Review: Tricyclic antidepressants, anticonvulsants, opioids, and capsaicin cream are effective treatments for diabetic neuropathy

Wong MC, Chung JW, Wong TK. **Effects of treatments for symptoms of painful diabetic neuropathy: systematic review.** BMJ. 2007;335:87.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Endocrinology ★★★★★☆☆ Neurology ★★★★★★☆

QUESTION

In adults with diabetes, how effective are treatments for painful diabetic neuropathy?

METHODS

Data sources: MEDLINE, EMBASE/Excerpta Medica, *Evidence Based Medicine Reviews—ACP Journal Club,* and Cochrane Central Register of Controlled Trials (to October 2006); and reference lists.

Study selection and assessment: Randomized, double-blind, placebo-controlled trials (RCTs) with sample size ≥ 10, published in English as full articles, that evaluated the analgesic effects of oral or topical pain-relieving drugs (excluding Chinese herbal medicines) in adults with diabetic neuropathy. Quality assessment of individual trials was based on the 5-point Jadad score; trials with scores ≤ 2 were excluded. 25 RCTs (n = 3290, range of mean ages 50 to 64 y) met the selection criteria; 17 RCTs assessed efficacy, and 21 RCTs assessed withdrawals for adverse events. Median duration of treatment was 6 weeks (range 2 to 16 wk).

Outcomes: ≥ 50% or "moderate" reduction in pain; study withdrawal because of adverse events.

MAIN RESULTS

Traditional anticonvulsants (sodium valproate, lamotrigine, and carbamazepine), newer-generation anticonvulsants (gabapentin, pregabalin, and oxcarbazepine), tricyclic antidepressants (desipramine, imipramine, and amitriptyline), a serotonin noradrenaline reuptake inhibitor (duloxetine), and opioids (controlled-release oxycodone and tramadol) were all more effective than placebo for reducing diabetic neuropathy pain (Table). Topical cream (capsaicin) was also effective (1 RCT, n = 277; odds ratio 2.4 [95% CI 1.3 to 4.3]). Study withdrawals for adverse events were more frequent in the treatment group than in the placebo group with newer-generation anticonvulsants (5 RCTs, n = 811), duloxetine (especially at 120 mg) (2 RCTs, n = 690), opioids (3 RCTs, n = 376), and capsaicin cream (1 RCT, n = 277); groups did not differ for withdrawal rates with traditional anticonvulsants (4 RCTs, n = 181) or tricyclic antidepressants (3 RCTs, n = 152).

CONCLUSION

Tricyclic antidepressants, traditional anticonvulsants, newer-generation anticonvulsants, opioids, duloxetine, and capsaicin cream are effective short-term treatments for painful diabetic neuropathy in adults, although side effects may result in discontinuation of treatment.

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Oral analgesics vs placebo for ≥ 50% or "moderate" pain reduction at 2 to 16 weeks in patients with painful diabetic neuropathy*

Type of analgesic	Number of trials (n)	Weighted event rates		RBI (95% CI)	NNT (CI)
		Analgesic	Placebo		
Traditional anticonvulsants	3 (111)	43%	13%	245% (61 to 457)	4 (2 to 13)
Newer-generation anticonvulsants	4 (623)	46%	21%	122% (80 to 165)	4 (3 to 7)
Tricyclic antidepressants	3 (122)	43%	3.3%	1211% (403 to 2162)	3 (2 to 8)
Duloxetine, 60 mg	2 (455)	49%	28%	79% (44 to 114)	5 (4 to 9)
Duloxetine, 120 mg	2 (455)	44%	28%	61% (2 to 124)	6 (3 to 169)
Opioids	2 (195)	66%	32%	110% (64 to 148)	3 (3 to 5)

*Abbreviations defined in Glossary. Weighted event rates, RBI, NNT, and CI calculated from data in article using a random-effects model.

COMMENTARY

Guidelines for effective and safe treatment of diabetic neuropathy are not available. From their systematic review, Wong and colleagues concluded that tricyclic antidepressants, anticonvulsants, and other agents are more effective than placebo in reducing neuropathic pain, although they acknowledged that the included trials had small sample sizes, poor precision, and short follow-up. Pooled estimates of efficacy may be overestimates because of publication bias, limiting searches to English-language trials, poor response rate from authors of original trials, and inability to obtain outcome data from 32% of eligible trials (1, 2).

Wong and colleagues offered a treatment algorithm, starting with topical treatment or tricyclic antidepressants. At face value, this approach appears appropriate based on expense and clinical experience with these agents. The choice of traditional or newer anticonvulsants is based on a small number of events pooled from 7 trials of agents with different mechanisms of action, efficacy, and side effects. The lack of head-to-head comparisons of agents does not allow true evaluation of relative safety and efficacy to inform decision making. Until such trials are done, treatment algorithms will be subject to the bias and experience of clinicians and patients.

Because of this limitation and the observation of only moderate efficacy of current pharmaceuticals compared with placebo, future trials need to include head-to-head comparisons, longer durations of follow-up, and use of standardized and validated pain assessment scales to permit pooling of results across trials. Furthermore, research is needed on other possible interventions for diabetic neuropathy that may include stabilization of glycemic control and modulation of oxidative stress and neurovascular dysfunction (3).

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