

Rintala DH, Holmes SA et al. Comparison of Effectiveness of Amitriptyline and Gabapentin on Chronic Neuropathic Pain in Persons With Spinal Cord Injury. Arch Phys Med Rehabil 2007;88:1547-59.

Design: Randomized crossover trial

Population/sample size/setting:

- 38 patients (36 men, 2 women, mean age 41) treated for neuropathic pain from spinal cord injury (SCI) at a department of Physical Medicine in Texas, including the VA hospital in Houston
- Eligible patients had an SCI at any level and any degree of completeness at least 12 months before entering the study, at least 6 months of chronic neuropathic pain rated at least 5 on a scale of 0-10
- Neuropathic pain diagnosis depended on location of pain at or below the level of injury, with quality of burning, stinging, or stabbing; with a nonradicular, diffuse pattern, made worse with movement, spasticity, or certain movements
- Exclusion criteria included several disorders: seizure, cardiac conduction, renal, hepatic psychological, or substance abuse, or allergy to study drugs; patients on MAO inhibitors were excluded

Main outcome measures:

- Three study drugs were administered to every patient in the study: amitriptyline, gabapentin, and diphenhydramine as an active placebo
- There were six possible sequences of the three drugs, and patients were randomized to one of the six sequences
- Each study drug was administered for 9 weeks: the first 4 weeks were for dose titration to the maximum tolerated dose, weeks 5 to 8 were for constant dose administration, and the last week was for dose tapering; week 10 was a washout period during which no study drug was taken
- Each patient was provided a packet of 8 tablets which could be used each day for breakthrough pain; the tablets had 5 mg of oxycodone and 325 mg of acetaminophen; these were to be taken only if necessary and a new packet was to be started each day to allow monitoring the amount used each day
- The maximum dose for amitriptyline was 50 mg tid; for gabapentin, 1200 mg tid, and for diphenhydramine, 25 mg tid
- Numerous follow-up visits were scheduled during the study: 8 clinic visits and 9 home visits by research assistants; at these visits, information was obtained about pain ratings, medication use, and adverse effects; in addition to these visits, telephone contacts were made twice per week by research assistants
- Most of the data analysis focused on two basic variables: the pain intensity score, and the Center for Epidemiologic Studies Depression Scale Short Form (CESD), which is a 10 item scale to measure symptoms of depression; it was administered at baseline and at weeks 4, 8, and 10 of each study period
- CESD was dichotomized into 2 groups: scores < 10 were considered less depressed, and scores \geq 10 were considered more depressed; response of pain to drug treatment was then considered separately for the two categories

of depression; 24 patients had low scores, 12 had high scores, and 2 had missing scores at baseline

- Of 38 patients randomized, only 22 completed all 3 phases of the study
- The main efficacy measure was the average VAS rating for pain during week 8 of each study period
- Mean VAS for pain during week 8 was 3.46 for amitriptyline, 4.85 for gabapentin, and 5.11 for diphenhydramine; there was a statistically significant difference between amitriptyline and gabapentin and between amitriptyline and placebo, but no difference between gabapentin and placebo; however, amitriptyline was statistically superior to diphenhydramine only in the group with high CESD scores, and in that group, there was only a “trend” toward a superiority of amitriptyline over gabapentin
- In the group with low CESD scores, there were no statistically significant differences between the three medications
- CESD scores did not change significantly from their baseline values during any of the three study periods, including those on amitriptyline
- Depression itself did have an effect on pain intensity scores (pain scores for any medication were higher in the group with higher CESD scores)
- Other secondary analyses were done, which showed statistically non-significant trends toward superiority of amitriptyline over the other two drugs
- The dropout rate was high (16 of the 38 patients randomized), but there was no difference between the three drugs with respect to the dropout rate
- More than half of the patients did not take medication for breakthrough pain during weeks 1 through 8 of the three drug study periods, and the majority of those who did take breakthrough medication took only 2 tablets per day
- Dry mouth was the most frequent adverse effect; it was more frequent with amitriptyline than with the other study drugs
- Spasticity occurred less often with gabapentin than with the other study drugs
- The cost of amitriptyline to the VA was \$1.76 for one month; the cost of gabapentin was \$31.59 for one month

Authors' conclusions:

- The most effective of the three study drugs was amitriptyline, which is efficacious and relatively economic for the treatment of neuropathic pain for spinal cord injury
- The pain was not completely eliminated by any study drug
- The lack of change of CESD scores when patients were taking amitriptyline may have been due to the fact that the 150 mg highest dose could be subtherapeutic for depression
- Combinations of treatments, including amitriptyline with other drugs, may be more effective than any one treatment

Comments:

- The pain scores of patients who withdrew because of intolerable side effects were not included in the analyses of that drug

- The estimates of the relative effectiveness of amitriptyline and gabapentin must be regarded as uncertain, since the analyses were done on completers, and the dropout rate was substantial
- Several analyses are reported as having a “trend” toward significance for amitriptyline; this may indicate a preference of the authors for a superiority of amitriptyline in their results
- The exclusion criteria list mistakenly lists MAO inhibitors as inhibiting “maximal acid output” rather than monoamine oxidase

Assessment: For evidence that amitriptyline is superior to gabapentin: inadequate (exclusion of pain scores for dropouts, high attrition rate).

For evidence that amitriptyline may be as effective as gabapentin: adequate

For evidence that gabapentin is not superior to placebo: inadequate