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# Diagnosis and Treatment of Pain in Small Fiber Neuropathy

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## Abstract

Small fiber neuropathy manifests in a variety of different diseases and often results in symptoms of burning pain, shooting pain, allodynia, and hyperesthesia. Diagnosis of small fiber neuropathy is determined primarily by the history and physical exam, but functional neurophysiologic testing and skin biopsy evaluation of intraepidermal nerve fiber density can provide diagnostic confirmation. Management of small fiber neuropathy depends on the underlying etiology with concurrent treatment of associated neuropathic pain. A variety of recent guidelines propose the use of antidepressants, anticonvulsants, opioids, topical therapies, and nonpharmacologic treatments as part of the overall management of neuropathic pain. Unfortunately, little data about the treatment of pain specifically in small fiber neuropathy exist because most studies combine mixed neuropathic pain syndromes in the analysis. Additional studies targeting the treatment of pain in small fiber neuropathy are needed to guide decision making.

### Keywords

Small fiber; Neuropathy; Pain; Peripheral nerve

## Introduction

Peripheral neuropathy is an expanding public health problem, seen in nearly 40 million individuals in the United States [1]. Many of these individuals will have specific damage to small myelinated and unmyelinated nerve fibers, either in isolation or in combination with injury to larger myelinated nerve fibers. There are a variety of diseases that may result in a small fiber neuropathy, including diabetes and other glucose dysregulation syndromes (eg, impaired glucose tolerance and metabolic syndrome), thyroid dysfunction, sarcoidosis, vitamin B12 deficiency, HIV, neurotoxic medications (including many chemotherapeutic agents and antiretroviral agents), celiac disease, paraneoplastic syndromes, and paraproteinemias [2•]. Despite extensive diagnostic evaluation, up to 50% of individuals with small fiber neuropathy ultimately may be given a diagnosis of “idiopathic” [3•]. Regardless of the underlying etiology, pain is a common and often problematic feature of small fiber neuropathies. Therefore, therapy is tailored toward identification and treatment of the underlying cause of the neuropathy, when possible, while simultaneously managing symptoms of pain.

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## Definition of Small Fiber Neuropathy

A small fiber neuropathy occurs when damage to the peripheral nerves predominantly or entirely affects the small myelinated (Aδ) fibers or unmyelinated C fibers. The specific fiber types involved in this process include both small somatic and autonomic fibers. The sensory functions of these fibers include thermal perception and nociception. These fibers also are involved in a number of autonomic and enteric functions.

Most small fiber neuropathies occur in a length-dependent fashion, resulting in loss of function in a stocking distribution in the lower extremities. When the condition is more advanced, a glove-like loss in the upper extremities also may occur. In rare cases, a non–length dependent neuropathy results in symptoms involving the trunk, face, proximal limbs, or other focal areas [2•,3•].

Anatomically, the small nerve fibers may be damaged or destroyed in these conditions, resulting in a loss of small nerve fibers and/or abnormal nerve fiber morphology. However, the pathogenesis of injury to small nerve fibers is not well understood. Small nerve fiber neuropathies can occur without large nerve fiber involvement, but in some cases they occur concomitantly or progress to involve large nerve fibers.

## Symptoms of Small Fiber Neuropathy

Symptoms of small fiber neuropathy can vary widely in severity. Many individuals report the gradual onset of distal symptoms that include vague disturbances of sensation in the feet. These symptoms may include the feeling of a wrinkle in a sock that cannot be removed or of small pebbles or sand in the shoe. Others may report a cold-like pain, tingling or a pins and needles sensation. More severe symptoms of small fiber neuropathy may include burning pain that often is persistent, although it may vary in intensity throughout the day. Many patients also report transient electric shock–like pain, usually lasting only seconds, but quite severe and potentially multiple times per day. Many symptoms worsen during periods of rest and at night. In addition to spontaneous pain, many individuals report allodynia and hyperesthesia. Patients with small fiber neuropathy frequently complain that the bedsheets are exquisitely painful, and therefore, wear socks or use “foot tents” to keep the sheets from making physical contact with the feet.

Small nerve fiber neuropathies also may result in autonomic and enteric dysfunction. Patients often do not identify the relationship of these symptoms to their sensory complaints; however, when asked, they may report dry eyes, dry mouth, postural lightheadedness, presyncope, syncope, abnormal sweating, erectile dysfunction, nausea, vomiting, diarrhea, constipation, early satiety, difficulty with urinary frequency, nocturia, and/or voiding [4,5].

## Examination Findings in Small Fiber Neuropathy

One of the hallmarks of a pure small fiber neuropathy is a normal or near normal physical and neurologic examination. The coordination, motor, and reflex examinations will be normal. Light touch, vibratory sensation, and proprioception also may be normal, resulting in diagnostic confusion in some situations. Patients may have decreased pinprick, decreased thermal sensation, or hyperalgesia in the affected region. There may be mildly decreased vibratory sensation in some individuals. Associated skin changes in affected areas may include dry, cracked, or shiny skin, with decreased moisture on the surface of these affected areas as well.

## Causes of Small Fiber Neuropathy

Diabetes and prediabetes (including both impaired glucose tolerance and impaired fasting glucose) frequently are associated with pure small fiber neuropathy; however, concomitant

large fiber involvement is seen more often [6]. Nearly half of all subjects with idiopathic small fiber neuropathy have abnormal 2-hour glucose tolerance tests or abnormal fasting glucose levels [6,7]. The abnormal glucose testing may be seen despite normal glycosylated hemoglobin. Several studies have also established a link between pain in small fiber neuropathy and abnormal glucose metabolism [8,9]. There also is a large overlap between prediabetes and metabolic syndrome. The metabolic syndrome is comprised of hyperlipidemia, hypertension, and obesity in addition to abnormal glucose metabolism with insulin resistance. Each of these separate factors appears to convey an increased risk of developing a small fiber neuropathy [10]. Individuals with diabetes and metabolic syndrome appear to have twice the risk of developing a small fiber neuropathy compared to those with diabetes alone [11]. Recent reports now are suggesting that the single largest contributing factor to neuropathy development is hyperlipidemia [12•,13••]. Some patients with diabetes also may experience an acute painful small fiber neuropathy associated with rapid glycemic control, also referred to as insulin neuritis or treatment-induced neuropathy [14•].

Other conditions associated with acquired small fiber neuropathy include HIV [15,16], inflammatory neuropathies (such as Guillain-Barre syndrome and chronic inflammatory demyelinating polyneuropathy) [17,18], celiac disease [19,20], hepatitis C [21], restless legs syndrome [22], complex regional pain syndrome type I [23], paraproteinemia [24], neurotoxic drug use [25–27], systemic lupus erythematosus [28], Sjogren's syndrome [29], abnormal thyroid function [2•], amyloidosis, and paraneoplastic syndromes [30,31]. This list is not comprehensive and there are many case reports describing small fiber neuropathies in other diseases. In addition, there are inherited conditions which cause small fiber neuropathies, such as Fabry's disease and the hereditary sensory and autonomic neuropathies.

## Diagnosis of Small Fiber Neuropathy

The history and physical examination findings still are considered the gold standard against which all tests are compared when making a diagnosis of a small fiber neuropathy. A detailed review of the symptoms, rate of progression, and complaints suggestive of autonomic fiber involvement is necessary. Generally, if a patient presents with a compelling history for a small fiber neuropathy and an appropriate clinical exam, further testing to confirm the diagnosis may be unnecessary. This scenario is particularly likely in the context of an associated disease, such as diabetes. However, in many cases, the diagnosis may be less clear and ancillary testing may provide additional guidance. Patients should always be screened for other treatable causes of small fiber neuropathy. Recently, scoring examinations have been developed, and may aid in diagnosis of small fiber neuropathies [32•]. In addition, the specific types of pain experienced by patients with small fiber neuropathy may need to be characterized. The Neuropathic Pain Symptom Inventory differentiates various aspects of neuropathic pain, and may aid in selection of treatments as clinical trials begin to select specific aspect of neuropathic pain as targets [33].

### Quantitative Sensory Testing

Quantitative sensory testing (QST) is an extension of the physical examination that can provide a threshold for detection of thermal sensation, thermal pain, and vibratory sensation. QST has been used in a number of longitudinal studies and clinical trials of neuropathy and is widely available [34]. There are some well-recognized limitations to QST; abnormalities in either the central or peripheral nervous system can result in the same deficit. In addition, QST requires conscious integration from the patient, and in conditions of cognitive impairment (due to disease or medication), the reliability of the test results are in question. Finally, QST is unable to distinguish between feigned and true loss of sensation [35].

There are few trials utilizing QST in the study of isolated small fiber neuropathies, most trials include patients with large fiber involvement as well [34,36]. Heat or heat-pain detection thresholds are considered the most useful and specific for evaluation of a small fiber neuropathy. Cold and cold-pain detection are transmitted through lightly myelinated Aδ fibers, while vibration detection thresholds are detected through large myelinated Aα and Aβ sensory fibers. Recent reports of contact heat evoked potentials (CHEPs), a device that provides rapid cycles of heat resulting in evoked potentials measured by electroencephalogram, show a linear correlation between CHEP amplitude and cutaneous nociceptive nerve fiber density [37]. Further study is required to determine the utility of new variations of QST on the diagnosis of a small fiber neuropathy.

## Quantitative Sudomotor Axon Reflex Testing

There are a variety of methods to quantify sudomotor function. The most frequently utilized and well-known test is quantitative sudomotor axon reflex testing (QSART), a measure of postganglionic sympathetic cholinergic function. Local sweating is produced through iontophoresis of acetylcholine; this method uses a mild electrical current to draw acetylcholine (a charged substance) into the skin, causing activation of local sweat glands. The stimulation also triggers an axon reflex resulting in neighboring sweat glands, not stimulated by acetylcholine, to produce sweat. The axon reflex–mediated sweat output is detected by passing dry gas over the nonstimulated region and quantifying the change in humidity of the gas. A study of patients with small fiber neuropathy revealed that QSART was abnormal in 74% of patients, and that sudomotor dysfunction may be the earliest manifestation of a distal small fiber neuropathy [38]. Another study reported QSART to be abnormal in 73% of patients with painful feet from a small fiber neuropathy. A variety of other tests, including sweat imprint tests, thermoregulatory sweat testing, and quantitative direct and indirect sudomotor testing, also detect abnormalities in patients with a small fiber neuropathy. To date, no prospective controlled study has evaluated the ability of these tests to diagnose a small fiber neuropathy.

## Skin Biopsy

Skin biopsy has become a widely accepted technique to investigate the structural integrity of small nerve fibers [39]. A standard 3-mm dermatologic punch biopsy can be taken from any location on the body, but typically is performed on sites of interest in evaluation of a distal small fiber neuropathy (the lateral distal leg, the lateral distal thigh, and the lateral proximal thigh to look for a length-dependent pattern). For clinical investigation, bright field immunohistochemistry is used with antibodies against protein gene product 9.5, a marker for all peripheral nerve fibers. The number of fibers crossing the dermal/epidermal junction is quantified through standardized means, and results are expressed as the number of intraepidermal nerve fibers per millimeter. Recently revised consensus statements have highlighted the utility of skin biopsy in the evaluation of small fiber neuropathy [40•]. The sensitivity (78%–92%) and specificity (65%–90%) of skin biopsy for diagnosing a small fiber neuropathy is fairly high across all studies. In early or mild cases of small fiber neuropathy, morphologic abnormalities of nerve fibers may aid in diagnosis if nerve fiber density is not reduced [41]. Unfortunately, there are no data on the utility of skin biopsy to diagnose the etiology of the small fiber neuropathy.

## Electromyography and Nerve-conduction Studies

Electromyography and nerve-conduction studies are well-established neurophysiologic techniques used to assess the integrity of larger myelinated sensory and motor fibers. These studies often are normal in pure small fiber neuropathies. If there is question of possible larger fiber involvement causing symptoms or occurring concomitantly with a small fiber

neuropathy, these studies can clarify if larger sensory and/or motor nerve fibers are involved.

## Treatment of Pain in Small Fiber Neuropathy

Treatment of any underlying causative etiology of a small fiber neuropathy is likely to be the most effective treatment of pain, when possible. Many cases of small fiber neuropathy will remain idiopathic, or will still require treatment of pain. There is very limited evidence for specific medications in the treatment of pain from small fiber neuropathies. Most clinical studies have examined drugs in the treatment of many neuropathic pain syndromes (such as postherpetic neuralgia and painful diabetic neuropathy). In some trials, the spectrum of neuropathic pain can be broad and include diagnoses such as central neuropathic pain, radiculopathy, or carpal tunnel syndrome. These disorders may respond to treatment differently than pain from small fiber neuropathy. This is a challenge when developing treatment recommendations for small nerve fiber pain because comparative effectiveness across different pain states is not known.

This issue is further complicated by evidence suggesting that some diseases causing neuropathic pain respond differently to the same medications. Neither HIV nor chemotherapy-related neuropathic pain respond to treatments that are effective for other forms of neuropathic pain. It is unclear if these discrepancies are methodological or due to differences in the underlying disease state. In addition, head-to-head trials of medications and long-term outcome data for small fiber neuropathies are lacking. When possible, disease-specific treatment guidelines should be selected for management of pain in small fiber neuropathy (eg, diabetes, HIV, or chemotherapy).

In patients with idiopathic small nerve fiber neuropathy pain physicians must select treatments based on evidence of safety, efficacy in other neuropathic conditions, tolerability, drug interactions, comorbid conditions, and cost [42]. There are a number of recent consensus guidelines for the treatment of neuropathic pain [43,44,45•,46,47 48••]. None of the guidelines specifically examine treatment of pain secondary to small fiber neuropathy. Several provide recommendations based on patterns of pain or underlying disease. Most of these guidelines are based on reviews of available randomized clinical trials published in MEDLINE and the Cochrane database, although some used additional resources. The criteria used to establish the guidelines varied somewhat, although all used randomized control trials. Other variables such as safety, efficacy, tolerability, number needed to treat (NNT), side-effect profile, comorbid conditions, effect on quality of life, cost and, ease of use also were considered. Certain guidelines also addressed population-specific issues such as availability and genetic features. These guidelines were published between 2006 and 2010; the older publications do not include the most recent trials. There is significant agreement about medications among these recommendations, although classifications of first-, second-, and third-line agents vary. Table 1 highlights the recommendations of these recent guidelines and consensus statements [43,44,45•,46,48••].

There are several different classes of medications commonly used to treat neuropathic pain. These include antidepressants, anticonvulsants, opioids, and topical treatments. Tricyclic antidepressants (TCAs) consistently are recommended as first tier drugs across all guidelines [43,44,45•,46–48]. The criterion for study inclusion varies amongst the guidelines; however, the number of studies for neuropathic pain reviewed ranged from 2 to 17. The NNT was 2.1 to 2.5 based on the type of TCA. None of the studies specifically treated patients with small fiber neuropathy. TCAs consistently were selected as first-tier choices based on their efficacy and other factors such as cost and availability. Their mechanism of action is inhibition of serotonin and norepinephrine reuptake. TCAs also have anticholinergic effects

that can cause significant side effects for some patients, and specifically should be avoided in elderly adults. They are contraindicated in patients with a significant cardiac history, glaucoma, or recent monoamine oxidase–inhibitor (MAOI) use. Guidelines note that safety and tolerability factors may limit the use of TCAs.

Serotonin–norepinephrine reuptake inhibitors (SNRIs) are another class of antidepressants commonly used for the treatment of neuropathic pain. Both duloxetine and venlafaxine are recommended as second-line agents in most guidelines. For duloxetine, most guidelines reviewed two to three studies [43,44,45•,46,47,48••]. It has been found to be effective in painful diabetic neuropathy and the NNT was 5.2. It has not been studied for other forms of neuropathic pain; therefore, it is frequently recommended as second- or third-line treatment. It has a rapid onset of action and is generally well tolerated. It should be avoided in patients with uncontrolled narrow-angle glaucoma or those being treated with MAOIs. In rare cases it has been associated with abnormal bleeding, hepatotoxicity, and serotonin syndrome.

Venlafaxine is another SNRI that typically is recommended as a second-line agent. Two studies have found it to be effective for painful diabetic neuropathy and for mixed neuropathy with a NNT of 4.6 [43,44,45•,46,47,48•]. In a study that compared imipramine and venlafaxine head to head, the imipramine group had a higher proportion of responders [49]. Generally, venlafaxine is well tolerated, but should be avoided in patients being treated with MAOIs. In some cases, it has been noted to increase blood pressure and cause ECG changes. Rare adverse events including bleeding, hyperlipidemia, and pulmonary complications (interstitial lung disease and eosinophilic pneumonia) have been reported. Due to differences in the NNT, TCAs are recommended over SNRIs in most guidelines except in elderly patients or others at risk for adverse events.

In addition to antidepressants, anticonvulsants also are routinely recommended for the treatment of neuropathic pain. Gabapentin frequently is utilized as a first-line treatment of neuropathic pain. Most guidelines reviewed two to four studies and the NNT was 3.9 to 4 [43,44,45•,46,47,48••]. It is effective for neuropathic pain (specifically postherpetic neuralgia and painful diabetic neuropathy). The mechanism of action is believed to be via the voltage-gated $\alpha_2\delta$ calcium channel, modifying the release of excitatory neurotransmitters. It is well tolerated and not known to cause significant drug–drug interactions. In rare circumstances, it has been associated with Stevens-Johnson syndrome.

Pregabalin is another anticonvulsant frequently used for first-line treatment of neuropathic pain. In the included guidelines, two to six studies on pregabalin in different types of neuropathic pain (postherpetic neuralgia, painful diabetic neuropathy, or both) were reviewed. For some guidelines, several studies were excluded based on concern that the methodology included enriched enrollment. The calculated NNT was 4.2 [43,44,45•, 46,47,48••]. Pregabalin's mechanism of action also is believed to be through the voltage-gated $\alpha_2\delta$ calcium channels and is a presynaptic inhibitor of the release of glutamate, substance P, and calcitonin gene–related peptide (CGRP). It also is typically well tolerated, but should be used with caution in patients with congestive heart failure. Angioedema rarely has been described as a side effect.

Topical lidocaine frequently is recommended as a first- or second-line treatment of focal neuropathic pain. These recommendations are typically for the lidocaine patch, although there also is evidence available for lidocaine gel. The guidelines included three or four studies (primarily for postherpetic neuralgia) and the NNT is 4.4 [43,44,45•,46,47,48••]. It is generally most effective for patients with focal regions of pain and offers the advantage of less systemic side effects and drug interactions. It also may be used for breakthrough pain. It is believed to act by decreasing neuronal membrane permeability to sodium ions. Topical

lidocaine is more expensive than some of the other treatments, but is generally well tolerated. It should be avoided in regions of skin breakdown. Rare allergic or anaphylactic reactions can occur.

Lastly, opioids and tramadol frequently are recommended as second- or third-line medications across all guidelines. Among expert opinions, there is consistent concern about the use of opioids for nonterminal neuropathic pain due to dependence. Some guidelines review different types of opioids (oxycodone, morphine, methadone, and levorphanol) as well as different types of neuropathic pain (painful polyneuropathy and post-herpetic neuralgia). The number of studies included ranged from five to eight and the NNT ranged from 2.5 to 2.7 based on the type of neuropathic pain and the drug [43,44,45•,46,47,48••]. Some guidelines suggest that opioids, typically oxycodone, be used for severe breakthrough pain either for acute exacerbations or during titration of another agent. While effective for pain, opioids pose the potential for many side effects as well as overdosing and dependence.

Tramadol is consistently recommended as a second- or third-line choice for treatment of neuropathic pain. Concerns for dependence also are raised with tramadol use. The number of reviewed studies ranged from two to three among the guidelines and included painful diabetic neuropathy, mixed polyneuropathy, or postherpetic neuralgia. The NNT ranged from 3.4 to 4.8 based on the type of neuropathic pain and criteria applied [43,44,45•, 46,47,48••]. Tramadol and its active metabolite bind to central μ-opiate receptors and inhibit ascending pain pathways. Tramadol also causes serotonin and norepinephrine–reuptake inhibition, another potential mechanism of pain relief. Side effects of tramadol can include dyspnea and respiratory depression, and it is rarely associated with myocardial infarction, pancreatitis, seizure, and serotonin syndrome. It should be avoided in patients who are actively using central nervous system depressants such as alcohol, hypnotics, opioids, or psychotropic drugs. In addition, tramadol does have the potential to interact with most antidepressant medications, and care is required due to the potential duplicative serotonin- and norepinephrine-reuptake inhibition. Also, up to 10% of Caucasians are poor cytochrome P450 2D6 metabolizers and, therefore, are unable to metabolize the drug effectively, resulting in poor efficacy [50].

In the only published study specifically examining treatment of small fiber neuropathy, both gabapentin and tramadol were found to be effective [51]. This study used an enrichment crossover design. Participants were included if they had biopsy-proven small fiber neuropathy and were self-identified as gabapentin responders. Patients first were treated with single-blinded gabapentin at their prestudy dose as well as matching diphenhydramine placebo, 50 mg, capsules for 1 week. Participants with a pain intensity score of 7.5 or higher were then allowed to continue to the second phase, in which patients were tapered off their gabapentin dose during the first week and continued on the diphenhydramine placebo for 2 weeks. Pain scores were assessed during the second week, and those participants with a pain score of 3 or higher and a 30% or greater increase from their initial phase pain scores then were randomized into a double-blind crossover phase. During the last phase of the trial, patients were randomized to three 2-week double-blind treatment periods with1-week washout periods between each treatment phase. Overall, 18 participants were treated in a randomized crossover design with 3 treatments: gabapentin at their prestudy dose, tramadol, 50 mg four times daily, and diphenhydramine 50 mg at bedtime. Three participants withdrew before completing all three treatment periods. There was a statistically significant improvement in pain scores for both gabapentin and tramadol groups when compared to diphenhydramine. The NNT for gabapentin was 4.6. The NNT for tramadol was 4.0. There was no statistically significant difference between the average pain scores during the gabapentin and tramadol treatment phases. There were no reported significant adverse events in either treatment group.

Other classes of medications have been used for the treatment of neuropathic pain including antiarrhythmics. This class typically is excluded from expert panel recommendations due to the large number of potential side effects. Selective serotonin reuptake inhibitors also are excluded as first- or second-line recommendations due to limited data on efficacy. For detailed descriptions of the guidelines, included studies, drugs and dosing, please refer to the recently published guidelines for neuropathic pain listed in Table 1 [43,44,45•,46,47,48••].

Nonpharmacologic options also are important for pain management. Some patients may benefit from cool or warm soaks, soft socks, and foot tents. Other treatments such as transcutaneous electrical nerve stimulation, acupuncture, physical therapy and massage also have been used, but have not been examined in clinical trials for small fiber neuropathic pain [43,44,45•,46,47,48••].

## Conclusions

Small fiber neuropathy frequently is associated with neuropathic pain. The clinical history and physical examination often are sufficient to make the diagnosis of a small fiber neuropathy; however, additional functional and pathological tests may help to confirm the diagnosis. Patients should be carefully screened for reversible causes of small fiber neuropathy. A variety of medications for treatment of pain exist, and there are a number of available consensus guidelines that can aid clinicians in selecting appropriate treatments. For some conditions, such as painful diabetic neuropathy, there are additional treatment guidelines available. However, additional studies specifically targeting the pain in small fiber neuropathy are necessary to support clinical decision making. With the advent of new medications coming to market, further review of the literature will be necessary.

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**Table 1**

Summary of Guidelines

| **Medication Class** | **Neuropathic Pain Special Interest Group (NeuPSIG) (2010)** | **Expert Panel Recommendations for the Middle East Region (2010)** | **European Federation of Neurological Societies (EFNS)[1] (2010)** | **Guidelines for the Diagnosis and Management of Neuropathic Pain: Consensus of a Group of Latin American Experts[2] (2009)** | **Canadian Pain Society (2007)** |
|---|---|---|---|---|---|
| Tricyclic Antidepressants | First Line | First Line | First Line for PPN and PHN | First Line | First Line |
| SNRIs | First Line | Second Line | First Line for PPN | Third Line | Second Line[3] |
| Anticonvulsants | First Line | First Line | First Line for PPN and PHN | Second Line | First Line |
| Topical Lidocaine | First Line for localized peripheral NP | First Line for PHN with focal allodynia | First Line for PHN for the elderly | First Line for localize peripheral neuropathies | Second Line for localized peripheral NP[4] |
| Opiods Analgesics | Second line except in selected Circumstances[5] | Second Line | Second line for PHN and Third Line for PPN | Second Line | Third line |
| Tramadol | Second line except in selected Circumstances[5] | Second Line | Second Line for PPN[6] | Second Line | Third line |

[1]Based on recommendations for painful polyneuropathy and postherpetic neuralgia

[2]Based on the recommendations for localized and diffuse peripheral neuropathies

[3]Duloxetine was not available in Canada per the authors at the time of this guideline

[4]The lidocaine patch was not available in Canada per the authors at the time of this guideline, however lidocaine gel was.

[5]Opioid analgesics and tramadol can be used as first-line options for the treatment of acute NP, episodic exacerbations of severe NP, neuropathic cancer pain, and during titration of a first-line medication in patients with substantial pain.

[6]Tramadol can be used as a second line agent for patients with painful polyneuropathy and painful exacerbations or patients with predominant coexisting non-neuropathic pain

NP=Neuropathic pain
PPN = painful polyneuropathy
PHN = postherpetic neuralgia
SNRIs= serotonin and norepinephrine reuptake inhibitors.