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Neuropathic pain is one of the most common types of pain, but it is often under-recognized and under-treated. It is defined by the International Association for the Study of Pain as pain “initiated or caused by a primary lesion or dysfunction in the nervous system.

Educational Objectives

- Describe the common nonmalignant neuropathic pain syndromes.
- Describe the pain assessment and management approaches for different nonmalignant neuropathic pain syndromes.

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This continuing medical education program is intended for primary care physicians and those physicians who care for patients experiencing pain.

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Pain is one of the most common reasons for patients to seek medical attention and one of the most prevalent medical complaints in the US.¹⁻³ According to the 2006 National Center for Health Statistics Report, one in 10 Americans overall and three in five of those 65 years or older said that they experienced pain that lasted a year or more.² More than one-quarter of adults said they had experienced low back pain, and 15% of adults experienced migraine or severe headache in the past three months. Between the periods 1988-94 and 1999-2002, the percentage of adults who took a narcotic drug to alleviate pain in the past month rose from 3.2 percent to 4.2 percent.

For the millions of Americans who experience persistent pain, the impact on function and quality of life can be profound.²⁻⁴ Pain is associated with high utilization of health care⁴ and the societal costs related to treatment are compounded by the loss in productivity associated with persistent pain. Lost productive time from common pain conditions among workers costs an estimated \$61.2 billion per year and most of this is related to reduced performance while at work.⁵ The total annual cost of poorly controlled persistent pain most likely exceeds \$100 billion.

Physicians and other clinicians need current, state-of-the-art education to assist them in developing the necessary skills to evaluate and manage patients with persistent pain. This CME program reviews assessment and management of persistent pain syndromes that are frequently seen in primary care.

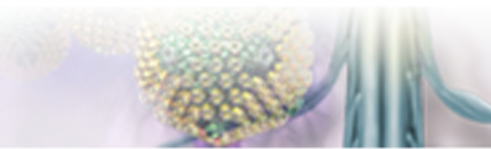
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Introduction

Neuropathic pain is one of the most common types of pain, but it is often under-recognized and undertreated. Neuropathic pain is defined by the International Association for the Study of Pain as pain initiated or caused by a primary lesion or dysfunction in the nervous system.¹ There are numerous syndromes that may be distinguished by the characteristics of the pain or the localization of the neurological injury responsible for the pain. Some neuropathic pains are categorized by dysfunction of neural systems (e.g., painful polyneuropathies) and others are categorized by specific sites of injury in the peripheral nervous system (e.g., painful entrapment mononeuropathy like meralgia paresthetica or lumbar radiculopathy from a herniated intervertebral disc) or central nervous system (e.g., post-stroke central pain syndrome or pain from spinal cord injury). Although the ‘generator’ of the pain often is assumed to be predominantly peripheral or central, it is likely that many syndromes involve an array of specific mechanisms that overlap peripheral and central phenomena.²⁻⁴ Some syndromes, such as complex regional pain syndrome (formerly called reflex sympathetic dystrophy or causalgia), postherpetic neuralgia and trigeminal neuralgia, are most clearly dependent on mechanisms that involve both the peripheral and central nervous systems.

Further augmenting this complexity is the high likelihood that neuropathic pains of different phenomenology actually share multiple pain-producing mechanisms at the cellular or synaptic levels.²⁻⁴ For example, pain may be dependent on a so-called channelopathy involving calcium or sodium channels, or others; receptor changes involving the glutamate or opioid receptors, or many others; or changes in levels of neurotransmitters or modulators affecting nociceptive processing, like serotonin or norepinephrine, nerve growth factor, bradykinin, prostaglandins, protons, and many others. This complex picture may underlie the overlap and the differences across specific pain syndromes.

Assessment of Neuropathic Pain

The assessment of a patient with neuropathic pain should consist of a thorough history with specific attention to the pain characteristics (see below Table: Patient History for Neuropathic Pain) and the neurological examination. The goals of this assessment, similar to all other types of chronic pain, are to characterize the pain; identify a syndrome and the likely etiology (*i.e.*, both the localization of any underlying neurological lesion and the cause of the damage); and clarify both the impact of the pain on multiple functional domains and relevant medical and psychiatric comorbidities.

Patient History for Neuropathic Pain

- Time of onset
- Location of pain
- Changes in pain (worsening, improvement, spread)
- Quality of the pain
- Discomfort (other abnormal sensations)
- Potential associated neurological symptoms (*i.e.*, numbness, weakness, trouble sleeping, bowel or bladder dysfunction)
- Exacerbating and alleviating factors
- Impact on ability to perform daily activities
- Complex regional pain syndrome-specific symptoms (*i.e.*, focal swelling, change in skin color, focal sweating abnormality, change in hair growth, change in nails, change in skin texture or subcutaneous fat)

Reproduced with permission from Gabb MG, Galer BS. A closer look at the tools used to diagnose and assess neuropathic pain. *Advance Studies in Medicine*. 2001;1:248-254.

The phenomenology of neuropathic pain is very diverse. Some patients present with continuous or intermittent pain that is consistent with the term “dysesthesia” (abnormal uncomfortable sensation). They may describe the pain as burning, shooting or electric. Other patients, however, have pain that seems clearly neuropathic (e.g., due to compression of a nerve root) but describe qualities that mimic nociceptive pain syndromes, e.g., sharp, aching, throbbing. Patients may or may not demonstrate abnormal stimulus-evoked pain, either in response to a non-noxious stimulus (allodynia, or pain with touch) or a noxious stimulus (hyperalgesia, or an exaggerated pain from a noxious stimulus). Some patients report abnormal nonpainful sensations (paresthesias), like tingling or itch and some develop an exaggerated pain response to some type of a stimulus, which itself may be characterized by spreading pain, after sensation and emotional over-reaction (hyperpathia). (See Table: Abnormal Sensory Symptoms and Signs with Neuropathic Pain States and Table: Neuropathic Pain Syndromes).

Responses to mechanical and thermal stimuli, brush, and cold can aid in the diagnosis of neuropathic pain when the distribution of the pain and the associated sensory abnormalities (see Table: Abnormal Sensory Symptoms and Signs with Neuropathic Pain) point to a discrete neurological condition. Subjective experience can be evaluated in more detail using a multidimensional pain assessment tool, such as the McGill Pain Questionnaire (MPQ)⁵ or the Brief Pain Inventory, or any of a number of other neuropathic pain-specific multidimensional questionnaires. The MPQ, for example, enables the patient to describe the quality of their pain, and takes into account the various aspects of pain, including sensory and affective components. The Neuropathic Pain Scale lists 8 descriptors of pain and was developed to evaluate treatment response in patients with central and peripheral neuropathic pain.^{6,7}

Neuropathic Pain Syndromes

Likely to have a Predominating Peripheral “Generator”

Painful polyneuropathy

Examples:

- Diabetic painful polyneuropathy
- Chemotherapy-induced neuropathy
- HIV sensory neuropathy

Painful mononeuropathy involving peripheral nerve

Examples:

- Post-traumatic/post-surgical neuropathies (e.g., post-mastectomy pain, post-thoracotomy pain, post-herniorrhaphy pain)
- Stump pain
- Entrapment neuropathy (e.g., meralgia paresthetica, carpal tunnel syndrome)
- Cervical or lumbar plexopathy from cancer

Painful mononeuropathy involving nerve roots

Examples:

- Radiculopathy due to disc disease
- Radiculopathy to leptomeningeal neoplasm

Likely to have a Predominating Central “Generator”

Pain from injury to the CNS

Examples:

- Pain from spinal cord injury
- Post-stroke central pain syndrome
- Pain from multiple sclerosis
- Deafferentation pain following peripheral nerve injury

Examples:

- Phantom limb pain

Uncertain or Likely to Involve Both Peripheral and Central “Generators”

Pain from injury to the CNS

Examples:

- Complex regional pain syndrome (e.g., reflex sympathetic dystrophy or causalgia)
- Postherpetic neuralgia
- Trigeminal neuralgia

Table: Abnormal Sensory Symptoms and Signs with Neuropathic Pain States

Type of Analgesic Strategy	Examples
Allodynia	Pain due to nonnoxious stimuli (<i>i.e.</i> , clothing, air movement, tactile stimuli) when applied to the symptomatic cutaneous area. Allodynia may be mechanical, static (<i>e.g.</i> , induced by a light pressure), dynamic (induced by moving a soft brush), and thermal (<i>e.g.</i> , induced by a nonpainful cold or warm stimulus).
Dysesthesias	Spontaneous or evoked unpleasant sensations, such as an annoying sensation elicited by cold stimuli or pinprick testing.
Hyperalgesia	An exaggerated pain response to a mildly noxious (mechanical or thermal) stimulus applied to the symptomatic area.
Hyperpathia	A delayed and explosive pain response to a noxious stimulus applied to the symptomatic area.
Paresthesias	Spontaneous intermittent painless abnormal sensations.

Source: Pappagallo M. Neuropathic pain in peripheral neuropathies. In: Tollinson CD, Satterwaite JR, Tollison JW, eds. *Practical Pain Management*. 3rd ed. Lippincott, Williams & Wilkins. Philadelphia: 2002;431-438.

Neuropathic Pain Syndromes

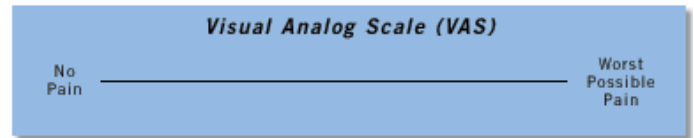
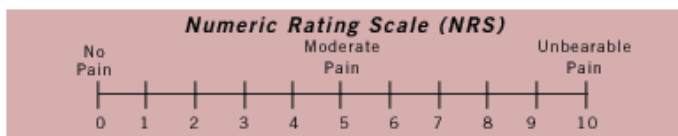
Neuropathic pain may be classified as predominantly peripheral or central based on the localization of the inciting lesion. Using this definition, central pain syndromes are considerably less common than peripheral neuropathic syndromes and include include poststroke pain, pain related to multiple sclerosis, and pain due to spinal cord injury.¹ Peripheral neuropathic pains include polyneuropathies and mononeuropathies, and the latter can be divided by the site of the lesion into painful peripheral mononeuropathies, painful plexopathies, and painful radiculopathies. Peripheral neuropathic pain syndromes often seen in primary care include entrapment neuropathies (*e.g.*, carpal tunnel syndrome), polyneuropathy due to diabetes, and postherpetic neuralgia (PHN). Perhaps one of the most difficult to manage neuropathic pain syndromes is complex regional pain syndrome (CRPS). Primary care physicians (and pain experts as well) also commonly see mixed syndromes, typically either lumbar or cervical post-laminectomy pain syndromes, which likely have a prominent neuropathic component.

It is important to recognize that this distinction between peripheral and central pains also can refer to the site of the presumed “generator” of the pain, and not just the localization of the inciting injury (see Table: Neuropathic Pain Syndromes).⁸ The term “deafferentation pain” has been used generically to refer to all neuropathic pain syndromes that are likely to be sustained by a pathogenesis in the central nervous system, whether or not the lesion that caused the pain was central (like a stroke) or peripheral (like nerve transection during amputation). Phantom pain, which the patient experiences in an area of the body that is fully denervated or absent, is the classic example of a deafferentation pain induced by a peripheral lesion. Presumably, any lesion that interrupts afferent input could potentially be complicated by the development of central dysfunction underlying the development of deafferentation pain.

Painful Diabetic Neuropathy

There are numerous types of polyneuropathy, of which diabetic neuropathy is one of the most prevalent.⁹ The most common type of diabetic neuropathy is a distal sensorimotor polyneuropathy. The sensory component usually predominates and pain is a very common accompaniment. Symptoms of the latter disorder typically begin insidiously in the feet. With progression, symptoms ascend into the legs and then appear in the fingers. Sensory symptoms, such as numbness or tingling, may be prominent, or pain may overshadow other symptoms from the start. Depending on the degree to which large sensory fibers and motor fibers are affected by the disease, any of a variety of neurological deficits may complicate the pain of this polyneuropathy. Some patients develop severe hypesthesia and some lose proprioception to the degree that the gait becomes ataxic. Some patients have marked distal weakness, predominating in the feet, and some have very little. Reflexes are usually lost, particularly at the ankles, but occasional patients with a predominating small fiber polyneuropathy may preserve deep tendon reflexes weakness everywhere.

Maintenance of tight glycemic control is key to delaying the onset of diabetic neuropathy and slowing its progression.¹⁰ However, approximately 45% of patients with diabetes will eventually develop some degree of neuropathy and 4% to 5% of all patients with diabetes will develop painful neuropathy. Diabetic polyneuropathy may be present in newly diagnosed patients, but it is most common in patients with longstanding diabetes. Painful diabetic neuropathy may lead to insomnia, anxiety, depression, weight loss, and decreased quality of life.



Assessment and Diagnosis of Painful Diabetic Neuropathy

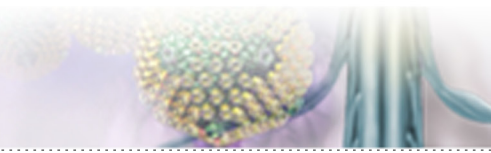
Typically, the history and examination provide information that strongly suggests a diagnosis of neuropathy in patients with diabetes. In some cases, referral to a neurologist for confirmation, often involving electrodiagnostic testing, is necessary. It is important to both exclude other causes of neuropathy, such as vitamin B12 deficiency, and evaluate the patient for concurrent sources of pain, such as the development of an entrapment syndrome or a traumatic arthropathy (Charcot joint).

Management of Painful Diabetic Neuropathy

Evidence-based guidelines developed by an international panel offer a broad approach to the management of neuropathic pain.¹¹ A multimodality strategy, usually including physical medicine interventions and cognitive-behavioral approaches, should be considered in all patients, particularly those whose pain is accompanied by functional impairments or a mood disorder. Pharmacologic management usually is the mainstay treatment for the pain.

NSAIDs and acetaminophen are generally considered to be ineffective against neuropathic pain. Occasional patients will indicate that they help, however, and in the absence of contraindications, it is reasonable to offer a trial. In most cases, however, treatment with the so-called adjuvant analgesics and opioid analgesics offer the greatest potential for benefit. The evidence-based guidelines¹¹ indicate that the first-line treatments for neuropathic pain are the gabapentinoids, gabapentin or pregabalin, or the analgesic antidepressants. Specifically, a trial of a gabapentinoid would be considered first, unless the patient has significant depressed mood, in which case an antidepressant would be tried.

Gabapentin and pregabalin are modulators of a protein—the alpha-2 delta subunit of the voltage-dependent calcium channel—and have broad efficacy in the treatment of neuropathic pains. They are approved for diabetic painful neuropathy and are widely used for this condition.¹² Most patients require a dose of gabapentin at least 900 mg per day and dosages of at least 1800 mg/day are commonly needed.¹³ Pregabalin has more stable pharmacokinetics than gabapentin and should be easier to titrate.¹⁴ The usual effective dose is 150-300 mg twice daily. Patients may respond, or respond better, to one or the other of these drugs and a poor response to one may be followed by a switch to the other.



Several tricyclic antidepressants (TCAs) have demonstrated efficacy in reducing the pain of diabetic neuropathy;^{11,12} nortriptyline or desipramine may be preferred over amitriptyline because they are associated with fewer anticholinergic adverse side effects. The serotonin and norepinephrine selective reuptake inhibitors (SNRIs), duloxetine (which is approved for this indication), and perhaps minalcipran and venlafaxine,¹⁵⁻¹⁹ have clear analgesic effects in neuropathic pain. Selective serotonin reuptake inhibitors (SSRIs) have not performed as well as TCAs and SNRIs, but there is evidence that paroxetine is analgesic.

The evidence-based guidelines¹¹ suggest that patients who present with severe pain may be offered an opioid immediately, but with the intention of reducing its use as other analgesic treatments are offered. This recommendation recognizes that there is good evidence that opioids can be helpful,²⁰⁻²³ but that long-term opioid therapy in this population should be reserved for those who have not responded to other, well-studied strategies. If patients do not benefit adequately from other drug trials and appropriate nonpharmacologic treatments, long-term opioid therapy can be considered (see module 2 and module 7).

Many other drugs categorized broadly under the so-called “adjuvant analgesics” may be considered for trials in patients with refractory pain from diabetic neuropathy (see module 2 and module 7). These drugs, most of which are approved for indications other than pain, include numerous agents in many classes, a large number of which may be tried for neuropathic pain (see Table: Adjuvant analgesics).²⁴ In addition to the analgesic antidepressants and gabapentinoids noted previously, this category includes 1) other anticonvulsants such as topiramate, oxcarbazepine, lamotrigine, lacosamide, clonazepam, and others, 2) alpha-2 adrenergic agonists such as tizanidine and clonidine, 3) sodium channel blockers such as mexiletine (and the novel lacosamide, which is a sodium channel modulator approved for the treatment of epilepsy), 4) other GABA agonists such as baclofen, 5) N-methyl-D-aspartate antagonists such as memantine, and 6) cannabinoids such as tetrahydrocannabinol and nabilone. In addition, topical therapies may be helpful. The lidocaine 5% patch or a topical local anesthetic cream, or topical capsaicin, are usually considered first, and typically in combination with oral agents. Poor adherence is common with capsaicin because of the need for frequent applications and burning at the application site. The lidocaine patch may have the added benefit of providing a barrier, which helps to protect an area of hypersensitive skin.

Postherpetic Neuralgia

Postherpetic neuralgia (PHN) is a serious complication of herpes zoster (shingles).²⁵⁻²⁷ A common definition indicates that PHN begins at four months after zoster eruption begins; prior to this, the pain may be called acute or subacute zoster.

Zoster occurs in patients previously infected with varicella. The presumably immune-related triggers that lead to a segmental recrudescence of the virus are not understood. Advancing age and immunosuppression for any reason clearly increase the risk of a zoster eruption. Also for unclear reasons, the trigeminal (usually V1) distribution and the thoracic dermatomes are the two most common sites of zoster eruption.

Pain occurs in virtually all patients with zoster and is relatively more severe among the elderly and those with worse rash. Although persistent pain affects fewer than 20% of those who develop acute zoster, there also is a relationship between age and the duration of pain among those whose pain eventually resolves and the proportion of those afflicted who develop persistent pain.²⁵⁻²⁷ There also are relationships between PHN and both the severity of the zoster eruption and the degree of distress and the occurrence of prolonged pain.

PHN is a highly variable disease, both in terms of clinical presentation and the likely pathophysiological mechanisms sustaining the pain.^{28,29} Patients may experience steady pain, which may be burning or sometimes sharp or aching, and lancinating, episodic pain like that of an electric shock. Some patients experience prominent itch. Allodynia, or pain with non-noxious stimuli, is sometimes a highly distressing symptom, which when extreme, may be associated with pain from wearing clothes or having a light breeze blow against the skin. It has been suggested that the allodynia reflects nociceptor dysfunction and distinguishes one type of PHN from another, which is associated with central changes known as deafferentation and is associated with sensory loss in the area of the pain.²⁷ This model reinforces the likelihood that PHN probably has multiple pathophysiologies related to overlapping sets of peripheral and central processes.

Prevention of Zoster and PHN

Primary prevention of zoster is now possible with the advent of a vaccine. The zoster vaccine is a live, attenuated strain of VZV, the same strain used in the varicella vaccine but with much higher potency. In a large trial, this vaccine reduced the incidence of zoster and reduced the severity and duration of pain among those who developed the infection. It is now recommended for all patients 60 years of age or older, who have no contraindications, including those who had a previous episode of zoster or who have chronic medical conditions.³⁰ Although it is clear that treatment with an antiviral drug, such as acyclovir, famciclovir or valacyclovir, at the time of a zoster eruption reduces pain, the evidence is not yet established that this treatment prevents PHN.^{31,32} Nonetheless, it may be recommended unless the zoster eruption is very mild.

Treatment of PHN

The acute pain of herpes zoster may be addressed using antiviral administration, opioid analgesics for moderate or severe pain, and in non-immunocompromised patients, a short course of systemic corticosteroid therapy.^{26,27,30,32} There is a large clinical experience suggesting that sympathetic nerve block at this time also provides effective analgesia. Referral to a consultant who is able to do this block should be considered if pain remains severe despite the initial drug therapy.³³

When pain persists, especially for a period long enough to designate the syndrome as PHN, the clinical strategy should address the problem like any other patient with chronic pain. The assessment should evaluate the nature of the pain to ensure that there are no complicating features. The impact of the pain on multiple domains of function and the existence of important physical and psychiatric comorbidities should be evaluated. Patients with severe pain or pain associated with functional decline should be considered for a multimodality approach to therapy.

In terms of pharmacotherapy, the strategy may derive from recent evidence-based guidelines for neuropathic pain.¹¹ A gabapentinoid may be considered first-line, unless there is significantly

depressed mood, in which case a trial of an analgesic antidepressant—a tricyclic antidepressant or a SNRI—should be considered first. Drugs that have been shown to be efficacious in PHN include TCAs, various anticonvulsants, and the opioid analgesics.^{11,24,26,34-38} At least two studies suggest that regular administration of an opioid may be more effective than one of the adjuvant analgesics, such as an antidepressant or anticonvulsant,^{37,38} and combination therapy may be most effective.³⁸ Patients with refractory pain have numerous options among many classes that have limited evidence of efficacy but are tried when pain does not respond to first-line approaches (Table: Adjuvant Analgesics Used for Painful Diabetic Neuropathy and Other Neuropathic Pains).²⁴

The 5% lidocaine patch was associated with reductions in pain intensity and pain interference with quality of life (QOL) in an open-label, nonrandomized effectiveness study.³⁹ The patch has FDA-approved labeling for PHN and has a good safety profile, even with continuous application of up to 3 patches per day, for 12 hours up to a 24-hour period.⁴⁰ Although capsaicin can be applied for pain in a circumscribed area and can be used in conjunction with oral analgesic agents, its use has been limited due to its burning sensation on application and the necessity of multiple daily applications for several weeks before pain relief is noted.

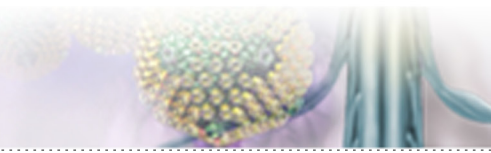
Table: Common Analgesics for Established Postherpetic Pain

Agent		Initial Dose	Comments	Potential Adverse Effects
Topical Agents	lidocaine (5% patch)	Applied to the painful area; up to 3 patches can be used at a time for a maximum of 12 hours, within a 24 hr period	Should be applied only to healed, intact skin; patches may be cut to one size; rapid onset of pain relief	Localized skin irritation; systemic toxicity from cutaneous absorption of lidocaine very rare
Opioids	oxycodone**	5 mg orally every 6 hours*	Titrate dose to whatever is needed to optimize balance between analgesia and side effects.	Sedation, nausea, dizziness, constipation
SNRI Antidepressants	duloxetine**	60 mg/d	Higher dosages have not shown to be more effective based on studies in diabetic neuropathic pain	Somnolence, dizziness, nausea
TCA Antidepressants	nortriptyline** desipramine**	10 to 25 mg/d orally at bedtime*	Total dose of up to 75 to 150 mg/d may be necessary; amitriptyline also proven effective, but may be poorly tolerated by elderly patients; less documented clinical experience with SSRIs	Sedation, confusion, anticholinergic effects (dry mouth, blurred vision, constipation, urinary retention)
Antiepileptic Agents	gabapentin	300 mg/d orally	Titration of dose as necessary over a 4-week period, to a total daily dose of 3600 mg (divided into 3 doses).	Somnolence, dizziness, ataxia, nystagmus
	pregabalin	75 to 150 mg/d orally bid, increasing to 300 mg/d orally after 1 week	In patients not experiencing sufficient pain relieve after 2 to 4 weeks treatment with 00 mg/d and tolerate the drug may be increased to a maximum of 600 mg/d.	Somnolence, dizziness, ataxia, blurred vision

*Other agents are also available for use.

** Does not have FDA-approved labeling for postherpetic neuralgia

Modified from Gnan JW, Whitley RJ. Herpes Zoster. *New Engl J Med*. 2002;347:340-346.



Patients with severe pain that does not respond well to pharmacological therapies may be candidates for any of a variety of interventional pain management approaches.⁴¹ These are performed by pain specialists and may include regional anesthesia techniques, interventional neurostimulation, or neuraxial analgesia. None of these approaches have been adequately studied and they are tried based on experience. There are some data supporting the use of neuraxial corticosteroids in reducing the pain of zoster and PHN, but the benefits and risks remain inadequately defined and the approaches are not routinely considered.

Complex Regional Pain Syndrome

The term complex regional pain syndrome (CRPS) has replaced the labels reflex sympathetic dystrophy (now CRPS type 1) and causalgia (now CRPS type 2) in an effort to be more generic and highlight the commonalities in these disorders. According to the International Association for the Study of Pain,¹ CRPS comprises a variety of regional painful conditions that usually, but not always, occur in the extremities, and usually but not always, are associated with overt trauma. The symptoms and signs exceed in both magnitude and duration the expected course of the inciting event. The following criteria are necessary for a diagnosis of CRPS:

- Spontaneous occurrence of pain in the absence of an external stimulus, allodynia, or hyperalgesia that is not limited to the territory of a single peripheral nerve, and is disproportionate to the inciting event.
- Evidence of edema, skin blood flow abnormality, or abnormal sudomotor (sweating) in the region of the pain.
- No existing condition that would otherwise account for the degree of pain and dysfunction.

The above criteria permit a diagnosis of CRPS type 1. A diagnosis of CRPS type 2 also requires that the syndrome develop after an initiating noxious event, typically one involving overt nerve injury.

In addition to these elements, patients with CRPS may have motor impairment, such as dystonia, hypertonicity, weakness or clumsiness; abnormal involuntary movements such as tremor, twitching or muscle spasm; or so-called trophic changes that may include thinning of the skin, loss of subcutaneous fat, relatively rapid or relative slowed growth of hair or nails, coarsening of the hair, or focal osteoporosis.

There have been several modifications of these criteria, but all include the syndromic constellation of pain disproportionate to injury and focal autonomic dysregulation. The pain often is burning, but may be described as throbbing, squeezing, aching, or shooting. The pain usually spreads beyond the area of the initial injury, and occasionally, patients develop spreading of the syndrome to a region that is very, and possibly even contralateral to the initial site.

The pathophysiology of CRPS is unknown. There is evidence that it is a neuropathic pain that involves both a central and a peripheral pathophysiology.⁴² A subpopulation of patients who meet clinical criteria for a diagnosis of CRPS will respond very favorably to interruption of sympathetic nervous system outflow to the pain site. These patients are said to have sympathetically-maintained pain as a contributing feature of CRPS. In clinical practice, a diagnosis of CRPS generally is viewed as an indicator of an increased likelihood of sympathetically-maintained pain. For this reason, sympathetic nerve block usually is considered among the early interventions for this condition. The goal of a block is to determine whether the patient is among the subpopulation of CRPS patients with this type of pain, and if so, whether the clinical response is sufficiently good to warrant including repeated sympathetic blocks as part of the ongoing plan of care. It is important to recognize that the response to sympathetic block does not determine whether or not the patient has CRPS.

Assessment and Diagnosis of CRPS

There is no specific diagnostic test for CRPS and thus, the diagnosis is made on the basis of patient history, clinical examination, and supporting laboratory findings.⁴³ To rule out other conditions, vascular and electrodiagnostic studies, radiographic imaging, blood tests, and rheumatologic studies may be needed. However, since not all CRPS is due to sympathetic nerve dysfunction, a positive response to a sympathetic block is not required to make a diagnosis.²⁹

Management of CRPS

Treatment of CRPS depends on the severity of symptoms and the degree of disability, and often requires an aggressive and multidisciplinary approach.^{43,44} Since pain and functional limitations are the principal clinical problems, physical rehabilitation and pain control are main treatment objectives. Pain management should be guided by pain severity and the presence or absence of sympathetic dysfunction. Comorbidities such as depression, sleep disturbance, anxiety, and general physical deconditioning should be treated aggressively.

Nonpharmacologic Approaches

Physical therapy is considered a cornerstone of the management of CRPS and has as its goal the restoration of function of the involved limb. Physical therapy is employed in a series of steps beginning with gentle desensitization, including various combinations of heat and cold, massage, and contrast baths (alternating heat and cold), and progresses (as tolerated) to gentle flexibility and isometric strengthening exercises. With improvement, range-of-motion exercises, stress loading, isotonic strengthening, and general aerobic conditioning can be added to the therapeutic regimen. Adequate pain control

must be achieved to support progress in physical therapy. If possible, physical therapy should be combined with cognitive-behavioral strategies that emphasize self-management, therapies such as biofeedback, and functional restoration.

The appropriateness of an early trial of a local anesthetic sympathetic nerve block was noted previously. There is no one definition of an effective block, but most experts would require substantial pain relief for a period of many hours if not days beyond the usual duration of the anesthetic. If a block is effective, it can be repeated in the hope that the period of benefit lengthens. If this happens, repeated blocks on a periodic basis can be used as part of the treatment plan. Some patients appear to benefit from a longer-acting block through a regional anesthetic technique like continuous epidural infusion anesthetic. Sympathectomy is now rarely considered and would only be appropriate if the benefits of each temporary block were substantial but persistently short-lived.

Pharmacologic Approaches

Most of the pharmacologic agents used for complex pain syndromes are those with demonstrated effectiveness in other neuropathic pain conditions.^{11,44} Although there have been a few trials of drug therapies specific for CRPS, most experts start with one of the analgesic antidepressants or one of the gabapentinoids in a manner similar to other conditions. Recently, trials have begun to explore the value of the NMDA receptor antagonist, ketamine, for this condition. Ketamine, in contrast to the oral NMDA receptor antagonists, appears to offer some promise. A recent controlled trial of an approximate 4-day infusion at a subanesthetic dose showed substantial benefit.⁴⁵ Brief infusion of anesthetic doses also are being explored for this indication. Other adjuvant analgesics and opioids are used empirically, as they are for other types of neuropathic pain.

Regional Anesthesia

Corticosteroids may provide relief in CRPS, but their long-term use is not recommended. An empirical trial may involve the administration of prednisone at a dose of 60 mg, which is tapered over two weeks. Although the mode of action is unknown, bisphosphonates, such as pamidronate, have been shown to be efficacious in several controlled trials.⁴⁶ Calcitonin, another osteoclast inhibitor, also has been suggested to be useful in some but not all trials.⁴⁷ Sympatholytic drugs, such as clonidine, phentolamine and prazosin, have been tried empirically based on the assumption (true in only a subpopulation) that the pain depends on sympathetic efferent activity. Calcium channel blockers, such as nifedipine, also have been used anecdotally.

Other Approaches

Spinal cord stimulation may be an effective modality for CRPS and should be considered whenever conservative therapies are not yielding satisfactory responses.⁴⁸ Neuraxial analgesia has not been studied in this condition but is considered by pain specialists in highly selected cases of refractory pain.

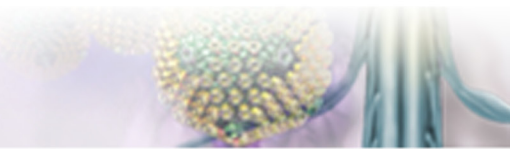
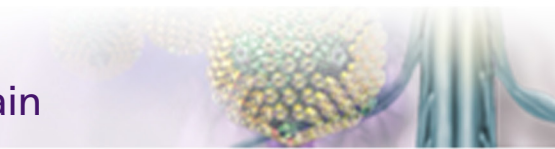


Table: Adjuvant Analgesics used for Neuropathic Pain Disorders

Drug Class	Starting Dose	Titration	Maximum Dose	Comments
Tricyclic anti-depressants				<p>TCAs are multipurpose analgesics and may be considered for a trial in any type of persistent pain.¹⁻⁶ The analgesic effect of TCAs is separate from their antidepressant effects.⁵ Depression also may be a target and doses sometimes require escalation to achieve this effect. The use of amitriptyline may be limited in many patients due to its side effects; desipramine and nortriptyline are preferred. A therapeutic response is usually seen within 3 to 10 days for neuropathic pain. TCA dosage should depend on the degree of pain relief balanced against the emergence of adverse effects. An adequate trial with a TCA needs to be given before determining treatment failure; some patients require higher dosages and several weeks of treatment before efficacy is evident. Failure of one TCA agent does not preclude a response to another, and two or more agents should be tried sequentially before selecting another class of adjuvant analgesic agents.</p>
amitriptyline	10 to 25 mg qd	10 to 25 mg qd 3 to 5 days	100 to 150 mg/day	
desipramine	10 to 25 mg qd	10 to 25 mg qd	100 to 150 mg/day	
nortriptyline	10 to 25 mg qd	10 to 25 mg qd 3 to 5 days	100 to 150 mg/day	
SNRI				<p>The newer norepinephrine/serotonin reuptake inhibitors (SNRIs) (e.g., duloxetine, venlafaxine) also may be considered multipurpose analgesics. Duloxetine has FDA-approved labeling for the management of pain caused by diabetic neuropathy. Side effects of SNRIs are usually less than those caused by the TCAs.</p>
venlafaxine*	25 mg tid*	25 mg tid q >4 days*	225 mg/day*	
duloxetine	60 mg qd	---	120 mg/day*	
SSRIs				<p>The selective serotonin reuptake inhibitors (SSRIs) have been used as adjunctive therapy for patients who are depressed. There is some evidence of analgesic efficacy (e.g., paroxetine, citalopram) but it is limited. SSRIs have fewer side effects than TCAs and are generally considered safer. In patients with depression and persistent pain who cannot tolerate TCAs, a trial with an SSRI is reasonable. Experience is greatest with paroxetine and citalopram.</p>
paroxetine*	20 mg/day*	10 mg/day q 7 days*	50 mg/day*	
citalopram*	20 mg/day*	20 mg/day q 7 days*	40 mg/day*	
	*antidepressant dose	*antidepressant dose	*antidepressant dose	
Antiepileptic drugs				<p>Antiepileptics are used in the management of neuropathic pain and are similar to TCAs in producing a graded analgesic effect.⁷</p> <p>Gabapentin and pregabalin have FDA -approved labeling for postherpetic neuralgia. Most who respond to gabapentin do so at total daily doses of 900 to 1800 mg/day, but some patients require higher doses. Dose- related sedation is a limiting factor with gabapentin.</p> <p>Pregabalin has FDA-approved labeling for neuropathic pain associated with diabetic peripheral neuropathy.</p>
gabapentin	300 mg/day	300 mg bid, day 2 300 mg tid, day 3	1800 to 3600 mg/day or higher	
pregabalin (For PNH)	50 mg tid 75mg bid or 50 mg tid	100 tid after 1 week 100 tid after 1 week	300 mg/day 300 mg/day	

carbamazepine	200 mg/day	200 mg/day q 12 h	1200 mg/day	Carbamazepine has FDA-approved labeling for trigeminal neuralgia. Lamotrigine, oxcarbazepine, topiramate, gabapentin, and valproate also may have analgesic effects but the evidence is inconsistent. All these agents are typically used at their antiepileptic doses.
GABA Agonist				
baclofen	5 to 10 mg bid or tid	5 to 10 mg/day q 2 to 3 days prn	80 mg/day	The analgesic effect of baclofen in trigeminal neuralgia has led to wider use in neuropathic pain of other types. Although less effective than carbamazepine, the adverse-reaction profile for baclofen is more favorable, making it an attractive initial drug to treat trigeminal neuralgia in select patients. The reported effective dosage range is 50 to 60 mg/d, but some patients benefit from higher doses. ⁸
Oral sodium channel blocker				
mexiletine	150 to 200 mg bid	50 mg q 2 to 3 days prn	1200 mg/day	Mexiletine, an oral analog of intravenous lidocaine has been used to treat difficult to control neuropathic pain secondary to diabetic neuropathy, spinal cord injury, persistent pain syndromes secondary to peripheral nerve injury. ⁹⁻¹³
Alpha-2-adrenergic				
agonist clonidine	0.1 mg bid	0.1 mg/day at weekly intervals prn	2.4 mg/day	Sympatholytic agents may be used for complex regional pain syndromes (also called reflex sympathetic dystrophy or causalgia). ^{4,15} The usual effective dosage is 0.3 mg/day. Transdermal clonidine may decrease swelling and pain in CRPS areas with hyperalgesia. Tizanidine is a muscle relaxant with centrally acting alpha-2 agonist activity. It can produce hypotension but this occurs less than with clonidine. Tizanidine may have some inherent analgesic activity and might be tried in refractory pains of other types.
tizanidine	4 mg initially	2 mg q 6 to 8 hours	36 mg/day	
NMDA receptor antagonist				NMDA receptor antagonists can be useful in intractable neuropathic pain. The experience with dextromethorphan for persistent pain syndromes has been disappointing. ¹⁶ One study has shown that dextromethorphan treatment improved pain assessment scores in patients with diabetic neuropathy but not PHN. ¹⁷ Ketamine, a dissociative anesthetic, has been used by pain specialists in some cases of intractable neuropathic pain. However, even with low (sub-anesthetic) doses, psychotomimetic side effects may limit its utility and safety, thus requiring careful patient selection.
ketamine	See comments	See comments	See comments	
dextro-methorphan	See comments	See comments	See comments	

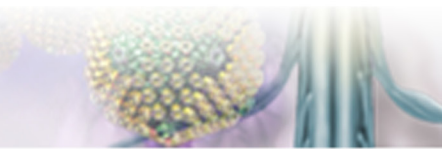


Topical agents			
capsaicin	0.025%to 0.075% qid	See comments	See comments
lidocaine patch	lidocaine 5%	Up to 3 patches applied at once, for up to 12 hrs in 24 hr period	See comments
Miscellaneous agent			
calcitonin, IM or SC	50 to 100 I.U./day	Maintenance dose 50 to 100 I.U.q 1 to 3 days	100 I.U./day

Topical capsaicin has been used to treat a number of persistent pain conditions including diabetic neuropathy, PHN, osteoarthritis, rheumatoid arthritis, and postmastectomy pain.¹⁸ One study concluded that topical capsaicin therapy for 22 weeks reduced pain in patients with diabetic neuropathy.¹⁹ Patients should be instructed to use the lower strength concentration qid before attempting to use the higher strength concentration. Initial burning is common, but most patients become tolerant within a few days. Patients should be advised to wash hands thoroughly after using capsaicin and avoid contact with eyes and mucous membranes. Topical local anesthetics are also used commonly and lidocaine patch (5%) is available, with labeled indications for PHN, but used for other conditions as well. Up to 3 patches/day can be used.

Calcitonin, has been reported to reduce persistent pain associated with osteoporotic fractures, bone metastases, complex regional pain syndrome and phantom limb pain. Although the long-term efficacy has not been established, a trial of calcitonin may be considered in patients with refractory pain.

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