Editorial

Varenicline for smoking cessation

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What can we learn from the story so far?

The public health burden of smoking is so enormous it is not surprising that varenicline—the most recently approved drug for smoking cessation—has been prescribed so widely and discussed extensively. A linked paper by Svanström and colleagues (doi:10.1136/bmj.e7176) further explores the association between use of varenicline and the occurrence of serious cardiovascular events, including myocardial infarction, unstable angina, ischaemic stroke, and death from cardiovascular disease.[1]

Varenicline (Champix, Chantix) was approved by the Food and Drug Administration (FDA) in May 2006, and from that date until July 2011 about 8.9 million patients received 21.8 million prescriptions for this drug from outpatient retail pharmacies in the United States.[2] Widespread prescribing of varenicline has also occurred elsewhere. In New Zealand, for example, its use increased steadily (to about 13 000 patients) during the first three years of marketing and then doubled in the fourth year (to almost 24 000 patients) after subsidisation by the government's pharmaceutical management agency (unpublished data from New Zealand Intensive Medicines Monitoring Programme).

Against this background of increasing worldwide use of varenicline, postmarketing surveillance and other research have identified and investigated several safety concerns. Reported adverse effects of varenicline include psychiatric effects,[3] [4] suicide and suicidal ideation,[5] [6] and cardiovascular effects.[7] [8] The FDA first issued a warning about psychiatric safety concerns in November 2007, and more recently it issued a safety announcement highlighting a small increase in the risk of adverse cardiovascular events associated with the use of varenicline.[9] However a subsequent meta-analysis of randomised clinical trials has reported no significantly increased risk of cardiovascular events in patients taking varenicline compared with those taking placebo,[10] and debate about a causal effect continues.

The primary endpoint of clinical trials of new drugs is efficacy, and the specific inclusion criteria of such trials often exclude patients at high risk of adverse events. Clinical trials may include too few patients to identify infrequent adverse events or may have too short a follow-up to detect latent events after treatment has stopped.

Svanström and colleagues' study was designed to overcome these limitations of data from randomised trials. They conducted a nationwide observational cohort study in Denmark, specifically to compare the risk of serious cardiovascular events of varenicline with another smoking cessation drug, bupropion. A strength of the study was that it investigated a large representative population who used drugs to aid smoking cessation and therefore analysed the risks associated with such drugs in "real life" circumstances. The authors compared about 18 000 patients in each group and found no significant difference in the risk of major cardiovascular events between varenicline and bupropion users (hazard ratio 0.96, 95% confidence interval 0.67 to 1.39).

But do these new findings further our understanding of the risks of varenicline? Lack of a comparator group of patients who were trying to quit without drugs means that the study can conclude only that the risk of serious cardiovascular events was similar in patients taking varenicline to that of those taking bupropion. This may not help us determine whether varenicline should be prescribed to patients at higher risk of cardiovascular disease, or to determine whether myocardial infarction in a patient who has taken varenicline is causally related to the drug. It is likely to remain difficult to pinpoint the role that varenicline may play in causing an adverse event in a particular patient against a background of pre-existing disease (diagnosed or undiagnosed). The effects of other factors such as stopping smoking (fully or partially), restarting smoking during treatment, and concomitant use of other drugs (prescribed or not) also complicate the matter.

At this point in the story of varenicline—about six years after its licence approval—do we need to re-evaluate its risk-benefit ratio and remind ourselves and our patients of the bigger picture? Let's start with what we know. Smoking causes major health problems and most patients' attempts to quit fail.[11] Randomised trials showed that varenicline is more effective than placebo in achieving smoking cessation and leads to similar abstinence rates to nicotine replacement therapy at 52 weeks.[12] [13]

Although varenicline can help some patients stop smoking, there are potential risks, including psychiatric and cardiovascular adverse events. The potential risks of varenicline should be weighed against the risks of other smoking cessation treatments and also against the risks of continuing to smoke. This is where it becomes difficult, because no studies have compared the risks of varenicline treatment with the risks of continued smoking, and it is hard to imagine how such a comparison could be made directly in a single study. We can therefore only speculate on what the relative risks for any outcome might be. However, speculation is not ideal, and when consulting with patients about smoking cessation it is better to state what we know and acknowledge what we don't.

For varenicline, there seem to be three key messages. Firstly, the drug is effective in some patients, but more studies are needed to confirm the proportion of patients it works for in real life. Secondly, there are risks, some serious, associated with the use of varenicline, as outlined in the product information,[14] which patients should be encouraged to read. Although a causal association between these events and varenicline has not been proved (and may never be), if a patient develops suicidal ideation or unstable angina while taking varenicline it is advisable to stop the drug while investigating further. Lastly, it is important to continue rigorous postmarketing monitoring of the safety of commonly prescribed drugs. Reporting to national pharmacovigilance programmes around the world will help us further evaluate the risk-benefit of varenicline and other approaches to smoking cessation.

Notes

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