



## Q/What medications are best for diabetic neuropathic pain?

### EVIDENCE-BASED ANSWER

**A/** **TRICYCLIC ANTIDEPRESSANTS**, duloxetine, pregabalin, oxycodone, and tramadol are all effective for the symptomatic treatment of painful diabetic neuropathy (strength of recommendation [SOR]: **A**, systematic reviews of randomized controlled trials [RCTs] and single RCTs).

Gabapentin is also effective (SOR: **B**,

systematic review of RCTs with methodologic flaws). Studies directly comparing tricyclic antidepressants with gabapentin or duloxetine show equivalent efficacy (SOR: **A**, systematic reviews of RCTs and single RCTs).

The outcome evaluated in all of these studies was pain.

### Evidence summary

A Cochrane review of antidepressants for neuropathic pain included 5 RCTs of tricyclic antidepressant use in patients with diabetic neuropathy. The strongest evidence of benefit was for the tricyclic antidepressants amitriptyline, imipramine, and nortriptyline<sup>1</sup> (TABLE).

Another Cochrane review of 3 RCTs of duloxetine for treating painful diabetic neuropathy found moderately strong evidence that duloxetine 60 mg/d was more effective than placebo. A 120 mg daily dose didn't result in significantly greater pain relief than 60 mg/d.<sup>2</sup>

### Antiepileptics alleviate pain, but with some drawbacks

A Cochrane review of 7 RCTs of pregabalin for acute and chronic pain in adults concluded that 600 mg/d was more effective than placebo for relieving diabetic neuropathic pain. However, as many as 28% of patients discontinued treatment because of dizziness and somnolence. Lower doses—150 and 300 mg—resulted in fewer adverse effects, but less relief.<sup>3</sup>

A Cochrane review of 4 RCTs that com-

pared gabapentin with placebo or active control found that gabapentin in daily doses >1200 mg provided pain relief superior to that of placebo.<sup>4</sup> An independent evaluation of manufacturer-sponsored gabapentin trials reported significant methodologic flaws, including selective outcome reporting.<sup>5</sup>

### Opioids also provide significant pain relief

A Cochrane review of studies of opioids for neuropathic pain identified 2 RCTs favoring oxycodone over placebo in patients with painful diabetic neuropathy. In the larger study (159 patients, mean age 59 years) subjects used a 0- to 10-point scale to evaluate pain intensity (0=none; 10=extreme). At 6 weeks, patients receiving oxycodone in doses of 10-120 mg/d had significantly lower pain scores than patients taking placebo ( $4.3 \pm 0.3$  for oxycodone vs  $5.3 \pm 0.3$  for placebo;  $P=.002$ ).<sup>6</sup>

An RCT that compared the benefit of tramadol at an average dose of 210 mg per day with placebo in 131 patients with diabetic neuropathy (mean age 59 years) found tramadol to be significantly better than placebo for treating pain. At 6 weeks, the mean

**Neil Page, MD**

Moncrief Army Community Hospital, Fort Jackson, SC

**Jesse P. DeLuca, DO**

Fort Belvoir Community Hospital, Fort Belvoir, Va

**Karen Crowell, MLIS**

Health Sciences Library, University of North Carolina, Chapel Hill

**ASSISTANT EDITOR**

**Anne L. Mounsey, MD**

University of North Carolina, Chapel Hill

TABLE

## Meta-analyses of drug therapy vs placebo for diabetic neuropathic pain

Drug and dose	Subjects (N)	Duration (wk)	Mean age (y)	Measured outcome	NNT (95% CI)	NNH (95% CI)
Various tricyclic antidepressants and doses <sup>1</sup>	177	3-12	50	Overall effectiveness	1.3 (1.2-1.5)	Treatment cessation: 28 (17.6-68.9)  Minor adverse effects: 6 (4.2-10.7)
Duloxetine <sup>2</sup> 60 mg/d 120 mg/d	655 655	12	N/A	50% pain reduction	6.0 (5-10) 6.0 (5-10)	Treatment cessation: 17 (12-50)
Pregabalin 600 mg/d <sup>3</sup>	1425	5-13	59	50% pain reduction	5 (4-6.6)	Somnolence: 8.8 (7-12)*  Dizziness: 2.8 (2.5-3.2)  Treatment cessation: 8.8 (6.8-12)
Gabapentin 1200-3600 mg/d <sup>4</sup>	829	4-12	58	50% pain reduction	5.8 (4.3-9.0)	Any adverse effect: 6.6 (5.3-9.0) <sup>†</sup>  Treatment cessation: 32 (19-100) <sup>‡</sup>
Oxycodone 20-80 mg/d <sup>6</sup>	36	4	63	Moderate pain relief (defined as a score of 3 on a 6-point scale)	2.6 (N/A)	Nausea: 4 (2-219)  Constipation: 4 (2-19)  Treatment cessation: 7 (4-87)

CI, confidence interval; NA, not available; NNH, number needed to harm; NNT, number needed to treat.

\*Six studies of pregabalin (N=1351) reported rates of somnolence and treatment cessation, whereas only 3 studies (N=1122) reported rates of dizziness.

<sup>†</sup>NNH calculated from 11 studies (N=2356) that included patients with other chronic pain diagnoses.

<sup>‡</sup>NNH calculated from 17 studies (N=3022) that included patients with other chronic pain diagnoses.

pain scores on a scale of 0 (mild pain) to 4 (extreme pain) were  $1.4 \pm 0.1$  for tramadol vs  $2.2 \pm 0.1$  for placebo ( $P < .001$ ).<sup>7</sup>

### Amitriptyline, gabapentin, duloxetine show similar benefit in some studies

A meta-analysis of 2 RCTs (N=77) comparing amitriptyline (25-90 mg/d) with gabapentin (900-2400 mg/d) found no significant difference between the 2 drugs in relief of diabetic neuropathic pain (relative risk=0.99; 95% confidence interval, 0.69-1.38).<sup>8</sup> A randomized, double-blind, crossover trial involving 58 patients with diabetic neuropathy compared duloxetine (20-60 mg/d) with amitriptyline (10-50 mg/d). After 6 weeks, 59% of

patients on duloxetine and 55% of patients on amitriptyline achieved a  $\geq 50\%$  reduction in pain. The 4% difference between the groups was not statistically significant.<sup>9</sup>

### Recommendations

The American Diabetes Association recommends tricyclic antidepressants as first-line agents, anticonvulsants as second-line treatment, and opioids as third-line therapy.<sup>10</sup>

The Diabetic Peripheral Neuropathic Pain Consensus Treatment Guidelines Advisory Boards recommend duloxetine, controlled-release oxycodone, pregabalin, and tricyclic antidepressants as first-tier agents and topical

capsaicin and lidocaine as alternatives.<sup>11</sup>

The American Academy of Neurology advocates pregabalin as the first-choice treatment and states that venlafaxine, duloxetine,

amitriptyline, gabapentin, valproate, opioids (morphine sulfate, tramadol, controlled-release oxycodone), and capsaicin are probably effective.<sup>12</sup>

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