

Gilron I, Bailey JM, et al . Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind randomized controlled crossover trial. Lancet 2009;374:1252-61.

Reviewed, no change to conclusions, November 2016

Design: Randomized crossover trial

Population/sample size/setting:

- 56 patients, 40 (26 men, 14 women, mean age 61) with diabetic neuropathy, 16 (9 men, 7 women, mean age 68) with postherpetic neuralgia (PHN), treated at a university hospital research clinic in Canada
- Eligible patients had daily pain score of at least 4 on a scale of 0-10 for at least 6 months, with normal renal and hepatic function, hemoglobin A1c less than 13%, and, for PHN, eruption or rash at least 6 months before enrollment
- Exclusion criteria included evidence of a neuropathy attributable to heredity, hypothyroidism, vitamin B12 deficiency, or other causes, any major organ system disease, psychiatric or substance abuse, or coexisting condition causing pain as severe as the neuropathic disorder
- Patients were eligible if they were taking sustained release opioids, NSAID, or acetaminophen at the time of entry, but procedural pain treatments were not allowed during the trial

Main outcome measures:

- Each participant received three interventions: gabapentin (G), nortriptyline (N), and a combination of both gabapentin and nortriptyline (C)
- The order of the treatments was randomly assigned, either GCN, NGC, or CNG
- Each treatment period lasted 6 weeks and had the same structure: days 1-24 for dose titration, days 25-31 for the maximum tolerated dose for that treatment, days 32-35 for dose tapering, and days 36-42 for drug washout
- Treatment efficacy was assessed from the average pain scores recorded three times/day during the maximum tolerated dose phase of the treatment period
- Several secondary measures included drug dose during each treatment period, drug serum concentration, McGill Pain Questionnaire, SF-36, Beck depression inventory, adverse events, global pain relief, and blinding questionnaires
- 45 of the 56 patients completed all three treatment periods, and 11 withdrew from at least 1 treatment period
- In the crossover analysis, no significant effects were observed for sequence, treatment period, or carryover; the drug effects were statistically significant
- Baseline average pain score was 5.4
- The combination of G and N had lower average pain scores (2.3) than G alone (3.2) or N alone (2.9); the combination also had a greater percentage pain reduction than for either drug given alone
- N and G monotherapies were similar to one another with respect to pain relief

- When the combination was being taken, the average dose of G was lower than when G was taken alone (2180 mg vs. 2433 mg), and the average dose of N was also lower in combination than alone (50.1 mg vs. 61.6 mg); however, the serum drug concentrations were not significantly lower in combination than with monotherapy for both G and N
- No serious adverse events were recorded, but dry mouth was commonly experienced with N, and inability to concentrate with G; these effects occurred during dose titration and at maximum dose; they were as common during combination drug therapy as with monotherapy
- At least moderate pain relief was reported at the maximum dose for 65% of patients taking G, 78% taking N, and 84% taking the combination; these differences were not statistically significant
- Most secondary measures (McGill questionnaire, SF-36) were not significantly different between the three treatments

Authors' conclusions:

- The combination of an antidepressant and an anticonvulsant drug seems to be superior to monotherapy for neuropathic pain
- Simultaneous drug titration, used in this trial, may be preferable to sequential drug titration
- Neuropathic pain is transmitted by several pathways, and new monotherapies may not deliver improvements as quickly as combination therapies
- A proportion (27-32%) of patients were taking either a tricyclic, gabapentin, or pregabalin when they entered the trial; this may have affected treatment response during the trial

Comments:

- No "serious" adverse effects were reported, but 11 of 56 patients did withdraw: the reasons included edema, ataxia, and chest pain
- The statistical model did not show a period effect, but in Figure 2, the spread in the graphs appears to be greater during period A than during periods B and C; this looks like a period effect, even if the statistical model did not report it
- The scores were approximately equal at the end of each washout period, returning close to the baseline values; this does suggest that the crossover design was suitable to the condition being treated, which remained more or less stable throughout the study

Assessment: Adequate for evidence that a combination of gabapentin and nortriptyline provides more effective pain relief than monotherapy with either drug, without increasing side effects of either drug