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Counseling is a must with this smoking cessation aid

For many smokers, the benefits of quitting will outweigh the risks associated with varenicline.

PRACTICE CHANGER

Inform patients who are interested in taking varenicline (Chantix) that there is a small cardiovascular (CV) risk associated with it, as well as neuropsychiatric risks—and consider recommending that smokers with a history of cardiovascular disease (CVD) use nicotine replacement therapy (NRT) or bupropion instead.[1]

STRENGTH OF RECOMMENDATION

A: Based on a meta-analysis.

Singh S, Loke YK, Spangler JG, et al. Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. *CMAJ*. 2011;183:1359-1366.

ILLUSTRATIVE CASE

A 53-year-old man asks you to prescribe Chantix to help him stop smoking. He has made several attempts to quit in the past, but never managed to stop for more than 6 months—and has smoked a pack a day for 30 years. The patient does not have a history of heart disease, but he is on statin therapy for hyperlipidemia. What should you tell him about varenicline's potential benefits and risks?

Tobacco use remains the largest preventable contributor to death and disease in the United States.[2] In smokers with coronary heart disease, smoking cessation is associated with a 36% reduction in all-cause mortality (relative risk [RR], 0.64; 95% confidence interval [CI], 0.58-0.71)—a risk reduction greater than that of statins (29%), aspirin (15%), beta-blockers (23%), or ACE inhibitors (23%).[3]

Varenicline now has 2 black box warnings

In its 2009 update on recommendations for smoking cessation, the United States Preventive Services Task Force cited NRT and controlled-release bupropion, as well as varenicline, as effective smoking cessation aids.[4] Varenicline received US Food and Drug Administration (FDA) approval in 2006. In 2009, the FDA added a black box warning based on evidence of its adverse neuropsychiatric effects, including suicidality.[5]

In July 2011, the FDA required another label change,[6] based on a double-blind RCT published in 2010 showing that for patients with CVD, varenicline is associated with an increased risk.[7] As a partial nicotine agonist, varenicline could confer some of the CV risk associated with nicotine abuse.[8] The FDA has asked its manufacturer, Pfizer Inc, to conduct further studies.[6] The meta-analysis reviewed below—which was not associated with Pfizer or the FDA—was published in September 2011, just a couple of months after the label change.[1]

STUDY SUMMARY

Risk of ischemic or arrhythmic event is small but significant

Singh et al searched for double-blind RCTs that tested varenicline against a control in tobacco users.[1] All included studies had to have reported adverse CV events. The primary outcome was any ischemic or arrhythmic CV event.

The researchers found 15 such studies (n=8216), which ranged in duration from 7 to 52 weeks. Most used a placebo control, but some

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included bupropion or NRT. The researchers used a Peto odds ratio (OR) for the meta-analysis, useful when combining uncommon events and including studies with no events.[9]

Compared with placebo, varenicline significantly increased the risk of CV events (odds ratio [OR], 1.72; 95% CI, 1.09-2.71). The incidence of CV events was 1.06% (52 of 4908) among varenicline users vs 0.82% (27 of 3308) in the controls (number needed to harm [NNH]=417).

The limited number of deaths (1.4% among patients taking varenicline vs 2.1% in the placebo groups) prevented analysis of mortality risk. The study with the most statistical power, which accounted for 57% of the overall effect, was the only one that included patients with known stable CV disease. (None included patients with unstable CV disease, whose risk may be greater.) Even when this study was removed, however, the outcome (OR, 2.54; 95% CI, 1.26-5.12) was consistent with the primary result for CV events. A sensitivity analysis comparing the risk associated with varenicline with that of either NRT or bupropion yielded similar results (OR, 1.67; 95% CI, 1.07-26.2). For a higher risk population with stable CVD (5.6% annual risk at baseline), the authors estimated an overall NNH of 28 per year (95% CI, 13-213).

In smokers with heart disease, quitting is associated with a greater risk reduction than that of statins, aspirin, beta-blockers, or ACE inhibitors.

WHAT'S NEW

Evidence of CV risk is cause for concern

This meta-analysis provides evidence that varenicline is associated with a small but significant harmful effect on CV outcomes. The methods Singh et al used for review and article selection appear to be sound, and analysis of the included studies reveals little likelihood of publication bias.

CAVEATS

For many, benefits of quitting outweigh the risks

The absolute risk of a CV event found in this meta-analysis was small—just 0.24%. What's more, the primary outcome was a composite of a diverse group of outcomes, some more serious than others. And, when compared with the highly positive effects of smoking cessation, the benefit-harm analysis still appears to favor varenicline for most patients. The estimated number needed to treat to get one person to stop smoking for ≥24 weeks is about 10 (95% CI, 8-13).[8]

CHALLENGES TO IMPLEMENTATION

Finding time to educate patients

The additional time needed to discuss the CV and neuropsychiatric risks of varenicline will be a challenge to physicians working in busy outpatient settings. Proper documentation of this discussion is prudent, however, given the increase in risk with this medication. **JFP**

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