Quitting Smoking Without a Psychotic Break

The Potential Link Between Nicotinic Acetylcholine Receptor Partial Agonists and Neuropsychiatric Adverse Events

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I am a CNS in a busy cardiac rehabilitation center. We often prescribe Varenicline (Chantix, Pfizer) to help patients quit smoking. I am aware of the new warnings regarding Varenicline. What is the link if any between Varenicline and depression, agitation, and suicide ideation? Furthermore, how effective is Varenicline in smoking cessation?

Tobacco use claims more than 440,000 lives a year, with nearly half dying premature death from tobacco-related illnesses. Approximately 47.5 million adults smoke. Seventy percent want to quit, and 42.5% attempt to quit each year. Smoking cessation is correlated with reduced mortality and morbidity. Benefits include reduced risk for lung cancer, chronic lung disease, myocardial infarction, stroke, and low-birth-weight infants. Many of the effects of nicotine are reversible, and after 10 years, life expectancy of a smoker approaches that of a nonsmoker. However, tobacco dependence is a chronic and difficult condition to treat, and smoking cessation usually requires many attempts to quit. Despite the availability of nicotine replacement therapy and bupropion, abstinence rates remain low.

THE PROMISE OF VARENICLINE

Varenicline (Chantix, Pfizer) was developed to address the addictive effects of nicotine and withdrawal symptoms, which make quitting smoking so difficult. Varenicline is the first in a new class of agents defined as nicotinic acetylcholine receptor partial agonists recently approved by the Food and Drug Administration (FDA) for smoking cessation. Nicotine addiction is mediated by stimulation of central α4β2 nicotinic acetylcholine receptors (nAChRs) by nicotine, which in turn causes the release of dopamine that provides the pleasurable effects of smoking. The partial agonist activity of Varenicline occurs at the α4β2 neuronal nAChR and promotes a sustained low-level dopamine release, which reduces withdrawal symptoms. Because of Varenicline affinity and long half-life compared with nicotine, Varenicline also acts as an antagonist by preventing nicotine from occupying α4β2 nAChRs during smoking, which reduces the pleasure or satisfaction associated with smoking. In summary, Varenicline, a nAChRs partial agonist, reduces the craving and withdrawal symptoms associated with abstinence and reduces the rewarding effects of smoking in patients who lapse.

Research Outcomes

Evidence from recent clinical trials suggests that Varenicline has superior efficacy over placebo and bupropion in achieving abstinence and reducing relapse. In phase 2 studies, the efficacy for Varenicline for short- and long-term tobacco abstinence was established. Phase 3 trials tested the safety and efficacy of 1 mg of Varenicline twice daily and maintenance therapy after 12 weeks of treatment compared with 12 weeks of treatment followed by placebo. Phase 3 trials also compared Varenicline with placebo and bupropion-sustained release. After 12 weeks of treatment, there was nearly a 4-fold increase in tobacco abstinence compared with that of placebo and almost a doubling of the odds of quitting smoking with Varenicline compared with bupropion-sustained release. Abstinence rates through week 52 ranged from 22% to 23% with Varenicline compared with 8% to 10% with placebo. Furthermore, symptoms of withdrawal, craving, and smoking satisfaction were significantly diminished for persons treated with Varenicline compared with those of placebo.
**PHARMACOKINETICS**

Varenicline is not affected by food, and steady state is achieved within 4 days of administration with a half-life of 24 hours. Therefore, Varenicline is not indicated for patients who must quickly abstain from smoking, which is the case for hospitalized patients. Varenicline has low protein binding and is not metabolized by the cytochrome P-450 isoenzyme 2A6.7 Maximum plasma concentration occurs 3 to 4 hours after oral administration, with a steady state achieved in 4 days. Elimination half-life is 24 hours, with 92% excreted unchanged in urine. Pharmacokinetics seem not to vary related to age, race, sex, smoking status, or use of concomitant medications. In persons with severe renal impairment (creatinine clearance <30 mL/min), Varenicline exposure was increased 2.1-fold. Caution is warranted with use in patients with renal impairment. Safety and effectiveness have not been established for pediatric patients, and Varenicline is not recommended for children younger than 18 years. The CNS may prescribe Varenicline to persons with liver disease since Varenicline does not undergo hepatic metabolism. The effects of combining bupropion and Varenicline have not been established.9

**Dosing and Adverse Effects**

Varenicline is available as 0.5 and 1 mg tablet. Adjust dosage from 0.5 mg once for days 1 to 3 and twice daily for days 4 to 7, with a final dosage of 1 mg twice daily beginning day 8. Dosing should begin 1 week before the scheduled quit date and continue for 12 weeks. Remember, Varenicline may be an option for those patients who concurrently smoke during therapy for cessation since Varenicline is a non-nicotine drug and will antagonize the effects of nicotine. However, patients should be warned that smoking during Varenicline use does increase nausea.7,9

Common adverse effects of Varenicline include nausea and vomiting. Taking Varenicline after a meal with a full glass of water seems helpful to decrease adverse effects, and dose reduction has been helpful. Less common adverse effects include headache, insomnia, abnormal dreams. No meaningful drug interactions have been identified.7,9

Twenty-four weeks of treatment may be more effective than that of 12 weeks to prevent relapse.9 Other dose-related adverse effects include sleep disturbance, constipation, flatulence, and vomiting with concomitant nicotine withdrawal symptoms. Monitor carefully patients taking theophylline, warfarin, and insulin who may require dose adjustment with the cessation of smoking.8

Other frequently reported adverse effects include diarrhea, gingivitis, edema, thirst, abnormal liver function tests, back pain, musculoskeletal pain, myalgia, polyuria, menstrual disorders, epistaxis, hypertension, and hot flushes.8 Varenicline is a pregnancy category C drug. Since there are no adequately controlled studies in pregnant women, Varenicline should only be used if the benefit justifies the potential risk to the fetus. It remains unknown whether Varenicline is excreted in breast milk; however, animal studies have demonstrated that Varenicline can be transferred to nursing pups. Therefore, a decision must be made whether to discontinue breastfeeding or drug therapy. Finally, patients should be warned that they may experience vivid, unusual, or strange dreams during therapy and should exercise caution in driving or operating machinery. Frequent nervous system disorders have been reported and include decrease in attention span, dizziness, sensory disturbances, anxiety, depression, irritability, and restlessness.8

**THE POSSIBLE LINK BETWEEN VARENICLINE AND MENTAL ILLNESS**

Varenicline has been associated with significant psychiatric adverse events in persons with and without preexisting mental illness.4 After the May 11, 2006, drug approval, reports of adverse events such as depressed mood, agitation, changes in behavior, suicidal ideation, and suicide began to emerge.7 The role of Varenicline in these adverse events remains unknown. Recent case reports suggest that Varenicline may induce mania and psychosis in vulnerable individuals with a history of depression. Varenicline displaces nicotine from acetylcholine receptors, produces moderate to low dopamine release, and stimulates the central mesolimbic dopamine system, which is believed to be responsible for the reinforcement and rewards associate with smoking. As a result, the equilibrium of cholinergic-adrenergic tone may be altered, which is also associated with physiology of mania. The dopaminergic agonist action of Varenicline may also trigger psychotic symptoms. Screening for family and individual past history of serious mood disturbances and life stressors before prescribing could reduce the risk of serious adverse effects. The CNS should remember that bupropion is also a dopamine agonist associated with suicidal ideation, depression, psychosis, and mania. It is proposed that the use of adrenergic agonist antidepressants such as bupropion in persons with bipolar depression may render patients at greater risk for mania and mood instability.8 Certainly, further research is needed to explore the role of nicotine addiction in the pathophysiology of mood and psychotic disorders.10

Preclinical studies reported the rare adverse events of agitation, aggression, and mood swings with Varenicline. Recent reports describe new onset of depressed mood, erratic behavior, agitation, suicidal ideation, and suicide within days to weeks of beginning Varenicline. Also reported are exacerbation of symptoms of schizophrenia and induction of a manic episode in a patient with bipolar disorder.11–13 Again, whether exacerbation of underlying psychiatric illness is related to smoking cessation or Varenicline is unknown. Some of the patients did not have preexisting psychiatric illness, and not all had stopped smoking. In addition, patients reported drowsiness significant enough that the ability to drive or operate machinery was decreased.14

As a result, on February 1, 2008, and May 16, 2008, the FDA issued alerts regarding the revisions to the “Warnings” and “Precautions” sections of the full prescribing information for Varenicline, warning patients to stop taking Varenicline if either the patient, the family, or the caregiver notices agitation, depressed mood, changes in typical behavior, or suicidal thoughts or actions.15,16
IMPLICATIONS FOR CNS PRACTICE

The most effective smoking cessation interventions are a combination of pharmacotherapy and behavioral counseling. Interventions should be tailored to the patient’s readiness to quit. For patients who do not intend to quit, provide information and teaching about smoking cessation. For smokers who are hesitant, use motivational strategies such as exploring barriers to quitting and ways to overcome obstacles. For those ready to quit, show strong support, help set a quit date, plan behavioral strategies, and consider prescribing pharmaceutical and nicotine replacement therapies.

Monitor carefully the patient’s mood and behavior when prescribing Varenicline. Assess for worsening pre-existing psychiatric illness in patients trying to quit smoking. Since the safety and efficacy of Varenicline use in persons with schizophrenia, bipolar disorder, or major depressive disorder have not been established, Varenicline should be avoided. Patients should be advised to stop Varenicline immediately if agitation, depressed mood, or changes in behavior occur or if the patient develops suicidal ideation or suicidal behavior, and the care provider should be notified.

Since patients will probably still want to smoke, help the patient design a plan to cope with situations where the desire to smoke is great. Instruct patients to call immediately for symptoms of chest pain or of seeing or hearing things that are not really there. The CNS can report adverse events to the FDA’s MedWatch reporting program at 1-800-FDA-1088 or online at http://www.fda.gov/medwatch or by mail to 5600 Fishers Lane, Rockville, MD 20852-9787.

Finally, offer hope to patients who fail to quit smoking. A recent meta-analysis of 70 placebo-controlled, double-blind randomized controlled clinical trials with 322,908 patients found that Varenicline, bupropion, and 5 nicotine replacement therapies were more effective than placebo in patients found that Varenicline, bupropion, and 5 nicotine replacement therapies.

References