Varenicline Does Not Appear to Increase Risk of Suicide or Depression

Gunnell D, Irvine D, Wise L, et al. Varenicline and suicidal behaviour: a cohort study based on data from the General Practice Research Database. BMJ 2009;339:b3805.

Study Overview

Objective. To determine whether varenicline is associated with increased risk of suicide, suicidal behavior, and depression as compared with bupropion and nicotine replacement therapy (NRT).

Design. Cohort study nested within the United Kingdom's General Practice Research Database (GPRD).

Setting and participants. The GPRD contains demographic, prescribing, medical record, referral, and health outcome data from approximately 500 general medical practices caring for over 3.6 million patients in the UK. Patients over age 18 years who were prescribed varenicline, bupropion, or NRT between September 2006 and May 2008 were included in the study. All patients with GPRD records of less than 365 days prior to first prescription or who took a smoking cessation product for more than twice the recommended treatment duration were excluded.

Main outcome measures. The primary outcomes were fatal and nonfatal self-harm, defined from 70 Read codes and Oxford Medical Information System (OXMIS) medical terms using a previously established GPRD algorithm. Secondary outcomes included suicidal thoughts, depression, and all-cause mortality defined through relevant Read and OXMIS terms. Depression was defined as the start of antidepressant therapy in people who had not previously been prescribed these medications within the past 6 months. Confounders included in the analysis were age, sex, previous psychiatric consultation, alcohol misuse, current or past psychotropic medication use, previous self-harm or suicidality, previous smoking cessation medication prescriptions, number of general practice visits annually, social deprivation index, region, and exposure before or after January 2008 (after which there was publicity about possible varenicline side effects). Adjusted Cox proportional hazard models were built to analyze the outcomes controlling for possible confounders as well as interactions between medication and age, sex, year, past use of psychotropic medications, and past psychiatric history.

Main results. The researchers identified a total of 80,660 patients prescribed smoking cessation medications during the study period: 63,265 received NRT, 6422 received bupropion, and 10,973 received varenicline. Patients prescribed varenicline and bupropion had similar sociodemographic and health characteristics; compared with patients given NRT they were more often male and less likely to have alcohol misuse, past psychiatric consultation, use psychotropic medications, and have past self-harm or suicidality. Over the follow-up period, 166 episodes of nonfatal self-harm, 2 suicides (both in NRT group), and 37 episodes of reported suicidal thoughts occurred. Standardized for age and sex, the incidence of self-harm was 533.1 per 100,000 person-years in patients prescribed varenicline, 498.7 per 100,000 among those receiving bupropion, and 751.7 per 100,000 for NRT. Compared with NRT, the hazard ratio (HR) for self-harm among patients prescribed varenicline was 1.12 (95% confidence interval [CI], 0.67–1.88), and it was 1.17 (95% CI, 0.59–2.32) for patients prescribed bupropion. The adjusted models showed no evidence that varenicline was associated with an increased risk of depression (n = 2244 patients; HR, 0.88 [CI, 0.77–1.00]) or suicidal thoughts (n = 37; HR, 1.43 [CI, 0.53–3.85]). Sensitivity analyses that censored follow-up to 10 weeks after treatment initiation or for patients who only took 1 cessation product during the study period showed no major outcome differences. During the study period, 208 patients died. There was no evidence that varenicline or bupropion were associated with increased risk of all-cause mortality compared with NRT (HR, 0.26 [95% CI, 0.13–0.53] and HR, 0.56 [95%, CI 0.26–1.19], respectively).

Conclusion. In a large sample of patients who took smoking cessation medications prescribed by general practitioners in the UK, varenicline was not associated with an increased risk of self-harm, suicide, suicidal thoughts, depression, or all-cause mortality.

Commentary

Varenicline is the newest smoking cessation medication approved for use in the United States and Europe. It is a partial

agonist that binds at the nicotinic α4β2 receptor in the brain, and it is likely the most effective smoking cessation product currently available, with a 6-month abstinence rate of 33.2% [1]. Beginning in late 2007, an increasing number of cases of suicidal thoughts and behavior and depression were reported in the mainstream press and to drug regulatory agencies worldwide. In July 2009, the U.S. Food and Drug Administration required the manufacturers of both varenicline and bupropion to add a new boxed warning to their products based on a review of postmarketing adverse event reports that suggested a possible increased risk of suicidality in patients taking these medications. However, smokers are more likely to have concomitant depression and suicidality than nonsmokers, and the risk of suicidality increases among smokers when they attempt to stop smoking regardless of whether medications are used [2]. Whether varenicline is associated with suicidality and depression independent of this possible confounding by indication is a key question in smoking cessation and primary care research.

This study sought to evaluate the risk of self-harm, suicidality, and depression among a large number of patients prescribed varenicline, bupropion, and NRT in the UK between 2006 and 2008. The database used to study this association was large, contained detailed medical and sociodemographic information, and was previously verified to study the risk of suicidality with certain medications. The authors were able to control for many key confounders including concomitant mental illness, past suicidality and depression, and multiple sociodemographic characteristics. They included multiple sensitivity analyses and interaction terms to help disentangle their complicated research questions.

A few key limitations deserve mention. First, the characteristics of patients taking varenicline differed from those taking NRT; those in the former group were less likely to have reported past self-harm symptoms, suicidality, or antidepressant use. This phenomenon was possibly associated with the negative publicity associated with varenicline after 2007 that highlighted risks among those with past depression, explaining the lower prevalence of associated factors in the group prescribed varenicline. Second, only 18 episodes of self-harm occurred in the varenicline group, highlighting a possible important power issue in the study. The study was only powered to detect a doubling or halving in risk for self-harm among the varenicline group at an 80% level. Thus, it is possible that if the risk is less than 2, the study might have been unable to detect it with the low number of events. Third, the study only included patients prescribed varenicline in a general practice setting. The UK has a robust network of Stop Smoking Services (SSS) linked to each of the primary care trusts that oversee care in the National Health Service. Many smokers access medications and counseling through the SSS, and these patients were not evaluated in this study. It is unclear whether these patients may differ from those accessing services from their general practitioners. Fourth, the observational nature of the study leaves open the possibility of unmeasured confounders that may have explained the findings seen, especially since the fully adjusted models showed slightly reversed (though statistically insignificant) HRs. Finally, death certificates were not obtained to verify all-cause mortality and the ratio of nonfatal self-harm to suicide was high in this study, suggesting that some cases of suicide may have been missed.

Applications for Clinical Practice

This large, well-conducted study of varenicline use in outpatient general practices in the UK does not show an association between varenicline and suicidality or depression. However, the observational nature of the study and the low power leave open the possibility that a small association may exist, pointing to the need for further large studies of varenicline safety, especially in patients with previous or concomitant mental illness. For now, physicians need to weigh the benefits of varenicline as the most efficacious smoking cessation medication available against a possible, though increasingly less likely, risk of psychiatric events. Physicians need to discuss these risks and benefits with their patients and come to a shared decision on the best course of action for the patient.

—Review by Asaf Bitton, MD

References

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