Review Article

Efficacy of Venlafaxine in Neuropathic Pain: A Narrative Review of Optimized Treatment

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ABSTRACT

Purpose: The prevalence of neuropathic pain is high in the general population, and high priority is given to the management of this pain condition. The treatment of neuropathic pain remains challenging, despite the publication of national and international recommendations. The purpose of this narrative review of venlafaxine (VLX) is to provide a better knowledge of the pharmacology of this drug and a clearer view of its efficacy and tolerability in neuropathic pain.

Methods: Two independent reviewers searched PubMed with the following search terms: *serotonin* and *noradrenalin reuptake inhibitors* OR *VLX hydrochloride* AND *pain*. The reviewers included all clinical studies that investigated VLX in neuropathic pain conditions and excluded animal studies, studies on fibromyalgia, studies that focused on the prevention of neuropathic pain, case reports, and studies that did not clearly describe neuropathic pain in the included patients. We describe the 13 studies that we analyzed.

Findings: Eleven were randomized clinical trials, and the comparator was placebo in 8 studies. Nine studies reported that VLX was effective against neuropathic pain. However, among the trials, only one against placebo included a large number of patients with >200 participants and one against prégabaline and carbamazepine had >200 patients. Most of the adverse events reported in the selected studies were consistent with known adverse events of VLX, and most were mild to moderate. However, most studies were of very short duration.

Implications: Most of the clinical studies found that VLX was effective and well tolerated. However, given the limited number of study and the limitations of all these studies, further large clinical trials are needed. Currently, considering the limited therapeutic options for treating neuropathic pain and the highly variable nature of responses to all drugs, VLX has a place as a treatment option for neuropathic pain. (*Clin Ther.* 2017;39:1104–1122)

Key words: chronic pain, narrative review, neuropathic pain, SNRI, venlafaxine.

INTRODUCTION

The International Association for the Study of Pain defines neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system."[1] Its causes may be peripheral or central and include physical trauma, diabetes, postherpetic neuralgia, HIV-related neuropathy, spinal cord injury, and chemotherapy.[2] Patients experience diverse symptoms,

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including pain and altered sensations, that profoundly affect quality of life.[3] Estimates of the prevalence of neuropathic pain range from 6.9% to 10% in the general population.[4–6] The management of this condition is therefore considered of high priority. However, neuropathic pain is difficult to treat. Recommendations and guidelines have been developed for the optimization of treatment with the limited options currently available for this condition. Our poor understanding of the pathophysiologic processes underlying neuropathic pain and the limited usefulness of many of the pharmacologic agents currently available have made it difficult to develop effective treatment options for neuropathic pain.

This review focuses on the potential usefulness of venlafaxine (VLX) for treating neuropathic pain. This antidepressant has been widely used to treat pain, without support from pharmaceutical companies. A Cochrane review[7] based on double-blind studies concluded that VLX was not effective for the treatment of neuropathic pain. However, several studies were absent from this analysis,[8–14] and the negative conclusions of this meta-analysis are not consistent with current recommendations[15] that VLX should be considered a first-line treatment. We therefore decided to perform a narrative review on VLX, including all studies on the use of this drug for the treatment of neuropathic pain, because a better knowledge of the pharmacology of this drug and of the studies performed to date might provide a clearer view of its efficacy and tolerability in neuropathic pain.

PHARMACOLOGY OF VLX

Pharmacodynamic Properties of VLX

Antidepressants and other psychotropic drugs have long been used to treat various pain syndromes, including migraine, fibromyalgia, and neuropathy.[7,16–19] Many studies have found them to be useful for pain management, regardless of whether the patient has clinical symptoms of depression.[7,16–19] Tricyclic antidepressants (TCAs) have the longest track record and are probably the group of psychotropic drugs most consistently effective for treating pain conditions.[16–19] These drugs were thought to exert their effects by increasing serotonin availability and then modulating the pain response. However, whereas low doses of amitriptyline or imipramine are effective, selective serotonin reuptake inhibitors (SSRIs) have proved disappointing for the management of several pain disorders, suggesting the involvement of other neurotransmitters in the effects of amitriptyline and imipramine on pain.[20]

VLX is increasingly widely used as a drug with an efficacy and mechanism of action similar to those of TCAs but without the adverse effects of these drugs, such as anticholinergic effects and cardiac conduction abnormalities. By contrast to what has been reported for serotonin reuptake inhibitors, the serotonin-blocking effects of VLX are complemented by mild norepinephrine transporter inhibition. The clinically significant antidepressant effect on norepinephrine usually requires a dose of at least 150 mg/d of VLX. The possible rapid downregulation of β-adrenergic receptor–coupled cyclic adenosine monophosphate levels observed with serotonin norepinephrine reuptake inhibitors (SNRIs) may be responsible for the earlier onset of action than for SSRIs.[21]

The effect of VLX on neuropathic pain, like that of other antidepressants, is not yet fully understood. In animal models, VLX acts via both the noradrenergic and serotoninergic systems through increases in serotonin and norepinephrine levels, leading to the relief of neuropathic pain through an intensification of the inhibitory descending pathway.[22,23] The noradrenergic system seems to be the dominant system in this effect,[24] as confirmed by studies of selective noradrenalin reuptake inhibitors.[25,26] VLX also reduces spinal hyperexcitability through a blockade of central 5-HT_{1A} receptors.[27] The antinociceptive effects of VLX also seem to be mediated by the α_2-adrenoreceptor[28] and, within the dorsal root ganglia, by β_2-adrenoreceptors, through a decrease in tumor necrosis factor α production.[29]

Then, it is supposed that the inhibition of presynaptic reuptake of serotonin and noradrenaline plays a major role in pain suppression because TCAs with balanced reuptake inhibition tend to work better than noradrenergic TCAs and SNRIs are more efficacious than SSRIs. Mirtazapine, a noradrenergic and specific serotonergic antidepressant that acts by antagonizing the adrenergic α_2-autoreceptors and α_2-heteroreceptors as well as by blocking 5-HT_2 and 5-HT_3 receptors, may also present advantages in pain relief.[30–32] It can be deduced that the noradrenergic mechanism appears to be most important. However, the apparent better effect of TCAs than SNRIs

indicates that other mechanisms contribute to the effect of TCAs, and the blockade of *N*-methyl-D aspartate receptors and sodium channels are obvious candidate mechanisms. The mechanism of action of TCAs in neuropathic pain is probably multimodal with contribution of monoamine reuptake inhibition and blockade of *N*-methyl-D aspartate receptors and sodium channels. In accordance, a recent study on bupropion, which is a noradrenaline and dopamine uptake inhibitor, indicated a surprisingly high efficacy of this drug in peripheral neuropathic pain.[33]

Pharmacokinetic Properties of VLX

The primary route of first-pass metabolism involves the demethylation of VLX to O-desmethyl VLX (ODV). Cytochrome P450 2D6 (CYP2D6) is the principal enzyme involved in ODV formation.[34] However, ODV is detectable in the plasma of individuals with no CYP2D6 activity, suggesting the probable involvement of other cytochrome P450 enzymes in ODV production, to a minor extent at least.[35] In vitro experiments have implicated CYP2C19 in the formation of ODV in human liver microsomes.[36] ODV also has antidepressant activity, and it has been suggested that this metabolite is a more potent inhibitor of norepinephrine uptake than VLX itself.

The *N*-demethylation of VLX to *N*-desmethyl VLX (NDV) is generally a minor metabolic pathway, catalyzed by CYP3A4 and CYP2C19.[36] NDV may weakly inhibit the uptake of serotonin and norepinephrine.[37] ODV and NDV are further metabolized by CYP2C19, CYP2D6, and/or CYP3A4 to other minor metabolites with no known pharmacologic effect. Finally, approximately 1% to 10% of the administered dose is excreted into the urine in an unchanged state.[38] ODV is excreted both in an unmodified form and as a glucuronide.[38]

At least 92% of VLX is absorbed after the administration of single oral doses of the immediate-release form. Absolute bioavailability is 40% to 45% attributable to presystemic metabolism.[39] Plasma concentrations of VLX and ODV peak at 2 and 3 hours, respectively, after the administration of immediate-release VLX.[39] VLX and ODV have minimal binding to human plasma proteins at therapeutic concentrations (27% and 30%, respectively), and the mean (SD) V_d of VLX at steady state is 4.4 (1.6) L/kg.[39] The mean (SD) plasma $t_{½}$ of VLX and ODV are 5 (2) and 11 (2) hours, respectively. Steady-state concentrations of VLX and ODV are reached within 3 days of oral multiple-dose therapy. These concentrations follow linear kinetics over the dose range of 75 to 450 mg/d.[39]

A standard dose of VLX does not have the same, predictable effects in all patients. This is partly because of the high degree of interindividual variability in the pharmacokinetic properties of VLX, which is related to variability in drug metabolism.[40] However, the association between efficacy and the sum of plasma VLX plus ODV concentrations remains unclear.[41,42] A correlation between the early response and the sum of VLX plus ODV concentrations has been found, but the overall response and nonresponse rates at the end of the study suggested that the pharmacokinetic properties of VLX had no effect on long-term response.[42]

Several studies have investigated the effect of CYP2D6 variability on VLX concentrations and pharmacodynamic properties, but additional studies are required to evaluate the contribution of CYP2C19 to VLX metabolism.[43] CYP2C19 activity is variable in most populations, and this variability might be expected to affect VLX metabolism, particularly in individuals with low levels of CYP2D6 activity. Finally, VLX inhibits CYP2D6 only weakly and therefore has a low potential for involvement in pharmacokinetic drug interactions.

Literature Search Method

Two independent reviewers searched PubMed in July 2016 with the following search terms: *serotonin* and *noradrenalin reuptake inhibitors* OR *VLX hydrochloride* AND *pain*. They included all clinical studies of VLX for neuropathic pain conditions and excluded animal studies, studies on fibromyalgia, studies that aimed to prevent neuropathic pain, case reports, and studies that did not clearly describe neuropathic pain in the included patients. In total, 13 studies were included and analyzed. They are described in the Figure. Eleven of these studies were randomized clinical trials,[8,9,11–13,44–49] one was a case-control study,[14] and one was an open study.[10]

RESULTS

Type of neuropathic pain

Five studies included patients with diabetic neuropathy.[8,9,12,47,49] Three studies concerned patients with

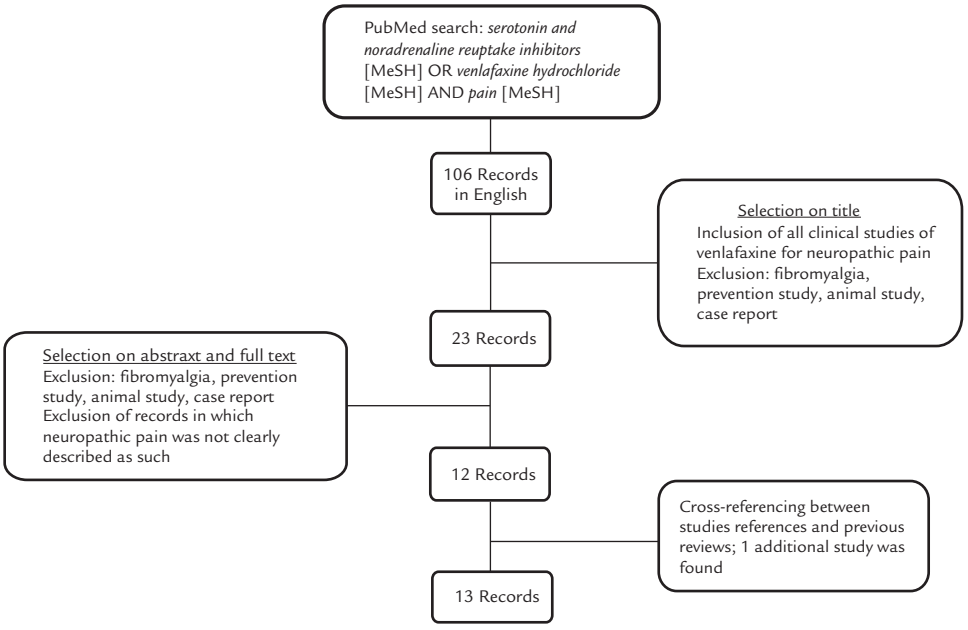

Figure. Flowchart of the literature search and study selection. MeSH = Medical Subject Heading.

peripheral neuropathy.[10,45,48] Two studies focused on patients with taxane- and oxaliplatin-induced neurotoxicity.[11,14] One study included patients with spinal cord injury.[13] One study focused on patients with atypical neuropathic facial pain.[46] One study concerned patients with neuropathic pain after the treatment of breast cancer.[44]

Design of the Studies

Ten studies were double-blind randomized clinical trials. The comparator was placebo in 8 of the studies investigating VLX. The other studies had gabapentin, pregabalin, carbamazepine, B_1 and B_6 vitamins, and imipramine as comparators. One of the studies included in the review was an open case-control study in which patients from the control group received no treatment for their neuropathic pain.[14] Study duration was 2 to 12 weeks, and the duration of follow-up was 6 months in the cohort study. Various doses, from 18.75 to 225 mg/d, were tested.

The main outcome was difference in pain intensity reduction, as assessed with a numerical rating scale (NRS) or a visual analog scale (VAS). Other outcomes considered included the proportion of patients presenting with 30%, 50%, 75%, or 100% pain relief.[11,13,14]

Studies Yielding Positive Results in Patients With Painful Diabetic Neuropathy

Painful diabetic neuropathy was the most frequently tested condition (Table I). In the randomized study by Razazian et al,[12] VLX was compared with carbamazepine and pregabalin. This study included a total of 257 patients and lasted 4 weeks. VLX was administered for 4 weeks at a dose of 75 mg/d during the first week and then at 150 mg/d. The mean VAS score for pain decreased significantly in the 3 groups from 74.5 to 46.6 of 100 mm in the VLX group, from 74.5 to 39.6 of 100 mm in the carbamazepine group, and from 82.3 to 33.4 of 100 mm in the pregabalin group. The degree of pain reduction was significant in all treatment groups, but pregabalin performed significantly better than VLX and carbamazepine, with no significant difference between these last 2 treatments.

Kadiroglu et al[9] randomized patients with painful diabetic neuropathy to 2 groups: one group of 30 patients receiving VLX and the other of 30 patients receiving vitamin B_1 and B_6. Patients received 75 mg/d of VLX during the first 2 weeks, subsequently increasing to 150 mg/d for patients with no decrease in pain severity. The patients were treated for 8 weeks. At the end of treatment, a significant decrease in pain severity was reported in the VLX group, for which the mean NRS score was 7.2 of 10 at baseline and 3.1 of

Table I. Description, design, results, and adverse events of the selected studies.

Study	Study Design	No. of Patients Receiving VLX or Other Treatment Arms (No. of Completers)	Comparator	VLX Dosage and Treatment Duration	Main Outcome and Main Results	AEs in the VLX Group
Razazian et al[12]	Double-blind RCT	VLX = 86 (69) Pregabalin = 86 (77) Carbamazepine = 85(78)	Pregabalin 150 mg/d Carbamazepine 400 mg/d	75 mg/d at week 1 then 150 mg/d for 4 weeks	Pain VAS: Significant reduction in all 3 treatment arms. Pain VAS reduction was significantly greater for pregabalin than for VLX and carbamazepine. (pain VAS score at baseline 74.5/100 for VLX and carbamazepine, 82.3/100 for pregabalin; pain VAS score on 35th day of 46.6/100 for VLX, 39.6/100 for carbamazepine, and 33.4/100 for pregabalin, $P = 0.0001$).	Mild to moderate AEs: somnolence, nausea, dizziness Discontinuation of treatment was significantly more common in the VLX group
Kadiroglu et al[9]	Nonblinded RCT	VLX = 30 (30) Vitamins = 30 (30)	Vitamin B_1 250-mg tablets and vitamin B_6 250-mg tablets	75 mg/d modified at week 2 to 150 mg/d (if ineffective) or 37.5 mg/d (if nausea) for 8 weeks	Pain NRS: Significantly larger decrease for VLX than for the comparator (pain score at baseline of 7.2/10 for VLX and 7.4/10 for control; pain score at week 8 of 3.1/10 for VLX and 5.5/10	No serious AEs Reported AEs: nausea

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Table I. (continued).

Study	Study Design	No. of Patients Receiving VLX or Other Treatment Arms (No. of Completers)	Comparator	VLX Dosage and Treatment Duration	Main Outcome and Main Results	AEs in the VLX Group
					for the control group ($P = 0.001$).	
Jia et al[49]	RCT double-blind	VLX = 66 (60) Carbamazepine = 66 (59)	Carbamazepine 0.1 g BID	25 mg BID for 2 weeks	Pain NRS: Significant decrease in both groups but larger for the VLX group (pain score at baseline of 6.7/10 for VLX and 6.7/10 for cabamazepine; pain score at day 14 of 2.2/10 for VLX and 3.6/10 for carbamazepine ($P < 0.05$ VLX vs carbamazepine).	Reported AEs: gastrointestinal discomfort, dizziness, and drowsiness Higher frequency of AEs in the VLX group
Rowbotham et al[47]	Double-blind RCT	VLX 75 mg = 82 (69) VLX 150/225 mg = 82 (64) Placebo = 81 (69)	Placebo	75 mg/d and 150–225 mg/d for 6 weeks	Pain VAS: VLX (150-225 mg) resulted in a significantly larger decrease in pain intensity than placebo, whereas the lower dose of VLX (75 mg) was not superior to placebo (reduction in mean pain intensity of 18.7/100 for placebo, 22.4/100 for 75 mg VLX, and 33.8/100 for 150–225 mg	Serious AEs: 9%–12% in all groups Reported AEs: nausea, dyspepsia, sweating, drowsiness, insomnia

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Table I. (continued).

Study	Study Design	No. of Patients Receiving VLX or Other Treatment Arms (No. of Completers)	Comparator	VLX Dosage and Treatment Duration	Main Outcome and Main Results	AEs in the VLX Group
					VLX ($P < 0.001$ for 150–225 mg VLX vs placebo).	
Simpson et al (part 2)[8]	Double-blind RCT on gabapentin plus VLX or gabapentin plus placebo	VLX = 6 Placebo = 5	Placebo	37.5 mg/d at week 1, 37.5 mg BID at week 2, 75 mg BID at weeks 3 to 8 for 8 weeks	Pain NRS: Two-point decrease after 8 weeks vs 0.5 points in the placebo group (difference in mean pain score, 2/10 for gabapentin plus VLX and 0.5/10 for gabapentin plus placebo).	AEs similar in the 2 groups Reported AEs: dizziness, drowsiness, headache, diarrhea, confusion, and nausea
Simpson et al (part 3)[8]	Prospective, open noncontrolled study	VLX = 42	None	37.5 mg/d at week 1, 37.5 mg BID at week 2, 75 mg BID at weeks 3 to 8 for 8 weeks	Pain NRS: Decrease of 2.1/10 after 8 weeks	Reported AEs: dizziness, drowsiness, headache, diarrhea, confusion, and nausea
Sindrup et al[45]	Double-blind, crossover RCT	VLX/imipramine = 40 (32)	Imipramine 25 mg BID in week 1, 50 mg BID in week 2, 75 mg BID in weeks 3 and 4 Placebo	37.5 mg BID at week 1, 75 mg BID at week 2, 112.5 mg BID at weeks 3 and 4 for 4 weeks for each treatment	Pain NRS: Significantly larger decrease for VLX and imipramine than for placebo (mean pain NRS score at baseline of 7/10, mean pain NRS score after week 4 of 6.3/10 after placebo, 5.3/10 after VLX, and 5/	Higher incidence of tiredness in the VLX group

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Table I. (continued).

Study	Study Design	No. of Patients Receiving VLX or Other Treatment Arms (No. of Completers)	Comparator	VLX Dosage and Treatment Duration	Main Outcome and Main Results	AEs in the VLX Group
					10 after imipramine (P = 0.0042 VLX vs placebo, P = 0.0004 imipramine vs placebo).	
Eardley et al[10]	Prospective, nonrandomized, open study	VLX monotherapy = 43 (33) VLX add-on = 45 (36) Gabapentin monotherapy = 52 (33) Gabapentin add-on = 64 (46) Control = 29 (29)	Gabapentin from 1200 to 2400 mg/d or none	From 75 to 300 mg/d for 6 months	Pain VAS: Significant decrease in both the VLX and gabapentin monotherapy group at 3 and 6 months (pain VAS score at baseline of 46/100 for VLX and 50.2/100 for gabapentin; pain VAS score at 3 months of 36.5/100 for VLX and 41.5/100 for gabapentin; pain VAS score at 6 months of 27.7/100 for VLX and 33.8/100 for gabapentin).	No serious AEs Reported AEs: sedation, dizziness/lightheadedness, and fatigue
Durand et al[11]	Double-blind RCT	VLX = 24 (20) Placebo = 24 (22)	Placebo	50 mg at day 1 before oxaliplatin, 37.5 mg BID for days 2 to 11, no VLX on days 12 to 13 for 3 months	Proportion of patients with 100% relief of neuropathy: Proportion significantly higher in the VLX armv (31.3% vs 5.3%, P = 0.03).	No serious AEs Reported AEs: nausea/vomiting, asthenia/somnolence

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Table I. (continued).

Study	Study Design	No. of Patients Receiving VLX or Other Treatment Arms (No. of Completers)	Comparator	VLX Dosage and Treatment Duration	Main Outcome and Main Results	AEs in the VLX Group
Kus et al[14]	Retrospective case-control	Case = VLX = 91 (84) Controls = 115 (not specified)	None	75 mg/d for 9 weeks	Rate of 75% symptomatic relief of acute neuropathy: Proportion of patients with 75% relief for pins and needles symptom significantly higher in the VLX group (rate of 45.2% vs 0%, $P > 0.001$).	No serious AEs Reported AEs: nausea/vomiting, asthenia/somnolence, dizziness and insomnia
Richards et al[13]	Double-blind RCT	VLX = 64 patients with 74 neuropathic pain sites (65 neuropathic pain sites completed) Placebo = 59 patients with 77 neuropathic pain sites (67 neuropathic pain sites completed)	Placebo	Starting at 37.5 mg/d, then 75 mg/d at week 1, 150 mg/d at week 3, 225 mg/d at week 6 for 12 weeks	Pain NRS: No difference in pain intensity between groups from baseline to 12 weeks (baseline mean pain NRS score of 6.6/10 for VLX and 6.5/10 for placebo; week 12 mean pain NRS score of 5.1/10 for both groups).	Serious AE: urinary tract infection, pressure ulcer, heart palpitations, suicide attempt in the VLX group
Yucel et al[48]	Double-blind RCT	VLX 75 mg = 20 (19)	Placebo	75 and 150 mg/d for 8 weeks	Pain VAS: Significant reduction in pain VAS	No serious AEs

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Table I. (continued).

Study	Study Design	No. of Patients Receiving VLX or Other Treatment Arms (No. of Completers)	Comparator	VLX Dosage and Treatment Duration	Main Outcome and Main Results	AEs in the VLX Group
		VLX 150 mg = 20 (17) Placebo = 20 (19)			scores in all treatment groups. No significant difference between groups (median pain VAS score at baseline of 8/10 for placebo, 7/10 for 75 mg VLX, and 8/10 for 150 mg of VLX; median pain VAS score at week 8 of 7/10 for placebo, 4/10 for 75 mg VLX, and 150 mg VLX).	Reported AEs: nausea/vomiting, dizziness, drowsiness Higher frequency of AEs in the VLX group (not significant)
Forssell et al[46]	Double-blind, crossover RCT	VLX/placebo = 30 (18)	Placebo	37.5 mg/d at weeks 1 and 2, 37.5 mg BID in weeks 3 and 4 for each treatment	Pain VAS: No significant difference in the decrease in pain intensity between VLX and placebo (pain VAS score at baseline of 42/100 before VLX and 45/100 before placebo, pain VAS score after week 4 of 34/100 after VLX and 47/100 after placebo ($P = .64$).	AEs: equally common for placebo and VLX, more severe sweating and dry mouth in symptoms in the VLX group
Tasmuth et al[44]	Double-blind, crossover RCT	VLX/placebo = 15 (13)	Placebo	18.75 mg/d at week 1, 18.75 mg BID at week	Pain VAS: No significant difference between VLX	No difference in the number or intensity of

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Table I. (continued).

Study	Study Design	No. of Patients Receiving VLX or Other Treatment Arms (No. of Completers)	Comparator	VLX Dosage and Treatment Duration	Main Outcome and Main Results	AEs in the VLX Group
				2, 18.75 mg morning and 37.5 mg evening at week 3, 37.5 mg BID in week 4 for 4 weeks for each treatment	and placebo (pain VAS at baseline of 49/100, pain score after week 4 after VLX of 0/100, and after placebo of 0.6/100).	AEs between treatments

AE = adverse event, NRS = Numerical Rating Scale, RCT = randomized clinical trial, VAS = visual analog scale, VLX = venlafaxine.

10 after 8 weeks of treatment. By contrast, the mean NRS score in the vitamin group was 7.4 at baseline and 5.1 at the end of the study.

Jia et al[49] compared VLX and carbamazepine in a randomized, double-blind trial that included 132 patients receiving 25 mg of VLX twice daily or 0.1 g of carbamazepine twice daily for 2 weeks. Mean pain intensity on the NRS at baseline was 6.79 of 10 for the VLX group and 6.72 of 10 for the carbamazepine group. A decrease in mean pain intensity was observed in both groups, but VLX was significantly superior to carbamazepine for pain relief, with a mean pain intensity at the end of the study of approximately 2.2 of 10 for VLX and 3.6 of 10 for carbamazepine group.

Rowbotham et al[47] performed a double-blind study comparing VLX and placebo. A total of 245 patients were randomized to receive placebo, 75 mg/d of VLX, or 150 to 225 mg/d of VLX for 6 weeks. Higher doses of VLX (150–225 mg) resulted in a significantly lower pain intensity than placebo, but the lower dose of VLX (75 mg) was not superior to placebo. The decrease in mean pain intensity at 6 weeks was 18.7 mm in the placebo group, 22.4 mm in the 75 mg of VLX group, and 33.8 mm in the 150 to 225 mg of VLX group.

Simpson[8] evaluated the efficacy and tolerability of VLX in a 3-part study on patients with painful diabetic neuropathy with no improvement while receiving gabapentin monotherapy. The second part of the study was a randomized, double-blind, controlled trial in which VLX was added to the maximum tolerated dose of gabapentin. Eleven patients were included, and the VLX dose was titrated up to 150 mg/d during the first 3 weeks and then maintained at this level for 5 weeks. The mean pain score decreased by 2 points on a 10-point NRS for the gabapentin group and by 0.5 points on the same scale in the gabapentin and placebo groups. The third part of the study was an open, uncontrolled trial in which 42 patients were given VLX in addition to the maximum tolerated dose of gabapentin. As in part 2, VLX dose was titrated up to 150 mg/d during a 3-week period and then maintained for 5 weeks. At the end of this 8-week trial, the mean pain score on the 10-point NRS had decreased by 2.1 points.

Studies Yielding Positive Results in Patients With Diverse Causes of Neuropathy

Sindrup et al[45] compared VLX with imipramine and placebo in a double-blind, crossover study.

Patients were included if they had a painful polyneuropathy of >6 months' duration. Forty patients were included, and each treatment sequence lasted 4 weeks, with a washout period of at least 1 week between treatments. Patients received VLX at a dose of 37.5 mg twice daily during first week, 75 mg twice daily during second week, and 112.5 mg twice daily during the third and fourth weeks. The dose of imipramine was 25 mg twice daily during the first week, 50 mg twice daily during the second week, and 75 mg daily for the last 2 weeks. The mean constant pain score at baseline was 7 of 10 on the NRS for pain. The mean constant pain score was 6.3 of 10 after 4 weeks of placebo, 5.3 of 10 after 4 weeks of VLX, and 5 of 10 after 4 weeks of imipramine. VLX and imipramine gave moderate pain relief that was significantly better than that achieved with placebo.

Eardley and Toth[10] conducted a prospective, nonrandomized, open study comparing VLX monotherapy or adjuvant therapy to gabapentin in patients with neuropathic pain attributable to polyneuropathy. Patients were assessed 1 week after treatment initiation and at 3 and 6 months. Ninety-five patients received VLX or gabapentin monotherapy, and 109 patients received VLX or gabapentin as adjuvant therapy. Mean VLX dose was approximately 220 mg/d at 3 and 6 months and was slightly higher in patients receiving VLX as monotherapy rather than adjuvant therapy. The decrease in the mean pain VAS score in the VLX group was 18.3 of 100 mm after 6 months in the monotherapy group and 19.7 of 100 mm after 6 months in patients receiving VLX as an adjuvant treatment.

Durand et al[11] compared VLX with placebo in acute oxaliplatin-induced neuropathy. Forty-eight patients presenting acute neurotoxicity after oxaliplatin chemotherapy received 50 mg of VLX (or placebo) on the day of oxaliplatin infusion, 37.5 mg twice daily from day 2 to day 11, no treatment on days 12 and 13, and then a new cycle of oxaliplatin treatment beginning on day 14, with 50 mg of VLX on the day of oxaliplatin administration. Treatment was continued until the end of chemotherapy. The study duration was 3 months. The proportion of patients experiencing 100% neurotoxicity relief was significantly higher in the VLX group (31.3%) than in the placebo group (5.3%).

In a retrospective case-control study, Kus et al[14] reported that VLX was effective against acute taxane- and oxaliplatin-induced neuropathy. In total, 206 patients with neuropathic pain were identified, 91 of whom were treated with 75 mg/d of VLX for mild depression. These patients were compared with the 115 patients without VLX treatment. Patients were assessed every 3 weeks for 9 weeks. The authors assessed 3 types of symptoms separately: burning, tingling, and stabbing; pins and needles; and pain triggered by cold. Each symptom was assessed on a numerical rating scale running from 0 to 10. For pins and needles (a symptom common to both taxane-induced and oxaliplatin-induced neuropathies), 45.2% of patients in the VLX group had 75% pain relief vs 0% in the control group.

Studies Yielding Negative Results

Four randomized, placebo-controlled studies reported that VLX was ineffective (**Table I**).[13,44,46,48] Richards et al[13] performed a study on 123 patients with spinal cord injury and major depression. Each patient could identify up to 3 separate pain sites, and each pain site was classified as nociceptive, neuropathic, or mixed. VLX treatment was initiated at a dose of 37.5 mg/d, with up-titration to 225 mg/d at week 6, if tolerated. Patients were treated for a 12-week period. VLX was found to be ineffective against pain in this study. Mean pain intensity at the sites of neuropathic pain was 6.6 of 10 in the VLX group and 6.5 in the placebo group at baseline and 5.1 of 10 in both groups at 12 weeks.

The study by Yucel et al[48] included 60 patients with neuropathic pain of various origins treated with 75 mg of VLX, 150 mg of VLX, or placebo daily for 8 weeks. Pain VAS score at baseline was 8 of 10 in the placebo group, 7 of 10 in the 75 mg/d of VLX group, and 8 of 10 in the 150 mg/d of VLX group. At the end of treatment period, pain VAS score was 7 of 10 in the placebo group and 4 of 10 in both VLX groups. Pain intensity decreased significantly in all 3 treatment arms, and the decrease was more pronounced in the 2 VLX arms than in the placebo arm, although this difference was not significant.

Forssell et al[46] included 30 patients with atypical facial pain in a 10-week crossover study that included a 2-week washout period. Patients received VLX at a dose of 37.5 mg/d during the first 2 weeks and then at a dose of 37.5 mg twice daily for the other 2 weeks or placebo for the entire 4-week period. Mean pain intensity on the VAS at baseline was 42 of 100 mm

in the group subsequently given VLX and 45 of 100 mm in the group subsequently given placebo. After 4 weeks, mean pain intensity on the VAS was 34 and 47 of 100, respectively. The difference between the 2 treatment periods was not significant. However, larger amounts of escape medication were taken during the placebo period. Moreover, patients rated pain relief, and their ratings were significantly higher during VLX treatment.

Finally, Tasmuth et al[44] compared VLX to placebo in 15 patients with neuropathic pain after breast cancer in a 10-week crossover study. Patients receiving VLX were treated as follows: tablets that contained 18.75 mg of VLX, 1 tablet at night during the first week, 2 tablets at night during the second week, 1 tablet in the morning and 2 at night during the third week, and 2 tablets morning and night during the fourth week. The washout period was 2 weeks long. The mean daily pain intensity, evaluated on a VAS (0–100 mm), was 49 of 100 at baseline and was significantly lower at the end of treatment in both treatment arms (0 of 100 after VLX and 0.6 of 100 after placebo). However, patients also reported pain levels in a computer program at baseline and at the end of each treatment period. The data obtained from this program indicate that maximum pain intensity was significantly lower on the maximum tolerated dose of VLX than placebo.

Tolerability of VLX in Patients With Neuropathic Pain

All studies reported adverse events. Most were consistent with the known adverse events associated with VLX, and most were mild to moderate. The adverse events associated with VLX have been described at length in multiple studies on psychiatric conditions.[50] The adverse events of VLX commonly observed are nausea, somnolence, dizziness, dry mouth, sweating, and headaches. In addition to these well-described events, Richards et al[13] reported several other serious adverse events in a population of patients with spinal cord injuries, including urinary tract infection, pressure ulcer, heart palpitations, and suicide attempt in the VLX group, but there was also a urinary tract infection and a suicide attempt in the placebo group. All the major adverse events reported in the selected studies are listed in Table I.

Rowbotham et al[47] reported a prevalence of serious adverse events of 10% in the placebo group, 9% in the 75 mg of VLX group, and 12% in the 150 mg of VLX group in their 6-week study. Razazian et al[12] (treatment duration of 4 weeks) reported a significantly higher rate of treatment discontinuation attributable to adverse events in the VLX group. Durand et al[11] (study duration of 3 months) also reported adverse events to be more frequent in the VLX group. According to Jia et al,[49]] during the 2 weeks of their study, the percentage of adverse events was higher in the VLX group than in the carbamazepine group, although this difference was not significant. Yucel et al[48] (treatment duration of 8 weeks) reported a higher frequency of adverse events in the 150 g/d of VLX group, with no significant difference in adverse event rates between the placebo and 75 mg/d of VLX groups. Sindrup et al[45] also reported a trend toward a higher rate of adverse effects in the VLX and imipramine groups than in the placebo group with treatment periods of 4 weeks for each treatment.

DISCUSSION AND CONCLUSION

We reviewed the studies published to date dealing with the issue of the efficacy of VLX against neuropathic pain. We observed that VLX treatment yielded positive results in most trials. This finding is consistent with current guidelines, recommendations, and literature for neuropathic pain, confirming the importance of VLX as a treatment option.[15,51–53]

VLX was recommended as a first-line treatment for neuropathic pain in the updated recommendations of the Neuropathic Pain Special Interest Group published in 2015 and in the 2014 recommendations of the Canadian Pain Society.[15,51] The other recommended first-line treatments for neuropathic pain are gabapentin, pregabalin, and TCAs.[15,51] The calculated combined number needed to treat for a 50% decrease in pain intensity reduction was 6.4 (range, 5.2–8.4) for the pooled results of trials on duloxetine and VLX. The VLX GRADE (Grading of Recommendations Assessment, Development and Evaluation) classification is, therefore, strong for doses of 150 to 225 mg/d.[15] In other recommendations, VLX is considered as a first- or second-line analgesic treatment.[52]

As mentioned in the Introduction section, a recent Cochrane review concluded that there was insufficient evidence to support the use of VLX for neuropathic pain.[7] However, this review included only double-

Table II. Main methodologic considerations for the 13 selected studies.

Study	Funding Source	Study Design	Analysis	No. of Patients Needed	Other Study Limitations
Razazian et al[12]	None mentioned	Double-blind RCT	Not specified (presumably per protocol)	Yes	1. Pain VAS score significantly greater in one of the treatment groups at baseline 2. Single-center study 3. Short follow-up (4 weeks)
Kadiroglu et al[9]	None mentioned	RCT not blinded	ITT (all included patients completed the study)	Not calculated	1. Small number of patients 2. Not blinded
Jia et al[49]	None mentioned	Double-blind RCT	Per protocol analysis for the primary outcome	Not calculated	1. Decrease in pain VAS score seemed to be large after only 2 weeks of treatment 2. Very short follow-up
Rowbotham et al[47]	Support by Wyeth Research	Double-blind RCT	ITT with LOCF	Yes	1. No clear mention of selection and allocation concealment 2. Short follow-up period
Simpson et al (part 2)[8]	None mentioned	Double-blind RCT of gabapentin plus VLX or gabapentin plus placebo	Not specified (presumably per protocol)	Not calculated	1. Very small number of patients
Simpson et al (part 3)[8]	None mentioned	Prospective, open, noncontrolled study	Not specified (presumably per protocol)	Not calculated	1. Open study
Sindrup et al[45]	Funded by Danish National Research Council and Research Foundation at Odense University Hospital; Wyeth Lederle and Nycomed provided study medication	Double-blind, crossover RCT	LOCF	Yes	1. Study stopped because too little treatment was supplied 2. Short follow-up period

(continued)

Table II. (continued).

Study	Funding Source	Study Design	Analysis	No. of Patients Needed	Other Study Limitations
Eardley et al[10]	None mentioned	Prospective, nonrandomized, open study	ITT with LOCF	Not calculated	1. Open study 2. Flexible dosing
Durand et al[11]	Funded by EUREKA: an academic research association receiving funds from Sanofi Aventis for this trial	Double-blind RCT	Per protocol	Targeted number not reached	1. Study stopped before reaching targeted number of included patients 2. Small number of patients
Kus et al[14]	None mentioned	Retrospective case-control	Per protocol	Not calculated	1. Retrospective study 2. Patients with neuropathy caused by various chemotherapies, hence various neuropathic symptoms
Richards et al[13]	Funded by Pfizer in the form of study drug	Double-blind RCT	Not specified (presumably per protocol)	Based on the primary outcome, depression, not on pain	1. Study and sample size powered for primary outcomes based on depression and not on pain reduction 2. Study based on up to 3 pain sites per patient and pain not only neuropathic 3. Flexible dosing plan
Yucel et al[48]	Funded by a grant from Wyeth; blinded drug preparations were supplied by Wyeth Pharmaceuticals	Double-blind RCT	Per protocol	Not calculated	1. Neuropathic pain of various origins with no stratification for cause 2. No clear mention of selection and allocation concealment 3. Small number of patients

(continued)

Table II. (continued).

Study	Funding Source	Study Design	Analysis	No. of Patients Needed	Other Study Limitations
Forssell et al[46]	Study financially funded by Helsinki University Central Hospital Research Fund; Wyeth Lederle provided the study medication	Double-blind, crossover RCT	Per protocol	Not calculated	1. Atypical facial pain without clear cause 2. Short follow-up period 3. Small number of patients completing study protocol
Tasmuth et al[44]	Funded by Helsinki University Central Hospital Research Funds	Double-blind, crossover RCT	Per protocol	Not calculated	1. Short follow-up 2. Small number of patients

ITT = intention to treat; LOCF = last observation carried forward; RCT = randomized clinical trial.

blind randomized clinical trials with a minimum of 10 patients per treatment arm and lasting for at least 2 weeks. All 6 studies included were considered to constitute third-tier evidence because all had a significant risk of bias. However, the conclusion of this Cochrane review goes against the latest Neuropathic Pain Special Interest Group recommendations published only a few months previously[15] and based on 4 of the studies selected for the Cochrane review.

All the studies presented methodologic limitations, regardless of the positive or negative nature of the results obtained. Even the largest study[47] did not provide a perfect description of its methods. The methods for random allocation sequence and allocation concealment or confirmation of the assessment of outcome blinding are not described. The study by Jia et al[49] mentions all the above risks of methodologic bias, but, unlike Rowbotham et al,[47] these authors did not describe the prior calculation of the number of participants needed, conferring a limited power on these studies. In the study by Richards et al,[13] pain relief was a secondary aim in a study of VLX for the treatment of major depressive disorder. The study had insufficient power to demonstrate a difference in pain outcome, potentially accounting for the negative results obtained. The other main methodologic considerations for the 13 selected studies are detailed in **Table II**.

In addition, most studies were performed with a low dose of VLX or during a short period. VLX may exert its effects earlier than other antidepressant agents when prescribed for major depressive disorder,[21] but a longer duration may be required for the correct assessment of its efficacy against neuropathic pain. In psychiatry settings, the correct duration for assessing antidepressant efficacy before switching to another treatment is considered to be 6 to 8 weeks. Only 4 studies on neuropathic pain involved VLX treatment >8 weeks, and only 2 of these studies were randomized clinical trials.[11,13] Given the characteristics of neuropathic pain and the limited treatment options available, we believe that studies should be performed in conditions in which the full pharmacodynamic effects of antidepressants against neuropathic pain can be assessed.

One of the physiologic hypotheses for VLX efficacy in neuropathic pain is based on action through the noradrenergic system. Because the noradrenergic system is involved only when VLX dose exceeds 150 mg,

VLX would be expected to be less effective at lower doses, calling into question the results of studies performed with doses of <150 mg/d.

Several principles should be respected, and caution is required when prescribing VLX. First, because VLX is a psychotropic agent with a risk of QTc prolongation, an ECG should be performed before its introduction and at steady state, although the risk of prolonged QT at the doses usually prescribed remains a matter of debate.[54,55] Second, VLX is a weak CYP2D6 inhibitor with a low potential for pharmacokinetic drug interactions, but these interactions should be taken into account when prescribing codeine, tramadol, and oxycodone, which are all substrates of CYP2D6, as active drugs.[56] A lack of efficacy of these drugs may be observed, and because tramadol is a parent drug that inhibits serotonin reuptake, it may increase the risk of serotoninergic syndrome when coprescribed with antidepressant.[57] Finally, if the pain relief achieved is considered inadequate, the treatment should be stopped gradually to prevent the withdrawal syndrome sometimes observed within hours of treatment cessation or a decrease in the usual dose.

In conclusion, most clinical studies found that VLX was effective against neuropathic pain and well tolerated. Given the limited therapeutic options for treating neuropathic pain and the considerable variability of responses to all drugs, VLX clearly has a place among the treatment options for neuropathic pain. VLX is no longer marketed by pharmaceutical companies, making it difficult to envisage any further large randomized clinical trials, but further studies should be encouraged to determine the right dose and to identify the patients most likely to respond to VLX for neuropathic pain.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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