mtDNA mutations are inherited by maternal transmission; we may therefore hypothesise that the mother either was affected or was an asymptomatic carrier. If the mother was not a carrier of the mutation, the authors should have determined whether the mutation detected in the patient was sporadic.

The high serum carnitine levels constitute another unusual finding.[1] Most patients with primary mitochondrial diseases display secondary carnitine deficiency in the blood, which explains why some patients benefit from L-carnitine supplementation.[4]

Patients with MELAS syndrome present not only muscle and brain alterations, but also endocrine, cardiac, and gastrointestinal manifestations. Therefore, the study by Pérez Torre et al. should have disclosed whether the patient presented short stature, hypothyroidism, hypoparathyroidism, diabetes, hypoaldosteronism, hypocortisolism, or hypogonadism. Patients with MELAS syndrome should also be screened for such heart conditions as arrhythmia or cardiomyopathy, which have diagnostic and therapeutic implications: the literature reports an increased risk of sudden cardiac death among patients with MELAS syndrome[5]; intractable heart failure requires heart transplantation.[6] There is also evidence that patients with mitochondrial diseases present greater risk of cardiac hypertrabeculation/left ventricular noncompaction cardiomyopathy,[7] which can be complicated by heart failure, ventricular arrhythmia, and cardiopulmonary failure.

In summary, the study would have been more informative if authors had gathered genetic data on the patient and his first-degree relatives and screened for mild or subclinical manifestations of multisystemic disease. Mitochondrial diseases are frequently associated with multisystem manifestations, which may present at disease onset or appear during the course of the disease.

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https://doi.org/10.1016/j.nrleng.2018.07.011
2173-5808/

Is there scientific evidence for the use of venlafaxine to treat neuropathic pain?☆

¿Existe evidencia científica para el empleo de venlafaxina en dolor neuropático?

Dear Editor:

Venlafaxine was the first serotonin—norepinephrine reuptake inhibitor (SNRI) to be marketed in Spain, in 1995. This antidepressant is indicated for the treatment of major depressive episodes, generalised anxiety disorder, social anxiety disorder, and panic disorder (with and without agoraphobia), as well as for preventing recurrence of major depressive episodes.[1] Although the summary of product characteristics does not list neuropathic pain among the drug's indications, venlafaxine is considered a first-line treatment in the latest clinical management guidelines.[2,3] After venlafaxine, other serotonin—norepinephrine reuptake inhibitors were authorised in Spain, including duloxetine, indicated for the treatment of painful diabetic peripheral neuropathy in adults, and desvenlafaxine, with no indication for neuropathic pain.

The antidepressant effects of venlafaxine result from increased neurotransmitter activity in the central nervous system.[4] Both venlafaxine and its active metabolite O-desmethylvenlafaxine are powerful serotonin-norepinephrine reuptake inhibitors and weak dopamine reuptake inhibitors. Neither drug has shown significant affinity for muscarinic, histamine, or $\alpha 1$ adrenergic receptors in vitro. Their action on these receptors is thought to be similar to the anticholinergic, sedative, and cardiovascular effects of other psychotropic drugs. Venlafaxine and O-desmethylvenlafaxine do not inhibit monoamine oxidase activity.[5]

Our literature review aimed to provide updated information on the use of venlafaxine for the treatment of neuropathic pain.

☆ Please cite this article as: Alcántara Montero A, González Curado A. ¿Existe evidencia científica para el empleo de venlafaxina en dolor neuropático? Neurología. 2020;35:522—530.

Development

We searched the PubMed, Medline, and Google Scholar databases in October 2017 using the following combinations of keywords: ''venlafaxine and pain,'' ''venlafaxine and neuropathic pain,'' ''venlafaxine and neuropathy,'' ''SNRI and neuropathic pain,'' ''SNRI and neuropathy,'' ''serotonin norepinephrine reuptake inhibitor and neuropathic pain,'' and ''serotonin norepinephrine reuptake inhibitor and neuropathy.''

The inclusion criteria were as follows: patients older than 18 years; neuropathic pain as the main indication for treatment with venlafaxine; venlafaxine in monotherapy; and studies and clinical trials (blinded and open-label randomised controlled trials and prospective, retrospective, and cross-sectional studies) published in English and reporting the effects of analgesic treatment with a scale and objectively analysing clinical response to venlafaxine. The exclusion criteria were as follows: review articles, case reports or case series, animal studies, studies published in any language other than English, studies using venlafaxine as a complementary treatment, and studies using venlafaxine for non-neuropathic pain or for conditions unrelated to pain.

We finally included 13 studies[6–18]: 11 randomised clinical trials (RCT),[6–13,15–17] a case-control study,[18] and an open-label study.[14] Table 1 summarises the main results of the studies included.

Discussion

Antidepressants are frequently used for the treatment of neuropathic pain,[19] for several reasons: the analgesic effects of these drugs are faster than their antidepressant effects; antidepressants have been found to be efficacious in clinical trials of patients with pain and no associated depression and in clinical studies with animal models of different types of pain; some antidepressants are particularly effective for neuropathic pain (serotonin and norepinephrine are involved in the modulation of descending pain pathways); and chronic pain and depression share certain biochemical and anatomical mechanisms.[20]

SNRIs have been shown to be useful for the treatment of neuropathic pain; their analgesic properties are thought to be explained by the inhibition of norepinephrine reuptake.[19] SNRIs bind to serotonin and norepinephrine transporters (SERT and NET) to inhibit presynaptic serotonin and norepinephrine reuptake, increasing the concentration of both neurotransmitters in the synaptic cleft and in postsynaptic neurotransmission. Serotonin and norepinephrine reuptake inhibition is sequential and dose-dependent, with inhibition of serotonin reuptake occurring first, followed by norepinephrine reuptake inhibition.[21] The dose needed to affect levels of these neurotransmitters in vitro depends on the drug's relative binding affinity and selectivity for the transporters.[22]

Affinity is defined as a drug's or a ligand's capacity to bind to its receptor. The lower a given receptor's binding affinity to human transporters (Ki), the stronger a drug's binding affinity to the receptor, indicating greater activity of said neurotransmitter. The efficacy of a ligand in inhibiting a molecular target is measured with the half maximal inhibitory concentration (IC_{50}), which is the concentration required to achieve 50% response. The molecular target of SNRIs is inhibition of SERT and NET. The selectivity of an antidepressant is the ratio of the relative potency values for each target (SERT and NET in this case).[23] The comparative affinities of SNRIs for SERT and NET are presented in Table 2. Venlafaxine presents 30 times greater affinity for reuptake inhibition of serotonin than for norepinephrine reuptake inhibition. A dose $\geq$ 150 mg/day is required for inhibiting norepinephrine uptake. Doses greater than 300 mg/day have been found to inhibit dopamine reuptake.[23]

The studies included in this review suggest that venlafaxine is effective for treating acute and chronic neuropathic pain. Richards et al.[17] analysed the reasons why venlafaxine is not as effective for treating neuropathic pain secondary to spinal cord injury as it is for neuropathic pain associated with other conditions. In their study, patients with spinal cord injuries displayed abnormal spontaneous neuronal activity in the dorsal horn above and below the level of injury, which may explain why this type of pain responds better to agents that interact with the alpha-2-delta subunits of voltage-gated calcium channels, such as gabapentin and pregabalin. Therefore, differences in the pathophysiology of the underlying pain may explain the possible inefficacy of venlafaxine. However, most studies into venlafaxine's efficacy for treating neuropathic pain focus on peripheral neuropathic pain syndromes, such as diabetic neuropathy.[17] In the other study reporting no improvement in pain with venlafaxine, Forssell et al.[9] gave several possible explanations for the drug's lack of efficacy for atypical facial pain. The authors suggested that the dose used (75 mg/day) may be too low, and that these patients may need higher doses (150-225 mg/day). They also suggested that heterogeneity in the diagnosis of atypical facial pain may have led to misdiagnosis, given the lack of unified diagnostic criteria for this type of pain.[9]

In any case, venlafaxine was not found to be superior to other drugs. This stands in contrast with the results of the study by Jia et al.,[12] who reported greater pain relief with venlafaxine than with carbamazepine. In the study by Razazian et al.,[16] venlafaxine was found to be inferior to pregabalin in relieving neuropathic pain in patients with diabetic neuropathy: not only was it less efficacious, but it also caused significantly more adverse effects than carbamazepine and pregabalin, which led to a significantly greater drop-out rate ($P = .01$).

Sindrup et al.[8] compared venlafaxine to imipramine in patients with diabetic neuropathy, observing no significant differences in efficacy between the 2 drugs. Although the number needed to treat was lower for imipramine (2.7 vs 5.2 for venlafaxine), the confidence interval was wide.

The studies in our review that compare venlafaxine against placebo demonstrate the analgesic potential of venlafaxine for neuropathic pain, and suggest that healthcare professionals involved in the management of neuropathic pain should consider the drug for treating these patients. However, venlafaxine has not been found to be superior to other agents.

A 2010 Cochrane review[24] on the use of antidepressants for neuropathic pain concluded that venlafaxine was efficacious for treating neuropathic pain with a number needed

Table 1 Summary of the studies on venlafaxine for the treatment of neuropathic pain included in the review.

Study	Design	Year	No. of patients receiving VLX/other treatments (no. of patients completing the study)	Control group	Diagnosis	VLX dose and treatment duration	Main outcomes	AEs in VLX group
Simpson[6] (part 2)	Double-blind RCT of gabapentin + VLX or gabapentin + placebo	2001	VLX: 6 Placebo: 5	Placebo	Diabetic neuropathy	37.5 mg/day in week 1; 37.5 mg bid in week 2; 75 mg bid in weeks 3 to 8	NPRS: 2-point decrease in VLX group vs 0.5-point decrease in placebo group after 8 weeks (mean change in pain score from baseline: 2/10 for gabapentin + VLX and 0.5/10 for gabapentin + placebo)	Similar in both groups Reported AEs: dizziness, somnolence, headache, diarrhoea, confusion, nausea
Simpson[6] (part 3)	Prospective, open-label, non-controlled trial	2001	VLX: 42	None	Diabetic neuropathy	37.5 mg/day in week 1; 37.5 mg bid in week 2; 75 mg bid in weeks 3 to 8	NPRS: decrease of 2.1/10 points after 8 weeks	Reported AEs: dizziness, somnolence, headache, diarrhoea, confusion, nausea
Tasmuth et al.[7]	Double-blind crossover RCT	2002	VLX/placebo: 15 (13)	Placebo	Neuropathic pain following treatment for breast cancer	18.75 mg/day in week 1; 18.75 mg bid in week 2; 18.75 mg in the morning and 37.5 mg in the evening in week 3, 37.5 mg bid in week 4 (same schedule for both VLX and placebo)	VAS: no significant differences between VLX and placebo (baseline: 49/100; at 4 weeks with VLX: 0/100; after treatment with placebo: 0.6/100)	No differences in number or intensity of AEs between treatment groups

Table 1 (*Continued*)

Study	Design	Year	No. of patients receiving VLX/other treatments (no. of patients completing the study)	Control group	Diagnosis	VLX dose and treatment duration	Main outcomes	AEs in VLX group
Sindrup et al.[8]	Double-blind crossover RCT	2003	VLX/imipramine: 40 (32)	Imipramine 25 mg/day in week 1; 50 mg bid in week 2; 75 mg bid in weeks 3 and 4 Placebo	Painful polyneuropathy (nearly half of patients had diabetic polyneuropathy)	37.5 mg bid in week 1; 75 mg bid in week 2; 112.5 mg bid in weeks 3 and 4 (same schedule for each treatment)	NPRS: significantly greater decreases in VLX and imipramine groups than in the placebo group (baseline: 7/10; mean score at 4 weeks: 6.3/10 for placebo, 5.3/10 for VLX, and 5/10 for imipramine [$P = .0042$ for VLX vs placebo; $P = .0004$ for imipramine vs placebo])	Higher incidence of tiredness in VLX group
Forssell et al.[9]	Double-blind crossover RCT	2004	VLX/placebo: 30 (18)	Placebo	Atypical facial pain	37.5 mg bid in weeks 1 and 2; 37.5 mg bid in weeks 3 and 4 (same schedule for both treatment groups)	VAS: no significant differences in pain relief between VLX and placebo (baseline: 42/100 before VLX and 45/100 before placebo; at 4 weeks: 34/100 for VLX and 47/100 for placebo) ($P = .64$)	Similar in both groups; sweating and dry mouth were more severe in VLX group
Rowbotham et al.[10]	Double-blind RCT	2004	VLX 75 mg: 82 (69) VLX 150—225 mg: 82 (64) Placebo: 81 (69)	Placebo	Diabetic neuropathy	75 mg/day and 150—225 mg/day for 6 weeks	VAS: VLX dosed at 150-225 mg achieved significantly greater pain relief than placebo, whereas VLX 75 mg was not superior to placebo (decrease in pain score: 18.7/100 for placebo, 22.4/100 for VLX 75 mg, and 33.8/100 for VLX 150-225 mg) ($P < .001$ for VLX 150—225 mg vs placebo)	Severe AEs: 9%-12% in all groups Reported AEs: nausea, dyspepsia, sweating, somnolence, insomnia

Table 1 (*Continued*)

Study	Design	Year	No. of patients receiving VLX/other treatments (no. of patients completing the study)	Control group	Diagnosis	VLX dose and treatment duration	Main outcomes	AEs in VLX group
Yucel et al.[11]	Double-blind RCT	2005	VLX 75 mg: 20 (19) VLX 150 mg: 20 (17) Placebo: 20 (19)	Placebo	Neuropathic pain (type not specified)	75 mg/day and 150 mg/day for 8 weeks	VAS: significant pain relief in all treatment groups. No significant differences between groups (baseline: 8/10 for placebo, 7/10 for VLX 75 mg, and 8/10 for VLX 150 mg; at 8 weeks: 7/10 for placebo and 4/10 for VLX 75 mg and VLX 150 mg)	No severe AEs Reported AEs: nausea/vomiting, dizziness, somnolence. Higher frequency of AEs in VLX group (non-significant differences)
Jia et at.[12]	Double-blind RCT	2006	VLX: 66 (60) Carbamazepine: 66 (59)	Carbamazepine 0.1 g bid	Diabetic neuropathy	25 mg bid for 2 weeks	NPRS: significant pain relief in both groups, but greater effect in VLX group (baseline: 6.7/10 for VLX and 6.7/10 for carbamazepine; at 14 days: 2.2/10 for VLX and 3.6/10 for carbamazepine; $P < .05$)	Reported AEs: gastrointestinal problems, dizziness, somnolence. Higher incidence of AEs in VLX group
Kadiroglu et al.[13]	Open-label RCT	2008	VLX: 30 (30) Vitamins: 30 (30)	Vitamin B_1 (250-mg tablets) and vitamin B_6 (250-mg tablets)	Diabetic neuropathy	75 mg/day for 8 weeks (in week 2, the dose was increased to 150 mg/day if ineffective or decreased to 37.5 mg/day if patients presented nausea)	NPRS: significantly greater pain relief in VLX group (baseline: 7.2/10 for VLX and 7.4/10 for vitamins; at 8 weeks: 3.1/10 for VLX and 5.5/10 in the control group; $P = .001$)	No severe AEs. Reported AEs: nausea

Table 1 (*Continued*)

Study	Design	Year	No. of patients receiving VLX/other treatments (no. of patients completing the study)	Control group	Diagnosis	VLX dose and treatment duration	Main outcomes	AEs in VLX group
Eardley et al.[14]	Prospective, open-label, non-randomised trial	2010	VLX in monotherapy: 43 (33) VLX as adjuvant therapy: 45 (36) Gabapentin in monotherapy: 52 (33) Gabapentin as adjuvant therapy: 64 (46) No treatment: 29 (29)	Gabapentin 1200-2400 mg/day or no treatment	Polyneuropathy	75-300 mg/day for 6 months	VAS: significant pain relief in the VLX and gabapentin monotherapy groups at 3 and 6 months (baseline: 46/100 for VLX and 50.2/100 for gabapentin; at 3 months: 36.5/100 for VLX and 41.5/100 for gabapentin; at 6 months: 27.7/100 for VLX and 33.8/100 for gabapentin)	No severe AEs. Reported AEs: sedation, dizziness/lightheadedness, fatigue
Durand et al.[15]	Double-blind RCT	2012	VLX: 24 (20) Placebo: 24 (22)	Placebo	Oxaliplatin-induced acute neurotoxicity	50 mg the day before oxaliplatin infusion, 37.5 mg bid on days 2 to 11, and no VLX on days 12 and 13, for 3 months	The VLX group showed a significantly greater percentage of patients achieving 100% relief of neuropathy (31.3% vs 5.3% in the placebo group; $P = .03$).	No severe AEs. Reported AEs: nausea/vomiting, asthaenia/somnolence

Table 1 (*Continued*)

Study	Design	Year	No. of patients receiving VLX/other treatments (no. of patients completing the study)	Control group	Diagnosis	VLX dose and treatment duration	Main outcomes	AEs in VLX group
Razazian et al.[16]	Double-blind RCT	2014	VLX: 86 (69) Pregabalin: 86 (77) Carbamazepine: 85 (78)	Pregabalin 150 mg/day Carbamazepine 400 mg/day	Diabetic neuropathy	75 mg/day in week 1 followed by 150 mg/day for 4 weeks	VAS: significant pain relief in all 3 treatment arms. Pregabalin achieved significantly greater pain relief than did VLX and carbamazepine (baseline: 74.5/100 for VLX and carbamazepine, 82.3/100 for pregabalin; at day 35: 46.6/100 for VLX, 39.6/100 for carbamazepine, and 33.4/100 for pregabalin; $P = .0001$)	Mild and moderate AEs: somnolence, nausea, dizziness. Treatment discontinuation was significantly more frequent in the VLX group.
Richards et al.[17]	Double-blind RCT	2015	VLX: 64 Placebo: 59	Placebo	Spinal cord injury	Starting dose of 37.5 mg/day, increasing to 75 mg/day in week 1, 150 mg/day in week 3, and 225 mg/day in week 6; treatment lasted 12 weeks	NPRS: no differences in pain relief between groups (baseline: 6.6/10 for VLX and 6.5/10 for placebo; at week 12: 5.1/10 for both groups)	Severe AEs: urinary tract infections, pressure ulcers, palpitations, and attempted suicide in the VLX group
Kus et al.[18]	Retrospective case-control study	2016	Cases (VLX): 91 (84) Controls: 115 (not specified)	None	Oxaliplatin- and taxane-induced acute neuropathy	75 mg/day for 9 weeks	The percentage of patients achieving a 75% relief of pins-and-needles sensation was significantly greater in the VLX group (45.2% vs 0% in controls; $P < .001$).	No severe AEs Reported AEs: nausea/vomiting, asthaenia/somnolence, dizziness, and insomnia

AE: adverse event; bid: twice daily; NPRS: Numeric Pain Rating Scale; RCT: randomised clinical trial; VAS: visual analogue scale; VLX: venlafaxine.

Table 2 Binding affinity of serotonin-norepinephrine reuptake inhibitors[a].

		Venlafaxine	Duloxetine	Desvenlafaxine
Affinity (Ki; nmol/L)	SERTNET	7.8 (0.28)1920 (158)	0.07 (0.01)1.17 (0.11)	40.2 (1.6) 558.4 (121.6)
Reuptake inhibition (IC_{50})	SERTNET	145 (18) 1420 (240)	3.7 (1.1) 20 (6)	47.3 (19.4)531.3 (113.0)
Approximate 5-HT/NE selectivity ratio[b]		30:1	10:1	14:1

5-HT: serotonin; IC_{50}: half maximal inhibitory concentration; NE: norepinephrine; NET: norepinephrine transporter; SERT: serotonin transporter.
[a] Values are based on in vitro studies of human monoamine transporters.
[b] 5-HT/NE selectivity ratio: based on ratio of IC_{50} values.
Adapted from Raouf et al.[23]

to treat of 3.1 for at least moderate pain relief. The number needed to harm for major adverse events (events leading to patient drop-outs) was 16.2.

A more recent Cochrane review on the use of venlafaxine for neuropathic pain in adults, including only 6 double-blind RCTs, concluded that there is little evidence on the efficacy of venlafaxine for neuropathic pain and that some studies had a considerable risk of bias.[25] Our review included a further 5 RCTs. Two of these concluded after the Cochrane review was published,[16,17] and another was an open-label trial[13] (the Cochrane review only included blinded RCTs).

The studies included in our review present several limitations. First, some studies include relatively small samples. Second, selection criteria varied between studies: although all the patients included had neuropathic pain, the differences in the type of neuropathic pain may have had an impact on results. The studies included also followed different research methodologies and used different pain assessment scales. They also used different doses of the drug, which may have had an impact on results; therefore, no conclusive evidence can be drawn from these results. Furthermore, treatment and follow-up times also varied between studies. Lastly, the available evidence on the topic is relatively limited, with only 13 studies and few empirical data.

In conclusion, while venlafaxine is not currently indicated for neuropathic pain, it has been found to be safe and well tolerated as a symptomatic treatment in these patients. The available evidence supports the efficacy of the drug (especially at doses of at least 150 mg/day), although further research is needed, particularly comparing the drug against other pharmacological agents.

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https://doi.org/10.1016/j.nrleng.2018.07.009
2173-5808/

Mild encephalopathy/encephalitis with a reversible splenial lesion associated with acute pyelonephritis: A case report*

Encefalitis/encefalopatía leve con lesión reversible del esplenio del cuerpo calloso asociada a pielonefritis aguda; a propósito de un caso clínico

Dear Editor,

MERS (mild encephalopathy/encephalitis with a reversible splenial lesion) is a reversible clinical—radiological syndrome associated with neurological signs and symptoms and restricted diffusion in the splenium on magnetic resonance imaging (MRI) studies. The precise pathophysiology remains unknown but the condition is mainly associated with infections.

We present the case of a 16-year-old girl with no relevant history who was assessed due to prostration and paraesthesia affecting the lower third of the right leg, progressing for 2 h.

The previous day she had been attended due to 24-h history of fever and dysuria, which was treated with antibiotics (oral cefuroxime). Physical examination revealed that the patient was oriented but unable to leave bed and showed psychomotor retardation (Glasgow Coma Scale [GCS] score of 14), with normal cranial nerve findings and no motor or sensory deficits in the upper limbs; we also observed monoparesis (grade 4+) and painful tactile hypoaesthesia in the distal part of the right leg. Deep tendon reflexes were normal and symmetrical and plantar reflexes were flexor. Cerebellar examination yielded normal results, and we observed no meningeal signs. A blood count revealed leukocytosis (20 080 cells/μL) with neutrophilia (17 630 cells/μL), normal biochemistry and electrolyte study findings (sodium 135 mmol/L), and increased inflammatory parameters (erythrocyte sedimentation rate 40 mm/h; C-reactive protein 24.66 mg/dL). Urine culture revealed growth of *Escherichia coli*. A lumbar puncture revealed clear, colourless cerebrospinal fluid with normal pressure, 6 leukocytes/μL (17% polymorphonuclear and 83% mononuclear), and normal biochemistry results; bacteriological, mycological, and mycobacteriological cultures, virus molecular biology (enterovirus, varicella zoster virus, and herpes simplex virus 1 and 2), and *Mycoplasma* culture yielded negative results. The polymerase chain reaction test for *E. coli* was not performed. Renal ultrasonography revealed an enlarged, globular left kidney, parenchymal hyperechogenicity, and perirenal fluid; these signs are suggestive of pyelonephritis. A head CT scan revealed no alterations. We started empirical treatment with intravenous ceftriaxone and aciclovir. A spinal and brain MRI scan (Fig. 1A—E) performed on the third day after admission showed an ovoid tumefactive lesion in the centre of the splenium, showing diffusion restriction. At that time, we observed complete

* Please cite this article as: Miranda J, Pereira I, Nunes J, Santos F. Encefalitis/encefalopatía leve con lesión reversible del esplenio del cuerpo calloso asociada a pielonefritis aguda; a propósito de un caso clínico. Neurología. 2020;35:530—534.