Reassessing the Safety of Varenicline

In this issue, in a meta-analysis of 17 randomized placebo-controlled clinical trials involving over 8,000 participants, Gibbons and Mann (1) report that varenicline improved tobacco abstinence rates and was not associated with increased rates of neuropsychiatric adverse events. The incidence of depression, aggression/agitation, or suicidal thoughts and behavior was no greater in study participants who received varenicline than in those who received placebo, whether or not they had a past or present comorbid psychiatric illness. Those who received varenicline had higher rates of nausea than those who received placebo, indicating that the analysis was sensitive enough to identify emergent adverse events associated with the treatment. Of note, smokers with a past or current comorbid psychiatric illness were more likely than those without to report a neuropsychiatric adverse event, but this effect did not differ between those who received varenicline and those who received placebo.

The authors also report on an expanded analysis of an observational study of over 35,000 smokers treated in the Military Health System with varenicline or nicotine replacement therapy for smoking cessation. In this retrospective cohort study, in the overall sample and the subsample with a comorbid psychiatric or addictive disorder, smokers who received varenicline had fewer diagnoses of anxiety, depression, drug-induced mental disorder, episodic mood disorder, other psychiatric disorder, posttraumatic stress disorder, schizophrenia, suicide attempt, or transient mental disorder in the subsequent 60 days than those who received nicotine replacement therapy.

Why do we find ourselves in the nearly impossible position of trying to prove the absence of an association between a medication and an important category of adverse events?

There is no signal in either of these large samples with active or placebo controls for varenicline to be associated with new or worsening neuropsychiatric symptoms. This is consistent with another large observational study in over 80,000 people with nicotine replacement therapy and bupropion comparators (2) and with other randomized placebo-controlled clinical trials of varenicline in stable outpatients with schizophrenia (3, 4) and major depressive disorder (5). In our group's experience with varenicline for smoking cessation in outpatients with stable, treated serious mental illness, 25%−30% of patients report generally mild to moderate transient symptoms of anxiety, irritability, agitation, or excitement that seldom lead to treatment discontinuation or need clinical intervention, although they may lead to resumption of smoking (6). Interestingly, study clinicians in a recent trial at our site performed no better than chance when guessing whether study participants were taking varenicline or placebo. To my knowledge, there is no published trial that shows a difference between varenicline and placebo in ratings of positive, negative, or depressive symptoms over the course of treatment, and rates of psychotic or depressive exacerbation have not differed between varenicline

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and placebo arms. It is not that there were no psychiatric adverse events in people who received varenicline to help them quit smoking; there were quite a few, most transient and mild, but the rate is no higher with varenicline than with placebo in the randomized controlled trials or with nicotine replacement therapy and bupropion in observational studies.

Why do we find ourselves in the nearly impossible position of trying to prove the absence of an association between a medication and an important category of adverse events? The large initial trials of varenicline excluded smokers with concurrent psychiatric or addictive disorders. Varenicline was found to be extremely effective and well tolerated in these trials, with few psychiatric adverse events. However, by excluding smokers with psychiatric illnesses, these trials had no opportunity to evaluate, with the aid of a control group, the psychiatric adverse event rate with varenicline in smokers with comorbid psychiatric illness. When varenicline came into use in the general population of smokers and particularly worrisome events such as agitated, aggressive, suicidal, or violent behavior and new-onset psychosis and mania in stable outpatients were observed, the medication was blamed, and the alarm bell sounded with sensationalism in the press, warnings by regulatory agencies, restriction of varenicline by many formularies, and reluctance on the part of many physicians to prescribe varenicline.

Case reports and postmarketing pharmacovigilance reports are critical sentinels that identify adverse events *possibly* associated with medical treatments in real-world practice, not seen in carefully selected samples in randomized controlled trials, that could change the risk-to-benefit assessment of a treatment in general practice. But because of reporting bias, confounding, multiple reporting, and the uncertain denominator inherent in these reports, controlled trials are essential to determine whether a causal association exists. Attempting to understand the association between neuropsychiatric adverse events and smoking cessation aids provides a classic example. The underlying diagnosis of nicotine dependence is strongly, independently associated with an increased risk for suicide attempts (7). A large proportion of smokers have a comorbid psychiatric or addictive disorder and are at risk for psychiatric adverse events independent of smoking cessation treatment. The nicotine withdrawal syndrome reliably includes transient and usually mild anxiety, irritability, difficulty concentrating, and depressed mood. So it is not surprising that uncontrolled postmarketing reports alerted us to psychiatric adverse events with varenicline treatment that may have been due to nicotine withdrawal, underlying nicotine dependence, or other psychiatric illness.

Our task now as clinicians is to weigh the known consequences of continued smoking against the risks of pharmacologic cessation aids. Smokers who don't quit have a 50% chance of dying prematurely, on average 10 years prematurely, from a smoking-related illness. The good news is that those who quit smoking in middle age avoid the bulk of the excess mortality in later life; for example, those who quit before age 40 avoid 90% of the excess risk for premature mortality from smoking. Thus, the risk of continued smoking is high, and the benefit of cessation is clear. Too many of our patients who smoke have not had a single aided cessation attempt, although a majority will have tried to quit on their own. But we now know that a substantial proportion of smokers with and without comorbid psychiatric and addictive disorders can quit smoking with available cessation aids and that psychiatric illnesses, by and large, remain stable during and after the cessation attempt (8, 9). Treatment guidelines recommend pharmacotherapy for every smoker willing to try quitting (10). Nicotine dependence is defined as a chronic, relapsing disorder;

the average smoker makes five cessation attempts before attaining sustained abstinence, so multiple cessation attempts following relapses to smoking should be expected and encouraged.

Clinicians should advise their patients who smoke to quit, prescribe a pharmacologic cessation aid, refer them to the telephone quit line in their area, and provide or refer them to any other behavioral support that is available. They should ask their patients to set a quit date and plan what to do that day, and advise them that they may experience craving, anxiety, irritability, agitation, excitement, and insomnia but that these are likely to be relatively mild and time limited. With varenicline, patients are also likely to experience nausea and vivid dreams. The trend from several studies is to see improvement in mood with varenicline.

Varenicline doubles to triples the likelihood of quitting smoking over placebo, and its most common side effects are nausea and vivid dreams. With the Gibbons and Mann report joining other published studies finding no increased incidence of psychiatric adverse events with varenicline over placebo or active controls, it is time to unring the alarm bell on varenicline and use this effective medication on a larger scale.

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