

Dogra S, Beydoun S, et al. Oxcarbazepine in painful diabetic neuropathy: a randomized, placebo-controlled study. Eur J Pain 2005;9:543-554.

Design: Randomized clinical trial

Population/sample size/setting:

- 146 diabetic patients (85 men, 61 women, mean age 60) treated for neuropathic pain at 22 diabetes and neurology pain clinics in the USA and Canada
- Eligible patients had type 1 or 2 diabetes, at least 6 months but less than 5 years of neuropathic pain, stable HbA1c <11% at baseline, a pain rating of at least 50 on a 100 point VAS scale on the first screening visit, and an average VAS of 50 or more during 4 of the last 7 days prior to randomization
- Exclusion was done if the patient had previous or current treatment with oxcarbazepine, amputations other than toes, renal insufficiency, serum sodium levels under 135, chronic infectious disease

Main outcome measures:

- Randomized to placebo (n=77) or to oxcarbazepine (n=69)
- The study period consisted of a 2 week pre-randomization screening phase, followed by a 16 week double blind treatment phase: 4 weeks for dose titration and a 12 week maintenance phase of the study drug
- Acetaminophen was authorized for breakthrough pain; no other analgesics were permitted
- Primary efficacy measure was average VAS in the final week of treatment compared to baseline
- Secondary measures were global assessment of therapeutic effect (GATE) on a 7 point scale (-3 is very much improved and +3 is very much worse); time to onset of pain relief (20 point decrease from baseline VAS sustained for 2 consecutive days); sleep and SF-36 quality of life scales were also secondary outcome measures
- Main analysis was intention to treat (ITT), but secondary analyses were done for per protocol (PP) population, which consisted of all patients in the ITT analysis, excluding those with protocol violations; a secondary analysis was done of completers, which consisted of all patients from the ITT population who stayed in the study through week 16 of the double blind phase
- The target dose of oxcarbazepine was 1800 mg/d in divided doses of 900 mg bid; the starting dose was 300 mg/d and titrated as tolerated to the maximum dose at the rate of 300 mg every 5 days; at the end of the 4 week dose titration, the dose was maintained for an additional 12 weeks
- Of the 69 patients randomized to oxcarbazepine, 25 withdrew before the end of the study, 19 (27.5%) for adverse effects; the placebo withdrawal rate was 15 of 77, with 6 withdrawals (7.8%) for adverse effects
- Of the ITT patients who completed the titration phase, 55% had reached the target dose of 1800 mg; the mean oxcarbazepine dose was 1445 mg/d

- In the main outcome analysis, the decrease from baseline of VAS in the oxcarbazepine group was 24.3 points, versus 14.7 for placebo; the estimated treatment difference between groups was 11.2 points in favor of oxcarbazepine
- The decrease in the PP population was similar to that for ITT analysis (25.3 versus 15.6 points), and the completers analysis was also similar (29.4 versus 16.9 points)
- In the ITT analysis, the percentage of patients with a 50% decrease in pain scores from baseline was 35.2% versus 18.4% for placebo; for a 30% reduction in pain, the percentages were 45.6% and 28.9%
- In the GATE, the percentage of patients with improvement (slight, much, or very much) was 73% for oxcarbazepine versus 40% for placebo
- Sleep scores (proportion of days that patients were awakened during the night by pain) also were different between groups in favor of oxcarbazepine over placebo (31% versus 49%)
- Most adverse events occurred during the titration phase, and dose reduction usually resolved the side effects before the study end; these were mild to moderate in intensity in 90% of patients in both groups
- Dizziness, somnolence, and gastrointestinal upset were the commonest adverse events; 4 patients in the oxcarbazepine group had serious adverse events (sinus bradycardia, erythema multiforme, and asthenia/dizziness/fatigue); 1 patient on placebo withdrew because of rectosigmoid cancer
- Mean sodium levels were unchanged overall, but 3 patients taking oxcarbazepine had sodiums less than 125 mmol/L; the sodium levels returned to normal after dose reduction in 2 patients and oxcarbazepine discontinuation in the third patient

Authors' conclusions:

- Compared to placebo, monotherapy with oxcarbazepine provides clinically meaningful pain relief and sleep improvement
- An individualized titration regimen based on patient tolerability may improve adherence to oxcarbazepine and by informing patients that many side effects will resolve with dose reduction and continued treatment
- Since oxcarbazepine treated patients who dropped out had their last observations carried forward for the ITT analysis, that analysis may have decreased the difference between oxcarbazepine and placebo

Comments:

- Of the three similarly designed oxcarbazepine trials in diabetic neuropathic pain (Grosskopf 2006 and Beydoun 2006 are the others), this is the most adequately reported and executed
- There is some lack of clarity in the blinding (we do not know if placebo was titrated in the same fashion as oxcarbazepine), but if the dose escalation was not replicated in the placebo group, the blinding could be compromised

- The ITT analysis was similar in effect size to the PP and completers analysis; the effect of early dropout on the difference between oxcarbazepine and placebo may not be as great as the authors speculate
- One important feature of this study is that the titration was done as tolerated by the patient and not on a fixed schedule; the dropout rate was 36% for oxcarbazepine in this study versus 54% in the Beydoun study which had a fixed titration to 1800 mg using the same 4 week titration phase
- The authors report that 55% of oxcarbazepine patients reached the target dose of 1800 mg, and that the mean dose was 1445 mg, but they do not report the actual distribution of doses, nor whether there was a dose-response curve for the main efficacy measure
- There was a separate per protocol analysis which excluded protocol violations, but the authors do not report what constituted a protocol violation that required a separate analysis

Assessment: Adequate for evidence that oxcarbazepine may be effectively relieve neuropathic pain, provided that the dose titration is carefully done according to patient tolerability of the drug