Exacerbation of Psychosis: A Case of Possible Varenicline-Mediated Effects in an Intellectually Disabled Adult

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Abstract

Varenicline represents a new agent available to aid smoking cessation. A twenty-five year old, white male with diagnoses of Psychosis Not Otherwise Specified, Antisocial Personality Disorder, nicotine dependence, and mild mental retardation with food obsession, paranoia, and a seizure disorder, was well controlled with a regimen of ziprasidone and haloperidol for paranoia and psychosis, escitalopram for obsessiveness, and carbamazepine for seizures. He became increasingly paranoid following the addition of varenicline for smoking cessation. An increase in ziprasidone resolved paranoid symptoms. Concurrent use of ziprasidone, haloperidol and carbamazepine may have provided more psychiatric stability in this patient. There may exist a subset of patients for whom use of varenicline may increase the risk of breakthrough psychosis or mania. This case report was accepted for a poster presentation at the 2008 College of Psychiatric & Neurologic Pharmacists Annual Meeting, April 13–16, 2008, Scottsdale, AZ.

Key Words: Varenicline, Psychosis, Developmentally Disabled, Intellectual Disability

Introduction

Varenicline represents a new agent available to aid smoking cessation. It is a partial agonist with high affinity and selectivity for the alpha-4-beta-2 nicotinic acetylcholine receptor subtype (1). Nicotinic receptors are thought to be critical in a number of cognitive processes and psychiatric conditions. These include memory and attention functions and schizophrenia (2). In addition, there exists a significant association with heavy smoking and schizophrenia (3).

Nicotine effects are expressed via selective activation of various nicotine acetylcholine receptor subtypes which presynaptically mediates release of dopamine, norepinephrine, serotonin, gamma-aminobutyric acid and glutamate (4). Individually, and in combination, these receptors mediate or regulate behavior.

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Several theories have been postulated to account for these differences, including the attenuation of nicotine on the side effect burden of antipsychotics, as one theory, in smoking behaviors between the general population and persons diagnosed with schizophrenia. McEvoy and colleagues found heavy nicotine use corresponded to nonresponse as a predictor of therapeutic response to haloperidol (5). A second theory is the possibility of nicotine for self-medication. Nicotine may help address psychomotor impairment and sensory deficits identified in persons with schizophrenia. Both auditory-evoked responses and abnormal smooth pursuit eye movements are normalized with nicotine use. These sensory deficits are noted in schizophrenics (4). A relationship is also identified between major depression and smoking, with higher rates in those with depression and schizophrenia (4).

An additional consideration is the use of antipsychotic agents in persons with psychoses. Interactions with nicotine and antipsychotic agents are reported (2). Several reports indicate the use of varenicline for smoking cessation is associated with a psychotic relapse (6), mania (7) and hypomania (8).

In November 2007, the U.S. Food and Drug Administration's release of safety information and adverse event reporting alerted healthcare professionals and consumers regard-

ing reports of suicidal thoughts and behavioral changes in persons who had taken varenicline for smoking cessation (9).

We report the first case of exacerbated behavioral changes and increased psychosis in an adult male with intellectual disabilities following use of varenicline for smoking cessation.

Case Report

The patient is a twenty-five year old, white male who resided in a long-term care facility for the intellectually disabled. Diagnoses included Psychosis Not Otherwise Specified, Antisocial Personality Disorder, nicotine dependence, and mild mental retardation. A behavior plan with psychotropic medication use was a component of his plan of care. Target behavior rates tracked prior to the addition of varenicline were physical aggression, self-injury, property destruction and verbal aggression. Rates were low for February and March 2007. Prior to initiation of varenicline, psychotropic medications included haloperidol 12.5 mg total daily dose for psychosis and escitalopram 30 mg mornings for depression and obsessive behavior.

In addition to medication use, a structured behavior program was also developed for this patient. He ruminated on several specific topics and access to cigarettes was also a control issue. The patient was a heavy smoker. His program allowed one cigarette per hour, up to 16 per day within a specific timeframe, if requested. Issues of control involved attempts to manipulate staff for earlier access. Requests for cigarettes were documented in staff notes. At the patient's request, varenicline was added the last week of March 2007. The dose was titrated according to the recommendations for smoking cessation. Increased interpersonal conflicts (including arguing, teasing, and noncooperation) and depressive symptomology were noted and added to the plan of care. These behaviors were originally attributed to changes in the milieu dynamic following a change in residential unit, starting a new job and conflict with peers in the new residential setting. In addition, during the initial treatment phase, criteria for transitioning into a community placement were met, and he was referred for placement. Smoking behaviors reflected no reduction in the total number of cigarettes requested daily. Varenicline was discontinued the second week of May 2007 following the patient's refusal to discontinue smoking. Behavior rates remained elevated and increased the following month.

Following discussions with the primary care physician and guardian, the patient again requested varenicline for smoking cessation. It was reinitiated the third week of July 2007. The next month, August 2007, increased psychiatric and behavioral disturbances of increased paranoia and aggression were documented. Noncooperation with reasonable requests were less than in July but continued to escalate. Additional changes in the milieu were not reported, no new admissions occurred to his living area, and the job remained stable. Behavioral and environmental interventions were unsuccessful. The patient reported he had stopped smoking completely in August. Ziprasidone 80 mg was added the second week of October and increased to 120 mg three days later secondary to escalating paranoia, which included auditory hallucinations. The severity of physical and verbal aggression continued to increase, and varenicline was discontinued the first week of November as the patient continued to be free of cigarette use since August. By the end of the month, rates for verbal aggression and arguing had declined, but were still significant. Rates for physical aggression decreased from twenty-two episodes in November to nine in December. Refusals to cooperate also declined from sixty-six episodes to thirty-eight. Other target behaviors remained relatively constant, with arguing increased slightly (twenty-seven episodes in November to thirty-five in December).

We report the first case of exacerbated behavioral changes and increased psychosis in an adult male with intellectual disabilities following use of varenicline for smoking cessation.

Discussion

Nicotinic receptors are thought to be critical in the functions of learning, memory, and attention, as well as in many postulated models of schizophrenia (2). In addition, there is a significant association with heavy smoking and schizophrenia, and interactions with nicotine and antipsychotic agents are reported (4). Several reports indicate use of varenicline for smoking cessation was associated with a psychotic relapse (6), mania (7) and hypomania (8). Prior to the addition of varenicline, these were well controlled by monotherapy with thiothixene and valproic acid, respectively. In each of the previously published case reports, behavioral changes were observed more quickly following therapy initiation.

Nicotine withdrawal was suggested as a contributing factor for behavioral changes. Discontinuation of nicotine included changes in mood such as irritability, depressed mood, restlessness, anxiety, interpersonal problems, and increased hunger and eating. Insomnia and tobacco craving were also reported (10). Symptom onset has been reported within twenty-four hours. The duration of withdrawl symptoms varies (11). Psychosis was not identified as a withdrawal symptom, and in this patient mood dysregulation occurred with tobacco use.

Compared to the general population, persons diagnosed with mental illness have a higher incidence of nicotine use than the general population (12). Grant and colleagues con-

ducted a population-based study and estimated people with comorbid nicotine dependence and mental illness, comprising 7.1% of the study population, smoked slightly more than one-third of the cigarettes purchased in the United States between 2001 and 2002 (13).

For the segment of the population diagnosed with schizophrenia, cognitive impairment was one of the essential features (14). A significant number of those with schizophrenia also smoke tobacco (2). The cognitive enhancing effects for nicotine are well reported. The positive association between smoking and a variety of psychiatric disorders was reported in retrospective and cross-sectional studies (4, 12, 13). In this patient, the initial changes in behavior were attributed to environmental changes which resulted from competition for staff attention and interpersonal conflict on the unit following the admission of peers of similar age and diagnoses. The receptor binding characteristics of haloperidol may have also attenuated the effects of varenicline use.

In this patient, the maintenance dose of haloperidol may have helped control the psychosis. Haloperidol, a butyrophenone, blocks mainly D2 receptors. The potency of typical antipsychotic agents positively correlates well with their D2 receptor binding affinity (15). The addition of ziprasidone, a benzisothiazolyl piperazine derivative, may have provided additional D2 binding activity. In the previously cited case reports, varenicline exposure ranged from five days to one month before changes in psychiatric stability were noted. In this patient, varenicline exposure occurred on two separate occasions and exceeded thirty days for each exposure. The first trial lasted approximately seven weeks, with a second trial duration of approximately fifteen weeks. The longer duration use of varenicline exposure may have contributed to the onset of psychosis.

The increased neurophysiological vulnerability of persons with intellectual disabilities cannot be overlooked. It has been reported that the incidence of mental illness in the intellectually disabled population is four to five times greater than that of the general population. In addition, the signs and symptoms of mental disorders in those with intellectual disabilities may be overlooked or underestimated as well as the indicators of mental illness attributed to cognitive deficits associated with intellectual disabilities (16).

Conclusions

Concurrent use of ziprasidone and haloperidol for psychosis may have minimized the rate and extent of exacerbation of psychiatric symptoms in this patient compared to those treated less aggressively. Varenicline use in persons with preexisting Axis I diagnoses, at greater risk or increased vulnerabilities, and in persons with suspected psychopathology may warrant increased monitoring for the emergence of psychiatric symptoms for the duration of therapy. Varenicline may increase the risk of breakthrough psychosis or mania in this susceptible population.

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