

Case Report

Induced psychosis after withdrawal of varenicline: a case report

López Arteaga MT, Amo C, Sánchez Morla EM, Sánchez Román M.
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Objective: Varenicline has been associated with psychiatric side effects, and cases with psychotic symptoms during treatment have been reported, few of them after the withdrawal. We describe a case with no current or previous medical or psychiatric history.

Method: A single case report.

Results: The patient without previous psychiatric pathology, following the withdrawal of treatment with varenicline, experiences delirium and behavioural disturbances. There was a remission of symptoms after 3 weeks of treatment with risperidone.

Conclusion: Discontinuation of treatment with varenicline due to poor tolerance for side effects (nausea and insomnia) could trigger psychotic symptoms in subjects with no personal or family psychiatric history.

María T. López Arteaga, Carlos Amo, Eva M. Sánchez Morla, Marina Sánchez Román

Department of Psychiatry, Hospital Universitario de Guadalajara, Guadalajara, Spain

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María Teresa López Arteaga, Department of Psychiatry, Hospital Universitario de Guadalajara, C/ Donante de sangre S/N, 19002 Guadalajara, Spain.
Tel: +34 949 209 200;
Fax: +34 949 209 218;
E-mail: mariatelarteaga@gmail.com

Introduction

Effective treatment for nicotine addiction is essential for reducing the morbidity and mortality associated with tobacco smoking (1). Varenicline tartrate represents the first nicotinic acetylcholine receptor partial agonist to be developed specifically for smoking cessation. It is highly selective for the alpha-4 beta-2 nicotinic acetylcholine receptor, which is responsible for mediating the reinforcing properties of nicotine in the brain (2). It is a partial agonist selective for the alpha-4 beta-2 nicotinic acetylcholine receptor subtype. It provides a low-to-moderate level of dopamine stimulation, which is believed to alleviate the craving and nicotine withdrawal symptoms. In addition, it is an antagonist at nicotine receptors, which may reduce the reinforcing effects of nicotine and decrease the risk of relapse (3).

The Food and Drug Administration (FDA) approved varenicline in 2006 as an aid to smoking cessation (3). November 2007, the FDA issued a safety alert to healthcare professionals regarding reports of suicidal thoughts and aggressive and erratic behaviour in patients on varenicline. In May 2008, the FDA advised that prescribing information for varenicline was revised to include information on serious neuropsychiatric symptoms in the

WARNINGS and PRECAUTIONS sections of the label (4).

In recent years, there have been several clinical cases in relation to psychotic symptoms produced as side effects of varenicline (Table 1). The aim of this paper is to make a brief descriptive review of these previous cases and comparing their characteristics with this new case that we describe.

Clinical case

A 33-year-old female, housewife, married and with two children, was brought to the psychiatric emergency section after presenting symptoms of disorganised thinking and associated anxiety symptoms. The patient had no previous personal or family psychiatric history, nor had suffered any significant illnesses. She showed no toxic consumption except tobacco consumption (20 cigarettes/day) for years. The patient was treated with varenicline for 12 days (0.5 mg/day for the first 3 days and 1 mg/day for the 9 following days) before going to hospital. On the fourth day of treatment, being the first day the patient took 1 mg/day, she began to feel headache, nausea and insomnia, so she decided to stop taking the prescribed medicine on her own. On arrival to the emergency department, the patient presented phenomena

Table 1. List of reported cases of psychosis induced by varenicline withdrawal

Authors	Patient gender and age	Previous psychiatric diagnosis	Psychiatric family history	Episode symptoms	Symptoms onset	Necessity of drug withdrawal	Symptoms arise during withdrawal	Reason for treatment withdrawal
Freedman (5)	Female 42	Schizophrenia	No	Psychotic episode lasting 5 days	During the fifth day of treatment	Yes	No	Possible causal relation between the medicine and this episode
Kohen and Kremen (6)	Male 63	Bipolar disorder	No	Manic episode lasting 7 days	During the seventh day of treatment	Not specified	No	Not specified
Pumariega et al. (7)	Female 50	Depressive syndrome	Bipolar disorder	Mixed episode with psychotic symptoms	3 months after starting of treatment	Yes	No	Possible causal relation between varenicline and this episode
Morstad et al. (8)	Female 41	Bipolar disorder (type II) and polysubstances abuse	No	Hypomania with agitation	A few days after the start of treatment. Florid episode a month after the medication	Yes	No	Possible causal relation between varenicline and this episode
Raidoo and Kutscher (9)	Male 61	Post-traumatic stress disorder, alcohol dependence and depressive disorder not otherwise specified	No	Visual hallucinations	During the 15th day of treatment	Yes	No	Patient's own decision at the start of this episode
Alhathen and Black (10)		Bipolar disorder	No	Manic episode	At the start of treatment	Yes	No	Possible causal relation between varenicline and this episode
Liu et al. (11)	Male 43	Schizoaffective disorder, bipolar subtype disorder	No	Mania with psychotic symptoms	During the 10th day of treatment	Yes	No	Possible causal relation between varenicline and this episode
Laine et al. (12)	Male 43	Without previous psychiatric history	Schizophrenia	Visual hallucinations and derealisation	On fourth day after the withdrawal of treatment	Yes	Yes	Effective response to treatment: smoking cessation
DiPaula and Thomas (13)	Female 45	Bipolar disorder (mixed type) with psychotic symptoms	No	Exacerbation, psychotic symptoms and agitation	During the second day of treatment	Yes	No	Possible causal relation between the medicine and this episode
May and Rose (14)	Female 32	No	Bipolar disorder and schizophrenia	Psychotic episode and delirium	Few days after treatment withdrawal	Yes	Yes	Side effects: insomnia
Cinemre et al. (15)	Male 25	Atypical psychosis	No	Delusions and auditory hallucinations	During the 20th day of medication	Yes	No	Patient's own decision for onset of clinical psychotic
The case presented in this study	Female 33	No	No	Delusions and auditory hallucinations	On fourth day after treatment withdrawal	Yes	Yes	Side effects: headache, nausea and insomnia

of thought insertion and delusion in relation to a conspiracy against her by her husband's family through her computer. She had not been able to tell which was the reality, which caused her anxiety and restlessness, etc. Her family thought that her condition could be related to taking a new medication that had been scheduled for days. Also explained that 4 days after the patient stopped varenicline, she changed her behaviour, showing behavioural disturbances, disorganised speech, insomnia, thought insertion, delusions and auditory hallucinations. The patient reported that through the Internet the information about her life had been spread, using messages she had sent a friend, all with marked feelings of guilt. No evidence of depressive symptoms and expansiveness. Given her state the patient was admitted in the psychiatric section of the hospital. On admission, a comprehensive study was performed to rule out other possible aetiologies of psychotic symptoms (toxic, cranial CT, EEG, complete blood test, etc.). During her hospitalisation, risperidone was prescribed to 10 mg/day, with adequate tolerance. Progressively proceeding, the psychotic symptoms remitted and subsequently she was discharged after 19 days of hospitalisation. The patient was referred to outpatient clinic to maintain ambulatory monitoring and at discharge, she was prescribed a risperidone 9 mg/day.

Four weeks after, risperidone was reduced and actually, 8 months after psychotic episode, she takes 3 mg/day.

Discussion

The interest of our case is that it is the first report of a psychotic episode in a subject without personal or family history, 4 days after the withdrawal of varenicline. We suggest the withdrawal of varenicline as a cause, but it is possible that it could have simply accelerated a process that would have occurred otherwise.

Following a review of previous literature in this regard, we note several cases of psychosis in relation to the varenicline, both during treatment and after making the withdrawal, and others in which various psychiatric symptoms occurred (Table 1).

From this comparison we observe: the use of nicotine is twice as high in patients with psychosis than among general population (16), so for a reduction of the adverse effects of tobacco, an antitobacco drug-like varenicline would be recommended. Patients with a history of schizophrenia may experience an activated psychotic relapse with taking it (5). However, there are also descriptions of cases of schizophrenia that after treatment with varenicline experienced no exacerbation of psychotic symptoms (17–19). We can interpret this clinical observation by

the indirect dopamine-releasing properties of varenicline (20).

We cannot say that there are gender differences regarding the psychiatric side effects of varenicline. As for the age range they occur, between 25 and 63 years, especially in the third and fourth decade of life, perhaps because they are the ages at which most secondary prevention on the harmful effects of tobacco are done.

In the three cases in which symptoms occurred after the medicine withdrawal, they were psychotic. These three cases have in common that they had no previous personal history; however, our case has no family history of schizophrenia. Psychosis may have occurred because of downregulation of the cholinergic system such that the abrupt lack of cholinergic stimulation, as a result of the withdrawal from varenicline, induced an anticholinergic response (12). Other possible mechanisms include dopaminergic overstimulation secondary to the alpha-2 beta-4 nicotinic receptor in an individual with genetic vulnerability (14).

In those with personal history of mood disorder, an exacerbation of the symptoms occurs and may be accompanied by psychotic symptoms, mainly manic episodes. 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 physiopathology of mania (21). In the case of Kohen et al. (6), they propose that the release of catecholamines, such as dopamine, was probably related to induction of mania in the patient.

Further research is needed to evaluate in depth the safety of varenicline, particularly among smokers with active or previous psychiatric history. Meanwhile, doctors should carefully monitor the use of this medicine.

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