Gabapentin or amitriptyline for painful diabetic neuropathy?

Tricia Rawn, PharmD  Christine Papoushek, PharmD  Michael F. Evans, MD, CCFP


Research question
Is gabapentin or amitriptyline more efficacious for treating the pain of diabetic peripheral neuropathy (DPN)?

Type of article and design
Prospective, randomized, double-blind, double-dummy, crossover study.

Relevance to family physicians
Painful peripheral neuropathy is a common long-term complication of diabetes that affects about 45% of diabetics after 25 years of disease. The pain, which occurs in the hands and lower extremities, ranges from mild to severe and is usually described as a shooting, burning, or tingling sensation in the affected area. The pain decreases patients' quality of life and presents an ongoing challenge for family physicians managing the complications of diabetes.

Neuropathic pain does not usually respond to traditional analgesics, such as nonsteroidal anti-inflammatory drugs or narcotics, so adjunctive treatment is often required. Several adjunctive treatment options are available, including amitriptyline, imipramine, carbamazepine, antiarrhythmics, and capsaicin cream. Amitriptylines and other tricyclic antidepressants are standard treatment for painful diabetic neuropathy and have shown efficacy in clinical trials. The variability of response and development of intolerable side effects, such as sedation, dry mouth, and weight gain, however, can limit use of this medication. Also, amitriptyline is contraindicated for patients receiving monoamine oxidase inhibitors, recovering from myocardial infarction (MI), or suffering acute congestive heart failure. Because of these limitations, alternative treatments with comparable efficacy to amitriptyline are needed.

Gabapentin has demonstrated efficacy in placebo-controlled trials involving patients with painful DPN. To evaluate its place in treatment relative to standard therapy (amitriptyline), we need comparative data, and this trial provides the first data of that kind.

Overview of study and outcomes
This single-centre study looked at 28 patients in an ambulatory care clinic. Patients were eligible for the study if they were 18 years or older, had diabetes mellitus with stable glycemic control (HbA1c at 0.043 to 0.079 within 3 months), had experienced chronic daily DPN pain (as diagnosed by a neurologist) for more than 3 months, and had a creatinine clearance rate of at least 30 mL/min. Patients were excluded if they had pain from another cause that was more severe than their DPN pain; had allergies or adverse reactions to study medications; were severely depressed; had cardiovascular symptoms (orthostatic hypotension, symptomatic coronary artery or peripheral vascular disease); or had previously used the study medications at doses higher than those used in the study.

After a 2-week washout period, patients were randomized to amitriptyline or gabapentin for 6 weeks of treatment. Following a 1-week wash-out period, patients were crossed over to the opposite treatment for another 6 weeks. Medication doses were titrated over 2 days according to pain relief and side effects. Doses of gabapentin ranged from 900 to 1800 mg/d (divided into three doses); doses of amitriptyline ranged from 25 to 75 mg (once daily with placebo twice daily). In

Ms Rawn was a student in the Doctor of Pharmacy Program at the University of Toronto (U of T) when this article was written. Dr Papoushek practises as a Clinical Pharmacy Specialist in the Department of Family and Community Medicine at the Toronto Western Hospital and is a cross-appointed lecturer in the Doctor of Pharmacy Program at U of T. Dr Evans is a staff physician at the Toronto Western Hospital and an Assistant Professor in the Department of Family and Community Medicine at U of T.
Results
Of the 28 patients eligible for the study, 25 were enrolled. Three patients then withdrew from the study due to adverse events (one taking gabapentin and two taking amitriptyline) and one due to protocol violation (gabapentin group). Of the 21 remaining patients, two were crossed over early to the opposite treatment arm (one in each group) due to adverse events. This left 19 patients who completed 6 weeks’ treatment with each study medication.

Patients were mostly white (92%) and male (96%) and had an average age of 60 years. Most patients (88%) had had type 2 diabetes for an average of 13 years.

Both treatments significantly reduced PSRS scores (P < .001) compared with baseline scores. No statistically significant difference in pain relief as measured by PSRS was seen between treatment groups (P = .26). A trend favoured amitriptyline.

No statistically significant difference between treatment groups appeared using the global pain rating scale (P > .1), but again, a trend favoured amitriptyline. Moderate or greater pain relief was seen in 52% (11/21) of gabapentin patients and 67% (14/21) of amitriptyline patients.

Adverse events were experienced by 17 patients taking amitriptyline and 18 patients taking gabapentin. Except for weight gain, which was more common with amitriptyline, there was no significant difference between treatment groups in occurrence of adverse events. Dry mouth due to amitriptyline worsened over time (P < .005). Pruritus due to amitriptyline was worse in the first week of treatment (P < .03), but not significantly worse by the fourth week of treatment.

Analysis of methodology
For the most part, the design of this study was appropriate to the research question. Amitriptyline is a suitable comparator because it is the standard adjunctive treatment for DPN pain. Prospective collection of data is preferable to retrospective collection for monitoring pain relief because it is difficult for patients to recall levels of pain up to 6 weeks in the past. Blinding was maintained with the help of identical tablets and placebos. Most importantly, the practical clinical outcomes of pain relief and adverse effects were evaluated. Also, the PSRS scale, which was used to evaluate pain control, is a validated tool.

This study, however, had several limitations. The main limitation was the small sample size. Only 19 patients (of the 28 eligible) completed the study. As a result, the sample size was probably too small to detect differences between treatment groups if, in fact, they existed. Although no significant differences in efficacy between treatment groups were found, trends on both the PSRS and the global rating scale favoured amitriptyline. This suggests that there are differences in effect; a larger trial might be required to appropriately detect them. In fact, the authors calculated a post-hoc analysis of sample size and found that about 260 patients would be needed to detect a significant difference between treatments.

The homogeneity of the population studied might prevent useful extrapolation to many diabetic patients with neuropathic pain. The mostly white, male patients evaluated in this trial had well controlled diabetes and mild-to-moderate neuropathic pain. It could be difficult, therefore, to apply results of this trial to patients with DPN who do not fit this profile, specifically patients experiencing severe or refractory pain.

Inclusion of patients who had previously used gabapentin or amitriptyline for neuropathic pain is another limitation. The patients evaluated in this trial were more likely to have experienced problems with therapy, since patients who respond well to therapy are less inclined to participate in trials that would require them to discontinue therapy. Unfortunately, it is difficult to assess the effect of including these patients because no information on the actual number of patients receiving either drug before the study is provided.

Although patient allocation and drop-outs were well described, there was no intention-to-treat analysis. Drop-out rates were similar in both treatment groups, but it would have better reflected “real life” to include both regular and intention-to-treat analyses.
The gabapentin dose of 900 to 1800 mg/d was based on the manufacturer’s recommended dose for treatment of seizures: 65% of the gabapentin group reached the maximum dose of 1800 mg. Higher doses of gabapentin (up to 3600 mg/d) have been shown effective for neuropathic pain; perhaps more patients would have had pain relief if gabapentin had been titrated to the maximum daily dose. Further studies are needed to compare higher doses of gabapentin with amitriptyline.

Finally, patient compliance with study medications or with medication restrictions was either not assessed or not reported by the authors.

**Application to clinical practice**

This study showed no significant differences in efficacy or side effects between amitriptyline and gabapentin. The small sample size prevented the trial from having the power to detect a difference between treatments, but at least this trial has set the stage for a larger randomized controlled trial to detect true differences.

For family physicians, results of this trial do not change the role of gabapentin as a second-line agent for treatment of painful DPN. Choice of therapy should still be individualized and based on evidence of benefit (amitriptyline has more evidence to support its benefit), adverse effects (amitriptyline causes more weight gain and, initially, more pruritus), drug interactions (gabapentin has no significant interactions while amitriptyline has several), convenience (amitriptyline is once daily, while gabapentin is three times daily), and cost (amitriptyline costs about $3 for a 30-day supply; gabapentin costs about $100).

**References**


**Bottom line**

- This small study found no significant differences between treatment with gabapentin and with amitriptyline in patients with mild-to-moderate DPN pain.
- There were limitations in study design, and the small sample size did not have the power to detect differences between treatments.
- This study does not provide justification for using gabapentin rather than amitriptyline as a first-line agent. It does provide more support, however, for using gabapentin as an alternative to amitriptyline (gabapentin is considerably more costly than amitriptyline).
- Larger comparative studies with more diverse populations (more women and non-whites) and patients with severe or refractory pain should be done to confirm the results of this trial.

**Points saillants**

- Cette étude de petite envergure n’a fait valoir aucune distinction majeure entre le traitement à la gabapentine et à l’amitriptyline chez les patients souffrant de douleurs faibles à modérées associées à une neuropathie périphérique d’origine diabétique.
- La conception de l’étude comportait certaines limites et le petit échantillonnage n’avait pas l’ampleur voulue pour déceler des différences entre les traitements.
- Cette étude ne justifie pas de préférer la gabapentine à l’amitriptyline comme médicament de première intention. Par ailleurs, elle appuie davantage le recours à la gabapentine comme solution de rechange à l’amitriptyline (la gabapentine est beaucoup plus coûteuse que l’amitriptyline).
- Des études comparatives de plus grande envergure portant sur des populations plus diversifiées (plus de femmes et de minorités visibles) et des patients souffrant de douleurs sévères ou réfractaires devraient être effectuées pour confirmer les résultats de la présente étude.