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Exacerbation of Schizophrenia by Varenicline

TO THE EDITOR: Schizophrenia is associated with heavy smoking. The replacement of tobacco by other forms of nicotine only occasionally achieves abstinence in persons with schizophrenia (1). The nicotinic agonist varenicline is a new alternative replacement agonist. There are no reports of its use in schizophrenia. We present the case of a patient with schizophrenia who received varenicline and experienced an activated psychotic relapse.

A 42-year-old woman with schizophrenia had been treated for 17 years with 1015 mg of thiothixene. She had several brief psychotic episodes per year, which seldom lasted for more than 3 days. She had no overt psychotic symptoms during an office visit one month previously. Her usual symptoms during acute psychotic episodes were voices commenting on her behavior, confusion, and angry outbursts. She smoked one to two packs of cigarettes per day and had made several attempts to discontinue the use of nicotine chewing gum and trandermal nicotine patches. The patient's mother reported a 5-day psychotic episode that began with increased activity, primarily the discarding of financial statements. At day 4, the patient ordered her daughter out of the house, and she threw away her thiothixene, which her daughter had insisted that she continue to take. She spent the next day screaming in her closet. Her mother administered thiothixene (20 mg) on the fifth evening and fed her because she had stopped eating. She appeared well groomed the next morning, without psychotic symptoms. She had no explanation for her sudden relapse and remission, but she announced with pride that her internist had prescribed a new medication, varenicline (2 mg), to help her stop smoking. The patient had been receiving varenicline for 5 days, and her quit day was the following day. She was advised to continue thiothixene, to avoid varenicline, and to return to nicotine chewing gum as a smoking substitute. She had no further exacerbations, but she continued to smoke cigarettes.

Nicotine activates several classes of brain cholinergic receptors. Many are high affinity presynaptic receptors, composed primarily of alpha4 and beta2 subunits, which cause the release of dopamine and other neurotransmitters. Nicotine produces profound tachyphylaxis at doses that are close to its agonist effect, which quickly ends its pleasurable effect. Heavy smokers, including persons with schizophrenia, respond by increasing their smoking to overcome the tachyphylaxis. Varenicline is principally an agonist at high affinity receptors, with a lower propensity to tachyphylaxis than nicotine (2). The more prolonged agonist effect of the drug was selected to increase its acceptance by smokers as a substitute for the briefer effects of cigarettes. Prolonged release of dopamine and norepinephrine may have resulted in the activated psychotic relapse in our patient. Her relatively low neuroleptic dose likely increased her vulnerability to this effect.

In addition to its pleasurable effects, smoking is a possible self-medication for cognitive dysfunction in schizophrenia. We have postulated the involvement of a different class of postsynaptic cholinergic receptors, composed primarily of alpha7 subunits, which activate inhibitory interneurons and thus inhibit response to extraneous sensory response. Pharmacological activation of these receptors by more alpha7-selective agonists improves cognitive performance in schizophrenia (3). Consideration of the unique neurobiological vulnerabilities of persons with schizophrenia is necessary in the design of cholinergic therapies for psychosis and smoking cessation.

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Varenicline-Induced Manic Episode in a Patient With Bipolar Disorder

TO THE EDITOR: We report a case of a manic episode in a patient with a history of bipolar disorder who was started on varenicline for smoking cessation. The case raises the possibility of inducing a manic episode with varenicline and using caution when prescribing it to patients with bipolar disorder.

A 63-year-old man with a history of bipolar disorder had been stable while receiving valproic acid for 5 years. The patient was admitted to an inpatient psychiatric unit and met criteria for a manic episode. He began exhibiting manic symptoms one week after starting varenicline (1 mg, twice daily) for smoking cessation. There was reported compliance with valproic acid, and his level on ad-

mission was 59.7. The patient had a negative urine drug screen; all other laboratory studies were normal. There were no other changes in his medication regimen, and he did not smoke cigarettes while on varenicline or after his admission to the hospital.

Varenicline was discontinued upon admission. The patient continued receiving valproic acid, up to a dose of 2 g per day. He was also started on olanzapine, up to 10 mg daily at bedtime. Within one week of admission, the patient was euthymic, without psychotic or manic symptoms.

Varenicline was approved by the Food and Drug Administration (FDA) in 2006 for smoking cessation. Varenicline binds with high affinity and selectivity at alpha4beta2 neuronal nicotinic acetylcholine receptors. Its efficacy is the result of its activity at a subtype of the nicotinic acetylcholine receptor, where its binding produces agonist activity while simultaneously preventing nicotine binding to the alpha4beta2 receptors. During abstinence, varenicline stimulates low-level dopamine release by binding to alpha4beta2 receptors located on dopamine neurons (1).

Agitation, aggression, and mood swings were reported as infrequent psychiatric adverse reactions in the preclinical studies for FDA approval of verenicline. In addition, euphoric mood, agitation, and psychosis were reported as rare psychiatric adverse reactions.

Several studies have shown that centrally active cholinergic agonists possess antimanic properties. Imbalance in cholinergic and adrenergic tone has been postulated in the pathophysiology of bipolar disorder, with relative cholinergic hypoactivity being implicated in the pathophysiology of mania (2). The release of catecholamines, such as dopamine, was likely related to the induction of mania in our patient.

Due to the high rate of smoking in bipolar disorder patients, smoking cessation agents may be used in a great number of patients with the disorder. However, our findings suggest a possible link between the onset of manic symptoms and treatment with varenicline in a patient with bipolar disorder. In this case, there was a temporal relationship between the beginning of therapy and the onset of symptoms. There were no other medication changes in our patient's regimen. A MEDLINE literature search revealed no case reports or studies regarding manic symptoms with varenicline. Our case highlights the need to use caution when prescribing the drug to patients with bipolar disorder.

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Alcohol Use and Anxiety

TO THE EDITOR: The Treatment in Psychiatry case study by Kathleen T. Brady, M.D., Ph.D., et al. (1), published in the February 2007 issue of the *Journal*, is a beautifully written clinical summary that utilized the presentation of a patient with commonly observed comorbid symptoms to review the most recent literature on the treatment of alcohol use disorders, anxiety spectrum disorders, and the overlap between the two. However, I cannot help but to notice that the authors chose not to address the controversial issue concerning the use of benzodiazepines with a patient such as "Ms. M." Although those of us who work in the field of addiction psychiatry are generally in agreement that benzodiazepines are contraindicated in managing symptoms other than alcohol withdrawal in individuals with alcohol use disorders who are actively drinking, many of my psychiatric colleagues would have prescribed either a benzodiazepine or a nonbenzodiazepine GABA-BZ receptor agonist hypnotic, such as zolpidem or eszopiclone, to treat the patient's insomnia. I feel that it is important to stress the risks of prescribing such treatment. These risks include 1) complicating the substance use picture with a cross-tolerant agent, thereby delaying diagnosis and treatment of potential alcohol dependence; 2) drug-drug interactions between sedatives and alcohol that can further impair motor function, resulting in a variety of untoward incidents, e.g., motor vehicle crashes, accidents in the home; 3) increasing rather than decreasing patients' craving for alcohol, making it less likely that he or she will be able to establish abstinence; and 4) worsening of depressive symptoms with possible suicide via a combination of sedatives and alcohol.

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Dr. Brady Replies

TO THE EDITOR: We would like to thank Dr. Zeigler for her insightful response to our case presentation. Dr. Zeigler appropriately points out some of the risks involved in prescribing benzodiazepines to individuals with substance use disorders. Unfortunately, insomnia is a common problem in individuals who are in early recovery from substance use disorders, and there is little empirical evidence to guide treatment of this problem. There are promising cognitive behavior strategies that have demonstrated efficacy in sleep disorders, but these strategies have not yet been tested in individuals who are in early recovery from substance use disorders. Additionally,