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*Chapter 1*

# An update on the pharmacological treatment of neuropathic pain

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## Abstract

Neuropathic pain is a debilitating, prevalent condition with substantial costs to individuals and society. Although the treatment strategies include interventional or behavioral procedures, pharmacological treatment remains the primary mode of therapy. Following a brief introduction, the review compiles and discusses findings from clinical trials utilizing the following classes of agents: anticonvulsants, antidepressants, opioids, topical agents, and adjuvants.

Results of the review indicate that numerous high-quality trials exist that investigate the efficacy of available agents for syndromes involving neuropathic pain. However, the trial protocols vary, and the findings often differ from study to study. The volume and diversity of existing evidence presents a challenge to clinicians attempting to ascertain the best treatment regimen. Also, many agents show promise, but require an additional

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research in larger trials before they can be integrated into the pool of standard treatment-strategies.

Moreover, all available pharmacologic agents are limited in their efficacy, side-effect profile, or both. The search for new agents balancing the satisfactory pain relief and still acceptable side-effects continues to be of high priority and clinical significance.

**Keywords:** Neuropathic pain, pain management, opioid medication, antidepressants, anticonvulsants

# 1. Introduction

The International Association for the Study of Pain (IASP) defines neuropathic pain as "pain initiated or caused by a primary lesion or dysfunction in the nervous system" (1). Criticizing this definition for its "lack of both diagnostic specificity and anatomic precision," an expert group (2) recently redefined neuropathic pain as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system".

This definition distinguishes neuropathic pain from that pain which may mimic neuropathic pain symptomatically but arises from tissue damage and secondary physiologic nociceptive activation.

Neuropathic pain is difficult to diagnose and notoriously difficult to treat (3-6). Neuropathic pain is characterized by stimulus-independent spontaneous pain, hyperalgesia, and/or allodynia.

It is often described as sharp, burning, shooting, stabbing, lancinating, electrical, hot, cold, shock-like, or fiery. It may arise from disease processes (e.g. herpes zoster, diabetes, HIV, stroke), surgical complications, medication side-effects (e.g. chemotherapeutic agents), injury, or unknown processes (e.g. trigeminal neuralgia) (30).

The sequential patho-physiological changes that result in chronic neuropathic pain have not yet been fully understood, though recent findings have begun to elucidate the involved mechanisms (7).

It has been shown that several causative pathways may result in similar symptomatology; for example, increased central firing from altered channel properties, decreased afferent inhibition of central structures, and central sensitization can all result in greater central activity, though through three distinct mechanisms (8-14).

The plurality of involved mechanisms underlies the difficulties to identify relevant cellular targets and to develop agents efficiently relieving pain in various neuropathic pain syndromes.

Although many interventional and experimental procedures are currently in use, medical treatment remains the mainstay of therapy.

Adjuvant analgesics are the pillar for this strategy and are defined as pharmacological agents developed for other uses but that have been shown to be analgesic, and include antiepileptics and antidepressants. In addition, other agents have been shown to have an analgesic effect in patients with neuropathic pain and include muscle relaxants, ketamine and lidocaine among others. Opioids, and oral or topical adjuvant analgesics currently constitute the major classes of medications (6).

# 2. Pharmacotherapy for neuropathic pain

## 2.1. Adjuvant analgesics

### *2.1.1. Anti-epileptics*

Anti-Epileptics (AED's), also known as anticonvulsants, have well-established efficacy in the treatment of neuropathic pain including painful diabetic neuropathy (PDN), post-herpetic neuralgia (PHN) and trigeminal neuralgia (TN). Proposed mechanisms of action include the enhancement of GABAergic inhibitory neurotransmission, decrease in glutamatergic excitatory neurotransmission directly or via inhibition of voltage-dependent sodium and calcium channels, and interference with intracellular signaling pathways (15-17). This class of drugs includes carbamazepine, phenytoin, gabapentin, pregabalin, lamotrigine, topiramate, oxcarbazepine, and lacosamide.

#### Carbamazepine and oxcarbazepine

Carbamazepine, the first AED studied in clinical trials for neuropathic pain, is still the drug of choice for trigeminal neuralgia (18, 19). Most studies that have examined its use were conducted in the 1960s-70s and found that 58-68% of patients had symptomatic relief as compared to a placebo (20). In a recent review of the literature (21), carbamazepine was shown to be superior to all other traditional analgesics. However, if patients are refractory to first-line treatment, or if there are unacceptable side effects, oxcarbazepine or lamotrigine may be used as second-line therapy (22, 23).

In addition to its role as a first-line agent for trigeminal neuralgia, carbamazepine, and to a lesser extent oxcarbazepine, have demonstrated efficacy in diabetic and post-herpetic neuropathies (24). However, additional head-to-head trials are needed to better characterize these agents' exact role in treating all kinds of neuropathic pain syndromes.

#### Gabapentin

Gabapentin, a drug designed to mimic the structure of gamma-aminobutyric acid (GABA) to treat partial seizures, has demonstrated analgesic effects in multiple neuropathic syndromes (25). Proposed mechanisms of action include increased synthesis of GABA, antagonism of the alpha2-delta protein subunit of voltage gated calcium channels, and reduction of monoamine neurotransmitter release (26). The involvement of the alpha2-delta protein in the dorsal horn may play a key mediating role in gabapentin's mechanism of action. Recent work has demonstrated that alpha2-delta mRNA expression in nerve crush injury resulted in allodynia (27). Furthermore, studies have shown that gabapentin, possibly secondary to modulating calcium release, results in decreased release of aspartate, glutamate and substance P (28). In addition, functional magnetic resonance imaging (fMRI) studies have shown gabapentin causes decreased central sensitization, shown in part by decreased stimulus-driven activation of the brainstem (29).

Numerous trials successfully demonstrate gabapentin's efficacy in treating multiple subgroups of neuropathic pain. In a prospective RCT involving twenty patients with traumatic spinal cord injury, gabapentin was shown to decrease pain intensity significantly by the fourth week of treatment ($p < 0.001$), as well as ameliorate other sensations of heat or sharp pain ($p<0.001$ at four weeks) (30). Another single-blinded, randomized, NSAID-controlled study

that enrolled 55 patients with lumbar spinal stenosis demonstrated increased walking distance at two months ($p<0.033$), decreased pain at three months ($p<0.039$), and improved sensory function at four months ($p<0.04$) (31).

In regards to PHN, a review looked at two randomized, placebo-controlled studies with a combined total of 563 patients; the studies demonstrated a significant decrease in pain with gabapentin treatment (32)). These results echo the findings of a previous multicenter, randomized, double-blind, placebo-controlled, parallel design study that enrolled a total of 229 subjects with PHN and found a significant decrease in overall pain measurements after two weeks of treatment ($p<0.001$) (33).

In addition to working alone, gabapentin has additive or synergistic effects when used with other analgesic medications. One open-label study looked at the combination of opioid analgesia and gabapentin in neuropathic cancer pain. A total of 75 patients were enrolled in the study, which compared gabapentin/opioid combination to opioid therapy alone. The combination group had decreased burning and shooting sensations ($p<0.0001$) between four to thirteen days of treatment (34).

Similar results were found in a RCT that compared combined therapy, opioid therapy alone, and a lorazepam control. A total of 57 patients (35 with diabetic neuropathy and 22 with PHN) were enrolled. Results demonstrated significantly less pain with combination therapy ($p<0.04$) at lower doses of each medication. This suggests that combination therapy could be used to decrease potential side effects of higher doses of monotherapy. However, there was increased constipation and dry mouth in the combination group ($p=0.006$ and 0.03, respectively) (35). A recent double-blind, double-dummy, crossover trial for patients with diabetic polyneuropathy and postherpetic neuralgia showed that gabapentin when combined with nortriptyline provides superior pain relief at lower doses than with either agent alone (2.3 on 0-10 numerical rating scale (NRS) for combination treatment, v. 2.9 for nortriptyline, 95% C.I. .02%, and 3.2 for gabapentin, 95% C.I. .001) (36).

In summary, gabapentin should be considered a first-line agent for neuropathic pain. Studies show that gabapentin generates analgesia in a variety of neuropathic settings, including diabetic, post-herpetic, spinal, and cancer-related neuropathies. It is generally safe to use with few clinically significant drug interactions. The main dose-limiting side effects of somnolence and dizziness can be reduced with gradual titration (37).

## Pregabalin

A newer gabapentinoid, pregabalin (an alpha2-delta ligand), has shown promise in treating PDN, PHN and fibromyalgia syndrome (39). In two separate double-blind, multicenter, placebo controlled studies, pregabalin demonstrated marked improvement in both endpoint mean pain scores ($p=0.0001$) and overall quality of life including improved sleep, and global impression of beneficial change (40, 41). Its use was generally well tolerated with no serious adverse events. The most common complaints were increased somnolence and dizziness, as well as increased cost. Improved tolerance is expected with gradual titration. Other studies support pregabalin's effectiveness for treating painful diabetic neuropathy (42, 43).

Like gabapentin, pregabalin also demonstrates synergism with other agents that target neuropathic pain. One recent study showed that pregabalin is effective in relieving neuropathic pain when used alongside controlled-release oxycodone, though oxycodone alone was more effective than pregabalin alone. The dosing required to achieve comparable relief was lower in combination than with either agent alone (44).

In summary, numerous studies support pregabalin's use in treating neuropathic pain for a variety of different conditions. It should be viewed along with gabapentin as a first-line agent for treating neuropathic pain.

## Topiramate

An additional AED, topiramate, has emerged as a possible therapeutic option for PDN and neuropathic pain in cancer patients. However, in three simultaneous double-blind placebo controlled studies, topiramate achieved nonsignificant but numerical pain relief when compared to placebo (45). The treatment groups experienced more side-effects, including weight loss, nausea, somnolence, confusion, fatigue or memory difficulties.

Other studies have since been more encouraging. A subsequent trial involving 323 subjects demonstrated that pain intensity scores were significantly reduced ($p=0.004$) when using topiramate as monotherapy (46). Furthermore, in a retrospective study looking at patients with neuropathic cancer pain, topiramate was shown to be beneficial as a second-line therapy when adequate pain control was unable to be maintained using first-line drug regimens (47). Similar results were also seen in an open-label extension study (48) involving 205 patients who were previously randomized to either topiramate or placebo. Pain scores were significantly lower for the topiramate arm ($n=117$) of the study, with a decrease in worst pain ($p<0.001$), current pain ($p=0.026$), and sleep disruption ($p=0.021$) as compared to placebo. However, a large number of subjects (39.5%) discontinued treatment because of intolerable side effects including upper respiratory tract infections, anorexia, nausea, and paresthesia.

## Lamotrigine

Lamotrigine is another AED with reported effectiveness in relieving pain from both PDN and complex regional pain syndromes (49). In a randomized, placebo-controlled study of 59 patients with PDN, lamotrigine demonstrated a significant ($p< 0.001$) decrease in overall pain scores as well as a decreased need for rescue medications after four weeks of use (50). Lamotrigine also has demonstrated efficacy in treating trigeminal neuralgia refractory to other first-line regimens, when used in combination with carbamazepine, but the evidence is weak (51, 52).

Lamotrigine was also assessed in a RCT of 12 patients with central pain secondary to multiple sclerosis. The study outcomes, including overall pain and quality of life, showed no significant benefit in using lamotrigine as compared to placebo (53). Similar results were found in one study comparing lamotrigine to placebo in the treatment of chemotherapy-induced peripheral neuropathy (54).

More recently, a number of RCTs looked at lamotrigine's efficacy in PDN as well as other painful neuropathies and found inconsistent benefits both as an adjunct and as compared to placebo (55, 56). Given the availability of more effective treatments, lamotrigine does not have a significant therapeutic role in neuropathic pain at this time. Its use should be reserved only after first-line therapy has been exhausted (57). While its use is generally safe and well-tolerated, it has been associated with skin rash, somnolence, ataxia and Steven-Johnson's Syndrome (58).

### Lacosamide

In a recent double-blind placebo-controlled trial for the treatment of painful diabetic neuropathy (59), lacosamide demonstrated statistically significant pain relief (p=0.02) over the 18-week study period at the target dose of 400 mg/day, but beyond that period during the last four weeks of the study it failed to reach significance (p=.0507). Adverse effects included nausea, dizziness, tremor, and somnolence. 24% of patients in the treatment group withdrew secondary to adverse effects as compared with 14% in the placebo group (59).

## *2.1.2. Antidepressants*

### Tricyclic antidepressants

Tricyclic antidepressants (TCAs), such as amitriptyline, nortriptyline, imipramine, and desipramine, have been used for over thirty years to treat a range of neuropathies including PDN, PHN, and traumatic neuropathy (60, 61). Their analgesic effect is thought to lie in their ability to modulate the endogenous opioid system (particularly the delta- and kappa-opioid receptors), as well as through the suppression of voltage-gated sodium channels (62-64). Clinical trials and extensive clinical experience have shown that TCAs, particularly amitriptyline, can reduce the severity of both PDN and PHN and lead to symptomatic relief (24). Their use is limited by their adverse side-effect profile, which includes cardiotoxicity, constipation, autonomic disturbances, and cross reactivity with many antihypertensive medications (65, 66). In a randomized, double-blind study, desipramine, amitriptyline, and fluoxetine were compared in the treatment of PHN in patients who never previously had been exposed to antidepressants (67). In the study, desipramine and amitriptyline were shown to be superior to fluoxetine (p=0.036), with desipramine providing pain relief in 80% of the patients (67).

In another randomized controlled trial (68), amitriptyline was compared to gabapentin and diphenhydramine in patients suffering from spinal cord neuropathy with concurrent depressive symptomatology. Amitriptyline was found to provide significantly more pain relief ($p<0.035$) than diphenhydramine, and may even be more efficacious then gabapentin (p=0.061) (68).

Considering the possible interactions of TCAs with the delta opioid receptor, studies have looked at the possible combination of TCAs and opioids for possible synergistic effects. One study that looked at the use of morphine, nortriptyline and their combination in treating chronic lumbar root pain demonstrated a degree of synergy between the two treatments. This randomized, single-blinded, placebo-controlled study showed that while there was no difference in average pain, combination therapy was superior to placebo for severe pain ($p< 0.04$) (69).

Considering the narrow therapeutic range of TCAs, studies have investigated novel methods to attain sufficient analgesia at the lowest possible doses. Therapeutic drug monitoring (TDM) has been studied in the use of imipramine for neuropathic pain (70). The doses ranged from 50 to 1400 nmol/L, with 70% subjects requiring less than 400 nmol/L in order to achieve 50% or greater pain relief (70). In addition, patients who had “failed” TCA previously were able to see benefit when using TDM.

In summary, TCAs are well-established as among the most efficacious of all available agents for the treatment neuropathic pain from various causes. However, undesirable side-effects limit their use.

## Nonselective serotonin-norepinephrine reuptake inhibitors (NSIRs)

### Venlafaxine

Venlafaxine is a nonselective serotonin-norepinephrine reuptake inhibitor approved for the treatment of depression and anxiety disorder. In recent years, its use has expanded to the off-label treatment of neuropathic pain, and several studies have investigated its efficacy (71-73).

A double-blind randomized trial (71) compared venlafaxine to imipramine and placebo in patients with painful polyneuropathy due to a variety of causes. The study found that both venlafaxine and imipramine were effective in reducing neuropathic pain ($p=0.006$, and 0.001 respectively), and no significant differences in pain relief were observed between the two treatment groups ($p=0.44$). Although side-effects were greater in both treatment groups than in the placebo group, more patients withdrew from the venlafaxine arm than the imipramine arm (71).

In another RCT examining venlafaxine in the treatment of peripheral diabetic neuropathy (PDN) (72), patients receiving high-dose venlafaxine (150-225 mg) experienced significant pain relief compared to placebo ($p<.001$).

The authors report that 5/77 patients in the low-dose group and 4/78 patients in the high-dose groups had EKG changes as opposed to 1/78 in the placebo group. Impotence, dyspepsia, nausea, vomiting, myalgia, insomnia, and somnolence were all more frequently reported in the treatment arms (72).

A randomized double-blind trial (73) investigating venlafaxine for the treatment of neuropathic pain failed to demonstrate a reduction in reported pain intensity when compared with placebo, though the authors noted that the treatment had a positive effect on hyperalgesia (73).

### Duloxetine

Duloxetine is a non-selective serotonin-norepinephrine reuptake inhibitor used in depression, generalized anxiety disorder, fibromyalgia, urinary incontinence, and pain conditions such as neuropathic pain (74).

Several trials have investigated its efficacy in the treatment of PDN (75-80). A double-blind multicenter study (75) demonstrated significant pain relief with duloxetine 60 mg/ day and 120mg/day at week 1 through week 12 of the treatment as compared to placebo ($p<.01$).

Significantly more patients in the treatment groups discontinued the study secondary to adverse effects, with increased somnolence and constipation being the two most common AEs ($p<.01$ v. placebo) (75). Two more trials (76, 77) supported these results in similarly designed 12-week studies in diabetic population. Additional industry-sponsored studies analyzing data pooled from these three original studies have since been published in support of duloxetine's "cost-effectiveness" (78), "efficacy and tolerability" (79), and "improvement in functional outcomes" (80).

Given the current evidence, duloxetine can be viewed as effective and relatively safe for the treatment of pain in PDN. However, additional corroborating reports from independent investigators are necessary. Furthermore, no studies exist that examine duloxetine's efficacy in treating non-diabetic causes of neuropathic pain.

### Serotonin selective reuptake inhibitors (SSRIs)

#### Escitalopram

Escitalopram is a serotonin-selective reuptake inhibitor used for depression and anxiety. A recent double-blind placebo-controlled study (81) examined its efficacy for the treatment of neuropathic pain. The results demonstrated statistically significant but clinically minimal pain relief as compared with placebo (.8 points on 6 point scale $p<0.001$), as well as significant improvement on a variety of other pain indices. Minimal differences were noted in terms of side-effects between groups. At this point, on the basis of only one study, any conclusion on the role of escitalopram in the treatment of neuropathic pain can't be drawn, and further evidence is needed.

### Other serotonin-selective reuptake inhibitors

Only limited data exists on the use of SSRIs in the treatment of neuropathic pain (60), and the RCTs (82-85) were conducted over a decade ago. All four trials showed minimal benefit of SSRIs over placebo in the treatment of idiopathic facial pain and painful diabetic neuropathy. SSRIs are safer than TCAs, but seem to be less efficacious than both SNRIs and TCAs (86). While they may be an option for patients unable to tolerate first-line agents, additional evidence is needed before SSRIs are used routinely for treatment of neuropathic pain.

### Non-selective norepinephrine-dopamine reuptake inhibitors

#### Bupropion SR

Bupropion is an antidepressant presumed to act by inhibiting neuronal norepinephrine reuptake and to a lesser extent dopamine reuptake. Only one double-blind randomized trial in neuropathic pain (87) is reported up to date. In this study, the bupropion treatment group experienced significant pain relief ($p<0.001$) and improved quality of life ($p<0.01$) when compared to the placebo group. The encouraging results from this trial justify exploring bupropion in larger controlled studies with longer follow-up period.

## 2.2. Opioids

Opiates are naturally occurring alkaloids with analgesic properties that modify the release of presynaptic neurotransmitters in the dorsal horn of the spinal cord and in peripheral tissues (88, 89) They may be classified by action as agonist, mixed agonist-antagonist, or antagonist, and by target receptor as kappa, delta and mu (90, 91). Opioid agonists have generally been reserved for patients who either failed or could not tolerate their first line medications (37, 92, 93). The most common limiting side-effects include constipation, respiratory depression, nausea and sedation (94).

### *Fentanyl*

Fentanyl is a strong synthetic opioid agonist. It primarily interacts with mu receptors and is approximately 80 times more potent than morphine. A number of studies have shown fentanyl to be an important treatment option in refractory neuropathic pain. In a randomized controlled trial (95) of 53 patients with neuropathic pain of various origin, the analgesic effect of the intravenous fentanyl was compared to diazepam and placebo. The results showed significant pain relief in 66% subjects in the fentanyl group, 23% of subjects within the diazepam group and 12% in the placebo group. Further, a large (n=529) prospective open-label study (96) evaluated the long-term efficacy of transdermal therapeutic system-fentanyl in relation to quality of life. In the study, 90% of patients showed significant ($p<0.0001$) improvement. The median period of effective pain management was 10 months (96). Similarly, another open-label trial of transdermal fentanyl evaluated efficacy and safety over a period of 12 months(97). 67% of patients reported positive outcomes, with 86% of patients reporting a preference of TDF over their previous drug regimens ($p<0.001$) (97). Further, a study in patients experiencing breakthrough pain (98) indicated an efficacy of fentanyl buccal tablets for relief of breakthrough pain.

### *Oxycodone*

Oxycodone is an opioid with activity at multiple opiate receptors. It is available in its pure form or in combination with tylenol or aspirin. Multiple studies have shown its usefulness in the treatment of neuropathic pain. For example, controlled-release (CR) oxycodone was evaluated in a RCT that looked at the efficacy, safety and health-related quality of life in patients with diabetic neuropathy (99). The treatment with CR oxycodone resulted in significantly lower ($p=0.0001$) mean pain scores as compared to placebo. Similarly, a multicenter RCT which included 159 diabetic neuropathy patients examined CR oxycodone's efficacy for moderate to severe pain. At an average dose of 37 mg per day, CR oxycodone provided significantly better relief ($p=0.002$) as compared to placebo (100). Furthermore, in a recent long-term trial of 233 non-cancer patients who continued to require opioid analgesia, CR oxycodone demonstrated prolonged relief in approximately 75% of patients (101). In summary, oxycodone is an effective tool in neuropathic pain treatment, though its use can be limited by side-effects common to opioids.

### *Morphine*

Morphine is the prototypical mu-receptor opioid. There are numerous trials documenting morphine efficacy in neuropathic pain. For example, a randomized controlled trial (102) evaluated morphine alone and in combination with gabapentin. Both drugs had equivocal decreases in pain scores as single agents, but achieved significantly greater analgesia when given together ($p<0.05$). Furthermore, when used in combination, they achieved therapeutic analgesia at lower doses than with each individual drug (102). In a study evaluating neuropsychological performance in patients with chronic non-cancer pain, morphine induced persistent (12 months) improvement in pain, function, and to a lesser extent also improvement of mood and quality of life (103).

### *Methadone*

Methadone is a potent mu receptor agonist with unique properties including weak N-methyl-D-aspartate (NMDA) antagonist activity, inhibition of norepinephrine and serotonin reuptake, and monoaminergic effects. It has demonstrated efficacy in the treatment of diverse range of chronic neuropathic pain syndromes (104-109). In 4 separate studies evaluating methadone in neuropathic pain, a total of 95 patients reported significant improvements in mechanical allodynia, quality of life, and overall pain relief (106-109). These studies looked at a diverse range of neuropathies and successfully demonstrated methadone role both in first-line therapy and for patients who respond poorly to traditional analgesic regiments. In summary, evidence indicates that methadone is a useful agent for treating neuropathic pain. However, in addition to the cautions already described for opioids as a class, prescribing clinicians must maintain awareness of methadone long half-life and the possibility of drug-drug interaction at the level of the cytochrome p450, specifically the isoenzymes 2A4 and 2D6 that also participate in the metabolism of certain antidepressants and antiretroviral agents. In addition prolongation of the QTc interval has been observed and the possibility of precipitation by methadone of torsades de pointes (TdP), a potentially fatal arrythmia, has been raised. Although the opinions are divided there is certain degree of consensus that patients taking over 100 mg/day of methadone should have an EKG to evaluate the duration of the QTc interval (110-111).

### *Tramadol*

Tramadol is a centrally acting weak mu-opioid agonist that inhibits both norepinephrine and serotonin reuptake (112, 113). In a recent study (114), tramadol/acetaminophen (APAP) was compared to placebo in painful diabetic peripheral neuropathy in 313 patients. Tramadol/APAP was associated with significantly greater improvement ($p<0.05$) in all measures of pain intensity, sleep interference, global impression and several measures of quality of life. It was well-tolerated and adverse events were equivalent to the placebo control (114). These results were similar to another study (115) that found tramadol to be significantly more effective than placebo ($p<0.017$). An open-label six-month study (116) indicated that tramadol provides long-term relief of PDN. Numerous other studies suggest that tramadol is also useful in the treatment of pain associated with postherpetic neuralgia (117, 118), fibromyalgia (119), post-spinal injury (120), and migraine headache (121).

The sustained-release (tramadol SR) and extended-release (tramadol ER, Ultram ER) formulations of tramadol show numerous benefits in the treatment of chronic neuropathic pain. A sustained-release (tramadol SR) capsule formulation of tramadol gradually releases active drug, allowing for twice-daily dosing (122). Compared with tramadol SR tablets, tramadol SR capsules produced a smoother plasma concentration profile with more gradual absorption and lower peak concentrations (123). An extended-release tablet formulation of tramadol (tramadol ER) allows gradual release of the active drug, permitting once-daily administration (124). Three RCTs established once-daily tramadol analgesic efficacy to be superior to that of placebo for pain management and functional improvement in patients with osteoarthritis (125-127). Three RCTs demonstrated similar rates of efficacy between one daily tramadol and immediate-release (IR) or sustained-release (SR) formulations, with a better adverse events profile (128-130). In general, the long-acting forms of tramadol offer higher patient compliance then immediate-release forms with the same level of efficacy and with an excellent tolerability (131). They also provide prolonged, more consistent plasma concentrations of drug compared to short-acting agents, minimizing fluctuations that can

contribute to the end-of-dose breakthrough pain (132). In summary, numerous studies support tramadol efficacy in the treatment of neuropathic pain from various sources. Despite to its unique mechanisms, tramadol is an opioid and has the potential for complications associated with other opioid agents (120, 133, 134).

### *Tapentadol*

The mu-opioid agonist and norepinephrine reuptake inhibitor tapentadol extended release (ER) was effective in a randomized, double-blind, placebo-controlled study in 591 patients with diabetic peripheral neuropathic pain. Patients entered the 12-week double-blind period after titration to an optimal tapentadol ER dose (100-250 mg b.i.d.) during a 3-week open-label period, with only patients achieving an improvement of at least one point in pain intensity randomized (n = 391). Mean pain intensity on an 11-point scale was 7.3 at the beginning at the open-label period, signifying severe pain (135). Tapentadol ER is not available yet in the USA but the IR formulation was approved in 2008.

## 2.3. Topical agents

### *Capsaicin*

Capsaicin (8-methyl-N-vanillyl-noneamid), a natural component of chili peppers, is the TRPV1 (transient receptor potential vanilloid subfamily, member 1) agonist. The therapeutic potential of capsaicin presumably stems from the fact that the initial excitation of sensory neurons by capsaicin (or other TRPV1 agonists) is followed by a lasting refractory state (desensitization) during which the previously excited neuron is unresponsive to stimuli. Desensitization is a complex process, the mechanisms of which are not yet fully understood. (136).

For therapeutic purposes, capsaicin can either be compounded at high concentrations (>1%) and administered under local or regional anesthesia, or applied topically in lower concentrations for an extended period of time. Numerous studies have suggested a potential usefulness of topical capsaicin in managing painful diabetic neuropathy (137-142), stump pain (143, 144), postherpetic neuralgia (145-147), trigeminal neuralgia (148, 149), headaches (150-156),osteoarthritis (157, 158), postmastectomy pain syndrome (159, 160) or oral mucositis (161). The use of capsaicin via creams and/or patches has some obvious therapeutic limitations, however a new patch formulation has trigger renewed enthusiasm for its use (162). Indications and applications are likely restricted to those few conditions where the expected pain generators and targets are anatomically superficial and circumscribed and thus amenable to topical treatment based on patches and creams. Site-specific injectable capsaicin therapy such as the administration of capsaicin directly into the pain targets (e.g. intraarticularly, perineurally, within soft tissues) in combination with regional anesthesia techniques could possible offer wider indications and more consistent therapeutic effects for moderate to severe pain of both cancer and non-cancer origin. It is possible that injectable and topical TRPV1 agonist-based agents that provide long-lasting analgesia with rapid onset following a single administration may emerge as viable options in the future.

### *Lidocaine*

Lidocaine is a local anesthetic that decreases ectopic neural activity by blocking voltage-gated sodium channels (163, 164). Direct application of lidocaine has a distinct advantage over systemic therapy as it obstructs neurotransmission in or near the skin where the abnormal ectopic impulses are generated, thereby minimizing systemic drug exposure and associated adverse effects (165). The most frequent side effect of lidocaine is mild skin irritation at the site of application, which quickly resolves when the lidocaine is removed.

In a prospective, randomized, placebo-controlled trial (166), lidocaine patch 5% was shown to be effective in reducing severe pain (p=0.017) and allodynia (p=0.023) during the first 8 hours after application, and it continued to produce relief for up to 7 days (p=0.018) in several focal neuropathic syndromes (166). These results were echoed in a 3-week open label study (167) that allowed up to four lidocaine 5% patches daily for 18 hours in patients with PDN. After 3 weeks of treatment, two-thirds of patients demonstrated a reduction of at least 30% in their mean daily pain scores. Similarly, in a study comparing topical lidocaine to amitriptyline and placebo, lidocaine demonstrated a significant reduction in pain intensity (p=0.045) and an overall improvement in Short Form McGill Pain Questionnaire (SF-MPQ) total scores and sensory subscores (p=0.023 and p=0.022 respectively) (168). It has also shown promise in refractory PHN when used in conjunction with other pharmacological regimens (24, 169). However, a recent multicenter, double-blind, randomized cross-over trial (170) comparing the use of lidocaine patch to placebo patch in post-surgical cancer-related neuropathic pain failed to find any difference in pain relief (p = 0.36). However, patients on the lidocaine patch did have significant improvement in physical and psychosocial parameters compared to placebo (p<.05).

The efficacy of lidocaine to relieve PHN has also been demonstrated for gel application. However, the gel application did not show any benefit in patients with HIV neuropathy (171, 172). Because of it's relatively ease of use and safety profile, lidocaine gel should be considered when the patch is unavailable, application of the patch is problematic, or cost precludes it use.

In summary, topical lidocaine can be an effective treatment for neuropathic pain from a variety of causes. Side-effects are minimal and localized. However, its use is limited to pain derived from superficial, circumscribed sources.

## 2.4.Others

### *Cannabinoids*

Delta (9)-Tetrahydorcannabinol/Cannabidiol (THC/CBD) is an endocannabinoid system modulator which is derived from the cannabis plant (173). It acts by suppressing nociceptive transmissions through the activation of CB1 and CB2 receptor subtypes both in the periphery and in the central nervous system (174, 175). Its analgesic properties have been widely recognized in the treatment of pain syndromes arising from nerve damage (176). In a study looking at the efficacy of cannabis in 50 patients with painful HIV-associated sensory neuropathy, there was a 30% reduction in overall pain by 52% of the cannabis study group as compared to only a 24% reduction in the placebo group (p=0.04). There was also a marked reduction in chronic pain by a median of 72% versus 15% with placebo (p=<0.001) (177). These results are comparable to results seen with Sativex, an oromucosal spray which delivers

THC 2.7mg and CBD 2.5mg with each application (178). In a five week RCT examining 125 patients with neuropathic pain, the mean reduction in pain intensity scores were statistically significant with a greater than 30% improvement as compared to placebo. The side-effect profile was relatively well-tolerated and initial pain relief was maintained without dose escalation or toxicity for 52 weeks (179-180).

### *Bisphosphonates*

Bisphosphonates are a group of pyrophosphate analogues which binds to bone surfaces and inhibit osteoclast bone resorption and remodeling (181). This class of drugs includes nitrogen-containing bisphosphonates (zoledronic acid, pamidronate, ibandronate and alendronate) as well as the non-nitrogen-containing compounds (etidronate and clodronate).

The therapeutic role of bisphosphonates in osteoporosis, Paget's disease and other pathologic states with resultant hypercalcemia has been well established (182). They are currently recommended as the gold standard therapy for breast cancer with bone metastases (183). While not strictly a neuropathic injury, cancer-induced bone pain (CIBP) is a unique state with features of both neuropathy and inflammation. This is likely a result of osteoclast over-proliferation with consequent damage to peripheral nerves (peptidergic C fibres and SNS) and deafferentation, as well as neuronal hyperexcitability within the dorsal horn. By reducing these activities, bisphosphonates affect the nociceptive primary afferents in the bone thereby augmenting primary pain perception (184).

The analgesic efficacy of bisphosphonates, particularly pamidronate and alendronate, has been well documented (185). Furthermore, their use as an adjunct therapy in Complex Regional Pain Syndrome I (CRPS I) has shown promising results (186). In a double-blind, placebo-controlled study involving 40 patients, alendronate-treated patients (n = 19) exhibited a marked and sustained improvement in levels of spontaneous pain, pressure tolerance, and joint mobility as compared to placebo (187). Adverse effects, including hypocalcemia and gastrointestinal complaints such as nausea and vomiting and rarely nephrotoxicity, are dose-related.

### *Ketamine*

Ketamine is a phencyclidine analogue that non-competitively inhibits N-methyl-D-aspartic acid (NMDA) receptors in the spinal column (188, 189). It has demonstrated efficacy in reducing both allodynia and hyperalgesic states (190-193). Ketamine has a favorable efficiency-tolerance relationship with opioids and can play an important role in opioid-sparing therapy (194). In an open-label trial looking at ketamine efficacy in refractory complex regional pain syndrome (CRPS), there was significant improvement in all outcome criteria including pain relief, quality of life, and ability to work for up to 6 months (195). Similarly, in a study looking at the neurocognitive effects of anesthetic ketamine at levels of 250–300 μg/dl for at least 4.5 days, there was marked reduction in both acute and overall pain scores (196). These findings are consistent with other CRPS trials which showed favorable outcomes with subanesthetic infusions (197, 198). In addition, ketamine has shown promise as an alternative option in patients with refractory PHN, PDN, and phantom limb syndromes (199-201). However, long-term parenteral use can lead to psychomimetic reactions and painful induration at the site of infusion.

### *Botulinum toxin type a (BoNT/A)*

A recent pilot study on the effects of BoNT/A in PDN demonstrated significant pain relief in the treatment group during the 12-week trial period ($p<.05$). In this randomized double-blind crossover study, 44% of the patients who received real injections had improvement of pain score of >3 points, whereas there was no improvement in the placebo group (202). These results are in line with other open-label preliminary studies demonstrating BoNT/A's efficacy in treating trigeminal neuralgia and carpel tunnel syndrome (203, 204). Larger placebo-controlled trials for a wider variety of conditions will be needed to establish optimal dosing and ensure long-term efficacy before BoNT/A can be recommended as a first-line treatment for neuropathic pain.

### *Vitamin C*

A recent study (205) demonstrated that a high-dose intravenous ascorbate was effective in pain reduction as compared to placebo in patients with postherpetic neuralgia ($p<.001$), although there was no difference in reported allodynia. The authors also found previously that low plasma vitamin C was associated with increased pain in patients with postherpetic neuralgia verses controls. They attributed vitamin C's effect to anti-viral properties (205).

### *Selective cyclooxygenase inhibitor (Cox-2)*

A small-sample RTC trial (206) indicated that the Cox-2 inhibitor, GW406381, produced greater reduction in pain scores than placebo in PHN over the three week trial period, though the difference did not reach statistical significance. GW406381 was generally well tolerated, with the most common adverse events being headache, diarrhea, nausea, and dizziness (206). More data is needed to draw any conclusions about the utility of this agent in treating neuropathic pain.

## Conclusion

There are numerous controlled trials that investigate the efficacy of available agents for syndromes involving neuropathic pain. However, the trial protocols vary, and the findings often differ from study to study. The volume and diversity of existing evidence presents a challenge to clinicians attempting to ascertain the best treatment regimen. Also, many agents show promise, but require an additional research in larger trials before they can be integrated into the pool of standard treatment-strategies. Moreover, all available pharmacologic agents are limited in their efficacy, side-effect profile, or both. The search for new agents balancing the satisfactory pain relief and still acceptable side-effects continues to be of high priority and clinical significance.

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