

**Gilron I, Bailey JM, et al. Morphine, Gabapentin, or their Combination for Neuropathic Pain. N Engl J Med 2005;352:1324-34.**

Design: Randomized crossover trial

Population/sample size/setting:

- 35 patients with diabetic neuropathy (DM, 18 men, 17 women, median age 60) and 22 patients with postherpetic neuralgia (PHN, 14 men, 8 women, median age 68) at two university settings in Canada
- Inclusion criteria were moderate pain for at least 3 months, age 18 to 89, normal renal and liver function, and (for DM) symmetric sensory deficits in both feet or decreased ankle-jerk reflexes; for PHN, at least 6 months since eruption of rash
- Exclusion criteria were hypersensitivity to study medications, comorbid heart, mood, or neurologic disorder, drug or alcohol abuse history, pregnancy, lactation, and lack of a primary care physician
- Current treatment with morphine or gabapentin was not an exclusionary criterion, but both drugs needed to be discontinued for 7 days before entry (4 patients were taking morphine or oxycodone, and 14 were taking gabapentin)

Main outcome measures:

- Crossover was complex due to the fact that each patient was observed for four treatment periods: low dose lorazepam as an active placebo (P), morphine (M), gabapentin (G), and a combination of morphine and gabapentin (C)
- Patients were randomized to one of four treatment orders: MPCG, PCMG, GMCP, and GCPM
- Blinding was maintained by dispensing blue and grey capsules which appeared identical but whose contents were known only to the pharmacist
- Each treatment period lasted 5 weeks: three weeks of titrating to the maximum tolerated dose, one week at the maximum tolerated dose, and one week with four days of dose tapering and three days of washout with no capsules taken
- The primary outcome measure was pain intensity on VAS during the fourth week of the treatment period, when the maximum dose was being taken
- Linear mixed models were used to identify treatment effects, period effects, sequence effects, and carryover effects
- 16 patients withdrew during the treatment periods, 13 during the first two periods (whose data were not analyzed) and 3 after the second treatment periods (whose data were analyzed; this left 41 patients who completed the entire trial, and 44 whose data were analyzed)
- For morphine, the mean maximum dose as a single agent was 45.3 mg, and was 34.4 mg when combined with gabapentin; for gabapentin, the mean maximum dose as a single agent was 2207 mg, and was 1705 mg when combined with morphine
- No sequence or period effects were observed, but one carryover effect was observed: morphine was more likely than placebo to carry over into the next treatment period

- For mean pain intensity, the main outcome measure, the scores were 5.72 at baseline, 4.49 with placebo, 4.15 with gabapentin, 3.70 for morphine, and 3.06 with the combination; this was statistically significant for the comparison of the combination with either component drug alone
- The combination was also superior for some of the secondary measures, such as the short form McGill Pain Questionnaire, mood, and some scales (vitality, social functioning) of the SF-36
- Moderate pain relief was recorded as a categorical variable for each of the four interventions: 31% for placebo, 61% for gabapentin, 80% for morphine, and 78% for the combination
- On the blinding questionnaire, correct guesses by patients were 66% for placebo, 42% for gabapentin, 44% for morphine, and 25% for the combination
- Commonest adverse effects were constipation and dry mouth; the frequency was higher during dose titration during weeks 1-3 than at the maximal tolerated dose in week 4 (e.g. 44% for gabapentin-morphine combination during dose titration but 21% at maximal tolerated dose)
- At the maximal tolerated dose, gabapentin-morphine combination also had lower rate of constipation (21%) than morphine alone (39%)

#### Authors' conclusions:

- The combination of gabapentin and morphine results in less pain than when either drug is used alone
- The same combination uses lower doses of each drug, and has adverse effect profiles similar to or less than the drugs used alone
- Therefore, the combination has a therapeutic profile superior to its component drugs
- Although gabapentin was not superior to placebo for the primary outcome, it was superior in several secondary outcomes; this may be attributable to the fact that lorazepam was used as an active placebo

#### Comments:

- Although the design of the study is complex, the analysis used safeguards against Type I error and should be expected to have a low risk of bias
- DM and PHN results were not reported separately, and may not have differed with respect to performance of the various interventions
- Gabapentin was used by 14 patients at the beginning of the study, and it was correctly identified by 42% of its users; morphine was used by only 4 patients but was identified correctly by 44% of its users; the constipating effects can easily compromise attempts at blinding
- The 13 withdrawals during the first two treatment periods are not described; it is not clear which treatments they received before withdrawing, and whether this occurred during titration or during the maximal tolerated dose phase
- A large proportion of the patients were not receiving analgesic treatment at the time of entering the trial; if these patients were not accustomed to drug treatment, they may have been more likely to drop out early in the study if adverse effects were more common in that group; this is not reported

- The study should have been adequately powered for the primary analysis, but because these calculations are an inexact science, the number of patients may not have been sufficient to show all of the relevant contrasts between treatments

Assessment: Adequate for evidence that the combination of gabapentin and morphine may allow lower doses with greater analgesic effect than the drugs given separately