

Neuropathic Pain: Principles of Diagnosis and Treatment

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Learning Objectives: On completion of this article, you should be able to (1) identify the key pathophysiologic mechanisms implicated in the development of neuropathic pain, (2) apply the necessary clinical tools to appropriately assess patients with neuropathic pain, and (3) formulate an evidence-based approach for the pharmacologic treatment of neuropathic pain.

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This review discusses a wide variety of treatment modalities, several of which are not necessarily labeled for use in the treatment of neuropathic pain in all countries. Therefore, readers are expected to determine the labeled indications in their country of clinical practice for any of the discussed treatments.

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Abstract

Neuropathic pain is caused by disease or injury of the nervous system and includes various chronic conditions that, together, affect up to 8% of the population. A substantial body of neuropathic pain research points to several important contributory mechanisms including aberrant ectopic activity in nociceptive nerves, peripheral and central sensitization, impaired inhibitory modulation, and pathological activation of microglia. Clinical evaluation of neuropathic pain requires a thorough history and physical examination to identify characteristic signs and symptoms. In many cases, other laboratory investigations and clinical neurophysiological testing may help identify the underlying etiology and guide treatment selection. Available treatments essentially provide only symptomatic relief and may include nonpharmacological, pharmacological, and interventional therapies. Most extensive evidence is available for pharmacological treatment, and currently recommended first-line treatments include antidepressants (tricyclic agents and serotonin-norepinephrine reuptake inhibitors) and anticonvulsants (gabapentin and pregabalin). Individualized multidisciplinary patient care is facilitated by careful consideration of pain-related disability (eg, depression and occupational dysfunction) as well as patient education; repeat follow-up and strategic referral to appropriate medical/surgical subspecialties; and physical and psychological therapies. In the near future, continued preclinical and clinical research and development are expected to lead to further advancements in the diagnosis and treatment of neuropathic pain.

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Neuropathic pain has most recently been redefined by the International Association for the Study of Pain as “pain caused by a lesion or disease of the somatosensory system.”¹ Nociceptive pain (eg, arthritis) involves peripheral sources of noxious stimulation (eg, inflammatory mediators) that are processed by an otherwise normal somatosensory system, whereas the primary cause of neuropathic pain is the lesion or disease that leads to an abnormal and dysfunctional somatosensory system.² Keeping this definition in mind, neuropathic pain refers to a broad range of clinical conditions (Table 1)³ that can be categorized anatomically (eg, peripheral vs central) and etiologically (eg, degenerative, traumatic, infectious, metabolic, and toxic).

The “positive” symptoms of neuropathic pain conditions include both stimulus-independent (“spontaneous”) and stimulus-dependent (“evoked”) pain and other symptoms such as tingling (ie, paresthesias).⁴ The “negative” signs and symptoms that may be observed include numbness, weakness, and loss of deep tendon reflexes in the involved nerve territory. Neuropathic pain can follow different temporal profiles (eg, continuous vs intermittent) and may be described with different pain quality descriptors.⁵⁻⁷ Stimulus-evoked pain includes *allodynia*, defined as pain in response to a normally nonpainful stimulus (eg, contact of clothing on skin), and *hyperalgesia*, defined as increased pain in response to a normally painful stimulus. These sensory abnormalities are often observed to extend beyond dermatomal or nerve territory distributions, leading to the inappropriate diagnosis of a functional or psychosomatic disorder.

Describing the epidemiology of neuropathic pain is particularly challenging given this diversity of related clinical entities. However, the validation of a number of assessment tools for the identification of pain with neuropathic characteristics^{5,6,8} has facilitated epidemiological studies that estimate the prevalence of neuropathic pain to be as high as 7% to 8% of the general population.^{9,10} Furthermore, quality-of-life studies indicate that in addition to the obvious pain-related suffering experienced by patients, neuropathic pain is associated with depression, disordered sleep, and impairments in physical function.¹¹⁻¹³ The purpose of this article was to review and describe current principles of neuropathic pain diagnosis and

neuropathic pain treatment with a focus on pharmacological therapy.

NEUROPATHIC PAIN MECHANISMS RELEVANT TO DIAGNOSIS AND TREATMENT

As illustrated in the Figure, an understanding of the diverse mechanisms of pain transmission and pain modulation is crucial for appropriate clinical assessment as well as the development and application of analgesic therapies. Development of several preclinical pain models involving injury (eg, surgical), or disease induction (eg, streptozocin-induced diabetic neuropathy), of peripheral or central neurons has facilitated many sophisticated investigations, providing a wealth of information about cellular and molecular mechanisms of neuropathic pain.¹⁴⁻¹⁷ Also, clinical manifestations of underlying neuropathic pain mechanisms (eg, sensitization and impaired descending inhibition) have emerged from human neuropathic pain studies involving quantitative sensory testing, electrophysiology, nerve and skin biopsy, and functional brain imaging studies.^{5,7} Prominent and well-characterized mechanisms observed to be important in neuropathic pain conditions include (1) ectopic activity, (2) peripheral sensitization, (3) central sensitization, (4) impaired inhibitory modulation, and (5) activation of microglia.^{14,15}

Ectopic Activity

Following nerve injury, hyperexcitability leading to ectopic action potentials in primary afferent neurons, and sometimes their central projections,¹⁸ is likely an important mechanism of spontaneous (stimulus-independent) paresthesias, dysesthesias, and pain,¹⁵ which may demonstrate different temporal patterns (eg, brief paroxysmal, continuous intermittent, or continuous constant).

TABLE 1. Classification of Neuropathic Pain According to Site of Major Pathology

Pathology	Peripheral	Spinal	Brain
Genetic	Fabry neuropathy	Syringomyelia	Syringobulbia
Metabolic	Painful diabetic neuropathy	B ₁₂ myelopathy	
Traumatic	Nerve injury	Spinal cord injury	Multiple sclerosis
Vascular	Vasculitic neuropathy	Spinal cord stroke	Brain stroke
Neoplastic	Tumor compression neuropathy	Tumor compression	Tumor compression
Immunological	Guillain-Barré syndrome	Multiple sclerosis	Multiple sclerosis
Infectious	HIV, Borreliosis	Infectious myelitis	Encephalitis
Toxic	Chemotherapy neuropathy		

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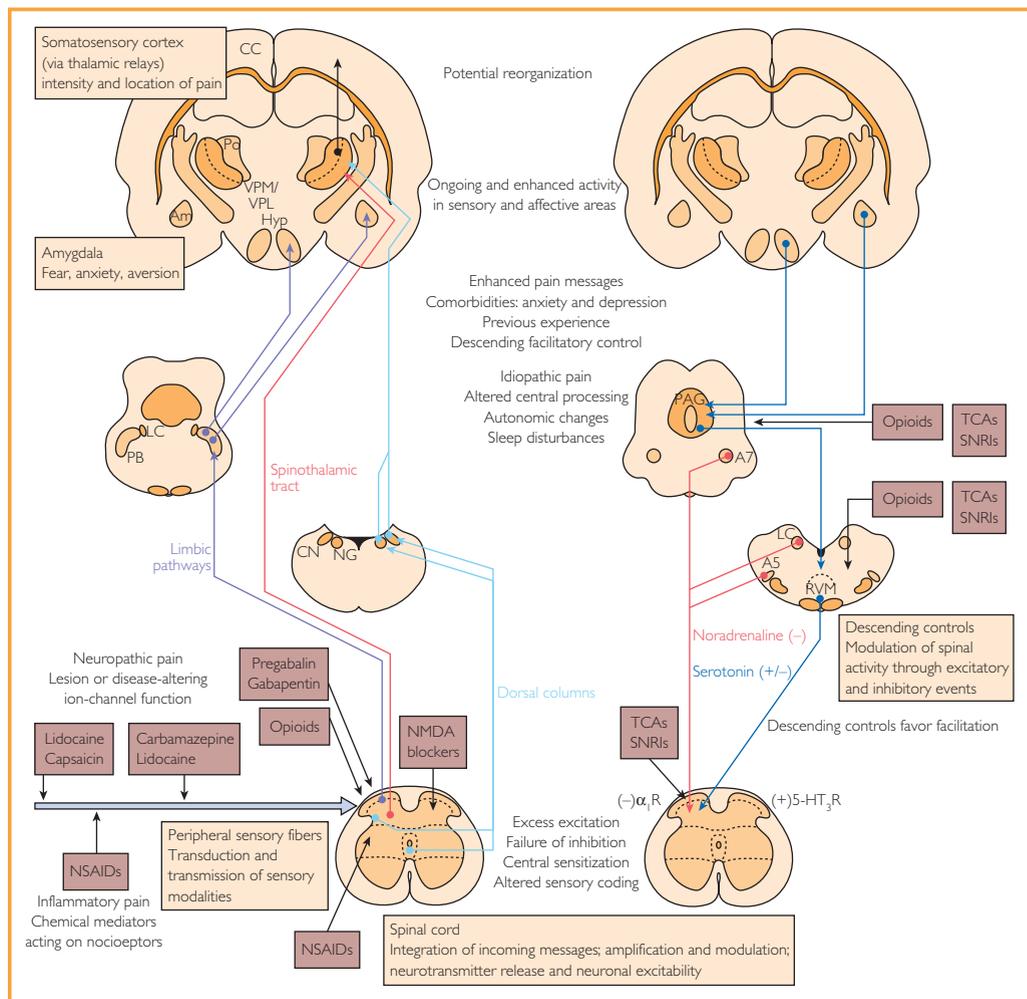


FIGURE. Main pathways and mechanisms by which pain is transmitted and modulated. The ascending pathways, by which sensory and affective components are generated, are shown on the left. Top-down modulation, by which higher centers can alter spinal function through changes in descending controls, is shown on the right. The major functional roles of different neural components in these pathways are summarized in yellow boxes. Changes that occur after tissue or nerve damage are listed, and pharmacological agents that modulate pain are shown at their sites of action in red boxes. Peripheral inputs are indicated by the horizontal purple arrow. The peripheral mechanisms of inflammatory and neuropathic pain are very different, and this difference is reflected in their different treatments. However, central mechanisms might be more common than peripheral mechanisms. (-) α_2 R = inhibition of neuronal activity. (+) 5-HT₃R = stimulation of neuronal activity; Am = amygdala; A5 and A7 = brain stem nuclei containing noradrenergic neurons; CC = cerebral cortex; CN = cuneate nucleus; Hyp = hypothalamus; LC = locus coeruleus; NG = nucleus gracilis; NMDA = N-methyl-D-aspartate; NSAID = nonsteroidal anti-inflammatory drug; PAG = periaqueductal gray matter; PB = parabrachial nucleus; Po = posterior nuclei of the thalamus; RVM = rostroventral medial medulla; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; VPM and VPL = ventrobasal thalamus, medial and lateral components. From *Lancet Neurol*,³ with permission from Elsevier, Inc.

Evidence points to various molecular changes that likely contribute to ectopic activity including postinjury alterations in voltage-gated sodium (eg, Na_v1.3, Na_v1.6, and Na_v1.9) channels, voltage-gated potassium (eg, KCNQ K_v7) channels, and hyperpolarization-

activated cyclic nucleotide-gated (eg, HCN2) channels.¹⁹

Peripheral Sensitization

Although thought to be one of the most important mechanisms of inflammatory pain,

peripheral sensitization—exhibited as hyperexcitability and reduced activation threshold of primary afferent neurons—is also an important mechanism of peripherally mediated hyperalgesia and allodynia after nerve injury.¹⁵ Postinjury changes in the transient receptor potential TRPV1 ion channel²⁰ and possibly other members of this ion channel family are thought to contribute to peripheral sensitization in neuropathic conditions, which has led to the clinical evaluation of the TRPV1 agonist capsaicin.²¹

Central Sensitization

A body of animal investigations has demonstrated that nerve disease or injury—as well as other peripheral nociceptive stimulation—can trigger central (ie, spinal and supraspinal) neuroplastic changes referred to as *central sensitization*.²² *Central sensitization* has been defined as “a prolonged but reversible increase in the excitability and synaptic efficacy of neurons in central nociceptive pathways” that manifests as allodynia (touch-evoked pain), hyperalgesia (pain experience that is exaggerated with respect to a standardized noxious stimulus), enhanced temporal summation (escalating pain in response to repeated application of a constant stimulus), and secondary hyperalgesia (pain and hypersensitivity beyond the dermatome of the nerve injury).²² Proposed mechanisms by which nerve injury results in central sensitization include phenotypic changes in A-beta touch fibers, which subsequently expressed increased levels of neuropeptides such as calcitonin gene-related peptide and substance P²³ and increased activity of excitatory amino acid transmission (eg, via *N*-methyl-D-aspartate [NMDA] receptors).²⁴ The latter mechanism has provided the therapeutic rationale for studying excitatory amino acid antagonists to treat neuropathic pain, although agents with an optimal therapeutic profile are yet to be identified.^{25,26}

Impaired Inhibitory Modulation

In addition to changes that enhance nociception, evidence has emerged to indicate that nerve injury can lead to the impairment of endogenous *inhibitory* mechanisms of nociception in some situations.^{14,15} For example, post-nerve injury excitatory transmission has been shown

to cause apoptosis (cell death) of GABAergic spinal inhibitory interneurons contributing further to postinjury pain sensitivity.²⁷

Activation of Microglia

Evidence has been mounting over the past 15 years to demonstrate that neuropathic conditions (and other pain states) are associated with activation of glia, and other nonneuronal cells in the central nervous system (CNS), and furthermore that changes in these activated glia may be important contributors to the phenomenon of central sensitization.²⁸ Several molecular changes resulting from postinjury glial activation have been identified to contribute to pain hypersensitivity and include phosphorylation of mitogen-activated protein kinase, upregulation of chemokine receptors, and release of glial cytokines and growth factors.²⁹

It is important to recognize that in patients with neuropathic pain, more than one mechanism, or pain phenotype, may be apparent and, furthermore, a seemingly singular condition (eg, postherpetic neuralgia) often includes a heterogeneous population, with patient subgroups exhibiting different mechanisms.^{30,31} For example, some patients with postherpetic neuralgia have been reported to exhibit hyperalgesia and/or allodynia thought to be due to peripheral sensitization (“irritable nociceptors”) but with minimal sensory loss. Another subgroup of patients exhibits deafferentation of small nociceptive fibers, resulting in impaired temperature sensation but profound allodynia thought to be due to central sensitization. Yet another subgroup exhibits sensory loss without hyperalgesia or allodynia but severe spontaneous pain thought to be related to ectopic activity in deafferented central neurons and/or central neuronal reorganization.³⁰ Perhaps even more relevant to individualizing therapy, it is also notable that multiple pain mechanisms may be involved in the same patient in some cases.³¹

PRIMARY CARE APPROACH TO NEUROPATHIC PAIN ASSESSMENT

In the setting of clinical care for a patient suspected of having neuropathic pain, careful history and physical examination and special laboratory tests serve to (1) aid in formulating a differential diagnosis of the presenting problem, (2) guide appropriate treatment selection, and (3) follow-up individual responses to

treatment.³²⁻³⁴ Diagnosis of neuropathic pain is primarily based on history and physical examination although other special investigations are often useful.^{6,32} Clinical assessment should focus on ruling out treatable conditions (eg, spinal cord compression and neoplasm), confirming the diagnosis of neuropathic pain, and identifying clinical features (eg, insomnia and autonomic neuropathy) that might help individualize treatment. As with other chronic pain conditions, evaluation of a suspected neuropathic condition should always include an assessment of pain location, quality, intensity and temporal variation, functional impact on mood, sleep, and other activities of daily living, responses to previously attempted treatments, and coexisting or previous alcohol or substance abuse.³

Signs and Symptoms Characteristic of Neuropathic Pain

Although no single sign or symptom is pathognomonic of neuropathic pain, research over the past 15 years or so has implicated a set of sensory signs and symptoms that are much more likely to be associated with a neuropathic pain condition versus other nonneuropathic conditions.^{4,5,8} Much of this information has emerged from the development and publication of several neuropathic pain (or neuropathy) screening tools including the Michigan Neuropathy Screening Instrument,³⁵ Neuropathic Pain Scale,³⁶ Leeds Assessment of Neuropathic Symptoms and Signs,³⁷ Neuropathic Pain Questionnaire,³⁸ Neuropathic Pain Symptom Inventory,³⁹ "Douleur Neuropathique en 4 questions,"⁴⁰ pain DETECT,⁴¹ Pain Quality Assessment Scale,⁴² and the Short-Form McGill Pain Questionnaire-2.⁴³ Although several differences exist, the sensory quality descriptors "tingling" (or "pins and needles" or "prickling"), "burning" (or "hot"), and "shooting" (or "electrical shocks") are included in nearly all these various tools, and these 3 descriptors are perhaps the most characteristic of neuropathic pain.^{4,6} The above, self-report, neuropathic pain assessment tools (some of which include a physical examination component) may be useful for the diagnostic characterization of neuropathic pain. However, some of these tools have also been used to describe subgroups of patients with neuropathic pain in whom unique underlying mechanisms are operant. For example, Baron et al⁴⁴ found 5 distinct

subgroups of sensory symptoms assessed using the pain DETECT instrument in 1623 patients with painful diabetic neuropathy and 498 patients with postherpetic neuralgia. Furthermore, pain quality descriptors can provide more detail in characterizing treatment effect beyond just global measures of pain intensity.⁴⁵ For example, secondary analyses of neuropathic pain clinical trials have demonstrated that drug therapy can preferentially reduce certain pain quality descriptors and have little effect on others.⁴⁶⁻⁴⁸

Basic Sensory Examination

Relatively simple bedside methods can be used to assess sensory abnormalities such as hypoesthesia (abnormally reduced sensation of a tactile stimulus) to touch or cold; hypoalgesia (abnormally reduced pain sensation to a noxious stimulus); hyperalgesia (abnormally increased pain sensation to a noxious stimulus) to pinprick, blunt pressure, heat, or cold; and, finally, allodynia (pain sensation to a nonnoxious stimulus).⁶ Sensory nerve fibers assessed by clinical examination include A-beta touch fibers (eg, with fingers, wisp of cotton, or soft brush), A-delta "fast" pain fibers (eg, with a metal straight pin or sharp wooden stick), and C "slow" pain fibers (eg, with a warm 40°C object).⁴⁹ Detection of abnormal sensory findings can often be validated by comparison with normal contralateral and/or other unaffected body sites. Efforts should be made to explain how observed sensory abnormalities relate to a suspected neurological lesion. For example, polyneuropathies such as diabetic neuropathy are often associated with distal and symmetrical sensory abnormalities,⁵⁰ whereas more focal neural conditions such as postherpetic neuralgia or lumbar radiculopathy are often associated with abnormalities along the affected dermatome.⁵¹

QUANTITATIVE SENSORY TESTING

Patients with neuropathic pain suffer from various sensory abnormalities that can occur in different combinations. It is thought that sensory signs and symptoms are closely linked to underlying mechanisms of pain generation, and it is therefore likely that precise analysis of the individual somatosensory pattern might facilitate a mechanism-based treatment strategy. Thus, it is important to assess the individual sensory phenotype as precisely as possible. In addition to the self-report instruments

discussed above, quantitative sensory testing to assess sensory signs has shown promising results in characterizing underlying “mechanistic clusters” in neuropathic pain as well as in predicting response to analgesic treatment with certain drugs. A standardized quantitative sensory testing protocol for routine use and clinical trials was introduced by the German Research Network on Neuropathic Pain (Deutscher Forschungsverbund Neuropathischer Schmerz [DFNS]) in 2006 because standardization is crucial to compare study results.⁵² Sensory stimuli are applied to the skin or deep somatic structures to elicit a painful or nonpainful sensation that can be quantified on a rating scale. Quantitative sensory testing uses a battery of mechanical and thermal stimuli (graded von Frey hairs, several pinprick stimuli, pressure algometry, quantitative thermal testing, etc) and assesses both minus signs (loss of function) and positive signs (gain of function) in the nociceptive and nonnociceptive afferent nervous systems. On the basis of quantitative sensory testing, a novel classification and subgroupings of neuropathic pain syndromes have been proposed. Similar to the way tumors are graded, patients are classified (LoGa classification) according to their function of small and large afferent fibers.⁵³ In the setting of neuropathic pain treatment, Demant et al⁵⁴ examined in a randomized, double-blind, placebo controlled trial the pain-relieving effect of oxcarbazepine in 72 patients with postherpetic neuralgia, surgical or traumatic nerve injury, or polyneuropathy. They performed quantitative sensory testing according to the LoGa classification in the beginning of the trial and stratified the patients according to their sensory profile into the following 2 groups: (1) “irritable nociceptor” with predominantly a “gain of function” and a preserved small-fiber nerve function and (2) “deafferentation type” dominated by sensory loss. This stratification is based on the assumption that ectopic activity from upregulated sodium channels is mainly responsible for hyperalgesia (“irritable nociceptor”), and therefore oxcarbazepine as a sodium channel blocker should have an effect in these patients.⁵⁴ Although oxcarbazepine is recommended as first-line therapy for trigeminal neuralgia, it plays a minor role in the treatment of other neuropathic pain syndromes because of equivocal study results. This study showed positive results and a treatment response depending on

the sensory phenotype. For all patients, the number needed to treat (NNT) for 50% pain relief was 6.9. The NNT in the group with the “irritable nociceptor phenotype” was only 3.9, whereas the NNT was 13 for the “nonirritable nociceptor” phenotype.⁵⁴

OTHER SPECIAL TESTS

Clinical neurophysiological examinations are vital assessment tools in establishing a diagnosis of neuropathic pain with peripheral nerve involvement.⁵⁵ However, clinical neurophysiology examines large fibers but is generally not useful in determining the possible involvement of small nerve fibers in neuropathic pain conditions. A number of other tests can be performed in patients with suspected small-fiber neuropathy. Apart from clinical and electrophysiological examination, other assessments include both structural tests such as various skin biopsy analyses, sural nerve biopsy, and structural imaging tests of, for example, larger nerves. The functional tests include, apart from quantitative sensory testing, sudomotor function test, heart rate variability, contact heat—evoked potentials (CHEPs), laser-evoked potentials (LEPs), and quantitative axon reflex measures. Dysfunction of the sudomotor nerves with changed sweat is an early neurophysiologic abnormality in neuropathies. There are different methods to determine sudomotor functionality. A commonly used one is the quantitative sudomotor axon reflex test (QSART).⁵⁶ The test measures resting skin temperature, resting sweat output, and iontophoretic-stimulated sweat output. The QSART can be used as a diagnostic tool for small-fiber neuropathy, and it has been shown that increased diagnostic yield can be obtained by incorporating the QSART into the diagnostic criteria for small-fiber neuropathy.⁵⁶ A recently devised objective “sweat test” has demonstrated the ability to detect and quantify early changes in sudomotor nerves by quantifying reduced water produced by partial denervation of individual sweat glands.⁵⁷ Contact heat—evoked potentials and LEPs assess noxious information of thermal nature that is mediated via C- and A-delta fibers.^{55,58} Contact heat—evoked potentials use contact heat stimulation and thereby stimulates a larger number of nociceptors in the skin, whereas LEPs use high-energy lasers to selectively activate single nociceptors.⁵⁹ Laser-evoked potentials have the advantage of requiring no skin contact, but they do not activate the nerve

fibers naturally. Despite these considerations, both CHEPs and LEPs are considered reliable methods to study nociceptive pathways.⁶ However, there is no clear correlation between LEPs and structural changes such as the intraepidermal nerve fiber density,^{60,61} indicating that loss of nerve fibers is not necessarily associated with loss of function of remaining nerve fibers. Casanova-Molla et al⁶² reported that in subgroups of 52 patients with small-fiber neuropathy and 40 patients with mixed (small-fiber and large-fiber) neuropathy, both showed in general reasonable correlation between intraepidermal nerve fiber density and the latency and amplitude of LEPs and CHEPs. Punch skin biopsy with a diameter of 2 or 3 mm is a fast and minimally invasive technique with a high diagnostic yield and is today a commonly used procedure in patients suspected of having small-fiber neuropathy.^{61,63-67} Following fixation and cutting, slices are immunostained with protein gene product 9.5 for visualization of the density of nerve fibers crossing from the dermis into the epidermis. Over the past decade, there has been some progress in extracting further quantitative measurements from the skin biopsies, including axonal swellings, nerve fiber length densities, and sweat gland innervation (Karlsson et al, unpublished data, 2014). An advantage of skin biopsies is that they can be repeated over time and allow the clinician to follow the disease course quantitatively, and they may disclose changes in the small nerve fibers, which a normal neurological examination is not capable of. A similar and completely noninvasive technique is confocal microscopy of the cornea in which corneal small nerve fibers are quantified.^{67,68} This technique developed by Malik⁶⁷ has been shown to be reproducible and sensitive and with a high degree of specificity not only in patients with signs of nerve damage but also in patients without neurophysiological signs of nerve abnormality.⁶⁸ The limitation of these structural nerve fiber measures is that they only demonstrate loss of nerve fibers, not the functionality of the remaining nerve fibers that can be intact, damaged, or overactive.

OVERVIEW OF TREATMENT GOALS AND STRATEGIES IN NEUROPATHIC PAIN

In addition to symptom control, management of patients with neuropathic pain requires periodic reevaluation to rule out other treatable underlying medical conditions, patient

education, and reassurance. Education about the natural history of the patient's underlying neuropathic condition as well as the limitations of currently available pain treatments helps generate appropriate treatment expectations; that is, current therapies are often not curative, and residual pain, even during treatment, is common. Because some patients may respond well to safer, less expensive, and less invasive treatments, a stepwise treatment approach is prudent.⁶⁹ However, in many cases, various challenges and complexities of individual cases may indicate the need for more intensive treatments as well as a multimodal, multidisciplinary pain management strategy. For example, referral to, and concurrent treatment by, an occupational, rehabilitation, or physical therapist may be helpful in cases in which pain interferes substantially with work and other daily activities. Furthermore, early assessment for coexisting depression, anxiety, and/or substance abuse disorders may facilitate early referral to a psychologist, psychiatrist, and/or tertiary care pain management clinic. Responses to initial patient trials of first-line pain treatments (discussed below) should be carefully evaluated and documented to help guide next management steps.

DRUG THERAPY FOR NEUROPATHIC PAIN

Various drug classes with analgesic effects have been compared to placebo in clinical trials involving patients with various neuropathic pain conditions including antidepressants, anticonvulsants, local anesthetic drugs, NMDA receptor antagonists, opioids, cannabinoids, botulinum toxin, topical capsaicin, and other agents.⁷⁰ Several of these drugs were first developed for other indications (eg, depression and epilepsy) and subsequently evaluated in neuropathic pain. Systematic review and meta-analysis of neuropathic pain trials—with careful consideration of both analgesic efficacy and treatment-related adverse effects—and development of recommendations by several societies and associations have led to the current strong recommendations (based on the Grading of Recommendations Assessment, Development, and Evaluation system) for tricyclic antidepressants, gabapentin, pregabalin, and serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants (first-line therapies); weak recommendations for lidocaine patches,

TABLE 2. Currently Recommended Neuropathic Pain Drugs^a

Drug	Total daily dose and dose regimen	Recommendations
Strong recommendations for use		
Gapabentin	1200-3600 mg, in 3 divided doses	First line
Gabapentin extended release or enacarbil	1200-3600 mg, in 2 divided doses	First line
Pregabalin	300-600 mg, in 2 divided doses	First line
Serotonin-norepinephrine reuptake inhibitors duloxetine or venlafaxine ^b	60-120 mg, once a day (duloxetine); 150-225 mg, once a day (venlafaxine extended release)	First line
Tricyclic antidepressants	25-150 mg, once a day or in 2 divided doses	First line ^c
Weak recommendations for use		
Capsaicin 8% patches	One to 4 patches to the painful area for 30-60 min every 3 mo	Second line (peripheral neuropathic pain) ^d
Lidocaine patches	One to 3 patches to the region of pain once a day for up to 12 h	Second line (peripheral neuropathic pain)
Tramadol	200-400 mg, in 2 (tramadol extended release) or 3 divided doses	Second line
Botulinum toxin A (subcutaneously)	50-200 units to the painful area every 3 mo	Third line; specialist use (peripheral neuropathic pain)
Strong opioids	Individual titration	Third line ^e

^aGRADE = Grading of Recommendations Assessment, Development, and Evaluation.
^bDuloxetine is the most studied, and therefore recommended, of the serotonin-norepinephrine reuptake inhibitors.
^cTricyclic antidepressants generally have similar efficacy; tertiary amine tricyclic antidepressants (amitriptyline, imipramine, and clomipramine) are not recommended at doses >75 mg/d in adults aged 65 y and older because of major anticholinergic and sedative adverse effects and potential risk of falls³²; an increased risk of sudden cardiac death has been reported with tricyclic antidepressants at doses >100 mg/d.³³
^dThe long-term safety of repeated applications of high-concentration capsaicin patches in patients has not been clearly established, particularly with respect to the degeneration of epidermal nerve fibers, which might be a cause for concern in progressive neuropathy.
^eSustained-release oxycodone and morphine have been the most studied opioids (maximum doses of 120 and 240 mg/d, respectively, in clinical trials); long-term opioid use might be associated with abuse, particularly at high doses, cognitive impairment, and endocrine and immunological changes.^{34,35}
From *Lancet Neurol*,⁷¹ with permission.

high-concentration capsaicin patches, opioids, botulinum toxin A, and combinations of selected first-line agents; strong recommendation *against* the use of levetiracetam and mexiletine; and weak recommendations *against* the use of cannabinoids and valproate.⁷¹ Table 2 describes recently recommended prescribing information, and Table 3 describes common adverse effects, precautions, and contraindications for first-line neuropathic pain drugs.⁷² Given the focus of this review, currently recommended first-line therapies, and also opioids, are reviewed below in further detail.

Antidepressants

Various pharmaceutical agents evaluated for the treatment of depression, and thus referred to as antidepressant drugs, have been classified according to their chemical structure and/or pharmacological mechanisms and include the older tricyclic antidepressants (TCAs; eg, amitriptyline, nortriptyline, and imipramine), selective serotonin reuptake inhibitors (eg, fluoxetine), SNRIs (eg, venlafaxine and duloxetine), monoamine

oxidase inhibitors (eg, moclobemide), and others.⁷³ Antidepressants reduce chronic pain in both depressed and nondepressed patients, suggesting independent analgesic mechanisms; however, additional benefits of these drugs may include treatment of comorbid depression and pain-related sleep interference.⁷⁴ Putative analgesic mechanisms of antidepressant drugs include increased supraspinal availability of norepinephrine (and enhancement of descending inhibitory bulbospinal control), activation of endogenous μ - and δ -opioid receptors, sodium channel blockade, and NMDA receptor inhibition.⁷⁵

More than a dozen randomized controlled trials (RCTs) of TCAs demonstrate efficacy in painful diabetic neuropathy,^{76,77} postherpetic neuralgia,^{78,79} and central poststroke pain.^{80,81} Meta-analyses of these trials resulted in estimated NNTs of 1.7 to 3.2 for imipramine, 1.9 to 4.5 for desipramine, and 2.5 to 4.2 for amitriptyline.^{71,82,83} Although efficacy in more than 1 peripheral neuropathic pain condition (eg, diabetic neuropathy and postherpetic neuralgia) may

TABLE 3. Common Adverse Effects, Precautions, and Contraindications for First-Line Neuropathic Pain Drugs^{a,b}

Medication	Major adverse effects	Precautions	Contraindications	Comments and recommendations
TCAs				
Nortriptyline and desipramine (amitriptyline, imipramine)	Cardiac conduction block, sedation, confusion, anticholinergic effects (dry mouth, constipation, urinary retention, blurred vision), orthostatic hypotension, weight gain	Use with caution in patients with history of seizures, prostatic hypertrophy, urinary retention, chronic constipation, narrow-angle glaucoma, increased intraocular pressure, or suicidal ideation; use with caution in patients receiving concomitant SSRI, SNRI, or tramadol treatment	Recovery phase after myocardial infarction, arrhythmias (particularly heart block of any degree), concomitant use of MAO inhibitors, porphyria	ECG screening recommended in adults older than 40 y; heart rate and blood pressure follow-up (both supine and standing measurements) recommended with dose escalation; ECG and blood concentration follow-up recommended at doses of >150 mg/d; follow-up of weight recommended, especially in diabetic patients
SNRIs				
Duloxetine	Nausea, loss of appetite, constipation, sedation, dry mouth, hyperhidrosis, anxiety	Use with caution in patients with history of mania, seizures, or bleeding tendency or those taking anticoagulants; use with caution in patients taking concomitant SSRI or tramadol treatment	Concomitant use of MAO inhibitors: uncontrolled hypertension	Blood pressure follow-up recommended in patients with known hypertension and/or other cardiac disease, especially during the first month of treatment. Smokers have almost 50% lower plasma concentrations of duloxetine than do nonsmokers
Venlafaxine	Nausea, loss of appetite, hypertension, sedation, insomnia, anxiety, dry mouth, hyperhidrosis, constipation	Use with caution in patients with hypertension; use with caution in patients taking concomitant SSRI or tramadol treatment	Concomitant use of MAO inhibitors	Blood pressure follow-up recommended
Gabapentinoids				
Gabapentin	Sedation, dizziness, weight gain, edema, blurred vision	Simple antacids reduce bioavailability		Follow-up of weight recommended, especially in diabetic patients
Pregabalin	Sedation, dizziness, weight gain, edema, blurred vision			Follow-up of weight recommended, especially in diabetic patients

^aECG = electrocardiogram; MAO = monoamine oxidase inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

^bAdapted from *Mayo Clin Proc*⁷² with permission.

provide evidence to consider a drug efficacious in all peripheral neuropathic pain conditions,⁸⁴ it should be noted that several high-quality RCTs failed to demonstrate the efficacy of TCAs in HIV-related neuropathy^{85,86} or in lumbar radiculopathy.⁸⁷ There are fewer trials of selective serotonin reuptake inhibitors in neuropathic pain; however, an estimated NNT⁷⁰ of 6.8 and at least 1 head-to-head comparative trial suggest inferior efficacy compared with that of TCAs.⁸⁸ The SNRIs venlafaxine and duloxetine have been

studied more recently, with NNTs estimated in the range of 3.4 to 14.^{70,83}

Anticonvulsants

Although several anticonvulsants have been studied in neuropathic pain, only the α -2- δ ligand calcium channel antagonists, gabapentin and pregabalin, are currently recommended as first-line treatments.⁷¹ Other anticonvulsants (eg, carbamazepine and oxcarbazepine) are often used as first-line therapy for trigeminal neuralgia, which

is discussed below. Several RCTs of gabapentin have been conducted in patients with diabetic neuropathy, postherpetic neuralgia, and other neuropathic conditions. Older meta-analyses estimated the efficacy of gabapentin with NNTs of 4.3 to 6.4^{70,89}; however, a recently updated Cochrane meta-analysis of gabapentin (for daily doses of 1200 mg or more) involving neuropathic pain as well as fibromyalgia provided NNTs of 9.6 for the patient global impression of change outcome of “very much improved” and 6.1 for “much or very much improved.”⁹⁰ The newer α -2- δ ligand anticonvulsant pregabalin was studied in many large trials in diabetic neuropathy, postherpetic neuralgia, and central neuropathic pain. A broad-ranging systematic review of most of these trials⁹¹ reported varying NNTs depending on daily doses ranging from 300 to 600 mg/d such that higher doses were associated with lower NNTs (ie, greater efficacy). The NNTs for pregabalin varied from 3.9 to 5.3 for postherpetic neuralgia, from 5 to 11 for diabetic neuropathy, and 5.6 for central neuropathic pain from 2 RCTs involving doses of 600 mg/d.⁹¹

Opioids

Opioids including morphine, oxycodone, tramadol, and several other agents have been evaluated in more than 30 RCTs of patients with neuropathic pain including peripheral conditions such as postherpetic neuralgia and diabetic neuropathy and central conditions such as poststroke pain.⁹²

Depending on different trial inclusion criteria and outcomes of interest (eg, 30% vs 50% pain reduction), recent meta-analyses have estimated the analgesic efficacy of opioids in neuropathic pain (expressed as NNTs) as ranging between 4.0 NNTs⁹² and 4.7.⁷¹ The degree of certainty of these efficacy estimates has come into question given potential risks of bias from included trials related to small trial size, short treatment duration, and study dropouts.⁹² Common, but not life-threatening, opioid-related adverse effects reported in these trials included constipation, sedation, nausea, and vomiting, and these were frequent causes of trial discontinuation.⁹² Recent consensus reports have recommended opioids as either second-line⁹³ or third-line⁷¹ therapy for neuropathic pain not only because of the above efficacy and tolerability results but also because of well-recognized concerns regarding

opioid abuse/misuse, diversion, and addiction potential.^{94,95}

INTERVENTIONAL MANAGEMENT OF NEUROPATHIC PAIN

Given that our treatment-related focus is on pharmacological therapy, an in-depth review of interventional management is beyond the scope of this review. However, we provide some brief comments here in context of other treatment modalities. Patients with neuropathic pain often do not respond adequately to pharmacologic treatments used alone or in combination with nonpharmacologic treatments and their pain is therefore called refractory.⁹⁶ Before patients continue endless pharmacological rotation that does not produce the desired pain relief or induces intolerable adverse effects, interventional strategies should be considered. Techniques of interventional pain management include neural blockade, spinal cord stimulation, intrathecal medication, and neurosurgical interventions. A recent systematic review assessed the effect of interventional treatments in many neuropathic pain syndromes, that is, herpes zoster and postherpetic neuralgia, painful diabetic and other peripheral neuropathies, spinal cord injury neuropathic pain and central poststroke pain, radiculopathy and failed back surgery syndrome, complex regional pain syndrome (CRPS), and trigeminal neuralgia and trigeminal neuropathy.⁹⁷ It was concluded that evidence for the effectiveness of interventional management of neuropathic pain is limited. No more than 40% to 60% of the patients obtain lasting, even though partial, pain relief. In summary, weak recommendations for chronic neuropathic pain were formulated—spinal cord stimulation for chronic radiculopathy (failed back surgery syndrome) and spinal cord stimulation for CRPS type 1. It is important to emphasize that rigorous evaluation of interventional, as well as surgical (see Trigeminal Neuralgia section below), pain treatments is fraught with several risks of bias related to ethical and practical challenges to treatment blinding and the use of optimal sham, or other, control interventions; study patient dropouts due to severity and intractability of treated patients; and cost/logistics of follow-up and study duration. Furthermore, it should be recognized that relative lack of evidence of efficacy does not necessarily suggest evidence of lack of efficacy and so, rational interventional management of

patients with chronic neuropathic pain should be considered an integral component of a more comprehensive approach that also includes pharmacologic and nonpharmacologic, noninterventional treatments.⁹⁷

SPECIAL CONDITIONS

Central Pain

Central pains are conditions caused by a lesion or disease affecting the somatosensory system within the CNS.¹ The diseases or lesions giving rise to central neuropathic pain are multiple and include stroke, multiple sclerosis, a syrinx within the cord or the brain stem, and an injury to the spinal cord. Even pains experienced by patients with Parkinson disease have been suggested to represent a central neuropathic pain state. Central pains are not rare. For example, central poststroke pain, formerly known as thalamic pain, occurs in 7% to 8% of the patients with stroke.^{98,99} In spinal cord injury, nociceptive and neuropathic pain is common. A recent prospective study found that 60% of the patients with spinal cord injury neuropathic pain have pain because of the CNS lesion.¹⁰⁰ Despite their etiological differences, these conditions share certain clinical characteristics: (1) partial or complete loss of spinothalamic functions (temperatures and pinprick sensation) and (2) the development of hypersensitivity in those body parts that have lost their normal somatosensory information because of a CNS lesion.¹⁰¹ Corresponding to these cardinal phenomena, patients have positive and negative signs and symptoms. The negative signs and symptoms reflect the damage to the CNS, resulting in partial or complete sensory loss and numbness in the distribution of the nervous structure that has been damaged. The positive phenomena such as allodynia, hyperalgesia, and hyperpathia are all manifestations of hyperexcitability in the nervous system.¹⁰² Central neuropathic pain is characterized by spontaneous ongoing pain and various types of evoked pain, often occurring in different combinations. Burning, pricking, lancinating, icy, tearing, cutting, and squeezing types of pain are often described, but there is no pathognomonic set of descriptors that permit a diagnosis of central pain. Importantly, in pain associated with central lesions, there is often a combination of factors that can contribute to the pain. For example, in pain after stroke, there may, in addition to the classical central poststroke pain

with its characteristic sensory manifestations, be headache, shoulder pain, musculoskeletal pain, and painful spasticity, which adds to the complexity of the clinical picture of central pain conditions.¹⁰³

Complex regional pain syndrome

Complex regional pain syndrome is a condition that usually develops after minor trauma or injury to a limb.¹⁰⁴ It is per tradition divided into 2 types: CRPS type 1, with no signs of nerve damage, and CRPS type 2, with evidence of nerve lesion. Per definition, CRPS type 1 does not fulfill the existing criteria for neuropathic pain.¹ The key element in CRPS is the presence of sensory, autonomic, and motor abnormalities.^{104,105} Less-specific symptoms of CRPS include abnormal posture, sometimes even contractures, neglect-like phenomena, and cognitive problems.^{104,105} The presence of these signs and symptoms varies between patients, and can change over time in a given individual patient. The distribution of pain and signs is important and is characterized by a distal distribution of symptoms and signs that can spread proximally in a glove stocking-like fashion, somewhat similar to what is seen in distal length-dependent neuropathies. In the acute phase, the injured limb is usually very painful, warm red, and edematous. In later stages, the affected limb continues to be painful, but is now colder with pale atrophic skin and often also has motor phenomena such as dystonia and tremor.

Trigeminal Neuralgia

Trigeminal neuralgia, a condition that is clinically distinct from other neuropathic pain conditions, responds differently to pharmacological therapy.¹⁰⁶ Meta-analysis of multiple positive RCTs of carbamazepine in trigeminal neuralgia, and the better-tolerated oxcarbazepine, resulted in estimated NNTs of 1.4 to 2.8.^{70,89} In drug-resistant cases, interventions such as gamma-knife nerve root destruction and surgical treatments such as microvascular decompression are often used, with a limited evidence base and variable results.¹⁰⁶

CONCLUSION

A diverse array of clinical conditions cause neuropathic pain in both the peripheral and central nervous systems. Several features of clinical presentation (eg, development of pain after nervous system injury/disease, certain pain quality

descriptors, allodynia, and sensory loss) and treatment response (eg, to anticonvulsant drugs) indicate that neuropathic pain is fundamentally different from inflammatory or nociceptive conditions such as osteoarthritis. Given the association between neuropathic pain and other clinical conditions, patients with suspected neuropathic pain require a thorough history and physical examination and, in many cases, special investigations to make a diagnosis and identify etiology as well as important comorbidities requiring intervention. A stepwise, multidisciplinary approach to neuropathic pain evaluation and treatment helps to promote comprehensive care and effective treatment with minimal risks, adverse effects, and costs. Currently, the best evidence of treatment safety and efficacy suggests first-line therapy with antidepressant and anticonvulsant drugs. However, even with these agents, efficacy is modest, with many patients failing to enjoy meaningful benefit. With the continued expansion of knowledge about the underlying causes and mechanisms of neuropathic pain, development of new and improved treatment is expected.

Abbreviations and Acronyms: CHEP = contact heat-evoked potential; CNS = central nervous system; CPRS = complex regional pain syndrome; LEP = laser-evoked potential; NMDA = N-methyl-D-aspartate; NNT = number needed to treat; QSART = quantitative sudomotor axon reflex test; RCT = randomized controlled trial; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant

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The Symposium on Pain Medicine will continue in an upcoming issue.

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