

Rowbotham MC, Goli V et al. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. Pain 2004;110:697-706.

Design: Randomized clinical trial

Population/sample size/setting:

- 244 patients (145 men, 99 women, mean age 59) treated for painful diabetic neuropathy at 12 centers in the United States
- Eligibility based upon at least 3 months of bilateral distal neuropathic pain at least 40 on a scale from 0-100, with metabolically stable type 1 or 2 DM
- Exclusion based on clinically significant psychiatric disorders or recent drug/alcohol abuse, medical comorbidity (heart, renal, hepatic), abnormal EKG or lab tests, or use of antidepressants, anxiolytic, sedative-hypnotic, or anticonvulsant drugs; analgesic drugs were permitted only if the patient was able to reduce their use to 1 dose per day at the start of the study (tramadol was not permitted, but opioids were allowed during the study)
- Exclusion was also based on Beck Depression Inventory scores of 13 or greater and a score of 9 or greater on the Raskin Depression Scale (representing moderate depression)

Main outcome measures:

- Randomized to placebo (n=81), low dose venlafaxine extended release (75 mg/d, n=81) or high dose venlafaxine XR (150-225 mg/d, n=82)
- In order to maintain blinding, a 2-bottle system was used, with capsules containing placebo, 37.5, 75 mg, 150 mg, or 225 mg venlafaxine, with dose titration occurring during the first 3 weeks of the double-blind phase; from week 4 to week 6, patients took 3 capsules per day of the targeted dose of the drug, based on individual tolerance
- Drug dose was tapered over a 2 week period following the 6th week of the double-blind study
- Primary outcome was reduction in mean weekly pain scores calculated from daily diary ratings between the baseline value and week 6
- Several secondary outcomes were also measured, both the clinicians' and patient global impressions of change, body weight, EKG, and laboratory determinations
- For the primary outcome, high-dose venlafaxine was more effective than low-dose venlafaxine and placebo; low-dose venlafaxine was not more effective than placebo
- Reduction in mean pain intensity from baseline to week 6 was 50% for high-dose venlafaxine, 32% for low-dose venlafaxine, and 27% for placebo
- For a 50% reduction in pain scores, high-dose venlafaxine was successful in 56% of patients, vs. 34% for placebo
- Clinicians' and patients global assessments of change were also in favor of high-dose venlafaxine

- Treatment-emergent adverse effects were reported by 75% of placebo patients, 88% of low-dose venlafaxine patients, and by 89% in the high-dose venlafaxine group; these were not significantly different
- The most common adverse events were mild to moderate: nausea, dyspepsia, sweating, somnolence, and insomnia
- Attrition was similar in the 3 groups: 15% for placebo, 15% for low-dose venlafaxine, and 22% for high-dose venlafaxine
- EKG changes occurred more often with venlafaxine than placebo: the medical monitor determined that 7 patients (4 on low-dose and 3 on high dose venlafaxine) had clinically important changes, and 3 patients were withdrawn from the study
- The high-dose venlafaxine group had an increase in the mean QRS interval, but no group had significant increase in the QT interval
- The low-dose venlafaxine group had postural decreases in systolic BP more often (20%) than the high-dose group (12%) or the placebo group (13%)

Authors' conclusions:

- Venlafaxine ER at doses of 150-225 mg effectively relieve diabetic neuropathic pain
- Lower doses of venlafaxine exert serotonergic effects, while the higher doses also have noradrenergic effects
- The 6 weeks of study in this trial do not necessarily predict whether the effect of venlafaxine will persist for longer periods, but this is a proof-of-concept study showing its efficacy and tolerability
- The fact that patients with depression were excluded from the study suggests that the changes in pain score are due to an analgesic effect of venlafaxine and not due to an antidepressant effect

Comments:

- Although the randomization is described as occurring in blocks of size 6, the method (if any) of concealment of allocation is not clearly described
- Two measures of pain response were used, both based on a visual analog scale (VAS); one is for pain intensity and one for pain relief; there is some redundancy between them, and it is expected that their correlation should be equal to -1; the need for the two scales is not clear
- The patients were metabolically stable at entry; but the meaning of this (and the laboratory measurements) are not clear; presumably, some peak level of HbA1c was an entry criterion, but this is not specified
- Efforts at blinding were done, but the success of blinding is not described
- A six week trial period, as the authors acknowledge, is long enough for proof-of-concept, but longer term effectiveness is not known

Assessment: Adequate for evidence that 150—225 mg of venlafaxine reduce neuropathic pain