ABSTRACT

Treatment of neuropathic pain poses unique treatment challenges because of its multiple etiologies and mechanisms. Potential peripheral and central nervous system (CNS) etiologies include a wide range of illnesses; examples are diabetes mellitus, cancer, infections, autoimmune and paraneoplastic disorders, nutritional and vitamin deficiencies, hereditary and idiopathic disorders, traumatic lesions for the peripheral nervous system, and multiple sclerosis and stroke for the CNS. Advances in preclinical and clinical research indicate that neuropathic pain involves multifactorial biomolecular and anatomical mechanisms, summarized within this article.

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CENTRAL MECHANISMS OF NEUROPATHIC PAIN

Chronic pain mechanisms are frequently complicated by temporary or long-term changes within the central nervous system (CNS). Central sensitization and microglia activation appear to be 2 relevant mechanisms. Dorsal horn central sensitization is a neurophysiologic phenomenon occurring in both acute and chronic pain states. Its clinical manifestation is called secondary hyperalgesia or allodynia (ie, the painful sensitivity to simple touch around the area of a burn or injury).

Microglia are glial cells that act as immune cells of the CNS. During nociceptors’ release of neuropeptides and excitatory amino acids within the dorsal horn, microglia not only undergo hypertrophy and hyperplasia, but also discharge substances, such as prostanoids, cytokines, and free radicals, which help to sensitize the CNS pain-transmitting neurons (PTN). Although the exact mechanism behind this response is unclear, it is believed that it may be a function of cross-talk between PTNs and microglia. Additional CNS mechanisms that contribute to neuropathic pain are the loss of inhibitory interneuron function and possible changes in the organization of pain pathways.

PERIPHERAL MECHANISMS OF NEUROPATHIC PAIN

Among the multiple peripheral mechanisms that contribute to neuropathic pain, one of recent scientific interest is the so-called phenotypic shift of affected pain pathways. Nerve injury and inflammation may induce transcriptional alterations in the dorsal root ganglia sensory neurons, prompting long-lasting biomolecular changes in tissue nociceptors, causing abnormal excitability and
enhanced responsiveness to inflammatory molecules. Recent research has focused on the discovery of novel subtypes of ion channels in patients affected by painful neuropathies and holds promise for new avenues of pain treatment in the years ahead.

**NEUROIMMUNE-INFLAMMATORY MECHANISMS OF NEUROPATHIC PAIN**

Pain is typically categorized as nociceptive or neuropathic. Nociceptive pain is a result of the activation of nociceptors by mechanical, chemical, or heat/cold stimuli. Neuropathic pain is caused by damage or dysfunction of the peripheral or CNS pain pathways.1

Neuroimmune-inflammatory mechanisms appear to play a relevant pathogenic role in some pain disorders, such as herpes zoster neuritis pain (Figure), complex regional pain syndrome, and cancer pain, but not in others, such as trigeminal neuralgia or postherpetic neuralgia. If a neuroimmune inflammatory process is present, descriptive terms, such as inflammatory nociceptive or inflammatory neuropathic, can be considered. Locally released diffusible factors, such as cytokines and growth factors can trigger a phenotypic shift in the nociceptors and cause a long-lasting neuropathic pain condition. An example of such pathophysiologic complexity is the acute pain state (initially nociceptive, inflammatory) that results from a trivial soft-tissue trauma that fails to resolve and may ultimately evolve into a neuropathic pain state called complex regional pain syndrome (CRPS)/reflex sympathetic dystrophy.

**TREATMENT OF NEUROPATHIC PAIN**

Traditional therapeutic targets of analgesics have included serotonin and norepinephrine reuptake mechanisms, opioid receptors, Na+ channels, and more recently the α-2 δ subunit of neuronal voltage-gated Ca++ channels. Current research is exploring additional neuropathic targets, shown in the Table. Areas of particular interest include the transient receptor potential vanilloid receptors, which are thought to play a role in pain elicited by noxious heat and protons (low pH). The growth factors are an active area of research in the setting of chronic cancer bone pain and postinflammatory neuropathic pain.2

Off-label drug use is common in the treatment of neuropathic pain. These are medications that have a US Food and Drug Administration (FDA)-approved non-pain indication. Research data sufficient to gain an additional pain indication may be lacking, and the manufacturer may not wish to spend resources to expand the medication indications. Only a few medications have US FDA-approved indication for neuropathic pain disorders. These are gabapentin, pregabalin, and the lidocaine patch for postherpetic neuralgia; duloxetine and pregabalin for painful diabetic neuropathy; and carbamazepine for trigeminal neuralgia. First-line

![Figure. Inflammatory Neuropathic Pain Induced by Herpes Zoster Virus](https://example.com/figure.png)

**Table. Emerging Neuropathic Targets**

- Voltage-gated Na+ channels (Nav1.7 in fam erythromelalgia)
- Transient receptor potential vanilloid receptors
- Nicotinic receptor subtypes (neuronal)
- Growth factors (ie, anti-nerve growth factor antibodies and glial-derived neurotrophic factor)
- Tumor necrosis factor-α and interleukin-1 receptor
- Central nervous system microglia (p38 mitogen-activated protein kinase)
- Cannabinoid receptors
- Sensory-neuron–specific adenosine triphosphate receptor (P2X3)
- Proteinase-activated receptor 2
medications for neuropathic pain are the gabapentinoids (eg, gabapentin and pregabalin), antidepressants (eg, duloxetine and tricyclic antidepressants), the lidocaine patch, opioids, and tramadol.2

Among the opioids, a particular role in the management of neuropathic pain is played by methadone. Methadone is a synthetic opioid that has been used for years to treat opioid dependence and now is increasingly being used to treat moderate-to-severe pain. Methadone is a racemic mixture of d- and l-methadone. L-methadone acts as a strong µ-opioid agonist as well as an N-methyl-D-aspartic acid (NMDA) antagonist; the d-methadone is only a pure NMDA antagonist. There is also some evidence that methadone can inhibit CNS reuptake of norepinephrine and serotonin. Advantages to methadone as an analgesic include its efficacy, high bioavailability, long half-life, and low cost. However, dosing methadone for pain management can be challenging. Because methadone is metabolized through the CYP3A4 pathway, inhibitors of that pathway, such as diazepam, fluoxetine, paroxetine, and verapamil, may increase methadone serum levels. CYP3A4 inducers, such as dexamethasone, carbamazepine, phenytoin, isoniazid, and topiramate, may decrease methadone serum levels and put a patient at risk for withdrawal. Methadone’s pharmacokinetic properties can be affected by plasma protein (α1) binding and gastric-urinary pH.3,4 Methadone has been associated with QTc prolongation, but the risk appears to be much greater with intravenous (IV) methadone than with the oral formulation.5 The nonlinear conversion ratio and QTc prolongation risks have led to a black box warning and a US FDA Public Health Advisory regarding the potential for methadone accumulation and fatal arrhythmia or respiratory depression. To prevent serious complications, healthcare professionals who prescribe oral or injectable methadone should read and carefully follow the methadone prescribing information.5-10 Medical evidence surrounding conversion rates is summarized by Lauren Shaiova, MD, and Craig D. Blinderman, MD, MA, in a case study later in this monograph.

Second-line agents with a modest body of evidence of efficacy for neuropathic pain include non-gabapentinoid antiepilepsy drugs, venlafaxine, bupropion, mexiletine, and clonidine. With the exceptions of epidural clonidine indicated for treating patients with cancer who have severe neuropathic pain11 and the 2 non-gabapentinoid antiepilepsy drugs, topiramate12 and divalproex sodium13 indicated for migraine prophylaxis, none of the other drugs have received US FDA indications for pain control. Therefore, their use for pain is still off-label. Steroids (eg, prednisone and IV methylprednisolone) are sometimes used for inflammatory neuropathic pain, particularly in cancer states. IV bisphosphonates and intranasal calcitonin are used for bone pain. In the setting of hyperalgesic pain states and/or opioid tolerance, NMDA antagonists are also occasionally used. The NMDA receptor in the pain-signaling neurons within the spinal cord dorsal horn mediates central sensitization and secondary hyperalgesia, thus agents that block this receptor may control some aspects of neuropathic pain. NMDA receptors are also therapeutic targets for opioid tolerance. Functional NMDA receptors are also present on primary afferents where they may play a role in pronociceptive plasticity.

Implantable devices, such as spinal cord stimulators, can be used to treat neuropathic pain. Another option is neuraxial analgesia that is based on intraspinally implanted tunneled catheters and pumps to deliver drugs intrathecally (IT). Implantable pumps can be used to deliver opioids, bupivacaine, clonidine, combinations of agents, and ziconotide into the cerebrospinal fluid. Morphine and ziconotide are the only US FDA-approved IT agents for chronic pain. IT baclofen has been effective in decreasing the severity of intractable painful dystonia associated with some forms of neuropathic pain, such as CRPS.

CONCLUSIONS

Pharmacotherapy for chronic pain is rapidly evolving. The objectives of pain pharmacotherapy are to balance efficacy, safety, and tolerability against the benefits of reduced pain, improved patient function, and optimal quality of life. Polypharmacy is often necessary to achieve these goals in the management of chronic disabling pain.

REFERENCES


