Is there a preference for venlafaxine over duloxetine in terms of treating chronic pain? Is 1 more effective than the other?
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Duloxetine (Cymbalta®) and venlafaxine (Effexor XR®) are both members of a class of drugs known as serotonin and norepinephrine reuptake inhibitors (SNRIs).[1,2] While the SNRIs are traditionally referred to as antidepressants, their use has been investigated for the treatment of pain.[3] The SNRIs are thought to enhance the inhibition of pain by blocking the reuptake of serotonin and norepinephrine. Duloxetine is approved by the Food and Drug Administration (FDA) to treat diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain, in addition to major depressive disorder (MDD) and generalized anxiety disorder (GAD).[1] In contrast, venlafaxine is not FDA-approved for the treatment of pain.[2] Venlafaxine is indicated for the treatment of MDD, GAD, social anxiety disorder, and panic disorder.

Several guidelines discuss the use of duloxetine and/or venlafaxine for treatment of various pain conditions, most commonly neuropathic pain.[4-12] SNRI-related recommendations are described in Table 1. Most of the guidelines that mention both duloxetine and venlafaxine do not assert that 1 agent should be used preferentially over the other. Of note, guidelines from the American Academy of Neurology (AAN), American College of Occupational and Environmental Medicine (ACOEM), American Pain Society (APS), National Opioid Use Guideline Group (NOUGG), and Veterans Affairs/Department of Defense (VA/DoD) are not included in Table 1 as there were no recommendations regarding SNRI use in these publications.[13-17]

Table 1. SNRI-related recommendations/statements from selected guidelines for chronic pain.[4-8]

Organization, year of publication	SNRI-related information
ACP 2017	• **Recommends duloxetine as a second-line pharmacologic treatment option for patients with chronic low back pain** (first-line options are NSAIDs). • States that duloxetine was associated with a small improvement in pain intensity and function compared to placebo, using data from 3 randomized controlled trials. • Duloxetine data: mean between group differences in 0-10 pain scale: range 0.58 to 0.74; for function, RDQ mean change from baseline: -2.69 vs. -2.22, p=0.26. • Also states that the risk for serious adverse events did not differ between duloxetine and placebo, but duloxetine was associated with nausea and an increased risk for treatment withdrawal due to adverse events. • **Does not mention venlafaxine.**
ASIPP 2017	• Discusses cost-effectiveness of duloxetine – refers to an analysis by Wielage et al, published in 2013, in which cost-effectiveness of various agents, including NSAIDs, duloxetine, and opioids were compared. They concluded that **duloxetine appeared to be a cost-effective post-first-line treatment option for chronic low back pain compared with all but generic NSAIDs**. • Also states that **SNRIs (agents not specified) have been recommended for neuropathic pain**.

Organization, year of publication	SNRI-related information
CDC 2016	• States that in patients with or without depression, TCAs and SNRIs provide effective analgesia for neuropathic pain, often at lower doses and with a shorter time of onset than for treatment of depression. Also states that patients with pain and depression are especially likely to benefit from antidepressant medication. • States that several guidelines (EFNS 2010, Canadian Pain Society 2007, AAN 2011) agree that first- and second-line drugs for neuropathic pain include anticonvulsants, TCAs, and SNRIs. • **States that duloxetine is FDA-approved for treatment of diabetic neuropathy and fibromyalgia. Does not specifically mention venlafaxine**.
ICSI 2016	• States that SNRIs may be useful for treatment of neuropathic pain. Antidepressants (TCAs, SNRIs, and SSRIs, to a lesser extent) may have a role in the treatment of pain, especially in patients with concomitant insomnia, anxiety, or depression. • **Lists duloxetine and venlafaxine as options for diabetic peripheral neuropathy, fibromyalgia, and neuropathic pain. Duloxetine also listed as an option for painful physical symptoms.**
WA State AMDG 2015	• Recommends consideration of TCAs, SNRIs, or anticonvulsants for neuropathic pain, other centralized pain syndromes, or fibromyalgia. • States that duloxetine has been shown to be effective in diabetic peripheral neuropathy, fibromyalgia, and chronic musculoskeletal pain. • Also states that a systematic review found no differences between venlafaxine and either gabapentin, pregabalin, or duloxetine on average pain scores or the likelihood of achieving significant pain relief.[18] • **Recommends duloxetine, specifically, as an option for fibromyalgia. Recommends either duloxetine or venlafaxine as options for 1) neuropathic pain conditions and 2) neuropathic pain conditions accompanied by depression or anxiety.** • Cautions serotonin syndrome, when SNRIs are used alone or in combination with other serotonergic agents, and leg movement disorders.

AAN=American Academy of Neurology; ACP=American College of Physicians; AMDG=Agency Medical Directors' Group; ASIPP=American Society of Interventional Pain Physicians; CDC=Centers for Disease Control and Prevention; EFNS=European Federation of Neurological Societies; FDA=Food and Drug Administration; ICSI=Institute for Clinical Systems Improvement; NSAIDs=non-steroidal anti-inflammatory drugs; RDQ=Roland Morris Disability Questionnaire; SNRI=serotonin and norepinephrine reuptake inhibitors; SSRIs=selective serotonin reuptake inhibitors; TCAs=tricyclic antidepressants; WA=Washington

Based on the recommendations regarding use of SNRIs for neuropathic pain identified in several of the guidelines in Table 1,[5-8] guidelines focusing on neuropathic pain were also reviewed (see Table 2).[9-12] The Canadian Pain Society[10] and European Federation of Neurological Societies (EFNS)[11] recommend both duloxetine and venlafaxine as first-line options for treatment of painful diabetic neuropathy (PDN), and the AAN suggests that either drug or amitriptyline be considered for PDN.[9] None of these organizations recommends preferential use of duloxetine or venlafaxine. However, in the United Kingdom guideline from the National Institute for Health and Care Excellence (NICE), clinicians are advised not to use venlafaxine unless consulting with a pain specialist.[12]

Table 2. SNRI-related recommendations from selected neuropathic pain guidelines.[9-12]

Organization, year of publication	SNRI-related information
AAN 2011	• **Recommends venlafaxine, duloxetine, and amitriptyline for treatment of PDN, stating that all 3 are probably effective for lessening the associated pain.** Further states that venlafaxine and duloxetine also improve quality of life in patients with PDN. • Also suggests that venlafaxine may be added to gabapentin for an improved response. • **States that data are insufficient to recommend 1 of these agents (venlafaxine, duloxetine, or amitriptyline) over the others.** Pregabalin recommended over these agents, based on level of evidence.
Canadian Pain Society 2014	• **Recommends duloxetine and venlafaxine as first-line options for treatment of neuropathic pain.** Other first-line options include TCAs and gabapentinoids. • States that both drugs have mainly been studied in PDN. Also mentions that duloxetine showed a significant reduction in pain intensity in patients with chemotherapy-induced peripheral neuropathy. Venlafaxine has shown efficacy in patients with mixed painful polyneuropathy. • Notes the safety concerns associated with these agents: ▪ Venlafaxine associated with nausea, dizziness, drowsiness, hyperhidrosis, and hypertension; dose adjustment required in renal failure. ▪ Duloxetine associated with sedation, nausea, constipation, ataxia, and dry mouth; contraindicated in patients with glaucoma.
EFNS 2010	• **Recommends duloxetine and venlafaxine as first-line options for PDN**. Other first-line options recommended include TCAs, gabapentin, and pregabalin.
NICE 2017	• Recommends duloxetine, gabapentin, pregabalin, or amitriptyline as initial treatment for neuropathic pain (except trigeminal neuralgia). • **Recommends not to start venlafaxine (as well as other agents) to treat neuropathic pain, unless advised by a specialist**.

AAN=American Academy of Neurology; EFNS=European Federation of Neurological Societies; GDG=Guideline Development Group; NICE=National Institute for Health and Care Excellence; PDN=painful diabetic neuropathy; SNRI=serotonin and norepinephrine reuptake inhibitors; TCAs=tricyclic antidepressants

From a search of the literature, few studies were identified comparing venlafaxine and duloxetine for treatment of pain. A clinical trial and 2 retrospective studies were identified;[19-21] notably, only 1 of these studies compared duloxetine specifically to venlafaxine.[20] In the others, comparisons were made between duloxetine and a group of other agents including venlafaxine.[19,21] Wang et al conducted a retrospective analysis evaluating adherence and persistence rates among patients with MDD and chronic pain using duloxetine, venlafaxine extended-release (XR), or escitalopram.[20] Data were derived from the MarketScan Commercial Claims and Encounters Database. The investigators identified adult patients, aged 18-64 years, who initiated 1 of the 3 study medications between July 1, 2006 and June 30, 2007, and followed the patients for 6 months. Adherence was assessed using medication possession ratio (MPR, ≥0.8), and persistence was measured using persistence rates (defined as proportions of patients who continuously refilled prescriptions during the 6-month period) and duration of therapy (defined as the number of days patients remained on the study medication before a prescription gap of >30 days).

In total, there were 15,523 patients included in the analysis, of which 6500 used duloxetine, 3405 used venlafaxine XR, and 5618 used escitalopram.[20] The majority of patients had low back pain (9301); other pain diagnoses included headache (n=6252), osteoarthritis (n=2966), fibromyalgia (n=2588), and diabetic neuropathy (n=399). Patients treated with duloxetine differed significantly from patients treated with venlafaxine XR in age (mean 47.97 vs. 46.02, p<0.0001), gender (male 21.57% vs. 23.37%, p=0.04), days' supply (36.12 days vs. 37.04 days, p=0.0352), number of prescription medications (mean 11.81 vs. 10.13, p<0.0001), and number of psychiatric conditions (mean 0.96 vs. 1.05, p=0.0002). Patients receiving duloxetine had a higher adherence rate (46.03%) compared to patients using venlafaxine XR (42.94%, p=0.0033) or escitalopram (37.27%, p<0.0001). Patients treated with duloxetine also had higher persistence rates (43.66%) compared to those treated with venlafaxine XR (40.38%, p=0.0017) or escitalopram (33.86%, p<0.0001). Those treated with duloxetine also had a longer duration of therapy (mean 117.82 days) than those treated with venlafaxine XR (mean 114.24 days, p=0.009) or escitalopram (mean 105.73 days, p<0.0001). Wang et al concluded that patients treated with duloxetine had higher adherence and persistence rates than patients treated with venlafaxine XR or escitalopram. Importantly, though the differences they reported were statistically significant, the clinical significance of their findings is questionable. Also, notably, this study was not designed to compare the efficacy or safety of these drugs.

In the clinical trial, Raskin et al evaluated adult patients with diabetic peripheral neuropathy who had completed a 13-week double-blind, placebo-controlled study of duloxetine and re-randomized these patients in a 2:1 ratio to receive duloxetine 60 mg twice daily or routine care for an additional 52 weeks, in an open-label manner.[19] Routine care was determined by providers and patients in the study and included gabapentin, amitriptyline, and venlafaxine. Outcomes evaluated were safety concerns, assessed using treatment-emergent adverse events (TEAEs) and patient-reported health outcomes, measured using the 36-item Short-Form Health Survey (SF-36) and Euro-Qol Questionnaire (EQ-5D). A total of 237 patients were included in this study; 161 received duloxetine and 65 received routine care. In the routine care group, the most commonly used medications were gabapentin (57.9% [n=44]) and branded amitriptyline (14.5% [n=11]); 7 (9.2%) patients received venlafaxine immediate-release and 9 (11.8%) received venlafaxine XR. A significantly higher proportion of patients in the routine care group experienced ≥1 serious adverse event (28.9% vs. 16.8%, p=0.039). Congestive heart failure was observed more frequently in the routine care group compared to the duloxetine group (5.3% vs. 0.6%). In terms of TEAEs, there were no significant differences between groups in overall incidence of these events (p=not reported). However, extremity pain (15.8% vs. 6.2%, p=0.029), peripheral edema (15.8% vs. 5.0%, p=0.010), balance disorder (5.3% vs. 0.6%, p=0.038), and erythema and localized infections (3.9% vs. 0.0%, p=0.032) were reported more frequently in the routine care group. The TEAE occurring most commonly in the duloxetine group was nausea (10.6%). Most TEAEs were mild or moderate. There were no statistically significant differences between groups in SF-36 or EQ-5D scores.

Raskin et al concluded that duloxetine was safe and well-tolerated compared to routine care options in the long-term management of patients with diabetic peripheral neuropathy.[19] However, because their control group included a number of other medications in addition to venlafaxine, the comparative effects between duloxetine and venlafaxine cannot be concluded.

Similarly, in the other retrospective study, investigators compared duloxetine to several agents, defined as "standard of care," comprising muscle relaxants, gabapentin, pregabalin, venlafaxine, and TCAs.[21] Andrews et al sought to characterize the use of these drugs in patients with chronic low back pain, using data from Surveillance Data, Inc Health (pharmacy and medical claims). Adults with chronic low back pain initiating duloxetine or standard of care between November 2010 and April 2011 were identified and matched using propensity scores, to select patients with similar baseline demographic and clinical

characteristics. Medication adherence was assessed using MPR and proportion of days covered (PDC) for 6 months following initiation. Opioid use was also compared between the cohorts.

A total of 6972 patients were identified, 766 of whom initiated duloxetine and 6206 initiated standard of care.[21] Among the 6206 patients, the majority initiated a muscle relaxant (61.8%); venlafaxine was initiated by 2.5% of patients. After matching, 743 patients from each group were included in the analyses. The number of venlafaxine users in the matched group was not specified. The duloxetine group was found to have higher adherence rates compared to the standard of care group, both by MPR (0.78 vs. 0.60, $p<0.001$) and PDC (0.50 vs. 0.31, $p<0.001$). The duloxetine group was also less likely to use opioids (45% vs. 61%, $p<0.001$) and used opioids for fewer days (median 0 vs. 7 days, $p<0.001$) compared to the standard of care group. Initiation of an opioid occurred later in the duloxetine group compared to the standard of care group (hazard ratio 0.77, 95% confidence interval [CI] 0.66 to 0.89). Andrews et al concluded that patients with chronic low back pain using duloxetine were more adherent and also less likely to use opioids compared to those using standard of care drugs. However, conclusions regarding comparative adherence and use of opioids between duloxetine and venlafaxine, specifically, cannot be drawn from this study, and the retrospective design precludes conclusions regarding a causal effect between medication initiation and use of opioids.

In addition to these studies, several systematic reviews and meta-analyses were identified evaluating the efficacy and safety of duloxetine and venlafaxine in patients with painful diabetic neuropathy[22-24] or neuropathic pain.[25,26] All clinical trials included in these articles were placebo-controlled or active-controlled involving other medications (i.e., there were no head-to-head trials comparing duloxetine and venlafaxine).[22-26] In the most recently published review,[22] Waldfogel et al identified studies evaluating treatment of diabetic peripheral neuropathy, published through May 24, 2016. They included a total of 106 randomized controlled trials which included anticonvulsants, TCAs, SNRIs, and opioids. The study durations ranged from 3 to 18 weeks (mean 10.5 weeks). Referring to findings from a meta-analysis by Griebeler et al,[23] Waldfogel et al stated that there were pain reductions with duloxetine (7 randomized trials [n=2203], standard mean difference [SMD] -1.33, credible interval [CrI] -1.82 to -0.86 calculated from the meta-analysis, and SMD -0.33, 95% CI -0.54 to -0.12 calculated from an additional trial) and pain reductions with venlafaxine (2 randomized trials [n=304], SMD -1.53, CRI -2.41 to -0.65).[22] Safety concerns were described by drug class; those reported for the SNRIs included dizziness, nausea, and somnolence. Study discontinuation rates due to adverse events were reported for the individual drugs: 4.3 to 19.3% for duloxetine, and 6 to 9.8% for venlafaxine – to compare, dropout rates ranged from 2.5 to 70% for all oral agents, including anticonvulsants, TCAs, and opioids. Waldfogel et al concluded that both agents were effective at reducing diabetic neuropathy pain with moderate strength of evidence. They also noted several limitations, including the lack of studies, lack of head-to-head trials, heterogeneity in reporting of outcomes, and short duration of most studies (<3 months).

In conclusion, venlafaxine and duloxetine are SNRIs that have been investigated for the treatment of chronic pain. At this time, only duloxetine is FDA-approved to treat pain – specifically, diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain.[1] Several guidelines discuss the use of duloxetine and/or venlafaxine for treatment of various pain conditions, most commonly neuropathic pain.[4-12] For chronic low back pain, the American College of Physicians only addresses use of duloxetine.[4] Most guidelines that mention both drugs do not explicitly state that 1 drug should be used preferentially, with the exception of NICE, which recommends use of venlafaxine only in consultation with a pain specialist.[12] From a literature search, no head-to-head trials were identified comparing duloxetine and venlafaxine. Among those reviewed, the most relevant comparison was in a retrospective analysis in which adherence rates and persistence rates were compared in patients with MDD and comorbid pain.[20] Though the investigators found statistically significant differences between groups

favoring duloxetine, the numeric differences were small and of questionable clinical significance; additionally, the data cannot be used to conclude comparative efficacy or safety of the drugs. Several meta-analyses and systematic reviews involving the 2 drugs have been published;[22-26] however, these suggest that the 2 drugs are effective in treating painful diabetic neuropathy, compared to placebo, and they are not without limitations.

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