotactic radiosurgery should be considered.⁸⁰ Neuroablative options attempt to create a focal injury of the trigeminal nerve afferents within the trigeminal (gasserian) ganglion. These procedures include radiofrequency ablation, glycerol rhizotomy, and balloon compression. A pooled

analysis reported that 19% to 58% of patients were pain free at 4 to 11 years after glycerol injection, 26% to 82% after radiofrequency ablation, and 55% to 80% after balloon compression.⁸⁰ The side-effect profile is notable for dysesthesia, corneal anesthesia, mastication weakness, and anesthesia dolorosa which can be very problematic and difficult to treat. Stereotactic radiosurgery is typically used for secondary trigeminal neuralgia associated with tumor, MS, or stroke.^{85,86} Nerve blocks, distal to the gasserian ganglion, can also be helpful in an acute setting. Their effect typically lasts only hours to days, but they can help manage severe exacerbations by allowing time for other administered medications to start working. They can also be considered in secondary trigeminal neuralgia.

KEY POINTS

- Classical trigeminal neuralgia is thought to be caused by neurovascular compression.
- About 15% of patients with trigeminal neuralgia symptomatology have secondary trigeminal neuralgia.
- The most common causes of secondary trigeminal neuralgia are multiple sclerosis and benign tumors.
- The goal of imaging in patients with trigeminal neuralgia is to look for evidence of vascular compression on the trigeminal nerve through nerve deviation, groove formation, or atrophy, and to exclude secondary causes.
- Treatment guidelines continue to suggest medical management as the first-line treatment of trigeminal neuralgia, with microvascular decompression being the most effective surgical option.
- Glossopharyngeal neuralgia causes similar pain to trigeminal neuralgia but is located in the ear, base of the tongue, roof of the mouth, and tonsillar fossa.

Other Neuralgias

Glossopharyngeal neuralgia uses the same terminology as trigeminal neuralgia and classic glossopharyngeal neuralgia is also suspected to be due to a vascular compression. The pain of this neuralgia is typically located in the ear, base of the tongue, tonsillar fossa, and roof of the mouth. The pain is similar to that of trigeminal neuralgia, being sharp, severe, stabbing, transient, and precipitated by specific triggers, most notably talking, swallowing, coughing, yawning, or chewing.⁸⁷ Similar to classic trigeminal neuralgia, classic glossopharyngeal neuralgia is also known to have an initially good response to carbamazepine. There are two types of pain distributions: pain starting in and around the ear (known as the tympanic form) and pain starting in the throat (known as the pharyngeal form). Vagal symptoms such as bradycardia, syncope, or even cardiac arrest have been observed in up to 10% of patients with glossopharyngeal neuralgia, which is then called vagoglossopharyngeal neuralgia.⁸⁸ The estimated incidence of 0.2 to 0.7 per 100,000 people per year is probably an underestimate due to the difficulty of diagnosis.^{89,90}

Epidemiologic studies of glossopharyngeal neuralgia are sparse; one study showed a female predominance and another showed a 25% bilateral presentation, but neither of these results have been confirmed by subsequent studies.⁶⁵ Age-specific incidence seems to be highest in the fifth and sixth decades.^{65,90} Secondary glossopharyngeal neuralgia may be due to Eagle syndrome and is attributed to an elongated styloid process and ossification of the stylohyoid ligament as the nerve passes behind the styloid process. Other secondary etiologies of secondary glossopharyngeal neuralgia are similar to secondary trigeminal neuralgia, including MS, tumors, trauma, and Chiari malformations.^{87,91}

Similar to trigeminal neuralgia, treatment of glossopharyngeal neuralgia involves neuromodulatory medication and workup should consist of imaging to look for vascular compression with possible consideration of surgery.⁹² Nerve blocks are not helpful for pain management in this setting due to the proximal nature of the lesion; however, blocks help distinguish between primary and secondary glossopharyngeal neuralgia.⁹² Vascular impingement of the posterior inferior cerebellar artery has been determined to be the most common vessel involved.^{93,94} Microvascular decompression is the most common technique for treatment, often performed with a concomitant rhizotomy of the nerve. Microvascular decompression alone has a low risk of complications and resolves pain in more than 85% of patients in the immediate postoperative setting and 65% to 90% of patients in the long term (>3 years). Concomitant rhizotomy appears to

CASE 5-2

A 65-year-old woman with no medical history presented with pain in her right upper teeth. She stated that the pain occurred 2 to 10 times a day and lasted only seconds, but was quite severe. The pain felt sharp and electric and was debilitating. She was convinced that it was an issue with her teeth and had seen three dentists, received x-rays, and had one tooth removed, but the pain continued. Pain triggers included rubbing the cheek and wind or air conditioning blowing on her cheek. On examination, there was no sinus pathology and no sensory loss in the face, but it was very sensitive to light touch in the right V2 and V3 distributions. Imaging showed possible but not obvious compression of the right trigeminal nerve by the superior cerebellar artery ([FIGURE 5-7](#)). She was diagnosed with trigeminal neuralgia, as supported by her history and essentially normal examination.

After a period of medication trials, including carbamazepine (which caused headache, dizziness, and low sodium) and gabapentin (which reduced the pain but was not tolerated at higher doses due to excessive fatigue and cognitive clouding), the patient elected to undergo microvascular decompression ([FIGURE 5-8](#)). This resulted in the separation of the superior cerebellar artery from the trigeminal nerve and allowed for complete pain resolution.

COMMENT

This patient's older age, sex, and distribution of pain on the right V2 and V3 distributions describe the most common presentation of trigeminal neuralgia. Distinguishing classic from secondary trigeminal neuralgia requires imaging to look for a neurovascular compression and rule out any other process. While this patient did not have frank morphologic distortion of the trigeminal nerve, the history and physical examination supported the diagnosis of classic trigeminal neuralgia.

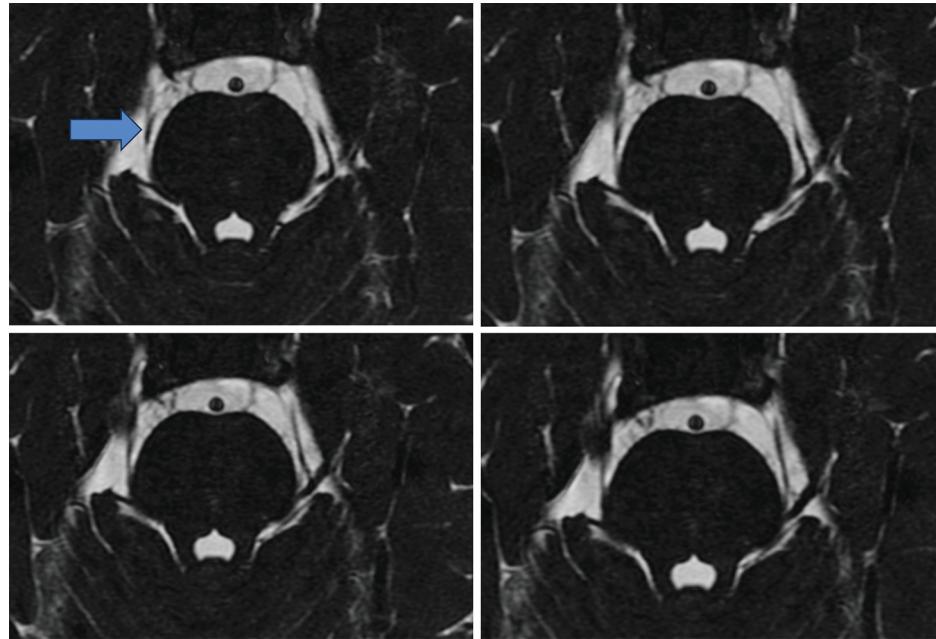


FIGURE 5-7

Imaging of the patient in **CASE 5-2**. Successive axial fast imaging employing steady state acquisition (FIESTA) images from a 3-T MRI with thin cuts through the brainstem show possible but not definite compression of the right trigeminal nerve by the superior cerebellar artery (arrow). While the blood vessel is clearly touching the nerve, the lack of atrophy or malformation of the nerve suggests that it may not be compressed.

Images courtesy of Michael Lim.

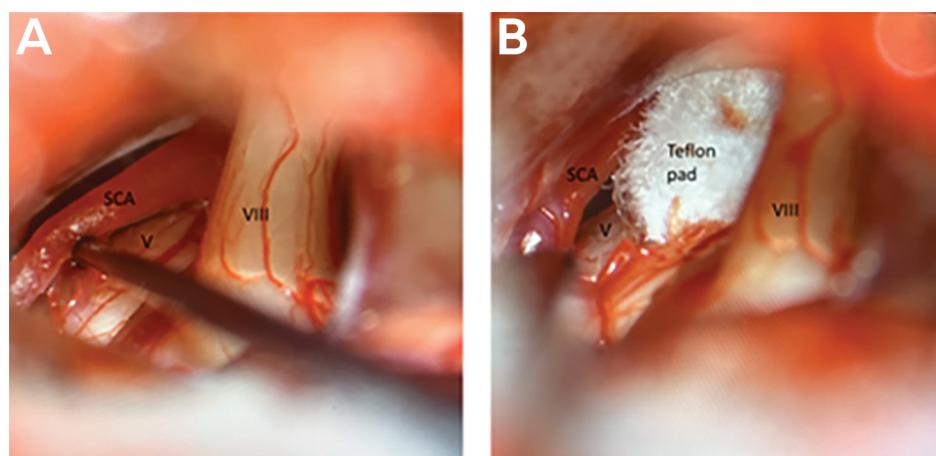


FIGURE 5-8

Imaging of the patient in **CASE 5-2**. A, Separation of the superior cerebellar artery (SCA) from the trigeminal nerve (V). B, A teflon pad is inserted between the SCA and trigeminal nerve, thus decompressing the nerve.

Images courtesy of Michael Lim.

TABLE 5-4

Medications Recommended for Trigeminal Neuralgia^a

Medication	Starting dose	Dose range	Titration/ tapering required	Precautions, side effects, and notes
Carbamazepine^b	200 mg/day to 400 mg/day in 2 to 4 divided doses based on formulation	Increase by 200 mg/day gradually; usual maintenance dose: 600 mg/day to 800 mg/day in 2 to 4 divided doses based on formulation; maximum dose: 1.2 g/day	Yes	Precautions: atrioventricular block, monoamine oxidase inhibitor (MAOI) use, bone marrow suppression Side effects: hyponatremia, leukopenia, ataxia, nausea, dizziness, fatigue, Stevens-Johnson syndrome For long-term use, check vitamin D and use calcium supplements
Oxcarbazepine^b	300 mg/day to 600 mg/day given in 2 divided doses; once-daily extended-release formulation available	Increase by 300 mg/day gradually; usual maintenance dose: 600 mg/day to 1200 mg/day in 2 divided doses; maximum dose: 1.8 g/day	Yes	Precautions: atrioventricular block, monoamine oxidase inhibitor (MAOI) use Side effects: hyponatremia, leukopenia, ataxia, nausea, dizziness, fatigue, Stevens-Johnson syndrome For long-term use, check vitamin D and use vitamin D and calcium supplements Incomplete allergic cross reactivity with carbamazepine and lamotrigine
Lamotrigine^b	25 mg once daily in the absence of other medications that significantly increase or decrease lamotrigine metabolism (eg, valproic acid, carbamazepine, phenytoin)	Increase by 25 mg every 2 weeks as tolerated; usual maintenance dose: 100 mg/day to 200 mg/day divided in 1 to 2 doses a day based on formulation; maximum dose: 400 mg/day	Yes: 25 mg every 2 weeks in the absence of other medications that significantly increase or decrease lamotrigine metabolism (eg, valproic acid, carbamazepine, phenytoin)	Precautions: hypersensitivity (eg, rash, angioedema, acute urticaria, extensive pruritus, mucosal ulceration) Side effects: blood dyscrasias, delayed hypersensitivity effects including Stevens-Johnson syndrome, hemophagocytic lymphohistiocytosis, aseptic meningitis

CONTINUED ON PAGE 1415

Medication	Starting dose	Dose range	Titration/ tapering required	Precautions, side effects, and notes
Gabapentin	300 mg to 600 mg divided 3 times a day; extended-release formulation available	Increase gradually by 300 mg/day as tolerated; usual maintenance dose: 1800 mg/day to 2700 mg/day divided 3 times a day; maximum dose: 3600 mg/day	Yes	Side effects: dizziness, fatigue, confusion, ataxia, increased risk of infection, gastrointestinal symptoms, weight gain, pedal edema Avoid concurrent use with opioids due to risk for respiratory depression, monitor for increased risk of suicidality
Pregabalin	50 mg to 150 mg divided 3 times a day; extended-release formulation available	Increase gradually by 50 mg/day as tolerated; usual maintenance dose: 300 mg to 450 mg divided 3 times a day; maximum dose: 600 mg/day	Yes	Side effects: dizziness, confusion, ataxia, increased risk of infection, gastrointestinal symptoms, weight gain, pedal edema Avoid concurrent use with opioids due to risk for respiratory depression, monitor for increased risk of suicidality
Baclofen	10 mg/day once a day or divided 2 times a day	Increase gradually by 5 mg/day to 10 mg /day; usual maintenance dose: 20 mg to 30 mg divided 2 to 3 times a day; maximum dose: 60 mg/day	Yes	Side effects: confusion, dizziness, drowsiness, gastrointestinal symptoms, euphoria, hallucinations

^a Modified with permission from Bendtsen L, et al, Eur J Neurol.⁸⁰ © 2019 European Journal of Neurology.

^b Lab testing required: EKG, complete blood count, comprehensive metabolic panel prior to start, and complete blood count and comprehensive metabolic panel at 1 month and annually; HLA-B*1502 testing recommended in patients of Asian descent (increased risk of Stevens-Johnson syndrome).

decrease the chances of symptom recurrence and potentially minimize the possibility of future pain, but it also introduces a greater possibility of glossopharyngeal deficits. Dysphagia and cough are more common when performing microvascular decompression and rhizotomy combined. Additionally, due to anatomic proximity, the vagus nerve is sometimes sectioned or irritated in surgery, resulting in hoarseness.⁹⁵

Nervus intermedius neuralgia is also known as geniculate neuralgia. The nervus intermedius travels alongside the motor fibers of the facial nerve, carrying the sensory and parasympathetic components of the nerve. It is considered part of the facial nerve. The most proximal segment of the nerve adheres to the vestibulocochlear nerve at the nerve root, and this area is thought

to be the most vulnerable to compression.⁹⁶ Nervus intermedius neuralgia is characterized by unilateral, brief paroxysms of pain felt deeply in the auditory canal, sometimes radiating to the parietooccipital region.⁹⁶ The symptoms may also be accompanied by disorders of lacrimation, salivation, or taste. Nervus intermedius neuralgia is also suspected to be due to neurovascular compression, yet to date, only a handful of microvascular decompression treatments for nervus intermedius neuralgia have been reported in the literature.^{97–99}

Sphenopalatine neuralgia (also known as Sluder neuralgia) comes from a disruption of the sphenopalatine ganglion, which is also known as Meckel's ganglion, the pterygopalatine ganglion, or nasal ganglion. It is a parasympathetic ganglion that sits below the maxillary branch of V2 in the pterygopalatine fossa. Sensory fibers from the maxillary nerve travel through the sphenopalatine ganglion and provide sensation to the nasal cavity, sphenoid sinus, palate, and some of the nasopharynx and oropharynx.¹⁰⁰ Sphenopalatine neuralgia has historically been very poorly defined and has no definite diagnostic criteria.

TABLE 5-5**Diagnosis of Sphenopalatine Neuralgia^a****Pain description**

- ◆ Moderately severe or severe, boring, burning, or nagging

Pain location

- ◆ Unilateral but possibly bilateral, located periorbital or intraorbital or at the root or lateral side of the nose, radiating to at least one of the following
 - ◇ Maxillary region or cheek and associated teeth
 - ◇ Mastoidal or occipital area
 - ◇ Neck, shoulder, or arm

Duration

- ◆ Either

- ◇ Episodic with attacks lasting hours to days, or
- ◇ Continuous for several weeks with or without exacerbations

Signs and symptoms

- ◆ At least one of the following

- ◇ Ipsilateral lacrimation or conjunctival injection
- ◇ Ipsilateral nasal congestion or rhinorrhea
- ◇ Hypoesthesia or hyperesthesia in maxillary distribution of trigeminal nerve
- ◇ Ipsilateral sore throat
- ◇ Ipsilateral delayed taste perception or parageusia
- ◇ Ipsilateral elevated palatine arch or contralaterally deflected uvula

Treatment

- ◆ Pain can be blocked by cocainization or infiltration anesthesia of the sphenopalatine ganglion

^a Data from the International Classification of Orofacial Pain, Cephalalgia.¹

TABLE 5-5 shares the most current diagnostic criteria as agreed upon by the ICOP.¹

The characteristics of sphenopalatine pain bear a resemblance to trigeminal autonomic cephalgias, resulting in increased interest in this ganglion for the management of these types of headaches. The 2013 development of a sphenopalatine ganglion implantable stimulator for the treatment of cluster headache has led to an exploration of procedures targeting this ganglion for other primary headache disorders as well.^{100,101} The mechanism of action lies in the trigeminal-autonomic reflex, where afferent fibers of the trigeminal nerve synapse on the superior salivatory nucleus and activate the sphenopalatine ganglion, resulting in parasympathetic activation of the nasal and pharyngeal mucosa, lacrimal glands, and meningeal vessels. This activation can in turn release peptides associated with neurogenic inflammation, leading to perpetuation of the pain. The most direct procedure for targeting the sphenopalatine ganglion is a direct infrayzygomatic block or radiofrequency ablation where it lies in the pterygopalatine fossa. Intraoral injections pass the local anesthetic up the greater palatine canal. A less direct but less invasive procedure is the intranasal deposition of local anesthetic, placed through intranasal catheters or soaked swabs at the back of the ethmoid sinus, in hopes that the medication will pass through the sphenopalatine foramen to reach the pterygopalatine fossa. Implantable stimulators are placed by approaching the sphenopalatine ganglion through the buccal mucosa.¹⁰²

CRANIAL NEUROPATHIES

Neuropathy of any of the aforementioned nerves is defined as pain in the distribution of one or more branches of the nerve caused by another disorder and indicative of neural damage. Unlike neuralgias, this pain is usually continuous and described as burning, squeezing, or “pins and needles.” While there may be paroxysms of pain, they are not as prominent as in neuralgias. In patients with trigeminal neuropathy, nerve conduction testing suggests sensory deficits within the trigeminal distribution, and mechanical allodynia and cold hyperalgesia are common. The known causes of trigeminal neuropathies include posttraumatic trigeminal neuropathy, acute herpes zoster or postherpetic neuralgia, MS, Sjögren syndrome, and space-occupying lesions. There is also a category for idiopathic painful trigeminal neuropathy.² The treatment approach for this type of pain should be specific to the condition, treating the underlying cause first and using neuropathic pain medications to help manage the pain. When painful anesthesia or dysesthesia is preceded by trauma to any of the branches of the trigeminal nerve (eg, dental surgery) or follows ablation procedures for trigeminal neuralgia, it is diagnosed as posttraumatic trigeminal neuropathy or painful posttraumatic trigeminal neuropathy.¹⁷ This pain is associated with somatosensory symptoms and can be persistent or recurring, follows a neuroanatomical pattern within the trigeminal distribution, and has an onset within 6 months after the injury event.¹ Treatment algorithms for posttraumatic trigeminal neuropathy and painful posttraumatic trigeminal neuropathy suggest the use of medications, namely tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), and gabapentinoids, as recommended by consensus studies for neuropathic pain,¹⁰³ and psychological support and education regarding coping strategies and cognitive behavioral therapy. Additionally, there may be a role for surgery, which seems to be more

KEY POINTS

- Secondary glossopharyngeal neuralgia may be caused by Eagle syndrome, multiple sclerosis, tumors, trauma, and Chiari malformations.
- Treatment for classic glossopharyngeal neuralgia is similar to that for classic trigeminal neuralgia, with medication management being the first-line treatment and consideration of microvascular decompression after that.
- Nervus intermedius neuralgia is felt deep in the auditory canal and may also be due to vascular compression.
- The sphenopalatine ganglion is a parasympathetic ganglion contributing to sensation to the nasal cavity, sphenoid sinus, palate, and some of the nasopharynx and oropharynx.
- Interventional procedures, including implantable neuromodulation, to the sphenopalatine ganglion have been examined to treat cluster headache and other primary headache syndromes.
- Neuropathic pain is the pain state represented by damage to the nerve. While it can be idiopathic, it can be caused by herpes zoster or postherpetic neuralgia, multiple sclerosis, or mass lesions.
- Burning mouth syndrome is most commonly seen in women 3 to 12 years postmenopause.

successful in injuries of the inferior alveolar nerve rather than the lingual nerve, injuries without neuromas, and earlier rather than later repair.¹⁰⁴

IDIOPATHIC OROFACIAL PAIN

Idiopathic orofacial pains are a group of disorders with a yet unidentified etiology and their diagnosis is made by exclusion of other diagnoses. The ICHD-3 categorizes these pains as idiopathic trigeminal neuralgia, idiopathic painful trigeminal neuropathy, persistent idiopathic facial pain, and burning mouth syndrome. ICOP notes the additional pain termed *persistent idiopathic dentoalveolar pain*. These disorders may present with or without neuropathic characteristics and their etiologies are still poorly understood.

Burning mouth syndrome is a rare, potentially disabling disease that is 7 times more common in women than in men. It typically affects women 3 to 12 years postmenopause, with a mean age of onset between 59 and 61 years, and rarely occurs before age 30 years.¹⁰⁴ The diagnostic criteria include a pain that is of burning quality, felt superficially in the oral mucosa daily for more than 2 hours a day, for longer than 3 months.² The pain typically presents bilaterally and is felt most commonly on the tongue, followed by the anterior hard palate and the labial mucosa. The pain is often described as scalding, tingling, and numb, and patients can experience a bitter or metallic taste.¹⁰⁵ Common comorbidities seen with burning mouth syndrome include anxiety, depression, and sleep disturbances. Factors that can contribute to burning mouth syndrome include tongue thrust and poorly fitting dentures. These can produce erythema, irritation, and microtrauma that can result in a burning sensation. Candidiasis and lichen

TABLE 5-6

Diagnostic Workup for Burning Mouth Syndrome¹¹²

Labs to consider

- ◆ Hemoglobin A_{1c} and fasting blood glucose
- ◆ Complete blood cell count with differential
- ◆ Thyroid function
- ◆ Serum iron and ferritin
- ◆ Vitamin B₆, vitamin B₁₂, vitamin D, folate, and zinc
- ◆ Serum antinuclear antibodies
- ◆ Anti-Sjögren syndrome-related antigen A and anti-Sjögren syndrome-related antigen B (SSA/Ro and SSB/La)
- ◆ Erythrocyte sedimentation rate

Consultations to consider

- ◆ Ear, nose, and throat: assessment for viral, fungal, bacterial causes
- ◆ Dentistry: assessment for oral candidiasis and other oral mucosal diseases as well as in patients using dentures, for the possibility of problems in fitting and dental and parafunctional contribution to pain
- ◆ Primary care: assessment for gastroesophageal reflux disease, treatment of diabetes, thyroid, anemia, and vitamin deficiencies
- ◆ Rheumatology: diagnosis and treatment recommendations

planus, geographic tongue, and local allergic reactions (possibly due to dental materials, toothpaste, or mouthwashes) can result in a burning sensation. Medications can cause burning in the mouth, including antihistamines, benzodiazepines, antihypertensives, and especially angiotensin-converting enzyme inhibitors and antiarrhythmics. Vitamin and mineral deficiencies, including vitamin B₁₂, vitamin B₆, vitamin D, iron, and zinc, can also cause a burning sensation in the mouth. Other systemic diseases that can cause oral burning include gastroesophageal reflux, diabetes, and hypothyroidism.¹⁰⁶

Therefore, it is important to identify primary (idiopathic) burning mouth syndrome when no secondary local or systemic source has been detected. Burning mouth syndrome is considered secondary when it is caused by oral mucosal lesions, fungal infections such as oral candidiasis (tongue thrust), poorly fitting dentures, allergies, medications, vitamin and mineral deficiencies, and systemic disorders. TABLE 5-6 describes the diagnostic workup for burning mouth syndrome. There are several theories on the pathophysiology of primary burning mouth syndrome. It has been suggested that it could be due to a small fiber neuropathy in the intramucosal epithelium, and a small number of biopsies have demonstrated decreased density of small fibers compared with controls¹⁰⁷ and increased density of TRPV1 receptors, which may heighten pain sensation.¹⁰⁸ It has also been suggested that it is a subclinical trigeminal neuropathy¹⁰⁹ or a dysfunction of dopamine receptors.¹¹⁰

Treatment trials have been limited and a 2018 Cochrane review found that the quality of prior research for burning mouth syndrome is poor, trials are limited, and bias is high, leading them to conclude that there is not enough data to support or refute any intervention for managing burning mouth syndrome.¹¹¹ However, a multidisciplinary approach is very useful in this population. Behavioral strategies include the minimization of alcohol, flavorings, and other common oral irritants. An examination of parafunctional behaviors including clenching, bruxism, and tongue movement habits is warranted. Education regarding self-regulatory behaviors is important, as is attention to psychiatric comorbidities that can compound the pain experience.¹¹² Medications can be divided into topical and systemic medications. Topical medications include sucking on a 1 mg tab of clonazepam for 3 minutes and then spitting, topical antifungals, topical capsaicin (either as 0.025% cream or 0.2% solution), salivary substitutes, or 0.15% benzydamine hydrochloride.^{105,112} Systemic options include clonazepam 0.5 mg daily at bedtime, gabapentinoids (eg, gabapentin, pregabalin), SNRIs, SSRIs, tricyclic antidepressants, α-lipoic acid, or the salivary stimulants pilocarpine and cevimeline.^{105,112} Some studies have examined low-level light therapy for burning mouth syndrome and onabotulinumtoxinA, both with some success.¹¹²

Persistent idiopathic facial pain, previously known as atypical facial pain, is defined by the ICHD-3 as daily recurring pain for more than 2 hours, for more than 3 months, in the absence of any clinical neurologic deficit.² It has also been described as dull, aching, nagging, burning, throbbing, and often stabbing, and is constant rather than episodic. It typically presents in the territory of the trigeminal nerve but does not follow any particular dermatomal pattern, can be unilateral, and can often spread to other regions. Forty percent of patients have bilateral pain, and there are no accompanying autonomic symptoms.^{2,113} Persistent idiopathic facial pain presents without abnormalities in qualitative or quantitative somatosensory testing, and it is more often associated with minor surgical or other invasive dental or otolaryngologic procedures than other facial

KEY POINTS

- Burning mouth syndrome is considered secondary when it is caused by tongue thrust, poorly fitting dentures, fungal infections, allergies, medications, vitamin and mineral deficiencies, gastroesophageal reflux disease, diabetes, and hypothyroidism.

- Burning mouth syndrome is primary (idiopathic) when no secondary local or systemic source has been detected.

- Persistent idiopathic facial pain and persistent idiopathic dentoalveolar pain are challenging medical conditions for which neuromodulating medications are at present the best form of treatment.

- Primary headache syndromes can present in the face alone.

pain disorders. In a longitudinal prospective study, 83.0% (78/94) of patients with persistent idiopathic facial pain, 54.8% (34/62) of patients with trigeminal neuralgia, and 44.2% (19/43) of patients with neuropathic pain underwent dental procedures on healthy teeth to reduce the pain, suggesting that this diagnosis is harder to make and leads to unnecessary interventions.¹¹⁴ If the pain is localized intraorally and circumscribed in a dentoalveolar site, the diagnosis becomes persistent idiopathic dentoalveolar pain, previously known as phantom tooth pain, atypical odontalgia, and primary dentoalveolar pain disorder. The diagnosis is made when no dental pathology is detected and in the absence of a history of a precipitating dental procedure or surgery.^{2,115} The mean age of onset is 43 to 44 years and there is a female predominance of 75%.¹¹⁴ Coexisting headache syndromes and remission periods also occur¹¹⁴ and treatment can be quite challenging. Guidelines suggest anticonvulsants, antidepressants, or a combination of both, but this was shown to be helpful in only 5.3% to 14.9% of patients.¹¹⁴ Thus, developing new treatments for this type of pain is necessary. Treatment considerations should focus on medications, namely, tricyclic antidepressants and SNRIs. Procedural considerations include low-level laser therapy and high-frequency repetitive transcranial magnetic stimulation targeting the right secondary somatosensory cortex. Psychological strategies should also be considered, including cognitive behavioral therapy and virtual reality-based therapies.¹¹³

PRIMARY HEADACHE SYNDROMES PRESENTING WITH OROFACIAL PAIN

It is important to mention that the ICOP differs from the ICHD-3 in acknowledging the presence of primary headache syndromes presenting as

TABLE 5-7

Orofacial Pain Resembling Presentations of Primary Headache Disorders^a

Pain type	Description
Episodic orofacial migraine	Recurrent orofacial pain attacks, without head pain, lasting 4 to 72 hours; typical characteristics of the pain are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with any combination of nausea, photophobia, or phonophobia
Chronic orofacial migraine	Facial pain, oral pain, or both occurring on 15 or more days per month for more than 3 months, which has the features of migraine on at least 8 days per month
Tension-type orofacial pain	Episodic or chronic pain exclusively in the orofacial region, without head pain, with the characteristics and associated features described under 2. <i>Tension-type headache</i> in the International Classification of Headache Disorders, Third Edition (ICHD-3)
Trigeminal-autonomic orofacial pain	Attacks of pain, exclusively in the orofacial region, without head pain, with the characteristics and associated features of a disorder described under 3. <i>Trigeminal autonomic cephalgias</i> in ICHD-3
Neurovascular orofacial pain	Attacks of variable duration of moderate or severe intraoral pain, without head pain, often accompanied by toothachelike symptoms, with mild autonomic symptoms, migrainous symptoms, or both; two subforms are represented by patients with relatively short attacks (1 to 4 hours) and those with longer attacks (>4 hours)

^a Data from the International Classification of Orofacial Pain, Cephalgia.¹

orofacial pain. The ICHD-3 alludes to this type of pain, noting that “[a] subset of otherwise typical patients have facial location of pain, which is called ‘facial migraine’ in the literature; there is no evidence that these patients form a separate subgroup of migraine patients.”² However, it has been shown that stimulation of the dura mater can induce pain in any of the three divisions of the trigeminal nerve. In addition, this orofacial presentation can be further supported as a result of the convergence of inputs of the trigeminal divisions, the upper cervical region, and the trigeminal-autonomic reflex into the trigeminocervical complex and their interactions with higher centers.^{116,117} The ICOP has responded to a growing awareness of primary headache syndromes presenting in primarily a V₂ and V₃ distribution,¹¹⁸ and has gone more in depth, dividing the patient presentation into three types:

- ◆ Type 1: Headache patients reporting headache plus additional ipsilateral facial pain during attacks
- ◆ Type 2: Headache patients reporting replacement of headache attacks with facial pain attacks of similar quality, length, and intensity and associated symptoms of headache attack
- ◆ Type 3: De novo facial pain attacks resembling a primary headache type in pain character, duration, and intensity, with or without the associated symptoms in a headache-naïve patient¹

A study looking at 2912 patients with primary headache disorders found that 10% reported a facial presentation. The prevalence of facial pain presentations differs among various primary headache diagnoses; for example, facial involvement was found in 2.3% of patients with migraine and 14.8% of patients with cluster headache or other trigeminal autonomic cephalgias.¹¹⁹ A 2022 review noted that orofacial presentation accounts for 6% to 10% of patients with primary headache disorders.¹²⁰ TABLE 5-7 lists the terminology for primary headache disorders presenting as facial pain.¹ Once the diagnosis is made, treatment should follow the standard recommendation for the primary headache syndrome.

The ICOP has an additional entry known as *neurovascular orofacial pain*. Coined by Benoliel and colleagues,¹¹⁸ neurovascular orofacial pain refers to a facial pain that is mostly unilateral and presents intraorally in the teeth and alveolar processes, with some referral to the perioral structures. This presentation may mimic dental pain since it can be described as a toothache and can be of throbbing quality; these characteristics stress the importance of ruling out the possibility of dentoalveolar pains. In addition, the clinician needs to be aware that these toothachelike symptoms are accompanied by some migraine and autonomic features that are not present with odontogenic pain; this awareness can help the patient avoid unnecessary dental procedures.

CONCLUSION

Neurologists need to be familiar with the presentation of pain throughout the mouth, face, and head and use this knowledge in diagnosis and treatment, and to develop an awareness of when it is necessary to screen for potential odontogenic pains, red flags, and potential sources of secondary headache disorders⁹ or other sources of pain that may resemble pain in the craniofacial region. Orofacial pain disorders span the realms of neurology and dentistry and greatly affect quality of

life. Increased awareness of these disorders and a multidisciplinary dialogue are needed for optimal diagnosis and care in this patient population.

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Chronic Widespread Pain

REVIEW ARTICLE

By Narayan R. Kissoon, MD



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ABSTRACT

OBJECTIVE: This article reviews the potential etiologies of chronic widespread pain syndromes and outlines a practical approach to the management of patients with these disorders.

LATEST DEVELOPMENTS: Recent updates to diagnostic criteria for primary chronic widespread pain syndromes have allowed for more effective diagnosis. Fibromyalgia is the most common presentation of chronic widespread pain, and the concept of nociceptive pain has been used to describe pain that is related to altered processing of pain sensory pathways. Research studies have provided a better understanding of the pathophysiology of the central augmentation that occurs in patients with nociceptive pain and fibromyalgia.

ESSENTIAL POINTS: Primary chronic widespread pain and fibromyalgia have established diagnostic criteria in which chronic pain involves multiple defined regions and occurs for longer than 3 months. Evaluation of chronic widespread pain should be directed by the clinical presentation. Neurologic disease can present with chronic widespread pain but is accompanied by associated signs and symptoms. Patients with chronic widespread pain benefit from effective communication that validates concerns, provides an understandable explanation of the presenting symptoms, and sets realistic expectations in outcomes using a comprehensive multimodal care plan.

INTRODUCTION

Pain is one of the most common chief concerns when people seek medical care, and the incidence of chronic pain is high compared with other conditions such as diabetes, depression, and hypertension.^{1,2} In patients with chronic pain, there is greater health care utilization, especially in the management of chronic widespread pain, and this is in part related to multisystem symptom presentations and a lack of diagnostic biomarkers.^{3,4} Neurologists are often involved in evaluating these patients; a large proportion of second opinions for tertiary neurologic care involve pain-related disorders (eg, musculoskeletal disorders, peripheral neuropathies, headache, radicular syndromes).⁵ Although most chronic widespread pain is related to nociceptive pain (eg, fibromyalgia), the neurologist is often called upon to ensure that the pain cannot be attributed to a structural neurologic cause because some nociceptive pain syndromes may present with neuropathic features (eg, burning or shooting quality, dysesthesia, allodynia) (**FIGURE 6-1**).⁶⁻⁸ *Nociceptive pain* can be mechanistically defined as “pain arising from the altered

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function of pain-related sensory pathways.”⁶ This differs from *nociceptive pain*, which “results from activity in neural pathways, secondary to actual stimuli or stimuli that might potentially damage tissue,” and *neuropathic pain*, which is defined by the International Association for the Study of Pain (IASP) as “pain caused by damage or disease affecting the somatosensory nervous system.”² With the overlap in presentations of nociceptive and neuropathic pain, the neurologic evaluation is important in identifying potentially modifiable factors in the clinical presentation and may be critical in changing the patient’s clinical course. For more information on the general approach to pain, refer to the article “Principles of Pain Management” by Beth B. Hogans, MS, MD, PhD,⁹ in this issue of *Continuum*.

NOCIPLASTIC CHRONIC WIDESPREAD PAIN AND FIBROMYALGIA

The terminology for nociceptive chronic widespread pain is challenging to navigate and dependent on the criteria used to define the disorder, whether it is considered chronic widespread pain or fibromyalgia. Fibromyalgia, which is the most common presentation of chronic widespread pain, has a prevalence of 2%

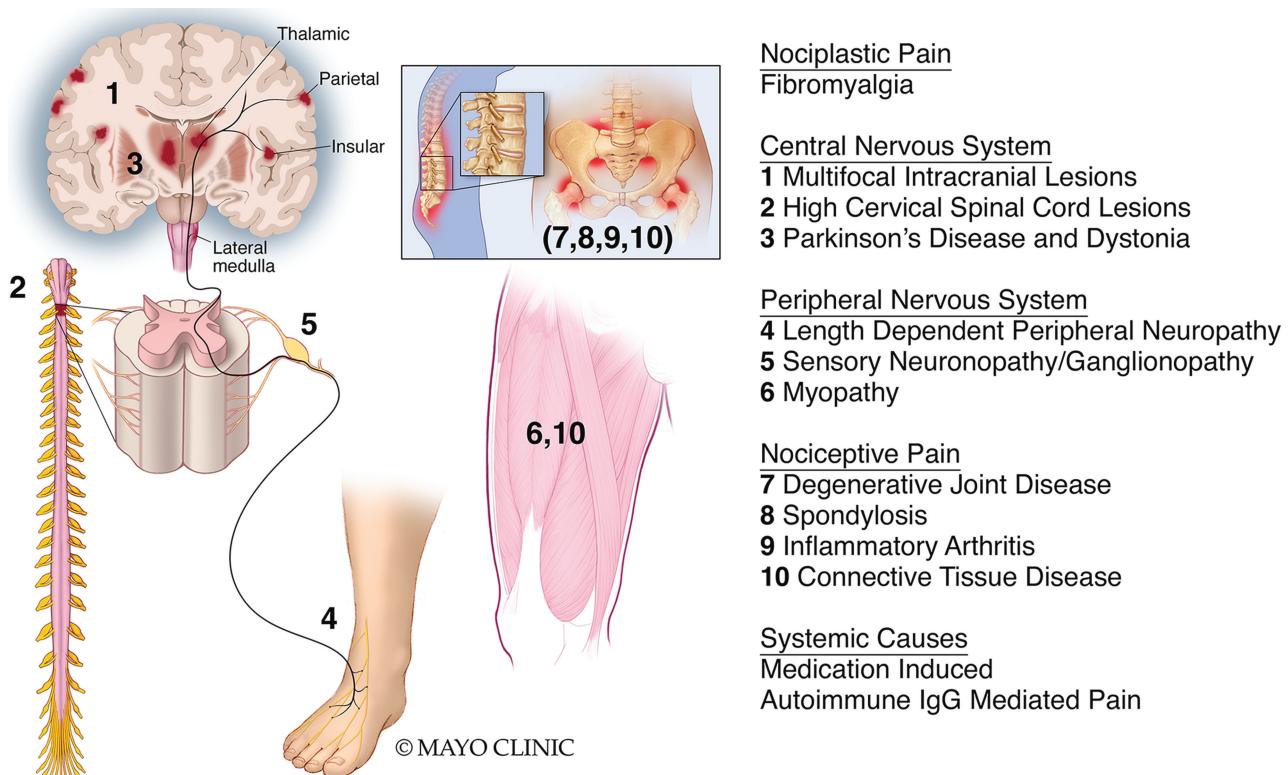


FIGURE 6-1

Localization and causes of chronic widespread pain. The numbers indicate the localization of the respective disorders. Autoimmune immunoglobulin G (IgG)-mediated pain can result from effects at all levels of the neuraxis and is dependent on the target antigens and receptors. In patients with fibromyalgia, augmentation occurs with diffuse physiologic changes involving the central nervous system. Medication effects may involve the brain and spinal cord (eg, opioid-induced hyperalgesia), peripheral nerves (eg, chemotherapy), bone and connective tissue (eg, bisphosphonates, aromatase inhibitors), or muscle (eg, statins, recreational drugs, antivirals, anti-inflammatory agents).

to 4% in the general population.¹⁰ The American College of Rheumatology (ACR) provided a set of research criteria in 1990 to define fibromyalgia that used the distribution of pain and location of tender points as part of the criteria.^{11,12} Over time, the research criteria were found to be impractical for clinical use and did not include associated symptoms, which led to the 2016 revised fibromyalgia diagnostic criteria from the ACR (**TABLE 6-1**).^{11,12} In 2019, the American Pain Society and the US Food and Drug Administration (FDA) created a fibromyalgia working group and proposed the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks—American Pain Society Pain Taxonomy diagnostic criteria for fibromyalgia.¹² At the same time, the IASP collaborated with the World Health Organization (WHO) to create a task force for the classification of chronic pain, which was incorporated into the *International Classification of Diseases, 11th Revision* (ICD-11).^{13,14}

In this IASP-WHO classification schema, chronic primary pain was defined as “chronic pain in one or more anatomical regions that persists or recurs for longer than 3 months and is associated with significant emotional distress and/or significant functional disability,” with chronic widespread pain being a subset of chronic primary pain defined as “diffuse musculoskeletal pain in at least 4 of 5 body regions and in at least 3 or more body quadrants (as defined by upper-lower/left-right side of the body) and axial skeleton (neck, back, chest, and abdomen).”^{13,15} In the IASP-WHO framework, fibromyalgia is considered a form of chronic widespread pain. Some experts have considered fibromyalgia and chronic widespread pain a spectrum disorder with the fibromyalgia denotation for severe presentations, but this relationship needs further validation.³ The ACR’s 2016 revised fibromyalgia diagnostic criteria, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks—American Pain Society Pain Taxonomy fibromyalgia diagnostic criteria, and IASP-WHO classification of chronic widespread pain are presented in **TABLE 6-2**. These diagnostic criteria for fibromyalgia and chronic widespread pain are similar in that the duration of pain is longer than 3 months and involves multisite pain, but they differ in that chronic widespread pain does not require the associated symptoms as part of the diagnostic criteria. The associated symptoms of fibromyalgia include fatigue, sleep disturbance, cognitive disturbance (eg, working memory, attentional control), and hypersensitivity to environmental stimuli (eg, bright lights, loud noises, strong smells, weather).^{6,15,16}

Clinical Features of Fibromyalgia

Aside from the associated symptoms (eg, fatigue, sleep disturbance, cognitive disturbance) that can alert the clinician to a diagnosis of fibromyalgia, the presentation of the pain syndrome can provide insight. In patients with fibromyalgia, the description of pain can vary from descriptors of nociceptive pain such as dull, deep, aching pain to descriptors of neuropathic pain such as burning or shooting in quality that potentially may be accompanied by dysesthesia.⁶ In the absence of overt findings for the cause of neuropathic pain on neurologic examination, patients with fibromyalgia have been shown to score high on the painDETECT questionnaire (a validated scale to identify neuropathic pain), and these findings correlated to the number of tender points and reduced pressure pain tolerances.⁷ However, in contrast with neuropathic pain, the nociceptive pain in fibromyalgia has fluctuations in location and intensity along with worsening by exertion and exposure to environmental stimuli (eg,

KEY POINTS

- Chronic widespread pain and fibromyalgia have established diagnostic criteria in which chronic pain involves multiple defined regions and occurs for longer than 3 months.
- For chronic widespread pain to be diagnosed as fibromyalgia, it must be accompanied by associated symptoms such as fatigue, sleep disorders that may include waking unrefreshed, and cognitive symptoms.

TABLE 6-1**Diagnostic Criteria for Fibromyalgia****ACR 2016 REVISED CRITERIA^{11,a}**

- ◆ Widespread pain index (WPI) ≥ 7 and symptom severity scale (SSS) score ≥ 5 OR WPI of 4-6 and SSS score ≥ 9
- ◆ Generalized pain, defined as pain in at least 4 of 5 regions, must be present; jaw, chest, and abdominal pain are not included in generalized pain definition
- ◆ Symptoms have been generally present for at least 3 months
- ◆ A diagnosis of fibromyalgia is valid irrespective of other diagnoses; a diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses

AAPT DIAGNOSTIC CRITERIA¹²

- ◆ Multisite pain defined as 6 or more pain sites from a total of 9 possible sites (head, left arm, right arm, chest, abdomen, upper back and spine, lower back and spine including buttocks, left leg, right leg)
- ◆ Moderate to severe sleep problems OR fatigue
- ◆ Multisite pain plus fatigue or sleep problems must have been present for at least 3 months

IASP CLASSIFICATION¹³

- ◆ Fibromyalgia syndrome is a form of chronic widespread pain, which is defined as pain in at least 4 of 5 body regions (in at least 3 or 4 body quadrants), and is associated with sleep disorders, cognitive dysfunction, and somatic symptoms
- ◆ The symptoms have been present at a similar level for at least 3 months and are not better accounted for by another diagnosis

ACR = American College of Rheumatology; AAPT = Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks (ACTTION)-American Pain Society (APS) Pain Taxonomy; IASP = International Association for the Study of Pain.

^aAscertainment

(1) **WPI:** note the number of areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19 and 1 point for each affected side in upper and lower regions.

(2) SSS score

Fatigue

Waking unrefreshed

Cognitive symptoms

For each of the 3 symptoms above, indicate the level of severity over the past week using the following scale:

0 = No problem

1 = Slight or mild problems, generally mild or intermittent

2 = Moderate, considerable problems, often present and/or at a moderate level

3 = Severe: pervasive, continuous, life-disturbing problems

The **SSS score** is the sum of the severity scores of the 3 symptoms (fatigue, waking unrefreshed, and cognitive symptoms) (0-9) plus the sum (0-3) of the number of the following symptoms the patient has been bothered by that occurred during the previous 6 months:

(1) Headaches (0-1)

(2) Pain or cramps in lower abdomen (0-1)

(3) And depression (0-1)

The final symptom severity score is between 0 and 12

Regions affected

Axial region: neck, upper back, lower back, chest, abdomen

Upper region: jaw (left or right), shoulder girdle (left or right), upper arm (left or right), Lower arm (left or right)

Lower region: hip (left or right), upper leg (left or right), lower leg (left or right)

photophobia, phonophobia, osmophobia), which may be a comorbid manifestation of or similar to what is observed in migraine.⁹ The diffuse nature of the pain, which by definition includes multiple body segments, is outside a dermatomal, myotomal, or sclerotomal distribution.^{6,10}

Patients with fibromyalgia in isolation have a normal neurologic examination, but some patients may have findings of diffuse allodynia supportive of the diagnosis. Often, patients present with an antecedent childhood or adolescent history of headache (typically migraine), abdominal pain, or low back pain. In addition, there is often a family history of chronic pain and mental health disorders.⁶ Patients with fibromyalgia can present with comorbid postural orthostatic tachycardia syndrome, persistent perceptual postural dizziness, and mood disorders (eg, anxiety, depression).^{10,17-19} Chronic pain can predispose patients to some of these associated hyperadrenergic disorders (eg, postural orthostatic tachycardia syndrome, anxiety).¹⁹ An antecedent history of traumatic life events or posttraumatic stress disorder is common, and anxiety can have an indirect effect on the impact of posttraumatic stress disorder symptoms on daily functioning in fibromyalgia.²⁰ With these complex multisystem symptom presentations, patients with fibromyalgia frequently demonstrate high utilization of health care services, delays in diagnosis, and poor tolerability or responsiveness to conventional medical management.^{6,10} Pain catastrophizing and maladaptive coping strategies can be common in patients with fibromyalgia and are associated with emotional distress and disability²¹; for more information, refer to the article “Chronic Pain Psychology in Neurology Practice” by Mirsad Serdarevic, PhD,²² in this issue of *Continuum*.

Pathophysiology of Fibromyalgia

The understanding of the pathophysiology of fibromyalgia is limited, but evidence suggests that the pain symptoms associated with fibromyalgia are related to the central augmentation of sensory input and disruption of the endogenous inhibition of pain.²³ When a known source of sensory disruption occurs, the term *central sensitization* is used (as observed commonly in neuropathic pain), but when no source is determined, *central augmentation* may be the better term.²³ In fibromyalgia, functional MRI (fMRI) studies have shown changes in the activation of brain regions involved in the processing of pain and other sensory afferents.²⁴ Interestingly, positron emission tomography (PET) scan studies demonstrated evidence of widespread microglial activation in patients with fibromyalgia.²⁵

IASP-WHO Classification for Chronic Widespread Pain^a

TABLE 6-2

- ◆ Chronic widespread pain is diffuse musculoskeletal pain in at least 4 of 5 body regions and in at least 3 or more body quadrants (as defined by upper-lower/left-right side of the body) and axial skeleton (neck, back, chest, and abdomen)
- ◆ Pain persisting for at least 3 months and associated with significant emotional distress, functional disability, or both.

IASP = International Association for the Study of Pain; WHO = World Health Organization.

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On μ -opioid PET imaging in patients with fibromyalgia, decreased μ -opioid receptor binding was observed in the nucleus accumbens, amygdala, and anterior cingulate, which was inversely correlated with affective pain scores.²⁶ In addition, μ -opioid PET binding was associated with pain-evoked neural activity observed on fMRI in the anterior cingulate and dorsolateral prefrontal cortex.²⁷ These findings, in conjunction with elevated CSF levels of endogenous opioids, have led to a hypothesis that high levels of tonic endogenous opioids, result in the downregulation of μ -opioid receptors. This subsequently causes inappropriate inhibition by γ -aminobutyric acid-mediated (GABAergic) interneurons resulting in antinociceptive neurons failing to activate after phasic endogenous opioid release from noxious stimulation.^{27,28} Dysregulation of glutamate and γ -aminobutyric acid (GABA) has been observed throughout the brain in patients with fibromyalgia, and specifically in the insula there is a noted decrease in GABA with increased GABA receptor concentration (likely secondary upregulation of GABA receptors).^{29,30} The elevated GABA receptor concentrations in the insula are associated with higher scores on fibromyalgia impact questionnaires.²⁹

In patients with chronic pain (including fibromyalgia), a meta-analysis showed reductions in gray matter volumes observed throughout the brain, which included the prefrontal cortex, cingulate, and insula. These regions are commonly referred to as the *pain matrix*.^{6,31} Other structures outside the pain matrix were noted to have a gray matter volume decrease of unclear significance, but it could be related to the heterogeneity of the pain disorders included in the meta-analysis and comorbidities.³¹ In the peripheral nervous system, studies have shown decreased intraepidermal nerve fiber density in fibromyalgia when compared with controls, but this finding was accompanied by reduced axonal diameter and Schwann cell abnormalities that are not seen in small fiber neuropathy.³² These changes in the central and peripheral nervous system are thought to be representative of neuroplasticity rather than atrophy or neuropathy, respectively.^{6,32} It is unclear why these changes in neuroplasticity occur, but in up to 30% of patients, a physical or psychological trigger is observed before the onset of fibromyalgia.³³ Whether the inciting incident is known or the pain has an insidious onset, fibromyalgia likely occurs as a result of central augmentation (or central sensitization in cases of a known trigger) resulting in widespread alterations of brain activity that include disruption of the endogenous opioid system and may be in part mediated by microglial activation.

CHRONIC FATIGUE SYNDROME

Although chronic fatigue syndrome does not include pain in clinical presentations or as part of the diagnostic criteria, the disorder is worth discussion because of the high comorbidity with fibromyalgia. More recently, specialties outside of neurology have termed the condition *myalgic encephalomyelitis* despite a lack of specific imaging evidence for encephalitis or myelitis, supportive biomarkers such as elevated cell counts in the CSF, or pathologic tissue findings in the central nervous system.³⁴ In patients with chronic fatigue syndrome, there is considerable overlap in the nonpain symptoms that are typically observed in fibromyalgia. For the diagnosis of chronic fatigue syndrome, the symptoms are required to be associated with a “substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities, that persists for more than 6 months and is accompanied by fatigue.”³⁵ This is accompanied by postexertional malaise, as well as unrefreshing

sleep and either cognitive symptoms or orthostatic intolerance.³⁵ Interestingly, an infectious episode before the onset of symptoms is described by more than 80% of patients diagnosed with chronic fatigue syndrome, similar to new daily persistent headache.³⁵

CONCURRENT NOCIPLASTIC PAIN SYNDROMES

Nociplastic pain can occur segmentally in the absence of chronic widespread pain and has been dichotomized by the IASP into broad categories of primary headache disorders, orofacial pain, chronic visceral pain, and chronic musculoskeletal pain. Patients with primary headache disorders are commonly evaluated by neurologists, and the association of migraine with chronic widespread pain has been the most studied.^{17,36-38} Migraine has been bidirectionally associated with fibromyalgia.³⁸ Patients presenting with chronic migraine and chronic tension-type headache have a higher probability of having comorbid fibromyalgia, and this association was not observed with trigeminal autonomic cephalgias.^{36,37} Predictors for an association of headache with fibromyalgia are higher headache frequency, worse severity, and allodynia.³⁷ The chronification of primary headache disorders is suspected to be related to central sensitization, and so this association with fibromyalgia is not surprising given the shared common underlying pathophysiology (see the Pathophysiology of Fibromyalgia section in this article). Orofacial pain syndromes include persistent idiopathic facial pain, burning mouth syndrome, and temporomandibular joint disorders; for more information, refer to the article “Orofacial Pain” by Meredith Barad, MD, and Marcela Romero-Reyes, DDS, PhD,³⁹ in this issue of *Continuum*.

Chronic primary visceral pain syndromes are categorized into six subcategories by the IASP, which are characterized by the symptoms of the organ system involved: chronic primary chest pain, chronic primary epigastric pain, chronic primary abdominal pain, chronic primary bladder pain, chronic primary pelvic pain, and irritable bowel syndrome.⁶ Irritable bowel syndrome, chronic primary pelvic pain, and chronic primary bladder pain (formerly interstitial cystitis) are the chronic primary visceral pain syndromes most associated with fibromyalgia.⁴⁰ In one study, when chronic visceral pain was treated in the context of superimposed fibromyalgia, the generalized body pain improved at all sites in patients after treatment of the concurrent chronic visceral pain syndrome.⁴¹

Patients may also present with chronic primary musculoskeletal pain with chronic primary low back pain being the most common; for more information, refer to the article “Spine Pain” by Vernon B. Williams, MD, FAAN,⁴² in this issue of *Continuum*. For all the segmental chronic primary pain syndromes mentioned here, the pain typically deviates from referral or dermatomal patterns of the respective organ systems and lacks correlates on imaging or other diagnostic testing.⁶ The nonpain symptoms observed in these segmental pain disorders are often like those observed in fibromyalgia. Some patients present with overlap in the segmental primary pain syndromes and chronic widespread pain. Pain that is confined to a single region typically has a better prognosis than when accompanied by chronic widespread pain.

COMPLEX REGIONAL PAIN SYNDROME

Complex regional pain syndrome (CRPS) has an association with fibromyalgia like the segmental primary pain syndromes mentioned earlier.⁴³ It is worth

KEY POINTS

- Fibromyalgia can present with pain that has neuropathic features and patients may have findings of allodynia on examination, but pain fluctuates and is outside dermatomal, myotomal, or sclerotomal distributions.
- Patients with fibromyalgia commonly present with comorbid disorders such as postural orthostatic tachycardia syndrome, persistent perceptual postural dizziness, mood disorders, migraine, and other chronic primary pain syndromes.
- Changes in gray matter volumes and small fiber intraepidermal nerve fiber density observed in patients with fibromyalgia are suspected to represent neuroplasticity rather than atrophy or neuropathy, respectively.

special mention given that it has both neuropathic and nociceptive features along with defined symptoms and signs. CRPS is characterized by persistent pain that does not follow a dermatome or nerve distribution and appears disproportionate to what is expected from any known trauma or identifiable lesion. The pain has a distal predominance and is accompanied by abnormal sensory, motor, sudomotor, vasomotor, and trophic findings.²⁷ The Budapest Criteria for CRPS have been validated and adopted by the IASP, which provided the recent Valencia adaptation (**TABLE 6-3**).^{44,45} CRPS is classified based on the onset: type 1 occurs in the absence of an identifiable nerve injury, and type 2 occurs after an identifiable nerve injury. Cases of innocuous trauma with no clear nerve injury are classified as type 1.¹³ Patients previously documented as having fully met CRPS criteria but who currently do not display enough CRPS features to fully meet the diagnostic criteria are classified as having CRPS with remission of some features.⁴⁵ Patients are classified as having CRPS-not otherwise specified if they never fulfilled the diagnostic criteria but no other diagnosis can better explain the clinical presentation.⁴⁵ Retrospective studies have shown that CRPS can spread to a contralateral or ipsilateral limb in 20% to 40% of patients with a history of CRPS,⁴⁶⁻⁴⁸ but pain affecting multiple limbs at onset should raise suspicion for an alternative etiology such as erythromelalgia.

The understanding of the pathogenesis of CRPS is limited and felt to be related to a proinflammatory response and impaired neuropeptide (eg, calcitonin gene-related peptide, substance P) signaling, resulting in sympathetic dysregulation along with both central and peripheral sensitization.^{43,49} The proinflammatory response is suspected to be related to the activation of CD4⁺

TABLE 6-3**Clinical Diagnostic Criteria for Complex Regional Pain Syndrome^a**

- ◆ Continuing pain that is disproportionate to any inciting event
- ◆ 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, skin color changes, or skin color asymmetry
 - ◆ Sudomotor/edema: reports of edema, sweating changes, or sweating asymmetry
 - ◆ Motor/trophic: reports of decreased range of motion, motor dysfunction (weakness, tremor, dystonia), or trophic changes (hair, nail, skin)
- ◆ Must display at least one sign at time of evaluation in two or more of the following categories
 - ◆ Sensory: evidence of hyperalgesia (to pinprick), allodynia (to light touch and/or deep somatic pressure and/or joint movement), or both
 - ◆ Vasomotor: evidence of temperature asymmetry, skin color changes, or asymmetry
 - ◆ Sudomotor/edema: reports of edema, sweating changes, or sweating asymmetry
 - ◆ Motor/trophic: evidence of decreased range of motion, motor dysfunction (weakness, tremor, dystonia), or trophic changes (hair, nail, skin)
- ◆ There is no other diagnosis that better explains the signs and symptoms

^a Reprinted with permission from Harden RN, et al, Pain Med.⁴⁴ © 2022 The Authors.

and CD8⁺ lymphocytes, resulting in cytokine release.⁴⁹ IgG antibodies to β₂-adrenergic receptors, muscarinic-2 receptors, or α_{1A} adrenoreceptors have been found in patients with CRPS, which is supportive of an autoimmune component of the pathogenesis of CRPS.⁴⁹

CRPS can present with different phenotypes: “warm CRPS” with a warm, red, dry, and edematous extremity and “cold CRPS” with a cold, blue, sweaty, and less edematous extremity.⁴⁴ The median duration of CRPS is 4.7 months in the warm CRPS phenotype and 20 months in the cold CRPS phenotype.⁴⁴

A patient-centered approach is typically used for the management of CRPS. For patients with an acute and warm CRPS presentation, a short course of oral steroids may be indicated.⁴⁴ Patients presenting acutely and with accompanied cold intolerance benefit most from lumbar sympathetic blocks.⁵⁰ For patients with CRPS that is accompanied by osteopenia, immobility, and trophic changes, calcitonin and bisphosphonate therapy may be indicated.⁴⁴ As with other nociceptive pain disorders, all patients with CRPS benefit from multidisciplinary care (see the Treatment in Widespread Pain Syndromes section in this article). Specifically, patients with CRPS benefit from comprehensive rehabilitation that includes mirror visual feedback, graded motor imagery, and exposure therapy along with management of clinical signs (eg, edema control, strengthening, range of movement). When a patient is unable to participate in or has a failure to progress with rehabilitation, sympathetic blocks, spinal cord stimulation, or dorsal root ganglion stimulation may be of benefit.⁴⁴

NEUROPATHIC WIDESPREAD PAIN SYNDROMES

Rarely, widespread pain can be neuropathic and related to lesions of the central or peripheral nervous system. Only a few central nervous system lesions (eg, upper cervical spinal cord lesions, brainstem lesions, bilateral thalamic lesions, multifocal bilateral cortical lesions) can potentially cause widespread pain, and these would be accompanied by other neurologic signs and symptoms that could guide localization; for more information, refer to the article “Central Neuropathic Pain” by Charles E. Argoff, MD,⁵¹ in this issue of *Continuum*. Cervical spondylopathy can present with vague and not well-defined pain and should be considered a potential etiology if other symptoms and examination findings are supportive, such as prominent neck pain, reflex changes, and gait impairment.⁵²

Aside from lesional central nervous system neurologic disease, movement disorders (specifically Parkinson disease) may present with widespread pain that is independent of musculoskeletal disease or dystonia and can have neuropathic features.^{52,53} It has been observed that improvements in symptomatic treatment of motor manifestations have resulted in improvements in pain outcomes in patients with Parkinson disease.⁵⁴ Pain is common in the setting of dystonia and reported in up to 80% of patients with variable responses to dystonia treatment (eg, onabotulinumtoxinA, deep brain stimulation).⁵⁵

Rarely, pain can be a presentation of processes affecting the nervous system diffusely through IgG-mediated autoimmune pain.^{49,52} A subacute temporal onset of multifocal neurologic signs and symptoms involving both the central and peripheral nervous system is a clinical presentation suggestive of autoimmune-mediated pain.⁴⁹ Specific neurologic manifestations include small fiber sensory loss or allodynia, neurogenic orthostatic hypotension, gastrointestinal dysmotility, sudomotor sweat impairment or paroxysms of

KEY POINTS

- Complex regional pain syndrome has validated diagnostic criteria that are useful in the diagnosis and include the presence of both symptoms and signs on examination.
- A patient-centered approach is used in the management of complex regional pain syndrome. When a patient is unable to participate in or has a failure to progress with rehabilitation, sympathetic blocks, spinal cord stimulation, or dorsal root ganglion stimulation may be of benefit.

hyperhidrosis, and encephalopathy with or without seizures or stereotyped spells.⁴⁹ **CASE 6-1** depicts a typical presentation of contactin-associated proteinlike 2 (CASPR2) IgG-mediated autoimmune pain. Other antibodies that have strong evidence for pain causality include leucine-rich glioma inactivated 1 (LGI-1) IgG, glutamic acid decarboxylase 65 (GAD65) IgG, amphiphysin IgG, glycine receptor IgG, and neuromyelitis optica (NMO) IgG; for further details on these clinical presentations, refer to the article “Autoimmune Neuromuscular Disorders Associated With Neural Antibodies” by Divyanshu Dubey, MD, FAAN,⁵⁶ in the August 2024 *Continuum* issue on Autoimmune Neurology. Pain

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CASE 6-1

A 65-year-old man with a medical history of melanoma presented with a 6-month history of burning and stinging pain that started in his extremities and progressed to his trunk and face. He noted painful muscle cramps, mood lability, and insomnia. The pain was intractable to medical management despite therapeutic doses of gabapentin and duloxetine and eventually required the use of opioid therapy with hydromorphone as needed for breakthrough pain. The patient was hospitalized after he developed focal seizures with secondary generalization. During hospital admission, he had persistent amnesia and confusion even after controlling his seizures with antiseizure medications. Interictal EEG showed bitemporal epileptiform discharges with diffuse slowing. MRI of his head showed bilateral mesial temporal lobe T2 hyperintensities. EMG showed evidence of peripheral nerve hyperexcitability with myokymic discharges, and a length-dependent sensorimotor peripheral neuropathy was identified by low amplitude compound muscle action potentials (CMAPs) and sensory nerve action potentials. Thermoregulatory sweat testing showed reduced sweat function in the distribution of neuropathic pain (FIGURE 6-2**⁵⁸). Serum contactin-associated proteinlike 2 (CASPR2) IgG was 0.1 nmol/L. The patient was treated initially with a 5-day course of IV immunoglobulin (IVIg) 0.4 gm/kg followed by weekly infusions. Following treatment with IVIg, his pain was substantially improved and accompanied by improved sweat function. He was tapered off the hydromorphone, and persistent pain was managed with duloxetine.**

COMMENT

This case illustrates an example of a patient presenting with characteristic features of Morvan syndrome (eg, neuromyotonia, confusion, insomnia, autonomic instability), which is associated with CASPR2 IgG positivity. Patients with CASPR2 IgG-associated autoimmune neurologic disease can have pain as the initial presenting symptom that may occur at first in isolation but typically manifests or progresses to include the other commonly associated signs and symptoms. The most common cancer association is with thymoma, but it has also been associated with melanoma. Pain dramatically improves with immunotherapy treatment, and early recognition can improve clinical outcomes.

can be the first symptom in more than 40% of patients with autoimmune peripheral neuropathy, and in 13% of these patients, pain was the sole first manifestation.⁵⁷

Widespread pain can be related to peripheral nervous system and muscle disease; for more information, refer to the article “Peripheral Neuropathic Pain” by Victor Wang, MD, PhD, and Miroslav Baćkonja, MD,⁵⁹ in this issue of *Continuum*. Large and small fiber peripheral neuropathies often present with neuropathic pain, typically in a length-dependent manner, so it is generally outside the scope of the discussion regarding widespread pain except when pain

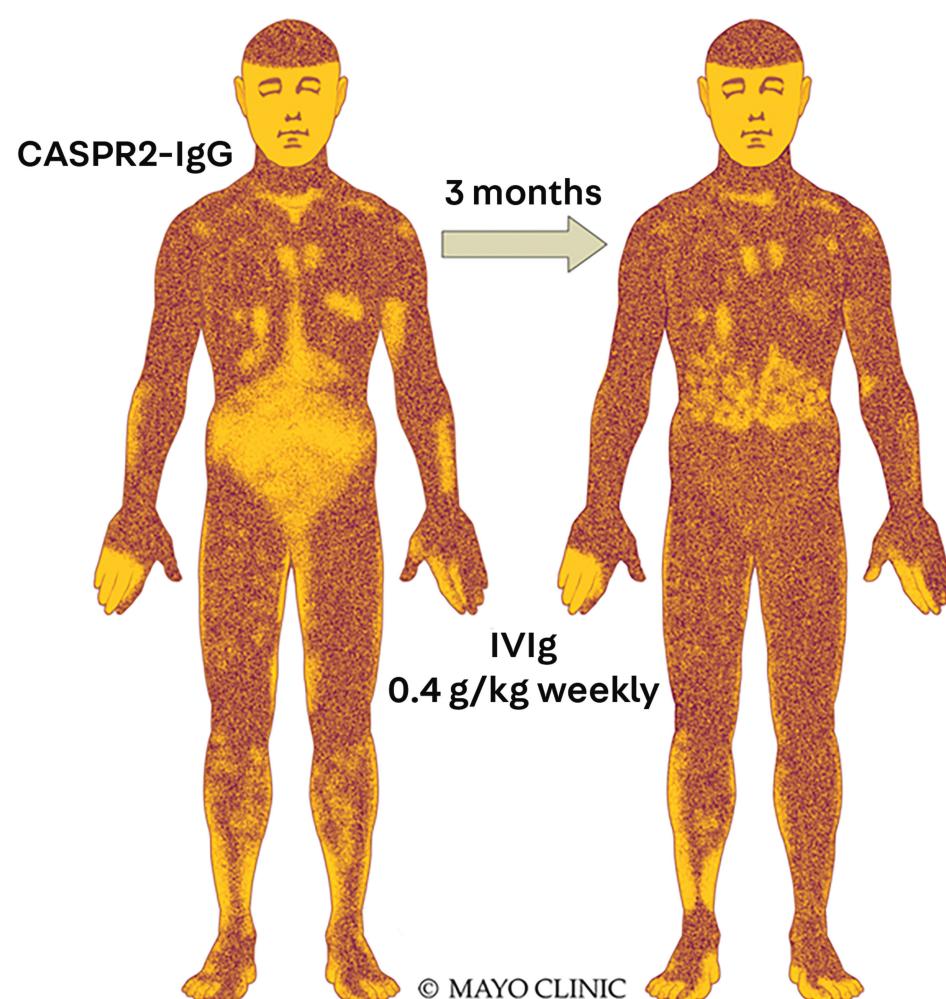


FIGURE 6-2

Example of findings on thermoregulatory sweat testing in a patient with contactin-associated proteinlike 2 (CASPR2)-immunoglobulin G (IgG)-mediated autoimmune pain. Yellow areas indicate locations of sweat loss after heat stimuli (the face is not typically tested). The distribution of pain is concordant with regions of decreased or absent sweat output. Following weekly treatment with IV immunoglobulin (IVIg), significant improvement was observed in pain that was accompanied by improved sweat function.

Data from Gadoth A, et al, Ann Neurol.⁵⁸

becomes more diffuse in severe presentations of peripheral neuropathy. In addition, a sensory ganglionopathy is typically painless, as are most large fiber ganglionopathies, but can present with diffuse neuropathic pain when there is small fiber involvement.⁶⁰

Myopathies can present with widespread pain; for more information on different presentations of myopathies, refer to the December 2022 *Continuum* issue on Muscle and Neuromuscular Junction Disorders.⁶¹ The presence of elevations in creatine kinase and proximal weakness should clue the clinician to a myopathy as a cause of the chronic widespread pain syndrome.^{52,62} In particular, inherited myopathies such as Pompe disease, mitochondrial myopathy, and myotonic dystrophy type 2 have been reported to masquerade as fibromyalgia.^{52,62,63} In patients with myotonic dystrophy type 2, pain can be the sole manifestation for years.⁶⁴ Inflammatory myopathies including polymyositis, dermatomyositis, and immune-mediated necrotizing myopathies can commonly present with diffuse myalgias.⁵² The presence of cutaneous manifestations in these patients (eg, heliotrope rash, Gottron sign, nail fold changes) suggests a diagnosis of dermatomyositis.⁵² Immune-mediated necrotizing myopathies often present with statin exposure, markedly elevated creatine kinase level (greater than 1000 U/L), characteristic distribution of weakness (proximal weakness with oropharyngeal and facial muscle involvement), and myotonic discharges and usually require the use of immunosuppressive medications.⁶⁵ Statins can also cause a toxic myopathy that occurs early in the treatment phase and usually resolves within 2 months of cessation of the offending medication.⁶⁶

NOCICEPTIVE WIDESPREAD PAIN SYNDROMES

Although a patient is typically referred to a neurologist for consideration of neuropathic pain or pain-related neurologic conditions, a nociceptive cause of the widespread pain syndrome should not be overlooked. When a questionnaire using modified 2010 ACR criteria for fibromyalgia was administered to 729 patients previously diagnosed with osteoarthritis, systemic lupus erythematosus (SLE), and rheumatoid arthritis, 16.8% of patients with osteoarthritis, 36.7% of patients with SLE, and 21.1% with rheumatoid arthritis fulfilled the criteria.⁶⁷ Chronic pain is becoming more prevalent in an aging population, and the progression of degenerative joint disease and spondylotic disease can be a presentation of chronic widespread pain, especially in older adults.⁶⁸

Diffuse idiopathic skeletal hyperostosis often coexists with osteoarthritis and in the past generally has been considered a nonpainful condition. However, patients diagnosed with diffuse idiopathic skeletal hyperostosis can present with nonarticular tenderness.⁶⁹ Systemic inflammatory rheumatologic disease can present with diffuse pain involving the joints and sites of enthesis (attachment sites of ligaments, tendons, fascia, and capsules to bone). Early in the course of the disease, diffuse pain can be present without clear findings of joint synovitis. Patients with inflammatory polyarthritis and spondyloarthritis may present with morning stiffness and pain for longer than an hour, and the pain improves with activity.⁵² The presence of a rash and constitutional symptoms such as fever and weight loss may be supportive. The age of onset and distribution of joint involvement helps differentiate between polyarthritis and spondyloarthritis.

In patients with inflammatory spondyloarthritis, the age of onset is typically younger than 45 years; axial pain and joint involvement are more common.⁵²

Inflammatory polyarthritis (most commonly rheumatoid arthritis) occurs in middle-aged and older adults (65 to 80 years) and has a predilection for peripheral joints but can also involve the axial spine (often the atlantoaxial joint). In adults older than 50 years with prominent shoulder and hip involvement, polymyalgia rheumatica is a consideration and can occur with temporal arteritis (headache, jaw claudication, visual disturbance) in up to 10% of patients.⁵² Infectious diseases such as hepatitis B, hepatitis C, human immunodeficiency virus (HIV), and Lyme disease can present with inflammatory arthritis and are considered in patients with risk factors or exposures. Of note, a post-Lyme disease syndrome can present with a combination of chronic fatigue, musculoskeletal pain, and cognitive symptoms despite appropriate antibiotic treatment and no evidence of persistent infection with *Borrelia burgdorferi*, which would best be described as a secondary fibromyalgia.⁵²

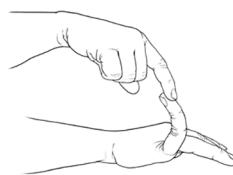
Systemic autoimmune rheumatologic diseases such as SLE or Sjögren disease can present with chronic widespread pain. SLE should be suspected in patients presenting with photosensitive skin lesions such as malar rash, and in the United States it is more common in people of African, Hispanic, or Asian ancestry.⁷⁰ Sjögren disease presents with sicca symptoms (eg, dry mouth, dry eyes) and has a female preponderance with an age of onset generally in the twenties or thirties or after menopause in the mid-fifties.⁷¹ Similarly, celiac disease is an autoimmune-mediated inflammatory enteropathy that can present with myalgias and fatigue that classically presents with diarrhea and signs of malabsorption accompanied by histologic findings on small bowel biopsy with or without serum IgA transglutaminase antibodies. This differs from nonceliac gluten sensitivity in which there is a high prevalence of joint and muscle pain resembling fibromyalgia.⁵²

Several disorders or traits are associated with chronic widespread pain, and it can be difficult to differentiate between the conditions being risk factors for the development of fibromyalgia or pain as a manifestation related to the underlying pathophysiology of the disorder. An example is the case of joint hypermobility, which can be commonly associated with pain. Clinically, joint hypermobility is determined by the Beighton criteria, which assesses joint hypermobility in the hands, elbows, lumbar spine, and knees (**FIGURE 6-3**).⁷² Joint hypermobility occurs in about 20% of the population but is more common in females, and the prevalence decreases with age.⁷³ The prevalence of pain in patients with joint hypermobility varies greatly; reports range from 2% to more than 80% of patients with joint hypermobility. Joint hypermobility is only one subset of the diagnostic criteria for Ehlers-Danlos syndrome, and a clear distinction is made between joint hypermobility syndrome and Ehlers-Danlos syndrome.⁷² Ehlers-Danlos syndrome is a broad spectrum of hereditary connective tissue diseases (eg, classical Ehlers-Danlos syndrome, vascular Ehlers-Danlos syndrome, myopathic Ehlers-Danlos syndrome) with distinct clinical features for each subtype and the genetic and molecular basis identified for all except for hypermobile Ehlers-Danlos syndrome. Although the genetic and molecular basis for hypermobile Ehlers-Danlos syndrome has not been identified, hypermobile Ehlers-Danlos syndrome has distinct clinical features such as skin fragility (eg, unusually soft or velvety skin, skin hyperextensibility, unexplained striae, recurrent or multiple abdominal hernias, atrophic scarring, pelvic floor dysfunction with or without rectal prolapse) and marfanoid features (eg, dental crowding and high arched or narrow palate, mitral valve prolapse, arachnodactyly, aortic root dilation).⁷² Joint hypermobility syndrome is defined

KEY POINTS

- Parkinson disease can present with chronic widespread pain that is independent of musculoskeletal disease or dystonia and can have neuropathic features.
- Autoimmune IgG-mediated pain should be considered in patients presenting with a subacute onset (weeks to months) of multifocal neurologic signs and symptoms involving both the central and peripheral nervous systems.

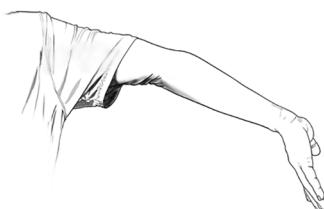
A Passive dorsiflexion of the little fingers beyond 90°; one point for each hand



B Passive apposition of the thumbs to the flexor aspect of the forearms; one point for each hand



C Hyperextension of the elbows beyond 10°; one point for each elbow



D Hyperextension of the knees beyond 10°; one point for each knee



E Forward flexion of the trunk with knees fully extended so that the palms of the hands rest flat on the floor; one point



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FIGURE 6-3

Beighton scoring system for joint hypermobility. A score of 5 out of 9 or greater in adults younger than 50 years or 4 out of 9 or greater in adults older than 50 years defines joint hypermobility. The total score is determined by the patient's ability to perform the following. **A**, Passive dorsiflexion of the little fingers beyond 90 degrees (1 point for each hand). **B**, Passive apposition of the thumbs to the flexor aspect of the forearms (1 point for each hand). **C**, Hyperextension of the elbows beyond 10 degrees (1 point for each elbow). **D**, Hyperextension of the knees beyond 10 degrees (1 point for each knee). **E**, Forward flexion of the trunk with knees fully extended so that the palms of the hands rest flat on the floor (1 point).

as joint hypermobility in the absence of the hallmark clinical features of hereditary connective tissue disorders. Other hereditary disorders of connective tissue such as Marfan syndrome and Loeys-Dietz syndrome also have distinct clinical features in addition to joint hypermobility and known genetic mutations to help differentiate them from joint hypermobility syndrome. In patients with hereditary disorders of connective tissue (eg, Ehlers-Danlos syndrome, Marfan syndrome, Loeys-Dietz syndrome), pain is a common presentation related to the underlying pathophysiology, whereas in joint hypermobility syndrome, the association of pain is not well defined, and the presence of joint hypermobility may be a risk factor for the development of fibromyalgia.

Patients with endocrinopathies can present with widespread pain and fatigue similar to fibromyalgia or that coexist with fibromyalgia. Screening evaluations for hypothyroidism, hyperparathyroidism, and vitamin D deficiency are commonly pursued as part of the initial evaluation of chronic widespread pain.⁷⁴ Autoimmune thyroid disease with and without hypothyroidism is associated with fibromyalgia. Severe vitamin D deficiency accompanied by osteomalacia and myopathy can present with generalized bone pain. However, the occurrence of severe vitamin D deficiency is rare in developed countries and typically only occurs in the context of malabsorption.⁵² Chronic widespread pain is associated with mild vitamin D deficiency. Vitamin D is thought to be involved in the regulation of prostaglandin synthesis and cytokine release. Vitamin D replacement provides benefits in the context of vitamin D deficiency with improvements in chronic widespread pain appreciated only when the 25-hydroxyvitamin D levels are less than 50 nmol/L.⁷⁵ In patients with increased size in hands and feet with coarse facial features associated with the onset of chronic widespread pain, an evaluation for excessive growth hormone production, including brain imaging, to assess for a pituitary adenoma is warranted.⁵²

KEY POINTS

- Hypermobile Ehlers-Danlos syndrome has distinct clinical findings of skin fragility and marfanoid features that allow it to be differentiated from joint hypermobility syndrome.
- All patients with chronic widespread pain should have a complete history and medical examination along with laboratory testing comprising a complete blood cell count and measurement of C-reactive protein, serum calcium, creatine phosphokinase, thyroid-stimulating hormone, and 25-hydroxyvitamin D levels.

MEDICATION-RELATED PAIN SYNDROMES

Several medications can be associated with widespread pain. Statins are associated with both an immune-mediated necrotizing myopathy and toxic myopathy but can also present with myalgias and a normal creatine kinase level that resolves with cessation of the offending medication.⁶⁶ Other agents such as recreational drugs (eg, cocaine), antiviral medications, and anti-inflammatory drugs can cause myopathies that may present with myalgias.⁷⁶ Following chemotherapy, patients can present with diffuse pain beyond what is expected from a chemotherapy-induced length-dependent peripheral neuropathy, and specifically, aromatase inhibitors can cause musculoskeletal pain in as many as one-half of patients treated with these agents for breast cancer.⁵² In addition, bisphosphonate therapy has been reported to cause musculoskeletal pain.⁵² Opioid-induced hyperalgesia is another consideration that could be a contributing factor to the clinical presentation if the pain is refractory and accompanied by allodynia in patients on opioid therapy.^{77,78} A medication-associated effect should be considered with the onset or worsening of pain symptoms temporally associated with the use of a medication known to cause generalized pain (eg, myalgias, hyperalgesia, musculoskeletal pain).

EVALUATION OF PATIENTS WITH WIDESPREAD PAIN SYNDROMES

All patients presenting with chronic widespread pain should have a screening evaluation for easily identifiable secondary causes of the pain as part of a

complete history and medical examination. Laboratory tests should include a complete blood cell count and measurement of C-reactive protein, serum calcium, creatine phosphokinase, thyroid-stimulating hormone (TSH), and 25-hydroxyvitamin D levels to screen for metabolic or inflammatory causes of chronic widespread pain.⁷⁴ Beyond the screening laboratory evaluation, the clinical presentation should guide any further evaluation based on the temporal profile of symptoms, syndromic presentation, and clinical examination findings. Conversely, a patient whose history suggests a nociceptive pain syndrome with a normal neurologic examination would not require further evaluation. It should also be noted that nociceptive, neuropathic, and nociceptive pain are not mutually exclusive, and patients may present with more than one pain type.

TREATMENT OF PATIENTS WITH WIDESPREAD PAIN SYNDROMES

Successful treatment of chronic widespread pain depends on thorough communication with a focus on patient education, validation of symptoms as part of the discussion, and realistic expectations that are set before the implementation of a treatment plan. When educating patients, it is important to use terminology appropriate for the patient's level of medical literacy, and terms such as "sensitized," "revved up," and a "fired-up nervous system" are often well received by patients when discussing the pathophysiology.⁶ It can be a challenge to set realistic expectations for improvement of symptoms focusing on quality of life rather than eradication of symptoms, but it is necessary for successful outcomes. A stepwise approach is preferred with the implementation of nonpharmacologic strategies first before pharmacotherapy.⁶ Empowering patients with a strong internal locus of control and promotion of good lifestyle habits (eg, physical activity, healthy diet with a focus on fruits and vegetables, sleep hygiene, stress reduction) are fundamental to positive outcomes.

When patients are ready, incorporating psychological treatments can provide benefits, and it helps to frame these treatments as part of a multidisciplinary care program to treat the whole person. Gauging the receptiveness of the patient to psychological treatments and using personalized medicine to guide the depth of psychological treatments are important; in one study, only about one-half of patients referred to pain psychologists ultimately established care with a pain psychology specialist.⁷⁹ If a patient appears receptive to psychological treatments, then direct referral to a psychotherapist for cognitive-behavioral therapy is ideal. For patients who do not appear receptive at first to referral to a psychotherapist, online resources may be of benefit, and preparing a list of websites or cognitive-behavioral therapy and mindfulness apps may be a good initial introduction to the principles that may maintain buy-in by hesitant patients. For patients with comorbid mood disorders, optimization of pharmacotherapy is important, and a referral to a psychiatrist may be indicated.

Duloxetine is FDA approved for the treatment of depression and fibromyalgia or musculoskeletal pain. Milnacipran has FDA approval for the treatment of fibromyalgia but is often used off-label for the treatment of depression. Pregabalin is also FDA approved to treat fibromyalgia, but typically a trial of gabapentin is required by most major insurers before use. Tricyclic antidepressants are commonly used in patients with chronic widespread pain. Aside from milnacipran, the pharmacologic approach is similar to that used to treat neuropathic pain. Opioids should be avoided for the treatment of nociceptive chronic widespread pain, and pathophysiologically, the use of opioids

may be detrimental given the observations of high endogenous opioids with low μ -opioid receptor binding observed in fibromyalgia.²⁷ Alternatively, low-dose naltrexone (1.5 mg/d to 4.5 mg/d), an opioid antagonist, has shown benefit in patients with fibromyalgia and may work by increasing the density of endogenous opioid receptors.⁶

Some patients may find complementary and integrative medicine approaches to be helpful (eg, osteopathic or chiropractic manipulation, acupuncture and other alternative medicine techniques, massage therapy, yoga). Systematic reviews and guidelines have shown the best evidence with the use of meditative movement therapies (eg, qigong, tai chi, yoga) and strongly recommended these therapies in the treatment of fibromyalgia but did not recommend acupuncture unless in the context of obesity, and there was insufficient evidence for the use of chiropractic treatment.^{80,81} These techniques are reasonable to incorporate if desired by patients and are generally not cost-prohibitive. Neuromodulation should generally be avoided in the treatment of chronic widespread pain because it is best applied to the treatment of focal pain syndromes that have identifiable targets for treatment. However, neuromodulation may be incorporated into the treatment plan for chronic overlapping pain conditions for which treatments such as spinal cord stimulation have evidence for benefit, as is the case with CRPS. Most important in the development of a multimodal treatment plan is a patient-centered approach with shared decision making and explanation of treatment options.

KEY POINTS

- Opioids should be avoided in the treatment of patients with nociceptive chronic widespread pain and pathophysiologically may be detrimental given the observations of high endogenous opioids with low μ -opioid receptor binding observed in the setting of fibromyalgia.
- Patients with chronic widespread pain benefit from effective communication that validates concerns, provides an understandable explanation of the presenting symptoms, and sets realistic expectations in outcomes using a comprehensive multimodal care plan.

CONCLUSION

Patients with chronic widespread pain frequently utilize health care services, which in many cases leads to neurologic referrals. Effective management of chronic widespread pain requires an in-depth understanding of the pathophysiology and diagnostic criteria of nociceptive pain syndromes, as well as the identification of clinical features that would lead one to suspect potential secondary etiologies. Regardless of etiology, patients with chronic widespread pain benefit from effective communication that validates concerns, provides an understandable explanation of the presenting symptoms, and sets realistic expectations in outcomes using a comprehensive multimodal care plan.

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Opioids and Cannabinoids in Neurology Practice

REVIEW ARTICLE



CONTINUUM AUDIO
INTERVIEW AVAILABLE
ONLINE

By Friedhelm Sandbrink, MD, FAAN; Nathaniel M. Schuster, MD

ABSTRACT

OBJECTIVE: Opioid and cannabinoid therapies for chronic pain conditions including neuropathic pain are controversial. Understanding patient and prescribing factors contributing to risks and implementing risk mitigation strategies optimizes outcomes.

LATEST DEVELOPMENTS: The ongoing transformation from a biomedical model of pain care toward a biopsychosocial model has been accompanied by a shift away from opioid therapy for pain, in particular for chronic pain. Opioid overdose deaths and opioid use disorder have greatly increased in the last several decades, initially because of increases in opioid prescribing and more recently associated with illicit drug use, in particular fentanyl derivatives. Opioid risk mitigation strategies may reduce risks related to opioid prescribing and tapering or discontinuation. Opioid therapy guidelines from the Centers for Disease Control and Prevention have become the consensus best practice for opioid therapy. Regulatory agencies and licensing medical boards have implemented restrictions and other mandates regarding opioid therapy. Meanwhile, interest in and use of cannabinoids for chronic pain has grown in the United States.

ESSENTIAL POINTS: Opioid therapy is generally not recommended for the chronic treatment of neuropathic pain conditions. Opioids may be considered for temporary use in patients with severe pain related to selected neuropathic pain conditions (such as postherpetic neuralgia), and only as part of a multimodal treatment regimen. Opioid risk mitigation strategies include careful patient selection and evaluation, patient education and informed consent, querying the state prescription drug monitoring programs, urine drug testing, and issuance of naloxone as potential rescue medication. Close follow-up when initiating or adjusting opioid therapy and frequent reevaluation during long-term opioid therapy is required. There is evidence for the efficacy of cannabinoids for neuropathic pain, with meaningful response rates in select patient populations.

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RELATIONSHIP DISCLOSURE:

Dr Sandbrink has noncompensated relationships as a Clinical Associate Professor of Neurology and Rehabilitation with George Washington University and as a Clinical Associate Professor in Neurology with Uniformed Services University that are relevant to American Academy of Neurology (AAN) interests or activities. Dr Schuster has received personal compensation in the range of \$500 to \$4999 for *Continued on page 1474*

UNLABELED USE OF PRODUCTS/ INVESTIGATIONAL USE

DISCLOSURE:

Drs Sandbrink and Schuster discuss the unlabeled use of opioids and the unlabeled and investigational use of cannabinoids for the treatment of pain.

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INTRODUCTION

While opioids are considered the most potent analgesic agents clinically available for acute pain, their benefit for treating chronic noncancer pain conditions is controversial and they are generally not recommended for the chronic treatment of neuropathic pain or headache disorders. A careful analysis of benefits versus risks is required when considering opioid therapy, taking patient factors and preferences into account. The most serious risks related to opioid therapy include respiratory depression, sedation resulting in overdose, and the development of opioid use disorder. Thus, nonpharmacologic and nonopioid pharmacologic pain treatment approaches should be maximized in all settings, and multimodal pain care is the best practice, particularly for chronic pain conditions where the risks of long-term opioid therapy are considerable and will likely outweigh the potential benefit.

This article addresses key clinical issues related to opioids, including the benefits and risks of their use in the treatment of neurologic conditions, and provides clinical strategies to optimize safety and effectiveness including risk mitigation standards.

There is interest among patients and neurologists in the potential of cannabinoids for chronic neuropathic pain conditions, and the legal status of cannabinoids across the United States continues to evolve. In addition to a review of opioid therapy, this article discusses the historical context of cannabinoids for pain from antiquity through today, an overview of the endocannabinoid system, the potential benefits and risks of cannabinoids for neuropathic pain, and practical considerations regarding the use of cannabinoids for pain.

THE CHANGING ROLE OF OPIOIDS IN THE TREATMENT OF CHRONIC PAIN

The use of opioids for pain has undergone major shifts in the last century, and the ongoing transformation from a biomedical model of pain care toward a biopsychosocial model has been accompanied by a shift away from opioid therapy for pain, in particular for chronic pain.

Before the 1980s, opioids were rarely used outside of severe acute injury or postsurgical pain, primarily due to concerns about tolerance, physical dependence, and addiction. With the hospice and palliative care movement during the 1980s, the emphasis on pain assessment and relief from pain, including the use of opioids for severe pain, was also applied to noncancer chronic pain, and opioid risks including addiction were underestimated. Opioid prescriptions in the United States increased fourfold from 1999 to 2010, with greater use of long-acting opioid formulations, higher dosages, and longer durations.^{1,2} The first reports highlighting the potential risks to patients included that of Franklin and colleagues,³ which described the association of overdose deaths with escalating opioid dosages and long-acting opioid medication in injured workers in the Washington State workers' compensation system. By 2007, overdose deaths from prescription opioids exceeded deaths from heroin and cocaine combined, and in 2008 opioid overdose became the leading cause of accidental death in the United States ahead of car accidents.⁴ Opioid medication misuse and the nonmedical use of opioids by people without a prescription emerged as major drivers of the overdose and opioid use disorder crisis in the US

population,^{5,6} and transitioning from prescription medication misuse toward the use of illicit substances such as heroin and fentanyl became more common.⁷

As the risks from opioids became more apparent, the potential benefits of pain reduction and improvement in quality of life were increasingly questioned as well, particularly when used as long-term opioid therapy for chronic noncancer pain. A 2014 systematic review found insufficient evidence to demonstrate long-term benefits of opioid treatment for chronic pain and instead documented the association of long-term and higher-dosage opioid prescribing with a greater risk of opioid overdose and misuse.⁸ The US Food and Drug Administration (FDA) subsequently required new safety labeling of opioids highlighting the “risks of addiction, abuse, and misuse, which can lead to overdose and death,” initially only for extended-release and long-acting opioids⁹ and 2 years later also for immediate-release opioids.¹⁰

In 2016, the Centers for Disease Control and Prevention (CDC) published the Guideline for Prescribing Opioids for Chronic Pain.¹¹ The CDC noted the need for a national guideline in recognition of the limited evidence of benefits from opioids for patients with chronic pain and the significant risks to patients and others using prescription opioids not prescribed to them.^{11,12} The guideline was intended to be voluntary, primarily for primary care providers in outpatient care settings, and stated the specific goal to improve communication between clinicians and their patients. The guidelines included recommendations regarding specific limitations for the dosage and duration of opioid therapy. Other organizations and agencies issued similar guidelines, including restrictive regulations by state licensing boards.¹³⁻¹⁵ While the Canadian Guideline, published in 2017, included the recommendation to offer a trial of opioids to selected patients with chronic noncancer pain who had not found sufficient relief with optimized nonopioid therapy, the jointly issued clinical practice guideline by the Department of Veterans Affairs (VA) and US Department of Defense (DoD), also published in 2017, made the recommendation against the initiation of long-term opioid therapy, not only due to the risk of overdose and opioid use disorder but in recognition of the challenges associated with opioid tapering once long-term opioid therapy had been established. In its 2022 update, the VA and DoD clinical practice guideline made a general recommendation against initiating opioid therapy for chronic pain.¹⁶ It also suggested the use of buprenorphine instead of full μ -agonist opioids in patients on daily opioid therapy.¹⁶

Opioid prescribing in the United States peaked around 2012, and the decline since then accelerated after the CDC published its 2016 guideline. Clinicians reacted with sometimes abrupt opioid dosage reductions or discontinuations in patients with chronic pain, in many patients without evidence of harm or misuse, and frequently unilaterally without regard to patient preferences.^{17,18} Subsequent studies documented how the tapering and discontinuation of long-term opioid therapy was correlated with illicit opioid use,¹⁹ emergency department visits and opioid-related hospitalizations,²⁰ mental health crises and overdose events,²¹ and increased risk of death from suicide or overdose.²² Studies also documented challenges in patient access to opioids for pain care,²³ patient abandonment,²⁰ and undertreatment of pain resulting in reductions in quality of life and functioning.¹⁹⁻²⁷

In 2022, the CDC updated and expanded its guideline to provide recommendations regarding the treatment of acute, subacute, and chronic pain, well beyond its prior focus on opioid therapy specifically.¹² The update incorporated feedback from many stakeholders, including the comprehensive

KEY POINTS

- Opioids for the treatment of chronic noncancer pain are generally not recommended for the chronic treatment of neuropathic pain or headache disorders.
- In 2022, the Department of Veterans Affairs/US Department of Defense recommended against initiating opioid therapy for chronic pain and suggested the use of buprenorphine instead of full μ -agonist opioids in patients on daily opioid therapy.
- The risks of tapering and discontinuing long-term opioid therapy include illicit opioid use, emergency department visits, opioid-related hospitalizations, mental health crises, and death from suicide or overdose.

Pain Management Best Practices Inter-Agency Task Force Report by the US Department of Health and Human Services. The updated CDC guideline provided extensive guidance including 12 specific recommendations. The CDC emphasized the patient-centered approach to decision making, the importance of clinician-patient communication, and strengthened the warning against the abrupt reduction or discontinuation of opioid therapy (unless there are indications of a life-threatening issue, such as warning signs of impending overdose).

For acute pain conditions of mild to moderate severity, opioid therapy is associated with similar or decreased effectiveness for pain and function versus nonopioid analgesics. If used for more severe acute pain, the CDC recommends keeping the dosage as low as possible and the duration as short as possible and as needed for the severity of the pain condition. In a 2023 blinded placebo-controlled study of opioids for acute or subacute low back or neck pain (12 weeks or less duration and at least moderate severity), the addition of an opioid analgesic to nonopioid guideline-concordant care did not confer any benefits; rather, there seemed to be some worsening of pain in the opioid group and a small but significant harmful effect on the risk of opioid misuse in the long term.²⁸

For chronic pain, there is mixed evidence regarding benefit. A systematic review and meta-analysis of 96 randomized controlled trials of 26,169 participants with chronic noncancer pain showed that opioid use was associated with statistically significant but small improvements in pain and physical functioning in the short to medium term (ie, 1 to 6 months), with overall benefit similar to nonopioid medications.²⁹

Specifically for neuropathic pain, evidence suggests at least a temporary benefit in pain reduction in selected neuropathic pain conditions, although risks may outweigh benefits, especially at higher dosages and with longer duration of use. According to a systematic review and meta-analysis by Sommer and colleagues,³⁰ some opioids (ie, buprenorphine, morphine, oxycodone, tramadol, and tapentadol) provide substantial pain relief compared with placebo in postherpetic neuralgia and peripheral neuropathies of different etiologies for 4 to 12 weeks. However, the authors noted that there is insufficient evidence for these drugs in other neuropathic pain conditions.³⁰ In contrast, a study of transdermal fentanyl that included patients with postherpetic neuralgia, complex regional pain syndrome, or chronic postoperative pain did not document any benefit compared with placebo.³¹

There is no clear evidence of long-term benefit (ie, for 12 months or longer) from opioid therapy for chronic pain. A single randomized (not blinded) trial evaluated outcomes at 1 year for opioid medications compared with nonopioid medications in patients with chronic musculoskeletal pain (low back and joint conditions).³² Treatment with opioids was not superior to treatment with nonopioid medications for improving pain-related function over 12 months. In contrast, pain intensity was slightly, but significantly better in the nonopioid group, and adverse medication-related symptoms were more common in the opioid group over 12 months. While the study had significant limitations including no blinding of patients and the use of tramadol (with weak opioid action) in the nonopioid group, this study supports the current understanding that over time, when opioids are used chronically, their benefits (if at all present) compared with nonopioid medication diminish, while their risks increase with the duration and dosage of opioid therapy, in particular when used daily and around the clock. Factors contributing to diminishing benefits include tolerance, physical dependence, sedative effects, and opioid-induced hyperalgesia.

OPIOID OVERDOSES IN THE UNITED STATES CONTINUE TO RISE

Despite the marked reduction in opioid prescribing for pain since 2012, deaths due to overdoses continue to escalate in the United States, with an annual rate of more than 100,000 overdose deaths since 2021.³³ Opioids are the most common cause of overdose deaths, and while the deaths from commonly prescribed opioids have been largely steady since 2010 and even decreased in recent years, there was an increase in overdoses from heroin after 2010 followed by a dramatic increase of overdoses from fentanyl and its derivatives since 2013, with further increase associated with the COVID-19 pandemic. Provisional data from the CDC's National Center for Health Statistics indicate that there were an estimated 99,684 drug overdose deaths during the 12-month period ending in March 2024. In the 12-month period ending August 2023, there were an estimated 80,609 overdose deaths from opioids. Of those, 73,845 were related to synthetic opioids other than methadone (ie, fentanyl and its derivatives), 10,456 were from natural and semisynthetic opioids (ie, prescription opioids), and 4386 were related to heroin.³³

REGULATORY AND LICENSURE CONSIDERATIONS IN OPIOID THERAPY

Most states have training requirements regarding pain management, opioid prescribing, or controlled substance prescribing for medical licensure. These requirements vary greatly between states; for example, California requires a one-time 12-hour training, whereas other states require training with each renewal cycle. Guidance is available,³⁴ but it is important to check directly with the state medical board for the latest training requirements.

Many regulatory agencies, insurers, health care delivery organizations, and other entities have imposed restrictions on opioid prescribing and mandates regarding risk mitigation, and the practicing neurologist must pay particular attention to adhere to their state's rules and licensure requirements.

Approximately one-half of all US states limit initial opioid prescriptions for acute pain to an up to 7-day supply.³⁵ Many states require coprescription of naloxone for high-dosage opioid therapy or when opioids are prescribed in the context of benzodiazepines.^{12,36,37}

The Controlled Substances Act, as amended by the Ryan Haight Online Pharmacy Consumer Protection Act of 2008,³⁸ defines requirements for prescribing controlled substances, including through telemedicine. The law is named after Ryan Haight, a 17-year-old honor student from California who died after obtaining a hydrocodone prescription from a doctor online and filled by an internet pharmacy. The Ryan Haight Act requires the completion of an in-person medical evaluation before prescribing a controlled substance, with few exceptions. One exception is the "covering practitioner," as long as the covering provider conducts a medical evaluation (other than an in-person evaluation) and acts at the request of a practitioner (such as being the assigned coverage) who has (1) conducted at least one in-person evaluation within the previous 24 months and (2) is temporarily unavailable (ie, the coverage is for a practitioner expected to resume the patient-provider relationship and future prescribing, if indicated). Another exception is during a public health emergency. During the public health emergency of the COVID-19 pandemic, significant federal telehealth-controlled substance prescribing flexibilities were implemented. New telehealth rules were proposed on March 1, 2023, that would in some situations allow the prescribing of Schedule III to V controlled substances via telemedicine without an in-person medical evaluation,³⁹ and the telemedicine flexibilities of the public health

KEY POINTS

- Despite the marked reduction in opioid prescribing for pain since 2012, deaths due to overdoses continue to escalate in the United States, with an annual rate of more than 100,000 overdose deaths since 2021.
- While the deaths from prescribed opioids have decreased in recent years, illicit fentanyl overdoses are now the leading cause of opioid-related death.
- Many states require coprescription of naloxone for high-dosage opioid therapy or when in the context of benzodiazepines.

emergency regarding controlled substance prescribing were extended until December 31, 2024.⁴⁰ However, prescribers also have to follow their state's licensing regulations, and many restrict controlled substance prescribing by telehealth. Details are available at the National Telehealth Policy Resource Center through the Center for Connected Health Policy.⁴¹ For more information, refer to the article "Navigating Federal and State Laws Regarding the Prescription of Opioids" by Joseph S. Kass, MD, JD, FAAN, and Rachel V. Rose, JD, MBA,⁴² in this issue of *Continuum*.

VULNERABLE POPULATIONS AND RISK FACTORS FOR LONG-TERM OPIOID THERAPY

Opioid therapy is associated with increased risk for serious harm (including overdose and opioid use disorder), in addition to other short-term and long-term risks. Risk factors include patient factors and medication or prescribing factors. In addition to opioid therapy dosage and duration, other risk factors include the concurrent use of sedative hypnotics, the use of extended-release or long-acting

TABLE 7-1

Patient Factors Associated With Opioid Risk

Age

- ◆ Younger and older adult patients

Medical comorbidities

- ◆ Sleep apnea or sleep disordered breathing
- ◆ Pulmonary disease
- ◆ Metabolic impairment (renal or hepatic)

Traumatic brain injury

Mental health comorbidities (risk of overdose, opioid use disorder, suicide)

- ◆ Anxiety
- ◆ Depression
- ◆ Bipolar disorder
- ◆ Posttraumatic stress disorder
- ◆ Psychotic disorder

Substance use disorder (SUD)

- ◆ Active or history of SUD, in particular opioid use disorder
- ◆ Family history of SUD

Tobacco use

Psychological factors

- ◆ Negative affect
- ◆ Catastrophizing

Suicidal risk, history of self-directed violence

Socioeconomic (risk of opioid use disorder)

- ◆ Being less educated
- ◆ Unemployed

opioids, and the presence of substance use and other mental health disorder comorbidities.^{12,16,43}

Patient Factors

Patients with substance use and other mental health disorder comorbidities as well as younger patients are particularly vulnerable to developing opioid misuse or opioid use disorder or to have overdoses. Older people and those with medical conditions such as sleep apnea, pulmonary conditions, or renal disease are more likely to experience sedation, cognitive impairment, or falls. Examples of patient factors and their associated risks are listed in TABLE 7-1.

Prescribing Factors

Higher opioid dosages are associated with a higher risk for opioid misuse, the development of opioid use disorder, and overdose-related death.^{2,29,44-54} There is no safe threshold without any risk of overdose. While risk increases at 50 morphine milligram equivalent (MME) and higher, many patients with opioid overdose and exposure to prescription opioid medication are on dosages below this level.⁴⁴ Dosage increases to greater than 50 MME/day are unlikely to substantially improve pain control for most patients, while overdose risk increases with dosage. Higher dosages, in particular above 90 MME/day, should be avoided without pain specialty consultation.^{11,12}

Longer duration of opioid therapy is associated with a higher risk of being treated for opioid use disorder and a higher risk of fatal opioid overdose.^{1,48,50,53,54} Of note, longer treatment duration is also associated with higher risk when tapering or discontinuing opioids, including overdose and suicide deaths, mental health crises, and emergency department visits and hospitalizations.¹⁹⁻²²

Long-acting or slow-release opioids are associated with a higher risk for opioid overdose and should not be used for acute pain, when initiating opioid therapy, or for as-needed medication use.^{9,12,16} Methadone has been associated with a particularly high risk for respiratory depression and overdose, whereas buprenorphine is associated with a lower risk of respiratory depression and overdose death.¹⁶

The risk for opioid overdose is increased for individuals on long-term opioid therapy who also receive concurrent long-term benzodiazepine therapy, with some risk, albeit lower, also noted for zolpidem.⁵⁵ There is possibly an increased risk when coprescribing gabapentinoids (eg, gabapentin, pregabalin).⁵⁶

Screening Tools to Assess Risk When Initiating Opioid Therapy

Several screening tools may be used to predict the risk of aberrant use behaviors or unhealthy opioid use for patients being considered for opioid therapy. These usually include patient factors such as history of substance use, psychiatric comorbidities, and family history. While these tools may indicate risk for aberrant behavior, their use has not been shown to reduce the risk of overdose or development of substance use disorder.⁵⁷ Common tools include the five-question Opioid Risk Tool,⁵⁸ the Opioid Risk Tool for Opioid Use Disorder (TABLE 7-2⁵⁹), the Screener and Opioid Assessment for Patients in Pain—Revised, a 24-item self-report,⁶⁰ and the Brief Risk Interview, a clinician-administered 12-item screen.⁶¹

Some health care systems employ predictive analytic tools that provide decision support to clinicians when considering opioid therapy, such as the

KEY POINTS

- Opioid overdose and opioid use disorder risk factors include the opioid therapy dosage and duration, concurrent use of sedatives, the use of extended-release or long-acting opioids, and the presence of substance use and mental health comorbidities.

- While overdose risk increases at 50 morphine milligram equivalent (MME) and higher, many patients with opioid overdose and exposure to prescription opioid medication are on dosages below this level.

- Dosage increases to greater than 50 MME/day are unlikely to substantially improve pain control for most patients, while overdose risk increases with dosage.

- Long-acting or slow-release opioids are associated with a higher risk for opioid overdose and should not be used for acute pain, when initiating opioid therapy, or for as-needed medication use.

- Methadone has been associated with a particularly high risk for respiratory depression and overdose, whereas buprenorphine has lower risk of respiratory depression and overdose death.

- The risk for opioid overdose is increased for individuals on long-term opioid therapy who also received concurrent long-term benzodiazepine therapy, with some risk, albeit lower, also noted for zolpidem.

Stratification Tool for Opioid Risk Mitigation in the Veterans Health Administration, which estimates the risk of death from opioid overdose or suicide.⁶² The Risk Index for Overdose or Serious Opioid-induced Respiratory Depression estimates the likelihood of life-threatening respiratory depression or overdose on opioid analgesic therapy and has been validated in different patient populations.^{45,63,64}

ADVERSE EFFECTS OF OPIOID THERAPY

Common acute physical side effects are sedation and cognitive dysfunction, respiratory depression, nausea and vomiting, constipation, urinary retention, and pruritus. Cognitive dysfunction and sedation are common, especially in older patients, and have been associated with an increased risk of falls and motor vehicle accidents. Sedation generally precedes respiratory depression and should always result in consideration for opioid cessation or reduction.

Respiratory depression is the usual mechanism for overdose from prescribed or illicit opioid use. The risk for respiratory depression is higher when opioid therapy is initiated or dosages increase, during opioid rotation, and when administered with other medications that reduce respiratory drive. Opioid-naïve patients, older adult patients, and patients with sleep-disordered breathing from obstructive or central sleep apnea are particularly vulnerable. The opioid antagonist naloxone can rapidly reverse respiratory depression and prevent

TABLE 7-2

Opioid Risk Tool for Opioid Use Disorder (ORT-OUD)^{a,b}

Risk factors	Yes	No
Family history of substance abuse of		
Alcohol	1	0
Illegal drugs	1	0
Rx drugs	1	0
Personal history of substance abuse		
Alcohol	1	0
Illegal drugs	1	0
Rx drugs	1	0
Age between 16-45 years		
	1	0
Psychological disease		
Attention deficit hyperactivity disorder, obsessive-compulsive disorder, bipolar disorder, schizophrenia	1	0
Depression	1	0
Scoring totals		

^a Reprinted with permission from Cheattle MD, et al, J Pain.⁵⁹ © 2019 Elsevier Ltd.

^b This tool should be administered to patients upon an initial visit prior to beginning or continuing opioid therapy for pain management. A score of 2 or lower indicates low risk for future opioid use disorder; a score of 3 or higher indicates high risk for opioid use disorder.

overdose death, and overdose education and the issuance of naloxone is considered an important risk mitigation strategy.^{65–67}

Constipation is common and is due to direct action on opioid receptors of the intestinal wall, resulting in hypomotility. It usually does not resolve without specific treatment and should be managed with both a stool softener and a bowel stimulant. The best strategy is often to reduce the opioid dosage. For some patients, transdermal instead of oral opioid administration reduces the gastrointestinal side effects.

Nausea, vomiting, and pruritus are common side effects that often improve by switching to a different opioid medication. Side effects of long-term opioid use include effects on the endocrine and immune systems. The most important hormonal effects are androgen deficiency and bone loss.⁶⁸ Low testosterone levels associated with long-term opioid use may cause low libido, erectile dysfunction, fatigue, and depressive symptoms,⁶⁹ and routine testing and treatment have been recommended.^{70,71} Osteopenia and osteoporosis contribute to the increased risk of fractures in older patients who may also be at higher risk of falls when taking opioids.⁷² Opioids have been associated with immunosuppressive effects, possibly linking opioid use, postoperative infection, and carcinogenesis. While the clinical relevance is not clear, it is an additional consideration to limit the use of opioids in acute and chronic pain treatment settings.⁷³

Physical dependence is a physiologic adaptation to the continuous presence of a drug that produces symptoms of withdrawal when the drug's effect significantly diminishes or stops,⁷⁴ due to rapid dose reduction or discontinuation, or from the administration of an antagonist. Physical dependence may develop within 2 to 10 days of opioid therapy initiation and is an expected outcome of long-term, around-the-clock opioid exposure.

Opioid withdrawal manifests with autonomic changes, diarrhea, piloerection, sweating, and mydriasis, and increases in heart rate and blood pressure. Irritability, anxiety, and sleeplessness contribute to patient discomfort. Withdrawal symptoms also include hyperalgesia (increased pain sensation) and anhedonia (inability to feel pleasure). While withdrawal symptoms are one of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* diagnostic criteria for opioid use disorder, withdrawal symptoms alone should not be considered diagnostic of opioid use disorder in individuals taking opioid medication as prescribed for pain.⁷⁵ It may be difficult to differentiate patients who are seeking opioid medication for pain relief and those seeking it as a result of opioid craving due to opioid use disorder.

Tolerance is indicated by the need for increasing doses of a medication to achieve the initial effects of the drug⁷⁴ and, at steady dosage, results in diminishing analgesic effect or reduced side effects over time, such as respiratory depression, sedation, or nausea. Tolerance to the analgesic effects of opioids administered continuously occurs over several days. A progressive gradual decline of the analgesic effects from opioids, over months to years, occurs in most patients.⁷⁶ While tolerance is one of the *DSM-5* diagnostic criteria for opioid use disorder, it should not be considered diagnostic of opioid use disorder in individuals taking opioids as prescribed for pain.⁷⁵

Hyperalgesia (increased sensitivity to pain) is due to sensitization to nociceptive stimuli resulting in a lowered pain threshold, decreased tolerance to pain, or both, and is mediated by aberrant glial activation.⁷⁷ Contributing factors are the long-term presence of pain and physiologic and psychological stressors

KEY POINTS

- Screening tools including the Opioid Risk Tool for Opioid Use Disorder may be used to predict the risk of aberrant use behaviors or unhealthy opioid use for patients being considered for opioid therapy.

- Patients developing opioid use disorder while on prescribed opioid therapy should be provided urgent access to evidence-based treatments for opioid use disorder such as methadone or buprenorphine, and other pain treatments should be optimized.

- Methadone or buprenorphine therapy for opioid use disorder, if prescribed in patients with concurrent pain conditions, should be given in divided doses, usually 3 times a day, for better analgesic efficacy.

such as sleep deprivation.⁷⁸ Central sensitization syndromes with hyperalgesia include fibromyalgia.⁷⁹ Opioid use may be a contributing factor to central sensitization and hyperalgesia, known as opioid-induced hyperalgesia. The relevance of opioid-induced hyperalgesia for patients on opioid therapy and contributing factors is not well understood.⁸⁰ It is increasingly appreciated that opioids may result in hyperalgesia and opioid therapy is generally not recommended in patients with central sensitization syndromes such as fibromyalgia.⁸¹

Opioid Use Disorder

The CDC describes opioid use disorder as a problematic pattern of opioid use that causes significant impairment or distress. According to the CDC, in 2016 approximately 2.1 million people in the United States suffered from an opioid use disorder related to prescription opioids and 262,000 had an opioid use disorder related to heroin.⁸² Estimates for opioid use disorder in patients taking opioids for chronic pain vary greatly depending on study methodology and population. One study indicated a 41.3% lifetime prevalence of any prescription opioid use disorder among patients with noncancer pain on opioid therapy.⁸³ When taking pain-related behavior into account (ie, behavioral or subjective criteria were not considered positive if pain relief was the sole motive), the rate of prescription opioid use disorder is lower.⁸⁴ Overall, according to a systematic review, rates of misuse averaged between 21% and 29%, and rates of addiction averaged between 8% and 12%.⁸⁵ Thus, the risk is likely somewhat higher than the 6.6% prevalence of illicit substance use disorders in the US population in general.⁸⁶ Factors contributing to the risk for opioid use disorder from opioids include young age, psychiatric comorbidity, a family history of substance use disorder, being less educated, and being unemployed.⁸⁷⁻⁹⁰

For patients who develop opioid use disorder while on prescribed opioid therapy, it is imperative not to abandon the patient, but to provide urgent access to evidence-based, usually pharmacologic treatment for opioid use disorder, and optimize other therapies for the effective treatment of the pain condition. Methadone (as provided by an opioid treatment program for opioid use disorder) and buprenorphine including the formulations approved for opioid use disorder provide opioid analgesic benefit in addition to evidence-based treatments for opioid use disorder that also include naltrexone. Transitioning to buprenorphine therapy for opioid use disorder may be facilitated by using a “microdosing” approach (see the Buprenorphine For Pain section in this article).^{91,92} Methadone or buprenorphine therapy for opioid use disorder, if prescribed to patients with concurrent pain conditions, should be given in divided doses, usually 3 times per day, for better analgesic efficacy.⁹³ For patients on long-term buprenorphine therapy for opioid use disorder and undergoing surgery, a multimodal analgesic strategy is suggested including the continuation of buprenorphine (with temporary dosage reduction if high dose) with added full μ -agonist opioid medication, if needed, in conjunction with nonopioid analgesics and regional anesthesia.⁹⁴

STRATEGIES WHEN PRESCRIBING OPIOID THERAPY FOR CHRONIC PAIN

The 2022 CDC Clinical Practice Guideline for Prescribing Opioids for Pain provides a guiding framework and recommendations for prescribing providers.¹²

TABLE 7-3 provides an overview of specific opioid medications used in the

Opioids Commonly Prescribed for Pain With Key Characteristics^a

TABLE 7-3

Opioid	Preparations and examples	Conversion factor (CF) (oral) ¹²	Morphine equivalent daily dosage compared with 30 mg morphine orally per day (MEDD 30)	Special considerations
μ-agonists				
Morphine	Immediate release (IR) 12-hour controlled release [CR] 24-hour CR Intermediate release Abuse-deterrent CR formulation available	CF 1.0	30 mg orally/day 10 mg IV	CR mechanism provides relatively stable blood levels Hepatic or renal disease: reduce dosage Metabolites accumulate in patients with renal disease, implicated in morphine-induced neurotoxicity, hyperalgesia, allodynia Avoid in patients with severe renal impairment
Oxycodone	IR 12-hour CR Abuse-deterrent CR formulations available	CF 1.5	20 mg orally/day	CR mechanism provides relatively stable blood levels Hepatic or renal disease: use caution, higher peak dosage in hepatic impairment; consider reducing dose and increasing frequency of dosing
Oxymorphone	IR CR Abuse-deterrent CR formulations available	CF 3.0	10 mg orally/day	CR mechanism provides relatively stable blood levels
Hydrocodone	IR, only as combination product	CF 1.0	30 mg orally/day	Most commonly prescribed opioid
Hydromorphone	IR CR Abuse-deterrent CR formulation available	CF 5.0	6 mg orally/day	Quick onset Oral and IV in preparations used in inpatient and emergency room settings, generally avoided in outpatient treatment settings due to higher risk of unhealthy use
Fentanyl	Transdermal, 72-hour CR patch Transmucosal immediate-release fentanyl (TIRF) sublingual tablet TIRF lozenge TIRF buccal tablet TIRF buccal soluble film	Transdermal, CF 2.4	Unknown Not to be used for opioid naive patients	Patch provides very stable blood levels when used as prescribed, but concentrated dosage is particularly dangerous when used in an inappropriate manner TIRF products are subject to FDA-mandated REMS program

CONTINUED ON PAGE 1458

CONTINUED FROM PAGE 1457

Opioid	Preparations and examples	Conversion factor (CF) (oral) ¹²	Morphine equivalent daily dosage compared with 30 mg morphine orally per day (MEDD 30)	Special considerations
Methadone	CR	CF 4.7, use with extreme caution	Unknown	Second analgesic mechanism: NMDA-receptor antagonist; possibly less tolerance and greater efficacy in neuropathic pain indications Complex pharmacologic properties and risk of accumulation due to long half-life; should only be used by clinicians with expertise in this drug Use in opioid treatment programs for opioid use disorder requires special authorization
Tapentadol	IR CR Abuse-deterrent CR formulation available	CF 0.4	Unknown	Second analgesic mechanism: reduces reuptake of norepinephrine Possible greater efficacy in neuropathic pain
Codeine	IR	CF 0.15	200 mg orally/day	Prodrug with ceiling effect
Partial μ-agonists				
Tramadol	IR	CF 0.2	150 mg orally/day	Schedule III Second analgesic mechanism (increase serotonin/norepinephrine); caution and dosage reduction advised when coprescribed with antidepressants Maximal total daily dosage is 300 mg Associated with risk of seizures; avoid in patients with elevated seizure risk
				May be used in patients with mild to moderate renal impairment or those on dialysis Slower initiation and titration improves tolerability; begin with 25 mg (one-half tablet) Relatively lower risk of unhealthy use and risk of respiratory depression

CONTINUED ON PAGE 1459

Opioid	Preparations and examples	Conversion factor (CF) (oral) ¹²	Morphine equivalent daily dosage compared with 30 mg morphine orally per day (MEDD 30)	Special considerations
Buprenorphine	Approved for pain: transdermal, transmucosal Approved for opioid use disorder: sublingual tablet, sublingual film, buccal film CR injection			Schedule III Partial agonist; ceiling effect; may cause precipitous withdrawal in patients already on opioids Formulations approved for pain are relatively lower dosed, may be used at lowest dosage in opioid-naïve patients Formulations for treatment of opioid use disorder may be used off label for pain Dosing is usually 3 times a day for buccal or sublingual forms when used for pain Considered safer than high-potency full μ -agonists regarding respiratory depression and overdose deaths, and thus may be considered lower risk compared with full μ -agonists in patients with high medical risk due to respiratory disease (eg, pulmonary disorders, sleep apnea) Some unhealthy use reported; may be used illicitly for prevention of withdrawal Useful agents in patients with pain and opioid use disorder

 κ -opioids, μ -antagonist actions

Butorphanol	IV Intranasal	Rapid onset of intranasal, ceiling analgesic effects Used for severe acute headache if opioid therapy is indicated
Nalbuphine	IV	Ceiling analgesic effects
Pentazocine	Oral	Ceiling analgesic effects

FDA = US Food and Drug Administration; IV = intravenous; NMDA = *N*-methyl-D-aspartate; REMS = Risk Evaluation and Mitigation Strategies.^a Data from Department of Defense and Department of Veterans Affairs.¹⁴

United States and their key characteristics. Based on the CDC¹² and other guidelines,^{13,16} the following strategies are suggested.

In general, nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. If used, opioids are usually combined with other modalities to reduce reliance on opioid medication and for improved outcomes related to pain and function.

Opioid therapy should only be considered if the benefits for both pain and function are anticipated to outweigh the risks to the patient. In general, any benefit from opioids for chronic pain may be expected to be only transient (not beyond 3 to 6 months, if at all present). Thus, an endpoint in the near future (eg, planned surgery) or a temporary use (eg, to allow someone to keep employment, for a limited duration while other pain measures are being instituted) may be considered.

Risk evaluation includes careful assessment of medical and mental health factors, as outlined above and in TABLE 7-1. It is advisable to document a careful assessment of patient risk including psychological factors, and screening tools as outlined above may facilitate this task.

Opioid therapy should not be initiated in a patient receiving a benzodiazepine due to the higher risk of respiratory depression and overdose death. Similarly, concurrent use of other sedating medications such as zolpidem should be avoided. However, for patients already on opioids and benzodiazepines, a careful individualized assessment is required to balance the risks of continuation with the risks of opioid or benzodiazepine tapering or discontinuation.

TABLE 7-4

Considerations for Prescribing Opioids for Chronic Pain^a

Risks do not outweigh potential functional benefit

Patient has a condition that is

- ◆ Causing severe chronic pain
- ◆ Interfering with function and quality of life
- ◆ Failing to adequately respond to indicated nonpharmacologic and nonopioid pharmacologic therapy
- ◆ Supported by objective data of diagnosis and severity, if applicable (eg, imaging)

Clear and measurable functional goals are established

Assessment of behavioral risk factors

- ◆ Include standardized assessment (eg, Opioid Risk Tool for Opioid Use Disorder)

Assessment of medical risk factors

Review of concurrent medications and substances

Initiate as a trial, with clear time limit and exit strategy depending on treatment response

Patient is willing and able to access adequate follow-up for prescribed opioids

Review information from prior treatment response if previously treated with opioids

Prescription drug monitoring program and urine drug testing are concordant with expectations

Patient is fully informed, expresses preference to initiate opioid therapy, and provides written consent to treatment with opioids

^a Modified with permission from Department of Defense and Department of Veterans Affairs.¹⁶

Before starting opioid therapy for chronic pain, the clinician should establish treatment goals with the patient, including realistic goals for pain and function. Improvement in function is the primary goal, even if there is no change in pain severity. The initiation of opioid therapy should be considered a trial, and it should be established with the patient that opioid therapy will be discontinued if benefits are not apparent (**TABLE 7-4**).

Patient Education and Informed Consent

Patient education must include the serious adverse effects of respiratory depression and potentially fatal overdose, the risk of opioid use disorder, and the expected effects of physical dependence and tolerance. The patient must be advised about the common adverse effects of constipation, nausea and vomiting, and pruritus, and in particular the risk for sedation and cognitive impairment such as when driving or operating heavy machinery. Many practitioners make use of an opioid treatment agreement (sometimes called an “opioid contract”) to facilitate and document the conversation about the risks and actions required by the patient, such as safeguarding the medication. In VA and DoD health care settings, written informed consent is universally used for patients on long-term opioid therapy (with exceptions for cancer pain and hospice settings). Written informed consent should carry an emphasis on patient education about the risks and benefits of opioid therapy in a patient-centered approach that fulfills high ethical standards. It includes information about alternatives to opioid medication for pain, guidance on opioid tapering and discontinuation, and documents the discussion of safety aspects and risk mitigation expectations in a patient-centered format.⁹⁴ The VA’s patient education guide is freely available.⁹⁵ Safety practices to discuss with the patient may include opioid prescribing from a single source, taking opioids only as prescribed, the refill policy, random urine testing, avoidance of other psychoactive drugs or substances (including alcohol), safeguarding the medication, and not sharing the medications with anyone.^{96,97}

Risk Mitigation

Examples of routine risk mitigation strategies are listed in **TABLE 7-5**. Querying the state prescription drug monitoring program database is a standard safety practice when initiating and renewing opioid therapy. State regulations vary greatly, with some states mandating prescription drug monitoring program queries for every controlled substance prescription event. An unexpected result

Routine Risk Mitigation Strategies for Long-term Opioid Therapy

TABLE 7-5

Education and written informed consent

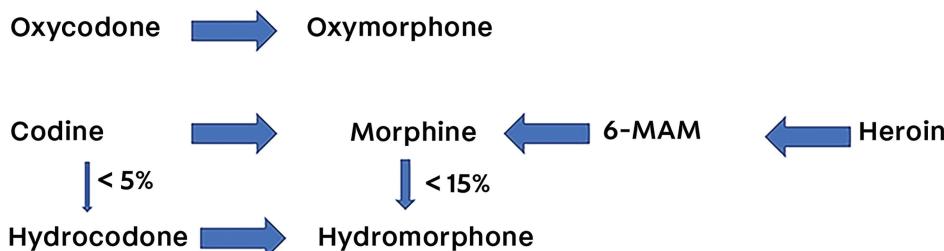
Querying the prescription drug monitoring program

Urine drug testing

Naloxone issuance

Follow-up (in person or audiovisual virtual care) with frequency determined by risk

- ◆ Usually within 1 to 4 weeks (maximum 30 days) after initiation and dosage increases
- ◆ During stable dosage therapy, at least quarterly review of treatment goals, adherence, and patient preferences

**FIGURE 7-1**

Basic opioid metabolic pathways. The basic metabolic pathway may explain the presence of a nonprescribed drug in a urine specimen. Codeine is metabolized to morphine, and in patients receiving codeine, both codeine and morphine are usually found. Similarly, the toxicology report of a patient receiving oxycodone will likely also show oxymorphone, and in those receiving hydrocodone it will also show hydromorphone. A small amount of hydrocodone or hydromorphone may be present in patients receiving codeine or morphine.

6-MAM = 6-monoacetylmorphine (an intermediate metabolite of heroin).

of a prescription drug monitoring program query should be discussed with the patient and not result in an interruption of care.

Urine drug testing should be considered before initiating opioid therapy, at least annually for patients on long-term opioid therapy and more often according to risk.^{12,16} The testing interval should be random. Urine drug testing includes urine drug screening and confirmatory testing if clinically indicated. Screening detects the presence of naturally occurring opioids (eg, morphine, codeine) rather reliably, with lower sensitivity for semisynthetic opioids (eg, oxycodone). Drug screening for synthetic opioids such as fentanyl or buprenorphine requires specific assays for detection, which in many settings requires sending the urine to a laboratory for additional testing. **FIGURE 7-1** shows the basic metabolic

TABLE 7-6

Differential Diagnosis of Unhealthy Use or Misuse of Opioids

Misunderstanding of dosing instructions

Self-medication due to pain

- ◆ Undertreatment
- ◆ During tapering or after recent opioid reduction
- ◆ Worsening of pain condition

Self-medication due to factors other than pain or opioid use disorder

- ◆ Mood
- ◆ Stress or anxiety
- ◆ Insomnia
- ◆ Disturbing memories

Compulsive use due to opioid use disorder

Diversion

- ◆ Sharing with family members or friends
- ◆ For profit
- ◆ Unauthorized access by others

pathways that explain the expected urine drug testing results during opioid therapy. Urine drug testing results must be used in a patient-centered approach, with unexpected findings triggering a conversation with the patient, leading to enhanced safety measures if clinically indicated, but not to patient abandonment.

In addition to overdose education, prescribing the opioid antagonist naloxone is considered an important risk mitigation strategy for patients on opioid therapy, especially in higher-risk situations, such as with high dosages (eg, 50 MME and above), benzodiazepine coprescription, those with a history of opioid use disorder or illicit drug use, or after recent opioid discontinuations. The patient's family, caregiver, or friends should also be educated to recognize the signs of opioid overdose and how to administer naloxone nasal spray. Training videos are widely available.⁹⁸ The FDA recently approved a higher-dose nasal spray formulation that may be considered, in particular for patients with a high risk of exposure to illicit opioids or stimulants that are commonly adulterated with fentanyl.

Prescribing Opioid Therapy and Follow-up

Immediate-release formulations should be used for initial opioid therapy. Long-acting or extended-release medication should never be used as initial opioid therapy, acute pain, or as-needed indications.

Opioid dosage should be kept at the lowest effective dose. The update of the 2022 CDC opioid guideline does not include specific dose limits within the formal recommendations; it continues to suggest that clinicians use extra caution, including increased frequency of follow-up, for patients on opioid dosages above 50 MME/day and should generally avoid increasing dosage to greater than 90 MME/day without careful justification based on diagnosis and individualized assessment of benefits and risks.¹²

Follow-up evaluation should usually occur within 1 to 4 weeks (up to 30 days) after the initiation of opioids or a dosage adjustment. During long-term opioid therapy, it is important to regularly reevaluate the opioid therapy, usually at an interval of every 3 months or less, regarding indication, risks and benefits, aberrant behavior, and patient preferences.

A common practice is to document the “four A’s”:

- ◆ **Analgesia:** effectiveness in reducing pain
- ◆ **Activities:** functional benefit
- ◆ **Adverse effects:** adverse effects from opioid therapy
- ◆ **Aberrant behavior:** adherence to care plan and compliance with risk mitigation strategies

In patients with evidence of aberrant behavior including opioid prescription misuse or illicit drug use, clinicians should carefully assess for the presence of opioid use disorder. Patients may run out of their medication early for a variety of reasons (**TABLE 7-6**). If there is concern for opioid use disorder, it is imperative to not abandon the patient but instead offer or arrange for treatment with evidence-based medications for opioid use disorder or hand off to a different provider. In this situation, buprenorphine may be used to treat both opioid use disorder and pain.

Buprenorphine For Pain

For patients on long-term opioid therapy who require daily opioids, the use of buprenorphine is an emerging practice due to its superior safety profile.^{16,23} As a

KEY POINTS

- Querying the state prescription drug monitoring program database is a standard safety practice when initiating and renewing opioid therapy.
- Urine drug testing should be considered before initiating opioid therapy, at least annually for patients on long-term opioid therapy, and more often according to risk.
- Prescribing of the opioid antagonist naloxone is considered an important risk mitigation strategy for patients on opioid therapy, especially in higher-risk situations.
- A common practice in opioid therapy monitoring is to document the “4 A’s”: analgesia, activities, adverse effects, and aberrant behavior.
- The use of the partial μ -opioid agonist buprenorphine for chronic pain is an emerging practice as it has a respiratory depression ceiling effect, unlike full μ -opioid agonists.

partial μ -opioid receptor agonist, it has a respiratory depression ceiling effect and is associated with less of an overdose risk than full μ -agonist opioids. It is particularly valuable in patients with medical comorbidities resulting in increased risk of respiratory depression and who require around-the-clock opioid therapy due to persistent pain. It is also suggested by recent guidelines to be used in patients with concurrent pain and opioid use disorder when opioid therapy for pain is clinically indicated due to the severity of pain despite optimization of other pain care approaches.

Buprenorphine products are classified as Schedule III controlled substances. Formulations approved for pain have relatively lower dosages, and while it is a long-acting medication, the buprenorphine transdermal system may be used at its lowest dosage in opioid-naïve patients. Formulations for the treatment of opioid use disorder have higher dosages and may be used off label for pain. Buprenorphine dosing is usually 2 to 3 times per day for the buccal or sublingual

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CASE 7-1

A 62-year-old man presented to the pain clinic for the treatment of painful diabetic neuropathy. He had a 10-year history of type 2 diabetes with obesity, obstructive sleep apnea, and chronic obstructive pulmonary disease. He reported intractable pain and numbness in his lower extremities distally, extending to above the ankles, and some tingling in his fingers. Consistent with the clinical impression of a fiber length-dependent peripheral neuropathy, prior nerve conduction studies and EMG demonstrated a moderate to severe sensory-predominant axonal neuropathy. His most recent hemoglobin A_{1c} was 8.5%.

He had been on opioid therapy for the previous 4 years and reported that he was currently using morphine continuous release 15 mg 2 times a day (about 12 hours apart) and oxycodone 5 mg/acetaminophen 325 mg 2 tablets up to 3 times a day. In addition, he was taking pregabalin 150 mg 2 times a day; he was switched to this from gabapentin approximately 1 year ago, without any clear additional benefit for pain control, but noted a weight gain of 9 kg (20 lbs) since then. He denied depression or suicidal thoughts.

The patient's treatment regimen was optimized by using nonpharmacologic and nonopioid pharmacologic approaches. In view of the significant weight gain since starting pregabalin, this was switched to duloxetine due to being weight neutral.

Regarding the opioid therapy, querying the prescription drug monitoring program provided objective documentation of his opioid therapy. The prior treatment records were obtained and did not document significant aberrant behaviors. Urine drug screening was obtained and was consistent with his prescribed regimen. His current morphine equivalent daily dosage (MEDD) was 75 mg (30 mg of morphine, plus 45 MEDD from the 30 mg of oxycodone; conversion factor 1.5), a fairly high dosage. His initial visit included a discussion about his goals, and he was educated about opioid-related risks and alternatives and signed an informed consent for opioid therapy. He was open to reducing the opioid dosage and possibly discontinuing in the future. With rather high amounts of as-needed medication, tapering the oxycodone/

forms when used for pain, in contrast to its single daily use when targeting opioid use disorder.

As a partial agonist with tight affinity to the opioid receptor, adding buprenorphine to ongoing opioid therapy (or in patients taking illicit opioids regularly) may precipitate withdrawal. A transition to a buprenorphine product from high-dose full μ -agonist opioid therapy may be facilitated by using a “microdosing” approach. As described in **CASE 7-1**, buprenorphine is initially added at a low dosage, followed by a gradual increase in dosage over several days to weeks, and delayed reduction and discontinuation of other opioids.^{91,92}

Opioid Rotation

In some instances, switching the patient from one opioid to another may be helpful, to reduce side effects or in the hope of improving the effectiveness

acetaminophen dosage was pursued initially, and reduction to a maximum of 4 tablets per day was feasible without him experiencing significant withdrawal symptoms. He was educated about and prescribed naloxone as rescue medication. Given the medical risk for respiratory depression, a switch to buprenorphine appeared medically advisable. While he was not ready to do this at the initial visit, it was planned for consideration upon follow-up.

This case highlights important considerations when taking over opioid prescribing for a patient already established on long-term opioid therapy by another provider. While opioids may not be recommended for chronic pain related to polyneuropathy, this patient was already established on fairly high-dose opioid therapy, and opioid reduction (tapering) is also associated with potential risks and must be done slowly, over months to years as feasible. In addition to querying the state prescription drug monitoring program, it is recommended to obtain urine drug testing. It is advisable to always obtain outside records if feasible and directly communicate with the prior prescriber to obtain additional information and avoid duplicate controlled substance prescribing. A conversation with his prior prescriber may provide information about aberrant behavior. The patient had a higher risk related to the fairly high-dose opioid therapy including being on long-acting medication in the context of medical risks due to respiratory disease and sleep apnea; providers should inquire about continuous positive airway pressure (CPAP) use and encourage compliance. With an MEDD of 75 mg, a direct switch to buprenorphine was not recommended due to the potential of causing withdrawal symptoms, and instead an overlapping conversion was considered using transdermal buprenorphine. A buprenorphine patch with a dosage strength of 10 μ g/hour may be added (for 7 days) and, when tolerated, the dosage may be increased further to then allow discontinuation of the full μ -opioid receptor agonist medications.

COMMENT

related to opioid therapy. This *opioid rotation* is associated with increased risk due to patient variability, in particular regarding incomplete cross-tolerance between different opioids. While opioid conversion factors or ratios (which are usually described in reference to morphine and often expressed in terms of morphine equivalent daily dosage) can provide guidance, published tables vary and were primarily developed based on single-use studies in acute pain. The CDC opioid therapy guideline is commonly used as a reference (**TABLE 7-3**).¹² It is imperative to reduce the opioid dosage of the new opioid by at least 25% to 50% from the calculated equivalent dosage due to incomplete cross-tolerance. A greater reduction may be needed in the elderly or with significant side effects from opioid therapy. If published guidelines exist (eg, in the package insert for transdermal fentanyl), these should be adhered to, even if they are considered conservative due to safety issues.

Opioid Tapering

If opioid therapy is not considered successful in improving function, if risks outweigh benefits for other reasons, or based on patient preference, opioid tapering should be considered. It is imperative that such tapering optimizes patient engagement and collaboration and is based on an individualized assessment of risk and tolerability. In general, more gradual tapers (eg, ≤10% per month) are often better tolerated than more rapid tapers, with pauses as needed. Sudden interruption of opioid prescribing should be avoided, with few safety exceptions. See **CASE 7-1** for an example of opioid tapering.

CANNABINOID

Cannabis use is common among US patients with chronic pain. This section discusses the historic context of cannabinoids for pain, an overview of the endocannabinoid system, clinical evidence for the use of cannabinoids for pain with a focus on neuropathic pain, practical considerations regarding the use of cannabinoids for pain, and a discussion of the risks of cannabinoids.

Historical Context of Cannabinoids for Pain

There is significant interest in cannabinoids as a treatment for painful neurologic conditions including spinal cord injury, multiple sclerosis, and peripheral neuropathy. In 2017, the National Academies Committee on the Health Effects of Marijuana concluded that there is “conclusive or substantial evidence” that cannabis is effective for the treatment of chronic pain in adults.⁹⁹ In 2024, the US Drug Enforcement Agency announced that it will move to reclassify marijuana to be a Schedule III drug.

Cannabis use among US patients with chronic pain is common. In a national survey of 1724 US patients with chronic pain living in areas with medical cannabis laws in 36 states and the District of Columbia, 31.0% reported ever using cannabis to manage pain, 25.9% reported using cannabis within the past 12 months, and 23.2% reported using cannabis in the past 30 days.¹⁰⁰

Cannabis was first used medicinally in China in 2900 BC and India in 1000 BC, and from 1843 to 1943 cannabis was a mainstay of treatment of migraine in Europe and North America and was reported to have benefit for both migraine prevention and acute treatment.^{101,102} In 1916, Sir William Osler wrote that cannabis was “probably the most satisfactory remedy” for migraine.¹⁰³

Overview of the Endocannabinoid System and Cannabinoids

The endocannabinoid system consists of the major ligands anandamide (also known as *N*-arachidonoyl ethanolamine anandamide) and 2-arachidonoylglycerol, as well as minor ligands. They bind to the CB₁ receptor in the central and peripheral nervous systems and the CB₂ receptor, which is predominantly found on splenic macrophages but is also found to a lesser degree in the brain. It also includes enzymes such as fatty-acid amide hydrolase, which degrades anandamide.

Cannabis contains hundreds of active components including the major phytocannabinoids delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), as well as minor cannabinoids, terpenes, and flavonoids. THC is a partial agonist at the CB₁ and CB₂ receptors and is believed to be both the primary antinociceptive compound in cannabis and its psychoactive component. CBD acts via multiple mechanisms and is nonintoxicating, and one CBD product is FDA-approved as an antiepileptic medication in patients with Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex. While there has been great interest in CBD as a pain treatment, the evidence to date has not demonstrated pain benefits from CBD.¹⁰⁴ Hemp-derived CBD has been legal nationally in the United States since 2018. The dosages available for purchase without a prescription are often approximately 10 mg/dose, which is much lower than the prescription antiepileptic dosages (maintenance dose of 10 mg/kg 2 times a day).

CBD is a negative allosteric modulator of the CB₁ receptor, a mechanism by which it is believed to decrease the psychoactivity of THC. High CBD-to-THC ratio products are typically better tolerated, especially by cannabis-naïve patients.¹⁰⁵

Clinical Evidence for Cannabinoids for Pain

The clinical evidence for cannabinoids for the treatment of pain includes studies of herbal cannabis, plant-derived products, and synthetic products. The plant-derived products include plant-derived THC (dronabinol), an oromucosal spray with a plant-derived combination of a 1:1 ratio of THC and CBD (nabiximols), and a synthetic cannabinoid mimicking THC (nabilone).

A Cochrane Library Review reviewed 16 studies with 1750 participants with various neuropathic pain conditions, including multiple sclerosis pain, spinal cord injury, plexus injury, diabetic peripheral neuropathy, human immunodeficiency virus (HIV)-associated peripheral neuropathy, chemotherapy-induced peripheral neuropathy, and mixed neuropathic pain conditions. It reported 50% responder rates (patients with 50% reduction in pain from baseline) of 21% with cannabis-based medications versus 17% with placebo, and 30% responder rates (patients with 30% reduction in pain from baseline) of 39% with cannabis-based medications versus 33% with placebo. Patient Global Impression of Change was 26% with cannabis-based medications versus 21% with placebo. As expected, central nervous system adverse events such as euphoria and sedation are common with cannabis-based medications.¹⁰⁶

Practical Considerations in Cannabinoids for Pain

Evidence suggests that THC has a narrow therapeutic window for neuropathic pain, with therapeutic benefit at subintoxicating dosages or dosages with limited psychoactive effects. THC may lead to hyperalgesia at higher dosages. THC also

KEY POINTS

- While there has been great interest in cannabidiol (CBD) as a pain treatment, the evidence to date has not demonstrated pain benefits from CBD.

- CBD is a negative allosteric modulator of the CB₁ receptor and reduces the psychoactivity of delta-9-tetrahydrocannabinol (THC). High CBD-to-THC ratio products are typically better tolerated, especially by cannabis-naïve patients.

has psychoactive effects at higher dosages, including dose-dependent effects on working memory and executive function.¹⁰⁷⁻¹⁰⁹ Overdosing can cause anxiety and panic attacks. It can also cause increased heart rate, changes in blood pressure, and arrhythmia.¹¹⁰

Inhaled cannabis has a fast onset and fast offset (maximum plasma concentration within minutes; psychotropic effect onset within seconds to minutes, peaking 15 to 30 minutes and wearing off within 2 to 3 hours), while oral products (liquid tinctures and oils, capsules, and edibles) have a slower onset and longer duration of effect (psychotropic effects starting after 30 to 90 minutes, peaking after 2 to 3 hours, and lasting 4 to 12 hours).¹¹⁰

At the University of California San Diego Center for Pain Medicine, for patients with refractory neuropathic pain conditions that have not responded to conservative treatment, a protocol that some providers recommend is an oral dose titration of 1:20 THC:CBD ratio starting with 1.25 mg THC 2 times a day and increasing every 3 days to 2.5 mg THC and then to 3.75 mg THC as needed and tolerated. For patients seeking a more sedating treatment at night, some University of California San Diego Center for Pain Medicine providers recommend a 1:1 THC:CBD ratio at nighttime, starting with 2.5 mg THC at bedtime and then after 3 nights if needed increasing to 5 mg.

Cannabis Use Disorder, Dependence, and Withdrawal

Cannabis use disorder is defined as the inability to stop consuming cannabis even when it is causing physical or psychological harm. Nearly 10% of people who used cannabis over the prior year were daily or near-daily users.¹¹⁰ Cannabis use disorder is present in nearly 10% of users and about one-third of daily users.¹¹¹ The lifetime risk of dependence among those who have ever tried cannabis is estimated at 9%, as compared with those of tobacco (32%) and alcohol (15%).¹¹¹ Withdrawal occurs with discontinuation in 12.1% of frequent cannabis users, with the most common withdrawal symptoms being anxiety, hostility, insomnia, and depressed mood.¹¹²

Cannabis Hyperemesis Syndrome

Cannabis hyperemesis syndrome presents with recurring episodes of nausea and vomiting in the setting of persistent high-dose cannabis use. It can be associated with abdominal pain and may result in frequent emergency department presentations. Compulsive hot water bathing or showering for symptomatic relief is pathognomonic for cannabis hyperemesis syndrome. Cannabis has a biphasic effect on nausea, where with intermittent or low-dose use it can have antiemetic and appetite stimulant effects, and dronabinol is an FDA-approved treatment for chemotherapy-induced nausea and vomiting. However, with persistent high-dose use cannabis can be proemetic.¹¹³

Pulmonary Risks

Pulmonary concerns with smoking cannabis include inhalation of carbon monoxide and tar.¹¹⁴ Pulmonary concerns with vaporized cannabis waxes and oils include electronic cigarette and vaping-associated lung injury due to the vitamin E acetate present in some of these substances.¹¹⁵ Vaporizing cannabis flower is believed to avoid these risks of electronic cigarette and vaping-associated lung injury due to vitamin E acetate.

Driving

When clinicians discuss cannabis use with patients they have an opportunity to educate about driving risks. Driving under the influence of cannabis is of course illegal. In a double-blind randomized controlled trial of a driving simulator study in which participants smoked either placebo cannabis, cannabis containing 5.9% THC, or cannabis containing 13.4% THC ad libitum, most participants' driving returned to normal after 3.5 to 4.5 hours.¹¹⁶ The duration of driving impairment due to orally administered formulations is longer than that of inhaled formulations.

KEY POINTS

- There is evidence suggesting that THC has a narrow therapeutic window for neuropathic pain, with therapeutic benefit at subintoxicating dosages or at dosages with limited psychoactive effects.
- Cannabis use disorder is present in nearly 10% of users and about one-third of daily users.
- Compulsive hot water bathing or showering for symptomatic relief is pathognomonic for cannabis hyperemesis syndrome.
- Cannabis has biphasic effects on nausea. With persistent high-dose use, it can be proemetic.

CONCLUSION

The continuing evolution of the role of opioids and cannabinoids in pain treatment requires ongoing education on the part of the practicing neurologist, with a need to keep abreast of both emerging medical evidence and changing regulations. Both opioids and cannabinoids can be part of the neurologist's armamentarium for the treatment of patients with painful neurologic disorders. Neurologists should consider the full breadth of pain treatments discussed in this issue of *Continuum*, including nonopioid medications, pain psychology, neuromodulation, physical therapy, and complementary and integrative therapies, when considering whether to initiate a trial of opioids or cannabinoids for a patient.

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DISCLOSURE

Continued from page 1447

serving as a consultant for Averitas Pharma and ShiraTronics, as an editor, associate editor, or editorial advisory board member for *Pain Medicine*, and on a scientific advisory or data safety monitoring board for Rapport Therapeutics, Inc and Vectura Fertin Pharma, Inc; in the range of \$5000 to \$9999 for serving as a consultant for Schedule 1 Therapeutics Inc and Vertex Pharmaceuticals Inc; in the range of \$10,000 to \$49,999 for serving as a consultant for Lohola Research Corporation; in the range of \$50,000 to \$99,999 for serving as a consultant for Syneos Health and on a speakers bureau for Averitas Pharma, Inc and Lilly; and

in the range of \$100,000 to \$499,999 for serving as an expert witness for various law firms and the State of California. The institution of Dr Schuster has received research support from the American Headache Society, the National Center For Complementary and Alternative Medicine (5R00AT009466-04, U24 NS115714), the National Institute of Neurological Disorders and Stroke (1 R01 AT012048-01A1), the National Institutes of Health Helping to End Addiction Long-term Initiative (EN21-01), and the University of California San Diego Academic Senate.

Neuromodulation for Neuropathic Pain Syndromes

REVIEW ARTICLE



CONTINUUM AUDIO
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By Prasad Shirvalkar, MD, PhD

ABSTRACT

OBJECTIVE: This article reviews the principles, applications, and emerging trends of neuromodulation as a therapeutic approach for managing painful neuropathic diseases. By parsing evidence for possible mechanisms of action and clinical trial outcomes for various diseases, this article focuses on five common therapy modalities: cutaneous, peripheral nerve, spinal cord, and brain stimulation, and intrathecal drug delivery.

LATEST DEVELOPMENTS: Recent advances in both invasive and noninvasive neuromodulation for pain have introduced personalized and closed-loop techniques, integrating real-time feedback mechanisms and combining therapies to improve physical and psychosocial function. Novel stimulation waveforms may influence distinct neural tissues to rectify pathologic pain signaling.

ESSENTIAL POINTS: With appropriate patient selection, peripheral nerve stimulation or epidural stimulation of the spinal cord can provide enduring relief for a variety of chronic pain syndromes. Newer technology using high frequencies, unique waveforms, or closed-loop stimulation may have selective advantages, but our current understanding of therapy mechanisms is very poor. For certain diagnoses and patients who meet clinical criteria, neuromodulation can provide profound, long-lasting relief that significantly improves quality of life. While many therapies are supported by data from large clinical trials, there is a risk of bias as most clinical studies were funded by device manufacturers or insurance companies, which increases the importance of real-world data analysis. Emerging methods like invasive or noninvasive brain stimulation may help us dissect basic mechanisms of pain processing and hold promise for personalized therapies for refractory pain syndromes. Finally, intrathecal delivery of drugs directly to segments of the spinal cord can also modify pain signaling to provide therapy for severe pain syndromes.

INTRODUCTION

Neuromodulation for chronic neuropathic pain involves electrical or chemical stimulation of specific neural targets to alter or interfere with abnormal pain signal processing and provide pain relief and improved quality of life.¹ Many therapies are approved by the US Food and Drug Administration (FDA) to target cutaneous nerve endings

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RELATIONSHIP DISCLOSURE:

Dr Shirvalkar has received personal compensation in the range of \$500 to \$4999 for serving as an expert witness for Keating Jones Hughes, P.C. and as faculty with the North American Neuromodulation Society. Dr Shirvalkar has a noncompensated relationship as a sponsor in collaboration with Medtronic that is relevant to American Academy of Neurology (AAN) interests or activities. Dr Shirvalkar has received intellectual property interests from a discovery *Continued on page 1500*

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:

Dr Shirvalkar discusses the use of deep brain stimulation, motor cortex stimulation, and transcranial magnetic stimulation to treat chronic pain; bupivacaine and nonmorphine opioids in intrathecal therapy; and spinal cord stimulation in motor recovery, none of which are approved by the US Food and Drug Administration (FDA).

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in the skin, peripheral nerve fibers, or the spinal cord to modify whatever maladaptive pathophysiology underlies chronic pain syndromes. However, many more therapies are under investigation for either directly stimulating the brain with electrodes or noninvasively with magnetic fields to influence central pain processing for pain relief.

Despite the explosion in technologic advances made in the last decade, there is still a lack of basic knowledge about both fundamental disease mechanisms that lead to chronic pain and how neuromodulation works to provide relief. Nevertheless, with appropriate patient selection, neuromodulation therapies can be offered as options for pain relief for a wide range of neuropathic pain syndromes (and for select other indications, such as nociceptive or myofascial pain syndromes). This article provides an overview of what is known about basic principles of neuromodulation applied to various targets ranging from the periphery to the central nervous system, and practical steps to using such therapies in the clinic (**FIGURE 8-1**). Beginning distally with direct peripheral nerve stimulation, this review progresses inward by discussing the role of spinal cord stimulation and deep brain stimulation (DBS) for chronic pain syndromes. Finally, noninvasive methods are highlighted, including transcutaneous electrical nerve stimulation (TENS), ongoing research using transcranial magnetic stimulation (TMS) for chronic pain, and future technology for circuit modulation. Intrathecal drug delivery is briefly discussed based on the International Neuromodulation Society's definition of neuromodulation, which also includes chemical or pharmacologic treatments such as intrathecal drug delivery under the umbrella of neuromodulation.²

PRINCIPLES OF ELECTRICAL NEUROMODULATION AND PATIENT SELECTION

Neuromodulation can modify nerve activity using implanted electrodes to deliver controlled electrical pulses, with modifiable parameters like contact selection, pulse width, frequency, and amplitude. Patient selection follows the SAFE principles (safety, appropriateness, fiscal neutrality, and efficacy), ensuring careful assessment of the patient's condition, psychological state, and potential benefits before treatment.

Electrical Stimulation of Nervous Tissue

In contrast to therapeutic lesions or the ablation of neural tissue, neuromodulation involves the reversible delivery of electrical or chemical stimuli to alter the electrical and cellular activity of both local and distal nerves.³ Since Hodgkin and Huxley's⁴ original description of the ionic basis of action potentials and electrical membrane currents among neurons, scientists have sought to both understand and modify the electrical properties of nerves for therapeutic benefit. Neuromodulation for pain most commonly involves electrical stimulation using constant, brief pulses through implanted electrodes close to the neural target to influence both membrane currents and action potentials.⁵ The effects of stimulation depend on the current delivered by the electrode array, electrical properties of the neural tissue medium into which current is delivered, and properties of the electrode-tissue interface.⁶ There are at least four important, clinician-adjustable stimulation parameters that control the effects of stimulation on the neural tissue: (1) contact selection and polarity, (2) pulse width, (3) frequency, and (4) amplitude (**FIGURE 8-2**⁷). A single electrode array typically consists of 2 to 16 electrical contacts, each of which can be programmed to a specific polarity: anode (positive charge, current source) or cathode

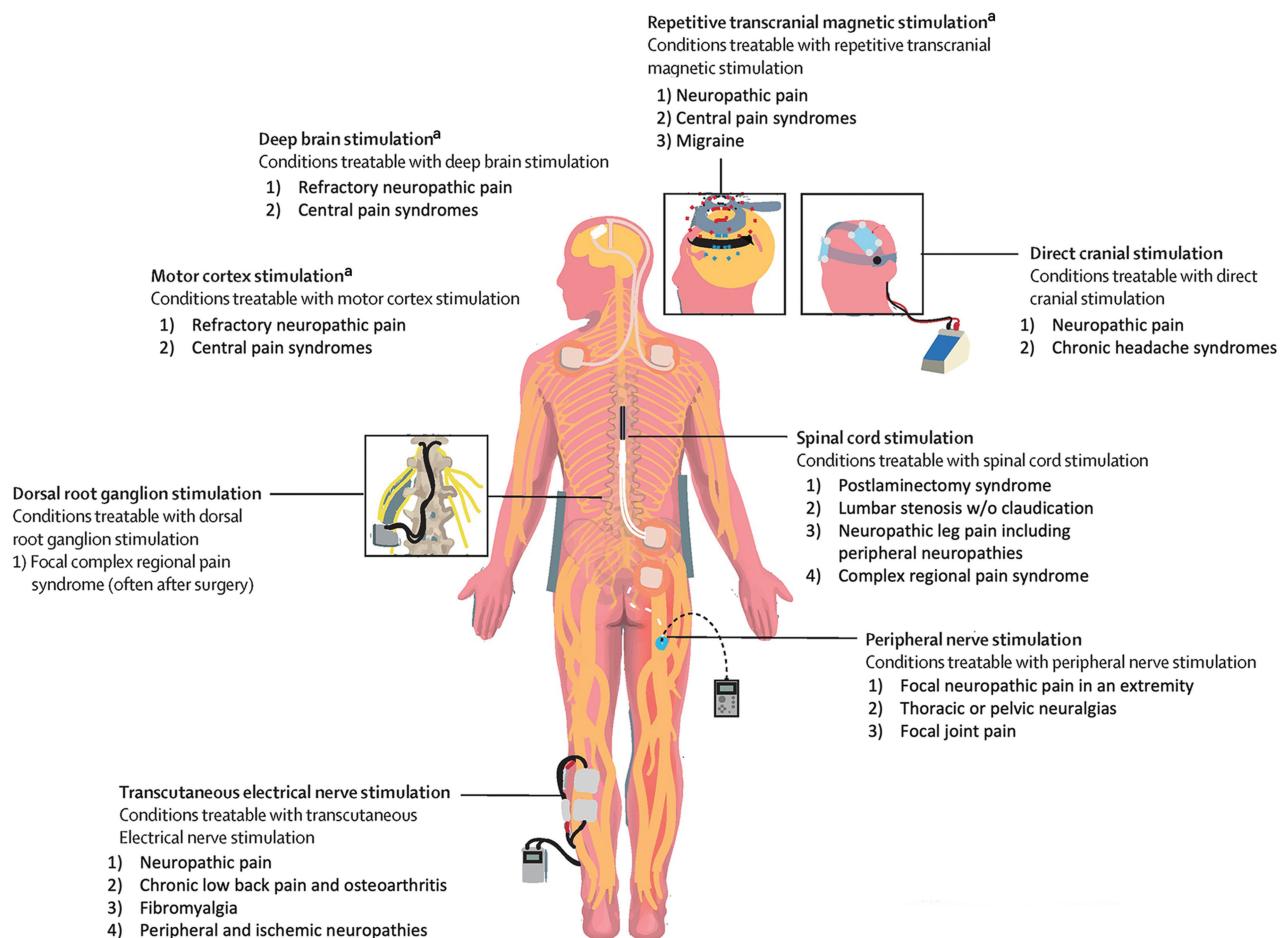


FIGURE 8-1

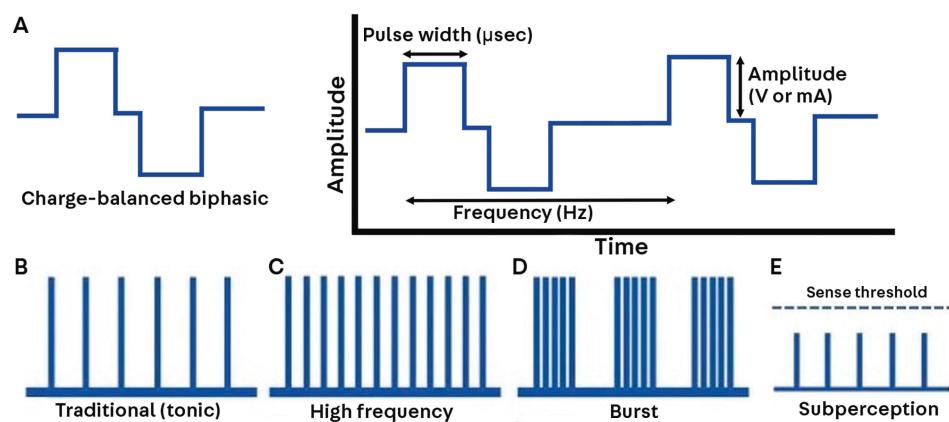
Schematic showing the different forms of neuromodulation and the conditions most amenable to treatment. Peripheral nerve stimulator pulse generators might be implanted or external. Note that transcranial and brain stimulation modalities are not US Food and Drug Administration (FDA) approved in the United States for chronic pain and direct-current stimulation is not regulated.

^a Indicates off-label use in the United States.

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(negative charge, current sink). Modern neuromodulation devices primarily use current-controlled cathodic stimulation, which more easily depolarizes nervous tissue than anodic stimulation.⁸ Neurostimulation is delivered in either a monopolar or bipolar configuration. In a monopolar scheme, a single contact is typically designated as a cathode and the implanted battery is designated as the anode, allowing for wider, less-selective energy delivery. A bipolar configuration (**FIGURE 8-3**)⁹ is more focal and involves local current flow through nearby tissue from at least one cathode to at least one anode.

To prevent electrode degradation or injury to adjacent tissues from current accumulation, modern devices chronically deliver electrical pulses in a charge-balanced manner, where a single pulse involves sequential positive and negative phases.⁶ The duration of each pulse is set by adjusting the pulse width, which typically ranges from 20 microseconds to 1 millisecond, depending

**FIGURE 8-2**

Electrical stimulation parameters and waveforms used in pain neuromodulation. **A**, The three parameters describing most waveforms are frequency (Hz), pulse width (μ sec), and amplitude (V or mA), which are typically delivered in a charge-balanced biphasic waveform. **B**, Traditional tonic spinal cord stimulation where the stimulus frequency occurs at a steady rate. **C**, "High frequency" usually refers to stimulation rates over 1000 Hz. **D**, Burst stimulation implies clusters of stimulation waves separated by pauses. **E**, Subperception stimulation is where the intensity is set below the perception threshold (reduced amplitude).

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on the application. As a rule of thumb, longer pulse widths provide more dispersion of the electrical field and so may stimulate a larger volume of tissue or excite dendrites, axons, and soma with lower amplitude thresholds. The frequency at which electrical pulses are delivered is a critical factor, but the impact of pulse frequency on neural tissue is still incompletely understood. Frequency is measured in cycles per second (hertz [Hz]) and for various applications in chronic pain can range from 10 Hz to 10 kHz. Recent experiments in animals suggest that conventional frequency stimulation (40 Hz to 60 Hz) applied to mechanosensitive afferents results in perceptual paresthesia due to synchronization of evoked action potentials in a manner not seen with high-frequency stimulation (greater than 1 kHz).¹⁰ Consistent with this observation, clinically, low-frequency stimulation typically replaces painful sensations with a tingling or vibratory paresthesia in the nerve distribution, while high-frequency stimulation can provide paresthesia-free pain relief.

The amplitude of stimulation refers to the intensity of current delivered with each pulse. Importantly, the total electrical energy delivered to tissues increases as a function of the square of the amplitude.¹¹ Therefore, higher amplitudes may produce greater excitation of neurons and axons but often result in unpleasant sensations or side effects if increased too high. By creatively manipulating stimulation parameters, various neuromodulation devices now deliver unique waveforms such as burst stimulation¹² (high-frequency packets of pulses with silent gaps between) (FIGURE 8-2D), simultaneous dual frequency stimulation¹³ (see the Spinal Cord Stimulation section in this article) or subperception amplitudes (FIGURE 8-2E).¹⁴

Concepts of Electrical Modulation of Pain

The most widely cited theoretical concept to explain how electrical nerve stimulation might improve pain is referred to as the *gate control theory*.¹⁵ First

KEY POINTS

- The four key adjustable parameters that control electrical stimulation are contact polarity, pulse width, frequency, and amplitude.
- Low-frequency stimulation typically replaces painful sensations with a tingling or vibratory paresthesia in the nerve distribution, while high-frequency stimulation can provide paresthesia-free pain relief.
- Gate control theory describes spinal cord mechanisms by which large-diameter and small-diameter fibers interact to “gate out” ascending pain signals.

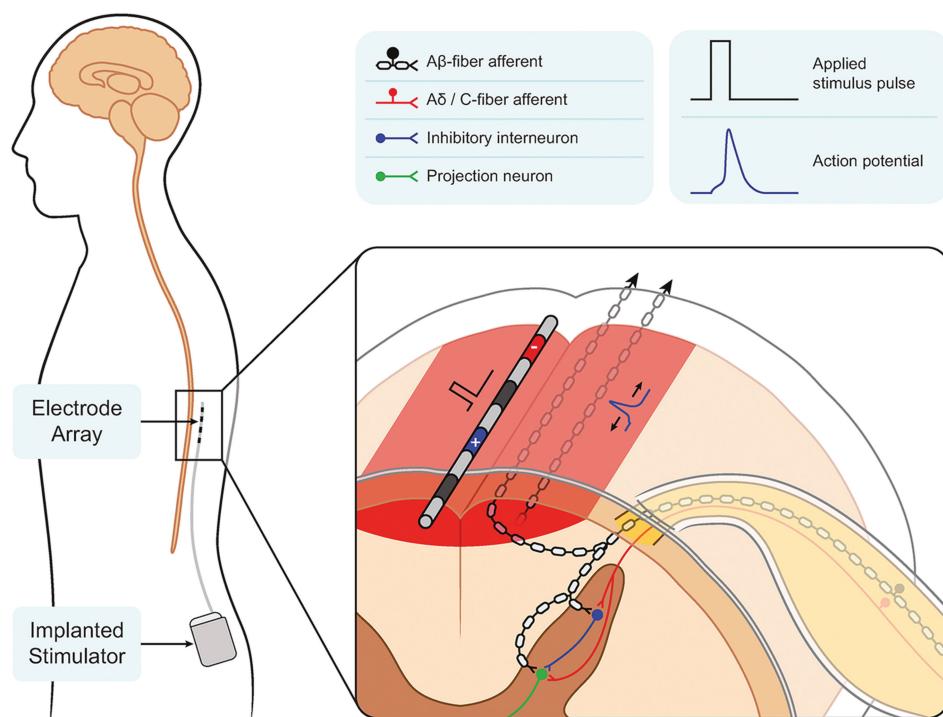


FIGURE 8-3

Example of spinal cord stimulation for pain. In conventional spinal cord stimulation, an electrode array(s) implanted in the epidural space applies electrical pulses at a moderate frequency (eg, 40 Hz to 60 Hz) to excite large-diameter A β somatosensory fibers in the dorsal columns. Antidromic action potential propagation is believed to inhibit the output of projection neurons in the dorsal horn via activation of inhibitory interneurons that close the “gate” and prevent the transmission of pain signals to the brain.

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proposed in 1956, it describes the selective activation of mechanosensitive and vibrosensitive large-diameter sensory fibers (ie, A β fibers) interacting with afferent inputs from painful small-diameter sensory fibers (eg, A δ and C fibers) in the spinal cord substantia gelatinosa (FIGURE 8-3). The activation of large-diameter fibers would effectively “gate out” pain signals that project to the same segmental dorsal horn neuron through feedforward inhibition, thus preventing peripheral pain signals from reaching the brain. Despite the wide appeal of this theory in explaining how paresthesia-based stimulation to peripheral nerves or the spinal cord dorsal horn might provide pain relief, it fails to account for the analgesic benefit of high-frequency paresthesia-free or subparesthesia stimulation protocols. While newer theories that explain analgesia from neuromodulation invoke possible glial cell mechanisms¹⁶ or the modulation of descending brain activity,¹⁷ fundamental circuit mechanisms of electrical stimulation for pain relief are incompletely understood. Despite this major knowledge gap in the basic science of neuromodulation, novel technologies for electrical nerve stimulation are still being developed using novel targets¹⁸ or measurements of evoked electrical activity to provide feedback control.¹⁹

Algorithms for Neuromodulation and Patient Selection

The SAFE principles offer clinical guidance for treatment algorithms involving implanted neuromodulation therapies.²⁰ To ensure safety, permanent

implantation of a neuromodulation device is typically considered only after a successful outpatient trial period and after less invasive treatments like medications or injections have failed. Further, it is critical to gauge comorbidities and surgical risks (**CASE 8-1**). Appropriateness refers to the suitability of both the patient (through a thorough psychological assessment for poor prognostic factors such as untreated depression or anxiety, poor coping skills, and unrealistic expectations) and the specific disease being treated with neuromodulation. The concept of fiscal neutrality aims to balance the initial costs of an intervention with expected future savings in health care spending so the long-term expenses of a new therapy do not exceed those of an equally effective alternative. Finally, the efficacy of any pain treatment should be assessed based on not just pain scores and subjective outcomes from published randomized clinical trials, but also significant improvements in functional ability and the attainment of prespecified activity goals. There is also a validated online, clinical decision tool for assessing the appropriateness of individual patients for spinal cord stimulation based on clinical pain and psychosocial characteristics (see the Useful Websites section in this article).²¹ This simple question-based website has shown prognostic validity in predicting which patients would benefit from a trial or receive significant pain relief. Selecting suitable candidates for neuromodulation and improving the chances of therapy success through medical optimization is just as important as selecting the appropriate neural target and modality for treatment.

STIMULATION MODALITIES

Neuromodulation therapies for pain can target the entire neuraxis from peripheral nerves to the brain using both implanted and noninvasive modalities. Intrathecal drug delivery offers a pharmacologic tool to directly modulate spinal neurons with various drugs.

Peripheral Nerve Stimulation

Peripheral nerve stimulation has undergone significant evolution over the last decade, transitioning from open neurosurgical techniques to contemporary percutaneous approaches where small-diameter wires (less than 1 mm) can be inserted through a needle within 1 cm proximity of a peripheral nerve (**FIGURE 8-4**). Peripheral nerve stimulation provides continuous pulses of electrical stimulation to modulate the activity of individual nerves or nerve bundles to treat focal pain syndromes such as neuralgia related to a mononeuropathy. While it is still common practice to apply peripheral nerve stimulation using hardware for other indications (eg, spinal cord stimulation systems used off label for peripheral nerve stimulation), contemporary peripheral nerve stimulation systems are now commercially available that consist of implantable electrode contacts, a microprocessor receiver, and a pulse generator, which could be external and wireless or internalized. Peripheral nerve stimulation is primarily indicated for neuropathic pain localized in an extremity but can also be used for focal pain in a joint (eg, suprascapular nerve for shoulder pain) or the thoracic and pelvic regions.²² Existing evidence for peripheral nerve stimulation at many targets is of varying quality but randomized, crossover clinical trials suggest that even temporary stimulation for 60 days¹ can provide enduring relief for low back pain in the intermediate term compared with conventional medical management, spanning over 1 year.¹⁸ Furthermore, peripheral nerve stimulation has shown potential in treating pain emanating

CASE 8-1

A 52-year-old woman presented with persistent low back pain radiating to the right leg in a dermatomal fashion, following an L5-S1 laminectomy and fusion performed 2 years earlier. Her pain was both inflammatory and neuropathic in character and refractory to physical therapy, nonsteroidal anti-inflammatory drugs, and opioid analgesics. She had a history of poorly controlled type 2 diabetes, with an elevated hemoglobin A_{1c} of 8.5%, alongside hypertension and obesity.

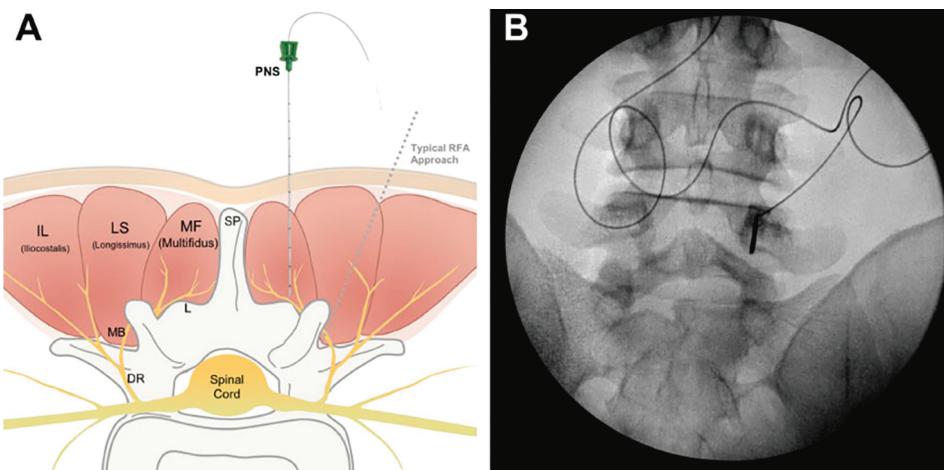
Given the refractory nature of her pain, a spinal cord stimulation trial was proposed. Before the trial, a comprehensive evaluation including a psychological assessment was conducted. The psychological evaluation was crucial to ascertain her candidacy for spinal cord stimulation, ensuring appropriate expectations and a lack of untreated psychological disorder before the procedure. Concurrently, her comorbid conditions were aggressively managed. Her diabetes regimen was intensified with the introduction of a GLP-1-receptor agonist, aiming for tighter glycemic control. This was essential to reduce the risk of postoperative infections and enhance wound healing. Her hypertension and obesity were managed with a combination of medication adjustments and a tailored exercise program.

The spinal cord stimulation trial involved the placement of two eight-contact cylindrical electrodes near the midline stimulating the T9/T10 spinal level in the epidural space. Over 1 week, she demonstrated 70% improvement in pain and function over the two different programs tested, and a permanent implant was subsequently placed at the same location. Notably, she preferred a low-frequency paresthesia-based program over a high-frequency program because the induced vibration and paresthesia let her “know that the device was working.” Postimplant, she reported a nearly 100% reduction in pain and a marked improvement in her quality of life. She was able to taper gabapentin and engaged more actively in physical therapy.

Two years postimplant, she reported a gradual return of her back pain. An x-ray revealed upward migration of the left-sided spinal cord stimulation lead. A revision surgery was scheduled, during which a new lead was implanted on the left side near T9. Postrevision, her pain relief improved but did not return to the initial postimplantation levels. She reported approximately 60% pain relief compared with the near-complete relief experienced initially.

This case highlights the potential of spinal cord stimulation in managing chronic pain in postlaminectomy syndrome, especially in patients with comorbid conditions; the importance of comprehensive preoperative evaluation including psychological assessment; and the vigilant management of lead migration, which may necessitate revision surgeries. The outcome postrevision may not always replicate initial success, indicating the need for ongoing management and realistic expectation setting with patients.

COMMENT

**FIGURE 8-4**

Example of peripheral nerve stimulation (PNS) application to medial branch (MB) nerves to treat chronic low back pain. **A**, Lead placement approach for PNS targeting the MB of the dorsal ramus (DR) of the spinal nerve root coursing over the bony lamina (L) just before it innervates the multifidus muscle. The target nerve is at the level of the patient's primary pain. **B**, Anteroposterior fluoroscopy image showing an example of lead placement with testing cable adjacent to the right L4/5 facet.

RFA = radiofrequency ablation.

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from specific conditions like poststroke shoulder pain,²³ phantom limb pain,²⁴ and thoracic postherpetic neuralgia, although these indications are mostly based on uncontrolled case series.²⁵ Peripheral nerve stimulation can also be applied directly to nerve terminals that innervate muscle, such as the medial branch nerve and multifidus muscle in cases of low back pain related to impaired neuromuscular control, with some patients experiencing remission of pain lasting up to 3 years.²⁶

Peripheral nerve stimulation has also been studied for the treatment of chronic migraine or cluster headache via greater occipital nerve or sphenopalatine ganglion stimulation.^{27,28} However, the use of peripheral nerve stimulation for these indications remains relatively limited in practice due to studies not achieving their primary endpoints, limited insurance coverage, off-label use, lack of familiarity, and high complication rates.

Identifying the right candidates for peripheral nerve stimulation is paramount. Generally, individuals experiencing pain in the distribution of one or two specific nerves, and who have not found relief through conventional care, could be considered for peripheral nerve stimulation. Those with widespread or diffuse pain syndromes might not benefit optimally from peripheral nerve stimulation. Likewise, patients exhibiting active psychiatric comorbidities are considered poor candidates due to potential complications and reduced efficacy.

The procedure involves the precise placement of the electrode contacts near the target nerve or nerves. The location is verified intraoperatively using sensory-evoking electrical stimulation. Once confirmed, the electrode is anchored in place, and the microprocessor receiver is implanted subcutaneously. The external pulse generator communicates with the implanted components, delivering preprogrammed electrical stimuli to modulate the nerve's activity. Compared with older systems like spinal cord stimulation devices, the cost is typically lower, making it a more economically viable option for many patients.

Clinicians employ various strategies for trialing the effectiveness of peripheral nerve stimulation. While some continue to prefer a local anesthetic nerve block trial, a subanalysis of results from an occipital nerve stimulation trial revealed that success from a nerve block does not reliably predict success from long-term nerve stimulation.²⁹ The most frequently reported complications include electrode migration, wherein the implanted electrode moves from its intended position, leading to reduced efficacy or adverse effects. Skin erosion, especially near the implant site, occurs less frequently; infections, although also rare, can also occur, necessitating the removal of the implanted device. With its refined techniques and purpose-built devices, peripheral nerve stimulation offers hope for many chronic pain sufferers. While the evidence on efficacy is still emerging, peripheral nerve stimulation is the most flexible and minimally invasive option for focal pain from mononeuralgia or polyneuralgia.

Spinal Cord Stimulation

Spinal cord stimulation is the most common type of electrical neuromodulation for chronic pain, with over 30,000 patients undergoing trial or permanent implant yearly worldwide.³⁰ Although the first report of spinal cord stimulation involved direct intradural stimulation of the dorsal horn of the spinal cord for cancer pain over 50 years ago,³¹ the modern approach uniformly involves stimulation behind the dorsal horn through the epidural space, through percutaneously implanted cylindrical electrodes or open placement of paddle-type electrodes, connected to an implanted battery.

The approved clinical indications for spinal cord stimulation are chronic low back pain from postlaminectomy syndrome (previously known as “failed back surgery syndrome”), lumbar stenosis without claudication, neuropathic leg pain (ie, radiculopathy), complex regional pain syndrome, and painful diabetic peripheral neuropathy. These indications can be somewhat open to interpretation in practice, and even though spinal cord stimulation is approved for neuropathic pain, studies have reported benefit in treating myofascial or nociceptive low back pain as well.^{14,32} In Europe, spinal cord stimulation is often used to treat chronic angina, and spinal cord stimulation was approved in 2021 by the FDA to treat diabetic peripheral neuropathy.³³ A variant of spinal cord stimulation, which uses flexible, thin electrodes to directly target thoracic and lumbar dorsal root ganglia, is also approved to treat causalgia (eg, complex regional pain syndrome type II). Despite the various approved indications for spinal cord stimulation therapy, group-level clinical outcome data remain controversial due to few studies with rigorous blinding or placebo control and the majority being funded by device manufacturers with very selective enrollment criteria. Nonetheless, subgroup analyses indicate that a proportion of patients obtain greater than 70% pain relief compared with baseline. Still, many spinal cord stimulation devices are implanted for “off-label” indications, including in the cervical spine for chronic neck pain, or for idiopathic lower back pain.⁵ The Neuromodulation Appropriateness Consensus Committee provides useful guidelines and considerations for clinical practice (**TABLE 8-1**³⁴⁻⁴²) (see the Useful Websites section in this article).⁴³

Spinal cord stimulation involves a trial period where patients are required to “test drive” potential benefit from temporarily implanted electrodes for up to 10 days before committing to a permanent implant. For chronic low back pain, two 14-gauge Tuohy needles are inserted just outside the dura in the epidural

KEY POINTS

- The SAFE principles offer clinical guidance for treatment algorithms involving implanted neuromodulation therapies: safety, appropriateness, fiscal neutrality, and efficacy.
- Peripheral nerve stimulation involves stimulating nerve axons by placing a fine electrode wire within 1 cm and is most appropriate for focal pain syndromes and neuralgias.
- Spinal cord stimulation is the most common type of electrical neuromodulation for chronic pain, with over 30,000 patients undergoing trial or permanent implant yearly worldwide.
- Despite the various approved indications for spinal cord stimulation therapy, group-level clinical outcome data remain controversial due to few studies with rigorous blinding or placebo control.
- Complex regional pain syndrome is a rare pain syndrome typically affecting one limb that involves neuroimmune, vasomotor, sudomotor, and trophic changes. Dorsal root ganglion stimulation is the only approved therapy for lower-extremity complex regional pain syndrome.

TABLE 8-1

Neuromodulation Appropriateness Consensus Committee Guidelines for the Use of Spinal Cord and Dorsal Root Ganglion Stimulation for Specific Disease Indications^a

Disease-specific indications	US Preventive Services Task Force (USPSTF) quality of evidence ^{34,b}	USPSTF recommendation strength ^{34,c}
The use of spinal cord stimulation early in the treatment algorithm for failed back surgery syndrome in the absence of neurological progression requiring surgical intervention with persistent axial and radicular complaints ³⁵⁻³⁸	I	A
The use of spinal cord stimulation should be either conventional spinal cord stimulation or dorsal root ganglion (DRG) stimulation when the pain is dominantly radicular in nature	II-2	B
The use of cervical spinal cord stimulation for the treatment of upper extremity pain of neuropathic pain syndromes affecting the upper extremities, including, but not limited to, radiculopathy	II-2	A
The use of spinal cord stimulation for the treatment of complex regional pain syndrome (CRPS)-I and CRPS-II	I	A
The use of spinal cord stimulation with pacemakers appears to be safe in most settings ³⁹	III	C
The use of neurostimulation has been shown to have a better outcome if used early in the course of the disease process; spinal cord stimulation and peripheral nerve stimulation would be considered earlier, when possible, and recommended to be trialed within the first two years of chronic pain ^{40,41}	II-3	B
High-frequency stimulation or burst stimulation may be helpful in treating axial back pain and those with tonic stimulation resistance	III	I, consensus panel strong
DRG stimulation should be trialed for discrete areas of neuropathic pain	II-1	B
The Neuromodulation Appropriateness Consensus Committee recommends spinal cord stimulation as an early intervention in patients with Raynaud's syndrome and other painful ischemic vascular disorders; if ischemic symptoms persist despite initial surgical or reasonable medical treatment, spinal cord stimulation should be trialed ⁴²	II-3	C

^a Reprinted with permission from Deer TR, et al, Neuromodulation.⁴³ © 2014 International Neuromodulation Society.

^b I: Evidence obtained from at least one properly randomized controlled trial.

II-1: Evidence obtained from well-designed controlled trials without randomization.

II-2: Evidence obtained from well-designed cohort or case control analytic studies, preferably from more than one center or research group.

II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III: Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

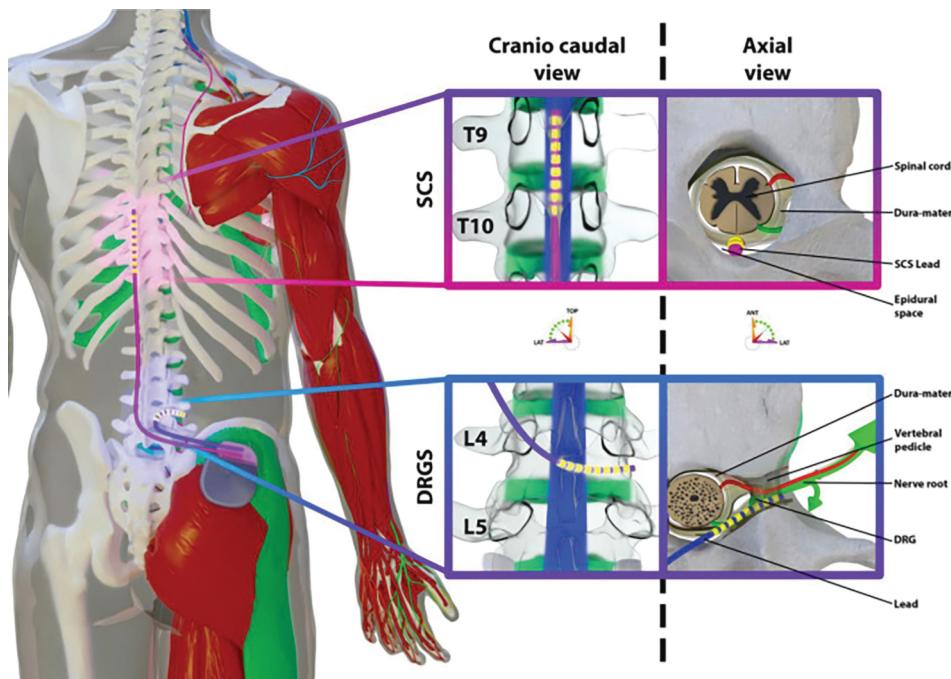
^c A: The USPSTF strongly recommends that clinicians routinely provide [the service] to eligible patients. (The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.)

B: The USPSTF recommends that clinicians routinely provide [the service] to eligible patients. (The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.)

C: The USPSTF makes no recommendation for or against routine provision of [the service]. (The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of the benefits and harms is too close to justify a general recommendation.)

D: The USPSTF recommends against routinely providing [the service] to asymptomatic patients. (The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.)

I: The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. (Evidence that [the service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.)



KEY POINTS

- In the case of a potential infection near spinal cord stimulator hardware, it is urgent to completely explant all hardware.
- While drug spread can be influenced by infusion rate or concentration, intrathecal drug delivery is typically best suited for focal pain syndromes involving one to two spinal levels.

FIGURE 8-5

Visual depiction of spinal cord stimulation (SCS) and dorsal root ganglion stimulation (DRGS) electrode placement. SCS for low back and leg pain (top panels) typically involves the placement of cylindrical epidural electrodes between the T9 and T10 vertebral levels, as shown in craniocaudal (top left) and axial (top right) views. Electrodes are placed vertically close to the midline to ensure activation of dorsal column fibers that topographically map to the midline lumbar region and legs. DRGS for focal pain (bottom panels) involves the oblique placement of thinner electrodes entering the epidural space and exiting the neural foramen from medial to lateral in very close proximity to the DRG within the foramen. A DRG electrode is shown here targeting the right L4 nerve root in craniocaudal (bottom left) and axial (bottom right) views, which is likely to produce paresthesia in the right L4 dermatome.

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space at spinal levels near the thoracolumbar junction. Cylindrical electrode wires are passed through these needles and advanced to T8-T10 to provide stimulation over dorsal horn fibers corresponding to a somatotopic representation of the low back (FIGURE 8-5⁴⁴). Spinal cord stimulation paddle electrodes can also be placed via a surgical laminectomy in select cases or to provide broader spatial coverage over the epidural space. Note that dorsal root ganglion stimulation, which is a special case of spinal cord stimulation, uses a very different anterograde transforaminal approach to deposit thinner wires adjacent to the dorsal root ganglion at relevant spinal levels. Using a combination of trial and error and educated guesses based on typical patient settings, various stimulation parameters are iteratively programmed using conventional tonic, high-frequency, or other waveforms to provide near-continuous stimulation. During a trial period, the distal electrode tails are externalized from the skin and connected to an external battery that is usually taped to the patient's flank. For permanent implants, the distal ends of electrodes are secured to underlying fascia with a silicone anchor, tunneled subcutaneously to the flank or buttock region, and connected to a primary cell or rechargeable implanted battery. Patients often require multiple reprogramming sessions to optimize stimulation parameters for maximal benefit.^{45,46}

Both the trial and permanent implant procedures for spinal cord stimulation carry significant risks. The most common risks are hardware related and involve possible lead fracture (up to 9% incidence), migration of the lead away from the intended target (up to 13%), or battery failure (1%).⁴⁷ Clinical risks and harm to the patient are more rare but involve possible infection (3% to 10%), epidural hematoma (0.3%), dural puncture (2%), or spinal cord injury (0.45%).⁴⁸ In the case of a potential infection near spinal cord stimulator hardware, it is urgent to completely explant all hardware. One challenging risk is the possible gradual loss of pain relief over time; up to 30% of patients elect to have the device explanted within 8 years, mostly due to loss of benefit.^{49,50} For a subgroup of patients, spinal cord stimulation has clear benefits for chronic low back pain, neuropathic leg pain, and other pain syndromes in the neck and thorax. Although therapeutic mechanisms are still unclear, by following the SAFE principles, well-selected patients may experience dramatically improved quality of life and function.

BIAS AND LONG-TERM BENEFIT OF SPINAL CORD STIMULATION. Most clinical trials on spinal cord stimulation have been funded by device manufacturers, which has raised concern around reporting bias or quantification of perceived patient benefit. For example, industry-sponsored clinical spinal cord stimulation studies have reported that around 80% to 90% of patients undergoing a spinal cord stimulation trial period obtain significant pain relief (usually 50% or more improvement in pain) to merit proceeding to a permanent implant.^{12,32,51,52} However, real-world data suggest that the trial-to-permanent implant ratio is closer to 50%.⁵³ Further, there is growing controversy around the potential benefit of spinal cord stimulation over time. Spinal cord stimulation is often promoted as an opioid-sparing pain management therapy that can reduce reliance on dangerous opioid medications in the long term. However, several retrospective reviews of insurance claim data challenge this hypothesis and the belief that spinal cord stimulation for low back pain might endure over many years. Specifically, a 2023 propensity-matched case control study found that patients with spinal cord stimulation devices used chronic opioids at a similar rate to those undergoing conventional medical management after 2 years.⁵⁴ However, prior studies have suggested that spinal cord stimulation becomes fiscally neutral with improved outcomes after 2.5 years and may be superior and more cost effective than spinal reoperation.^{37,55} Although such retrospective reviews on spinal cord stimulation outcomes have their limitations, including lacking analysis of actual pain or functional outcome metrics, there is a pressing need to better understand real-world outcomes of spinal cord stimulation over the long term.

Intrathecal Drug Delivery

Intrathecal drug delivery for chronic pain involves the controlled delivery of small volumes of pharmacologic compounds directly into the CSF through a permanently implanted spinal catheter connected to a subcutaneously implanted pump and battery. The only FDA-approved drugs for intrathecal infusion in chronic pain are morphine and ziconotide (an N-type calcium channel toxin derived from snails), and baclofen is also approved for neurogenic spasticity.⁵⁶ However, in clinical practice, it is common to use off-label medications for neuropathic pain such as bupivacaine (local anesthetic), fentanyl, or clonidine either alone or in combination.

The main target of action of intrathecally infused drugs for pain are receptors on dorsal horn neurons in lamina II of the spinal cord. The Polyanalgesic

Consensus Committee has published regularly updated guidelines on key efficacy and safety considerations for patient care, disease indications, spinal anatomy, and recommended drug doses and concentrations.⁵⁷ High-quality evidence supports the use of intrathecal drug delivery as a palliative treatment in cancer pain for either nociceptive or visceral pain from tumor burden or neuropathic pain resulting from nerve involvement.⁵⁷ Less commonly, intrathecal drug delivery is used to treat nonterminal chronic pain conditions. Due to the restricted oscillatory fluid dynamics of CSF and pial and subarachnoid barriers to laminar flow, intrathecally infused molecules have very limited rostrocaudal spread from the catheter tip where they are delivered. While drug spread can be influenced by infusion rate or concentration, intrathecal drug delivery is typically best suited for focal pain syndromes involving one to two spinal levels.⁵⁶ Intrathecal drug delivery is FDA approved for moderate to severe trunk and limb pain and chronic pain intractable to conservative management. Other example indications include axial neck or back pain from multiple causes, abdominal or pelvic visceral pain, and complex regional pain syndrome.⁵⁷ Because intrathecally infused molecules are minimally present in systemic circulation, intrathecal opioids are an appealing option for patients who receive significant benefit from oral opioids but have intolerable systemic side effects.

Intrathecal drug delivery therapy involves careful consideration of patient comorbidities and psychological and social support, disease indications, relevant anatomical target spinal levels, and the selection of the most appropriate drug compounds. Before permanent implant, patients typically undergo an intrathecal drug infusion trial period using either a single-shot test dose or a temporary catheter infusion to observe analgesic effects over the following 8 to 12 hours. Modern drug pumps are capable of variable rates of continuous infusion and include a patient-controlled option where a small bolus of drug can be administered with the push of a button on a remote controller device. Drug pumps can be refilled by inserting a needle through the skin and an outward-facing port on the device, which is typically required every few months. Intrathecal drug delivery involves many possible risks including infection, a spinal CSF leak, nerve or spinal cord injury, temporary loss of neurologic function from excess dosing, respiratory depression from cerebral flow of drug, or possible interactions with other central nervous system (CNS) active medications.^{57,58} Excess concentration of some drugs can also lead to the formation of a granuloma in the subarachnoid space, causing neurologic complications. An unsuccessful, misplaced refill of a drug pump can result in a “pocket fill,” a large injection of drug to the subcutaneous space causing clinical overdose and requiring hospitalization. Finally, although intrathecally delivered medications are minimally present in systemic circulation, abruptly discontinuing the infusion due to pump malfunction or a missed refill appointment could precipitate withdrawal. This can be life-threatening if using intrathecal baclofen. While complications are uncommon, possible obstruction of the catheter or malfunction of the device can require surgical revision. Intrathecal drug delivery therapy is generally reserved for treating neuropathic pain after neurostimulation options have failed; however, many forms of nociceptive or cancer pain can also respond well. Overall, it is an established tool for the treatment of severe and refractory pain syndromes. The existence of intrathecal infusion technology presents an open opportunity for new drug development to treat many other CNS diseases.

Deep Brain Stimulation

DBS is an advanced neuromodulatory procedure wherein electrodes are implanted within specific brain structures to deliver controlled electrical impulses. These impulses can modulate neural activity, providing therapeutic benefits for various neurologic and psychiatric disorders. DBS is often referred to as a “brain pacemaker” and is most used in movement disorders such as Parkinson disease. DBS for chronic pain has a history stretching back even earlier, but the long-term failure of clinical trials has remained an obstacle to FDA approval in the United States. Initial intraoperative microstimulation in human subjects highlighted the potential of modulating the somatosensory and nociceptive network to influence pain perception. From as early as 1960,⁵⁹ many small case series have explored DBS by targeting specific neural nodes (**TABLE 8-2**⁶⁰): the ventral (or caudal) thalamus, internal capsule, and periventricular and periaqueductal gray.⁶¹⁻⁶³ The reported efficacy of these interventions ranged from 23% to 59%.

The 1990s marked a significant phase in chronic pain DBS research with the first two large-scale, multicenter, randomized controlled trials.⁶⁴ These studies aimed to extend the earlier case series findings by involving a heterogeneous cohort of chronic pain patients. The surgical procedure involved implanting bilateral electrodes targeting both the ventral thalamus and periaqueductal gray regions. The primary endpoint, which has since become a benchmark in many

TABLE 8-2**Historic Brain Targets and Results for Deep Brain Stimulation for Chronic Pain^{a,b}**

	Average pain reduction			Responder rates ^c			
	Mean (%)	SD (%)	Studies (patients)	Mean (%)	SD (%)	Studies (patients)	Responder criteria
Single target							
VPL/VPM	60.8	12.4	2 (28)	78.3	16.7	3 (43)	>50% to 80%
PAG/PVG	62.5	-	1 (2)	87.5	17.7	2 (6)	
ACC	40.9	18.1	4 (49)	59.5	35.6	3 (42)	
VS/ALIC	-	-	-	11	-	1 (10)	>50%
M1	45	-	1 (2)	58	-	1 (8)	
Multitarget							
CMpf, PVG, or both	65.9	5.02	2 (6)	65.9	5.02	2 (6)	
PAG/PVG, VPL/VPM, or both	45.7	10.8	6 (149)	64.9	26.9	8 (220)	

ACC = anterior cingulate cortex; CMpf = centromedian parafascicular thalamic nucleus; M1 = primary motor cortex; PAG = periaqueductal gray; PLIC = posterior limb of the internal capsule; PVG = periventricular gray; VPL = ventral posterolateral thalamus; VPM = ventral posteromedial thalamus; VS/ALIC = ventral striatum/posterior limb of internal capsule; SD = standard deviation.

^a Reprinted with permission from Motzkin JC, et al, *Front Pain Res*.⁶⁰ © 2023 Motzkin, Kanungo, D'Esposito, and Shirvalkar.

^b Single-target PLIC and CMpf are excluded.

^c Response thresholds are variably defined. Some studies use percent relief criteria, whereas others include response thresholds such as “satisfactory reduction in symptoms” or “decision to keep implanted pulse generator.”

KEY POINTS

- Although intrathecally delivered medications are minimally present in systemic circulation, abruptly discontinuing the infusion due to pump malfunction or a missed refill appointment could precipitate withdrawal. This can be life-threatening if using intrathecal baclofen.

- Deep brain stimulation for chronic pain has been studied since 1960 but remains off label due to the lack of a single “best target” for all patients and the development of tolerance to stimulation over time.

contemporary chronic pain trials, was a reduction of more than 50% in the pain visual analog score at the 1-year mark. However, these large-scale trials faced numerous challenges, leading to their premature termination. Primary among these was poor enrollment and high participant attrition. Concurrently, the FDA approved DBS in managing Parkinson disease and essential tremor. Given the challenges in the pain trials and successes in movement disorders, market approval for DBS in pain indications was not commercially pursued.

Several critiques emerged regarding the design and execution of these two DBS pain trials. First, the heterogeneity of the pain conditions studied, spanning nociceptive pain, neuropathic pain, thalamic pain, visceral pain, and more, might have muddled the results. Second, purely neuropathic pain syndromes, which many believe to be more amenable to DBS, constituted only approximately 30% of the patient population. Finally, there was a notable lack of rigorous patient follow-up. Technologically, the DBS devices used fixed, tonic stimulation parameters between 100 Hz to 130 Hz, which were optimized only at the study’s onset. Although the modulation of targeted regions initially appeared promising, the long-term analgesic effect diminished. This decline in efficacy over time is postulated to be due to neural adaptation to the constant stimulation, leading to tolerance development. The potential advantages of DBS over other interventions became evident when contrasted with ablative procedures. While DBS is reversible and adjustable, interventions like ablation or resection of brain tissue, which showed limited analgesic efficacy, were permanent.

Early attempts at direct somatosensory cortex stimulation were not fruitful in pain alleviation.⁶⁵ However, interventions targeting the adjacent motor cortex demonstrated therapeutic promise in specific pain syndromes, including pelvic pain,⁶⁶ trigeminal neuralgia,⁶⁷ and phantom limb pain.⁶⁸ Efficacy rates for motor cortex stimulation were reported between 40% and 60% (see the Motor Cortex Stimulation section in this article). However, comprehensive long-term studies are still required to establish its durability and broader applicability, and so its use remains off label.

A paradigm shift in DBS for pain in the 21st century is the focus on modulating brain regions associated with emotional and affective dimensions of pain. Advanced imaging modalities like positron emission tomography (PET) and functional MRI (fMRI) pinpointed regions like the dorsal anterior cingulate cortex,^{69,70} insula, and dorsolateral prefrontal cortex as central to the subjective pain experience.⁷¹ In particular, the anterior cingulate cortex appears to be important for the affective component of pain. Two cases of anterior cingulate cortex stimulation for spinal cord injury yielded promising results but lacked comparison with sham control and may have been influenced by placebo effect.⁷² Additionally, a groundbreaking clinical trial on open-loop DBS in the anterior cingulate cortex demonstrated a significant decrease in visual analog score pain ratings at both the 1-year and 2-year marks, but again lacked a control group.^{73,74}

While open-loop DBS refers to the conventional approach of delivering electrical stimulation continuously, around-the-clock, without regard to underlying physiology, newer “closed-loop” DBS approaches use feedback from neural signals to adaptively adjust stimulation parameters in real time, much like how a thermostat operates. Closed-loop DBS is actively being developed for many disorders but has not yet been tested in chronic pain.

The only rigorous, randomized controlled, and blinded DBS trial for chronic pain (central poststroke pain) to date attempted to modulate the affective

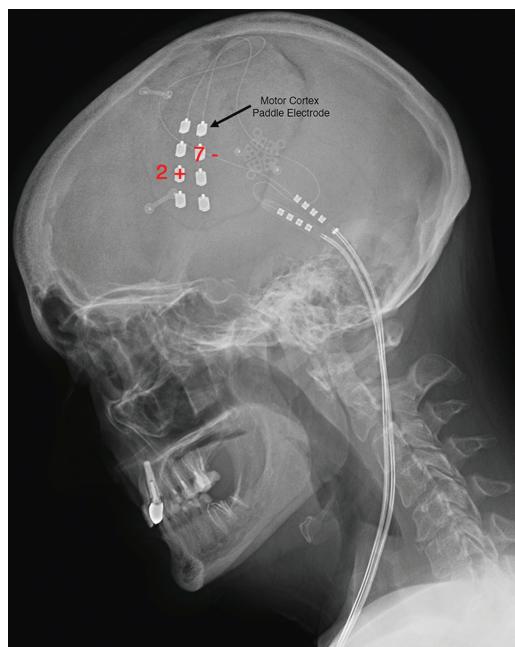


FIGURE 8-6
Example of implanted motor cortex stimulator. X-ray of the lateral view of a patient's skull implanted with a left-sided motor cortex stimulator demonstrating two paddle electrodes. Red text indicates the final anode and cathode contacts chosen for stimulation.

(**FIGURE 8-6**). The electrode wire is subcutaneously tunneled through the neck and connected to an infraclavicular-placed battery, similar to DBS. Motor cortex stimulation garnered attention as a potential treatment avenue for chronic pain following the fortuitous observation that primary motor cortex (M1) stimulation mitigated bursting activity in the ischemic penumbra of a feline thalamic stroke model.⁷⁶ Early clinical trials reported promising outcomes with motor cortex stimulation, yet its reliability in alleviating pain was comparable to DBS targets, exhibiting varied results across studies.^{77,78}

In the 1990s, advancements in TMS techniques permitted noninvasive stimulation of the M1 region contralateral to pain, demonstrating replicable pain relief outcomes reminiscent of invasive motor cortex stimulation techniques.⁶⁸ Typically, paddle electrodes originally designed for spinal cord stimulation are used to chronically deliver motor cortex stimulation. Excess stimulation can result in evoked motor responses or induce seizures at high amplitudes.⁷⁹ The main indication for motor cortex stimulation, which is off label, is refractory neuropathic pain in the face or arm resulting from central pain syndromes such as poststroke pain. Otherwise, motor cortex stimulation has a similar risk profile to DBS and requires similar patient care considerations. While motor cortex stimulation is rarely discussed in conventional circuitry models of chronic pain, evidence reinforces that M1 stimulation interacts with and activates a nexus of brain regions crucial to pain with variable clinical benefit.⁸⁰ In line with this observation, recent investigations highlight M1 as a central hub interlinking brain lesions causing pain, positing M1 as a pivotal network node exerting influence over various associated brain regions. Notwithstanding, the nuanced efficacy of M1

dimension of pain by stimulating the ventral striatum and anterior limb of the internal capsule.⁷⁵ Although this did not lead to improved pain scores, there was a notable enhancement in mood metrics. In summary, DBS offers a promising avenue for chronic pain management, albeit with challenges. A more nuanced understanding of its mechanisms, rigorous trial designs, and patient-specific approaches could pave the way for DBS to become a mainstream therapeutic strategy for chronic pain syndromes.

Motor Cortex Stimulation

Motor cortex stimulation involves the stimulation of superficial motor cortex, in the contralateral hemisphere to pain locations, using either epidural or subdural implanted paddle electrode arrays

stimulation across different pain syndromes points to a possibly more intricate somatotopic interplay with other brain circuits. As basic science mechanisms are uncovered regarding the role of the motor cortex in pain, we may be able to better select candidate patients and more precisely target key cortical circuits in the future.

KEY POINTS

- Motor cortex stimulation involves stimulating the superficial motor cortex with implanted electrode arrays. Potential response for pain control may be identified by first using transcranial magnetic stimulation noninvasively.
- Transcranial magnetic stimulation for pain uses noninvasive magnetic fields through the scalp to induce electrical field stimulation on the primary motor cortex over repeated daily sessions.
- Although therapeutic effects of transcranial magnetic stimulation for pain are short lived, usually dissipating by 1 month, transcranial magnetic stimulation can be used to identify candidates who would benefit from the permanent implant of a motor cortex stimulator.

Noninvasive Stimulation Methods

Several noninvasive neuromodulation devices can generate electrical or magnetic fields in the vicinity of peripheral nerves or the brain to modulate pain signaling. TENS is an intervention for many different syndromes that provides stimulation to the skin and subcutaneous tissues using repeated pulses through adhesive pads placed on the skin. TMS is a noninvasive neuromodulation technique that uses magnetic fields to induce electrical currents beneath the skull.⁸¹ Although limited to research use, MRI-guided low-intensity focused ultrasound is an emerging form of noninvasive neuromodulation that is capable of precisely modulating brain activity in deep subcortical regions that are out of reach of conventional TMS probes.⁸² Additional stimulation modalities such as transcranial direct current stimulation have been described for chronic pain but are currently unregulated and lack large clinical studies.

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION. TENS is an inexpensive tool that is available for purchase over the counter and FDA cleared for a host of neuropathic, myofascial, and inflammatory pain syndromes. TENS operates on focal areas of the body by administering transcutaneous electrical stimulation associated with a strong but comfortable vibration sensation under the applied pad. Some TENS devices have multiple contact pads that can provide electrical stimulation to multiple body parts in parallel. The sensitivity of TENS to electrode pad placement has ignited a research interest in electroacupuncture.⁸³ TENS is approved for various indications including chronic low back pain, osteoarthritis, fibromyalgia, tendonitis and bursa pain, diabetic neuropathy, and peripheral arterial disease.

Mechanisms supporting TENS are widespread. While blockade of peripheral α -noradrenergic or spinal γ -aminobutyric acid (GABA) and muscarinic receptors abolishes TENS analgesia, TENS promotes the activation of central descending pain inhibitory circuits and the release of endogenous opioids such as β -endorphins and enkephalins in the brain, spinal cord, and CSF.⁸⁴ Electrical pulses can be applied using either low-frequency (1 Hz to 8 Hz, activating μ -opioid receptors) or high-frequency trains (25 Hz to 150 Hz, activating δ -opioid receptors); high-frequency TENS may be more appropriate for opioid-tolerant patients. Although both frequencies have been tested in over 200 randomized clinical trials, one key to proper usage is applying a sufficiently strong amplitude to produce a strong but comfortable paresthesia. Variable amplitudes or frequencies have resulted in conflicting outcome results, a feature overlooked by Cochrane reviews on TENS.⁸⁴

Side effects and risks related to TENS are relatively minimal, with the main concerns being related to skin irritation. However, applying TENS near implanted hardware can cause unpleasant sensations and the repeated use of identical stimulation parameters can result in tolerance or habituation over days to weeks. One way to avoid tolerance may be to alternate low and high frequencies every other day.⁸⁴ Among all neuromodulation modalities, TENS provides the least invasive and safest option for short-term pain relief. Although

analgesia is limited to the duration of stimulation or shortly thereafter, various noninvasive TENS-like devices are commercially available to treat a plethora of pain syndromes,⁸⁵ including many headache types.⁸⁶ The ability to simultaneously recruit peripheral and central mechanisms of pain relief positions TENS as a time-tested treatment that should be considered among other first-line pain therapies.

TRANSCRANIAL MAGNETIC STIMULATION. A variety of cortical regions have been explored as targets for chronic pain using high-frequency repetitive TMS, but multiple rigorous studies identify M₁ as one of the more reliable targets for both invasive and noninvasive pain modulation.^{87,88} Depending on stimulation frequency, TMS can excite or inhibit superficial cortical structures.⁸⁹ High-frequency (ie, greater than 5 Hz) excitatory repetitive TMS is FDA approved as a treatment for major depression at the left dorsolateral prefrontal cortex⁹⁰ and for obsessive-compulsive disorder at the dorsomedial prefrontal cortex.⁹¹ Despite accumulating evidence that high-frequency repetitive TMS at M₁ can be effective for chronic neuropathic pain in select patients,⁸⁸ it is approved for use in the European Union but not the United States. A simplified single-pulse TMS system is FDA approved for the

CASE 8-2

A 61-year-old man presented with a 3-year history of chronic trigeminal distribution neuropathic pain after a dental procedure, involving stinging, burning, and stabbing sensation in the right side of his face including the cheek and lower jaw. His physical examination was significant only for loss of sensation to light touch and pinprick in the right V₂ and V₃ distributions. Brain MRI with contrast including thin cuts through the brainstem did not reveal any compressing vessel near the territory of the trigeminal nerves, so he was not a candidate for microvascular decompression surgery. He had previously been trialed on multiple medications, including nortriptyline, gabapentin, carbamazepine, duloxetine, and opioids, without significant relief. A gasserian ganglion steroid injection provided 40% relief which only lasted for 2 weeks. Before considering neuromodulation, he underwent a brief psychological evaluation by a pain psychologist and was deemed a suitable candidate for further interventions. As an initial noninvasive approach, he underwent transcranial magnetic stimulation (TMS) targeting the left (contralateral) primary motor cortex.

Initially, there was a substantial decrease in his pain ratings post-TMS sessions after 3 daily sessions lasting 30 minutes each. However, this relief was transient and began to wane over subsequent weeks. Given the transient success with TMS, a decision was made to proceed with the implantation of a permanent motor cortex stimulator to provide sustained relief. Two four-contact paddle-type electrodes were placed over the left central sulcus, orthogonal to the axis of the sulcus (**FIGURE 8-6**). Postsurgery, the initial settings on the motor cortex stimulator were as follows: contacts 2+ (anode) and 3- (cathode) were chosen based on their proximity to the primary motor cortex region

treatment of migraine with aura. For chronic pain, the primary indications for repetitive TMS are refractory neuropathic pain syndromes such as trigeminal neuralgia, atypical facial pain, poststroke pain, or others including fibromyalgia and chronic headache syndromes.

TMS generally involves the patient sitting in a chair with their head lightly stabilized. The TMS probe is then positioned over the patient's M1 (eg, hand knob) and the amplitude is slowly increased until an observable twitch is achieved in the thumb (**FIGURE 8-1**). This amplitude value is taken to represent their motor threshold and the actual therapy is applied using 80% of the resting motor threshold or below. High-frequency repetitive TMS involves delivering 3000 pulses or more at 10 Hz or 20 Hz.⁸⁸ Modern systems also use neuronavigation, whereby the patient's structural MRI is used in combination with skull landmarks to target magnetic field therapy more precisely onto a cortical region. Repetitive TMS involves multiple sessions, each usually lasting for 30 to 60 minutes, repeated either daily or every other day for about 1 week. There are new, intensive protocols that provide multiple daily sessions in a condensed format, which were recently FDA approved for major depression.⁹² Although the exact underpinnings through which M1 stimulation alleviates pain remain elusive, there are several plausible theories.^{93,94} Compelling data from

associated with trigeminal nerve representation; frequency: 50 Hz; amplitude: 4 mA; pulse width: 200 μ s. Over the subsequent 3 months, the patient's device settings underwent multiple adjustments based on his feedback and pain relief. While he reported a 30% reduction in pain in the first month, he experienced occasional tingling in his face. Contacts were switched to 1+ (anode) and 3- (cathode) to shift the stimulation slightly, the frequency was increased to 75 Hz, and the amplitude was adjusted to 3.5 mA to mitigate tingling sensations. By the second month, pain reduction was maintained at 40%. He desired further optimization for better daily functioning. Through trial and error, contacts were further optimized to positions 2+ (anode) and 7- (cathode), and the amplitude was increased to 5 mA, given the patient's tolerance and lack of side effects. By the third month, he indicated a pain reduction of up to 70%. However, battery consumption was high, so the frequency was reduced to 60 Hz to conserve battery power and the amplitude was fine-tuned to 4.8 mA. By the end of the third month, with iterative adjustments to the motor cortex stimulator's parameters, he reported a sustained 70% reduction in his trigeminal neuropathy pain without significant side effects.

This case highlights how motor cortex stimulation, an extensively studied but off-label therapy, can be used in select cases to treat refractory facial pain even when the causative injury occurred in a peripheral nerve. By performing an initial noninvasive therapy trial with TMS, positioning of the surgical electrode paddles and prognostication of long-term relief can be personalized for each case. Determining the optimal stimulation parameters for pain relief often requires iterative reprogramming over many months.

COMMENT

high-frequency excitatory M1 repetitive TMS coupled with neuroimaging paints a picture of M1 stimulation igniting a cascading response across a network of brain regions pivotal in pain processing. This includes, but is not limited to, the thalamus, periaqueductal gray, insula, anterior cingulate cortex, and medial prefrontal cortex, a region increasingly associated with the chronicification of pain.⁹⁵ Human studies note the release of endogenous opioids in the anterior cingulate cortex and periaqueductal gray post-motor cortex stimulation, a phenomenon directly associated with pain mitigation.⁹⁶ Concordantly, M1 TMS is reversed by naloxone, akin to some outcomes from periventricular and periaqueductal gray DBS.^{97,98} Delving deeper, some literature suggests a specificity in M1 stimulation's efficacy: it appears more potent for pain localized to the contralateral face and arm while demonstrating reduced outcomes for pain syndromes afflicting the lower extremities or manifesting more diffusely, hinting at potential somatotopic influences.⁹⁹ However, it is also possible that the relative loss of precision with repetitive TMS at deeper targets may contribute to the lack of clinical efficacy.

Compared with other neuromodulation modalities, TMS is generally safer with the main side effect related to scalp irritation. However, TMS is relatively contraindicated in epilepsy, as repeated stimulation could provoke a seizure. Although the therapeutic effects of TMS for pain are short lived, usually dissipating by 1 month, TMS can be used to identify candidates who would benefit from the permanent implant of a motor cortex stimulator (**CASE 8-2**).

DISPARITIES IN NEUROMODULATION CARE

Disparities in access to neuromodulation for pain are significant, particularly for patients using Medicaid who may face reduced access to specialists performing SCS. Patients who were dual-eligible for Medicaid and Medicare in the United States were 62% less likely to receive SCS compared with patients eligible for Medicare alone.¹⁰⁰ In turn, hospitalized patients with private insurance were more than 3 times as likely to receive SCS for a diagnosis of complex regional pain syndrome compared with those with Medicare.¹⁰¹ The specific influence of race on SCS remains unclear, as some studies have found higher utilization rates among White people compared with minority groups,¹⁰¹ while others have found the opposite.¹⁰² Socioeconomic disparities are also reflected in the costs of surgery and outcomes after SCS. While a large observational study found no differences in the 90-day complication rate or overall reoperation rate between Medicaid and commercially insured patients, those with Medicaid had significantly more inpatient hospital days, more trips to the emergency room, more clinic visits, and higher use of prescription medications 2 years after implant.¹⁰³ Future policy efforts at the state and national levels are needed to help identify and mitigate systemic biases that contribute to such health care disparities around neuromodulation therapies.

EMERGING TRENDS AND FUTURE DIRECTIONS

Neuromodulation for chronic pain is experiencing an explosion in research, technology development, and clinical application, while basic underlying mechanisms remain murky. Emerging technologies in peripheral nerve stimulation and spinal cord stimulation use unique proprietary waveforms that may improve efficacy but represent incremental advances over existing methods. Intrathecal drug delivery has been used clinically since the 1980s, but there has been a lack of new drug development or changing clinical practice over recent decades. Spinal cord

stimulation technology developed for the treatment of chronic pain has been used investigationally in patients with complete spinal cord injury to stimulate anterior motor neurons and restore motor function such as walking above ground against the full force of gravity (ie, not in a pool or other supportive environment) in patients with paraplegia.⁴⁵ In some cases, motor function remained restored even after turning spinal cord stimulation off. These findings hold promise for tonic or patterned spinal cord stimulation to be developed for future applications in motor rehabilitation and restoring function after severe neurologic injury.⁴⁶

For spinal cord stimulation and DBS, a recent trend has been to use simultaneously recorded electrophysiologic signals that track stimulation effects or symptoms to control stimulation parameters in real time with “closed-loop” protocols.^{51,104} Such feedback control holds promise to provide personalized optimization of therapy, but evidence for superior efficacy is nascent. In the future, intrathecal drug delivery may theoretically be able to adaptively control drug infusion in response to putative serum pain biomarkers, much like how modern insulin pumps operate.

All brain stimulation technologies for chronic pain are still off label in the United States, but a greater appreciation for central mechanisms in chronic pain suggests that modulating brain networks will be critical to the future of pain neuromodulation, especially for treating refractory cases. There is emerging interest in low-intensity focused ultrasound as a novel noninvasive brain neuromodulation tool for chronic pain and other disorders. Advances in neuroimaging and the discovery of novel pain biomarkers may also help to improve anatomic targeting of neuromodulation therapies. Modern controversies surrounding the efficacy and safety of pain neuromodulation devices largely result from mixed results from limited sham-controlled trials and possible bias from conflicts of interest related to trial funding. Future clinical trials in pain neuromodulation would benefit from adhering to the rigorous guidelines developed by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials¹⁰⁵ and assessing key functional activity metrics together with patient-specific goals in addition to pain symptom ratings.

CONCLUSION

Neuromodulation devices for pain currently offer myriad strategies to modulate the electrical and chemical activity of the nervous system, without a comprehensive understanding of how that activity reflects pain or key mechanisms of action of electrical stimulation. Therefore, in many ways, the technology is ahead of the science. Further research into mechanisms of action of electrical stimulation is needed before most neuromodulation therapies can help most patients with chronic pain. However, modulating neural activity from peripheral nerves to the brain has undoubtedly improved the lives of many individual patients and restored physical and social functioning in ways that medication alone cannot achieve. It is important to emphasize that neuromodulation devices are not a panacea, but instead are most effectively used as part of a multimodal pain treatment plan. By working with an interdisciplinary team (ie, pain specialists, psychologists, and neurologic surgeons) and using evidence-based guidelines, neurologists can aid in selecting the right neuromodulation therapy for the right patient.

USEFUL WEBSITES

INTERNATIONAL NEUROMODULATION SOCIETY

A nonprofit professional organization for clinicians, scientists, and engineers promoting neuromodulation research, education, and accessibility, and publisher of the journal *Neuromodulation*.

neuromodulation.com (International Neuromodulation Society)

NEUROMODEC

A website featuring news and editorial pieces on neuromodulation technology and policy, educational topics, and patient resources for locating neuromodulation specialists.

neuromodec.org

NORTH AMERICAN NEUROMODULATION SOCIETY

The North American chapter of the International Neuromodulation Society.

neuromodulation.org

SCS e-HEALTH TOOL

A web-based clinical decision tool for assessing the appropriateness of spinal cord stimulation.

scstool.org

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DISCLOSURE

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Chronic Pain Psychology in Neurology Practice

By Mirsad Serdarevic, PhD

REVIEW ARTICLE



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ABSTRACT

OBJECTIVE: This article reviews the latest literature regarding chronic pain epidemiology and describes pain-specific psychological factors associated with the development and maintenance of chronic pain, mental health conditions that co-occur with chronic pain, and advances in the psychobehavioral treatment of chronic pain, including established treatments (ie, cognitive behavioral therapy [CBT], acceptance and commitment therapy, and mindfulness-based stress reduction) and emerging treatments (ie, pain reprocessing therapy).

LATEST DEVELOPMENTS: In addition to CBT and acceptance and commitment therapy for pain, numerous other psychological treatment modalities have been integrated into chronic pain management, including mindfulness-based stress reduction, mindfulness meditation, chronic pain self-management, relaxation response, pain neuroscience education, biofeedback, hypnosis, and, more recently, integrative psychological treatment for centralized pain. This article gives an overview of these methods and contextualizes their use within the standard psychological treatment of chronic pain.

ESSENTIAL POINTS: Guided by the biopsychosocial treatment model, pain psychologists use numerous evidence-based psychological methods to treat patients with chronic pain conditions. Familiarity with the psychological tools available for pain management will aid neurologists and their patients in navigating the psychological aspects of living with chronic pain.

INTRODUCTION

The incidence of chronic pain is 52.4 cases per 1000 people per year and it affects approximately one-fifth to one-quarter of the US population.^{1–4} Pain is the most common presenting symptom in the emergency department and often the initial symptom that brings a patient to the physician's office.³ Neurologists commonly see patients with neuropathic pain, low back pain, myofascial pain, complex regional pain syndrome, and other painful conditions covered in this issue of *Continuum*. Given that chronic pain is a complex biopsychosocial disease that can affect all aspects of life including mood, social life, cognition, physical health, and functioning, an interdisciplinary approach is the preferable treatment for chronic pain, as medication alone cannot break the pain cycle.⁵ Indeed, both psychological

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KEY POINTS

- The incidence of chronic pain is 52.4 cases per 1000 people per year.
- Given that chronic pain is a complex biopsychosocial disease that can affect all aspects of life including mood, social life, cognition, physical health, and functioning, it comes as no surprise that interdisciplinary treatment is the only reliable treatment for chronic pain as medication alone and procedures alone cannot break the pain cycle.
- Acceptance and commitment therapy and cognitive behavioral therapy are the psychological pain interventions that have shown the strongest evidence of benefit and cost effectiveness.
- Research on the effectiveness of cognitive behavioral therapy for pain in patients with chronic pain has shown gray matter volume increases in the posterior parietal cortex, bilateral dorsolateral prefrontal cortex, and other sensory, motor, and affective regions of the brain also associated with pain control.

and biological factors contribute to the dynamic, multidirectional relationship between pain, anxiety, and depression. Advances in real-time imaging have enabled neuroscientists to observe that “suffering from both physical injury and psychological trauma share circuits in the brain.”⁶ For example, the amygdala, hypothalamus, and anterior cingulate cortex, regions of the brain implicated in anxiety and depression, interact with the somatosensory cortex to produce the psychological and biological experience of pain. **TABLE 9-1** summarizes how psychotherapeutic treatments correlate with psychological changes.⁷

Given the complex interplay between the biological, psychological, and social factors contributing to chronic pain, the biopsychosocial model is the most optimal theoretical approach to comprehensive chronic pain care. Indeed, according to the National Institutes of Health (NIH) Interagency Pain Research Coordinating Committee, “chronic pain is a biopsychosocial condition”⁸ and as such it requires a multidisciplinary treatment approach.

It is helpful to think of pain as a continuum, with the two ends representing acute pain (lasting 0 to 3 months) and chronic pain (greater than 6 months), with transitional pain (lasting 3 to 6 months) lying in the middle. Acute-onset pain affects patients’ behavior almost instantaneously (eg, when experiencing the initial onset of lumbar radiculopathy, patients may alter regular daily activities, miss work or school, or stop exercise programs). When patients continue to think of their pain as an acute pain that has not been resolved beyond 6 months after the onset of pain, they will likely engage in common avoidant behaviors and experience the characteristic components of chronic pain syndrome, including fear of movement, deconditioning, muscular atrophy, sleep disturbance potentially progressing to insomnia, depression and anxiety, weight gain, sexual dysfunction, and addiction. Pain psychology interventions involve psychoeducation, including providing basic pain neuroscience education using a conceptual model (eg, the gate control theory of pain; see **TABLE 9-2**⁹) that illustrates the multidimensionality of chronic pain. Specifically, the key elements of psychological interventions for pain are the following:

- ◆ Decrease pain focus
- ◆ Increase goal-oriented and value-oriented living
- ◆ Improve perceptions of control
- ◆ Address any mental health comorbidities
- ◆ Adopt pacing strategies
- ◆ Improve relationships and increase support systems
- ◆ Increase function
- ◆ Improve physical fitness

Unlike acute pain, which is defined as lasting less than 3 months and which serves the adaptive role of initiating protective behaviors that prevent further tissue damage, chronic pain does not have an adaptive function as it persists long after tissue has healed. Research literature has demonstrated that, in addition to numerous medical factors, psychosocial factors are associated with the development and maintenance of chronic pain. For example, *pain catastrophizing* occurs when patients have unhelpful, negative, or exaggerated thoughts about their pain (eg, “This pain is awful, horrible, and will only get worse.”); this

catastrophizing and the fear of pain are common psychological factors associated with pain persistence following an acute injury or surgery.

This article provides an overview of the pain-specific psychological factors involved in the development and maintenance of chronic pain, the most common mental health conditions that co-occur with chronic pain, and evidence-based psychological treatments for patients with chronic pain, with a special focus on acceptance and commitment therapy and cognitive behavioral therapy (CBT). Finally, this article provides policy and communication strategies to help patients who are reluctant to see pain psychologists.

PAIN-SPECIFIC PSYCHOLOGICAL FACTORS

The International Association for the Study of Pain (IASP) defines pain as “[a]n unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.”¹⁰ The term *emotional experience* places psychological factors into the IASP’s definition of pain for a reason. Indeed, pain catastrophizing, fear of pain, fear of movement, pain-related anxiety, and pain self-efficacy are some examples of pain-specific psychological factors that are also potent targets for psychological treatments for patients with chronic pain. Furthermore, these pain-specific psychological factors correlate with volumetric changes seen on brain MRI. For example, people who catastrophize show atrophy in the regions of the brain associated with pain control, including volumetric decreases in the prefrontal cortex.¹¹ Research on the effectiveness of CBT for pain in patients with chronic pain has shown gray matter volume increases in the posterior parietal cortex, bilateral dorsolateral prefrontal cortex, and other sensory, motor, and affective regions of the brain also associated with pain control.¹¹ Seminowicz and colleagues¹¹ found that increased gray matter volume in prefrontal and parietal areas was related to decreased pain catastrophizing. These findings showed that following CBT for pain, the brain has better top-down regulation of pain, a cognitive reevaluation of pain, and a shift in how noxious signals are perceived.¹²

Correlation Between Psychological Treatments and Psychological Functions^a

TABLE 9-1

Psychological treatments and interventions	Psychological functions
Cognitive behavioral therapy (CBT), acceptance and commitment therapy (ACT), mindfulness	Cognition, attention, interoception
Progressive muscle relaxation, sleep hygiene	Stress, autonomic dysregulation, sleep
Goal setting	Motivation, sensorimotor processing
Exposure treatment (CBT, ACT)	Fear and anxiety
CBT, cognitive reappraisal	Depression, anxiety
Behavioral activation (CBT, ACT)	Anhedonic state

^a Data from Simons LE, et al, Neurosci Biobehav Rev.⁷

In addition to pain catastrophizing, many patients with chronic pain engage in fear-avoidance behaviors, which frequently involve the avoidance of physical activities patients believe will lead to pain, but which actually lead to deconditioning and often more pain. Education about the neurophysiology of pain has been shown to lead to a better understanding of pain, which is associated with a decrease in fear-avoidance behaviors and better outcomes.¹³ Furthermore, patient engagement in CBT for pain and other psychological treatment modalities may be facilitated by patient education on the science of pain psychology treatment.¹⁴ TABLES 9-3A and 9-3B summarize how pain-specific psychological factors impact patients with chronic pain and how psychological treatments can change emotions, behaviors, and the perception of pain by focusing on changing unhelpful beliefs about the pain (eg, pain catastrophizing).

The assessment of pain catastrophizing is an important part of both preprocedure (eg, evaluations for candidacy for implantable devices such as spinal cord stimulators, peripheral nerve stimulators, or intrathecal pumps) and general psychological evaluations. Pain catastrophizing is associated with worse health behaviors, including reduced physical capacity,¹⁵ reduced engagement with exercise,¹⁶ and, among patients with acute low back pain, reliance on bed rest and rejection of exercise, which over time lead to deconditioning.^{17,18} The Pain Catastrophizing Scale is a 13-item questionnaire describing different thoughts and feelings that may be associated with pain and includes subscales assessing for rumination, magnification, and the degree of helplessness.¹⁹ A total score of 30 or greater represents a clinically significant level of pain catastrophizing. Greater levels of pain catastrophizing are associated with emotional distress, muscle tenderness,²⁰ muscle tension, and pain intensity.²¹

COGNITIVE BEHAVIORAL THERAPY FOR CHRONIC PAIN

According to the literature,²²⁻²⁴ CBT is considered the standard psychosocial intervention for chronic pain. CBT for pain is about changing one's relationship with and response to pain to lessen its impact on functioning and quality of

TABLE 9-2

Gate Control Theory of Pain^a

Factors	Open the pain gate	Close the pain gate
Physical	Extent of the injury, readiness of the nervous system to send pain signals, inappropriate activity level	Application of heat or cold, massage, relaxation skills (to lower readiness of the nervous system), appropriate activity level
Emotional	Depression, worry, anxiety, tension, anger	Avoiding excessive emotions, positive emotions, managing stress
Mental	Focusing on the pain, boredom due to minimal involvement in life activities, nonadaptive attitudes	Distraction from pain, increased social activities, positive attitudes
Behavioral	Withdrawal from positive life activities, poor health habits	Increased positive life activities, appropriate exercise, healthy eating, refraining from unhealthy habits

^a Data from Hunter CL, et al, American Psychological Association.⁹

Common Pain Beliefs and Consequences^a

TABLE 9-3A

Belief	Emotional consequences	Behavioral consequences
"This pain is the worst. It will never get better."	Low mood, anxiety, irritability	Withdrawal from general activity (leading to deconditioning and more pain), social withdrawal, reliance on pain medication
"Any physical activity is harmful."	Fear of pain, fear of movement	Avoidance of activity, stopping physical therapy or other treatments and medical regimens, withdrawal from most activities
"This is a medical condition and I will find a medical cure."	Feeling of helplessness or anxiety, dependence on doctors and medical system to alleviate anxiety	Delay in pain self-management at home, overly relying on pain medication, delays in physical therapy and other medical regimens
"When I find the right surgeon, this pain will finally be resolved and I will be my old self."		

^a Data from Darnall BD.¹⁴

Common Pain Beliefs and Consequences Following Psychological Treatments

TABLE 9-3B

Belief	Emotional consequences	Behavioral consequences
"This pain is 9 out of 10. I dealt with it before and I can do it again."	Less decrease in mood, less increase in anxiety, less irritability	Engaging in some activity, engaging in social activities, focusing on problem solving (eg, heating pad, stretches, appropriate use of medication)
"If I practice activity pacing and have realistic expectations of what I can do, activity is good for me."	Less fear of movement, less fear of pain	Less avoidant behaviors, continuous engagement in physical therapy or other treatments and medical regimens, engaging in activities
"This is a biopsychosocial condition that requires me to work on things that I'm able to work on, like keeping my stress low through relaxation strategies, managing my mood, and keeping positive relationships. I will continue to see my doctors to work on improving physical aspects of pain, but in the meantime, there is a lot I can do for myself."	Lessened feeling of helplessness, less anxiety, less dependence on doctors and medical system to alleviate anxiety	Engagement in pain self-management at home, less reliance on pain medication, engagement in physical therapy and other medical regimens

^a Data from Darnall BD.¹⁴

life.^{25,26} The focus of CBT for pain is on how one's beliefs, emotions, physiologic responses, and behaviors affect the experience of pain, and it extends beyond the forms of CBT used to treat depression and anxiety.

First, CBT for pain includes pain education that introduces patients to a conceptual model, such as the gate control theory of pain (TABLE 9-2). This theory suggests that pain signals do not automatically or directly reach the brain; rather, a “gate mechanism” that controls the amount of pain signals that reach the brain is located within the spinal cord, and more pain signals pass through when the gate is open than when it is closed.

CASE 9-1

A 46-year-old woman with a lumbar radiculopathy was referred to the pain clinic for help managing her ongoing chronic pain. Her pain fluctuated in severity, so during periods of relatively low pain, she felt pressure to complete tasks that had been neglected for weeks. However, a day of intense productivity would lead to another pain flare that required her to take time off and would frequently leave her feeling frustrated, helpless, and anxious. She had already pursued numerous pharmacologic and procedural interventions, which were incompletely effective, and she was not a candidate for spine surgery.

After beginning cognitive behavioral therapy (CBT) for pain, she learned several important things about chronic pain and self-management of chronic pain. First, she was provided with basic pain neuroscience education and discovered that chronic pain is a complex biopsychosocial disease that can affect all aspects of life, including mood, social life, cognition, and physical health and functioning. By using a conceptual model (ie, the gate control theory of pain; TABLE 9-2), she was able to understand how physical, psychological, and social factors are interrelated. She also learned about the dynamic relationship between pain, anxiety, and depression, and how unhelpful thoughts (eg, pain catastrophizing) could lead to irritability, anxiety, or lower mood, all of which can make the experience of pain more intense. By managing her stress and anxiety she was indirectly lowering pain volume as well. Second, she learned to set realistic expectations for herself rather than pushing to do too much at once. Third, she learned about activity pacing principles and focused on keeping a steady and consistent pace rather than the intensity of the activity. Pacing principles helped the patient develop a daily activity routine at the right level of intensity and prevented deconditioning. Finally, she developed a better awareness of her thoughts; for example, when she was unable to cook meals at home, she had self-critical thoughts, which she learned to challenge through CBT for pain-specific homework and experienced an improvement in her mood.

COMMENT

This case illustrates the basic principles of CBT for pain: pain education, discussing pain catastrophizing, activity pacing, pain beliefs, pain-specific cognitive reframing, relaxation training, pain-specific mood regulation, pain-specific problem solving, exercise and movement, and goal setting.

These types of conceptual models teach the skills needed to manage maladaptive cognitive and behavioral processes related to chronic pain. Patients are also educated on the dynamic, bidirectional relationship between pain and stress and are provided with an overview of stress management strategies, helping them understand that by managing stress they will, indirectly, manage pain too.

Second, patients learn about activity pacing, which helps them focus on consistency of activity rather than intensity. For example, patients are taught that by pacing activities they can avoid pain flares and fatigue.

Third, special focus is placed on pain catastrophizing, pain beliefs, and cognitive reframing specific to pain. For example, patients are taught how to decrease pain catastrophizing through cognitive reappraisal. Topics unique to CBT for pain include relaxation training and problem-solving and mood regulation strategies specific to pain.

Fourth, given the dynamic relationship between pain and sleep, with high rates of insomnia among patients with chronic pain, CBT for pain includes a focus on sleep hygiene.

Finally, exercise, movement, and goal setting are emphasized. Patients are also expected to do structured homework and implement the skills learned during sessions. For a clinical application of key features of CBT for pain, see **CASE 9-1**.

ACCEPTANCE AND COMMITMENT THERAPY

Acceptance and commitment therapy extends previous forms of CBT and integrates many CBT-related variables into core therapeutic processes. Indeed, acceptance and commitment therapy is often described as a modified form of CBT and, like CBT, it has achieved the status of a well-established treatment for chronic pain.²⁷ Acceptance and commitment therapy emphasizes how suffering emerges predominantly within the context of thought and language.²⁸ Specifically, acceptance and commitment therapy consists of six core therapeutic processes: psychological flexibility, flexible present-focused attention, cognitive diffusion, self-as-context, values, and committed action.

Although chronic pain symptom reduction can happen in acceptance and commitment therapy, it is not the primary focus; the goal is to increase psychological flexibility and reduce the dominance of pain in a person's life.²⁷ The capacity to persist and change behavior, including open contact with discomfort and other discouraging experiences while being guided by value-based goals, are defining characteristics of psychological flexibility. Acceptance and commitment therapy suggests that by developing psychological flexibility, patients with chronic pain become better able to actively accept pain while engaging in their value-based goals and daily activities. By practicing mindfulness, acceptance is further bolstered, which helps patients become nonjudgmental observers of their feelings, thoughts, and sensations, which helps reduce their reactivity and increase their psychological flexibility. Further, acceptance and commitment therapy is a process-based therapy that fosters awareness, openness, and engagement through methods such as the use of therapeutic metaphors (ie, metaphors used as a tool to help patients express their experiences symbolically), experiential and exposure methods, and values clarification. The final subprocess that is theorized to underlie psychological flexibility involves separating the self from the experiences that the self is having and is termed *self-as-context*.²⁸

KEY POINTS

- Cognitive behavioral therapy for pain is about changing one's relationship with and response to pain to lessen its impact on functioning and quality of life and focuses on how one's beliefs, emotions, physiologic responses, and behaviors affect the experience of pain.

- The gate control theory of pain suggests that pain signals do not automatically or directly reach the brain; rather, a "gate mechanism" that controls the amount of pain signals that reach the brain is located within the spinal cord, and more pain signals pass through when the gate is open than when it is closed.

- Acceptance and commitment therapy is a psychological intervention that integrates many cognitive behavioral therapy-related variables into core therapeutic processes. The goal of acceptance and commitment therapy is to increase psychological flexibility and reduce pain's dominance in a person's life.

- Mindfulness-based treatments of chronic pain, including most widely used mindfulness-based stress reduction techniques, aim to cultivate acceptance through nonjudgmental, purposeful attention to the present moment.

- Mindfulness-based treatments for chronic pain can be used alone or in combination with other treatments, such as cognitive behavioral therapy and acceptance and commitment therapy.

Literature supports the effectiveness of acceptance and commitment therapy for chronic pain and many studies focused on specific processes derived from the psychological flexibility model.²⁷ The most recent meta-analyses and systematic reviews have shown that acceptance and commitment therapy produced medium to large effects on pain acceptance and psychological flexibility compared with control.²⁹⁻³¹ These studies have also shown small effects on quality of life, pain intensity, physical functioning, and disability favoring acceptance and commitment therapy at 3-month and 6-month follow-ups. For examples of clinical applications of acceptance and commitment therapy, see [CASE 9-2](#).

MINDFULNESS-BASED TREATMENTS

Although originating from Buddhist practices, contemporary and westernized mindfulness-based treatment protocols are typically presented as secular meditation practices and aim to cultivate acceptance through nonjudgmental, purposeful attention to the present moment.³² Through mindfulness practices, patients learn to use breath or other sensory perceptions as an anchor to the present moment. Focusing on the breath helps patients become more distant observers of their thoughts and emotions. Mindfulness-based stress reduction was among the early psychological treatments used in chronic pain management.³³ Overall, a meta-analysis of 30 randomized controlled trials found that mindfulness-based treatments for chronic pain produced medium effects on physical and mental health and quality of life and small effects on depression.³⁴

Mindfulness meditation practices have also been integrated into other treatments. For example, mindfulness-based cognitive therapy integrates cognitive restructuring with mindfulness meditation practices. Mindfulness is also an important component of acceptance and commitment therapy as it bolsters acceptance, helping patients become more accepting and nonjudgmental observers of their thoughts, emotions, and painful sensations, thereby increasing their psychological flexibility while reducing reactivity.³²

OTHER PSYCHOLOGICAL TREATMENTS FOR CHRONIC PAIN

Although it is beyond the scope of this article to report on the details of all psychological treatments used for chronic pain, it is important to summarize some key features of biofeedback, clinical hypnosis, and integrative psychological treatment for centralized pain and discuss the components of psychological treatments shared across all interventions. While acceptance and commitment therapy and CBT are the most established psychological treatments,³⁵ other psychological treatments have also shown varying evidence of benefit.³⁶⁻³⁸

Biofeedback provides immediate audible or visual cues to the patient regarding changes in physiologic activity (eg, heart rate, muscle tension, respiration) using precise instrumentation. Patients gain awareness and control of their physiologic responses through such feedback, leading to improved psychological and physiologic functioning.³⁹ Combining biofeedback interventions with CBT or physical therapy demonstrated better outcomes than biofeedback treatment alone³⁶; however, due to the need for precise measurements and additional provider training requirements, implementing biofeedback therapy across larger health care systems remains challenging.

Clinical hypnosis involves the patient entering a state of focused attention, allowing for more openness to suggestions for changes in behaviors, sensations, and thoughts.³² Hypnosis is divided into two phases: an induction phase, followed by specific suggestions for therapeutic change.³² During the induction phase, the clinician asks the patient to suspend critical thinking and focus their attention, followed by hypnotic suggestion targeting decreased pain sensation or intensity and increased comfort and ability to function even in the presence of pain.³² The literature supports the use of clinical hypnosis for chronic pain⁴⁰; however, given that clinical hypnosis requires specialized training, its implementation in health care systems remains challenging.

Unlike other psychological treatments, which rarely differentiate different types of chronic pain, integrative psychological treatment for centralized pain acknowledges the heterogeneity of chronic pain.⁴¹ Further, given that

CASE 9-2

A 38-year-old woman had postlaminectomy syndrome and associated chronic pain. She pushed herself at work and home and ignored early signs of pain and exhaustion until she ran out of energy entirely. She was on a short-term disability leave from work and expressed significant anxiety related to the uncertainty of her health status, being away from work, and whether she would be able to go back. After many medical treatments and numerous procedures, she expressed a lack of trust in the medical system and a good deal of frustration with health care insurance, noting the “many appointments” with different doctors that left her exhausted at the end of the week.

The patient was also hesitant to start psychotherapy but shared that she was willing to try it. Understanding that the patient was ambivalent about treatment, her psychologist did not try to convince her of what she “should” do, and instead validated her concerns and provided a supportive environment in which the patient gradually started to feel safe and comfortable. Establishing strong therapeutic rapport allowed the psychologist to share basic psychoeducation on the dynamic and often bidirectional relationship between pain and psychological factors. The patient was educated on acceptance and commitment therapy methods and was informed that, while acceptance and commitment therapy may lead to a reduction of pain symptoms, this was not its primary purpose. Rather, she would learn to reduce the dominance of pain in her life by increasing psychological flexibility and learning to actively accept pain while engaging in her value-based goals and daily activities.

The patient also expanded on her already existing elementary knowledge of mindfulness practices, which led to reduced reactivity, more patience in her relationships, and improvement in daily task performance.

This case illustrates the integration of common factors in psychotherapy (eg, rapport-building, validation, reflective listening) and mindfulness practices into acceptance and commitment therapy.

COMMENT

KEY POINTS

- Biofeedback provides immediate audible or visual cues to the patient regarding changes in physiologic activity (eg, heart rate, muscle tension, respiration) using precise instrumentation. Patients gain awareness and control of their physiologic responses through such feedback, leading to improved psychological and physiologic functioning.
- Clinical hypnosis for chronic pain treatment involves the patient entering a state of focused attention, allowing for more openness to suggestions for changes in behaviors, sensations, and thoughts. Clinical hypnosis is divided into two phases: an induction phase, followed by specific suggestions for therapeutic change.
- Integrative psychological treatment for centralized pain, which includes pain reprocessing therapy, focuses on treating patients whose pain is either partially or completely centralized (ie, nociceptive or somatoform).

psychological factors are more strongly associated with the etiology and maintenance of nociceptive pain than other types of pain (ie, neuropathic, inflammatory, or nociceptive),⁴² it was proposed that integrating emotional processing and interpersonal changes into treatment would help patients with adverse life experiences and psychological conflicts, two factors that play an important role in centralized pain.⁴¹ Centralized pain presents as diffuse sensation (eg, fibromyalgia), functional visceral pain (eg, irritable bowel syndrome, bladder pain syndrome), or regional somatic sensitization.⁴³ For more on nociceptive pain syndromes, refer to the article “Chronic Widespread Pain” by Narayan R. Kissoon, MD,⁴⁴ in this issue of *Continuum*.

Specifically, researchers have argued that integrative psychological treatment for centralized pain is best suited for patients dealing primarily with centralized pain.⁴¹ The five major components of the treatment are education about pain, reduction of perceived danger, increasing adaptive behaviors, facilitating emotional processing, and encouraging adaptive interpersonal communication.⁴¹ Education helps the patient understand that pain is real and caused by central processes. Reduction of perceived danger is achieved through retraining the brain’s neural pathways and reducing the pain alarm. This is sometimes referred to as *pain reprocessing therapy*.⁴¹ Patients learn to view their pain through a “safety lens” and remind themselves that there is no danger, and while the sensations are real, they are also temporary.⁴¹ Patients also learn to gradually increase adaptive behaviors and reduce avoidance of activities due to pain. The facilitation of emotional processing is especially important for patients whose pain is linked to a broader pattern of avoided places, memories, relationships, and other emotion-eliciting experiences stemming from conflicts or adverse life experiences.⁴¹ Expressive writing exercises (eg, “unsent letters,” “free writing”) facilitate access to feelings, memories, and current stressors by facilitating in-session processing of avoided emotions.⁴¹ Finally, as in acceptance and commitment therapy, patients are encouraged to reengage with valued activities. Patients learn to set boundaries and express desires within their social settings. Roleplaying involving how patients might interact with key people in their lives is a common intervention that encourages adaptive interpersonal communication.⁴¹ However, the integrative approach faces a range of challenges, including the fact that many patients experience pain with a combination of centralized and noncentralized (nociceptive and neuropathic) processes. For a summary of psychological treatments for patients with chronic pain, see **TABLE 9-4**.⁴⁵

In addition to the specific psychological treatments mentioned above, it is important to acknowledge common factors across psychological treatments that have been shown to contribute to improvements in treatment outcomes.³² Specifically, therapeutic alliance, patient expectations, and specific intervention ingredients have been shown to contribute to meaningful improvements in outcomes across psychological interventions.³² Empathy and positive regard are components of therapeutic relationships that contribute to stronger therapeutic alliance and, along with psychological interventions for chronic pain, are related to improved treatment outcomes.³² Research has also shown that patients who perceive that their medical provider demonstrates active listening, collaboration, empathy, and patient-centered communication report higher self-efficacy for managing chronic disease, which is related to lower pain severity and interference.⁴⁶

Psychological Treatments for Chronic Pain^a

TABLE 9-4

Psychological treatment	Description of treatment strategy	Key features	Painful conditions	Outcomes
Acceptance and commitment therapy	Aims to reduce the dominance of pain in a patient's life while increasing value-based activities	Acceptance and psychological flexibility	Broadly applied to chronic pain	Small to medium effects on physical functioning and mood
Cognitive behavioral therapy	Aims to challenge and change maladaptive thoughts and behaviors	Reduction in maladaptive cognitions (eg, pain catastrophizing), better coping with pain, and improved sleep	Musculoskeletal pain, neuropathic pain, headache	Small to moderate improvements in functional disability, mood, and pain
Mindfulness-based interventions	Aims to separate pain from emotional suffering by nonjudgmentally focusing on the moment-to-moment experiences and using the breath as an "anchor" to the present moment	Acceptance and psychological flexibility	Broadly applied to chronic pain	Pain outcomes vary by condition; improvements in emotional well-being; reduction in pain-related distress
Clinical hypnosis	Aims to induce openness to suggestions for changes in behaviors, thoughts, and sensations	Dampens neural activity responsible for pain and its transmission	Fibromyalgia, arthritis, back pain, mixed pain conditions, and temporomandibular disorders	Small to moderate improvements in physical functioning, mood, and pain intensity
Biofeedback	Uses sophisticated equipment to monitor physiologic activity and helps the patient improve control of automatic bodily functions	Regulation of the stress response, self-efficacy	Back pain, fibromyalgia, headache	Small to moderate improvements in physical functioning, muscle tension, depression, and pain intensity
Integrative treatment for centralized pain (which includes pain reprocessing therapy)	Focuses on working with patients whose pain is either partly or completely centralized (eg, nociceptive, somatoform)	Education about pain, reduction of perceived danger, increasing adaptive behaviors, facilitating emotional processing, encouraging adaptive interpersonal communication	Diffuse sensitization (fibromyalgia) and other nociceptive pain	Recently developed treatment; future studies needed to evaluate effects, although its component parts (eg, acceptance and commitment therapy, pain education) have been shown to be effective

^a Data from Driscoll MA, et al, *Psychol Sci Public Interest*⁴⁵ and Lumley MA and Schubiner H, *Psychosom Med*.⁴¹

STRATEGIES FOR IMPROVING PAIN PSYCHOLOGY TREATMENT INITIATION RATES

Given that research has shown that approximately 50% of patients referred to pain psychology do not initiate treatment,⁴⁷ it is important to discuss communication strategies that referring neurologists can use and clinical operations and scheduling strategies that have been shown to increase referral initiation rates.

Referring neurologists could consider introducing pain psychology services early on in treatment, even before thinking of a referral, as that will help patients view these services as part of comprehensive pain management, thereby reducing the stigma often associated with mental health services. Providing information and psychoeducation (eg, a summary of the gate control theory of pain) has also been associated with improvements in initiation rates.⁴⁸

The following is an example of framing pain psychology as an important part of multidisciplinary pain treatment: “As part of your pain management multidisciplinary team, we have a pain psychologist who provides support with managing pain in daily life and helping people still live valued lives even when living with chronic pain. Sometime in the future, we might recommend you meet with a pain psychologist for an evaluation to see what additional treatment supports they might recommend.” Also, consider normalizing psychology services by using the following example: “Athletes use sports psychologists to help them with their performance, and you can think of a pain psychologist as helping you with living a valued life even when faced with chronic pain. Pain psychology also uses general health and wellness approaches, like mindfulness-based stress reduction, which are frequently used by the general public and are not exclusive to mental health services.”

In addition to communicating about pain psychology early on in treatment, it is important to identify barriers to seeking psychology services, including socioeconomic and cultural barriers (eg, cost, transportation, language, health insurance). Patients facing transportation problems could use telehealth treatment services when appropriate, and those for whom language is a potential barrier could use professional translation services.

DISPARITIES IN PAIN MANAGEMENT

Although everyone experiences pain, there are known differences in how ethnic, racial, gender, socioeconomic, and other sociodemographic groups are assessed and treated for pain.⁴⁹ For example, compared with White patients, Black patients are less likely to be prescribed opioids and referred to pain specialists.⁴⁹ Similarly, those who self-identify as women are prescribed opioids less frequently and receive less intensive treatment for their pain, despite experiencing and reporting more severe pain than men.⁴⁹ There are also differences in health care coverage and access, geographic location, and socioeconomic status, as patients of lower socioeconomic status who report higher levels of postoperative pain receive fewer opioid prescriptions than patients of higher socioeconomic status.⁴⁹ Also, when it comes to managing chronic pain, lesbian, gay, bisexual, transgender, and queer (LGBTQ+) patients have different needs than straight, cisgender people.⁵⁰ Compared with heterosexual adults, sexual minority adults are more likely to have multiple pain sites and experience more frequent functional limitations as a result of pain.⁵⁰ Lesbian, gay, and bisexual adults

experience higher rates of depressive symptoms and disorders than heterosexual individuals.⁵¹

Wang and Jacobs⁴⁹ proposed five approaches to promote fairness in pain treatment and enhance overall patient outcomes via research, policy, advocacy, and delivery of health care. The first approach is to standardize pain assessment guidelines and protocols to assess multiple dimensions of pain.⁴⁹ For example, standardized assessment tools such as numeric rating scales and visual analog scales have demonstrated greater reliability in quantifying pain across language and cultural barriers.⁴⁹ The second approach is to adapt pain management approaches and contextualize care for diverse populations. For example, when asking about pain, rather than solely relying on a numerical scale, it may be more informative to ask patients to describe their current pain compared with previous experiences or how their pain impacts daily living activities. The third approach is to promote collaborative provider-patient decision making and support patients as part of a larger community.⁴⁹ This collaborative approach involves including key individuals such as family members in developing care strategies to mitigate risk and discomfort at home and connect patients with available support systems and community resources.⁴⁹ The fourth approach is to invest in and support intervention research to inform evidence-based practices. Indeed, researchers should recruit diverse study populations and develop intervention approaches and evaluation methods in collaboration with key stakeholders, such as patients and patient advocates.⁴⁹ Finally, researchers emphasize the importance of advocating for policies that promote better access to and care in pain management. For example, systemic and broader structural factors need to be addressed, such as advocating for insurance coverage of evidence-based pain treatment and improving access to comprehensive pain management.⁴⁹

The ADDRESSING approach⁵² (**a**ge and generational influences, **d**evelopmental and acquired **d**isabilities, **r**eligion and spiritual orientation, **e**thnicity, **s**ocioeconomic status, **s**exual orientation, **i**ndigenous heritage, **n**ational origin, **g**ender) is a practical framework that clinicians can use when working with diverse populations that begins with an emphasis on understanding the impact of a clinician's worldview of diverse cultural influences (eg, the clinician's age and generational experiences, experience with disability, religious or spiritual upbringing, ethnicity). By recognizing areas in which they are members of dominant groups (eg, being nondisabled), clinicians will become more aware of ways in which such identities can limit their knowledge base and experience, particularly regarding cultures different than their own.

KEY POINTS

- In pain reprocessing therapy, patients learn to view their pain through a “safety lens” and remind themselves that there is no danger, and while the sensations are real, they are also temporary.
- The ADDRESSING approach (age and generational influences, developmental and acquired disabilities, religion and spiritual orientation, ethnicity, socioeconomic status, sexual orientation, indigenous heritage, national origin, gender) provides a framework for understanding the impact of a clinician's worldview of different cultures on patient care.

CONCLUSION

Psychological interventions for chronic pain have emerged as integral components of effective multidisciplinary treatment thanks to establishing the biopsychosocial model of pain⁴⁵ as a consensus best practice. These interventions are effective at improving psychological, social, and physical functioning.⁵³ Acceptance and commitment therapy, CBT for pain, and mindfulness-based stress reduction are well-established, evidence-based psychological treatments for patients with chronic pain. These treatments, as well as biofeedback, clinical hypnosis, and integrative psychological treatment for centralized pain, focus on facilitating patients' ability to develop useful strategies to cope with pain and its related impact on mood.⁵⁴ With well-established evidence for the effectiveness

of psychological interventions in the management of chronic pain, neurologists can improve the care they provide patients with chronic pain by integrating pain psychology into their care.⁴⁵

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Pediatric Pain

REVIEW ARTICLE

By Alyssa Lebel, MD; Nathaniel M. Schuster, MD



CONTINUUM AUDIO
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ABSTRACT

OBJECTIVE: This article reviews pain disorders encountered in pediatric neurology practice and provides current information regarding the assessment and treatment of pediatric chronic pain.

LATEST DEVELOPMENTS: Data about pediatric pain management remain sparse, owing to a dearth of controlled trials and longitudinal studies in these patients. However, the field of pain management and understanding of central and peripheral pain processing has expanded to allow more effective treatment of a broad group of children and adolescents with pain associated with neurologic disease. Neuroimaging visualizes sensory and nonsensory systems, and genetic markers of sensitivity and disease may guide specific therapy. The concept of central sensitization in chronic pain disorders has supported the development of multidisciplinary paradigms for the comprehensive care of these patients.

ESSENTIAL POINTS: Pain involves sensory activation and central nervous system modulation in pediatric patients. Pediatric neurologists should be prepared to define, investigate, and treat pain disorders in this complex patient population. Appropriate interventions during childhood may attenuate or prevent chronic pain later in life. Current interventions include behavioral, physical, and pharmacologic approaches, as well as potential noninvasive tools for neuromodulation. Research is progressing in sensory measurement, neuroimaging, genetics, and neuroinflammation to guide future targeted therapies.

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RELATIONSHIP DISCLOSURE:

An immediate family member of Dr Lebel has received personal compensation for serving as an employee of Stoke Therapeutics, has received personal compensation in the range of \$100,000 to \$499,999 for serving as an officer or member of the board of directors for Cytokinetics, and has stock in Cytokinetics and Stoke Therapeutics. Dr Schuster has received personal

Continued on page 1535

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:

Drs Lebel and Schuster discuss the use of amitriptyline, atomoxetine, buprenorphine, chloroprocaine, clonazepam, clonidine, duloxetine, gabapentin, guanfacine, hydromorphone, methadone, methylnaltrexone, metoclopramide, mexiletine, midazolam, morphine, nalbuphine, nortriptyline, pregabalin, and ropivacaine for pain management, none of which are approved by the US Food and Drug Administration (FDA) for use in pediatric patients.

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INTRODUCTION

Pain assessment and treatment of pediatric patients can be a daunting task. This article covers developmental and biopsychosocial pediatric assessment; examination pearls specific to pain disorders; primary, peripheral, and central neuropathic pain syndromes; secondary injury to the nervous system (eg, postcancer therapy); pain of unclear etiology in patients with intellectual delay; and future considerations.

The global prevalence of chronic recurrent pain in children is estimated at 40% to 50%.¹ Overall, the prevalence of pain increases in the adolescent population with a female predominance.² Data on the prevalence of pain over the past few decades in high-income countries are available from reports from the International Association for the Study of Pain³ and a study by King and colleagues.² A 2022 meta-analysis of data from low-income and middle-income countries estimated a pooled mean of 8% (95% confidence interval, 6% to 10%).⁴ In a Danish study of pain prevalence in hospitalized children, 37% of children

reported moderate to severe pain and 43% would have preferred an intervention to alleviate pain but did not have a documented pain assessment.⁵ A 2021 Lancet review called for improvement in the assessment, understanding, and treatment of global pediatric pain.⁶

Chronic pain in patients with rare diseases, often the domain of pediatric neurology, has historically been underrecognized and often undertreated, with research and clinical care instead focusing on appropriate novel metabolic and genetic therapies. Some examples (**TABLE 10-1**)⁷ include hereditary and metabolic disorders, such as Charcot-Marie-Tooth disease type 1, neurofibromatosis type 1, Gaucher disease, Fabry disease, and sodium channelopathies (eg, erythromelalgia). These patients may have significant nociceptive, neuropathic, and visceral pain involving the skeleton, viscera, and extremities (**TABLE 10-1**).

ASSESSMENT OF PEDIATRIC PAIN

Pediatric pain evaluation uses validated pain intensity scales that are developmentally appropriate for children of different ages (**TABLE 10-2**).⁸ There is currently no objective measure of pain, although the search for biomarkers has advanced with the use of brain-derived measures such as functional MRI (fMRI), near-infrared spectroscopy, EEG, and quantitative sensory testing. Pain history requires information regarding intensity, location, and time course, as well as factors that relieve or exacerbate pain.⁹ Electronic pain diaries employing innovative self-reported pain outcome tools, such as eOuch, SUPER-KIDZ, and iPadVAS, are now available and have largely replaced paper inventories.¹⁰ These applications are accepted and understood by most pediatric patients, with the caveats of incomplete access to devices and necessary attention to patient

TABLE 10-1**Pediatric Chronic Pain in Rare Diseases^a**

Disease	Pathophysiology	Pain type	Location	Onset and development
Gaucher disease	Glucosylceramide accumulation with neuropathy	Nociceptive, neuropathic, visceral	Viscera and bones	10 to 20 years and lifelong
Fabry disease	Globotriaosylceramide accumulation in viscera and nerves (small fibers)	Neuropathic	Hands and feet	6 to 9 years and lifelong
Charcot-Marie-Tooth disease type 1A	Protein variations in motor and sensory nerves	Neuropathic	Extremities	First and second decade and lifelong
Neurofibromatosis type 1	Neurofibromas affecting nerves	Neuropathic	Nervous system, skin, skeleton	At birth and lifelong
Sodium channelopathies	Variations in SCN9A, which encodes the NaV1.7 protein subunit	Neuropathic	Hands and feet	5 to 18 years and lifelong episodes

^a Modified with permission from Sieberg CB, et al, Neurosci Biobehav Rev.⁶ © 2021 Elsevier Ltd.

privacy. Previously evaluated scales of pain intensity (**TABLE 10-2**) are incorporated into these tools. Additionally, activities of daily living, such as diet, physical activity, and sleep, are recorded, along with scales measuring disability, fear of pain, catastrophization, anxiety, and depression.

Assessment is influenced by developmental stages. As a general guide, this developmental understanding of pain is based on piagetian developmental theory.¹¹ During hospitalization and illness, children may often regress to an earlier cognitive level. In patients able to understand a rank order, the unidimensional self-report scales are the primary tools. In some patients younger than 6 years old and those with intellectual delay, proxy reporting by caregivers and behavioral scales are used. The measures used in neonatal pain may overlap with observational and caretaker tools for patients with intellectual delay. Drawings of pain locations and coloring in a blank figure with pain sites are useful adjuvants. In preverbal and nonverbal patients, a proxy scale (**FIGURE 10-1**¹¹⁻¹³) does not indicate pain intensity and is best used for acute and procedural pain. The behaviors recorded by the observer include vocalizations, facial expression (eg, furrowed brow), large body movements (eg, rapid limb withdrawal to touch), and changes in social interactions, appetite, and sleep-wake states. Multidimensional tools, such as the Patient-Reported Outcomes

Self-report Pain Intensity Measures^a

TABLE 10-2

Tool	Age range (years)	Type of pain
Faces Pain Scale- Revised (FPS-R)	4 to 12 years	Acute, procedural, postoperative, disease-related
Numeric Rating Scale (NRS)	8 years and older	Acute, procedural, postoperative, disease-related
Oucher	3 years and older	Acute, procedural, postoperative, disease-related
Pediatric Pain Questionnaire (PPQ)	5 years and older	Disease-related, chronic
Visual Analog Scale (VAS)	8 years and older	Acute, procedural, postoperative, disease-related, chronic
Wong-Baker FACES Pain Scale (WBPRS)	3 years and older	Acute, procedural, postoperative, disease-related
Faces, Legs, Activity, Cry, and Consolability Observational Tool (FLACC)	0 to 18 years	Acute, procedural, postoperative, disease-related
Revised Faces, Legs, Activity, Cry, and Consolability Observational Tool (rFLACC)	4 to 19 years with mild to severe intellectual disabilities	Acute, postoperative
Individualized Numeric Rating Scale	6 to 18 years with severe intellectual disabilities in acute care settings	Postoperative
Paediatric Pain Profile	1 to 18 years with severe physical and neurologic impairments	Acute, disease-related, chronic

^a Modified with permission from Manworren RC and Stinson J. Semin Pediatr Neurol.⁸ © 2021 Elsevier Ltd.

Measurement Information System, are best for patients with chronic pain. Many of these measures are in the public domain and available in multiple languages.

EXAMINATION PEARLS

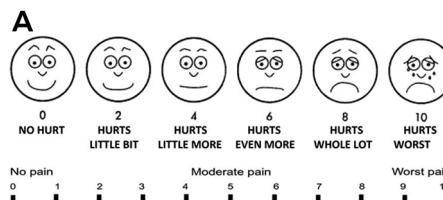
In addition to lesion localization, the neurologic examination in pediatric patients with pain requires additional elements for a complete assessment. This comprehensive approach is indicated in patients with severe neurologic impairment, central sensitization, autonomic nervous system dysfunction, and overlapping pain syndromes.^{15,16}

General Examination

If possible, the patient should be observed while undressing, climbing onto the examination table or bed, walking, and running. Clothing should be removed to perform a sensory examination (especially shoes), and neurologists should assess for signs of autonomic nervous system sensitivity (eg, clammy palms and soles, livedo reticularis, orthostatic pallor, mydriasis with postural changes), postural and gait asymmetry, and inconsistencies in motor and sensory performance possibly suggestive of functional neurologic disorders or elaboration. Patients with functional neurologic disorders show changes in intrinsic resting brain function in regions implicated in arousal, energy regulation, motivation, emotion processing, self-referential functions, and motor function.¹⁷ In patients with severe neurologic impairment, the face should be observed for grimacing or other signs recognized by the caregiver that indicate distress while moving the limbs or observing abnormal postures.

The examination of patients with pain includes the following basic information:

- ◆ Vital signs: sympathetic excitation (eg, tachycardia, hypertension), autonomic nervous system dysfunction (eg, hypotension, orthostasis)
- ◆ Posture: scoliosis, kyphosis, lordosis, truncal flexion
- ◆ Face: grimace, asymmetry, flushing
- ◆ Gait: antalgia with limp, genu valgus (hypotonia), use of assistive devices, coordination
- ◆ Extremities: color and temperature irregularity (autonomic nervous system dysfunction); skin, hair, and nail dystrophy (complex regional pain syndrome [CRPS]); atrophy and tremor (neuropathy)



FLACC (Face, Legs, Activity, Cry, Consolability)			
Categories	0	1	2
Face	No particular expression or smile	Occasional grimace or frown; withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless; tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth; tense	Arched, ridged, or jerking
Cry	No cry (awake or asleep)	Means or whimpers; occasional complaint	Crying steadily, screams or sob; frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to; distractible	Difficult to console or comfort

Each category is scored on the 0-2 scale, which results in a total score of 0-10.

0: Relaxed and comfortable
1-3: Mild discomfort
4-6: Moderate pain
7-10: Severe discomfort or pain, or both

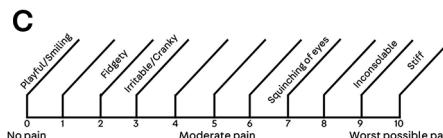


FIGURE 10-1

Examples of numeric rating scales. In children with cognitive delay, using behavioral changes well known to the caretaker can help care providers develop an individualized rating scale. **A**, The FACES Scale. **B**, The Faces, Legs, Activity, Cry, and Consolability Observational Tool (FLACC). **C**, Individualized Numeric Rating Scale.

Reprinted with permission from Wong DL and Baker CM, *Pediatr Nurs*,¹² Ahn Y and Jun Y, *Early Hum Dev*,¹³ and Solodiuk J and Curley MAQ, *J Pediatr Nurs*.¹⁴

Neurologic Examination

Although a complete assessment is appropriate, the focus should be on cranial nerve function (eg, headache disorders and self-injurious behavior), the spinal nerve root and peripheral nerve territories, and a detailed sensory exam including clinical features of neuropathic pain.

In a region of possible neuropathic pain, one should examine for the following:

- ◆ **Allodynia:** All stimuli are perceived as painful.
- ◆ **Analgesia:** absence of pain to a painful stimulus
- ◆ **Dysesthesia:** unpleasant, abnormal sensation
- ◆ **Hyperalgesia or hypoalgesia:** Pain threshold to painful stimuli is decreased or increased.
- ◆ **Hyperesthesia or hypoesthesia:** increased or decreased sensitivity to stimulus
- ◆ **Hyperpathia:** Once the pain threshold to painful stimuli is exceeded, the sensation of pain increases more rapidly and to a greater degree than expected (summation).

Quantifying the sensory and motor examination using nerve conduction studies and EMG is often uncomfortable for pediatric patients and not sensitive in the identification of small fiber sensory dysfunction, which may be present in challenging pain cases. Nerve conduction studies and EMG are informative for patients with large fiber sensory and motor disorders, radiculopathies, and myopathies. Quantitative sensory testing is feasible and valid for cooperative patients 5 years old and older but is still predominantly a research tool. Reference values differ from those in adults. In general, children ages 6 to 9 years have higher sensory thresholds to thermal and mechanical stimuli and lower thresholds to pain stimuli compared with children ages 9 years and older.

Pediatric patients younger than 14 years old with diabetes may have subclinical neuropathy per quantitative sensory testing.¹⁸ Quantitative sensory testing abnormalities may be measured in children reporting “growing pains.”¹⁹ C-fiber dysfunction has been described in patients older than 8 years and quantitatively measured in the skin by epidermal biopsy and, more recently, confocal corneal microscopy, a less invasive and possibly repeatable measure of alteration in corneal fibers.²⁰ Using neuroimaging and EEG, central measures of interacting peripheral and central pain mechanisms have increasingly shown changes in brain connectivity indicating developmental changes in pain systems, delineated communicating networks specific for some pain disorders, and presented provocative regional differences in cortical or subcortical thickness and brain chemistry.²¹ These studies emphasize that pain disorders are brain disorders.

GENETIC TESTING

Chronic pain often runs in families, which can be due to genetic predisposition to pain sensitivity, nongenetic factors including parental behavioral modeling and environmental milieu, or both. There are limited data for genes involved in pain sensitivity, such as catechol-O-methyltransferase (*COMT*) (TABLE 10-3²²).

The first study of genetic variants and experimental thermal pain in children and adolescents included 136 subjects aged 8 to 18 years. Cold and heat pain thresholds were determined with a thermal sensory analyzer, and the gene *OPRM1* was highlighted.²³ Specifically, based on expected pain sensitivity, the combined genotype *OPRM1* 118AA/*COMT* 472 GA was associated with lower

KEY POINTS

- The prevalence of chronic pain in children is widespread and is more common in females. Pediatric chronic pain prevalence in low-income and middle-income countries is underreported in the literature, and yet is a leading cause of morbidity.
- Pain is a frequent component of rare neurometabolic diseases.
- Chronic pain assessment can be individualized through self-report measures depending on the patient’s needs and developmental and cognitive levels.
- The neurologic examination for patients with pain includes assessment of small sensory fiber function.
- Neuroimaging studies illustrate that pain disorders are, at their root, disorders of the brain.

pain thresholds (ie, higher pain sensitivity) than the *OPRM1* 118GA or GG/COMT 472GG genotypes.²³ Thus, the *OPRM1* rs1799971 polymorphism and the combined *OPRM1*/COMT genotype could serve as biomarkers for pain sensitivity.

In contrast, patients who report minimal pain after nerve injury may be homozygous for the gene *GCH1* or may have an *SCN9A* variation that can cause congenital insensitivity to pain. Research into erythromelalgia and *SCN9A* variations have led to clinical trials studying sodium channel antagonists for the treatment of acute and chronic pain disorders. This research has also advanced knowledge of the broader spectrum of sodium channel disorders, including sporadic or inherited variations associated with epilepsy, cardiac conduction, and muscle contraction abnormalities.²⁴ Nav 1.7 channels are present in small sensory fibers, dorsal root ganglia, the trigeminal nerve, the olfactory nerve, and the sympathetic chain. They are a common link in cases of small fiber neuropathy concurrent with autonomic nervous system sensitivity or idiopathic dysautonomia. Channel function may also be modulated by cytokines and protein kinases and may be related to neuroinflammation. A gain-of-function

TABLE 10-3

Genes Involved in the Experience of Pain^a

Genes facilitating or amplifying pain

- ◆ *KCNS1*
- ◆ *SCN9A*
- ◆ *ADRB2*
- ◆ *H2TRA*
- ◆ *CACNG2*
- ◆ *IL16*

Genes that confer protection from or decrease in pain

- ◆ *COMT*
- ◆ *OPRM1*
- ◆ *TRPV1^b*
- ◆ *MC1R*
- ◆ *GCH1*
- ◆ *CACNA2D3*

Genes involved in the modulation of analgesic efficacy

- ◆ *COMT*
- ◆ *MC1R*
- ◆ *OPRM1*
- ◆ *CYP2D6*
- ◆ *ABCB1*

^a Data from Binder A, et al, PLoS One.²²

^b The 1911 A > G polymorphism of *TRPV1* was significantly associated with altered heat pain thresholds.

variation may result in erythromelalgia, paroxysmal extreme pain disorder, and paroxysmal itch.²⁴ A loss-of-function variation produces congenital insensitivity to pain.²⁴ Genetic testing of pediatric patients with variable symptoms referable to a channelopathy or additional sodium channel variants is expanding, as are trials of specific sodium channel ligands. In the clinical setting, nonspecific sodium channel blockade is achieved with topical and IV lidocaine, antiseizure medications including carbamazepine, and mexiletine.

PEDIATRIC NEUROPATHIC PAIN

Neuropathic pain is defined as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.”²⁵ Alterations in the structure and function of the peripheral and central pain transmission systems or neuroplasticity produce spontaneous pain, loss of normal function, and hypersensitivity to noxious and innocuous stimuli.²⁶ In children, these maladaptive and plastic changes within the nociceptive network coincide with the normal maturation of the nervous system. Therefore, pediatric neuropathic pain disorders may differ from adult conditions regarding presentation, prognosis, and treatment. Effective treatment of pediatric neuropathic pain is multimodal.

Oral Medications

Effective treatment of pediatric neuropathic pain includes direct inhibition of peripheral and central neuronal activity rather than nonspecific modulation of opioid and nonsteroidal pathways. Therapeutic targets and medications include the following:

- ◆ Sodium, calcium, and potassium neuronal channels: local anesthetics and antiseizure medications
- ◆ Neurotransmitters: tricyclic, tetracyclic, serotonin-norepinephrine reuptake inhibitors (SNRIs), or other known antidepressant agents
- ◆ Central N-methyl-D-aspartate (NMDA) receptors: magnesium and ketamine
- ◆ Intrinsic brain circuits: cognitive behavioral therapy (CBT), physical therapy, and acupuncture with or without medications

Data supporting the treatment of patients with pediatric neuropathic pain disorders, compared with the treatment of cancer-related pain in children, are limited. Due to ethical concerns, there are fewer placebo-controlled randomized controlled trials to inform pediatric pain treatment. The effectiveness of medications may vary during different stages of brain development. Some common neuropathic pain disorders in the adult population, such as diabetic peripheral neuropathy, brachial plexopathies, radiculopathy, trigeminal neuralgia, and postherpetic neuralgia, are uncommon in children. Posttraumatic brachial plexus neuralgia is also rare in children, even with a history of shoulder dystocia or brachial plexus traction injury during difficult delivery. Other painful neuropathic disorders present in early childhood, such as hereditary and metabolic neuropathies (eg, Fabry disease, mitochondrial disorders, lead exposure) and primary erythromelalgia.

Given the limited evidence to inform pediatric pain treatment, adult data are sometimes used to inform pediatric pain management. Some safety and efficacy information from the use of medications such as antiepileptics and

antidepressants in epilepsy, cancer pain, and depression may be reassuring.^{27,28} However, suicidal ideation is an infrequent but important safety concern and should be part of the discussion with patients and families when using antiseizure and antidepressant agents in children and adolescents (see the Useful Websites section in this article).²⁹ Parents may access the websites of the European and American Psychological and Psychiatric Associations for additional information.

Amitriptyline has been used clinically for more than 40 years, especially in patients with headache and chronic abdominal pain, and is frequently the initial choice when selecting first-line agents for neuropathic pain. The initial dosage should be low, such as 0.1 mg/kg, with an increase to a maximum of 1 mg/kg per day to 2 mg/kg per day. ECG is ordered before initial dosing to exclude occult cardiac arrhythmia or prolonged QTc. Adverse effects are usually seen with high dosages (such as >50 mg/day to 75 mg/day) and may include constipation, weight gain, sedation, and anticholinergic autonomic effects. Sedation with nighttime dosing may be beneficial for patients with insomnia. Nortriptyline may confer less sedation but carries a greater risk of palpitations and tachycardia. Tricyclic antidepressants act by reducing reuptake of norepinephrine and serotonin within neuronal synapses in the endogenous (endorphin and encephalin) descending pain modulation pathways at the brain and spinal cord levels. SNRIs, such as duloxetine and venlafaxine, have not been well studied in children but are often used in adolescents when first-line agents have failed. SNRIs have the best data for use in adults with diabetic neuropathy and postherpetic neuralgia,³⁰ and selective serotonin reuptake inhibitors (SSRIs) alone are infrequently effective for neuropathic pain. SNRIs may be modestly more effective than SSRIs in adults with neuropathic pain, and they are often chosen for patients with concurrent anxiety and depression; however, there are limited data on SNRIs in pediatrics.³¹ In this author's clinical experience, SNRIs are not always optimal for patients with neuropathic pain and comorbid anxiety and depression. The combined effect of SNRIs and SSRIs may be subtractive, necessitating higher SSRI dosages if anxiety or depressive symptoms are more prominent.

Safety and efficacy data for antiseizure medications are available from pediatric epilepsy trials, but data are limited for neuropathic pain. Gabapentin is most frequently used in children and adolescents with neuropathic pain. Dosing of antiseizure medications is based on weight, and serum drug levels do not predict pain effect but may be used for patient safety, especially if the patient reports adverse effects. Adverse reactions of antiseizure medications may be anticipated based on the specific medication choice and include rash, sedation or mental clouding, renal calculi formation, and severe gastrointestinal distress. Laboratory testing for possible hematologic and hepatic changes is indicated in patients using first-generation antiseizure medications. Second-generation and third-generation agents are often titrated based on pain relief. These newer formulations also potentially bind to a greater variety of receptors, with activity at sodium and calcium channels as well as NMDA and γ -aminobutyric acid (GABA) receptors.

Additional medications for the treatment of neuropathic pain include NMDA-receptor ligands (eg, ketamine) and α_2 agonists (eg, clonidine). Ketamine is generally used for procedural sedation and with induction of general anesthesia. Low-dose ketamine may be used in inpatient settings to enhance analgesia and limit the adverse effects of opioids, such as in patients with sickle cell disease. The most common challenges in high-dose or long-term treatment include increased

salivation, nausea, sedation, short-term memory loss, increased intracranial pressure, cardiac dysrhythmia, and respiratory depression. Clonidine oral dosing is suggested at 2 µg/kg to 4 µg/kg every 4 to 6 hr, adjusted regarding potential hypotension and sedation. Rebound hypertension may be seen with abrupt discontinuation after greater than 2 weeks of treatment.³² Pediatric dosing ranges and common side effects of various neuropathic pain medications are listed in TABLE 10-4. There is extensive literature from palliative care regarding the use of adjuvant medications for spasticity, nausea, constipation, sedation, pruritus, and fatigue (TABLE 10-5), which may direct the choice of neuropathic medication based on potential adverse effects.

KEY POINT

- Maladaptive changes within the nociceptive network coincide with maturation of the nervous system, and thus pediatric neuropathic pain disorders may differ from adult conditions regarding presentation, prognosis, and treatment.

ADDITIONAL TREATMENTS FOR PEDIATRIC PAIN

Additional treatments and routes of medication administration are available in the management of pain in pediatric patients.

Local Anesthetic Agents

Lidocaine, the prototypical local anesthetic, is a blocker of fast voltage-gated sodium channels in cell membranes of postsynaptic neurons, a type IB antiarrhythmic contraindicated in patients with cardiac conduction disorders, and a local anesthetic that has been used as an anesthetic and analgesic for over 60 years. It was first synthesized in 1943 and approved for regional anesthesia in 1948.³³ It may be administered by transdermal 5% patch, 700 mg lidocaine in an aqueous base, every 12 hours per 24 hours in areas of focal allodynia. Data are predominantly from adult trials, such as for postherpetic neuralgia. Lidocaine IV infusion was reviewed for adults in a 2005 Cochrane review³⁴ and has been studied in pediatric patients with erythromelalgia, neuropathy, and refractory headache. It may be opioid sparing in postoperative pain, cancer pain, and sickle cell disease. The frequency and duration of effective infusions in pediatric patients require further study. However, short-term (120-minute) infusions in a pediatric outpatient infusion unit or hospital have shown safety and efficacy with a dosage of 25 µg/kg/min and a maximum dosage of 33 µg/kg/min, not to exceed adult dosing of 1.7 mg/min. This rate has been associated with serum lidocaine levels less than 3 µg/ml to 5 µg/ml. In addition to cardiac contraindications, restrictions include local anesthetic allergy, pregnancy, age younger than 1 year (immature hepatic metabolism), recent seizure history, renal and hepatic dysfunction, and concurrent medications that induce CYP1A2 and CYP3A4 enzymes.^{33,35} It is advised to withhold tricyclic antidepressants and mexiletine the day before treatment due to arrhythmia concerns if there is an underlying conduction pathway abnormality or ventricular hypofunction. If the patient has a history of congenital heart disease, it is best to consult a pediatric cardiologist. Oral mexiletine,³⁶ a sodium channel blocker, is a neuropathic pain option at 150 mg 2 times a day for IV lidocaine responders, but may not be tolerated due to frequent heartburn.

Topical agents such as lidocaine patches and topical nonsteroidal anti-inflammatory therapies such as topical diclofenac gel are usually not potent enough for intense neuropathic pain beyond the dermal afferents. Interventional treatments may be indicated after initial treatment fails. Data are quite limited for these interventions and are often limited to case studies. The adult literature is well populated but not readily transferrable to pediatric cases.³⁷ Peripheral nerve blocks using long-acting anesthetics, such as ropivacaine and bupivacaine,

may decrease the likelihood of postsurgical pain (eg, preamputation and periamputation; **CASE 10-1**), and tunneled catheter infusions may be used for up to 3 to 6 months. Sites include the femoral, sciatic, axillary, supraclavicular, infraclavicular, and interscalene nerves.³⁸ These interventions are particularly effective for patients with bony tumors and somatic bony pain.

Procedural Pain Management

In pediatric palliative care, the intrathecal administration of opioids, anesthetics, and α_2 agonists via implantable catheter and pump systems has been shown to be pain sparing and safe in pediatric patients with visceral and limb pain.^{39,40} The management of catheters at home is preferable but requires specialized nursing care. Sympathetic peripheral nerve blockade has been helpful in patients with severe peripheral vascular disease (eg, sepsis, thrombosis) and visceral pain within the distributions of the celiac (innervating the inferior part of the esophagus, stomach, pancreas, spleen, kidneys, liver, gallbladder, and small intestine) and hypogastric plexuses (superior innervating the distal rectum, distal portion of the ureter, urinary bladder, reproductive tract and associated accessory glands, and blood vessels; inferior innervating the pelvic and perineal organs). Epidural analgesia per single-shot or continuous infusion, with the catheter tunneled subcutaneously, may provide some relief for patients with solid tumors. Risks include bleeding, infection, and dural puncture.

Pediatric case reports describe neurolytic procedures in end-of-life care, such as intrathecal neurolysis and cordotomy, which require further study to accurately assess duration and efficacy. The risks of neurolytic procedures

TABLE 10-4

Pediatric Dosing and Side Effects of Neuropathic Pain Medications

Medication	Dosing	Maximum dose	Side effects
Amitriptyline	0.1 mg/kg/day to 0.4 mg/kg/day	100 mg/day	Sedation, weight gain, constipation, dizziness
Nortriptyline	0.05 mg/kg/day to 1 mg/kg/day	75 mg/day	Tachycardia, weight gain
Gabapentin	5 mg/kg/day to 10 mg/kg/day	2400 mg/day to 3600 mg/day, but start low at 300 mg in the evening, with a slow titration of increases by 300 mg/day until reaching the desired analgesic effect and tolerable dose	Fatigue, nausea, confusion
Pregabalin	50 mg 2 times a day to 3 times a day	300 mg/day	Fatigue, confusion
Topiramate	1 mg/kg/day to 3 mg/kg/day	400 mg/day	Confusion, weight loss, acidosis, kidney stones
Zonisamide	2 mg/kg/day to 4 mg/kg/day	400 mg/day	Weight loss, kidney stones, rash, acidosis
Clonidine	2 μ g/kg/day to 4 μ g/kg/day	0.4 mg/day	Sedation, bradycardia, hypotension
Mexiletine	2 mg/kg/day to 3 mg/kg/day	600 mg/day	Dizziness, tremor, gastrointestinal distress

include paralysis, bowel and bladder dysfunction, and new neuropathic pain disorders.⁴⁰

Pediatric regional anesthesia for noncancer-related pain is increasingly used in the perioperative period, enhanced by the use of ultrasound for precision and minimally toxic local anesthetics (eg, ropivacaine, chloroprocaine) administered with synergistic adjuvants (eg, clonidine, dexmedetomidine). The adverse effects of local anesthetics are additive. Neurologists may be consulted in the postoperative period for persistent sensory or motor deficits, especially in patients with cancer following solid tumor surgeries, to differentiate between preexisting vulnerability to nerve injury, intraoperative nerve trauma, and infusate toxicity. Generally, if nerve injury or neurapraxia occurs (possibly due to patient positioning, anesthetic technique, or surgical trauma), recovery, with physical therapy support, will typically occur within 3 months.⁴¹

Data from The Pediatric Regional Anesthesia Network documented the overall incidence of neurologic complications of 2.4 per 10,000 blocks, which were predominantly neuraxial and similar for single injection or continuous catheter techniques.⁴² As in a patient undergoing cancer therapies, overlapping pain sites and pathophysiologies are common and require multimodal care. Many nonchemotherapy neuropathies may also benefit from the approach to cancer pain, as there are shared sensory mechanisms.

Expanding beyond more typical neuropathic pain interventions, short-term IV infusions of lidocaine and ketamine have shown variable efficacy in patients with CRPS but have little benefit for somatic symptom disorder or functional neurologic disorders.^{39,40}

Ketamine

Ketamine is a phencyclidine derivative synthesized in the early 1960s as an anesthetic agent. The mechanism of action for analgesia is antagonism at

Adjvant Medications in Pediatric Pain Management

TABLE 10-5

Side effect	Medication	Dose
Nausea	Ondansetron	10 kg to 30 kg 1 mg to 2 mg IV every 8 hours; >30 kg 2 mg to 4 mg IV every 8 hours
	Naloxone infusion	0.25 mcg/kg/hr to 1 mcg/kg/hr
	Metoclopramide	0.1 mg/kg to 0.2 mg/kg oral/IV every 6 hours
Pruritus	Naloxone infusion	0.5 mcg/kg/hr to 1.0 mcg/kg/hr
	Nalbuphine	0.02 mg/kg to 0.05 mg/kg IV every 4 hours
	Cyproheptadine	2 mg to 4 mg orally every 8 hours (maximum 16 mg/day)
	Diphenhydramine	1 mg/kg to 2 mg/kg IV or oral every 4 to 6 hours
	Hydroxyzine	0.5 mg/kg to 1.0 mg/kg IV or oral every 4 to 6 hours
Constipation	Methylnaltrexone	0.15 mg/kg IV single dose
	Docosate	10 mg to 40 mg orally 1 time a day
	Bisacodyl	5 mg to 10 mg orally or rectally 1 time a day

the NMDA receptor, which is expressed in the dorsal horn of the spinal cord but also active in the cortex and subcortical regions, especially within the hippocampus. Its use may decrease the wind-up phenomenon at tertiary neurons in the dorsal horn, decreasing central sensitization in chronic pain. Ketamine is not a specific and “clean” antagonist, as it is also active at nicotinic, muscarinic, opioid, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and kainate receptors, and inhibits serotonin and dopamine reuptake and additional calcium channels.⁴³ Low dosing is maintained to reduce dissociative and amnestic effects. Somewhat surprisingly, it may reduce postoperative delirium, possibly counteracting intraoperative opioids. In pediatric pain management, ketamine requires additional study to support widespread use for chronic neuropathic pain, despite some reported

CASE 10-1

A 16-year-old boy presented for pain associated with a previous below-knee amputation of the left lower extremity following total resection of osteosarcoma of the tibia. Pulmonary metastases were identified preoperatively, and his chemotherapy protocol included doxorubicin, cisplatin, and methotrexate. Mucositis in the setting of neutropenia was initially managed with an antacid mouthwash, antihistamine, topical anesthetic, and IV opioids. He reported cramping and dysesthesia in the phantom foot and ankle and burning and electrical pain with numbness in the remaining distal extremities. He did not report sensitivity to light touch and had stable renal and cardiac function. He had no analgesia with IV ketorolac and acetaminophen.

The patient was diagnosed with phantom limb pain and chemotherapy induced peripheral neuropathy. His neurologist instituted a multidisciplinary team approach to his care, including physical therapy and psychology for cognitive behavioral therapy and hypnosis. His neurologist managed ongoing assessment of his pain and pharmacotherapy with gabapentin, with eventual improvement of his pain at follow up.

COMMENT

Although tissue damage and persistent peripheral inflammatory mediators may remain after surgery, this is a case of phantom limb pain, with underlying pathophysiology including both central sensitization of dorsal horn neurons and connected networks in the thalamus and sensory cortices following amputation and deafferentation. The patient also had chemotherapy-induced peripheral neuropathic pain due to chemotherapeutic toxicity. Nerve blockade, intrathecal medication, or transcranial magnetic stimulation are available if initial interventions are ineffective. The neurologist should start with the least invasive interventions without delaying escalation if distress is severe, beginning with physical therapy and neuropathic pain medications. Antiseizure medications are first-line medication choices, with guidance from the epilepsy literature regarding dosing and adverse effects.

enthusiasm for use in intractable CRPS. It is best chosen for cancer, sickle cell disease, and burn-related pain in children unresponsive to other interventions. It also has promise as an adjunct to multimodal perioperative analgesia.⁴⁴

The current pediatric dosing recommendations for IV ketamine are listed below:

- ◆ Low-dose ketamine infusions may be initiated at 0.12 mg/kg/hr (2 µg/kg/min)
- ◆ Patient may be titrated up by 0.05 mg/kg increments every 4 hours as needed to 0.42 mg/kg/hr (7 µg/kg/min)
- ◆ If greater than 0.42 mg/kg/hr is needed, the patient must be in an intensive care or step-down unit for monitoring
- ◆ To discontinue the infusion, consider the days of exposure to ketamine
 - ◆ If the patient has been on the infusion for less than 5 days, stop the infusion and observe
 - ◆ If the patient has been on ketamine infusion for longer than 5 days, wean infusion by 0.05 mg/kg increments every 4 hours

Cannabinoids

The persistent, dependent use of marijuana before age 18 years has been shown to cause lasting harm to a person's intelligence, attention, and memory.⁴⁵ The use of delta-9-tetrahydrocannabinol (THC) is generally limited to cancer and palliative care in pediatrics. There are minimal pharmacokinetic and pharmacodynamic data to guide dosing in children and adolescents. Cannabidiol preparations, often including trace doses of THC, have minimal analgesic effects when compared with primarily THC agents. There is some experience with synthetic THC use (including dronabinol and nabilone) in pediatrics for the treatment of chemotherapy-induced nausea and vomiting postchemotherapy.

Opioids

Opioids remain effective therapy in pediatrics for postoperative pain and cancer-related symptoms. However, in postoperative pain, multimodel therapy is preferred, with minimal opioid use and adjuvant neuropathic medications, muscle relaxants, anxiolytics, regional anesthesia, and behavioral therapies (**TABLE 10-6**).

Prescribing opioids requires an understanding of equianalgesic dosing, the consideration of likely adverse effects with acute and subacute dosing (eg, sedation, constipation, nausea, respiratory suppression), and monitoring of vital signs with treatment initiation. In some chronic pain conditions such as skeletal

Opioid Equianalgesic Dosing

TABLE 10-6

Drug	Oral dose	IV dose
Oxycodone	30 mg	NA
Morphine	30 mg	10 mg
Hydromorphone	7.5 mg	1.5 mg
Fentanyl	25 µg/hr patch	100 µg

dysplasias, stable dosing of an opioid with a long half-life may be chosen, such as methadone.

It is important to avoid codeine and tramadol in children younger than 12 years, particularly in those with obstructive sleep apnea, obesity, and severe lung disease. The metabolism of these opioids is genetically determined by the highly polymorphic CYP2D6 pathway, with patients ranging from poor to ultrarapid metabolizers.

Opioid side effects primarily fall into four categories—nausea, pruritus, constipation, and sedation—which may be treated with adjuvant medications.

PAIN PSYCHOLOGY

Chronic pain often insufficiently responds to pharmacotherapy alone. Conditions such as CRPS and functional neurologic disorder require the addition of physical and cognitive interventions, which activate central pain processing systems. In a 2002 study, 28 pediatric patients with CRPS of the lower limb participated in physical therapy 1 versus 3 times per week, with CBT once per week, for a total of 6 weeks. Outcome measures included pain scores, gait testing, stair climbing, psychological inventories, regional and systemic autonomic examination, and quantitative sensory testing. Both groups had a greater than 50% improvement in visual analog pain scale scores, improved gait and stair climbing, and no need for assistive devices by 6 weeks.⁴⁶ Strong evidence supports psychological treatments for chronic and episodic pain, most notably CBT. CBT is a structured, goal-oriented psychological therapy used to effectively manage behavioral health conditions, such as depression and anxiety, as well as health-related concerns including chronic pain and insomnia.⁴⁷ Numerous research studies suggest that CBT leads to significant improvement in functioning and quality of life. In many studies, CBT has been demonstrated to be as effective as, or more effective than, other forms of psychological therapy or psychiatric medications.⁴⁸

Acceptance and commitment therapy focuses on engaging in valued activities in the presence of pain, rather than attempting to alleviate the uncomfortable sensations, through enhanced psychological flexibility. For more information on pain psychology, refer to the article “Chronic Pain Psychology in Neurology Practice” by Mirsad Serdarevic, PhD,⁴⁹ in this issue of *Continuum*.

OTHER CHRONIC PAINFUL CONDITIONS IN PEDIATRIC NEUROLOGY

Pediatric pain management is important in a variety of clinical settings. This section outlines treatment strategies for other common causes of pain in the child neurology setting, including cerebral palsy and CRPS.

Cerebral Palsy and Genetic Encephalopathies

Pain prevalence is estimated at 14% to 76% in patients with cerebral palsy.⁵⁰ Dysregulated sleep patterns, myoclonus, and seizures may complicate the presentation in patients with cerebral palsy. Somatic pain etiologies may include joint dislocation, muscle spasm, infections, vocal cord dysfunction, heartburn, constipation, and general abdominal pain. Neuropathic etiologies include dystonia with traction of sensory fibers, radiculopathy, and neuralgia.

Similar pain sources may be present in patients with more progressive degenerative and genetic encephalopathies, such as the leukodystrophies.

Affecting 1 in 7500 individuals, these conditions present in infancy and early childhood and include X-linked adrenoleukodystrophy, Krabbe disease, metachromatic leukodystrophy, Pelizaeus-Merzbacher disease, and Alexander disease. Leukodystrophies are heritable diseases affecting the white matter of the central nervous system, with and without peripheral nervous system involvement. The approach to pain management in this population is similar to patients in the chronic pain clinic, with an early focus on improving quality of life through multidisciplinary care, often including early input from specialists in palliative care.⁵¹

Nonpharmacologic approaches include⁵²:

- ◆ Rocking, repositioning, music, lighting, and warm water (especially in patients with spasticity)
- ◆ Aquatherapy, especially to temporarily relieve the need for pressure and support
- ◆ Feeding support, hydration, and dietary changes to relieve constipation
- ◆ Improved sleep, with weighted blankets, decreased nursing care interruption at night, and aromatherapy
- ◆ CBT

Other age-appropriate periprocedural comfort measures include:

- ◆ Infants: rocking, singing, music, holding, skin-to-skin contact, tucking, gentle massage, pacifier, sucrose
- ◆ Toddlers: rocking, holding, music, blowing bubbles, playing, pet therapy
- ◆ Preschoolers: talking about the procedure, blowing bubbles, telling stories, watching movies, distracting with pop-up books, toys, video games, acting out the procedure, pet therapy
- ◆ School-aged children: breathing techniques, visual imagery, movies and video games, music, reading, massage, explaining the procedure, pet therapy

The approach to pharmacologic management emphasizes medications considered to have fewer possible adverse effects and interactions, such as nonsteroidal anti-inflammatory drugs and acetaminophen, unless there is known hepatic or renal comorbidity. The next steps include the conservative use of opioids, neuropathic pain medications, and adjuvants such as benzodiazepines, antispasmodics, and clonidine.

Regarding pharmacologic approaches, one may take advantage of the sedating and analgesic effects of the patient's muscle relaxants and antiseizure medications. Note that SSRIs and stimulants may disrupt sleep. The first choices for concentration include guanfacine and atomoxetine. Melatonin is often an initial selection for sleep, and clonazepam may aid in both nocturnal myoclonus and sedation. Gabapentin may aid in sleep, irritability, and neuropathic pain. Clonidine may be used as an adjuvant for symptoms of dysautonomia and restlessness.^{50,53}

FUTURE DIRECTIONS

Pediatric neurologists are well equipped to research the underlying mechanisms and provide additional studies of targeted treatments, supported by ongoing neuroimaging, combining near-infrared spectroscopy and magnetoencephalography (MEG), in addition to fMRI, as more flexible instruments to define neurocircuitry. Additional opportunities include using

KEY POINTS

- Studies support psychological treatment for chronic pain, with cognitive behavioral therapy recommended as a best practice.
- Studies have shown that targeting the patient's relationship with their pain in therapy is a powerful intervention.
- The evaluation of patients unable to assess or verbalize their pain due to intellectual delay relies heavily on provider assessment.
- Pain assessment in patients with cerebral palsy is often complicated by dysregulated sleep patterns, myoclonus, and seizures.

mRNA extraction to identify neuroinflammatory genes, and applying machine learning to identify classifiers of pediatric pain disorders. Child neurology education should include education about pain psychology and pain management techniques to optimize child neurologists' treatment capabilities for the care of their many complex patients with neurologic diseases and chronic pain. Neurologic screening tools for pediatric patients require development and assessment. Controlled and longitudinal trials to evaluate function and treatment response are critical for evidence-based management of pediatric pain. Collaboration through multicenter and international trials will be necessary to increase sample sizes for this patient population.⁶

CONCLUSION

Pediatric neurologists are often consulted for patients with pain from both central and peripheral nervous system dysfunction as well as combined nociceptive, neuropathic, and psychological etiologies. Common scenarios include patients with a history of treated cancer, chronic spasticity and motor disorders, or rare genetic and neurodegenerative diseases, nonverbal patients with unexplained irritability, patients with unexplained pain disorders, and patients with neurologic diseases with comorbid central sensitization. Multimodal treatment is the consensus best practice. Future investigations will hopefully advance clinical care including targeted care utilizing biomarkers for specific pain disorders.

USEFUL WEBSITES

FEAR OF PAIN QUESTIONNAIRE, CHILD REPORT

A self-report inventory assessing youth pain-related fear and associated avoidance behaviors. Responses are rated on a five-point Likert-type scale, ranging from "Strongly Disagree" to "Strongly Agree."

[jpain.org/article/S1526-5900\(10\)00860-6/pdf](http://jpain.org/article/S1526-5900(10)00860-6/pdf)

FUNCTIONAL DISABILITY INVENTORY

A 15-item self-report measure assessing children's perceived difficulty in physical and psychosocial functioning that is due to physical health.

downloads.aap.org/AAP/PDF/FDI_Child_and_Parent.pdf

PAIN CATASTROPHIZING SCALE-CHILD

A 13-item inventory that assesses a child's maladaptive thinking patterns associated with pain. physiotutors.com/questionnaires/pain-catastrophizing-scale-pcs/

PROMIS PEDIATRIC SHORT FORM v2.0 – ANXIETY 8a

An 8-item self-report measure that assesses anxiety in children and adolescents.

healthmeasures.net/images/PROMIS/manuals/PROMIS_Anxiety_Scoring_Manual.pdf

PROMIS PEDIATRIC SHORT FORM v2.0 – DEPRESSIVE SYMPTOMS 8a

An 8-item self-report measure that assesses depressive symptoms in children and adolescents.

healthmeasures.net/images/PROMIS/manuals/PROMIS_Depression_Scoring_Manual.pdf

TEENS HEALTH

Emergency resources for teens experiencing suicidal ideation and their families, including contact information for the 988 Suicide & Crisis Lifeline and The Trevor Project.

kidshealth.org/en/teens/stop-suicide.html

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Continued from page 1517

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Navigating Federal and State Laws Regarding the Prescription of Opioids

By Joseph S. Kass, MD, JD, FAAN; Rachel V. Rose, JD, MBA

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ABSTRACT

Since 2000, the opioid epidemic has claimed the lives of more than 500,000 people and policies regarding the prescription of opioids for chronic pain have undergone drastic changes. While neurologists account for a small number of overall opioid prescriptions, they may treat patients on opioids, prescribed by other physicians or obtained illicitly, and need to be aware of the latest practice guidelines and the legal regime regulating opioid prescriptions.

INTRODUCTION

Since 2000, opioids have claimed the lives of more than 500,000 people in the United States.¹ In response, legislatures and regulatory agencies have dramatically changed policies regarding the prescription of controlled substances, including opioids. This article reviews the complex and evolving landscape of federal and state laws regarding the prescription of opioids for the management of pain.

EVOLUTION OF THE OPIOID CRISIS

The opioid crisis emerged in 1996 as a tragic side effect of the commercial and regulatory push to treat chronic pain aggressively with opioids, most notoriously oxycodone hydrochloride, despite the lack of evidence for opioids to treat chronic, noncancer pain effectively. Purdue Pharma, the first manufacturer of oxycodone hydrochloride, aggressively marketed the drug and saw its sales climb from \$48 million in 1996 to more than \$1 billion in 2000.² A devastating byproduct of the approximately fourfold increase in opioid prescribing between 1999 and 2010 was "...an approximately fourfold increase in overdose deaths involving prescription opioids during the same period and increases in prescription opioid use disorder."³ Opioid prescription practices also changed during this period. For example, "...opioids increasingly were prescribed at higher dosages and for longer durations, prescribing behaviors associated with opioid use disorder and overdose."³ The dramatic spike in access to opioids fed addiction and facilitated the diversion and illegal distribution of prescribed narcotics. Opioid prescriptions peaked in 2011,¹ just as heroin emerged as an opioid of choice, followed shortly by fentanyl and related synthetic opioids. Recently, illegally manufactured opioids combined with psychostimulants

such as cocaine and methamphetamine are propelling the fourth wave of the opioid crisis.

Although prescribers and lawmakers have tightened the spigot on opioid prescriptions, people in the United States are the world's largest per capita consumers of prescription opioids.¹ Approximately 10 million people in the United States misuse or abuse opioids.⁴ In 2020, approximately 48,000 people in the United States experienced an opioid overdose. According to the National Institute on Drug Abuse, in 2020 there were 16,416 opioid deaths, and in 2022 the number of deaths decreased to 14,716, with a significant number of deaths being attributed to synthetic opioid ingestion.⁵ Although West Virginia has the highest per capita rate of overall opioid overdose deaths, Utah and Wyoming have the highest per capita rate of opioid overdoses involving prescription opioids in the United States.⁴

Chronic pain, defined as pain lasting 3 or more months, continues to be an enormous public health challenge because it affects approximately 21% of the US adult population, with almost 7% experiencing high-impact chronic pain.⁶ In 2014, the Agency for Healthcare Research and Quality "...found insufficient evidence to demonstrate long-term benefits of prescription opioid treatment for chronic pain, and long-term prescription opioid use was found to be associated with increased risk for overdose and opioid misuse."³ That same year, the US Food and Drug Administration (FDA) required new safety labeling changes for extended-release and long-acting opioids, which were expanded in 2016 to include immediate-release formulations. The boxed warning cautions about addiction, abuse, misuse, overdose, and death risks as well as the risk of neonatal abstinence syndrome.³

In 2016, the Centers for Disease Control and Prevention (CDC) issued the *CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016*, which included 12 recommendations for prescribing opioids for chronic pain in outpatient settings, excluding active cancer treatment, palliative care, and end-of-life care.³ The CDC guideline impacted state regulation of opioid prescriptions, with approximately one-half of states now limiting initial opioid prescriptions for acute pain to a 7-day or less supply. Some states also require or recommend coprescription of naloxone for patients receiving high-risk opioid prescriptions. Some lawmakers were overzealous in their attempts to curtail inappropriate opioid prescriptions by failing to carve out exceptions for patients with cancer and those receiving palliative care. The duration limitation rules also led to many patients discontinuing opioids abruptly, causing them to experience severe withdrawal or search out nonprescription opioids. In 2022, the CDC updated this guideline to address some of the shortfalls and unintended consequences of the 2016 guideline. The 2022 guideline helps practitioners determine whether to initiate opioids for pain, select opioids and determine opioid doses, decide the duration of initial opioid prescription and conduct follow-up, and assess opioid-related risk and address potential harms.³

RELEVANCE TO NEUROLOGISTS

In 2018, the American Academy of Neurology (AAN) issued a position statement on opioids that cautioned neurologists against prescribing opioids for chronic pain.

There is insufficient evidence that opioids are effective for the treatment of chronic pain, particularly neuropathic pain, and clear evidence that

they often worsen migraine. ...It may be acceptable to consider opioids for weakness, pain, or other symptoms at the end of life as part of a palliative care treatment plan. However, the risks of opioid therapy for most chronic conditions outweigh the benefits.⁷

Although US neurologists rank only 14th among medical professionals prescribing opioids, they care for patients prescribed opioids for non-neurologic conditions by non-neurologists.⁷ Neurologists account for approximately 2% of US physicians⁸ and wrote 1.2% of the 209.5 million opioid prescriptions in the United States between July 1, 2016, and June 30, 2017 (not including buprenorphine or veterinary prescriptions).⁹ This statistic translates into 10,896 neurologists issuing 2,482,777 opioid prescriptions.⁹ In 2015, there were 13,392 active neurologists in the United States.¹⁰ Although neurologists contribute a relatively small percentage to overall US opioid prescriptions, a relatively large percentage of US neurologists do prescribe opioids; therefore, neurologists must be familiar with the latest practice guidelines and the legal regime regulating opioid prescription.

FEDERAL OVERSIGHT OF THE PRESCRIPTION OF CONTROLLED SUBSTANCES

Whereas the FDA approves new opioids, the US Drug Enforcement Administration (DEA) is responsible for enforcing controlled substance laws in the United States.¹¹ To control the production and distribution of drugs, the Controlled Substances Act of 1970 categorizes drugs with abuse and dependence potential into five categories or drug schedules based on the drug's medical value, addiction risk, and potential to cause harm. The schedules range from Schedule I (most potential for addiction or use disorder) to Schedule V (least potential for addiction or use disorder). The law requires healthcare professionals prescribing scheduled drugs and pharmacists filling them to obtain a DEA license. This licensure requirement ensures that only qualified individuals prescribe controlled substances and facilitates tracking of prescription practices.

Illicit drugs such as heroin are Schedule I, whereas fentanyl, hydromorphone, meperidine, methadone, morphine, and oxycodone are Schedule II. Schedule II drugs, the prescription drugs with the highest potential for both physical and psychological dependence, may be prescribed with either a paper prescription or electronically, but refills are not allowed. Schedule III drugs, such as ketamine, buprenorphine, and products containing no more than 90 mg of codeine per dosage unit, are believed to have a lower misuse potential than Schedule I and II drugs and incur a greater risk of psychological rather than physical dependence. Schedule III drugs can be prescribed verbally over the phone, electronically, or with a paper prescription. They can be prescribed with only five refills in a 6-month period. Schedule IV drugs, which include tramadol and benzodiazepines, pose a more limited risk of physical or psychological dependence, and prescribers can order them for as long as they believe the drugs are medically necessary. Refills are permitted up to five times in a 6-month time frame from the issuance date. Schedule V drugs, including cough medicines with codeine containing less than 200 mg of codeine per 100 mL, antidiarrheal medications that contain atropine/diphenoxylate, and several antiseizure medications such as cenobamate, ezogabine, lacosamide, and pregabalin, have low abuse potential but still require careful management. Partial prescription fills for Schedule V

drugs cannot occur more than 6 months after the issue date. When a partial fill occurs, it is treated in the same manner and with the same rules as a refill of the drug.¹²

The Controlled Substances Act places all substances that were in some manner regulated under existing federal law into one of the five schedules. The DEA, in coordination with the Department of Health and Human Services, has the authority to change a drug's designated schedule. For example, in 2014, the DEA published a final rule moving hydrocodone combination from Schedule III to the more restrictive Schedule II.¹³ This placement is based on the substance's medical use, potential for abuse, and safety or dependence liability.¹¹ Under the Controlled Substances Act, prescription labels are required to contain the following items: (1) pharmacy name and address; (2) prescription number; (3) patient name; (4) initial dispensing date; (5) name of the prescriber; (6) directions for use; and (7) cautionary statements, if applicable.¹⁴ The FDA further requires that medications falling under Schedule II to IV include the following statement on the container: "CAUTION: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed."¹⁴

Even the method of prescribing is very specific for controlled substances. Effective June 1, 2010, the DEA promulgated its interim final rule that added to existing rules related to electronic prescriptions for controlled substances.¹⁵ In addition to enabling providers, who within the scope of their license can prescribe controlled substances, to write electronic prescriptions for controlled substances, "[t]he regulations will also permit the pharmacies to receive, dispense, and archive these electronic prescriptions."¹⁵ On July 27, 2023, the DEA published its *Final Rule: Transfer of Electronic Prescriptions for Schedules II-V Controlled Substances Between Pharmacies for Initial Filing*.¹⁶ In amending existing regulations, the DEA's final rule

explicitly state[s] that an electronic prescription for a controlled substance in schedule II-V may be transferred between retail pharmacies for initial filling on a one-time basis only, upon request from the patient, and clarifies that any authorized refills included on a prescription for a schedule III, IV, or V controlled substance are transferred with the original prescription. The final rule requires that: the transfer must be communicated directly between two licensed pharmacists; the prescription must remain in its electronic form; and the contents of the prescription required by 21 CFR part 1306 must be unaltered during the transmission. The final rule also stipulates that the transfer of EPSCS [electronic prescribing for controlled substances] for initial dispensing is permissible only if allowable under existing State or other applicable law.¹⁶

Notably, 21 CFR Parts 1306 and 1311 remained unchanged. Electronic prescribing, transmitting, and archiving also provide a trail for easier tracking by pharmacies and government agencies. This same notion applies to prescribing buprenorphine to treat opioid use disorder, which is diagnosed using the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* assessment criteria.¹⁷ As the Substance Abuse and Mental Health Services Administration (SAMHSA) indicates, buprenorphine is an FDA-approved drug and "...the first medication to treat opioid use disorder that can be prescribed or dispensed in physician offices, significantly increasing access to treatment."¹⁸ SAMHSA also

lists the following, among other items, that physicians should consider when prescribing buprenorphine: (1) it is often a safe choice for those with tolerance to opioids; (2) it acts as a partial mixed opioid agonist at the μ -receptor and as an antagonist at the κ -receptor; (3) it is dosed daily and has a long half-life; and (4) many formulations also contain naloxone.¹⁹

As a result of the opioid epidemic, states enacted prescription drug monitoring programs, which have proven successful in mitigating the risk of abuse in opioid prescribing. A prescription drug monitoring program "...is an electronic database that tracks controlled substance prescriptions. Information from [prescription drug monitoring programs] can help clinicians identify patients who may be at risk for overdose and provide potentially lifesaving information and interventions."²⁰ For example, Florida law requires that each prescriber or their designee consult the prescription drug monitoring program system to review a patient's controlled substance dispensing history every time a controlled substance is prescribed or dispensed to a patient age 16 years or older unless a statutory exception applies.²¹ While all 50 states, the District of Columbia, and most US territories have enacted prescription drug monitoring programs,²² the sharing of information across state borders, especially when a state borders multiple states (eg, Tennessee, California, Texas), is lacking.²³ Finally, when prescribing opioids via telehealth, although the DEA and the Department of Health and Human Services have extended the "...full set of telemedicine flexibilities regarding the prescribing of controlled medications as were in place during the COVID-19 public health emergency, through December 31, 2024," it is imperative to check state law requirements to ensure compliance with both federal and state laws.²⁴

THE FDA'S RISK MITIGATION STRATEGY

Because prescription opioids fueled the opioid crisis, as well as US Department of Justice enforcement actions,²⁵⁻²⁷ the FDA was forced to reexamine its processes for drug approval. Section 1003(b) of the Federal Food, Drug, and Cosmetic Act states that the FDA's role is to "protect the public health by ensuring that . . . drugs are safe and effective," and "promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner."²⁸ The FDA accomplishes this mission using its drug approval authority. In reviewing a new drug application, the FDA must determine that a drug is safe and effective for its proposed indication, which it does by weighing the benefits of the drug against its risks, including the potential for misuse. The FDA may require manufacturers to implement a Risk Evaluation and Mitigation Strategy (REMS) for certain approved drugs as a way of reducing the risk of serious adverse drug reactions, ensuring that the drug's benefits outweigh its risks. REMS may cover either an individual drug or an entire drug class.²⁹ REMS may include provider education, specific communications to patients, special training for physicians, certain preadministration testing, or limitations on the venue where the medication can be dispensed. In response to the public health crisis of opioid drug misuse, the FDA's approach to balancing benefit and risk with opioid analgesics evolved to include a greater analysis of the potential for medication misuse and overdose deaths. The FDA considers "...addiction, misuse of FDA-approved products, and transitions between use of FDA-approved opioid analgesics and illicit opioids—while at the same time FDA has kept in mind the need for patients to access effective medications for pain."³⁰

Opioids are managed through the Opioid Analgesic (OA) REMS, which is:

...one strategy among multiple national and state efforts to reduce the risk of abuse, misuse, addiction, overdose, and deaths due to prescription opioid analgesics. The OA REMS requires that education be made available to all health care providers (HCPs) who are involved in the management of patients with pain, including nurses and pharmacists. To meet this requirement, drug companies with approved opioid analgesics provide unrestricted grants to accredited continuing education providers for the development of education courses for HCPs based on the 2018 version of FDA's Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain (also referred to as the "FDA Blueprint").³¹

Although the FDA's OA REMS did not mandate prescriber education, in 2023 the federal government imposed on prescribers a formal requirement for opioid-related education tied to DEA licensure. Section 1263 of the Consolidated Appropriations Act of 2023 requires new or renewing DEA registrants, starting June 27, 2023, upon submission of their application, to have at least one of the following:

- ◆ A total of 8 hours of training from certain organizations on opioid or other substance use disorders for practitioners renewing or newly applying for a registration from the DEA to prescribe any Schedule II to V controlled medications;
- ◆ Board certification in addiction medicine or addiction psychiatry from the American Board of Medical Specialties, American Board of Addiction Medicine, or the American Osteopathic Association; or
- ◆ Graduation within 5 years and status in good standing from medical, advanced practice nursing, or physician assistant school in the United States that included successful completion of an opioid or other substance use disorder curriculum of at least eight hours.³²

Additionally, the Mainstreaming Addiction Treatment Act of 2021 now allows all DEA-licensed health care professionals with a Schedule III prescribing authority to prescribe buprenorphine for opioid use disorder,³³ just as they prescribe other Schedule III drugs as allowed by state law. The law eliminated the DATA-Waiver (X-Waiver) program, which previously required "practitioners to file a Notice of Intent (have a waiver) to prescribe medications, like buprenorphine, for the treatment of opioid use disorder."³³ Federal restrictions on the number of patients with opioid use disorder a practitioner may treat with buprenorphine were eliminated, and separate tracking of patients treated with buprenorphine and written prescriptions are no longer required. Likewise, unless restricted by state law, pharmacists can now fill buprenorphine prescriptions using the prescribing authority's DEA number and do not need a DATA 2000 waiver from the prescriber.^{33,34}

CONCLUSION

Neurologists routinely care for individuals experiencing pain syndromes, and these patients may be taking opioids, even if the neurologist is not the prescriber

of these controlled substances. With the expanded availability of buprenorphine, neurologists should familiarize themselves with appropriate prescription practices and the potential for drug-to-drug interactions that could adversely affect patients either by precipitating opioid withdrawal or potentiating opioids' central nervous system depressant effects. A new DEA requirement for 8 hours of opioid-related training can be an opportunity to fill the knowledge gap about opioids for those who do not routinely prescribe them. Given the prevalence of opioid use disorder, neurologists may be caring for more patients taking opioids than they realize. Neurologists will also need to work closely with the other health care practitioners caring for the patient to ensure the patient is receiving the safest and most effective care possible. Whether required by state law or not, checking the prescription drug monitoring program should be a routine part of a neurologist's process for prescribing a controlled substance. When caring for a patient taking opioids, the neurologist should incorporate counseling about safe opioid use and overdose prevention.

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Postreading Self-Assessment and CME Test

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AND CME

By Nuri Jacoby, MD; James M. W. Owens Jr, MD, PhD

PAIN MANAGEMENT IN NEUROLOGY

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ARTICLE 1: PRINCIPLES OF PAIN MANAGEMENT

- 1** Which of the following potential side effects is a boxed warning of duloxetine and should be discussed with all patients?
- A gastrointestinal hemorrhage
 - B increased risk of mania
 - C Stevens-Johnson syndrome
 - D suicidal ideation
 - E teratogenicity
- 2** A 70-year-old woman with a medical history of chronic right L5 radiculopathy and epilepsy presents for follow-up. Her medications include gabapentin 900 mg 3 times daily, topiramate 100 mg 2 times daily, and amitriptyline 50 mg 1 time daily. Which of the following medication side effects is this patient particularly at risk for?
- A cognitive dysfunction
 - B leg edema
 - C near angle glaucoma
 - D peripheral neuropathy
 - E withdrawal
- 3** Which of the following changes to coding will occur with the upcoming *International Classification of Diseases, Eleventh Edition* classification system?
- A alleviating factors to pain will be considered
 - B different pain mechanisms will need to be distinguished from each other
 - C pain severity will need to be included with the diagnosis
 - D pain syndromes will be less emphasized
 - E the types of complex regional pain syndrome will be expanded
- 4** Which of the following are strongly associated with lower rates of chronic pain?
- A anxiety and depression
 - B moderate physical activity
 - C obesity
 - D poor sleep
 - E social determinants of health

ARTICLE 2: SPINE PAIN

- 9B6vmzj4RAT1RqJBz5vmQ6bjYts4rZHominWNX0H3U65GurdNee3T25dQe6XNmvyCGabTods9Wqj4Xu38PhBKDAOyyxDHbzda8
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- 5 Which of the following potential correlating factors should be considered in a patient whose pain is exacerbated by prolonged sitting?
- A anterior compartment or muscles
 - B canal or foraminal stenosis
 - C facet joint, sacroiliac joint, or both
 - D muscle fatigue or deconditioning
 - E vertebral disk
- 6 If a patient's pain is relieved by gently pulling upward on the head and neck with the patient in a spine-neutral position, which of the following processes is implicated as a possible source of pain?
- A acromioclavicular joint arthritis
 - B brachial plexopathy
 - C cervical instability
 - D cervical radiculopathy
 - E shoulder girdle myopathy
- 7 Which of the following patterns of pain would suggest cluneal nerve targets for injection therapy?
- A axial pain
 - B low back pain with radiation into the buttock
 - C lower lumbar and gluteal pain
 - D paraspinal pain without radiation
 - E radiating radicular pain

ARTICLE 3: PERIPHERAL NEUROPATHIC PAIN

- 8 Which of the following treatments target central sensitization that contributes to neuropathic pain?
- A amitriptyline
 - B duloxetine
 - C gabapentin
 - D topical lidocaine
 - E tramadol

-
- 9** Which of the following patient-reported outcome tools primarily assesses the severity of neuropathic pain symptoms?
- A Brief Pain Inventory
 - B Comprehensive Pain Evaluation Questionnaire
 - C Neuropathic Pain Questionnaire
 - D Neuropathic Pain Symptom Inventory
 - E painDETECT Questionnaire
-
- 10** A 72-year-old man with a medical history of painful diabetic neuropathy presents with severe 8/10 constant pain. The pain was previously 10/10 but has improved slightly with the addition of gabapentin 900 mg 3 times daily and duloxetine 60 mg daily, but it still significantly affects his quality of life. He had previously tried nortriptyline but experienced significant side effects. Which of the following is the next best step in management?
- A addition of amitriptyline 25 mg daily
 - B increase the gabapentin dose to 1200 mg 3 times daily
 - C photobiomodulation therapy
 - D spinal cord stimulation
 - E transcutaneous electric nerve stimulation
-

ARTICLE 4: CENTRAL NEUROPATHIC PAIN

-
- 11** Abnormal function of which of the following structures appears to be a nearly universal requirement in the emergence of central neuropathic pain?
- A central tegmental tract
 - B dorsomedial nucleus of the thalamus
 - C nucleus accumbens
 - D spinothalamic tract
 - E superior parietal lobule
-
- 12** Which of the following stroke locations is associated with the highest risk of central poststroke pain?
- A anterior watershed territory
 - B cerebellum
 - C midbrain
 - D middle cerebral artery territory
 - E thalamus
-

13 Which of the following antiseizure medications has been shown in multiple randomized controlled trials to benefit the management of spinal cord injury-related pain?

- A lamotrigine
- B phenytoin
- C pregabalin
- D topiramate
- E valproic acid

14 Which of the following medications should be considered for first-line treatment of central neuropathic pain?

- A baclofen
- B cannabidiol
- C carbamazepine
- D duloxetine
- E mexiletine

15 Which of the following terms is used to describe pain occurring following a stimulus that is not normally painful?

- A allodynia
- B causalgia
- C hyperalgesia
- D nociceptive pain
- E referred pain

ARTICLE 5: OROFACIAL PAIN

16 A 44-year-old woman presents for the evaluation of 1 month of left facial pain. The pain is moderate, aching, and occurs in the left jaw and radiates to the teeth and above the eye. It is constant, and can be exacerbated by chewing hard and chewy foods and by speaking for prolonged periods of time. She does not report any noises of the temporomandibular joint or episodes of locking. In addition, she does not report pain at the palpation of the temporomandibular joints; however, she experiences soreness when opening her mouth wide, in addition to tenderness to palpation of the left masseter muscle that replicated the familiar referral pattern. Her cranial nerves and the rest of the neurologic examination are normal. Which of the following is the most likely diagnosis?

- A hemicrania continua
- B migraine headache
- C myofascial pain with referral
- D temporomandibular joint pain
- E trigeminal neuralgia

- 17** Which of the following disorders is one of the most common causes of secondary trigeminal neuralgia?
- A arteriovenous malformation
 - B connective tissue disease
 - C dural arteriovenous fistula
 - D multiple sclerosis
 - E stroke
-
- 18** A 35-year-old woman with multiple sclerosis presents with a 5-month history of severe paroxysmal pain in the right V2 and V3 distributions that significantly affects her quality of life. Her brain MRI demonstrates a plaque in the right ventral pons and no evidence of compression of the right trigeminal nerve. She has previously tried carbamazepine, oxcarbazepine, gabapentin, and lamotrigine without benefit. Which of the following treatments are most appropriate for this patient?
- A balloon decompression
 - B glycerol rhizotomy
 - C microvascular decompression
 - D radiofrequency ablation
 - E stereotactic radiosurgery
-
- 19** Which of the following blood vessels is most commonly implicated in classic glossopharyngeal neuralgia?
- A anterior inferior cerebellar artery
 - B posterior communicating artery
 - C posterior inferior cerebellar artery
 - D superior cerebellar artery
 - E vertebral artery

ARTICLE 6: WIDESPREAD PAIN SYNDROMES

-
- 20** According to current diagnostic criteria, which of the following features is required for the diagnosis of fibromyalgia but is not required for the diagnosis of chronic widespread pain?
- A different regions of the body affected
 - B duration of pain greater than 3 months
 - C exclusion of any other neurologic diagnosis
 - D normal neuroimaging and electrodiagnostic evaluation
 - E presence of associated symptoms

21 Which of the following features helps to differentiate the nociceptive pain of fibromyalgia from neuropathic pain?

- A constant in intensity
 - B constant in location
 - C dull, deep, aching pain
 - D improved by exertion
 - E worsened by environmental stimuli
-

22 A 40-year-old woman comes to the clinic with a 2-month history of burning pain in her left leg. Approximately 2 weeks before the pain began, she had sprained her left ankle playing soccer and was in a compression bandage for 1 week with resolution of the ankle pain. She notes that the skin is cooler and more purple in color below the knee on the left and that her left foot is more swollen than her right, findings which are verified on exam. She also feels weak on the left when trying to stand on her toes. On examination, she has allodynia in response to light touch over her left leg. Which of the following conditions is most likely in this patient?

- A complex regional pain syndrome
 - B erythromelalgia
 - C fibromyalgia
 - D Lyme disease
 - E Morvan syndrome
-

23 Which of the following medications is approved by the US Food and Drug Administration (FDA) for the treatment of both depression and fibromyalgia or musculoskeletal pain?

- A duloxetine
 - B fluoxetine
 - C gabapentin
 - D naltrexone
 - E pregabalin
-

24 Which of the following regions are part of the *pain matrix*, demonstrating reductions in gray matter volumes in patients with chronic pain?

- A precuneus
- B prefrontal cortex
- C putamen
- D somatosensory cortex
- E superior temporal gyrus

ARTICLE 7: OPIOIDS AND CANNABINOIDs IN NEUROLOGY PRACTICE

25 What are the “four A’s” that should be documented when seeing a patient for follow-up who is on opioids?

- A aberrant behavior, activities, adverse effects, analgesia
 - B abstinence, action, alertness, anxiety
 - C abuse, acceptance, assure, attest
 - D adherence, agitation, ameliorate, appeal
 - E alcohol use, alliance, aggression, autonomy
-

26 Which of the following was the most common cause of opioid overdose in 2022 and 2023?

- A fentanyl
 - B heroin
 - C methadone
 - D morphine
 - E oxycodone
-

27 A 73-year-old man with a medical history of chronic obstructive pulmonary disease and severe obstructive sleep apnea presents with constant 10/10 low back pain due to postlaminectomy syndrome. His pain has not responded to nonpharmacologic and nonopioid pharmacologic therapy including gabapentin, pregabalin, and duloxetine. Treatment with opioid medications is being considered. Which of the following is the best medication option for this patient?

- A buprenorphine
 - B hydrocodone
 - C methadone
 - D morphine
 - E oxymorphone
-

28 A 55-year-old woman with a medical history of diabetic neuropathy with severe neuropathic pain presents to the emergency department with recurrent episodes of nausea, vomiting, and abdominal pain. She notes that with prior episodes, taking a hot bath was helpful, although this time her symptoms were severe enough to warrant the emergency department. Which of the following is the most likely cause of the patient’s symptoms?

- A buprenorphine
- B cannabis
- C fentanyl
- D heroin
- E tramadol

ARTICLE 8: NEUROMODULATION FOR NEUROPATHIC PAIN SYNDROMES

29 Which of the following spinal cord stimulation parameter changes would be most likely to shift a patient's experience from a tingling or vibratory paresthesia to paresthesia-free pain relief?

- A change from cathodic to anodic stimulation
- B change from monopolar to bipolar stimulation
- C decreased stimulation pulse amplitude
- D increased stimulation frequency
- E increased stimulation pulse width

30 Which of the following neuromodulation modalities would be the best choice for a patient with a painful ulnar neuropathy that is unresponsive to medical management and without any detectable area of compression?

- A deep brain stimulation of the periaqueductal gray nucleus
- B dorsal root ganglion stimulation
- C peripheral nerve stimulation
- D spinal cord stimulation
- E transcranial magnetic stimulation of the motor cortex

31 Which of the following neuromodulation approaches should be considered first in a patient with complex regional pain syndrome?

- A deep brain stimulation
- B direct cranial stimulation
- C repetitive transcranial magnetic stimulation
- D spinal cord stimulation
- E transcutaneous electrical nerve stimulation

32 Which of the following is approved by the US Food and Drug Administration (FDA) for intrathecal infusion to treat chronic pain?

- A baclofen
- B bupivacaine
- C clonidine
- D fentanyl
- E ziconotide

33 Which of the following deep brain stimulation targets has been identified as central to the subjective pain experience and particularly the affective component of pain?

- A amygdala
- B anterior cingulate cortex
- C orbitofrontal cortex
- D periaqueductal grey nucleus
- E ventral thalamus

ARTICLE 9: CHRONIC PAIN PSYCHOLOGY IN NEUROLOGY PRACTICE

34 Which of the following is a strategy utilized by cognitive behavioral therapy for pain?

- A acceptance
- B activity pacing
- C mindfulness
- D psychological flexibility
- E self-as-context

35 Increasing a patient's psychological flexibility is the goal of which of the following psychological interventions?

- A acceptance and commitment therapy
- B biofeedback
- C cognitive behavioral therapy
- D dialectical behavioral therapy
- E hypnosis

36 Which of the following psychological treatments specifically targets nociceptive pain?

- A biofeedback
- B clinical hypnosis
- C cognitive behavioral therapy
- D integrative psychological treatment for centralized pain
- E mindfulness-based stress reduction

37 Which of the following psychological treatments has the strongest evidence of benefit in treating chronic pain?

- A acceptance and commitment therapy
- B biofeedback
- C clinical hypnosis
- D integrative psychological treatment for centralized pain
- E mindfulness-based stress reduction

ARTICLE 10: PEDIATRIC PAIN

38 Which of the following rare diseases is associated with chronic visceral pain?

- A Charcot-Marie-Tooth disease type 1
- B Fabry disease
- C Gaucher disease
- D neurofibromatosis type 1
- E SCN9 variations

39 Which of the following medications is frequently the initial choice in treating pediatric neuropathic pain?

- A amitriptyline
- B clonidine
- C duloxetine
- D phenytoin
- E pregabalin

40 Which of the following medications has a noted side effect of confusion?

- A amitriptyline
- B clonidine
- C gabapentin
- D mexiletine
- E zonisamide

Postreading Self-Assessment and CME Test—Preferred Responses

By Nuri Jacoby, MD; James M. W. Owens Jr, MD, PhD

PAIN MANAGEMENT IN NEUROLOGY

Following are the preferred responses to the questions in the Postreading Self-Assessment and CME Test in this *Continuum* issue. The preferred response is followed by an explanation and a reference with which you may seek more specific information. You are encouraged to review the responses and explanations carefully to evaluate your general understanding of the article topic. The comments and references included with each question are intended to encourage independent study.

US PARTICIPANTS: Upon completion of the Postreading Self-Assessment and CME Test and issue evaluation online at continpub.com/CME, participants may earn up to 20 AMA PRA Category 1 Credits™ toward SA-CME. US participants have up to 3 years from the date of publication online to earn SA-CME credits.

CANADIAN PARTICIPANTS. This program is an Accredited Self-Assessment Program (Section 3) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada and approved by the University of Calgary Office of Continuing Medical Education and Professional Development. Refer to the CME tab on ContinuumJournal.com for dates of accreditation. Canadian participants should visit MAINPORT (mainport.org) to record learning and outcomes. Canadian participants can claim a maximum of 20 hours per issue (credits are automatically calculated).

ARTICLE 1: PRINCIPLES OF PAIN MANAGEMENT

- 1 The preferred response is **D (suicidal ideation)**. Of the answer choices, only an increased risk of suicidal ideation is a boxed warning of duloxetine. For more information, refer to **page 1333** of the *Continuum* article "Principles of Pain Management."
- 2 The preferred response is **A (cognitive dysfunction)**. Older adult patients with polypharmacy, as is the case with this patient, are susceptible to serious side effects, including cognitive dysfunction and increased risk of falls. This patient uses multiple medications that can cause cognitive dysfunction, particularly amitriptyline, although topiramate can as well. For more information, refer to **page 1334** of the *Continuum* article "Principles of Pain Management."
- 3 The preferred response is **B (different pain mechanisms will need to be distinguished from each other)**. With the *International Classification of Diseases, Eleventh Edition*, it is expected that providers will need to distinguish pain mechanisms in addition to underlying pathologies. For more information, refer to **page 1325** of the *Continuum* article "Principles of Pain Management."
- 4 The preferred response is **B (moderate physical activity)**. Moderate physical activity is associated with reduced rates of chronic pain. The other conditions and factors are associated with increased rates of chronic pain. For more information, refer to **page 1330** of the *Continuum* article "Principles of Pain Management."

ARTICLE 2: SPINE PAIN

- 5 The preferred response is **C (facet joint, sacroiliac joint, or both)**. Pain worsened by prolonged sitting suggests a condition affecting the facet joint, sacroiliac joint, or both. Worsened pain with weight bearing and bending backward or extension can also implicate the facet joints. For more information, refer to **page 1349** of the *Continuum* article "Spine Pain."

- 6** The preferred response is **D (cervical radiculopathy)**. Cervical pain relieved by gently pulling upward on the head and neck with the patient in a spine-neutral position suggests a cervical radiculopathy. The Spurling test, performed by extending, laterally flexing, and rotating the neck to one side, would tend to reproduce or exacerbate symptoms, implicating nerve root tension from compression or inflammatory irritation. For more information, refer to **page 1351** of the *Continuum* article “Spine Pain.”
-
- 7** The preferred response is **B (low back pain with radiation into the buttock)**. Low back pain with radiation into the buttock or groin would suggest cluneal nerve targets for injection. For more information, refer to **page 1355** of the *Continuum* article “Spine Pain.”

ARTICLE 3: PERIPHERAL NEUROPATHIC PAIN

- 8** The preferred response is **B (duloxetine)**. Duloxetine and spinal cord stimulation are treatment options that target central sensitization, a key pathophysiologic mechanism of neuropathic pain. For more information, refer to **page 1366** of the *Continuum* article “Peripheral Neuropathic Pain.”
-
- 9** The preferred response is **D (Neuropathic Pain Symptom Inventory)**. Patient-reported outcome tools can be valuable tools to help assess neuropathic pain, including the severity and quality of pain and associated comorbid symptoms. Of the responses listed, the Neuropathic Pain Symptom Inventory specifically assesses the severity of neuropathic pain symptoms. For more information, refer to **page 1369** of the *Continuum* article “Peripheral Neuropathic Pain.”
-
- 10** The preferred response is **D (spinal cord stimulation)**. Of the possible options, spinal cord stimulation, which is approved by the US Food and Drug Administration (FDA) for the treatment of painful diabetic neuropathy, is most likely to help the patient’s pain. Given the patient’s age and prior side effects to nortriptyline, the addition of amitriptyline is not recommended. Increasing the dose of gabapentin from 900 mg 3 times daily to 1200 mg 3 times daily is unlikely to significantly alter the patient’s severe pain. For more information, refer to **page 1375** of the *Continuum* article “Peripheral Neuropathic Pain.”

ARTICLE 4: CENTRAL NEUROPATHIC PAIN

- 11 The preferred response is **D (spinothalamic tract)**. Abnormal function of the spinothalamic tract appears to be a nearly universal requirement in the emergence of central neuropathic pain. For more information, refer to **page 1382** of the *Continuum* article “Central Neuropathic Pain.”
- 12 The preferred response is **E (thalamus)**. Strokes involving the thalamus and the lateral aspect of the medulla are associated with the highest risk of central poststroke pain. For more information, refer to **page 1384** of the *Continuum* article “Central Neuropathic Pain.”
- 13 The preferred response is **C (pregabalin)**. Pregabalin has been shown in multiple randomized controlled clinical trials to benefit the treatment of spinal cord injury-related pain. For more information, refer to **page 1387** of the *Continuum* article “Central Neuropathic Pain.”
- 14 The preferred response is **D (duloxetine)**. First-line treatment of central neuropathic pain would include duloxetine, as well as venlafaxine, pregabalin, and gabapentin. For more information, refer to **page 1392** of the *Continuum* article “Central Neuropathic Pain.”
- 15 The preferred response is **A (allodynia)**. Allodynia refers to pain following a stimulus that is not normally painful. For more information, refer to **page 1383** of the *Continuum* article “Central Neuropathic Pain.”

ARTICLE 5: OROFACIAL PAIN

- 16 The preferred response is **C (myofascial pain with referral)**. This patient presents symptomatology of a myogenous temporomandibular disorder. The two main diagnostic categories of temporomandibular disorders are temporomandibular joint disorders and masticatory muscle disorders. The patient’s tenderness to palpation of the masseter muscle and referral pattern points to myofascial pain with referral (masticatory muscle disorder) as the cause of the patient’s temporomandibular disorder. For more information, refer to **page 1412** of the *Continuum* article “Orofacial Pain.”

-
- 17 The preferred response is **D (multiple sclerosis)**. The two most common causes of secondary trigeminal neuralgia are multiple sclerosis and benign tumors of the cerebellopontine angle, which include acoustic neuromas, meningiomas, cholesteatomas, and epidermoid cysts. The other responses can cause secondary trigeminal neuralgia, although less commonly than multiple sclerosis. For more information, refer to **page 1409** of the *Continuum* article "Orofacial Pain."
-
- 18 The preferred response is **E (stereotactic radiosurgery)**. Microvascular decompression, stereotactic radiosurgery, and neuroablative procedures are all options for refractory trigeminal neuralgia. For secondary trigeminal neuralgia due to multiple sclerosis, tumors, or stroke, stereotactic radiosurgery is the preferred method, especially if there is no evidence of trigeminal nerve compression on imaging. For more information, refer to **page 1411** of the *Continuum* article "Orofacial Pain."
-
- 19 The preferred response is **C (posterior inferior cerebellar artery)**. Classic glossopharyngeal neuralgia, similar to classic trigeminal neuralgia, is thought to be caused by vascular compression. The posterior inferior cerebellar artery is the most common vessel involved. For more information, refer to **page 1411** of the *Continuum* article "Orofacial Pain."

ARTICLE 6: WIDESPREAD PAIN SYNDROMES

- 20 The preferred response is **E (presence of associated symptoms)**. The presence of associated symptoms such as fatigue or sleep problems is required for the diagnosis of fibromyalgia but not for the diagnosis of chronic widespread pain. Different regions of the body affected by pain and a pain duration of more than 3 months are required for both diagnoses. The exclusion of any other neurologic diagnosis and a normal neuroimaging and electrodiagnostic evaluation are not required for either diagnosis. For more information, refer to **page 1430** of the *Continuum* article "Widespread Pain Syndromes."

- 21** The preferred response is **E (worsened by environmental stimuli)**. Patients with fibromyalgia may report worsening of pain by environmental stimuli. Their pain will tend to fluctuate in intensity and location and be worsened by exertion. It may be described as dull, deep, and aching (nociceptive in quality) or burning and shooting (neuropathic in quality). For more information, refer to **page 1429** of the *Continuum* article “Widespread Pain Syndromes.”
- 22** The preferred response is **A (complex regional pain syndrome)**. This patient meets the Valencia adaptation of the Budapest Criteria for complex regional pain syndrome given her associated vasomotor, edematous, and motor symptoms with sensory, vasomotor, and edematous signs. For more information, refer to **page 1434** of the *Continuum* article “Widespread Pain Syndromes.”
- 23** The preferred response is **A (duloxetine)**. Duloxetine has been approved by the US Food and Drug Administration (FDA) for the treatment of both depression and fibromyalgia or musculoskeletal pain. Milnacipran is FDA approved for the treatment of fibromyalgia but not for depression, though it is often used off label for this purpose. For more information, refer to **page 1442** of the *Continuum* article “Widespread Pain Syndromes.”
- 24** The preferred response is **B (prefrontal cortex)**. The prefrontal cortex, together with the cingulate and insula, have been shown to have decreased gray matter volume in patients with chronic pain and are commonly referred to as the *pain matrix*. For more information, refer to **page 1432** of the *Continuum* article “Widespread Pain Syndromes.”

ARTICLE 7: OPIOIDS AND CANNABINOIDs IN NEUROLOGY PRACTICE

- 25** The preferred response is **A (aberrant behavior, activities, adverse effects, analgesia)**. The four A's to document and assess when seeing patients for follow-up who are on opioids are analgesia, activities or functional benefit, adverse effects from the opioids, and aberrant behavior or the patient's adherence to the care plan and risk-mitigation strategies. For more information, refer to **page 1463** of the *Continuum* article “Opioids and Cannabinoids in Neurology Practice.”
- 26** The preferred response is **A (fentanyl)**. Synthetic opioids other than methadone, including fentanyl and its derivates, were the most common cause of opioid overdoses in 2022 and 2023, followed by natural and semisynthetic opioids and heroin. For more information, refer to **page 1451** of the *Continuum* article “Opioids and Cannabinoids in Neurology Practice.”

27 The preferred response is **A (buprenorphine)**. This patient has medical risk factors for respiratory depression due to opioid use. Therefore, if the clinician decides to start opioid medication, buprenorphine would be the best option because of its respiratory depression ceiling effect. For more information, refer to **page 1464** of the *Continuum* article “Opioids and Cannabinoids in Neurology Practice.”

28 The preferred response is **B (cannabis)**. This patient is presenting with symptoms consistent with cannabis hyperemesis syndrome. Hot water bathing or showering for symptomatic relief is pathognomonic for this syndrome. For more information, refer to **page 1468** of the *Continuum* article “Opioids and Cannabinoids in Neurology Practice.”

ARTICLE 8: NEUROMODULATION FOR NEUROPATHIC PAIN SYNDROMES

29 The preferred response is **D (increased stimulation frequency)**. Increasing stimulation frequency from 40 Hz to 60 Hz to greater than 1 kHz is most likely to shift from a tingling or vibratory paresthesia to paresthesia-free pain relief. For more information, refer to **page 1478** of the *Continuum* article “Neuromodulation for Neuropathic Pain Syndromes.”

30 The preferred response is **C (peripheral nerve stimulation)**. Peripheral nerve stimulation would be the best first neuromodulatory choice for a patient with a focal pharmacoresistant painful mononeuropathy that is not otherwise surgically amenable. For more information, refer to **page 1480** of the *Continuum* article “Neuromodulation for Neuropathic Pain Syndromes.”

31 The preferred response is **D (spinal cord stimulation)**. Spinal cord stimulation would be the first neuromodulation therapy considered and is US Food and Drug Administration (FDA) approved for the treatment of complex regional pain syndrome. For more information, refer to **page 1483** of the *Continuum* article “Neuromodulation for Neuropathic Pain Syndromes.”

32 The preferred response is **E (ziconotide)**. Ziconotide, an N-type calcium channel toxin, is approved by the US Food and Drug Administration (FDA) for intrathecal infusion in chronic pain. Morphine is also FDA approved, while bupivacaine, fentanyl, and clonidine are used off label. Baclofen is FDA approved for neurogenic spasticity but not for chronic pain. For more information, refer to **page 1486** of the *Continuum* article “Neuromodulation for Neuropathic Pain Syndromes.”

33 The preferred response is **B (anterior cingulate cortex)**. The anterior cingulate cortex appears to be central in mediating the affective component of pain. Other regions implicated in the subjective pain experience include the insula and dorsolateral prefrontal cortex. For more information, refer to **page 1489** of the *Continuum* article “Neuromodulation for Neuropathic Pain Syndromes.”

ARTICLE 9: CHRONIC PAIN PSYCHOLOGY IN NEUROLOGY PRACTICE

34 The preferred response is **B (activity pacing)**. The basic principles of cognitive behavioral therapy for pain include pain education, activity pacing, cognitive reframing with an emphasis on decreasing pain catastrophizing, sleep hygiene, and an emphasis on exercise and movement. Activity pacing refers to teaching patients to focus on consistency of activity rather than intensity to help avoid pain flares and encourage movement. For more information, refer to **page 1507** of the *Continuum* article “Chronic Pain Psychology in Neurology Practice.”

35 The preferred response is **A (acceptance and commitment therapy)**. Psychological flexibility, defined as the ability to be present in the moment regardless of unpleasant feelings and sensations while being guided by value goals, is an overarching therapeutic process targeted in acceptance and commitment therapy. For more information, refer to **page 1507** of the *Continuum* article “Chronic Pain Psychology in Neurology Practice.”

36 The preferred response is **D (integrative psychological treatment for centralized pain)**. Nociplastic pain is defined as pain arising from altered function of pain-related sensory pathways causing increased sensitivity. Although all of the responses can be used to treat nociplastic pain, integrative psychological treatment for centralized pain specifically targets nociplastic rather than nociceptive or neuropathic pain. For more information, refer to **page 1511** of the *Continuum* article “Chronic Pain Psychology in Neurology Practice.”

- 37** The preferred response is **A (acceptance and commitment therapy)**. Acceptance and commitment therapy and cognitive behavioral therapy are the two psychological treatment interventions that have the strongest evidence of benefit. The other responses have demonstrated varying evidence of benefit. For more information, refer to **page 1503** of the *Continuum* article “Chronic Pain Psychology in Neurology Practice.”

ARTICLE 10: PEDIATRIC PAIN

- 38** The preferred response is **C (Gaucher disease)**. Chronic visceral pain is associated with Gaucher disease. The other conditions are associated with hand and foot pain (Fabry disease and SCN9 variations), more general extremity pain (Charcot-Marie-Tooth disease type 1), and more diffuse nerve, skin, and skeletal pain (neurofibromatosis type 1). For more information, refer to **page 1518** of the *Continuum* article “Pediatric Pain.”
- 39** The preferred response is **A (amitriptyline)**. While all the agents listed can be used to treat neuropathic pain in children, amitriptyline is often considered the initial choice given the extensive experience with the medication and its reasonable efficacy and tolerability. For more information, refer to **page 1524** of the *Continuum* article “Pediatric Pain.”
- 40** The preferred response is **C (gabapentin)**. Gabapentin can cause fatigue, nausea, and confusion. For more information, refer to **page 1526** of the *Continuum* article “Pediatric Pain.”

LEARNING OBJECTIVES AND CORE COMPETENCIES

Learning Objectives

Upon completion of this *Continuum: Lifelong Learning in Neurology* Pain Management in Neurology issue, participants will be able to:

- ◆ Discuss pain classification, assessment, and management, including the use of a differential diagnosis that addresses biological, psychological, and social factors and reflects the substantive progress in pain research and clinical care
- ◆ Identify strategies for a comprehensive assessment and intervention plan for patients experiencing spine pain
- ◆ Describe the current assessment and measurement, diagnosis, and treatment approaches for peripheral neuropathic pain
- ◆ Describe the diagnosis and treatment of central neuropathic pain associated with spinal cord injury, stroke, and multiple sclerosis
- ◆ Describe the multiple etiologies, diagnosis, and management of orofacial pain
- ◆ Discuss the clinical features, pathophysiology, diagnostic criteria, differential diagnoses, and treatment for chronic widespread pain syndromes
- ◆ Delineate the current state of opioid and cannabinoid prescribing for neurologic pain conditions and describe risk mitigation strategies to optimize outcomes for patients with chronic pain
- ◆ Discuss different modalities of neuromodulation for chronic neuropathic pain and understand factors that influence patient selection and common long-term complications
- ◆ Describe established and emerging psychological treatments for patients with chronic pain
- ◆ Identify pain disorders frequently encountered in pediatric practice and implement effective treatment approaches

Core Competencies

This *Continuum: Lifelong Learning in Neurology* Pain Management in Neurology issue covers the following core competencies:

- ◆ Patient Care and Procedural Skills
- ◆ Medical Knowledge
- ◆ Practice-Based Learning and Improvement
- ◆ Interpersonal and Communication Skills
- ◆ Professionalism
- ◆ Systems-Based Practice

LIST OF ABBREVIATIONS

Pain Management in Neurology

AAN	American Academy of Neurology	HIV	Human immunodeficiency virus
AAAPT	Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks—American Pain Society Pain Taxonomy	IASP	International Association for the Study of Pain
ACR	American College of Rheumatology	ICD	International Classification of Diseases
ACT	Acceptance and commitment therapy	ICHD	International Classification of Headache Disorders
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid	ICOP	International Classification of Orofacial Pain
ATP	Adenosine triphosphate	IgG	Immunoglobulin G
CBD	Cannabidiol	IR	Immediate release
CBT	Cognitive behavioral therapy	IV	Intravenous
CDC	Centers for Disease Control and Prevention	IVIg	intravenous immunoglobulin
CF	Conversion factor	LGBTQ+	Lesbian, gay, bisexual, transgender, and queer
CISS	Constructive interference in steady state	LGI-1	Leucine-rich glioma inactivated 1
CMAP	Compound muscle action potential	M1	Primary motor cortex
CNS	Central nervous system	MEDD	Morphine equivalent daily dosage
COMT	Catechol-O-methyltransferase	MEG	Magnetoencephalography
COVID-19	Coronavirus 2019	MME	Morphine milligram equivalent
CPAP	Continuous positive airway pressure	MRA	Magnetic resonance angiography
CR	Controlled release	MRI	Magnetic resonance imaging
CRPS	Complex regional pain syndrome	mRNA	Messenger ribonucleic acid
CSF	Cerebrospinal fluid	MRV	Magnetic resonance venography
CT	Computed tomography	MS	Multiple sclerosis
DBS	Deep brain stimulation	NIH	National Institutes of Health
DEA	US Drug Enforcement Administration	NMDA	N-methyl-D-aspartate
DNA	Deoxyribonucleic acid	NMO	Neuromyelitis optica
DoD	US Department of Defense	OA	Opioid Analgesic
DSM-5	<i>Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition</i>	PET	Positron emission tomography
DWI	Diffusion-weighted imaging	PROMIS	Patient-Reported Outcomes Measurement Information System
ECG	Electrocardiogram	PT	Physical therapy
EEG	Electroencephalogram	REMS	Risk Evaluation and Mitigation Strategy
EMG	Electromyography	SAFE	Safety, appropriateness, fiscal neutrality, and efficacy
FABER	Flexion, abduction, and external rotation	SAMHSA	Substance Abuse and Mental Health Services Administration
FDA	US Food and Drug Administration	SLE	Systemic lupus erythematosus
FIESTA	Fast imaging employing steady state acquisition	SNRI	Serotonin-norepinephrine reuptake inhibitor
FLACC	Faces, Legs, Activity, Cry, and Consolability Observational Tool	SPECT	Single-photon emission computed tomography
FLAIR	Fluid-attenuated inversion recovery	SSRI	Selective serotonin reuptake inhibitor
fMRI	Functional magnetic resonance imaging	SSS	Symptom severity scale
GABA	γ -aminobutyric acid	TENS	Transcutaneous electric nerve stimulation
GABAergic	γ -aminobutyric acid-mediated	THC	Delta-9-tetrahydrocannabinol
GAD65	Glutamic acid decarboxylase 65	TIRF	Transmucosal immediate-release fentanyl
GRE	Gradient recalled echo	TMJ	Temporomandibular joint
HCP	Health care provider	TMS	Transcranial magnetic stimulation
		TRPV1	Transient receptor potential cation channel subfamily V member 1
		TSH	Thyroid-stimulating hormone
		US	United States
		VA	Department of Veterans Affairs
		WHO	World Health Organization
		WPI	Widespread pain index

PAIN MANAGEMENT IN NEUROLOGY

ARTICLE 1: PRINCIPLES OF PAIN MANAGEMENT

Beth B. Hogans, MS (Biomath), MD, PhD. Continuum (Minneapolis). October 2024; 30 (5 Pain Management in Neurology):1318–1343.

ABSTRACT

OBJECTIVE:

This article introduces the general principles of assessing, diagnosing, and managing pain relevant to neurologic practice.

LATEST DEVELOPMENTS:

Scientific understanding of and clinical practices related to pain and pain management are advancing. The field is remarkable for the diversity of health professions engaged in this effort, including physicians, scientists, psychologists, pharmacists, and many others. Pain classification is transforming with pending changes to the *International Classification of Diseases* diagnostic coding system, and pain assessment has moved toward consistent application of the biopsychosocial model. The diagnosis of pain has continued to become more sophisticated with the development of additional testing modalities, clearer classification systems, and diagnostic criteria. Pain management requires both pharmacologic and nonpharmacologic elements; systematic review evidence for both of these and interventional and surgical management are increasingly available. The context of treatment remains important given the impact of social determinants of health and limitations of access to diagnostic and treatment resources. Due to global and interprofessional collaborations as well as new research funding, the outlook is positive.

ESSENTIAL POINTS:

Pain is a protean experience for humans; functional MRI (fMRI) and other research modalities show that pain perception is highly multifocal, and modulation occurs at many nervous system levels. Neurologists bring special skills to pain evaluation and management, are well equipped to appreciate both the focal and diffuse nature of pain, and can envision how pain attenuates sleep, cognitive function, mobility, motivation, and social connection. By operationalizing expert knowledge of the nervous system, implementing relevant therapies, and collaborating with diverse health professions to manage pain, neurologists can succeed at and find meaning in optimizing patient outcomes.

KEY POINTS

- The systematic classification of facial pain and headache disorders in the International Classification of Headache Disorders allows for relatively detailed diagnoses of these disorders in both inpatient and outpatient neurology settings that are consistent from one location to another.
- The neurologic management of headache and facial pain includes acknowledging the patient's experience of pain and related symptoms; seeking diagnostic information through neurologic examination and diagnostic testing; and integrative management including pharmacologic and nonpharmacologic therapies, potentially incorporating lifestyle modifications using a "whole-health" approach and interprofessional collaboration.
- Pathologic processes giving rise to spine pain can be biomechanical, musculoskeletal, neuropathic, nociceptive, central sensitization mediated, infectious, and immune mediated.
- Common neuropathic pain patterns include a distal symmetrical gradient-type pattern, neuropathy affecting only small fibers (typically diffusely distributed), "named nerve" patterns, radicular (dermatomal) patterns, and visceral involvement patterns.
- There are no well-established clinical tests currently used to determine the presence of central sensitization.
- Given the frequency with which patients with complex pain conditions are encountered in clinical practice, neurologists need to know that several pain mechanisms may be active at any phase of treatment.
- It is often necessary to initiate symptomatic pain treatment concurrently with the diagnostic workup so that patients do not continue to experience uncontrolled pain while awaiting test results.
- New pain classification systems will require a major revision to coding practices as practitioners will be expected to distinguish both pain mechanisms and underlying pathologies.
- Features of pain presentation of particular interest include symptom quality, region, severity, and timing, as well as identifying factors that alleviate and worsen the symptoms.
- In the diagnosis of pain-associated conditions, there is a role for the assessment of musculoskeletal dysfunction.
- Pain may impact motor, cerebellar, and cognitive function, but these effects will vary by etiology.
- Health systems vary in terms of both the opportunities for interprofessional collaborative care for patients with chronic pain and the provision of a broad range of therapies.
- Interprofessional collaboration and the principles of teamwork, communication, ethics and values, and the responsibility and roles of other professions can deliver pain care that is patient-centered and responsive to the community's needs.
- Normal nociceptive processing, like all somatosensory signals, involves (1) transduction, the process of translating external energy (eg, heat, cold, pressure) into action potentials; (2) transmission, which carries information from the peripheral sensing structures to the spinal and supraspinal centers; (3) modulation, which tempers the flow of information; and (4) perception, which for pain is highly multicentric.
- The development of an appropriate differential diagnosis requires knowledge of the most relevant common pain-associated conditions as well as those that are potentially catastrophic.
- For structural spine lesions, imaging is typically considered the definitive diagnostic test, although, in the context of suspected nerve or root compression, nerve conduction studies and EMG may be necessary to appraise functional impact.
- For many patients, a helpful approach is to invite the patient to identify the psychosocial factors that they believe are important to their current pain management.
- Neurologists should be vigilant and diligent in screening for affective disorders and suicidality as the risk for suicide is increased for patients with chronic pain.
- Even modest amounts of pain may worsen sleep quality and limit sleep duration; at the same time, poor quality and limited duration of sleep will limit patients' self-modulatory pain mechanisms.
- Motivational interviewing and acceptance and commitment therapy, which focuses on pursuing activities that have the greatest personal meaning, can be very helpful for prioritizing activities and selecting therapies for patients who have pain.

- Disability related to pain can be the most important aspect of a patient's experience of pain. For some patients, pain entails motor impairment, dyscoordination, or autonomic dysregulation.
- Pharmacologic and nonpharmacologic management are both important to optimize pain control while minimizing problematic side effects.
- All pain-active antidepressants carry a boxed warning for suicidality risks; these should be explained to patients and instructions for how to respond in the event of suicidal ideation should be provided.
- Nonpharmacologic therapies for pain-associated conditions managed in neurology practice continue to accrue evidence of measurable benefits.
- Physical activity is important for many reasons, including the upregulation of endogenous analgesic mechanisms and preservation of function, and psychological support is important to reduce pain-related interference with function, suffering, and pain intensity.
- Incorporating coordinated nonpharmacologic therapies can reduce pharmacologic focus and polypharmacy, which is associated with cognitive interference and increased falls in older adults and accidental injury, substance use disorders, and long-term dependency in passive pain relief strategies.
- By working with collaborating providers (eg, physical therapists and clinical psychologists), patients will make important and helpful connections that foster a proactive dynamic toward pain, including increased pain self-efficacy.
- Neurologists bring a special skill set to pain management, with advanced training in neurologic localization, familiarity with issues pertaining to impairment and disability, and expert knowledge of several medications used for chronic pain.

ARTICLE 2: SPINE PAIN

Vernon B. Williams, MD, FAAN. Continuum (Minneapolis Minn). October 2024; 30 (5 Pain Management in Neurology):1344–1362.

ABSTRACT

OBJECTIVE:

Spine pain is one of the most common presenting concerns in health care settings. This article reviews clinical strategies for evaluating and managing patients with spine pain.

LATEST DEVELOPMENTS:

Minimally invasive interventional procedures, virtual reality, predictive analytics, neuromodulation, and other evolving technologies are significantly impacting the management of spine pain. Advances in modern pain science have also led to effective skills and treatment strategies, including patient interviews and queries for insight regarding pain, education, and cognitive restructuring, and adjusting the timing of examination (after reeducation) and examination techniques to encourage the experience of movement in the absence of assumed tissue damage. An evolving understanding of the influence of patient-centric thoughts, framing, emotional status, and cognitive restructuring's influence on the brain's response to perceived threat are important aspects of spine pain management.

ESSENTIAL POINTS:

The correlation of clinical presentations with structural abnormalities is necessary but insufficient to evaluate and manage spine pain. Modern pain science acknowledges pain as a subjective experience but recognizes a critical distinction between tissue damage, nociception, and the experience of pain. What and how we communicate with patients, as well as evolving neuromodulation technologies, augment conventional approaches.

KEY POINTS

- Many patients with spine pain conceive of and frame their experience as the direct and sole result of physical stimuli (“pain signals”) resulting from tissue damage. Modern pain science recognizes the inadequacy of this simplistic concept.
- Modern pain science establishes additional factors such as expectation, the brain’s processing and interpretation of sensory input, variations in nociceptive thresholds, and other factors that are critical to the pain experience.
- Modern pain science and emerging theories related to the experience of pain involve far more complex physiologic activity than the ascending and descending pain nervous system pathways typically used to show nociceptive and modulating signals.
- Pain is defined as an unpleasant sensory and emotional experience associated with or resembling that associated with actual or potential tissue damage.
- Communication with patients who have spine pain should reinforce concepts related to modern pain science. Without vigilant attention, actions and words can negatively impact patient insight, framing, and outcome.
- When devising spine pain management strategies, the consideration of neuroplasticity will involve an expanded appreciation of biological factors (at the level of the spinal cord, within the brain, and distributed throughout the body) contributing to the pain experience and prevent inappropriate and sole focus on the simple treatment of a peripheral anatomic spine “pain generator.”
- Likely owing to the maladaptive effects of neuroplasticity with time, chronic pain becomes less specific relative to location.
- Axial pain without significant radiation into the legs (particularly below the knee) suggests vertebral body, diskogenic, facet, sacroiliac, or muscular conditions.
- Radicular or radiating pain from the spine into one arm or leg suggests nerve root compression, whereas pain radiating from the spine into both arms or both legs symmetrically suggests an intraspinal condition.
- Provocative testing is a crucial aspect of the clinical evaluation of spine pain.
- Routine imaging for individuals with spine pain who have nonspecific symptoms, no red flags, and have not had appropriate trials of conservative treatments can be costly, ineffective, and may contribute negatively to patient outcomes.
- Cultural beliefs, past experiences, personal values, family or financial concerns, or other priorities may reasonably influence management decisions for patients with spine pain.
- Alternative routes of administration and nontraditional forms of analgesics should be considered to minimize risk, minimize side effects, maximize safety profile, and optimize effect in patients with spine pain.
- Drug formulations with rapid onset of action, long-acting or gradual absorption, or those that do not require traditional gastrointestinal absorption (eg, intranasal, transmucosal, and transdermal versions of anti-inflammatories, partial agonist opioids) may be safer and more effective alternatives to consider in appropriate candidates with spine pain.
- Diagnostic injections for spine pain should be limited to local anesthetic and not include steroids, which can confound the interpretation of results.
- Pain diaries or other strategies that allow for the review of the patient’s response as documented in real time may be more accurate than retrospective description, memory, or the misinterpretation of a temporary effect as ineffective.
- Increasingly, and in concert with increasing experience and insight regarding neuroplasticity, neuromodulation strategies are being successfully employed in the treatment of spine pain. Moreover, the use of these strategies is no longer limited to a “last resort” or in the event of inadequate response to other intervention trials.
- Surgical intervention in the spine can be categorized relative to the goal of decompression, fusion to reduce maladaptive motion, or disk replacement to facilitate motion.
- Health equity, health disparities, and social determinants of health must be recognized in light of the

inevitable and inarguable effects on spine pain and addressed in all approaches to spine pain evaluation and management.

ARTICLE 3: PERIPHERAL NEUROPATHIC PAIN

Victor Wang, MD, PhD; Miroslav Baćkonja, MD. Continuum (Minneapolis). October 2024; 30 (5 Pain Management in Neurology):1363–1380.

ABSTRACT

OBJECTIVE:

This article synthesizes current knowledge on neuropathic pain, with a brief review of mechanisms, diagnostic approaches, and treatment strategies to help neurologists provide effective and individualized care for patients with this complex condition.

LATEST DEVELOPMENTS:

The most promising developments in peripheral neuropathic pain are related to the molecular biology of the peripheral nervous system. Systematic molecular and genetic analyses of peripheral nerve terminals and dorsal root ganglia have advanced our understanding of the genetics of function and disease of peripheral nerves, as well as their physiology and clinical manifestations.

ESSENTIAL POINTS:

Peripheral neuropathic pain, similar to central neuropathic pain, is primarily influenced by the biology and pathophysiology of the underlying structures, peripheral sensory nerves, and their central pathways. The clinical course is widely variable in sensory symptoms and intensities, natural history, and response to treatments.

KEY POINTS

- When discussing painful peripheral neuropathies, patients usually describe typical painful sensations such as tingling, pins and needles, burning, and stabbing, termed *paresthesia* and *dysesthesia*, as most bothersome.
- In addition to paresthesia and dysesthesia, neuropathic pain frequently includes components of hyperalgesia (worsened pain from noxious stimuli) and allodynia (pain caused by innocuous stimuli).
- Most peripheral neuropathic pain disorders are chronic, with variability in symptom manifestations and disease course.
- There is no curative therapy for peripheral neuropathic pain and, in all cases, the therapy and management are primarily symptomatic, to relieve pain and improve function and quality of life.
- A wide range of disorders may present with peripheral neuropathic pain as a clinical feature.
- Several large clinical studies have demonstrated that painful neuropathies share distinct sensory pain phenotypes regardless of etiologic pathology, pointing to shared pain pathophysiologic mechanisms.
- To understand the dual peripheral and central nature of peripheral neuropathic pain pathophysiology, the diagnostic workup must account for peripheral nerve pathology and the sensory manifestations of peripheral and central sensitization.
- It is important to translate an understanding of the complexity of the pathophysiology of peripheral neuropathic pain into clinical evaluation, assessment, and treatment planning.
- Initial assessment of patients with neuropathic pain begins with taking a history of pain and its course, affected sensory and pain domains, and psychological and social aspects, including the impact of pain on function and quality of life.

- Several patient-reported outcome tools have been developed to help clinicians assess the severity of neuropathic pain symptoms and response to treatment.
- Negative sensory phenomena almost always conform to the peripheral nerve anatomy, following the nerve, plexus, or root distribution, whereas positive sensory phenomena are frequently detectable outside of the peripheral nerve distribution because of the central sensitization phenomenon.
- There is no known curative therapy for peripheral neuropathic pain, and the main focus of neuropathic pain therapy is symptom control and improvement of function and quality of life.
- Neuropathic pain is best managed with a multimodal and multidisciplinary approach, which, in addition to pharmacotherapy, can include psychological support, training, and a comprehensive range of physical therapy modalities.
- Antiseizure medications are usually the first-line treatment for painful neuropathies.
- Duloxetine is the only US Food and Drug Administration (FDA)-approved antidepressant for use in painful diabetic neuropathy treatment, although several other antidepressants have been widely prescribed for painful neuropathy.
- Managing peripheral neuropathic pain requires a comprehensive and integrative approach that addresses the diverse aspects of the condition. This multidisciplinary and multimodal approach involves combining various therapeutic strategies to improve pain relief, enhance function, and promote overall well-being.
- Structured exercise programs tailored to individual needs can improve strength, flexibility, and coordination in patients with neuropathic pain. Low-impact exercises, such as swimming or tai chi, are often recommended to minimize stress on affected nerves.

ARTICLE 4: CENTRAL NEUROPATHIC PAIN

Charles E. Argoff, MD. Continuum (Minneapolis). October 2024; 30 (5 Pain Management in Neurology):1381-1396.

ABSTRACT

OBJECTIVE:

This article provides an approach to the assessment, diagnosis, and treatment of central neuropathic pain.

LATEST DEVELOPMENTS:

Recent studies of the pathophysiology of central neuropathic pain, including evidence of changes in the expression of voltage-gated sodium channels and N-methyl-D-aspartate (NMDA) receptors, may provide the basis for new therapies. Other areas of current research include the role of cannabinoid-receptor activity and microglial cell activation in various animal models of central neuropathic pain. New observations regarding changes in primary afferent neuronal activity in central neuropathic pain and the preliminary observation that peripheral nerve blocks may relieve pain due to central neuropathic etiologies provide new insights into both the mechanism and treatment of central neuropathic pain.

ESSENTIAL POINTS:

In the patient populations treated by neurologists, central neuropathic pain develops most frequently following spinal cord injury, multiple sclerosis, or stroke. A multimodal, individualized approach to the management of central neuropathic pain is necessary to optimize pain relief and may require multiple treatment trials to achieve the best outcome.

KEY POINTS

- The development of central neuropathic pain may occur following an injury of or in association with a disorder affecting the spinal cord or brain.
- Abnormal spinothalamic tract function is nearly always present in a person experiencing central neuropathic pain.
- Non-neuropathic pain may exist concurrently in a person experiencing central neuropathic pain.
- Mechanisms underlying central neuropathic pain include those involving both the peripheral and central nervous systems.
- Approximately 70% of spinal cord injuries are associated with a motor vehicle accident or a fall.
- Central neuropathic pain associated with spinal cord injury may occur concurrently with non-neuropathic pain associated with spinal cord injury, emphasizing the need for a formal neurologic assessment.
- Central poststroke pain is the most common type of central neuropathic pain.
- Stroke location is an important risk factor for the development of central poststroke pain.
- Chronic pain occurs in the majority of patients diagnosed with multiple sclerosis (MS).
- Central neuropathic pain is one of several types of pain that a person with MS may experience, and formal assessment for each type of MS-related pain should be completed.
- MS-related central neuropathic pain is more likely to occur in patients with a progressive MS course, older age, greater disability, and longer MS duration.
- Formal diagnostic criteria for central neuropathic pain associated with spinal cord injury, MS, or central poststroke pain have been recently proposed.
- There is a scarcity of large, high-quality randomized trials for central neuropathic pain.
- Multiple antiseizure medications have been evaluated for different central neuropathic pain states with mixed results.
- Based upon the results of two randomized controlled trials, duloxetine may be considered for MS-related neuropathic pain.
- Small studies suggest the potential role of IV lidocaine infusions for the treatment of central neuropathic pain.
- In addition to its role in the treatment of spasticity, onabotulinumtoxinA has been demonstrated to reduce pain in patients with spinal cord injury-related neuropathic pain when injected subcutaneously.
- Insufficient evidence is currently available regarding the effect of cannabinoids on central neuropathic pain.
- Insufficient evidence is available to broadly recommend chronic opioid therapy for the management of central neuropathic pain.
- Insufficient evidence is currently available to define the role of various neuromodulation approaches in the management of central neuropathic pain.
- Limited high-quality evidence exists for the treatment of central neuropathic pain, with the exception of pregabalin for spinal cord injury-related neuropathic pain. Commonly prescribed medications for central neuropathic pain do not have significant published evidence to support their use in general but may be considered on an individual basis.
- Nonpharmacologic treatments for central neuropathic pain may be considered in addition to or in place of pharmacologic therapies for people with central neuropathic pain.

ARTICLE 5: OROFACIAL PAIN

Meredith Barad, MD; Marcela Romero-Reyes, DDS, PhD. Continuum (Minneapolis). October 2024; 30 (5 Pain Management in Neurology):1397-1426.

ABSTRACT

OBJECTIVE:

This article explores the multiple etiologies, diagnosis, and management of orofacial pain.

LATEST DEVELOPMENTS:

Published in 2019, the International Classification of Orofacial Pain has become the internationally accepted classification system for primary and secondary facial pain. New discoveries in temporomandibular disorders have demonstrated that they are far more complex than the traditional dental mechanistic point of view. A 2020 consensus report released by the National Academies of Sciences, Engineering, and Medicine entitled "Temporomandibular Disorders: Priorities for Research and Care" highlighted this paradigm shift and its importance for patient care, education, and research.

ESSENTIAL POINTS:

Orofacial pain comprises many disorders with different etiologies and pathophysiologies. The subjectivity of the pain experience and the interrelated anatomy and physiology of the craniofacial area add to the complexity of diagnosis when the source and etiology of pain are not clear. As orofacial pain straddles the expertise of multiple disciplines, a multidisciplinary approach combining medication, physical therapy, and procedural and psychological strategies is essential in treating patients with orofacial pain.

KEY POINTS

- Given the complexity and difficulty in diagnosis, a multidisciplinary approach is the best strategy for diagnosing and treating orofacial pain.
- Odontogenic pain is the most common acute source of orofacial pain and is usually the result of pulp or periapical tissue pathology.
- Odontogenic pain can be referred to adjacent craniofacial structures as a form of secondary headache.
- Other painful oral problems include oral mucosal lesions, cancer-related pain, salivary gland pain, or mandibular or maxillary bone pain.
- Temporomandibular disorders are a constellation of musculoskeletal disorders involving the temporomandibular joint, the muscles of mastication, and their associated structures.
- Temporomandibular disorders are the most prevalent chronic orofacial pain.
- Temporomandibular disorders are comorbid with depression, poor sleep, primary headaches, and other chronic pain problems.
- Bruxism may influence temporomandibular disorder symptomatology in some individuals, but more research is necessary to establish evidence of causality.
- OnabotulinumtoxinA is not indicated as first-line management and is not US Food and Drug Administration (FDA) approved for the treatment of temporomandibular disorders, but it may be explored in refractory cases in consultation with an orofacial pain specialist.
- Trigeminal neuralgia is more common in women, appears to increase with age, and presents most frequently in the V2 distribution on the right side.
- One-half of patients with trigeminal neuralgia experience concomitant continuous pain.
- The examination in patients with classic trigeminal neuralgia is usually normal, and deficits in the distribution of the trigeminal nerve suggest trigeminal neuropathy.

- Classical trigeminal neuralgia is thought to be caused by neurovascular compression.
- About 15% of patients with trigeminal neuralgia symptomatology have secondary trigeminal neuralgia.
- The most common causes of secondary trigeminal neuralgia are multiple sclerosis and benign tumors.
- The goal of imaging in patients with trigeminal neuralgia is to look for evidence of vascular compression on the trigeminal nerve through nerve deviation, groove formation, or atrophy, and to exclude secondary causes.
- Treatment guidelines continue to suggest medical management as the first-line treatment of trigeminal neuralgia, with microvascular decompression being the most effective surgical option.
- Glossopharyngeal neuralgia causes similar pain to trigeminal neuralgia but is located in the ear, base of the tongue, roof of the mouth, and tonsillar fossa.
- Secondary glossopharyngeal neuralgia may be caused by Eagle syndrome, multiple sclerosis, tumors, trauma, and Chiari malformations.
- Treatment for classic glossopharyngeal neuralgia is similar to that for classic trigeminal neuralgia, with medication management being the first-line treatment and consideration of microvascular decompression after that.
- Nervus intermedius neuralgia is felt deep in the auditory canal and may also be due to vascular compression.
- The sphenopalatine ganglion is a parasympathetic ganglion contributing to sensation to the nasal cavity, sphenoid sinus, palate, and some of the nasopharynx and oropharynx.
- Interventional procedures, including implantable neuromodulation, to the sphenopalatine ganglion have been examined to treat cluster headache and other primary headache syndromes.
- Neuropathic pain is the pain state represented by damage to the nerve. While it can be idiopathic, it can be caused by herpes zoster or postherpetic neuralgia, multiple sclerosis, or mass lesions.
- Burning mouth syndrome is most commonly seen in women 3 to 12 years postmenopause.
- Burning mouth syndrome is considered secondary when it is caused by tongue thrust, poorly fitting dentures, fungal infections, allergies, medications, vitamin and mineral deficiencies, gastroesophageal reflux disease, diabetes, and hypothyroidism.
- Burning mouth syndrome is primary (idiopathic) when no secondary local or systemic source has been detected.
- Persistent idiopathic facial pain and persistent idiopathic dentoalveolar pain are challenging medical conditions for which neuromodulating medications are at present the best form of treatment.
- Primary headache syndromes can present in the face alone.

ARTICLE 6: CHRONIC WIDESPREAD PAIN

Narayan R. Kissoon, MD. Continuum (Minneapolis Minn). October 2024; 30 (5 Pain Management in Neurology):1427–1446.

ABSTRACT

OBJECTIVE:

This article reviews the potential etiologies of chronic widespread pain syndromes and outlines a practical approach to the management of patients with these disorders.

LATEST DEVELOPMENTS:

Recent updates to diagnostic criteria for primary chronic widespread pain syndromes have allowed for more effective diagnosis. Fibromyalgia is the most common presentation of chronic widespread pain, and the concept of nociceptive pain has been used to describe pain that is related to altered processing of pain sensory pathways. Research studies have provided a better

understanding of the pathophysiology of the central augmentation that occurs in patients with nociceptive pain and fibromyalgia.

ESSENTIAL POINTS:

Primary chronic widespread pain and fibromyalgia have established diagnostic criteria in which chronic pain involves multiple defined regions and occurs for longer than 3 months. Evaluation of chronic widespread pain should be directed by the clinical presentation. Neurologic disease can present with chronic widespread pain but is accompanied by associated signs and symptoms. Patients with chronic widespread pain benefit from effective communication that validates concerns, provides an understandable explanation of the presenting symptoms, and sets realistic expectations in outcomes using a comprehensive multimodal care plan.

KEY POINTS

- Chronic widespread pain and fibromyalgia have established diagnostic criteria in which chronic pain involves multiple defined regions and occurs for longer than 3 months.
- For chronic widespread pain to be diagnosed as fibromyalgia, it must be accompanied by associated symptoms such as fatigue, sleep disorders that may include waking unrefreshed, and cognitive symptoms.
- Fibromyalgia can present with pain that has neuropathic features and patients may have findings of allodynia on examination, but pain fluctuates and is outside dermatomal, myotomal, or sclerotomal distributions.
- Patients with fibromyalgia commonly present with comorbid disorders such as postural orthostatic tachycardia syndrome, persistent perceptual postural dizziness, mood disorders, migraine, and other chronic primary pain syndromes.
- Changes in gray matter volumes and small fiber intraepidermal nerve fiber density observed in patients with fibromyalgia are suspected to represent neuroplasticity rather than atrophy or neuropathy, respectively.
- Complex regional pain syndrome has validated diagnostic criteria that are useful in the diagnosis and include the presence of both symptoms and signs on examination.
- A patient-centered approach is used in the management of complex regional pain syndrome. When a patient is unable to participate in or has a failure to progress with rehabilitation, sympathetic blocks, spinal cord stimulation, or dorsal root ganglion stimulation may be of benefit.
- Parkinson disease can present with chronic widespread pain that is independent of musculoskeletal disease or dystonia and can have neuropathic features.
- Autoimmune IgG-mediated pain should be considered in patients presenting with a subacute onset (weeks to months) of multifocal neurologic signs and symptoms involving both the central and peripheral nervous systems.
- Hypermobility Ehlers-Danlos syndrome has distinct clinical findings of skin fragility and marfanoid features that allow it to be differentiated from joint hypermobility syndrome.
- All patients with chronic widespread pain should have a complete history and medical examination along with laboratory testing comprising a complete blood cell count and measurement of C-reactive protein, serum calcium, creatine phosphokinase, thyroid-stimulating hormone, and 25-hydroxyvitamin D levels.
- Opioids should be avoided in the treatment of patients with nociceptive chronic widespread pain and pathophysiologically may be detrimental given the observations of high endogenous opioids with low μ -opioid receptor binding observed in the setting of fibromyalgia.
- Patients with chronic widespread pain benefit from effective communication that validates concerns, provides an understandable explanation of the presenting symptoms, and sets realistic expectations in outcomes using a comprehensive multimodal care plan.

ARTICLE 7: OPIOIDS AND CANNABINOIDs IN NEUROLOGY PRACTICE

Friedhelm Sandbrink, MD, FAAN; Nathaniel M. Schuster, MD. Continuum (Minneapolis). October 2024; 30 (5 Pain Management in Neurology):1447–1474.

ABSTRACT

OBJECTIVE:

Opioid and cannabinoid therapies for chronic pain conditions including neuropathic pain are controversial. Understanding patient and prescribing factors contributing to risks and implementing risk mitigation strategies optimizes outcomes.

LATEST DEVELOPMENTS:

The ongoing transformation from a biomedical model of pain care toward a biopsychosocial model has been accompanied by a shift away from opioid therapy for pain, in particular for chronic pain. Opioid overdose deaths and opioid use disorder have greatly increased in the last several decades, initially because of increases in opioid prescribing and more recently associated with illicit drug use, in particular fentanyl derivatives. Opioid risk mitigation strategies may reduce risks related to opioid prescribing and tapering or discontinuation. Opioid therapy guidelines from the Centers for Disease Control and Prevention have become the consensus best practice for opioid therapy. Regulatory agencies and licensing medical boards have implemented restrictions and other mandates regarding opioid therapy. Meanwhile, interest in and use of cannabinoids for chronic pain has grown in the United States.

ESSENTIAL POINTS:

Opioid therapy is generally not recommended for the chronic treatment of neuropathic pain conditions. Opioids may be considered for temporary use in patients with severe pain related to selected neuropathic pain conditions (such as postherpetic neuralgia), and only as part of a multimodal treatment regimen. Opioid risk mitigation strategies include careful patient selection and evaluation, patient education and informed consent, querying the state prescription drug monitoring programs, urine drug testing, and issuance of naloxone as potential rescue medication. Close follow-up when initiating or adjusting opioid therapy and frequent reevaluation during long-term opioid therapy is required. There is evidence for the efficacy of cannabinoids for neuropathic pain, with meaningful response rates in select patient populations.

KEY POINTS

- Opioids for the treatment of chronic noncancer pain are generally not recommended for the chronic treatment of neuropathic pain or headache disorders.
- In 2022, the Department of Veterans Affairs/US Department of Defense recommended against initiating opioid therapy for chronic pain and suggested the use of buprenorphine instead of full μ -agonist opioids in patients on daily opioid therapy.
- The risks of tapering and discontinuing long-term opioid therapy include illicit opioid use, emergency department visits, opioid-related hospitalizations, mental health crises, and death from suicide or overdose.
- Despite the marked reduction in opioid prescribing for pain since 2012, deaths due to overdoses continue to escalate in the United States, with an annual rate of more than 100,000 overdose deaths since 2021.

- While the deaths from prescribed opioids have decreased in recent years, illicit fentanyl overdoses are now the leading cause of opioid-related death.
- Many states require coprescription of naloxone for high-dosage opioid therapy or when in the context of benzodiazepines.
- Opioid overdose and opioid use disorder risk factors include the opioid therapy dosage and duration, concurrent use of sedatives, the use of extended-release or long-acting opioids, and the presence of substance use and mental health comorbidities.
- While overdose risk increases at 50 morphine milligram equivalent (MME) and higher, many patients with opioid overdose and exposure to prescription opioid medication are on dosages below this level.
- Dosage increases to greater than 50 MME/day are unlikely to substantially improve pain control for most patients, while overdose risk increases with dosage.
- Long-acting or slow-release opioids are associated with a higher risk for opioid overdose and should not be used for acute pain, when initiating opioid therapy, or for as-needed medication use.
- Methadone has been associated with a particularly high risk for respiratory depression and overdose, whereas buprenorphine has lower risk of respiratory depression and overdose death.
- The risk for opioid overdose is increased for individuals on long-term opioid therapy who also received concurrent long-term benzodiazepine therapy, with some risk, albeit lower, also noted for zolpidem.
- Screening tools including the Opioid Risk Tool for Opioid Use Disorder may be used to predict the risk of aberrant use behaviors or unhealthy opioid use for patients being considered for opioid therapy.
- Patients developing opioid use disorder while on prescribed opioid therapy should be provided urgent access to evidence-based treatments for opioid use disorder such as methadone or buprenorphine, and other pain treatments should be optimized.
- Methadone or buprenorphine therapy for opioid use disorder, if prescribed in patients with concurrent pain conditions, should be given in divided doses, usually 3 times a day, for better analgesic efficacy.
- Querying the state prescription drug monitoring program database is a standard safety practice when initiating and renewing opioid therapy.
- Urine drug testing should be considered before initiating opioid therapy, at least annually for patients on long-term opioid therapy, and more often according to risk.
- Prescribing of the opioid antagonist naloxone is considered an important risk mitigation strategy for patients on opioid therapy, especially in higher-risk situations.
- A common practice in opioid therapy monitoring is to document the “4 A’s”: analgesia, activities, adverse effects, and aberrant behavior.
- The use of the partial μ -opioid agonist buprenorphine for chronic pain is an emerging practice as it has a respiratory depression ceiling effect, unlike full μ -opioid agonists.
- While there has been great interest in cannabidiol (CBD) as a pain treatment, the evidence to date has not demonstrated pain benefits from CBD.
- CBD is a negative allosteric modulator of the CB1 receptor and reduces the psychoactivity of delta-9-tetrahydrocannabinol (THC). High CBD-to-THC ratio products are typically better tolerated, especially by cannabis-naïve patients.
- There is evidence suggesting that THC has a narrow therapeutic window for neuropathic pain, with therapeutic benefit at subintoxicating dosages or at dosages with limited psychoactive effects.
- Cannabis use disorder is present in nearly 10% of users and about one-third of daily users.
- Compulsive hot water bathing or showering for symptomatic relief is pathognomonic for cannabis hyperemesis syndrome.
- Cannabis has biphasic effects on nausea. With persistent high-dose use, it can be proemetic.

ARTICLE 8: NEUROMODULATION FOR NEUROPATHIC PAIN SYNDROMES

Prasad Shirvalkar, MD, PhD. Continuum (Minneapolis). October 2024; 30 (5 Pain Management in Neurology):1475–1500.

ABSTRACT

OBJECTIVE:

This article reviews the principles, applications, and emerging trends of neuromodulation as a therapeutic approach for managing painful neuropathic diseases. By parsing evidence for possible mechanisms of action and clinical trial outcomes for various diseases, this article focuses on five common therapy modalities: cutaneous, peripheral nerve, spinal cord, and brain stimulation, and intrathecal drug delivery.

LATEST DEVELOPMENTS:

Recent advances in both invasive and noninvasive neuromodulation for pain have introduced personalized and closed-loop techniques, integrating real-time feedback mechanisms and combining therapies to improve physical and psychosocial function. Novel stimulation waveforms may influence distinct neural tissues to rectify pathologic pain signaling.

ESSENTIAL POINTS:

With appropriate patient selection, peripheral nerve stimulation or epidural stimulation of the spinal cord can provide enduring relief for a variety of chronic pain syndromes. Newer technology using high frequencies, unique waveforms, or closed-loop stimulation may have selective advantages, but our current understanding of therapy mechanisms is very poor. For certain diagnoses and patients who meet clinical criteria, neuromodulation can provide profound, long-lasting relief that significantly improves quality of life. While many therapies are supported by data from large clinical trials, there is a risk of bias as most clinical studies were funded by device manufacturers or insurance companies, which increases the importance of real-world data analysis. Emerging methods like invasive or noninvasive brain stimulation may help us dissect basic mechanisms of pain processing and hold promise for personalized therapies for refractory pain syndromes. Finally, intrathecal delivery of drugs directly to segments of the spinal cord can also modify pain signaling to provide therapy for severe pain syndromes.

KEY POINTS

- The four key adjustable parameters that control electrical stimulation are contact polarity, pulse width, frequency, and amplitude.
- Low-frequency stimulation typically replaces painful sensations with a tingling or vibratory paresthesia in the nerve distribution, while high-frequency stimulation can provide paresthesia-free pain relief.
- Gate control theory describes spinal cord mechanisms by which large-diameter and small-diameter fibers interact to “gate out” ascending pain signals.
- The SAFE principles offer clinical guidance for treatment algorithms involving implanted neuromodulation therapies: safety, appropriateness, fiscal neutrality, and efficacy.
- Peripheral nerve stimulation involves stimulating nerve axons by placing a fine electrode wire within 1cm and is most appropriate for focal pain syndromes and neuralgias.
- Spinal cord stimulation is the most common type of electrical neuromodulation for chronic pain, with over 30,000 patients undergoing trial or permanent implant yearly worldwide.

- Despite the various approved indications for spinal cord stimulation therapy, group-level clinical outcome data remain controversial due to few studies with rigorous blinding or placebo control.
- Complex regional pain syndrome is a rare pain syndrome typically affecting one limb that involves neuroimmune, vasomotor, sudomotor, and trophic changes. Dorsal root ganglion stimulation is the only approved therapy for lower-extremity complex regional pain syndrome.
- In the case of a potential infection near spinal cord stimulator hardware, it is urgent to completely explant all hardware.
- While drug spread can be influenced by infusion rate or concentration, intrathecal drug delivery is typically best suited for focal pain syndromes involving one to two spinal levels.
- Although intrathecally delivered medications are minimally present in systemic circulation, abruptly discontinuing the infusion due to pump malfunction or a missed refill appointment could precipitate withdrawal. This can be life-threatening if using intrathecal baclofen.
- Deep brain stimulation for chronic pain has been studied since 1960 but remains off label due to the lack of a single “best target” for all patients and the development of tolerance to stimulation over time.
- Motor cortex stimulation involves stimulating the superficial motor cortex with implanted electrode arrays. Potential response for pain control may be identified by first using transcranial magnetic stimulation noninvasively.
- Transcranial magnetic stimulation for pain uses noninvasive magnetic fields through the scalp to induce electrical field stimulation on the primary motor cortex over repeated daily sessions.
- Although therapeutic effects of transcranial magnetic stimulation for pain are short lived, usually dissipating by 1 month, transcranial magnetic stimulation can be used to identify candidates who would benefit from the permanent implant of a motor cortex stimulator.

ARTICLE 9: CHRONIC PAIN PSYCHOLOGY IN NEUROLOGY PRACTICE

Mirsad Serdarevic, PhD. Continuum (Minneapolis, Minn). October 2024; 30 (5 Pain Management in Neurology):1501–1516.

ABSTRACT

OBJECTIVE:

This article reviews the latest literature regarding chronic pain epidemiology and describes pain-specific psychological factors associated with the development and maintenance of chronic pain, mental health conditions that co-occur with chronic pain, and advances in the psychobehavioral treatment of chronic pain, including established treatments (ie, cognitive behavioral therapy [CBT], acceptance and commitment therapy, and mindfulness-based stress reduction) and emerging treatments (ie, pain reprocessing therapy).

LATEST DEVELOPMENTS:

In addition to CBT and acceptance and commitment therapy for pain, numerous other psychological treatment modalities have been integrated into chronic pain management, including mindfulness-based stress reduction, mindfulness meditation, chronic pain self-management, relaxation response, pain neuroscience education, biofeedback, hypnosis, and, more recently, integrative psychological treatment for centralized pain. This article gives an overview of these methods and contextualizes their use within the standard psychological treatment of chronic pain.

ESSENTIAL POINTS:

Guided by the biopsychosocial treatment model, pain psychologists use numerous evidence-based psychological methods to treat patients with chronic pain conditions. Familiarity with the psychological tools available for pain management will aid neurologists and their patients in navigating the psychological aspects of living with chronic pain.

KEY POINTS

- The incidence of chronic pain is 52.4 cases per 1000 people per year.
- Given that chronic pain is a complex biopsychosocial disease that can affect all aspects of life including mood, social life, cognition, physical health, and functioning, it comes as no surprise that interdisciplinary treatment is the only reliable treatment for chronic pain as medication alone and procedures alone cannot break the pain cycle.
- Acceptance and commitment therapy and cognitive behavioral therapy are the psychological pain interventions that have shown the strongest evidence of benefit and cost effectiveness.
- Research on the effectiveness of cognitive behavioral therapy for pain in patients with chronic pain has shown gray matter volume increases in the posterior parietal cortex, bilateral dorsolateral prefrontal cortex, and other sensory, motor, and affective regions of the brain also associated with pain control.
- Cognitive behavioral therapy for pain is about changing one's relationship with and response to pain to lessen its impact on functioning and quality of life and focuses on how one's beliefs, emotions, physiologic responses, and behaviors affect the experience of pain.
- The gate control theory of pain suggests that pain signals do not automatically or directly reach the brain; rather, a "gate mechanism" that controls the amount of pain signals that reach the brain is located within the spinal cord, and more pain signals pass through when the gate is open than when it is closed.
- Acceptance and commitment therapy is a psychological intervention that integrates many cognitive behavioral therapy-related variables into core therapeutic processes. The goal of acceptance and commitment therapy is to increase psychological flexibility and reduce pain's dominance in a person's life.
- Mindfulness-based treatments of chronic pain, including most widely used mindfulness-based stress reduction techniques, aim to cultivate acceptance through nonjudgmental, purposeful attention to the present moment.
- Mindfulness-based treatments for chronic pain can be used alone or in combination with other treatments, such as cognitive behavioral therapy and acceptance and commitment therapy.
- Biofeedback provides immediate audible or visual cues to the patient regarding changes in physiologic activity (eg, heart rate, muscle tension, respiration) using precise instrumentation. Patients gain awareness and control of their physiologic responses through such feedback, leading to improved psychological and physiologic functioning.
- Clinical hypnosis for chronic pain treatment involves the patient entering a state of focused attention, allowing for more openness to suggestions for changes in behaviors, sensations, and thoughts. Clinical hypnosis is divided into two phases: an induction phase, followed by specific suggestions for therapeutic change.
- Integrative psychological treatment for centralized pain, which includes pain reprocessing therapy, focuses on treating patients whose pain is either partially or completely centralized (ie, nociceptive or somatoform).
- In pain reprocessing therapy, patients learn to view their pain through a "safety lens" and remind themselves that there is no danger, and while the sensations are real, they are also temporary.
- The ADDRESSING approach (age and generational influences, developmental and acquired disabilities, religion and spiritual orientation, ethnicity, socioeconomic status, sexual orientation, indigenous heritage, national origin, gender) provides a framework for understanding the impact of a clinician's worldview of different cultures on patient care.

ARTICLE 10: PEDIATRIC PAIN

Alyssa Lebel, MD; Nathaniel M. Schuster, MD. Continuum (Minneapolis). October 2024; 30 (5 Pain Management in Neurology):1517–1535.

ABSTRACT

OBJECTIVE:

This article reviews pain disorders encountered in pediatric neurology practice and provides current information regarding the assessment and treatment of pediatric chronic pain.

LATEST DEVELOPMENTS:

Data about pediatric pain management remain sparse, owing to a dearth of controlled trials and longitudinal studies in these patients. However, the field of pain management and understanding of central and peripheral pain processing has expanded to allow more effective treatment of a broad group of children and adolescents with pain associated with neurologic disease.

Neuroimaging visualizes sensory and nonsensory systems, and genetic markers of sensitivity and disease may guide specific therapy. The concept of central sensitization in chronic pain disorders has supported the development of multidisciplinary paradigms for the comprehensive care of these patients.

ESSENTIAL POINTS:

Pain involves sensory activation and central nervous system modulation in pediatric patients. Pediatric neurologists should be prepared to define, investigate, and treat pain disorders in this complex patient population. Appropriate interventions during childhood may attenuate or prevent chronic pain later in life. Current interventions include behavioral, physical, and pharmacologic approaches, as well as potential noninvasive tools for neuromodulation. Research is progressing in sensory measurement, neuroimaging, genetics, and neuroinflammation to guide future targeted therapies.

KEY POINTS

- The prevalence of chronic pain in children is widespread and is more common in females. Pediatric chronic pain prevalence in low-income and middle-income countries is underreported in the literature, and yet is a leading cause of morbidity.
- Pain is a frequent component of rare neurometabolic diseases.
- Chronic pain assessment can be individualized through self-report measures depending on the patient's needs and developmental and cognitive levels.
- The neurologic examination for patients with pain includes assessment of small sensory fiber function.
- Neuroimaging studies illustrate that pain disorders are, at their root, disorders of the brain.
- Maladaptive changes within the nociceptive network coincide with maturation of the nervous system, and thus pediatric neuropathic pain disorders may differ from adult conditions regarding presentation, prognosis, and treatment.
- Studies support psychological treatment for chronic pain, with cognitive behavioral therapy recommended as a best practice.
- Studies have shown that targeting the patient's relationship with their pain in therapy is a powerful intervention.
- The evaluation of patients unable to assess or verbalize their pain due to intellectual delay relies heavily on provider assessment.
- Pain assessment in patients with cerebral palsy is often complicated by dysregulated sleep patterns, myoclonus, and seizures.

Issue Overview

Pain Management in Neurology, Volume 30, Number 5, October 2024

Continuum: Lifelong Learning in Neurology® is designed to help practicing neurologists stay abreast of advances in the field while simultaneously developing lifelong self-directed learning skills.

Learning Objectives

Upon completion of this *Continuum: Lifelong Learning in Neurology* Pain Management in Neurology issue, participants will be able to:

- Discuss pain classification, assessment, and management, including the use of a differential diagnosis that addresses biological, psychological, and social factors and reflects the substantive progress in pain research and clinical care
- Identify strategies for a comprehensive assessment and intervention plan for patients experiencing spine pain
- Describe the current assessment and measurement, diagnosis, and treatment approaches for peripheral neuropathic pain
- Describe the diagnosis and treatment of central neuropathic pain associated with spinal cord injury, stroke, and multiple sclerosis
- Describe the multiple etiologies, diagnosis, and management of orofacial pain
- Discuss the clinical features, pathophysiology, diagnostic criteria, differential diagnoses, and treatment for chronic widespread pain syndromes
- Delineate the current state of opioid and cannabinoid prescribing for neurologic pain conditions and describe risk mitigation strategies to optimize outcomes for patients with chronic pain
- Discuss different modalities of neuromodulation for chronic neuropathic pain and understand factors that influence patient selection and common long-term complications
- Describe established and emerging psychological treatments for patients with chronic pain
- Identify pain disorders frequently encountered in pediatric practice and implement effective treatment approaches

Core Competencies

This *Continuum: Lifelong Learning in Neurology* Pain Management in Neurology issue covers the following core competencies:

- Patient Care and Procedural Skills
- Medical Knowledge
- Practice-Based Learning and Improvement
- Interpersonal and Communication Skills
- Professionalism
- Systems-Based Practice

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Schuster discusses the unlabeled use of opioids and the unlabeled and investigational use of cannabinoids for the treatment of pain, and the use of amitriptyline, atomoxetine, buprenorphine, chlorprocaine, clonazepam, clonidine, duloxetine, gabapentin, guanfacine, hydromorphone, methadone, methylnaltrexone, metoclopramide, mexiletine, midazolam, morphine, nalbuphine, nortriptyline, pregabalin, and ropivacaine for pain management, none of which are approved by the US Food and Drug Administration (FDA) for use in pediatric patients.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Argoff discusses several therapies, none of which are approved by the US Food and Drug Administration (FDA) for the treatment of central neuropathic pain.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Hogans discusses the use of several pain-active antidepressants and antiseizure medications, none of which are approved by the US Food and Drug Administration (FDA) for the management of pain.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Lebel discusses the use of amitriptyline, atomoxetine, buprenorphine, chloroprocaine, clonazepam, clonidine, duloxetine, gabapentin, guanfacine, hydromorphone, methadone, methylnaltrexone, metoclopramide, mexiletine, midazolam, morphine, nalbuphine, nortriptyline, pregabalin, and ropivacaine for pain management, none of which are approved by the US Food and Drug Administration (FDA) for use in pediatric patients.

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