

Review: Clonidine is more effective than placebo for long-term smoking cessation but has side effects

Gourlay SG, Stead LF, Benowitz NL. Clonidine for smoking cessation. Cochrane Database Syst Rev. 2004;(3):CD000058.

QUESTION

Is oral or transdermal clonidine more effective than placebo for achieving long-term smoking cessation?

METHODS

Data sources: Cochrane Tobacco Addiction Group trials register, MEDLINE, and PsycLIT (up to May 2004); and the e-mail newsgroup of the Society for Research on Nicotine and Tobacco for unpublished studies.

Study selection and assessment: Studies were selected if they were randomized placebo-controlled trials that compared oral or transdermal clonidine (maximum daily dosage ≥ 0.2 mg) with placebo. Methodological quality of individual studies was assessed for randomization procedure and blinding.

Outcomes: Smoking cessation at ≥ 12 weeks (biochemical verification of sustained abstinence assessed ≥ 12 wk after the end of treatment).

MAIN RESULTS

6 trials ($n = 776$) met the inclusion criteria. Assessment of blinding and details of the ran-

domization procedure were not reported in any of the studies. 4 of the 6 trials used biochemical verification of smoking abstinence using plasma cotinine (< 15 μ mL), salivary cotinine (< 20 μ mL), expired carbon monoxide (< 10 ppm), or random plasma thiocyanate monitoring. Volunteer participants were recruited from community settings (5 trials) and an internal medicine clinic and were described as smokers (> 10 cigarettes/d, 2 trials) or heavy smokers (> 20 cigarettes/d or > 1 pack/d for 3 years, 4 trials). Clonidine was taken orally (dosage varied from a maximum of 0.15 to 0.45 mg/d) (3 trials) or transdermally (dosage 0.1 to 0.3 mg/d) (3 trials). Dosage was individualized according to tolerance or body weight, and built up before quit day. Participants in 5 trials received behavioral therapy or counsel-

ing, and 1 trial randomized half the clonidine and control groups to behavior therapy. More patients who received clonidine stopped smoking than did those who received placebo (Table). However, clonidine was associated with such dose-dependent side effects as dry mouth and sedation.

CONCLUSION

Oral or transdermal clonidine is more effective than placebo for achieving long-term smoking cessation but is associated with side effects including dry mouth and sedation.

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Clonidine vs placebo for smoking cessation at ≥ 12 months*

Number of trials	Number of patients	Weighted event rates		RBI (95% CI)	NNT (CI)
		Clonidine	Placebo		
6	776	23%	14%	63% (22 to 118)	12 (7 to 25)

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

COMMENTARY

Although clonidine has been used to treat the symptoms of substance withdrawal for several decades (1), its use for smoking cessation has only recently been recommended. The systematic review by Gourlay and colleagues supports the conclusions of a U.S. Public Health Service clinical guideline on treating tobacco use and dependence (2). Clinicians should now have confidence that clonidine, along with nicotine replacement therapy (NRT) (gum, patch, inhaler, intranasal spray, or tablets) and antidepressant therapy (bupropion or nortriptyline), is an effective option for helping tobacco users quit.

Clonidine is best for patients who have agitation or anxiety that is unrelieved by NRT or antidepressants, and should be specifically considered when treating patients with withdrawal symptoms who use multiple drugs (e.g., opiates, benzodiazepines, or alcohol).

Clonidine is considered a "second-line" medication for several reasons. Special care should be taken when prescribing clonidine to older patients because of such well-known side effects as drowsiness, dry mouth, and postural hypotension. The dose should be tapered at the end of therapy to avoid the withdrawal effects of clonidine itself. Although the level of evidence for effectiveness is high, only data from 1 of the 6 small studies that were pooled showed a statistically significant difference. The U.S. Food and Drug Administration considers the use of clonidine for tobacco cessation to be an "off-label" indication.

While it is not clear which dose or route of administration is the most effective, oral dosing has the added attraction of being relatively inexpensive (< 50 ¢/d) compared with NRT or bupropion, which can cost $> \$3.00$ /d.

All the studies in the review by Gourlay and colleagues included substantial amounts of behavioral support, which underscores the imperative that clinicians should always focus on behavior change issues when addressing tobacco dependence.

Helping patients quit smoking is one of the most important things that health care providers can do. While clonidine may not be for everyone, it might be useful for patients who have extreme withdrawal symptoms or for those who do not improve with nicotine replacement or antidepressant therapy.

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