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Varenicline increases smoking abstinence at six months to a year compared with placebo or bupropion; nausea is the most commonly reported adverse effect

Mehmet Sofuoglu,
VA Connecticut Healthcare System & Yale Department of Psychiatry

Dianne Duffey, and
VA Connecticut Healthcare System & Yale Department of Psychiatry

Marc E. Mooney
University of Minnesota

Commentary

Context

Cigarette smoking is the leading cause of preventable premature death in the world, with an estimated five million smoking-related deaths worldwide. Quitting substantially reduces the health risk associated with smoking. Treatments available for smoking cessation include nicotine replacement therapies (NRTs), bupropion, and the most recently marketed, varenicline. Varenicline, an analogue of cytisine, is a partial agonist for the α4β2 subtype of nicotinic cholinergic receptors, which are associated with the addictive effects of nicotine. Varenicline may help smokers quit smoking by both reducing the rewarding effects of nicotine as well as attenuating the withdrawal symptoms.[1] This meta-analysis evaluated the efficacy and safety of partial nicotine agonists, varenicline or cytisine, compared to placebo or other treatments in clinical trials conducted worldwide.

Methods

Cahill and colleagues conducted a Cochrane review evaluating the efficacy of partial nicotine agonists, varenicline or cytisine, for smoking cessation. Randomised controlled trials comparing active drug with placebo were included in the analyses. The review also included studies comparing the efficacy of varenicline to bupropion or NRT. Studies were excluded if they did not have a minimum of six month follow-up data from the beginning of treatment. Literature searches were conducted using the Cochrane trial register and other databases including Medline, up to September 2010. The main outcome was the smoking abstinence rate at six months or more. Biochemical measures of smoking abstinence were the preferred outcome. One author extracted the data and another author checked them. The

Correspondence address: 950 Campbell Ave, Bldg 35, Mailcode 151-D, West Haven, CT 06516, Mehmet.sofuoglu@yale.edu.

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MS AND DD have no conflicting interests.

authors used a meta-analysis to produce a risk ratio (RR), using the Mantel-Haenszel fixed-effect model. The heterogeneity of the studies and publication bias were also assessed.

Findings

A total of 16 studies were included in the analyses, 15 for varenicline and one study for cytisine. Twenty-one studies were excluded. The main finding of the review was that the usual recommended dose of varenicline, 1mg twice daily, was more effective than placebo for continuous abstinence at six months or longer (RR 2.31, 95% CI 2.01 to 2.66). Lower or variable doses of varenicline were also more effective than placebo (RR 2.09, 95% CI 1.56 to 2.78). Results also indicated that varenicline was more effective than bupropion at one year after the initiation of treatment (RR 1.52, 95% CI 1.22 to 1.88). Similarly, varenicline was more effective than NRT at 24 weeks, although this effect was not statistically significant (RR 1.13, 95% CI 0.94 to 1.35). Overall, varenicline was well-tolerated even beyond the 12-week recommended treatment period. Nausea was the most common side effect, with a dose-dependent effect. The results did not show the behavioural adverse events reported in the post-marketing stage including depressed mood, agitation, and suicidal behaviour or ideation. The single trial of cytisine was inconclusive.

Commentary

The results demonstrate the efficacy of varenicline, relative to placebo, as a pharmacological treatment for smoking cessation both in the usual recommended dose as well as at lower or flexible-dosing schedules. The results also suggest that varenicline may be more effective than bupropion. However, this comparison of efficacy was based on only a few studies. Future studies specifically designed to compare the efficacy of NRTs, bupropion, and varenicline are needed.

What remains to be determined is whether varenicline will have similar efficacy in samples representative of all smokers. The clinical trials included in the meta-analyses excluded smokers with medical or psychiatric comorbidity or with other addictions. It has been estimated that at least one third of smokers in the U.S. have a psychiatric disorder or another addiction.[2] Thus, it will be important to conduct studies including these subject populations as well. Indeed, the authors identified numerous ongoing trials in these areas. In addition, clinical trials generally provide more psychosocial treatment than those provided in clinical settings. It will also be important to show the efficacy of varenicline in real-world settings.

This meta-analysis supports the safety of varenicline up to one-year duration. These findings do not support the post-marketing reports of depressed mood, agitation, and suicidal behavior or ideation associated with varenicline treatment. However, due to the selection biases of the included studies, the absence of these putative severe adverse events in this review is by no means dispositive. The causal relationship of these side effects to varenicline treatment or smoking cessation effect remains to be determined.

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