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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-**