Irving G, Jensen M, et al. Efficacy and Tolerability of Gastric-retentive Gabapentin for the Treatment of Postherpetic Neuralgia. Clin J Pain 2009;25:185-92.

Design: Randomized clinical trial

Population/sample size/setting:

- 158 patients (74 men, 84 women, mean age 70) treated for postherpetic neuralgia (PHN) in a university rehabilitation department in Seattle
- Eligible patients had pain intensity of at least 4 on a scale of 0-10 at least 3 months after healing of a herpes zoster rash, had previously responded to treatment for PHN with gabapentin >=1200 mg/d without dose-limiting adverse effects
- Exclusion criteria were immunocompromised status, renal, hepatic, or gastrointestinal disease, severe pain from causes other than PHN, or significant abnormal laboratory results
- Before entering the trial, patients had to discontinue antidepressants, benzodiazepines, muscle relaxants, oral steroids, capsaicin, NSAID, and strong opioids; a washout period of 5 half lives of the drug was required

Main outcome measures:

- The experimental treatment was gabapentin extended release (ER), which enters the circulation slowly and is thought to overcome the saturable transport mechanism that limits the availability of ordinary gabapentin
- Three randomization groups were generated: one group (n=55) took gabapentin ER once daily, 1800 mg at hs; the second (n=52) took gabapentin ER bid, 600 mg in the morning and 1200 mg at bedtime; the third (n=51) took placebo
- The use of rescue medication in the form of acetaminophen with hydrocodone up to 8 tablets per day was allowed during the trial
- The main efficacy end point was the mean change in average daily pain from baseline to week 4 of treatment
- Dose titration was done over a period of 2 weeks to reach 1800 mg per day; the dose was maintained at that level for 2 weeks, and was tapered over 7 days
- 158 patients started the study, and 15 withdrew early, 11 of them for adverse events (4 on gabapentin once daily, 6 on gabapentin bid, and 1 on placebo)
- The mean average daily pain at baseline was 6.5 for all patients
- All groups had a decrease in pain during the trial
- Gabapentin bid was statistically superior to placebo in the mean percent change from baseline (34.7% vs. 18.6% decrease); gabapentin at hs was not statistically superior to placebo (30.1% decrease)
- 50% decrease in pain from baseline occurred in 14 (25.5%) of gabapentin at hs, 15 (28.8%) of gabapentin bid, and in 6 (11.8%) of placebo group
- 30% decrease in pain occurred in 24 (43.6%) of gabapentin at hs, 25 (48.1%) of gabapentin bid, and in 16 (31.4%) of placebo group

- Some secondary outcomes were measured; including patient's global impression of change, which was much or very much improved in 32.7% of gabapentin at hs, 40.8% of gabapentin bid, and in 20.8% of placebo group
- Rescue medication was used by 65.5% of the gabapentin hs group, by 51.9% of the gabapentin bid group, and by 60.8% of the placebo group; only 16.5% of patients used hydrocodone (group data not reported)
- Adverse effects did not differ statistically significantly between treatment groups; the most common were dizziness, somnolence, fatigue, and headache
- 11 patients (10 on gabapentin and 1 on placebo) had 1 or more adverse events leading to discontinuation of the study drug, and 8 of these discontinuations were considered possibly or probably related to the study drug

Authors' conclusions:

- Gabapentin ER given in a divided dose of 1800 mg, is significantly more effective than placebo at alleviating pain from PHN
- There was a relatively high placebo response, which may account for the lack of statistical significance of gabapentin at hs; the fact that rescue medication containing hydrocodone was allowed may account for this high placebo response rate
- Once daily dosing may cause trough plasma levels to fall below the therapeutic range
- The study was relatively short and long-term effects are not known

Comments:

- Patients were excluded if they "had previously not responded" to gabapentin at doses up to 1200 mg/d or had dose-limiting adverse effects; it is not clear whether "responded" means a substantial reduction in a validated pain scale, or if it only means that the patients had been able to reach a dose of 1200 mg in a dose titration study
- Although the overall adverse effects did not have a statistically significant difference between groups, the discontinuation due to adverse effects might be significant if the sample size were larger
- The high placebo response rate could be due to the use of acetaminophen, which was approximately equal in the three groups; however, the lack of group data on the use of hydrocodone precludes a better exploration of this issue
- The study was sponsored by the drug maker, but there is no registry protocol with the study in order to compare the reported outcomes with those which were planned at the outset of the study
- Randomization was done by computer generation, but nothing is said about allocation concealment; however, in a study design with previous response to the study drug as an entry criterion, this is not necessarily a source of bias
- The effects observed with extended release gabapentin do not appear to differ greatly from those in immediate release preparations of the drug

Assessment: Adequate for evidence that gabapentin is superior to placebo for relief of neuropathic pain