

Possible varenicline withdrawal-induced akathisia: A case report

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Abstract

Akathisia is a relatively common adverse effect that may emerge during treatment with antipsychotics and other medication classes. We present a case of akathisia that may have been induced by the abrupt discontinuation of varenicline and review existing literature related to this phenomenon. A 46-year-old female with a past psychiatric history of bipolar disorder and borderline personality disorder was admitted to the acute psychiatric services department for suicidal ideation after 3 weeks of a new course of varenicline. This was prescribed for smoking cessation and titrated to 1 mg twice daily. Upon admission, the varenicline was discontinued. Roughly 3 days later, the patient began to complain of akathisia. The patient had experienced akathisia previously while taking antipsychotics for her bipolar disorder and was able to recognize its emergence. As the akathisia worsened, propranolol 10 mg 3 times daily was ordered and was effective in relieving her symptoms. A PubMed search using the terms *varenicline*, *akathisia*, *withdrawal*, and *discontinuation* was conducted. No literature of this phenomenon was found; however, reports of other extrapyramidal symptoms were noted. Considering the timing of varenicline's discontinuation and its mechanism, a pharmacological link between its use and akathisia is possible. Akathisia is a severely uncomfortable sequela of medications that may produce severe outcomes, such as suicidal ideation. In this case, it is possible that the discontinuation of varenicline after 3 weeks of therapy led to akathisia, which was successfully treated with propranolol.

Keywords: varenicline, akathisia, withdrawal, adverse effect

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Background

Varenicline is a smoking-cessation aid that acts as a partial neuronal α_4 β_2 nicotinic receptor agonist. Varenicline stimulates dopamine activity in a similar but reduced fashion to nicotine while also blocking nicotine's ability to produce this effect. This results in decreased craving and

withdrawal symptoms.¹ Akathisia is an extrapyramidal movement disorder consisting of difficulty staying still and a subjective sense of restlessness. According to the *Diagnostic and Statistical Manual of Mental Disorders* (5th edition),² medication-induced acute akathisia is the development of subjective complaints of restlessness after exposure to antipsychotic medication or the reduction of dosage or withdrawal of a medication used to treat extrapyramidal symptoms (EPS). Typically, excessive movements are also observed and usually consist of fidgeting or swinging of the legs, rocking while standing, pacing to relieve restlessness, or inability to sit or stand still for at least several minutes. The onset of symptoms typically occurs within weeks of initiating or increasing the dose of an antipsychotic agent. Risk factors may include advanced age, female gender, iron deficiency,



negative symptoms in schizophrenia, cognitive dysfunction, and/or a mood disorder.³ Akathisia can cause significant patient distress, including suicidal thoughts.⁴ Thus, its proper identification and treatment is crucial for patient wellbeing and safety.

Multiple neuropsychiatric adverse effects, but not akathisia, are listed in varenicline's prescribing information.⁵ These include changes in mood (depression or mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, suicidal ideation, suicide attempt, and completed suicide.

Varenicline has a somewhat lengthy and controversial history regarding psychiatric side effects, including the addition and eventual removal of the US black box warning related to serious psychiatric sequela.⁶ These concerns have somewhat been counterbalanced from results of the EAGLES trial by Anthenelli et al,⁷ which indicated that varenicline did not have an inherent increased risk of neuropsychiatric adverse effects compared to placebo. However, the study found participants with a history of psychiatric illness generally reported greater neuropsychiatric adverse events and suicidal ideation compared to those without psychiatric illness in all treatment groups, including varenicline. Adverse events included anxiety, agitation, and restlessness. Therefore, varenicline's absolute risk of psychiatric adverse effects and specific reactions are somewhat unclear. It is possible that some adverse events are rare and not well described. The following case describes the possibility of one of these rare events: akathisia following discontinuation of varenicline.

Case Report

A 46-year-old female presented to the emergency department seeking acute psychiatric services subsequent to significant changes in mood, including suicidality, irritability, sleep disturbance, and an inability to utilize coping skills to feel safe. The patient had an extensive past psychiatry history notable for bipolar I disorder, borderline personality disorder, posttraumatic stress disorder, and nicotine use disorder. Her past medical history was significant for a number of chronic illnesses, including hypertension, thyroid disease, and chronic obstructive pulmonary disease—none of which were exacerbated in the previous weeks.

The mental status exam found the patient to be calm with appropriate speech, language, and attention. No abnormal movements were found although some restlessness was noted. Suicidal ideations were present although hallucinations and delusions were absent. Basic laboratories and the physical exam were unremarkable.

Medications prior to admission included cyclobenzaprine, gabapentin, lamotrigine, quetiapine, venlafaxine, trazodone, and vortioxetine. The only change noted in these in the previous 5 months leading to admission was a decrease in the dose of venlafaxine. One new medication, varenicline, was added to her regimen 3 weeks prior to presenting. This was prescribed by the patient's pulmonologist in regards to her continued smoking despite her chronic obstructive pulmonary disease. The doses were titrated per approved labeling up to 1 mg by mouth twice daily. Due to the patient endorsing concerns that varenicline may have induced her current symptoms, the attending psychiatrist discontinued this agent and admitted the patient to the inpatient psychiatric unit.

On the second day of admission (3 days since the last varenicline dose), the patient reported intense anxiety and restlessness, which she described as similar in nature to a previous episode she developed after initiation of an antipsychotic. The patient was diagnosed with akathisia because of this description and the psychiatrist's assessment. No changes had been made to her antipsychotics, and no medication known to cause akathisia was added. The clinical pharmacist on the team was asked to investigate varenicline as a possible cause of this extrapyramidal reaction and recommend treatment. No specific literature describing this was found, and the patient's akathisia was subsequently treated per usual. Propranolol 10 mg by mouth 3 times daily provided relief within 24 hours.

Discussion

Although akathisia is most typically seen with new or increased antipsychotic exposure, varenicline was suspected as the primary cause in this case as it was the only medication changed at the time of symptoms, and its discontinuation timeline aligned with symptom onset.

The Naranjo Nomogram⁸ was utilized to assign the likelihood of this speculation. As shown in Table 1, the application of the Naranjo Nomogram had to be altered from its traditional use because the adverse effect witnessed in this case was suspected to stem from withdrawal of the medication rather than the introduction of the medication. With this approach, the tool produced a score of 5, which indicates probable cause of akathisia via varenicline discontinuation. We acknowledge that the application of this tool is limited as it had to be applied differently than its original intent, and 4 of these questions were assigned *do not know* as information related to these were not available. Additionally, there exists a level of subjectivity in answering these questions, and a lower score is within the spectrum of possibility in

TABLE 1: Naranjo Nomogram^a tool to assess the likelihood of varenicline causing akathisia in this case

Original Naranjo Nomogram Question	Modified Question to Reflect Drug Withdrawal				Score Given to Case
		Yes	No	Do Not Know	
Are there previous conclusive reports on this reaction?		+1	0	0	0
Did the adverse event appear after the suspected drug was administered?	Did the adverse event appear after the suspected drug was withdrawn?	+2	-1	0	+2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	Did the adverse reaction improve when the drug was readministered or a specific treatment for the effect was administered?	+1	0	0	+1
Did the adverse reaction reappear when the drug was readministered?		+2	-1	0	0
Are there alternative causes (other than the drug) that could on their own have caused the reaction?		-1	+2	0	+2
Did the reaction reappear when a placebo was given?		-1	+1	0	0
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?		+1	0	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?		+1	0	0	0
Did the patient have a similar reaction on the same or similar drugs in any previous exposure?		+1	0	0	0
Was the adverse event confirmed by any objective evidence?		+1	0	0	0
Total Score: 5 (probable)					

^aOriginal questions are listed as well as how the questions were modified to reflect the adverse drug reaction due to drug withdrawal. Scoring is based on modified question when applicable.⁸

this case. For example, other medications, although unchanged, could have been linked to the patient's akathisia, possibly with a delayed presentation (eg, quetiapine). Therefore, the final score and assignment of *probable* by the tool should be interpreted with some degree of skepticism.

A PubMed search for literature describing this adverse effect with varenicline was conducted. The terms *varenicline*, *Chantix*, *akathisia*, *EPS*, *withdrawal*, *discontinuation*, and *restlessness* did not produce literature describing reports of akathisia resulting from abrupt discontinuation. However, case reports of other movement symptoms that manifested after withdrawal of varenicline were found (Table 2).⁹ Both of these cases involved excessive movement that developed after cessation of varenicline. These differ from akathisia in that they were involuntary, whereas excessive movements in relation to akathisia tend to be consciously initiated by the patient; however, movement may be involuntary during extreme akathisia.

A search of the database EHealthMe¹⁰ showed a relationship between akathisia and varenicline in a small number of patients along with 1 of the following drugs: metoclopramide, venlafaxine, quetiapine, pantoprazole, and gabapentin (venlafaxine, quetiapine, and gabapentin were medications the presented patient was prescribed as well). EHealthMe¹⁰ is a data analysis tool that uses information from various sources, including the Food and Drug Administration to report on outcomes for drugs and supplements. Although evidence of this adverse effect preferably would be found in other sources, the use of ancillary tools was necessary after primary methods revealed little information. This tool revealed a possible association between varenicline and akathisia but does not indicate causality.

Akathisia is a phenomenon that can be challenging to identify and diagnose. Patients may have difficulty in expressing their restlessness, and it may be mistaken for agitation or anxiety.¹¹ Therefore, it is possible that varenicline's discontinuation can induce an akathisia that is either not reported or not properly diagnosed. A limitation in

TABLE 2: Case reports of withdrawal dyskinesias with varenicline⁸

Age, y	Sex	Dyskinesia	Varenicline Dose	Varenicline Length of Therapy	Other Medications	Diagnoses
51	Female	Involuntary chorea of the hands, feet, neck, face, mouth and jaw	1 mg/d	1 y	Lamotrigine, fluoxetine, alprazolam, lithium, bupropion, aripiprazole	Mood disorder, anxiety, nicotine dependence
65	Female	Involuntary movements/dystonic tics of the head and neck	1 mg/d	Intermittently over 3 y	Not reported	Nicotine dependence

this case report includes the lack of a scoring tool, such as the Barnes Akathisia Rating Scale. This is not typically utilized by the providers at the unit, but would have provided additional descriptions and assessment of akathisia if it were truly present. Considering varenicline's mechanism as a partial dopamine agonist and the understanding that akathisia typically stems from reduced dopamine activity, it is plausible that decreased dopamine action resulting from discontinuation of varenicline could produce akathisia. This is similar to akathisia that develops from withdrawal of drugs of abuse such as nicotine and opiates.¹

Furthermore, symptoms improved and eventually resolved with the addition of propranolol, a common effective akathisia treatment.¹¹ However, with the complex nature of the patient's symptoms (eg, anxiety that may respond to propranolol) and other medications that act on the central nervous system (including antipsychotics), varenicline's discontinuation as the true cause cannot be absolutely established. Nonetheless, considering that this may be a phenomenon not reported in the literature, increasing awareness of this serious adverse effect is warranted.

Conclusion

This case highlights the possibility of akathisia following discontinuation of varenicline. Although not reported in existing literature, elements that do support this possible adverse effect include its mechanism, the Naranjo Nonogram indicating probability, and previous published reports of other types of movement symptoms stemming from discontinuation. Additionally, although data seem to indicate that previous concerns over neuropsychiatric risks with varenicline may have been exaggerated, the concern for psychiatric side effects of this drug still exist.⁶ Akathisia can cause significant patient distress. Therefore, recognition of this adverse effect beyond the typical cause of antipsychotics is critical.

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