

Goldstein DJ, Lu Y, et al. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain 2005;116:109-118.

Design: Randomized clinical trial

Population/sample size/setting:

- 457 patients (281 men, 176 women, mean age 60) treated for painful diabetic neuropathy at the University of Indiana
- Eligibility based on daily pain caused by type 1 or 2 DM, beginning in the feet with a symmetrical onset, an average pain score of at least 4 on a scale from 0-10, and a score of at least 3 on the Michigan Neuropathy Screening Instrument (MNSI)
- Exclusion based on pain that could not be clearly differentiated from diabetic neuropathy (such as ischemic pain), mood disorders, neurological disorders unrelated to DM, skin conditions that could alter sensation, history of substance abuse in the past year, treatment with an MAOI or with fluoxetine, or use of an opioid within 3 days of baseline
- Use of acetaminophen up to 4 g per day was allowed, but no other analgesic medication for treatment of neuropathic pain

Main outcome measures:

- Randomized to daily use of placebo (n=115), 20 mg duloxetine (n=115), 60 mg duloxetine (n=114), or 120 mg duloxetine (n=113)
- Main efficacy measure was the change in 24 hour average pain scores between baseline and week 12 of the study, using pain diaries recorded at the evening dose
- Safety was assessed with week 1 and week 12 measurements of systolic BP, blood chemistry, lipids, HbA1c, and hematology
- Compared to placebo, duloxetine 60 mg and 120 mg demonstrated significantly reduced pain severity, beginning at week 1 and persisting through week 12; duloxetine 20 mg did not differ significantly from placebo
- A 50% reduction in pain score was achieved by 26% of the placebo group, 41% of the 20 mg duloxetine group, 49% of the 60 mg group, and 52% of the 120 mg group
- Several secondary outcome measures, such as the SF-36 and global impression of improvement, were also significantly better in the 60 and 120 mg duloxetine group than in the placebo group
- Use of acetaminophen was lower in the 60 and 120 mg duloxetine groups (74 and 80 mg/d) compared with the 20 mg duloxetine group (178 mg/d) or placebo groups (335 mg/d)
- Attrition was approximately 25% in all 4 groups, but there were differences in discontinuation due to adverse effects: 6 patients in the placebo group, 5 in the 20 mg duloxetine group, 15 in the 60 mg group, and 22 in the 120 mg group
- Nausea, somnolence, and dizziness were the most common adverse effects; in addition, in the 120 mg duloxetine group, appetite loss was reported by 14 patients and anorexia by 9 patients

- Glycemic control, QT intervals, and lipid profiles were not affected by duloxetine at any of the dose levels
- The groups did not differ in the incidence of hypertension

Authors' conclusions:

- In pain due to polyneuropathy caused by Type 1 or Type 2 diabetes, duloxetine at doses of 60 and 120 mg/d is more effective than placebo for most pain measurements
- Less supplemental analgesic was used by patients treated with duloxetine as well; quality of life improved and pain interference with activity decreased
- Duloxetine appears to be safe and well tolerated during the 12 weeks of the study
- The analgesic effects of duloxetine did not appear to be dependent on its mood effects
- Because diabetic neuropathic pain requires prolonged treatment, evaluation longer than 12 weeks is necessary

Comments:

- Risks of selection bias (allocation concealment and method of randomization) are adequately described; the risk of bias here is low
- The study is designated as double-blind, but the description of blinding (and assessment of its success) is lacking; the risk of bias here is not clear
- Strengths of the study include a large sample size (more than 100 patients randomized to each group) and clear flow diagram for withdrawals and follow-up
- The caveat concerning the need for more than 12 weeks of follow-up is justified

Assessment: Adequate for evidence that duloxetine at doses of 60 or 120 mg per day reduces pain and analgesic use for up to 12 weeks in diabetic neuropathic pain