

**Vinik AI, Tuchman M, et al. Lamotrigine for treatment of pain associated with diabetic neuropathy: Results of two randomized, double-blind, placebo-controlled studies. Pain 2007;128:169-179.**

Design: 2 randomized clinical trials done at the same time

Population/sample size/setting:

- 720 patients with diabetic neuropathy (386 men, 334 women, mean age 60) treated in two separate randomized trials with 360 patients in each trial in the United States
- Eligible patients were over 18, with screening HbA1c  $\leq 11\%$  for at least 3 months before study entry, with diabetic neuropathy defined by decreased ankle reflexes or abnormal bilateral deficits in vibration, pinprick, fine touch, or temperature sensation; associated pain had lasted at least 6 months but less than 5 years; mean weekly pain score was at least 4 on a scale of 0-10
- Exclusion criteria were severe pain not associated with diabetic neuropathy, pain arising from mononeuropathy, nerve block or acupuncture for pain relief within 30 days, or previous use of lamotrigine

Main outcome measures:

- Central randomization was done at both study centers, where the 360 patients were randomized to 4 groups: placebo (n=90), lamotrigine 200 mg/d (n=90), lamotrigine 300 mg/d (n=90), and lamotrigine 400 mg/d (n=90)
- For each group, there were 2-4 weeks of screening for eligibility and 19 weeks of treatment: 7 weeks of dose escalation and 12 weeks of fixed-dose maintenance
- Acetaminophen was allowed for breakthrough pain, and patients taking gabapentin (n=167), tricyclics (n=40), or both (n=9) were allowed to continue
- The primary analysis was the decrease in pain score from baseline, measured during week 19 by averaging the daily pain scores for a minimum of 4 days
- Secondary analyses included the numbers of patients with 30% and 50% pain relief, pain improvements between baseline and week 19, patient global impression of change (PGIC), and clinician global impression of change (CGIC)
- The analysis was planned to first compare lamotrigine 400 mg vs. placebo; if this was not significant, the 200 and 300 mg comparisons would not be made
- The primary analysis showed a greater change in pain scores for lamotrigine 400 mg than placebo (2.7 points vs. 1.6 points) in Study 2 but not in Study 1
- Some secondary analyses showed greater decreases in pain between baseline and week 19 for lamotrigine vs. placebo
- There was significant failure to reach the target dose for the 180 patients in each treatment group, and these failures were equally distributed; the number of patients reaching the target dose was: for placebo, n=151; for lamotrigine 200 mg, n=149; for lamotrigine 300 mg, n=152; for lamotrigine 400 mg, n=149

- Responder rates defined by attainment of 30% or 50% pain relief did not differ between the treatment groups in either study; less than half of the participants had a 30% reduction in pain
- Adverse events occurred more often in lamotrigine than placebo; headache and rash occurred most often, and 1 rash was serious enough to require hospitalization; rashes occurred in 12-16% of the lamotrigine groups

Authors' conclusions:

- The two studies showed mixed results for lamotrigine in diabetic neuropathic pain; lamotrigine 400 mg differed from placebo in the primary analysis in one study but not the other
- The results did not vary as a function of the patient taking gabapentin or a tricyclic during the study
- The high dropout rate may have influenced the results, and may have underestimated the efficacy since patients who withdrew were likely not to have been on an effective dose of lamotrigine at the time they dropped out
- Lamotrigine was generally well tolerated, but was not consistently effective for diabetic neuropathic pain

Comments:

- The authors state in the last page that the manufacturer has discontinued trials of lamotrigine for neuropathic pain
- The fact that patients dropped out before reaching the target dose of lamotrigine should not be interpreted as likely to underestimate the efficacy of lamotrigine, since dropout due to intolerance of the drug is a valid endpoint for analysis
- The use of acetaminophen as a rescue medication could account for a high response rate in the placebo group; its use in the 4 randomized groups is not described, but would have been of use in interpreting the study

Assessment; Adequate for evidence that lamotrigine is unlikely to be effective for neuropathic pain