Varenicline for Smoking Cessation in Patients With Coronary Heart Disease

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Despite the decline in cigarette smoking over the past 40 years, self-reported data from the National Health Interview Survey show that 19.8% (43.4 million) of US adults were still smokers in 2007. Attempts to quit during the previous year in the general population decreased from 47% in 1993 to 38.8% in 2007, and only 4% to 7% of smokers trying to quit each year will eventually succeed.

Cardiovascular diseases are the leading cause of death in Western countries, and cigarette smoking has a clear cause-and-effect relationship with atherosclerotic disease, with the risk of myocardial infarction (MI) increasing with the number of cigarettes smoked. Similarly strong evidence indicates that smoking cessation alone can result in a 36% reduction in the crude relative risk of mortality in smokers who quit versus those who do not. The risk decreases rapidly: after only 1 year of cessation, quitters have a lower relative risk (RR = 0.63) of death from coronary heart disease (CHD) than do nonquitters, which decreases even further (RR = 0.38) after 3 years of cessation. Consequently, efforts to find effective treatments to enhance smoking cessation are of great importance. Psycho-social, pharmacological, and combined psychosocial and pharmacological intervention have been studied. Psycho-social interventions, including phone or internet support, behavioral therapy, and self-help programs are effective in promoting abstinence. In a meta-analysis of 19 randomized clinical trials conducted in older men with MI, odds ratios (OR) for abstinence at 1 year were 1.65 (CI 1.28, 2.13) for behavioral therapies, 1.58 (1.26, 1.98) for telephone support, and 1.47 (1.10, 1.97) for self-help. Efficacy was strongly associated with intensity of treatment, and intensive interventions started in the hospital after an acute cardiovascular event can have an even stronger effect, with several studies showing 12-month cessation rates of 50% to 70%. However, many individuals continue to smoke, and multiple studies have shown pharmacological aids to be of value. First-line pharmacological interventions approved by the US Food and Drug Administration for treatment of tobacco dependence include bupropion SR, varenicline, and nicotine replacement therapy administered in different forms. Pharmacological interventions are more effective when combined with counseling, and smokers trying to quit should receive both.

Varenicline, a partial agonist of the α4β2 nicotinic acetylcholine receptor, is the most recent addition to the repertoire of pharmacological interventions. In 2006, 3 clinical trials were published, of which two included an active treatment comparison group. They showed a positive effect on smoking cessation rates versus placebo at 1 year, whereas comparison with bupropion showed a positive effect in 1 study, and less convincing evidence in another (OR versus bupropion at 1 year: 1.46; 95% CI, 0.99 to 2.17; P = 0.057). Higher abstinence rates were shown for varenicline versus placebo at 6 and 12 months, but with concerns regarding study design. All trials involved a population of otherwise healthy volunteer smokers; had multiple exclusion criteria, thus limiting generalizability; and were conducted in academic centers. In 2006, the US Food and Drug Administration approved varenicline for the treatment of tobacco dependence.

The study published in the current issue of *Circulation* was designed to address some of the problems left open by previous research. The first was to evaluate the safety of the drug in cardiovascular patients. Inasmuch as varenicline binds to the α4β2 nicotinic receptor, and given that the effects of nicotine on the cardiovascular system are mediated by a different receptor, it is reasonable to expect that the drug may be safe in patients with CHD. Nevertheless, it was important to gather information about possible side effects in cardiovascular patients. Second, it focused on the incidence of psychiatric adverse events, a concern that had been raised with regard to this agent.

This multicenter, double-blind, randomized clinical trial compared varenicline (2 mg/daily for 12 weeks) with placebo in 714 smokers with stable CHD. Follow-up duration was 1 year. Smokers in both arms received in-person counseling followed by phone calls up to week 44. An intention-to-treat analysis was used; ie, patients who withdrew or were lost to follow-up were counted as smokers. The continuous abstinence rate (CAR) at 9 to 12 weeks, confirmed by expired air carbon monoxide (CO), was 47.0% in the varenicline group versus 13.9% in the control group (OR, 6.11, CI 4.18, 8.93). The CAR at weeks 9 to 52 (secondary outcome) was more than twice the CAR in the placebo group (19.2% versus 7.2%). The authors conclude that varenicline is well tolerated and does not increase cardiovascular events or mortality. Rates of severe psychiatric adverse events were very low and similar in both groups.

As noted above, as many as 50% to 70% of cigarette smokers remain abstinent for at least a year after an acute
Patients in the varenicline arm more often reported gastrointestinal side effects such as vomiting (8.2 versus 1.1), nausea (29.5 versus 8.6), and constipation (6.5 versus 2.0), or sleep disturbances (22.1 versus 9.7). These side effects led to drug discontinuation in almost 10% of patients.

Multiple characteristics of the study limit generalizability. Patients were recruited primarily from academic centers. Women and minorities were underrepresented. Patients with recent cardiac events or procedures, who were clinically unstable, or who had comorbidities common in CHD patients such as chronic obstructive pulmonary disease, severe diabetes, and depression were excluded.

Finally, despite the evidence from European studies that varenicline may be cost effective when compared with other available treatments, the cost of the treatment may be problematic, considering that the prevalence of smoking is higher among the less educated and among adults with incomes below the federal poverty level. These patients are often uninsured and may not be able to afford the drug.

In conclusion, varenicline is a useful drug for the treatment of tobacco dependence, and it seems to be reasonably safe in patients with chronic, stable CHD without a history of depression or psychiatric disease. Nevertheless, more research is needed before it can be safely prescribed to all patients with CHD, in particular those with comorbid depression and unstable cardiovascular disease. Its risk/benefit profile also needs to be evaluated in equivalence trials where varenicline is compared to current treatments, including intensive counseling. Finally, interventions combining multiple strategies, pharmacological and psychosocial, may have better long-term efficacy, in particular for patients who do not respond to the drug alone.

Disclosures

None.

References


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