

Beydoun A, Shaibani A, et al. Oxcarbazepine in painful diabetic neuropathy: results of a dose-ranging study. Acta Neurol Scand 2006;113:395-404.

Design: Randomized clinical trial

Population/sample size/setting:

- 347 diabetic patients (192 men, 155 women, mean age 61) treated for painful diabetic neuropathy at 37 centers in the United States
- 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 40 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, drug or alcohol abuse in past year, hyponatremia, or hypersensitivity to oxcarbazepine or its metabolites

Main outcome measures

- Randomized into 4 groups: placebo (n=89), oxcarbazepine 600 mg/d (n=83), oxcarbazepine 1200 mg/d (n=87), and oxcarbazepine 1800 mg/d (n=88)
- The study period consisted of a 2 week pre-randomization screening phase, followed by a 16 double blind week treatment phase: 4 weeks for dose titration and a 12 week maintenance phase of the study drug
- Primary efficacy measure was average VAS in the final week of treatment compared to baseline using intention to treat (ITT) analysis, in which any patient who was randomized and provided at least one day of VAS data
- 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
- Acetaminophen was authorized for breakthrough pain; no other analgesics were permitted
- Titration was done with a starting dose of oxcarbazepine 300 mg/d, increased by 1 tablet every 5 days until the target dose (600 mg, 1200 mg, or 1800 mg) was reached; drug was given in divided doses bid
- Only 67% of patients completed the study; and attrition was related to treatment group; dropout rate was 19% in the placebo group, 19% in the 600 mg group, 39% in the 1200 mg group, and 54% in the 1800 mg group
- Most dropouts occurred in the dose titration phase, and were related to adverse effects; the most common adverse effects were dizziness, digestive complaints, fatigue, ataxia, headache, somnolence, tremor and confusional states
- The primary efficacy measure (mean decreases in pain VAS from baseline in the last week of treatment, using ITT analysis) did not differ between groups in a statistically significant way; the percent changes were: placebo, 27.1%;

oxcarbazepine 600 mg, 33.7%; oxcarbazepine 1200 mg, 38.2%; and oxcarbazepine 1800 mg, 37.2%

- In addition to ITT analysis, a comparison was made of patients who completed the study; for the completers, oxcarbazepine 1800 mg was superior to placebo ($p=0.034$), and the reduction in VAS in the 1800 mg group who completed the study was 52.7%, greater than the 37.2% in the ITT analysis
- The VAS averaged over the entire 16 weeks of the study favored oxcarbazepine 1200 and 1800 mg ($p<.05$)
- For “much” or “very much improved” scores on the GATE, the placebo, 600 mg, 1200 mg, and 1800 mg improvements were: 37.3%, 36.4%, 50%, and 49.3% respectively; this did not reach statistical significance
- The percentages of patients whose GATE showed a worsening of pain in the placebo, 600 mg, 1200 mg, and 1800 mg groups were 14.5%, 10.4%, 8.3%, and 10.4% respectively
- For GATE scores of “much” or “very much” improved, the Number Needed to Treat (NNT) could not be calculated for oxcarbazepine 600 mg, but was 7.9 for 1200 mg and 8.3 for 1800 mg of oxcarbazepine
- Adverse effects leading to withdrawal (7% in placebo group, 11% in 600 mg group, 23.5% in 1200 mg group, and 41.4% in 1800 mg group), the numbers needed to harm (NNH) were 24.4 in 600 mg, 6.2 for 1200 mg, and 2.9 in 1800 mg
- Hyponatremia ($Na<125$) was observed in 4 patients taking 1200 mg and in 2 patients taking 1800 mg of oxcarbazepine; it resolved after discontinuation of the drug

Authors' conclusions:

- This is one of 3 similarly designed studies of oxcarbazepine as monotherapy for diabetic neuropathic pain; one study of oxcarbazepine 1800 mg vs. placebo showed significant pain reduction, and one study of oxcarbazepine 1200 failed to show significant pain reduction over placebo
- Although 1200 and 1800 mg of oxcarbazepine were favored over placebo, the difference failed to reach statistical significance
- A high placebo response rate (27.1% improvement) may in part account for the absence of statistical significance in this study
- The high withdrawal rate during the titration phase of the study could lead to underestimating the true treatment effect of oxcarbazepine, the titration may have been too rapid, and titration rates must be individualized
- Although the primary efficacy variable was not statistically significant, oxcarbazepine may provide clinically meaningful pain relief to patients who can tolerate doses of 1200 or 1800 mg

Comments:

- The comparison of benefits (NNT) and harms (NNH) needs to be re-analyzed
- Because the differences in the proportion of patients who improved or greatly improved in the GATE were not statistically significant, the confidence intervals for NNT will include the null value

- For example, GATE was improved in 49.3% of oxcarbazepine 1800 mg and in 37.3% of placebo patients; the difference is about 12%, and its reciprocal is 8.3, which appears in Table 3 as the NNT for the 1800 mg dose
- However, the standard error of the difference can be calculated as about 14.4%; the 95% confidence interval for the difference in proportions would be between 2.4% in favor of placebo and 26.4% in favor of oxcarbazepine 1800 mg
- The NNT of 8.3 is not interpretable in this context
- However, the NNH for adverse effects leading to withdrawal of 2.9 is interpretable; similar calculations yield a 95% confidence interval for NNH between 2.2 and 4.3
- This means that the NNT is greater than the NNH; the data are compatible with the hypothesis that oxcarbazepine does more harm than good
- 6 patients taking oxcarbazepine had hyponatremia with sodium less than 125 mmol/L; it was not reported how often sodium was measured, but this may be a mechanism for some of the frequent adverse effects, and the number of patients with sodium between 125 and 135 (mild hyponatremia) is not reported, nor is the lowest sodium laboratory value reported
- Some results are reported only with p values; this is not an acceptable substitute for numerical values with standard deviations
- There is not sufficient evidence to conclude that the harms are greater than the benefits for oxcarbazepine, since the problem may have been that 300 mg every 5 days is too fast a rate of titration
- Details of randomization and blinding are lacking, but in a study which does not show group treatment differences, this is not likely to be a source of bias

Assessment: Inadequate for evidence of benefit (a marginally significant secondary analysis has the appearance of an attempt for statistically significant results; NNT are incorrectly presented, and are greater than NNH)

Inadequate for evidence that harms are greater than benefits, but concerns are raised that this could be the case

Adequate for the precaution that dose titration must be individualized, and that rapid dose escalation may produce adverse effects sufficient to limit the use of oxcarbazepine