

Raskin P, Donofrio PD, et al. Topiramate vs. placebo in painful diabetic neuropathy. Neurology 2004;63:865-873.

Design: Randomized clinical trial

Population/sample size/setting:

- 317 diabetic patients (157 men, 160 women, mean age 59) treated for painful neuropathy at 39 centers in the USA
- Eligibility criteria included symmetric neuropathic pain in the lower extremities for ≥ 3 months but ≤ 10 years with stable HbA1c $\leq 11\%$
- Exclusion criteria included non-diabetic causes of peripheral neuropathy, other conditions more painful than the qualifying neuropathic pain, degenerative neurological disorders, ongoing treatment with anticonvulsants or antipsychotics, use of narcotics, and topiramate treatment in past 30 days

Main outcome measures:

- Randomized to topiramate (n=208) or placebo (n=109)
- Randomization was preceded by a 28 day screening/washout phase, during which the patients discontinued TENS, acupuncture, anticonvulsants, antidepressants (other than SSRI), alpha-lipoic acid, and capsaicin
- Following the 28 day washout phase, a 12 week double-blind study was done, with 8 weeks for dose titration and 4 weeks of maintenance
- Starting dose of topiramate (or placebo) was 25 mg at hs, with increments of 25 mg on weeks 2, 3, and 4; then by 50 mg on weeks 5 and 6; then by 100 mg on weeks 7 and 8; the final dose was 400 mg or the maximum tolerated dose during titration phase
- The mean daily dose of topiramate during the maintenance phase was 320 mg
- Pain intensity was measured at baseline and at 4, 8, and 12 weeks of treatment, with the change in pain intensity from baseline to the last evaluation as the primary efficacy measure
- In the topiramate group, 112 of 214 patients completed the study; in the placebo group, 80 of 109 completed the study
- 102 topiramate patients discontinued early: 52 for adverse effects, 31 for lack of efficacy, and 19 for other reasons
- 29 placebo patients discontinued early: 9 for adverse effects, 16 for lack of efficacy, and 4 for other reasons
- Pain intensity decreased at 12 weeks in both groups, but the decrease was greater (from 68.0 to 46.2) in the topiramate group than in the placebo group (from 69.1 to 54.0)
- A 30% reduction in pain was reported in 49.5% of topiramate patients and in 33.9% of placebo patients
- A 50% reduction in pain was reported in 35.6% of topiramate patients and in 21.1% of placebo patients
- There were differences in treatment groups as early as week 8 (the end of the titration phase); and additional analyses which account for missing observations also showed topiramate superior to placebo

- Topiramate improved sleep disruption scores better than placebo
- Topiramate improved the physical component summary of the SF-36 by a small amount (33.2 to 37.2), but the mental component was slightly worse (from 49.0 to 46.9); the topiramate group had higher levels of reported somnolence, fatigue, loss of appetite, and diarrhea
- In the topiramate group, one patient had convulsions and one patient had bradycardia with syncope, but no deaths occurred in either group
- Topiramate was associated with weight loss (mean 2.6 kg weight decrease compared to 0.2 kg weight gain in placebo group); no other metabolic effects of topiramate were reported (HbA1c did not change from baseline in either treatment group)

Authors' conclusions:

- The pain of diabetic neuropathy responds favorably to topiramate, with about half of patients achieving a clinically meaningful pain reduction during 12 weeks of treatment
- These results contrast with those of another trial of three doses (100 mg, 200 mg, and 400 mg) of topiramate versus placebo, in which no advantage of topiramate over placebo was reported
 - o The placebo response in the negative study was greater than the placebo response in the current study; since a high placebo response makes it more difficult to detect a true treatment effect, this may account for the different results in the studies
 - o The patients in the negative study were asked "How would you rate your pain?" and in the current study they were asked to rate the pain they were currently experiencing in their lower extremities; this more specific question may have yielded a more precise response
 - o There were improvements in pain intensity with topiramate which were similar in the studies, suggesting that there was a true analgesic effect from topiramate
- The small decrease in the psychological component of the SF-36 in the topiramate group may have been due to the somnolence and dizziness effects of the drug
- The high dropout rate in the topiramate group may have been a limitation of the study; the high target drug dose may account for some of the attrition, and the result may be an underestimation of the effectiveness of the study drug

Comments:

- Although it is true that a high dropout rate due to difficulties in titrating the dose may lead to an underestimation of the potential analgesic effect of the study drug, tolerability is an important outcome in itself, and the high dropout rate may predict difficulties with compliance in clinical practice
- The dropout rate due to lack of efficacy was nearly equal in the two groups, as seen in Figure 1: 14.5% in the topiramate group and 14.7% in the placebo group

- For a 50% pain reduction, achieved by 35.6% of the topiramate group and by 21.1% of the placebo group, the number needed to treat (NNT) is about 6.9
- For a 30% pain reduction, the NNT is about 6.4
- For adverse effects leading to withdrawal, reported by 24.3% of the topiramate group and by 8.3% of the placebo group, the number needed to harm (NNH) is about 6.25, approximately the same as the NNT for a 30% and for a 50% pain reduction
- The overall balance of harms and benefits is a matter of judgment which would need to be considered carefully on an individual basis by the treating physician

Assessment: adequate for evidence that topiramate is marginally better than placebo for diabetic neuropathic pain