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## PSYCHOPHARMACOLOGY & NEUROBIOLOGY

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### COMMENTARY

# Varenicline Should Be Used as a First-Line Treatment to Help Smokers With Mental Illness Quit

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Despite reductions in smoking in the general population in the last 40 years, cigarette smoking is still the number one preventable cause of death in the United States. Smoking-related health care costs and associated productivity losses exceed \$167 billion per year in the United States (Centers for Disease Control and Prevention, 2007). All health care providers, but particularly those in behavioral health, should be more aggressive in providing first-line treatments for tobacco dependence. Clinical practice guidelines recommend a combination approach of both medications and counseling to give smokers the greatest chances to quit successfully. As a result of warnings published by the FDA, clinicians and policy makers have been questioning whether to recommend varenicline as part of a first-line treatment plan for smoking cessation. A few authors have been very outspoken in their reluctance to use this medication despite strong efficacy data and a lack of findings of significant neuropsychiatric side effects from clinical trial data. Even the FDA acknowledges that the risks that are known to be associated with smoking must be balanced against the small but real risk of serious adverse effects associated with medicines that can help patients quit smoking when making the decision on whether to use a medicine to help stop smoking. Given the devastation of tobacco addiction and struggles that patients experience trying to quit, the risk-benefit ratio

for many may be in favor of using varenicline as a first-line treatment approach.

#### IT MAY BE THE MOST EFFECTIVE SMOKING CESSATION PHARMACOTHERAPY AVAILABLE

Varenicline is a selective nicotinic receptor partial agonist that binds potently to the alpha4beta2 receptor, the main nicotinic receptor subtype implicated in nicotine addiction. As a partial agonist, varenicline mimics the effects of nicotine, resulting in the release of some dopamine in the nucleus accumbens; it concomitantly blocks the effects of the full agonist, nicotine (Coe et al., 2005). Because of its mixed agonist–antagonist properties, varenicline offers the therapeutic benefit of relieving the symptoms of nicotine withdrawal and cigarette craving during abstinence while also blocking the reinforcing effects of nicotine. The most frequently reported treatment-emergent adverse events associated with varenicline are nausea, insomnia, abnormal dreams, and headache (Cahill, Stead, & Lancaster, 2011).

Many trials have shown that varenicline is efficacious as an aid for smoking cessation in the general population (Gonzales et al., 2006; Jorenby et al., 2006). In well-designed head-to-head studies, varenicline was more effective than sustained-release bupropion (Cahill et al., 2011; Eisenberg et al., 2008; Wu, Wilson, Dimoulas, & Mills, 2006). One open-label trial has also demonstrated that varenicline is more effective than nicotine patch treatment (Aubin et al., 2008), and other retrospective analyses have indicated that it is more effective than other monotherapy treatments for smoking cessation (Stapleton et al., 2008).

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## SMOKERS WITH MENTAL ILLNESS ARE DYING OF TOBACCO-RELATED DISEASE AT AN ALARMING RATE

Individuals with serious mental illness smoke at higher rates and have higher levels of nicotine dependence than smokers in the general population (Lasser et al., 2000; Hagman, Delnevo, Hrywna, & Williams, 2008). Clinical samples of individuals trying to quit smoking in community-based cessation programs also reveal sizeable percentages (about 50%) with mental health issues (Piper et al., 2010; Han et al., 2006; McClure et al., 2010). The consequences of these elevated smoking rates are considerable. Smokers with mental illnesses incur significant tobacco-caused medical illnesses and lose up to 25 years of life expectancy (Brown, Inskip, & Barraclough, 2000; Lichtermann, Ekelund, Pukkala, Tanskanen, & Lonnqvist, 2001; Miller, Paschall, & Svendsen, 2006). Smoking-caused cardiovascular and respiratory diseases are common and cigarettes are responsible for much of the early mortality seen in schizophrenia, with 12 times more cardiac-related death in smokers relative to non-smokers (Kelly et al., 2011).

Smoking cessation rates in many of these groups are also lower compared with those in the general population (Tsoi, Porwal, & Webster, 2010; Lasser et al., 2000; Hagman et al., 2008). The quit ratio is calculated as the ratio of former to ever smokers and is considered a measure of total cessation in a population. In a sample of adults in the US population, 47% of ever smokers have quit whereas the quit ratio for those with serious mental illness was 0.29 (i.e., 29% have quit or were former smokers), indicating that they are less likely to quit smoking in their lifetime (Hagman et al., 2008). National treatment guidelines recommend that all smokers should be offered counseling and pharmacotherapy, and given that smokers with a mental illness tend to be heavier smokers, these recommendations should be followed more aggressively in this population, not less (Fiore et al., 2009).

## CASE REPORT DATA INDICATING NEUROPSYCHIATRIC SIDE EFFECTS HAS NOT BEEN BORNE OUT FROM CLINICAL TRIAL DATA AND THE OVERALL RISKS MAY BE SIMILAR TO OTHER TREATMENTS

Case reports in the post-marketing period raised questions about a possible association between varenicline and neuropsychiatric symptoms including depressed mood, psychosis, agitation, and suicidal behavior or ideation (Moore, Glenmullen, & Furberg, 2010). The FDA amended the labeling for varenicline and a boxed warning was added in July 2009. The contribution of varenicline to these conditions is not clear because smoking cessation, with or without treatment, causes nicotine withdrawal symptoms including depression, anxiety,

and irritability in addition to insomnia, which can be difficult to clinically distinguish from symptoms of an underlying psychiatric condition (Hughes, 2006). Moreover, interpretation of some neuropsychiatric adverse events is complicated because of the known higher rates of lifetime psychiatric illnesses in smokers versus nonsmokers. In addition, the early trials were conducted in highly selected smoking populations including predominately White smokers and excluding smokers with significant medical and psychiatric illnesses. This makes interpretation of some clinical trial data difficult since, in clinical practice, many smokers have significant medical and behavioral comorbidity and come from diverse racial and ethnic groups. Finally, smoking has been linked to suicidal thoughts and behavior in many studies, although the mechanism is unclear (Clarke et al., 2010; Breslau, Schultz, Johnson, Peterson, & Davis, 2005; Ostacher et al., 2006; Oquendo et al., 2007; Moriya, Hashimoto, & Furumiya, 2007). More studies of this emerging area are needed because the effect of successful and unsuccessful smoking cessation on depressed mood, anxiety, and suicide risk outcomes is unclear and further complicated by the use of pharmacotherapy.

Several post hoc analyses have now been published to better examine neuropsychiatric safety data. Pooled results from 10 placebo-controlled studies (Tonstad, Davies, Flammer, Russ, & Hughes, 2010) found no evidence that varenicline use was associated with more neuropsychiatric adverse events including depression and suicidality. Perhaps the best study to date was an analysis of more than 80,000 smokers treated with a smoking cessation medicine in primary care settings throughout the United Kingdom, including 10,973 treated with varenicline, 6,422 treated with bupropion, and 63,265 treated with nicotine replacement therapy (Gunnell, Irvine, Wise, Davies, & Martin, 2009). The incidence of self-harm, standardized for age and sex, was no different in patients receiving varenicline compared to bupropion or nicotine replacement products.

Although there is a published case report of an individual who experienced clinical worsening of schizophrenia while taking varenicline (Freedman, 2007), other case reports in smokers with schizophrenia, several of whom were successful in quitting smoking, indicated good tolerability with no clinical worsening (Evins & Goff, 2009; Fatemi, 2008; Anghelescu, 2009). Our review of published cases of neuropsychiatric symptoms attributed to varenicline found only one case of new-onset symptoms in a smoker with no prior psychiatric history (Kutscher, Stanley, & Oehlke, 2009). Most of the other cases are complicated by preexisting psychiatric conditions and complex polypharmacy (Williams et al., 2011). Other small studies have suggested improvements in cognitive test scores associated with verbal learning and memory with varenicline treatment (Smith et al., 2009).

In medicine, all treatments have an inherent risk and the risk-benefit ratio for determining whether treatment with varenicline is warranted should be balanced with the risk of continued smoking. In considering the comparative risk

between different smoking cessation treatments current data do not support an increased risk for varenicline versus nicotine replacement or bupropion (Gunnell et al., 2009). In addition, bupropion received the same boxed warning (risk of serious neuropsychiatric effects) by the FDA on the same day as varenicline, yet there have not been widespread calls to discontinue its use or relegate it to a second-line treatment.

### EMERGING STUDIES CONTINUE TO SUPPORT THE SAFETY OF VARENICLINE

In this issue, Pachas et al. (2012), report on the safety and effectiveness of varenicline in an open-label trial for smoking cessation in schizophrenia. The sample included 112 participants who were fairly typical for smokers with schizophrenia and comparable to participants from other smoking cessation studies. These authors report no worsening of psychiatric symptoms or nicotine withdrawal symptoms from baseline to week 12 or the end of treatment assessment. Although dropouts were fairly common, this is again not unusual in studies of schizophrenia and the authors reported a high rate of final assessment completion in early terminators (77%).

This study also found a fairly high rate of abstinence (34%) for 4 or more consecutive weeks of continuous abstinence at week 12. This relatively large, prospective, open study suggests that varenicline combined with cognitive behavioral therapy may be well tolerated and effective for smoking cessation in stable, treated outpatient smokers with schizophrenia and nicotine dependence. Over 12 weeks, participants demonstrated increased abstinence rates and decreased withdrawal symptoms, depressive symptoms, and psychosis. Although limited by the absence of a placebo control, the strengths of this study include the relatively large number of smokers with schizophrenia assessed and detailed follow-up measures used. This study was also funded by the National Institutes of Health and not by Pfizer, which has been another criticism of previously published varenicline studies.

Studies continue to be published that demonstrate the safety and efficacy of varenicline in a broader range of tobacco users with medical, behavioral, and diverse demographic characteristics as summarized in Williams et al. (2011). The risk-benefit ratio of using varenicline to quit smoking must be weighed against the sizeable evidence of cancer and cardiovascular and respiratory disease in smokers with mental illness and the risk of not taking aggressive action to treat tobacco dependence.

### DISCLOSURES

Dr. Jill Williams has received grant support from Pfizer and has also served as an advisory board member for Pfizer.

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