MAYO CLINIC

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		

From *Lancet Neurol*,[3] with permission.