

FROM THE FAMILY PRACTICE INQUIRIES NETWORK

What is the best treatment for diabetic neuropathy?

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■ EVIDENCE-BASED ANSWER

Tricyclic antidepressants, anticonvulsants, and capsaicin reduce the pain of diabetic neuropathy; limited data suggests that lidocaine patches may also be efficacious. Both tricyclic antidepressants and anticonvulsants are superior to placebo in relieving painful diabetic neuropathy. Compared with placebo, patients taking tricyclic antidepressants report reduced pain (number needed to treat [NNT] for at least 50% reduction= 3.5) (strength of recommendation [SOR]: **A**). Similarly, patients taking anticonvulsants report reduced pain (NNT for at least 50% reduction in pain=2.7) (SOR: **A**).

Limited evidence suggests that selective serotonin reuptake inhibitors (SSRIs) are no more efficacious than placebo (SOR: **C**). Both anti-depressants and anticonvulsants have a high rate of minor adverse effects (number needed to harm [NNH]=2.7 for both). Tricyclic antidepressants have an NNH of 17 for side effects severe enough that patients withdrew from the study.

Compared with placebo, topical capsaicin also reduces pain (NNT=4) (SOR: **A**); however, there are no systematically collected data on side effects for capsaicin. A single case series demonstrates that lidocaine patches are efficacious for neuropathic pain, though expensive (SOR: **B**). Almost no trials comparing different classes of treatments have been performed.

■ EVIDENCE SUMMARY

A recent well-done meta-analysis¹ summarized available randomized placebo-controlled trials of antidepressants (including tricyclics and SSRIs) and anticonvulsants (including phenytoin, carbamazepine, and gabapentin). Almost all trials compare individual agents against placebo, and there have been no head-to-head trials that address functional outcomes, quality of life, patient satisfaction, or cost. Most trials do not describe diagnostic criteria, consider causes of pain other than diabetes or address diabetic control, which is known to predict frequency of neuropathy. Finally, very few trials include typical primary care patients in a primary care

setting or control for important confounding variables such as over-the-counter medications or comorbid illnesses.

Within the constraints of this literature, placebo have a substantial impact, with an aggregate 32% of patients receiving placebo reporting at least 50% reduction in pain. A total of 16 trials have addressed the efficacy of antidepressants for diabetic neuropathy. Compared with placebo, tricyclic antidepressants have an aggregate NNT of 3.5 (95% confidence interval [CI], 2.6–4.7) for patients reporting at least 50% reduction of pain, along with an NNH of 2.7 (95% CI, 2.1–3.9) for minor adverse effects (typically the muscarinic effects of dry mouth, constipation, and blurred vision) and 17 (95% CI, 10–43) for side effects severe enough to cause withdrawal from a trial. Dosages were in the low to middle range of those used to treat depression; there was no significant difference in efficacy between trials less than 3 weeks and those greater than 3 weeks. No evidence supports differences among different tricyclic agents, and limited evidence suggests that SSRIs are no more efficacious than placebo.

A total of 4 randomized placebo-controlled trials (1 each for phenytoin [Dilantin], carbamazepine [Tegretol], gabapentin [Neurontin], and valproate [Depakote]) have extractable data about the efficacy of anticonvulsants for the pain of diabetic neuropathy. As a class, the NNT for patients reporting at least a 50% reduction in pain was 2.7 (95% CI, 2.2–3.8); the NNH for minor adverse effects (typically transient central nervous system effect such as dizziness, somnolence, or disturbance in gait) was 2.7 (95% CI, 2.2–3.4).

These summary estimates do not include the valproate trial,² which was reported after the meta-analysis was completed; the report did not allow calculation of NNT, but the findings were consistent with these results. Phenytoin dosage was 300 mg/d; carbamazepine dosage was titrated to 200–600 mg/d, gabapentin from 300–3600 mg/d, and valproate 1200 mg/d. Patients taking anticonvulsants did not have a higher rate of withdrawal compared to those taking placebo. Limited evidence suggests no significant differences among anticonvulsants; there is insufficient evidence to determine optimal dosage of any of these agents.

Studies involving topical agents are also limited. According to an information summary,³ a total of 4 trials have addressed the efficacy of topical capsaicin for neuropathic pain. Compared with placebo, capsaicin reduces pain (NNT=4; 95% CI, 2.9–6.7), but no pooled information is available on side effects or rate of study withdrawal. Finally, 1 case series has suggested that lidocaine patches are efficacious for diabetic neuropathy.⁴

A variety of other interventions have been reported for diabetic neuropathy, including non-steroidal anti-inflammatory drugs, transcutaneous electrical nerve stimulation (TENS), angiotensin-converting enzyme inhibitors, and Tramadol, but there have been no published systematic evaluations of them.

The **Table** characterizes the agents, the number of trials that address each, the NNT, NNH, typical effective dose, and approximate retail cost per month with the average effective dose.

Efficacy of drug treatments for diabetic neuropathy

Drug	Number	NNT (95%	NNH	Efficacious	Typical
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	of controlled trials	CI) for 50% pain reduction	(95% CI)	dose	cost
Antidepressants	16	3.4 (2.6–4.7)	2.7 (2.1–3.9)		
Tricyclics	8	3.5 (2.5–5.6)	3.2 (2.3–5.2)	Amitriptyline 50–100 mg/d; Nortriptyline 50–75 mg/d	\$12
SSRIs	3	Not efficacious		N/A	N/A
Anticonvulsants*	3	2.7 (2.2–3.8)	2.7 (2.2–3.4)		
Phenytoin	1	Not available	3.2 (2.1–6.3)	300 mg/d	\$18
Carbamezapine	1	Not available	Not available	400 mg 2x daily	\$28
Gabapentin	2	Not available	2.6 (2.1–3.3)	600–900 mg 3x daily	\$333
Valproate [†]	1	Not available	Rare	400 mg 3x daily	\$36
Topical capsaicin	4	4 (2.9–6.7)	Not available	0.075% 4x daily	\$39
Lidocaine patch	0	Not available	Not available	1 patch each foot, daily	\$272
Costs based on 30 days of typical efficacious dose. Retail prices from www.drugstore.com, December 2003, except for capsaicin, which was obtained from Walmart.					
*This summary does not include results from Kochar et al.					
†Data from this trial cannot be summarized within this framework; however, results were statistically significant and similar in magnitude to other trials.					
NNT, number needed to treat; NNH, number needed to harm; CI, confidence interval					

■ RECOMMENDATIONS FROM OTHERS

American Diabetes Association practice guidelines do not address neuropathy; UptoDate emphasizes prevention through glycemic control, with initial treatment using amitriptyline or nortriptyline, followed by capsaicin and anticonvulsants.⁵

CLINICAL COMMENTARY:

Anticonvulsants and antidepressants effective at reducing perception of pain

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The management of patients with chronic pain requires a combination of artistry and skill. As each individual's perceptions, expectations and response to therapy differ, dynamic treatment approaches are required. The relative dearth of evidence supporting effective treatments for chronic pain compounds the problem. This evidence review helps to lessen some of the guesswork for patients with diabetic neuropathy. Anticonvulsants and antidepressants are impressively effective at reducing patients' perceptions of pain at a favorable benefit to significant harm ratio, NNT of 2–4 vs. NNH of 18. Several things however, aren't clear from the literature: as these were all placebo comparisons, which drug is more effective? As well, were reductions in functional limitation and disability measures or improvements in quality of life scores demonstrated? Will other newer agents prove to be superior? Despite these unanswered questions, for patients with diabetic neuropathy good evidence now supports what has likely been many clinicians' preference for the treatment of most chronic pain conditions; any alternative to narcotics.

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