

**Thienel U, Neto W, et al. Topiramate in painful diabetic polyneuropathy: findings from three double-blind placebo-controlled trials. Acta Neurol Scand 2004;110:221-231.**

Design: Randomized clinical trial

Population/sample size/setting:

- 1269 diabetic patients (736 men, 533 women, mean age 58) treated for painful neuropathy at 195 centers in the US and Europe
- Eligible patients had at least 6 months of pain of at least moderate intensity (2 or more on a scale from 0-4), with stable glycemic control for at least 3 months, HgbA1c less than 11%, creatinine clearance at least 60ml/min, and not pregnant
- Exclusion criteria included neuropathy from other diseases, diabetic ulceration of extremities, non-traumatic amputation, history of hepatitis or HIV, history of alcohol or drug abuse in previous year, significant psychiatric or mood disorders, tricyclic antidepressants, MAO inhibitors, anticonvulsants
- Other exclusion criteria were related to previous analgesic treatment: patients requiring chronic use of simple analgesics (e.g., acetaminophen), or opioids to control pain, and patients who had failed 3 or more previous pain control regimens other than simple analgesics or opioids

Main outcome measures:

- Three separate trials (NP-001, NP-002, and NP-003) with the same inclusion/exclusion criteria were done, each trial comparing topiramate with placebo
- NP-001 randomized patients to placebo (n=136), topiramate 100 mg (n=128), topiramate 200 mg (n=130), and topiramate 400 mg (n=130)
- NP-002 randomized patients to placebo (n=119), topiramate 200 mg (n=116), and topiramate 400 mg (n=129)
- NP-003 randomized patients to placebo (n=126), topiramate 100 mg (n=122), or topiramate 200 mg (n=123)
- The trials had similar completion rates; for placebo the completion rate was 50% for NP-001, 62% for NP-002, and 63% for NP-003
- For topiramate 100 mg, the completion rate was 52% for NP-001 and 56% for NP-003
- For topiramate 200 mg, the completion rate was 46% for NP-001 and 47% for NP-002 and NP-003
- For topiramate 400 mg, the completion rate was 38% for NP-001 and 45% for NP-002
- The mean VAS decreased in all treatment groups in all 3 trials, but the differences between topiramate and placebo was not statistically significant in any of the comparisons between the two; however, in NP-001, topiramate was more effective than placebo in decreasing the median VAS

- In NP-001, topiramate 100 mg and 200 mg was superior to placebo on two of the quality of life scores (bodily pain and physical functioning); in NP-002 and NP-003, this superiority of topiramate over placebo was not observed
- Discontinuation due to adverse effects occurred more often with topiramate than with placebo (8%); the discontinuations were dose-dependent (16% for 100 mg, 25% for 200 mg, and 31% for 400 mg of topiramate)
- The most common adverse effects with topiramate were nausea, fatigue, dizziness, somnolence, and loss of appetite
- Most patients taking topiramate lost weight, and HbA1c levels also improved; however, no correlation was observed between weight loss and improvement in glycemic control

#### Authors' conclusions:

- The measured analgesic effect of topiramate was not significantly greater than that of placebo
- This may have occurred because the placebo response was high, and a high placebo response rate can obscure a true effect of topiramate
- Given the intra-and inter-individual variability in self-ratings of pain, and the fluctuating nature of neuropathic pain, it is possible for studies to produce inconsistent results
- The patients were asked only "How would you rate your pain?" rather than more specific questions about the level of pain in the extremities; this too may have increased the variability of the responses and decreased the power of the study to detect a difference between topiramate and placebo
- The short-term effects of improved diabetic control is not understood; it is possible that this could slow the degeneration of nerve fibers and stimulate axonal regeneration, which could increase pain in the short term
- Although one entry criterion was that there be at least a score of 2 (moderate pain) on a scale from 0-4, this may not have produced the same level of baseline pain as in studies requiring a score of at least 40 on a scale from 0-100; the correlation between the two pain scales is only 0.44, suggesting that there may be considerable disagreement between the two pain scales
- The failure to describe a treatment effect for topiramate does not exclude the possibility that it is effective; future studies need to consider inclusion criteria, the sensitivity of the scale to detect treatment effects, the specificity of the questions used, and the use of rescue analgesics during the study

#### Comments:

- The discussion section points to several factors that may underestimate a treatment effect for topiramate; one other possible factor is that the actual dosages taken during maintenance seem not to have been taken into account (only the assigned doses were considered)
- There is some lack of clarity in the inclusion criteria regarding previous use of analgesics; it is stated that patients were excluded if they required chronic use of simple analgesics such as acetaminophen or opioids, or if they had vailed 3

or more pain control regimens; it is not clear what criteria were applied to determine whether these exclusions had occurred

- The study was done in 195 centers, which introduces an additional source of variability into the data; this may decrease the power of the study to detect treatment differences, but it is still unlikely that a large treatment effect of topiramate was overlooked

Assessment: Adequate for evidence that topiramate has at best a marginal effect on neuropathic pain (study is inconclusive, but is not compatible with a large treatment effect for topiramate)