

An integrated perspective on diabetic, alcoholic, and drug-induced neuropathy, etiology, and treatment in the US

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Abstract: Neuropathic pain (NeuP) is a syndrome that results from damaged nerves and/or aberrant regeneration. Common etiologies of neuropathy include chronic illnesses and medication use. Chronic disorders, such as diabetes and alcoholism, can cause neuronal injury and consequently NeuP. Certain medications with antineoplastic effects also carry an exquisitely high risk for neuropathy. These culprits are a few of many that are fueling the NeuP epidemic, which currently affects 7%–10% of the population. It has been estimated that approximately 10% and 7% of US adults carry a diagnosis of diabetes and alcohol disorder, respectively. Despite its pervasiveness, many physicians are unfamiliar with adequate treatment of NeuP, partly due to the few reviews that are available that have integrated basic science and clinical practice. In light of the recent Centers for Disease Control and Prevention guidelines that advise against the routine use of μ -opioid receptor-selective opioids for chronic pain management, such a review is timely. Here, we provide a succinct overview of the etiology and treatment options of diabetic and alcohol- and drug-induced neuropathy, three different and prevalent neuropathies fusing the combined clinical and preclinical pharmacological expertise in NeuP of the authors. We discuss the anatomy of pain and pain transmission, with special attention to key ion channels, receptors, and neurotransmitters. An understanding of pain neurophysiology will lead to a better understanding of the rationale for the effectiveness of current treatment options, and may lead to better diagnostic tools to help distinguish types of neuropathy. We close with a discussion of ongoing research efforts to develop additional treatments for NeuP.

Keywords: small-fiber neuropathy, pain, alcohol use disorder, diabetes mellitus, chemotherapy, opioid receptors

Introduction

Neuropathic pain (NeuP) arises from aberrant or incomplete regeneration of damaged nerves, and is characterized by hyperalgesia and allodynia, enhanced sensitivity to pain, and exaggerated pain response to normal stimuli.¹ The prevalence of NeuP varies around the world, but has been cited as at a minimum of 3%,^{2–4} and true prevalence has been estimated to be around 7%–10%.⁵ The incidence of NeuP also varies by type, as categorized by the mechanism of injury: diabetic neuropathy, alcoholic neuropathy, and medication-induced neuropathy.⁶ A concerning trend in the US is the rise in diagnosis of neuropathies caused by type 2 diabetes.⁷ This may in part be fueled by increased health care costs hampering proper management of diabetes (diabetes.org).⁸ Alcoholic neuropathy in the US occurs in roughly 65% of patients diagnosed with an alcohol-use disorder.⁹ Anticancer medications, especially taxanes, are also known to cause neuropathy. A study found that 100% of patients receiving paclitaxel developed

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symptoms of neuropathy.¹⁰ On a clinical level, NeuP translates to a complex syndrome that is often multidrug-resistant and unresponsive to alternative therapies. Therefore, it is imperative that clinicians understand the etiology of NeuP and the mechanism and effectiveness of the current repertoire of treatments.

Significance and limitations

In this integrative review, an internal medicine physician and preclinical behavioral pharmacologist summarize differences and overlap in etiologies and treatment options for NeuP. This review focuses on three of the most common neuropathies – diabetic, alcohol-induced, and drug-induced neuropathy – describes the specific nerve fibers associated with each neuropathy, and lists recommended treatment options for NeuP. The review is purposely succinct, aimed at providing clinicians with insight into the etiology of NeuP and educating preclinical scientists on the diagnosis and choice of treatment for NeuP. The review favors conciseness over an extensive in-depth analysis of the available literature, thus limiting its scope.

Materials and methods

A PubMed search was performed to identify clinical and preclinical studies detailing etiology and treatment of NeuP. Emphasis was given to articles published in the last 10 years,

with older articles used primarily to provide a frame of reference.

Basic anatomy of pain

Comprehending the pathophysiology of peripheral neuropathy and the mechanism of action for drugs requires a basic appreciation of the anatomy of the somatosensory system, especially with respect to pain. Noxious stimuli, such as thermal, chemical, and high-threshold mechanical stimuli, are detected in the periphery and conducted to the spinal cord via two types of small fibers. The C fibers are unmyelinated, slow-conducting, and localize pain poorly. The A δ fibers are thinly myelinated, faster-conducting, and localize pain better.^{11,12} Larger and more thickly myelinated than A δ fibers are A α and A β fibers, which primarily transmit information about proprioception and vibration.¹³ It is primarily the A δ and C fibers that are indiscriminately affected in the different types of neuropathies (Figure 1). Measuring which type of fibers are impacted is not trivial, but can be attempted by clinical examination; loss of tactile or vibratory skin sensation or tendon reflexes are indicative of large-fiber neuropathy, whereas alterations in lower-limb pinprick sensation and a visual analog scale pain score >40 suggest small-fiber neuropathy.¹⁴ Small-fiber neuropathy can also be determined by measuring intraepidermal nerve-fiber density following biopsy.¹⁵ A δ -fiber neuropathy can be mea-

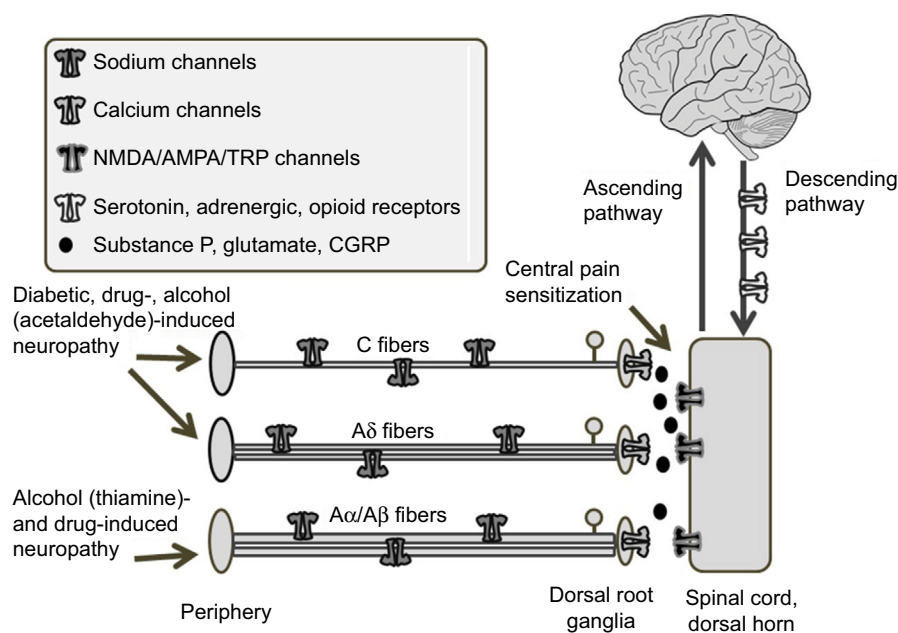


Figure 1 Overview of neuropathies affecting pain pathways.

Notes: C and A δ fibers are affected by diabetes, drugs, and alcohol (and its metabolite acetaldehyde), whereas large, myelinated A α and A β fibers are affected by drugs and thiamine deficiency. Channels (sodium, calcium) and receptors (NMDA, serotonin, adrenergic, opioid) along the pain pathway serve as drug targets for treatment of chronic neuropathic pain.

Abbreviations: NMDA, N-methyl-D-aspartate; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; TRP, transient receptor potential; CGRP, calcitonin gene-related peptide.

sured noninvasively by laser evoked-potential^{16,17} and contact heat-evoked potential.^{18,19} Nerve-conducting studies are a useful technique for NeuP research, but less relevant for clinical studies, as they primarily measure A β -fiber function, which supersedes small-fiber neuropathy²⁰ and is laborious.²¹

Receptors on primary sensory neurons convert environmental stimuli, such as pain, into an electrical signal that is transmitted to the dorsal root ganglia, with an important role for sodium channels.^{22,23} In the terminals of the dorsal root ganglia, neurons subsequently convert this electric signal into chemical signals by releasing neurotransmitters and neuropeptides, including glutamate, substance P, and calcitonin gene-related peptide into the dorsal horn (Figure 1). A significant event that occurs during the development of a chronic pain state is central sensitization, where postsynaptic glutamate (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA] and *N*-methyl-D-aspartate [NMDA]) receptors become increasingly more adaptive in transmitting pain signals.^{24–28} Activation of presynaptic calcium channels can reduce the release of neurotransmitters and dampen central sensitization (Figure 1).^{29,30} In the spinal cord, this nociceptive signal can be modulated by inhibitory interneurons using γ -aminobutyric acid (GABA) and glycine as their main neurotransmitters. Following the reception of a pain signal in the cortical structures of the brain, the experience of pain can still be suppressed by a descending system that originates from the brain stem. This efferent system attenuates the afferent signal via neurotransmitters, such as endogenous opioids, serotonin, and noradrenaline.^{31–33}

Diagnosis of neuropathic pain

The diagnosis of NeuP is usually made on clinical grounds. Screening questionnaires are available for NeuP, including the Leeds Assessment of Neuropathic Symptoms and Signs,³⁴ PainDetect,³⁵ and Douleur Neuropathique 4 (DN4).³⁶ Of these, the DN4 has the higher sensitivity and specificity. The DN4 is a questionnaire that consists of four questions and incorporates both subjective and objective information, namely the patient's perception of pain and the physician's exam findings. It has been validated as a screening tool for different types of NeuP, including diabetic neuropathy, and has sensitivity and specificity of 80% and 92%, respectively, at a score cutoff of 4.³⁶ At a score cutoff of 3, sensitivity and specificity are 84%.³⁶ While these screening tools are useful, the diagnosis ultimately hinges on the clinician's intuition from effective interviewing and physical examination. Symptoms of neuropathy can range from hypoalgesia and paresthesia (tingling) to hyperalgesia, especially prominent

in the distal extremities, known as the “stocking and glove” distribution. Patients with neuropathy may exhibit a painful response to benign stimuli, such as light touch from a cotton swab or a finger. Patients may also exhibit an attenuated/exaggerated response to a pinprick. These phenomena are known as allodynia and hypo/hyperalgesia, respectively. As the neuropathy progresses, more severe symptoms, including burning sensations and electric shocks, can arise. Symptoms are aggravated during rest and prolonged weakness and sensory loss in extremities; particularly feet can culminate in gait impairment.³⁷ Because the diagnosis is based on subjective data, it can sometimes be challenging for the physician to track response to therapeutics. With this said, the threshold to treat NeuP is exceedingly low, given the good side-effect profile of most drugs. In our experience, most physicians would trial a serotonin–norepinephrine reuptake inhibitor (SNRI) if a patient complained of burning pain, even if no other findings were present.

Three major types of neuropathy

Diabetic neuropathy

Peripheral neuropathy is one of the most common microvascular complications of diabetes. It has been estimated that ~50% of diabetics suffer from peripheral neuropathy,³⁸ and 50% of these neuropathies are considered at least moderate in severity.^{39–41} Histological studies suggest that primarily small C fibers are affected by diabetes and glucose intolerance,^{42–45} although A δ fibers have also been shown to be affected by type 1 and type 2 diabetes.^{46–48} Morbidities associated with diabetic neuropathy amount to more than \$10 billion in the US.⁴⁹

Diabetes or glucose intolerance can impair vasodilation and lead to ischemia, which is thought to be central to the pathogenesis of peripheral neuropathy, including trigeminal neuralgia.^{50,51} A recent study demonstrated that patients with glucose intolerance, even without carrying the diagnosis of diabetes, exhibited C-fiber neuropathy, highlighting the devastating effect of prolonged hyperglycemia on neuronal health.⁵² On a molecular level, there are at least five prevailing mechanisms of how hyperglycemia leads to different complications of diabetes, with the polyol and PARP pathways being the most relevant to neuronal death.⁵³ In the polyol pathway, the influx of glucose into the cell activates aldose reductase to convert glucose to sorbitol. Sorbitol is then converted to fructose via sorbitol dehydrogenase. Both of these steps generate oxidative species that contribute to neuronal injury.^{53,54} In Schwann cells, endothelial cells, and sensory neurons, PARP is stimulated by oxidative species and induces

further oxidative stress in a feedback mechanism.^{55–59} PARP is a nuclear enzyme that can also alter gene expression, leading to impairment of neuronal conduction velocity, small-fiber neuropathy (Figure 1), hyperalgesia, and allodynia, as well as other diabetic complications.^{53,55,60–64}

Alcoholic neuropathy

The prevalence of alcohol-related peripheral neuropathy has been estimated to occur in two-thirds of chronic alcoholics.⁹ Alcohol-related peripheral neuropathy is historically regarded as a large-fiber neuropathy from thiamine deficiency (Figure 1).^{65–69} In contrast to small sensory fibers, large fibers are responsible for vibration and proprioception. However, advances in scientific techniques have reshaped the pathophysiology of alcoholic neuropathy. Observations that neuropathy can develop even in the setting of normal thiamine levels⁷⁰ and that the early stages of alcoholic neuropathy are characterized by painful paresthesia⁷¹ have led scientists to postulate that alcohol and its metabolites have direct neurotoxic effects on small C fibers (Figure 1).^{72,73} Acetaldehyde is a known neurotoxin that is formed when alcohol is metabolized by alcohol dehydrogenase. The precise mechanism underlying alcoholic neuropathy is yet to be fully elucidated. Some proposed explanations include direct neurotoxic effects of alcohol or its metabolite acetaldehyde⁷⁰ through activation of spinal cord microglia,⁷⁴ involvement of metabotropic glutamate 5 and opioid receptors^{74,75} in the spinal cord, promotion of oxidative stress by the activity of alcohol-metabolizing enzymes in the liver,⁷⁶ and release of proinflammatory cytokines coupled with phosphorylation of protein kinase C⁷⁷ and extracellular signal-regulated kinases.⁷⁸ Taken together, these different initiating events may ultimately lead to DNA fragmentation and neuronal apoptosis.⁷⁹ Once formed, acetaldehyde is metabolized by ALDH into a much less harmful acetate. Interestingly, pharmacological and genetic data suggest that reducing ALDH activity can precipitate peripheral neuropathy, whereas increasing its activity may carry therapeutic potential. As such, disulfiram, an ALDH inhibitor, has the side effect of causing NeuP.⁸⁰

Medication-induced neuropathy

Disulfiram is not unique in causing NeuP; in fact, many and more commonly prescribed drugs, which span the spectrum of chemotherapy to cardiovascular medications, are known to induce neuropathy. This section focuses on taxanes, with mention of statin-induced neuropathy. Paclitaxel and docetaxel are antineoplastic taxanes used to treat numerous types of solid tumors, including ovarian, breast, lung, and head and neck

malignancies. Paclitaxel has its chemotherapeutic effect by promoting microtubule assembly in a disorganized manner, thereby prohibiting mitotic division. It is by this very same mechanism that paclitaxel causes peripheral neuropathy, one of the most common and limiting side effects of the drug. In vivo studies have demonstrated that paclitaxel causes abnormal microtubule accumulation, leading to demyelination,^{81,82} and inhibits the regenerative capacities of neurons.^{83,84} In a non-dose-dependent manner, paclitaxel causes hyperalgesia and allodynia without affecting motor performance.⁸⁵ Clinically, patients have complained of sensory neuropathy and decreased vibration and proprioception, indicating that both small C and A δ fibers are affected (Figure 1).^{86–89} One of the original articles on paclitaxel-induced neuropathy studied paclitaxel infusion at three doses, and found that neuropathy developed in >80% of the patients at all doses and was dose-limiting in 70% of patients at the highest dose.⁹⁰

It is noteworthy that diabetes is a predisposition to drug-induced neuropathy. In a retrospective study comparing the rates of taxane-induced neuropathy, chronic diabetics (defined by >5 years) developed neuropathy more frequently compared to nondiabetics.⁹¹ With regard to treating chemotherapy-induced peripheral neuropathy, SNRIs have been shown to be superior to placebo.⁹² These drugs are also used in the treatment of diabetic neuropathy. Together, these data suggest that taxanes and diabetes act differently but synergistically in causing peripheral nerve damage and NeuP.

Statins are prescribed to >40 million patients in the US alone (<https://meps.ahrq.gov>), and are frequently prescribed to diabetics to reduce their cardiovascular risk. It is interesting to note that there have been reports of statin-induced peripheral neuropathy.^{93,94} Though statins are demonstrated to have pleiotropic effects, preclinical studies suggest that they can attenuate NeuP by potentiating antioxidation.^{95,96} Promising data have also been found in human studies where rosuvastatin improved both the intensity of diabetic neuropathy pain and nerve conduction.⁹⁷ In combination with the rarity of statin-induced neuropathy, these data suggest that this potential side effect of statin should minimally influence the physician's decision to prescribe statins for vascular protection.

Current neuropathic pain therapies

Based on a 2015 analysis of a systemic review and meta-analysis performed by the Neuropathic Pain Special Interest Group on clinical studies of NeuP pharmacotherapy, a new guideline for treatment of NeuP was recently proposed.⁹⁸ The guidelines highlight the difficulty in adequately treating NeuP,

but recommend the use of tricyclic antidepressants (TCAs), SNRIs, pregabalin, and gabapentin as first-line treatment options for NeuP.⁹⁸ In the following section, we discuss these medications in more detail.

Tricyclic antidepressants

A number of randomized controlled trials have shown that TCAs may exert their NeuP-relieving effect via multiple mechanisms of action.^{99,100} The potential of TCAs in pain relief is primed by their inhibition of presynaptic reuptake of serotonin and norepinephrine^{101,102} and activity at NMDA receptors and sodium channels,¹⁰³ all of which are involved in pain transmission. Amitriptyline and nortriptyline are two of the oldest TCAs on the market. Although their use to treat depression has declined with the increased popularity of SNRIs and selective serotoninreuptake inhibitors, they continue to be used off-label to treat NeuP. However, according to recent Cochrane meta-analyses, no high-quality evidence exists to support the analgesic effect of both amitriptyline and nortriptyline, despite an extensive history of anecdotal success.^{104,105} A factor for the declining use of TCAs, whether for depressive disorders or NeuP, is that TCAs have a higher risk for fatal overdose and require careful dosing. Therefore, TCAs should not be advocated for use as first-line treatment of NeuP.

Serotonin–norepinephrine reuptake inhibitors

Venlafaxine and duloxetine are SNRIs that are prescribed to treat depression, anxiety, and NeuP. Serotonin and norepinephrine play integral parts in the descending pain pathway to suppress pain.^{106–108} Preclinical and clinical research has shown that drugs that increase serotonergic and noradrenergic neurotransmissions exert antinociceptive properties. For example, SNRIs significantly attenuated pain-related behaviors in the formalin model of persistent pain and the L5–L6 spinal nerve ligation model of NeuP in rats.¹⁰⁹ SNRIs are also efficacious in the treatment of pain and functional impairment associated with fibromyalgia, as per a number of randomized controlled trials.^{110–113}

Pharmacological studies have demonstrated that for certain SNRIs, serotonin reuptake inhibition predominates at low drug concentration, whereas inhibition of norepinephrine reuptake occurs only at much higher doses.¹¹⁴ Unlike treating depression, the treatment for NeuP with SNRIs is achieved at higher doses and more rapidly. For venlafaxine, the usual antidepressant dosage is much lower than what is needed for pain relief,¹¹⁵ suggesting that norepinephrine contributes

more strongly to attenuating pain. The importance of norepinephrine is further exemplified by the effect of clonidine and the adrenergic receptor agonist in alleviating pain.¹¹⁶ However, a Cochrane review found that venlafaxine had limited efficacy compared to placebo.³² Despite relatively similar pharmacology, duloxetine was effective for the relief of NeuP.¹¹⁷ Duloxetine is a much more potent inhibitor of the serotonin- and norepinephrine reuptake transporters than venlafaxine.¹¹⁴ Therefore, when choosing an SNRI, we would favor the use of duloxetine.

Calcium-channel blockers

Changes in the expression and activity of voltage-gated calcium channels are known to modulate neuronal excitability and synaptic plasticity in the dorsal horn, culminating in pain processing.^{118–120} The $\text{Ca}_v\alpha_2\delta_1$ subunit, an important accessory subunit for calcium channels, plays an important role in NeuP development, based on reports of increased expression in the dorsal root ganglia and spinal neurons during NeuP states.^{121–123} Further supporting evidence shows that blockade of the $\text{Ca}_v\alpha_2\delta_1$ subunit could reverse tactile allodynia in nerve-injured animals.^{124,125} Interestingly, the $\text{Ca}_v\alpha_2\delta_1$ subunit is the binding site for pregabalin and gabapentin.¹²⁶ Pregabalin and gabapentin were developed and US Food and Drug Administration (FDA) approved for treatment of epilepsy, but have become first-line treatments for NeuP.

A Cochrane review using randomized double-blind trials found pregabalin to be effective for the treatment of NeuP. Pregabalin at doses of >300 mg provided moderate pain relief (50% improvement from baseline) in different types of pain.¹²⁷ Another Cochrane review investigated the efficacy of gabapentin on NeuP using randomized double-blind controlled studies, and concluded that 1,200 mg daily was needed to achieve 50% pain relief. This effect was found in 35% of study participants compared to 21% in the placebo group.¹²⁸ To avoid sedating effects, gabapentin is divided into three doses, and patients are routinely instructed to titrate the dose, starting at 300 mg daily. However, compliance is a major issue in patients on gabapentin, usually as they dismiss the medications as ineffective and discontinue the medications before reaching the therapeutic dose. Therefore, it is prudent to educate patients of this therapeutic range. Moreover, a recent study has shown that the endogenous lipid palmitoylethanolamide has synergistic effects with gabapentin to relieve chemotherapy-induced allodynia in mice, which makes it possible to reduce the dosage of gabapentin and lower its side effects.¹³

To illustrate further the vital role of calcium channels in pain transmission, ziconotide is a selective calcium-channel blocker and potent analgesic. Ziconotide is FDA approved for the treatment of refractory chronic pain.¹²⁹ As ziconotide is a large peptide that cannot readily cross the blood–brain barrier, it can thus only be administered intrathecally. Intrathecal drug delivery can be used to manage chronic pain effectively, and may provide the most targeted approach with the fewest side effects.^{130–133}

Opioids and drug development

Although opioids are intended for short-term use for acute pain, they have repeatedly been used to treat chronic pain. For example, tramadol has been used to treat chronic pain, in part due to its dual action as a μ -opioid agonist and SNRI.⁹⁸ Patients frequently cite failures of different adjunctive therapies to alleviate their pain, and revert to the use of opioids. In light of the rapid increase in patients suffering from opioid-dependence/use disorders, the Centers for Disease Control and Prevention (CDC) has recently published guidelines to avoid routinely prescribing narcotics for the management of chronic pain. In addition to dependence, opioids also cause other serious side effects, including tolerance, ileus, and respiratory depression. The latter side effect explains the high hospitalization and mortality rate associated with opioid overdose, which has increased concomitantly with the rise in opioid dependence. Moreover, prolonged use of (escalating doses of) opioids can lead to paradoxical pain, also known as opioid-induced hyperalgesia, and discontinuation of opioids leads to withdrawal of hyperalgesia. While the CDC guidelines are helpful for guiding narcotic use, it will be challenging to unearth the culture of pain management that is heavily rooted in narcotics. The CDC currently excludes these guidelines from patients with active malignancy, which remains a challenge to treat, despite rapidly escalating doses of opioids. Clearly, safer and more potent and selective therapeutics are necessary and overdue. Although the CDC raised concerns regarding the use of μ -opioids in chronic pain, it is important not to dismiss completely their analgesic potential for acute pain and palliative care.¹³⁴ Importantly, other opioid-receptor subtypes like μ are also expressed along descending pain pathways, and increasing research efforts have identified these non- μ -opioid receptors as potential analgesic targets for chronic pain.

While current analgesic opioids target μ -opioid receptors, there are three other opioid-receptor subtypes. One of the most intriguing new developments in the use of opioids for NeuP comes from work focused on δ -opioid receptors (DORs), κ -ORs (KORs), and nociception ORs (NORs). DORs, KORs, and NORs are expressed in several levels

of pain pathways, including the periphery, spinal cord, and supraspinal regions.^{135–141} The expression of opioid-peptide messenger RNA also increases under conditions of chronic pain.^{142–144} Preclinical evidence has demonstrated that inhibition of DORs or KORs via either opioid antagonists or genetic ablation in mice enhances allodynia and hyperalgesia following spinal cord injury.^{145–148} Additionally, both DOR and KOR agonists have elicited antinociceptive and antiallodynic effects in animal models of NeuP.^{142,149–151} An intriguing recent study identified 6-methoxyflavanone as a positive allosteric modulator of GABA_A channels that can alleviate streptozotocin-induced diabetic NeuP in female rats in a naloxone-reversible manner, potentially via direct interaction with DORs and KORs.¹⁵² In contrast, the role of NORs in nociception is less linear: analgesic actions of the nociceptin system in rodents are bidirectional, depending upon the doses and assays.^{153–156} Encouragingly, the activation of NORs produces only attenuated and not intensified pain in primates regardless of experimental conditions,^{157,158} and thus their therapeutic potential in humans remains.

Summary

NeuP results from nerve damage, and can be classified based on the inciting factors, such as hyperglycemia (as in diabetes), toxins from alcohol metabolism, and drugs like chemotherapy. In basic pain anatomy, noxious stimuli are detected in the periphery, and are transmitted via small fibers to the central nervous system, where they are converted into the experience of pain (Figure 1). This afferent system is modulated by an efferent system via GABAergic neurons and neurotransmitters, such as serotonin and norepinephrine. Opioids that act on GABAergic neurons have been used in pain relief for millennia. However, the side effects of opioids, especially their addictive properties, have recently led the CDC to advise against their use in chronic pain. Therefore, an understanding of adjunctive therapies for NeuP is essential. Meta-analyses show the most promising efficacy in calcium-channel ligands and SNRIs over older TCAs, but these medications still leave a number of patients untreated. Sodium-channel blockers may represent a broadly applicable strategy for many types of NeuP.^{159–162} However, improved diagnosis of symptoms paired with increased understanding and detection of the exact fibers affected by disease-specific neuropathies may guide the development of more precise therapeutics.¹⁶³ Targeting receptors or ion channels that are uniquely expressed in A β , A δ , or C fibers, including DORs and transient receptor-potential (TRPV, TRPA1) channels^{164–166} may represent a new direction for NeuP treatment.

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Disclosure

The authors report no conflicts of interest in this work.

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