Combined Treatment with Gabapentin and Nortriptyline Improves Pain Control in Peripheral Neuropathy More than Either Agent Alone

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

Study Overview

Objective. To determine whether gabapentin, nortriptyline, the combination, or both are better for treatment of neuropathic pain.

Design. Double-blind, randomized controlled, crossover trial.

Setting and participants. 56 patients at 1 site with diabetic polyneuropathy or postherpetic neuralgia with a pain score of at least 4 on a 0–10 scale. Patients were randomized in a balanced Latin square design in equal proportions. All subjects received each of the 3 treatments for 6 weeks at a time—gabapentin alone, nortriptyline alone, or gabapentin and nortriptyline in combination—according to a sequence designated by the randomization. Exclusion criteria included abnormal laboratory values (creatinine, alanine aminotransferase), evidence of neuropathy or other significant pain from another cause, major organ system disease, hypersensitivity to the drugs used in the trial, and symptoms commonly found as side effects from the medications being used in the trial.

Main outcome measures. Mean daily pain at the maximum tolerated dose of the drug.

Main results. Most of the patients (71%) had diabetic polyneuropathy. Demographic details of patients were reported separately for diabetic polyneuropathy and postherpetic neuralgia patients. Respectively, the mean age of subjects was 61 and 68 years, 35% and 44% were women, and 20% and 25% were using opiates. 47 patients completed at least 2 treatment periods, and 45 completed all periods. Mean daily pain at baseline was 5.4 (95% confidence interval [CI], 5.0–5.8). Treatment with any of the medication regimens improved pain control compared to baseline (P = 0.004). There was no significant effect from the treatment period or treatment sequence in the main analysis. Pain was lower with the combination treatment than with either individual agent alone. With combined therapy, mean daily pain was –0.9 lower (95% CI, –1.4 to –0.3; P = 0.001) compared with gabapentin and –0.6 lower (95% CI, –1.1 to –0.1; P = 0.02) compared with nortriptyline. Moderate to severe dry mouth was higher in both the combined and nortriptyline periods than the gabapentin period. Depression was higher in the nortriptyline period compared with the combination period, and vitality was lower compared with the combination and gabapentin periods. The maximum tolerated dose of gabapentin and nortriptyline were 2180 mg (standard deviation, ~~SD~~ 108) and 50.1 mg (standard deviation, ~~SD~~ 3.5) when the medications were used in combination. The maximum tolerated dose of medications was significantly higher when used alone.

Conclusion. The combination of nortriptyline and gabapentin decreases pain more than either medication alone in the treatment of neuropathic pain from diabetic polyneuropathy or postherpetic neuralgia.

Commentary

Peripheral neuropathy is a challenging condition that has important negative effects on quality of life [1]. Many agents have been utilized and studied for treatment. Anticonvulsants and tricyclic antidepressants have emerged as mainstays of therapy and are usually recommended as first-line treatment because of repeated success in clinical trials [2,3]. Specific medications used most commonly among these classes include gabapentin and pregabalin for anticonvulsants and nortriptyline and amitriptyline for the tricyclics. Limited research is available on medication combinations, which hold promise for more effective therapy at doses that could decrease potential side effects.

This trial found a significant benefit to the combined treatment of gabapentin and nortriptyline as compared with monotherapy, both in the primary endpoint of mean daily pain as well as secondary endpoints of percent change in pain from baseline, reduced pain intensity, increased pain relief, and improved sleep. Some improvement in the enjoyment of life was evident as well, with a significant improvement compared to nortriptyline and a nearly significant

improvement compared to gabapentin. Side effects were limited in all groups.

Results for this study are comparable to a trial of a similar crossover design which used gabapentin and morphine, alone or in combination [4]. In that trial, the combination of moderate doses of morphine (maximum, 60 mg) and gabapentin (maximum, 2400 mg) was superior to morphine alone (maximum, 120 mg), gabapentin alone (maximum, 3200 mg), and placebo. These prior results were compelling; however, treatment with opiates still leads to challenges, especially with the potential for abuse of opiates. The present data, using 2 therapies without addictive potential, improve the options available for treatment of peripheral neuropathy.

This study had a few limitations. First, the sample size was small though adequately powered to detect clinically meaningful differences. Second, some trouble with blinding emerged. More than one third of the subjects correctly identified that they were taking nortriptyline, and the research nurse correctly identified the treatment regimen for more than 50% of participants. Third, the sample was 100% white, limiting the applicability of these results to diverse populations. Fourth, there was no placebo group with which to compare the regimens.

It is hard to determine whether the findings in this study have meaningful clinical significance. The difference in median daily pain between the combination treatment periods and the monotherapy treatment periods was –0.9 and –0.6 only on the 0 to 10 pain scale. These differences translated into very weak improvements in quality of life only. However, even a small benefit may be an important contribution, especially because the side effects from combined therapy were limited.

Applications for Clinical Practice

Combined treatment with gabapentin and nortriptyline is better than either agent alone for control of pain from diabetic polyneuropathy and postherpetic neuralgia. Use of these agents together should be strongly considered, especially when monotherapy does not achieve adequate pain control.

—Review by Jason P. Block, MD, MPH

References

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