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REVIEW OF DRUGS/PHARMACOTHERAPY Open Access

Evidence and clinical considerations for the use of serotonin and norepinephrine reuptake inhibitors for the treatment of painful neuropathy

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Abstract

Introduction: Peripheral neuropathy is a painful condition that can lead to a reduction in quality of life. The pain, which stems from damaged, hyperexcitable neurons, does not respond to traditional analgesics. However, due to the underlying mechanism of pain, some antidepressants are effective in managing peripheral neuropathy. The purpose of this review is to evaluate the available literature on serotonin-norepinephrine reuptake inhibitors for the management of peripheral neuropathy and outline clinical considerations for choosing an agent.

Methods: PubMed, Ovid/MEDLINE, and Scopus queries were conducted for relevant literature. Search types were limited to keyword searches and articles were limited to those published prior to March 31, 2015.

Results: There were 19 randomized controlled trials included in this review. No articles were found investigating the use of desvenlafaxine, milnacipran, or levomilnacipran for treatment of neuropathy. Both duloxetine and venlafaxine improved pain severity scores for patients suffering from painful peripheral neuropathy compared to placebo.

Discussion: Duloxetine and venlafaxine are able to decrease the severity of peripheral neuropathic pain. None of the trials found that either one of the therapies was able to completely eliminate pain for the patients, which should be an important counseling point for patients to understand. Additionally, patient-specific factors should be considered when choosing an agent, including comorbid disease states and potentially interacting medications.

Keywords: neuropathy, neuropathic pain, painful neuropathy, serotonin-norepinephrine reuptake inhibitor (SNRI), duloxetine, venlafaxine, desvenlafaxine, milnacipran, levomilnacipran

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Introduction

Peripheral neuropathy can be a debilitating condition for many patients. As a chronic disease state, the incidence of neuropathy is on the rise. More than 220 million patients worldwide are estimated to have diabetes with the development of neuropathy occurring in more than half of these patients, and up to 20% of the patients experiencing neuropathy have painful peripheral neuropathy.[1,2] However, diabetes is not the only inciting cause of peripheral neuropathy. Some other common causes of peripheral neuropathy include alcohol abuse, human

immunodeficiency virus, vitamin B12 deficiency, uremia, and hypothyroidism. In addition to various disease states, medications can also be the culprit. Medications known to cause peripheral neuropathy include amiodarone, bortezomib, carboplatin, cisplatin, dapsone, docetaxel, ethambutol, isoniazid, metronidazole, nitrofurantoin, paclitaxel, phenelzine, phenytoin, pyridoxine, tranylcypromine, and vincristine.[3]

The pathophysiology of neuropathy stems from 3 types of nerve fibers: large myelinated nerve fibers, small myelinated nerve fibers, and small unmyelinated nerve fibers. When large myelinated nerve fibers are affected, the neuropathy manifests as numbness, impaired light touch, decreased sensation of vibration, and loss of ankle reflexes. If small myelinated and unmyelinated nerve fibers are affected, pain and impaired pain sensation can result.[3] The mechanisms leading to damage of nerve fibers have not all been elucidated, but diabetic neuropathy is thought to develop from glycemic excursions leading to alterations in the sodium channels, causing peripheral sensitization and altering peripheral blood flow.[4] Dysfunction of the inhibitory endogenous pain routes could lead to central sensitization and hyperexcitability of the spinal and supraspinal areas in the pain pathway, resulting in painful neuropathy.[5] Both serotonin and norepinephrine play a role in endogenous inhibitory pain signals in the descending pain route. With a disparity in the concentrations of these neurotransmitters, hyperexcitability of the pain pathway may occur.[6]

Although neuropathy can be painful for many patients, typical pain regimens used for nociceptive pain (eg, nonsteroidal anti-inflammatory medications, opioids, etc) do not provide adequate relief.[7] Alternative agents, such as antidepressants and anticonvulsants, have been used to provide additional relief.[7,8] Anticonvulsants have been found to decrease neurotransmission in hyperexcited neurons in the ascending pain pathway, providing pain relief for patients.[4] Specific classes of antidepressants that have been associated with neuropathic pain respite include tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). These antidepressants provide alleviation of pain by increasing the availability of serotonin and norepinephrine in the descending pain pathway, resulting in inhibition of pain signaling.[4,8]

Although TCAs are a valid treatment option for patients experiencing painful neuropathy, use is limited by anticholinergic effects, toxicity risk with overdose, and risk with comorbid conditions (glaucoma and cardiovascular disease).[4] SNRIs may be better tolerated than TCAs and still provide adequate pain response in patients. The purpose of this review is to evaluate the existing literature for the efficacy and safety of SNRIs used to treat painful peripheral neuropathy.

Methods

This review was conducted by completing literature searches through PubMed, Ovid/MEDLINE, and Scopus queries. The search terms used in the various databases included "neuropathy," "neuropathic pain," "painful neuropathy," "serotonin-norepinephrine reuptake inhibitors," "SNRI," "duloxetine," "venlafaxine," "desvenlafaxine," "milnacipran," and "levomilnacipran." All searches were limited to adults, humans, and only articles written in the English language. The search was conducted for all trials published before March 31, 2015. The bibliographies of the trials selected were reviewed for additional references. Drug interactions and side effects were reviewed in primary literature, as were package inserts, to assist with recommendations for clinical decision making. The results of the selected trials are summarized below.

Results

The following articles were assessed for inclusion in the review and were deemed eligible after reviewing article titles and abstracts. In total, there were 19 randomized controlled trials. One systematic review and meta-analysis of milnacipran for neuropathic pain and fibromyalgia was excluded from this review as none of its studies included cohorts of patients with neuropathy. No articles were found for desvenlafaxine, milnacipran, or levomilnacipran being investigated for treatment of neuropathy.

Duloxetine

Three 12-week, parallel, double-blind, randomized, placebo-controlled trials of duloxetine were used to support the FDA-approved indication for diabetic painful neuropathy (DPN). Patients were included in these studies if they had moderately severe bilateral pedal DPN associated with Type 1 or Type 2 diabetes mellitus. Patients were excluded for any comorbid psychiatric illness, substance use disorder, serious or unstable illness, or chronic use of various medications (antidepressants, analgesics, anxiolytics, sedative hypnotics, steroids, topical analgesics, or anticonvulsants). The key outcomes of these studies are summarized in Table 1.[9-11] Although some studies showed dose-dependent improvement, there was also a dose-dependent increase in side effects. An additional 12-week study demonstrated benefit at 1 to 4 weeks of treatment but no difference from placebo at week 8.[12]

Four studies compared duloxetine to other treatment modalities for DPN (see Table 1 for a summary of

TABLE 1: Duloxetine for peripheral neuropathy

Study	Duration/Arms	Primary Outcome	Results
Raskin[9] DPN 2005	12 weeks Placebo Duloxetine 60 mg daily Duloxetine 60 mg BID	Change in 11-point VAS pain score	Duloxetine 60 mg daily > placebo Duloxetine 60 mg BID > placebo
Wernicke[10] DPN 2006	12 weeks Placebo Duloxetine 60 mg daily Duloxetine 60 mg BID	Change in 11-point VAS pain score	Duloxetine 60 mg daily > placebo Duloxetine 60 mg BID > placebo
Goldstein[11] DPN	12 weeks Placebo Duloxetine 20 mg daily Duloxetine 60 mg daily Duloxetine 60 mg BID	Change in 11-point VAS pain score	Dose-dependent improvement and discontinuation due to side effect
Gao[12] DPN 2010	12 weeks Duloxetine 60 to 120 mg Placebo	Brief pain inventory	Significant improvement at weeks 1, 2, and 4 Duloxetine = placebo at week 8
Kaur[13] DPN 2011	6 week crossover N = 58 Amitriptyline 10 to 50 mg Duloxetine 20 to 60 mg	Change in 100 mm VAS	No significant difference between groups
Boyle[14] DPN 2012	28 days Amitriptyline 50 to 75 mg Duloxetine 60 to 120 mg Pregabalin 300 to 600 mg	Pain Sleep Daytime functioning Quality of life	No significant differences between active treatments
Tesfaye[15] DPN 2013	Phase 1 (N = 804) 8 weeks Duloxetine 60 mg daily Pregabalin 300 mg daily Phase 2 (N = 343) 8 weeks Duloxetine 120 mg daily Duloxetine 60 mg + pregabalin 300 mg Pregabalin 600 mg daily	Brief pain inventory scores Nonresponders entered phase 2	Phase 1 duloxetine > pregabalin Phase 2 no significant differences between any groups Trend toward combination > high dose pregabalin > high dose duloxetine
Raskin[16] DPN 2006	52-week extension study Routine care (n = 76) Duloxetine 60 mg BID (n = 161)	Impact on health outcome measure questionnaires (SF-36 and EQ-5D)	No significant differences between groups
Wernicke[17] DPN 2007	52 week extension of Raskin[9] Routine care (n = 96) Duloxetine 120 mg (n = 197)	Impact on SF-36 and EQ-5D	Duloxetine > routine care on SF-36 subscales including bodily pain No significant difference on EQ-5D
Smith[18] CIPN	5 weeks, crossover Placebo Duloxetine 60 mg daily	Change in 11-point VAS pain score	Duloxetine > placebo Less robust effect than with DPN studies
Vranken[19] SCI/stroke pain 2011	8 weeks Placebo (n = 24) Duloxetine 60 to 120 mg (n = 24)	Change in 11-point VAS pain score	Duloxetine = placebo on VAS Duloxetine > placebo SF36 questionnaire pain item

CIPN = chemotherapy-induced peripheral neuropathy; DPN = diabetic painful neuropathy; SCI = spinal cord injury; VAS = visual analog scale.

outcomes).[13-16] In a crossover trial consisting of 6 weeks each of duloxetine or amitriptyline with a 2-week washout between arms, there were neither clinically or statistically significant differences in pain outcomes on the visual analog scale (VAS).[13] Boyle and colleagues compared amitriptyline, duloxetine, and pregabalin with an 8-day placebo run in, 2 weeks at low dose, and 2 weeks at high dose treatment.[14] There were no significant differences across outcomes of pain severity, daytime functioning, or quality of life. The low doses of pregabalin, duloxetine, and amitriptyline and the medium doses of duloxetine and amitriptyline were statistically significant ($P < .05$) compared to baseline placebo pain severity scores. Tesfaye et al compared duloxetine and pregabalin low-dose monotherapy (60 mg and 300 mg, respectively), then randomized non-responders to high dose monotherapy (120 mg and 600 mg, respectively) or combination therapy (60 and 300 mg). The combination therapy was not statistically significant compared to monotherapy ($P = .370$).[15] Finally, Raskin and colleagues completed a 52-week extension study, randomizing subjects from a 12-week duloxetine study to continue duloxetine or switch to routine care (including gabapentin in 58%, amitriptyline in 22%, and venlafaxine in 20% of patients).[16] There were no

significant differences between groups in the health outcome questionnaires. In an additional 52-week extension study by Wernicke et al comparing duloxetine against routine care, statistically significant benefits were shown for duloxetine on specific subscales of the SF-36, including improvement in physical functioning, bodily pain, mental health, and vitality ($P < .05$ for all except bodily pain $P < .01$).[17]

In assessing the potential for duloxetine to manage patients with chemotherapy-induced peripheral neuropathy, Smith et al conducted a randomized, double-blind, placebo-controlled, crossover trial. There were 220 patients who received duloxetine 30 mg daily for 1 week and then 60 mg daily for an additional 4 weeks. Patients were randomized in a 1:1 fashion; those in Group A received active treatment for weeks 1 to 5 and then placebo for weeks 8 to 12, and Group B received placebo first, followed by duloxetine. The majority of patients received either paclitaxel or oxaliplatin and had some form of gastrointestinal cancer. Patients receiving duloxetine for 5 weeks had a mean decrease in their average pain score of 1.06 (95% confidence interval [CI]: .72-1.40; $P = .003$). In the duloxetine group, 59% of patients reported a reduction in pain versus only 38% of patients on placebo. When addressing pain scores for different neurotoxic chemotherapy agents, duloxetine fared better for platinum-based agents but did not reduce pain significantly for taxane-based chemotherapy. However, this finding was not statistically significant (mean difference in pain scores for platinum versus taxane users: 1.06 versus .19; $P = .13$). The authors concluded that duloxetine was associated with significant improvement in pain related to neurotoxic chemotherapy.[18]

A small 8-week study comparing duloxetine to placebo for neuropathic pain associated with spinal cord injury or stroke found no significant difference between groups on VAS pain scores at end point. There was a significant benefit of duloxetine on the bodily pain item of the SF-36 health survey ($P = .035$ after adjusting for baseline differences).[19]

Venlafaxine

Venlafaxine has studies demonstrating efficacy in treating neuropathy due to a variety of causes (diabetes, polyneuropathy, postmastectomy pain syndrome, and chemotherapy-induced neuropathy).[20-26] The only published study that demonstrated no benefit was in experimentally induced pain in patients with neuropathy.[27] See Table 2 for a summary of these studies.

For venlafaxine therapy in patients with DPN, there are 3 clinical trials. One compared low-dose and high-dose venlafaxine to placebo; one compared venlafaxine 150 mg to B1/B6 vitamin-based placebo; and one compared venlafaxine, carbamazepine, and pregabalin. Venlafaxine ER 75 mg and 150 to 225 mg were compared to placebo in a randomized, double-blind, placebo-controlled trial with higher doses of venlafaxine titrated to full treatment doses by week 3 and for total study duration of 6 weeks. The primary objective of efficacy was measured through mean weekly pain scores according to the VAS-Pain Intensity. At the end of 6 weeks, the placebo arm had a 27% reduction in pain scores compared to 32% from venlafaxine 75 mg and 50% from the venlafaxine extended release 150 to 225 mg. The higher doses significantly improved pain scores compared to both the lower doses of venlafaxine and placebo ($P < .001$ and $P = .006$, respectively). The authors noted that, overall, the safety was similar between the venlafaxine arms and placebo.[20] Kadiroglu found similar results with venlafaxine 150 mg providing more benefit than a placebo arm of vitamin B1 and B6.[21] The final DPN study is one of few comparing different active treatments with different mechanisms (carbamazepine, pregabalin, and venlafaxine). Although pregabalin had a significantly higher response rate (> 50% reduction in VAS), the baseline score was approximately 8 points higher than other groups, which may have biased results in favor of a more robust drop in score.[22]

In a crossover study, venlafaxine 112.5 mg BID was found to have a similar effect on pain scores as imipramine 75 mg BID for polyneuropathy.[23] This is the only published study comparing venlafaxine to another antidepressant agent other than the duloxetine versus routine care, in which patients were not specifically randomized to venlafaxine.[16]

Venlafaxine has demonstrated efficacy in patients with chemotherapy-induced peripheral neuropathy with venlafaxine 50 mg 1 hour prior to an infusion of oxaliplatin, then venlafaxine extended release 37.5 mg twice daily from days 2 to 11, compared to placebo. There was a statistically significant difference between the venlafaxine and placebo arm ($P = .03$). Notably, venlafaxine also improved the functional status of patients compared to placebo ($P < .001$).[24]

Perioperative venlafaxine has also demonstrated benefit in preventing chronic neuropathic pain associated with mastectomy. In one study, venlafaxine was started the evening before mastectomy surgery and continued for 2 weeks after the surgery. Although there was no initial benefit of venlafaxine over placebo, at 6 months there were significantly better pain outcomes in the venlafaxine group.[25] A study comparing 10 days of gabapentin, venlafaxine, and placebo demonstrated similar results. The venlafaxine group did have lower pain scores

TABLE 2: Venlafaxine for peripheral neuropathy

Study	Duration/Arms	Primary Outcome	Results
Rowbatham[20] DPN 2004	6 weeks Placebo (n = 81) Venlafaxine ER 75 mg (n = 81) Venlafaxine ER 150 to 225 mg (n = 82)	Change in VAS pain scores	150 to 225 mg > 75 mg venlafaxine 150 to 225 mg > placebo Venlafaxine 75 mg no better than placebo No significant difference in opioid or NSAID use
Kadiroglu[21] DPN 2008	8 weeks Placebo (vitamin B1 and B6) (n = 30) Venlafaxine ER 150 mg daily (n = 30)	Change in pain questionnaire	Venlafaxine > vitamin B1/B6 placebo
Razazian[22] DPN 2014	35 days, 28 days full dose Carbamazepine 400 mg (n = 86) Pregabalin 150 mg (n = 86) Venlafaxine 150 mg (n = 85)	VAS pain score	All groups significant improvement over baseline Pregabalin > carbamazepine Pregabalin > venlafaxine Carbamazepine = venlafaxine
Sindrup[23] Polyneuropathy 2003	3-way crossover 4 weeks each arm (n = 30) Placebo Imipramine 75 BID Venlafaxine 112.5 mg BID	Change in 11-point VAS pain score	Imipramine = venlafaxine > placebo Better response with higher serum concentrations of venlafaxine
Durand[24] CIPN 2012	11 days Placebo (n = 24) Venlafaxine 37.5 mg BID (n = 24)	Percentage with 100% pain relief	Venlafaxine 37.5 mg BID (31%) > placebo (5%)
Reuben[25] Postmastectomy pain syndrome 2004	2 weeks perioperatively Venalfaxine 75 mg daily (n = 50) Placebo (n = 50)	Incidence of pain at 6 months	No significant difference at time of surgery or at 30 days Significant benefit at 6 months: - analgesic use 17% versus 55% - chronic pain 72% versus 39%
Amr[26] Postmastectomy pain syndrome 2010	10 days Placebo (n = 50) Gabapentin 300 mg (n = 50) Venlafaxine 37.5 mg (n = 50)	Change in VAS pain score	Short term venlafaxine = gabapentin > placebo Benefit at 6-month follow up: Venlafaxine > gabapentin = placebo
Yucel[27] Experimentally induced pain in patients with neuropathy 2005	8 weeks Placebo (n = 19) Venlafaxine XR 75 mg (n = 19) Venlafaxine XR 150 mg (n = 17)	Change in 11-point VAS pain score	No difference between groups Allowed to use up to 2 grams acetaminophen daily

CIPN = chemotherapy-induced peripheral neuropathy; DPN = diabetic painful neuropathy; ER = extended release; VAS = visual analog scale.

associated with movement at 6 months compared to gabapentin and placebo ($P < .0001$)[26]

Discussion

Peripheral neuropathy can be painful and debilitating for many patients. A review of the literature illustrates the specific role of SNRI therapy in treating painful peripheral neuropathy. It has been suggested that antidepressant therapy is beneficial in neuropathic pain due to pain suppression via monoaminergic links in diffuse noxious inhibitory control induced by inhibition of presynaptic reuptake of serotonin and norepinephrine.[28] An evidenced-based guideline by the American Academy of Neurology for the management of painful diabetic neuropathy gives a Level B recommendation for use of duloxetine and venlafaxine.[29] Both duloxetine and venlafaxine have been studied and have been shown to be beneficial and offer a preferred safety and tolerability profile compared to tricyclic antidepressants. However, there are currently no head-to-head trials to determine superiority of one agent over another.

Clinical Considerations

Patient-specific factors must be taken into consideration when using these agents, and it should be noted that the clinical trials had extensive exclusion criteria, especially for those with diabetes-related neuropathy. Due to the risk of hypertension with SNRIs, baseline blood pressure should be evaluated for all patients, and those with uncontrolled hypertension should avoid SNRIs until their blood pressure is better controlled. On the other hand, comorbid depression or anxiety disorders could be considered compelling indications to use SNRIs rather than other

agents (eg, anticonvulsants) as first line treatment for peripheral neuropathy, minimizing pill burden.

There are multiple pharmacokinetic considerations when choosing an SNRI. Duloxetine is contraindicated in hemodialysis, is not recommended in patients with significant renal impairment (creatinine clearance $<$ 30 mL/min), and may need a dose reduction with less severe renal impairment. As patients with DPN have already developed end organ damage, renal impairment should be monitored closely. Additionally, duloxetine is not recommended in patients with hepatic impairment. Venlafaxine, on the other hand, may be used with a 25% to 50% dose reduction for patients with a glomerular filtration rate of 10 to 70 mL/min and a 50% dose reduction for patients receiving hemodialysis or those with mild to moderate hepatic impairment.

Duloxetine is a delayed-release capsule. Venlafaxine is available as an immediate-release tablet, extended-release tablet, and an extended-release capsule. These dosage forms must be considered for patients who are unable to or have difficulty swallowing. The immediate-release venlafaxine tablets may be crushed without impacting absorption; however, crushing the extended-release products (either duloxetine or venlafaxine) would result in a more rapid peak in serum concentration. One study with duloxetine capsules demonstrated that mixing the capsule contents with pudding (but not apple sauce) damaged the enteric coating of the capsule pellets.[30]

Venlafaxine is a substrate of cytochrome (CYP) 2D6, which converts it primarily to the active metabolite desvenlafaxine. Venlafaxine is neither a potent inhibitor of 2D6 nor are its effects significantly altered by 2D6 inhibitors. Duloxetine is a substrate of CYP 1A2 and 2D6 and is also a potent inhibitor of 2D6. The inhibitory properties are important in patients with peripheral neuropathy when concomitant medications are considered. For example, 2D6 inhibitors may prevent the breakdown of tramadol and hydrocodone to their metabolites and may result in suboptimal analgesic effect when used with potent 2D6 inhibitors, such as duloxetine. Tramadol, a substrate of 2D6, has SNRI properties as the parent compound with more potent opioid activity as the metabolite. Inhibition of 2D6 has been shown to decrease the analgesic efficacy of tramadol as well as increase the serotonergic side effects, resulting in an increased risk of serotonin syndrome. Hydrocodone efficacy may also be diminished when used with 2D6 inhibitors as it is metabolized via 2D6 to a more potent metabolite. Tamoxifen is another important agent to consider as SNRIs have been studied for postmastectomy pain because tamoxifen requires CYP 2D6 for activation. Other 2D6 substrates to consider are beta-blockers (metoprolol, carvedilol, and propranolol) and antipsychotics (aripiprazole, fluphenazine, haloperidol, and iloperidone) as effects may be increased with duloxetine.

Although duloxetine and venlafaxine share the mechanism of SNRI, venlafaxine has additional mechanisms that may prove beneficial for the treatment of neuropathy. Venlafaxine also acts at both mu and sigma opioid receptors.[19]

Finally, cost of medication differs between the SNRIs with venlafaxine products typically being lower in price than duloxetine.

In summary, use of an SNRI for the treatment of painful neuropathy has sufficient evidence showing a decrease in pain severity with minimal adverse effects. Future studies investigating agents compared to one another as well as combination therapy compared to monotherapy are warranted to determine the most appropriate therapy to decrease pain severity and increase quality of life for patients suffering from painful peripheral neuropathy.

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