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Tobacco Smoking Is a Medical Problem We Ought to Treat It Like One

The number of premature deaths caused by cancer, cardiovascular and metabolic disease, and respiratory disease among cigarette smokers is substantial (1). The stakes, to both individual and population health, could not be higher when it comes to helping people quit smoking. Indeed, achieving abstinence from smoking results in a variety of health benefits, including reduced mortality. In a U.S. population-based study, quitting smoking resulted in 4–6 years of life gained, even when quitting after age 50 years (2). Fortunately, there are several effective pharmacologic therapies to help patients stop smoking, the most effective of which appears to be the $\alpha 4\beta 2$ nicotinic receptor partial agonist, varenicline (3, 4).

Although varenicline's efficacy is well established, there have been ongoing concerns about its safety in terms of risk for both cardiovascular and neuropsychiatric events. In this issue of the *Journal*, Gershon and colleagues (pp. 913–922) address the question of the safety of varenicline in a real-world setting (5). Using the Ontario (Canada) Drug Benefit Database, the authors captured all outpatient prescriptions for varenicline and linked them to national reporting databases for hospitalizations and emergency room visits. Through a self-controlled risk interval design, they ascertained cardiovascular and neuropsychiatric events in patients during the 12 weeks after a prescription for varenicline compared with other time intervals when these same individuals were presumably not taking the drug. Varenicline use was associated with a 34% increased risk for cardiovascular events in the population, with an estimated 3.95 cardiovascular events per 1,000 individuals attributable to varenicline use during the 12-week risk interval. Because a recent cardiovascular event during the “induction interval” might trigger prescription for varenicline in smokers and artificially inflate risk, an important sensitivity analysis was performed among individuals without a history of a cardiovascular event. In this group, Gershon and colleagues document a 12% increased risk for cardiovascular events in the

12 weeks after prescription for varenicline. Thus, in this real-world study using administrative health data, varenicline was associated with a small, yet statistically significant, risk for cardiovascular events.

The article by Gershon and colleagues has the distinct strength of using a real-world population, which likely captures the spectrum of use of varenicline using a national health database. This stands in contrast to several publications that rely on pooled analyses of data from randomized clinical trials to yield conflicting results regarding the cardiovascular safety of varenicline (6, 7). Many of the studies included in these meta-analyses excluded participants with significant underlying medical conditions and, as a result, may have underestimated risk when the drug is prescribed to individuals with the many comorbidities encountered in clinical practice.

In contrast, the data presented should be interpreted in the context of limitations in their study design. First, it is worth noting that a placebo-controlled randomized clinical trial evaluating the efficacy and safety of varenicline specifically in participants with stable cardiovascular disease did not document an increased rate of cardiovascular events among the varenicline group (8). A 2016 meta-analysis conducted by Sterling and colleagues (9), which involved 38 randomized clinical trials, observed no difference in cardiovascular adverse events when comparing varenicline and placebo treatment among patients with or without a history of cardiovascular disease. The discordance between adverse outcomes reported in the study by Gershon and colleagues and randomized clinical trials are likely a result of differences in the populations under study and/or biases inherent in the study design.

Observational studies of medication safety are particularly prone to bias, as residual confounding attributable to unmeasured factors that influence the prescription of a medication is difficult to account for. For example, in the self-controlled design employed by Gershon and colleagues, one wonders whether the prescription of varenicline was driven by any number of healthcare events that might enhance interest on the part of both providers and/or patients in making a quit attempt. The idea that an antecedent cardiovascular event in

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the induction interval might be the trigger is accounted for in a sensitivity analysis, but perhaps other noncardiovascular events such as respiratory events were the drivers. Such events certainly may be associated with increased short-term risk for cardiovascular events that would occur in the interval after a prescription for varenicline (10–12). The potential for confounding by indication (in this case, factors that increased cardiovascular event risk around the time when an individual was prescribed varenicline versus other periods in their life when they were smoking but varenicline was not prescribed) is an additional major challenge in interpreting the true risk associated with medication use when reported in pharmacoepidemiologic studies. The issue surrounding time-varying confounders cannot be solved through the use of the self-controlled design employed by Gershon and colleagues (13). Thus, in this study, varenicline prescription could be a marker, not a mediator, of increased risk for cardiovascular disease events.

Given the conflicting data derived from real-world observation studies such as that of Gershon and colleagues, and the meta-analyses of randomized clinical trials, it stands to reason that a very large-scale, pragmatic, prospective randomized controlled clinical trial of varenicline use compared with other smoking cessation therapies embedded in real-world clinical practice is a necessary step to truly understand the risks of varenicline relative to the many obvious benefits of successful smoking abstinence.

Absent data from a pragmatic trial to inform decision making, what should a clinician do? Our opinion is that smoking cessation should be approached similar to any other medical diagnosis, whereby treatment decisions require integration of both risks and benefits. There are several examples of common complex medical conditions in which therapies are associated with significant risks, often at a low event rate such as that seen in the current study with varenicline, but the potential benefits are great. The benefits of varenicline and a higher rate of smoking abstinence in reducing a variety of health outcomes need to be balanced against any potential risks in careful and coherent conversations between patients and providers.

It is reassuring to note that if a clinician, when faced with selection of smoking cessation therapies, determines that an individual patient is at excess risk and does not want to prescribe varenicline, combined mode nicotine replacement (i.e., transdermal patch combined with a fast-onset form such as that delivered via gum, lozenge, or inhaler) has comparable efficacy to varenicline (14). Just like any other condition encountered in clinical practice, treatment of tobacco dependence should be viewed through the lens of risks and benefits. In our view, the greatest risk is continued smoking and the largest benefit in terms of overall health to be derived is through the delivery of effective smoking cessation therapy. Varenicline is one therapy documented to be effective for long-term cessation but, similar to most medical therapies, might have some concurrent risks. Given the current evidence, clinicians should counsel patients about such risks, but not lose sight of the tremendous benefits that can be gained through helping our patients quit smoking. ■

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