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 2007.1 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.1

Cardiovascular diseases are the leading cause of death in Western countries, and cigarette smoking has a clear cause-and-effect relationship with atherosclerotic disease,2,3 with the risk of myocardial infarction (MI) increasing with the number of cigarettes smoked.4 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.5 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 nonquitters, which decreases even further (RR=0.38) after 3 years of cessation.6 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,7 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,8 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.9 Pharmacological interventions are more effective when combined with counseling, and smokers trying to quit should receive both.9

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,10–12 of which two10,11 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,11 and less convincing evidence in another10 (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,12 but with concerns regarding study design.13 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 Circulation14 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.15

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 death from cardiovascular disease, with mortality decreasing 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. Ph...
cardiovascular event.\textsuperscript{16} Inasmuch as all the participants in this study had stable cardiovascular disease, and patients with a history of recent MI or cardiac operation were excluded, the study population was made up of “resistant” cases—patients who did not quit despite the onset of cardiovascular disease, or those who had already resumed smoking despite having experienced a cardiac event. In such a population, a point prevalence abstinence of almost 28% at 1 year is a considerable success.

Clearly, varenicline does better than placebo as long as patients keep receiving the drug. With cessation of the medication, the prevalence of patients who were abstinent during the previous 7 days drops from 54.1% at the end of treatment to 34.9% at 24 weeks (a 35% decrease in 3 months) and to 27.9% at 52 weeks (a 48.4% decrease). In the control group, the point prevalence abstinence is lower, but more stable over time (18.1% to 15.9% at both 24 and 52 weeks), and this is consistent with the effect of psychosocial interventions. The effect at 1 year is lower than that generally reported in studies of psychosocial interventions: pooled OR of quitting versus usual care at 12 months=1.66 (CI 1.24, 2.21); quit rates=48.7% versus 38.4%.\textsuperscript{7} This may reflect a population that is relatively resistant to counseling, or it may be related to a less effective counseling intervention; the article does not provide details with regard to the content of each session.

Varenicline was compared to a placebo plus counseling instead of to an active treatment arm (ie, bupropion or NRT). Consequently, we do not know whether in patients with CHD varenicline is as effective, safe, and well tolerated as current (and less expensive) treatments.

The authors used CO sampling to confirm abstinence. CO samples have the benefit of being immediately analyzable, but CO’s relatively short half-life (3 to 5 hours) allows only the reliable detection of smoking within the past 9 hours, whereas nondaily smokers are more difficult to identify.\textsuperscript{17} The measurement of cotinine, a main metabolite of nicotine, is a more accurate measure of nicotine intake, and it is appropriate for validating 24- to 48-hour point prevalence measures.\textsuperscript{18,19} Continuous abstinence rates cannot be reliably validated biochemically.\textsuperscript{20} In this study, smokers who did not show up for a scheduled visit were counted as nonsmokers if they showed CO-confirmed abstinence at the next visit. Consequently, an occasional smoker would end up being considered abstinent, leading to an overestimation of continuous abstinence rates in both groups.

The authors conclude that varenicline did not increase CV events or mortality. Table 1 shows that the prevalence of most CV conditions was slightly higher in patients enrolled in the placebo group: 52.4% versus 46% had a previous MI, 51% versus 46% had revascularization, 4.2% versus 2.8% had atrial fibrillation, 6.7% versus 4.5% had a stroke, 16.7% versus 13.2% had diabetes (probability values not presented). Consequently, even though the crude number of adjudicated CV events was similar in both groups, it cannot be excluded that the some of the events in the placebo arm were due to a more unfavorable profile at baseline. Moreover, as the authors comment in the discussion, the study may not have been powered to detect small differences in cardiovascular events.

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,\textsuperscript{21} 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.\textsuperscript{1} 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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