Withdrawal-Emergent Dyskinesia Related to Benztropine: A Case Report

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ABSTRACT

Introduction: Benztropine is an anticholinergic drug used as a therapy for Parkinson's disease and treatment for extrapyramidal side effects. While tardive dyskinesia is an involuntary movement disorder that often occurs gradually after long-term use of medications, it does not commonly present acutely.

Case Presentation: A 31-year-old White woman experiencing psychosis presented with spontaneous, acute-onset dyskinesia induced with the withdrawal of benztropine. She had been followed in our academic outpatient clinic for medication management and intermittent psychotherapy.

Discussion: The pathophysiology of tardive dyskinesia is not fully understood, but several hypotheses exist, including the involvement of changes in basal ganglia neuronal systems. To our knowledge, this is the first case report to document acute-onset dyskinesia associated with the withdrawal of benztropine.

Conclusion: This case report, which describes an atypical response to discontinuing benztropine, might offer the scientific community potential clues to better understand the pathophysiology of tardive dyskinesia.

INTRODUCTION

Dyskinesia refers to involuntary muscle movements that can range from slight tremor to uncontrollable full body movements.[1] The tardive form of dyskinesia refers to the slow, or tardive, onset of involuntary movements of the face, lips, tongue, trunk, or extremities.[1] Tardive dyskinesia is defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as involuntary athetoid or choreiform movements of the tongue, lower part of the face, chin, arms, or legs secondary to the use of a neuroleptic medication for at least a few months.[2] It is often a side effect of antipsychotic medications thought to be related to blockage of dopamine D2 receptors. Although often developing gradually, a handful of cases have been noted wherein dyskinetic movements presented spontaneously with rapid onset. There are case reports of acute-onset dyskinesia from a single dose of metoclopramide, a dopamine blocking agent.[3]

Withdrawal dyskinesia[4] is a form of tardive dyskinesia in adults that occurs immediately after discontinuing or reducing the dose of a dopamine receptor-blocking agent; DSM-5 defines the dyskinesia presenting after changing, dose alteration, or stopping neuroleptic agents, as "withdrawal-emergent dyskinesia."[2] Research supports the occurrence of acute-onset dyskinesia related to withdrawal from second generation antipsychotics.[5-7] The term "masked TD" refers to tardive movements that resolve when a dopamine receptor-blocking agent is resumed or its dose is increased.

Benztropine is an anticholinergic drug approved by the US Food and Drug Administration for the adjunctive therapy for all forms of Parkinsonism. It is also used for medication-induced extrapyramidal side effects, as well as prevention and treatment of dystonic reactions.[8] There is literature that suggests that withdrawing anticholinergic agents may lead to the emergence of akathisia and to transient worsening of psychosis.[9] However, to the best of the authors' knowledge, there has been no doc-

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umented case of acute-onset withdrawal-emergent dyskinesia from benztropine.

CASE PRESENTATION

This case describes a 31-year-old divorced White woman who lived in a group home and had been followed in an academic outpatient clinic for medication management and intermittent psychotherapy. She had a diagnosis of schizoaffective disorder, bipolar type, most recent depressive episode, and generalized anxiety disorder. She was diagnosed with attention deficit hyperactivity disorder in childhood. Past diagnoses also include obsessive compulsive disorder, although she did not show any signs or symptoms during the time period described in this case report. Of note, at age 15, after being prescribed paroxetine, she was described as having a history of exophoria of both eyes (an abnormal muscle coordination likely central nervous system mediated). Selective serotonin reuptake inhibitors (SSRI) and mixed amphetamine salts reportedly worsened psychosis. Other past medications include methylphenidate, citalopram, escitalopram, sertraline, venlafaxine, bupropion, mirtazapine, trazodone, zolpidem, quetiapine, aripiprazole, divalproex, lithium carbonate, clonazepam, tiagabine, gabapentin, and buspirone. She has had a total of approximately 25 treatments of electroconvulsive therapy since her 20s. All labs were generally within normal range during the time period described in this case report.

Around the time the withdrawal-emergent dyskinesia occurred, the patient was taking risperidone 4 mg orally at bedtime, haloperidol 12 mg orally at bedtime, and benztropine 1 mg orally twice daily. On this regimen, she was relatively stable with respect to psychosis, mania, and depression; however, she reported concerns regarding cognitive issues. Since literature suggests cognitive problems can improve with discontinuing benztropine,[9] and since she was no longer on the original offending antipsychotic (aripiprazole), it was decided to try a slow taper off the benztropine—0.5 mg per week—with the plan to reinstate it if extrapyramidal side effects emerged. She was assessed every week and was displaying no signs of side effects when she was assessed at a dose of benztropine 0.5 mg orally per day. However, within 2 weeks of stopping the final 0.5 mg of benztropine, she developed slow, writhing movements affecting her tongue and head. On examination, she met criteria for dyskinesia. Benztropine was subsequently restarted and increased over the next 2 weeks all the way back to 1 mg orally twice daily; unfortunately, dyskinesia persisted. Newer medications that target tardive dyskinesia via the vesicular monoamine transporter 2[10,11] were considered; however, these were so costly to the patient that they were infeasible.[12] Therefore, over the next 2 weeks, she was cross tapered between benztropine and amantadine, which was increased to 200 mg orally twice daily.

Over the next 6 weeks, the patient showed steady improvement and gradual, complete resolution of dyskinesia. Thus, from the time of acute onset of this withdrawal-emergent dyskinesia, the involuntary movements persisted for a total of 10 weeks, at which point they subsided. Three months later, the amantadine was tapered off, with no signs of return of dyskinesia 1 year later. In retrospect, it is unclear whether amantadine helped resolve the dyskinesia or whether it gradually dissipated over 10 weeks spontaneously and would have done so even without amantadine.

DISCUSSION

The pathophysiology of tardive dyskinesia is not fully understood, and several hypotheses exist. Some theories propose the role of nicotinic cholinergic pathways.[13] However, the most commonly proposed mechanisms suggest that dopamine receptor hypersensitivity and/or an imbalance between dopamine type 1 (D1) and type 2 (D2) receptor-mediated effects in the basal ganglia are primarily responsible.[10,15] According to the dopamine hypothesis, antipsychotics preferentially block D2 receptors, resulting in excessive activity of D1-mediated striatopallidal output, altered firing patterns in medial globus pallidus, and eventual evolution of the clinical features of tardive dyskinesia. Its development also may involve changes in other basal ganglia neuronal systems. Tardive dyskinesia could result from loss of striatal interneurons that exert a feedback influence on nigrostriatal dopamine neurons and form part of an efferent output pathway from the basal ganglia. Such interneurons may utilize gamma-aminobutyric acid (GABA),[10,15] acetylcholine, or peptides as their neurotransmitter.[16]

Withdrawal-emergent dyskinesia has been observed as early as 1973 after sudden cessation of chronic antipsychotic treatment in children.[17] Its pathophysiology remains unclear, even though some theories have been put forth. For instance, Lo and Peng[18] hypothesize that hyperdopaminergic processes in basal ganglia secondary to the termination of the medications blocking dopaminergic receptors are believed to underlie the phenomenon. Teo et al[19] postulate that, similar to tardive dyskinesia, the development of D2 receptor hypersensitivity on the nigrostriatal dopaminergic pathway may be involved in withdrawal-emergent dyskinesia, and the indirect reversal of the inhibition on the globus pallidus internus and subthalamic nucleus by the D2 receptor hypersensitivity is believed to result in a hyperkinetic movement disorder. Yet another theory attributes withdrawal-emergent dyskinesia to the GABAergic hypofunction, as well as the increase in dopamine D3 receptors.[20]

The story of this clinical case includes several interesting features, which may or may not have contributed to the atypical withdrawal-emergent dyskinesia upon discontinuing benztropine.

- The patient has a history of exophoria coincident with the use of paroxetine. It is not entirely clear whether the exophoria was related to an oculogyric reaction; however, if it was, then this could increase the risk for future extrapyramidal side effects.[21]
- The patient has a history of "involuntarily swing[ing] her arms, back and forth, and muscle spasm" that was reported as an adverse reaction to paroxetine. Although abnormal movements

can occur from paroxetine, they are relatively uncommon (<1%, according to paroxetine drug information, Lexicomp).[22] Muscle spasm (dystonia) is even more rare, and when it has been described in case reports, it is hypothesized to be related to the decreased neuroplasticity of aging neurons and to previous exposure to neuroleptic medications, neither of which was true for this patient.[23] Nonetheless, if these symptoms represented some form of extrapyramidal side effects, this puts her at a higher risk for future side effects.[21]

- The patient has a history of being on several antipsychotics, and at the time of the withdrawal-emergent dyskinesia, she was on 2 potent antipsychotics (risperidone and haloperidol). If an atypical medication has been associated with extrapyramidal side effects in the past (in this case, paroxetine), it may be worth considering if there is increased risk that a different atypical medication (in this case, dense tropine) might lead to extrapyramidal side effects in the future.
- Finally, the patient also has a history of obsessive-compulsive disorder, which, like extrapyramidal side effects, has long been associated with basal ganglion dysfunction.[24] It might be worth considering whether some common underlying mechanism could be related to all three (obsessive-compulsive disorder, extrapyramidal side effects, and in a typical response to benztropine withdrawal).

One possibility considered by the authors is that this incident was not withdrawal-emergent dyskinesia, but "masked dyskinesia" from risperidone and haloperidol. In other words, the authors considered if the rapid-onset dyskinesia could be related to the fact that the patient was no longer on the antidote for tardive dyskinesia, and discontinuing the medication unmasked underlying, preexisting tardive dyskinesia. However, the fact that the patient continued to suffer from the dyskinesia long after the benztropine was reintroduced would speak against this theory. Additionally, although benztropine is known to improve extrapyramidal side effects, such as parkinsonism and dystonia, it is not known to improve dyskinesia generally.[25] Therefore, withdrawal from benztropine should not cause the emergence of dyskinesia.

The atypical response to discontinuing benztropine may offer potential clues to better understand the pathophysiology of dyskinesia. Additionally, given that the DSM-5 definition of tardive includes "persisting beyond 4 to 8 weeks," it may be worth considering if the term "tardive withdrawal" or "tardive withdrawal syndrome" should be utilized for instances like these, where involuntary movements, including dyskinesias, persist beyond 4 to 8 weeks after discontinuing certain medication—whether they be antipsychotics, benztropine, or some other medication.

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