A medication change, then involuntary lip smacking and tongue rolling

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Ms. X, age 65, requests to change her antipsychotic to one her insurance covers. Within a few weeks, she experiences involuntary lip smacking and tongue rolling. How would you manage her?

CASE Insurer denies drug coverage

Ms. X, age 65, has a 35-year history of bipolar I disorder (BD I) characterized by psychotic mania and severe suicidal depression. For the past year, her symptoms have been well controlled with aripiprazole, 5 mg/d; trazodone, 50 mg at bedtime; and citalopram, 20 mg/d. Because her health insurance has changed, Ms. X asks to be switched to an alternative antipsychotic because the new provider denied coverage of aripiprazole.

While taking aripiprazole, Ms. X did not report any extrapyramidal side effects, including tardive dyskinesia. Her Abnormal Involuntary Movement Scale (AIMS) score is 4. No significant abnormal movements were noted on examination during previous medication management sessions.

We decide to replace aripiprazole with quetiapine, 50 mg/d. At a 2-week follow-up visit, Ms. X is noted to have euphoric mood and reduced need to sleep, flight of ideas, increased talkativeness, and paranoia. We also notice that she has significant tongue rolling and lip smacking, which she says started 10 days after changing from aripiprazole to quetiapine. Her AIMS score is 17.

What could be causing Ms. X's tongue rolling and lip smacking?

a) an irreversible syndrome usually starting after 1 or 2 years of continuous exposure to antipsychotics
b) a self-limited condition expected to resolve completely within 12 weeks
c) an acute manifestation of an antipsychotic that can respond to an anticholinergic agent
d) none of the above

The authors' observations

Tardive dyskinesia (TD) refers to at least moderate abnormal involuntary movements in ≥1 areas of the body or at least mild movements in ≥2 areas of the body, developing after ≥3 months of cumulative exposure (continuous or discontinuous) to dopamine D2 receptor-blocking agents.[1] AIMS is a 14-item, clinician-administered questionnaire designed to evaluate such movements and track their severity over time. The first 10 items are rated on 5-point scale (0 = none; 1 = minimal; 2 = mild; 3 = moderate; 4 = severe), with items 1 to 4 assessing orofacial movements, 5 to 7 assessing extremity and truncal movements, and

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How would you handle this case?

Answer the challenge questions throughout this article

Table 1

Types of dyskinesia related to antipsychotics

Type	Onset	Course of illness	Management options[a]
Tardive dyskinesia	After 3 months of antipsychotic use	Commonly irreversible especially without intervention; some cases may show some improvement over time	• Discontinue or lower the dosage of the offending agent in patients who can tolerate it without psychotic decompensation or worsening of dyskinesia because of withdrawal • Gradual taper of anticholinergic medications prescribed for EPS • Switch from a typical to an atypical antipsychotic, such as risperidone, olanzapine, clozapine and quetiapine (although the American Academy of Neurology advises caution because these drugs can mask tardive dyskinesia rather than treat it) • Symptomatic treatment
Withdrawal dyskinesia	Within 4 to 6 weeks of antipsychotic discontinuation	Complete resolution in 1 to 3 months of onset	• Watchful waiting with reassurance in milder cases • Short-term symptomatic treatment, eg, short-term clonazepam • Reintroduction of the offending antipsychotic followed by more gradual taper or cross-taper
Covert dyskinesia	Within 4 to 6 weeks of antipsychotic discontinuation	Commonly irreversible but some cases may show gradual improvement over extended period of time	• Symptomatic treatment • Gradual taper of anticholinergic medications prescribed for EPS • Reintroduction of the offending antipsychotic if other measures fail and the patient has disabling dyskinesia, then gradual taper or cross-taper to atypical antipsychotic with lower D2 receptor blockade

[a]Management options are not listed in a step-wise order and can be chosen on a case-by-case basis

EPS: extrapyramidal symptoms

Clinical Point

AIMS is a 14-item, clinician-administered questionnaire designed to evaluate abnormal involuntary movements and track their severity over time

8 to 10 assessing overall severity, impairment, and subjective distress. Items 11 to 13 assess dental status because lack of teeth can result in oral movements mimicking TDs. The last item assesses whether these movements disappear during sleep.

HISTORY Poor response

Ms. X was given a diagnosis of BD I at age 30; she first started taking antipsychotics 10 years later. Previous psychotropic trials included lamotrigine, divalproex sodium, risperidone, and ziprasidone, which were ineffective or poorly tolerated. Her medical history includes obstructive sleep apnea, narcolepsy, type 2 diabetes mellitus, hypertension, dyslipidemia, fibromyalgia, gastroesophageal reflux disease, and hypothyroidism. She takes metformin, omeprazole, pravastatin, carvedilol, insulin, levothyroxine, methylphenidate (for hypersomnia), and enalapril.

What is the next best step in management?

a) discontinue quetiapine
b) replace quetiapine with clozapine
c) increase quetiapine to target manic symptoms and reassess in a few weeks
d) continue quetiapine and treat abnormal movements with benztropine

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TREATMENT Increase dosage

We increase quetiapine to 150 mg/d to target Ms. X's manic symptoms. She is scheduled for a follow-up visit in 4 weeks but is instructed to return to the clinic earlier if her manic symptoms do not improve. At the 4-week follow-up visit, Ms. X does not have any abnormal movements and her manic symptoms have resolved. Her AIMS score is 4. Her husband reports that her abnormal movements resolved 4 days after increasing quetiapine to 150 mg/d.

The authors' observations

Second-generation antipsychotics are known to have a lower risk of extrapyramidal adverse reactions compared with older first-generation antipsychotics.[2,3] TD differs from other extrapyramidal symptoms (EPS) because of its delayed onset. Risk factors for TD include:

- female sex
- age >50
- history of brain damage
- long-term antipsychotic use
- diagnosis of a mood disorder.

Gardos et al[4] described 2 other forms of delayed dyskinesias related to antipsychotic use but resulting from antipsychotic discontinuation: withdrawal dyskinesia and covert dyskinesia. Evidence for these types of antipsychotic discontinuation syndromes mostly is anecdotal.[5,6] ***Table 1*** highlights 3 different types of dyskinesias and their management.

Withdrawal dyskinesia has been described as a syndrome resembling TD that appears after discontinuation or dosage reduction of an antipsychotic in a patient who does not have an earlier TD diagnosis.[7] The prevalence of withdrawal dyskinesia among patients undergoing antipsychotic discontinuation is approximately 30%.[8] Cases of withdrawal dyskinesia are self-limited and resolve in 1 to 3 months.[9,10] We believe that Ms. X's movement disorder was withdrawal dyskinesia from aripiprazole because her symptoms started 10 days after the drug was discontinued, and was self-limited and reversible.

Similar to TD, withdrawal dyskinesia can present in different forms:

- tongue protrusion movements
- facial grimacing
- ticks
- chorea
- tremors
- athetosis
- involuntary vocalizations
- abnormal movements of hands and legs
- "dyspnea" due to involvement of respiratory musculature.[5,11]

There may be a sex difference in duration of withdrawal dyskinesias, because symptoms persist longer in females.[9]

Although covert dyskinesia also develops after discontinuation or dosage reduction of a dopamine-blocking agent, the symptoms usually are permanent, and could require reintroducing the antipsychotic or management with evidence-based treatments for TD, such as tetrabenazine or amantadine.[6,12]

What is the cause of Ms. X's abnormal involuntary movements?

a) quetiapine-induced D2 receptor hypersensitivity
b) aripiprazole-induced cholinergic overactivity
c) quetiapine-induced cholinergic overactivity
d) aripiprazole-induced D2 receptor hypersensitivity

The authors' observations

Pathophysiology of this condition is unknown but different theories have been proposed. D2 receptor up-regulation and hypersensitivity to compensate for chronic D2 receptor blockade by antipsychotics is a commonly cited theory.[7,13] Discontinuation of an antipsychotic can make this D2 receptor up-regulation and hypersensitivity manifest as withdrawal dyskinesia by creating a temporary hyperdopaminergic state in basal ganglia. Other theories implicate

Clinical Point

Cases of withdrawal dyskinesia are self-limited and resolve in 1 to 3 months

Clinical Point

Look carefully for dyskinetic movements in patients who have recently discontinued or decreased the dosage of their antipsychotic

Table 2

Medication options for symptomatic treatment of tardive dyskinesia and withdrawal dyskinesias

Amantadine (200 to 300 mg/d in divided dosing; adjust dosage based on renal function; could be considered with Grade C recommendation[a])
Botulinum toxin (insufficient data)
Branched chain amino acids (insufficient data)
Clonazepam (dosing range from 0.5 to 4 mg/d in divided fashion based upon response; Grade B recommendation for use up to 3 months)
Deep brain stimulation (insufficient data)
Donepezil (5 to 10 mg/d; insufficient data)
Ginkgo biloba extract (240 mg/d; probably useful, Grade B recommendation)
Levetiracetam (500 to 3,000 mg/d; insufficient data)
Melatonin (10 to 20 mg/d; Grade C recommendation)
Omega-3 fatty acids, particularly eicosapentaenoic and docosahexaenoic acids (classified as experimental therapy and proposed to have significant potential for managing tardive dyskinesia)
Tetrabenazine (100 to 200 mg/d in divided dosing; sedation, parkinsonism, and depression are dose-dependent; Grade C recommendation)
Vitamin B6 (1,200 mg/d; insufficient data)
Vitamin E (600 to 1,600 units/d in divided dosing; insufficient data)

[a]See reference 19 for definitions of grades of recommendation and levels of evidence

decrease of γ-aminobutyric acid (GABA) in the globus pallidus (GP) and substantia nigra (SN) regions of the brain, and oxidative damage to GABAergic interneurons in GP and SN from excess production of catecholamines in response to chronic dopamine blockade.[14]

It has been proposed that patients with withdrawal dyskinesia might be in an early phase of D2 receptor modulation that, if continued because of use of the antipsychotic implicated in withdrawal dyskinesia, can lead to development of TD.[4,7,8] A feature of withdrawal dyskinesia that differentiates it from TD is that it usually remits spontaneously within several weeks to a few months.[4,7] Because of this characteristic, Schultz et al[8] propose that, if withdrawal dyskinesia is identified early in treatment, it may be possible to prevent development of persistent TD.

Look carefully for dyskinetic movements in patients who have recently discontinued or decreased the dosage of their antipsychotic. Non-compliance and partial compliance are common problems among patients taking an antipsychotic.[15] Therefore, careful watchfulness for withdrawal dyskinesias at all times can be beneficial. Inquiring about recent history of these dyskinesias in such patients is probably more useful than an exam because the dyskinesias may not be evident on exam when these patients show up for their follow-up visit, because of their self-limited nature.[8]

Treatment options

If a patient is noted to have a withdrawal-emergent dyskinesia, a clinician has options to prevent TD, including:

- decreasing the dosage of the antipsychotic
- switching from a typical antipsychotic to an atypical antipsychotic
- switching from one atypical to another with lesser affinity for striatal D2 receptor, such as clozapine or quetiapine.[16,17]

In addition, researchers are investigating the use of vitamin B6, *Ginkgo biloba*, amantadine, levetiracetam, melatonin, tetrabenazine, zonisamide, branched chain amino acids, clonazepam, and vitamin E as treatment alternatives for TD.

Tetrabenazine acts by blocking vesicular monoamine transporter type 2, thereby inhibiting release of monoamines, including dopamine into synaptic cleft area in basal ganglia.[18] Clonazepam's benefit for TD relates to its facilitation of GABAergic neurotransmission, because reduced GABAergic transmission in GP and SN has been associ-

Table 3

Striatal D2 receptor occupancy data (atypical antipsychotics vs haloperidol) in steady-state conditions

Antipsychotic	Dosage range	D2 receptor blockade (mean % ± SD)
Haloperidol	5 to 20 mg/d	85% ± 9
Olanzapine	10 to 25 mg/d	74% ± 8
Risperidone	3 to 8 mg/d	70% ± 9
Clozapine	300 to 600 mg/d	33% ± 17
Quetiapine	300 to 700 mg/d	20% ± 13

ated with hyperkinetic movements, including TD.[14] *Ginkgo biloba* and melatonin exert their beneficial effects in TD through their antioxidant function.[14]

The agents listed in ***Table 2***[19] could be used on a short-term basis for symptomatic treatment of withdrawal dyskinesias.[1,18,20]

Withdrawal dyskinesia has been reported with aripiprazole discontinuation and is thought to be related to aripiprazole's strong affinity for D2 receptors.[21] Aripiprazole at dosages of 15 to 30 mg/d can occupy more than 80% of the striatal D2 dopamine receptors. The dosage of ≥30 mg/d can lead to receptor occupancy of >90%.[22] Studies have shown that EPS correlate with D2 receptor occupancy in steady-state conditions, and occupancy exceeding 80% results in these symptoms.[22]

Compared with aripiprazole, quetiapine has weak affinity for D2 receptors (***Table 3***), making it an unlikely culprit if dyskinesia emerges within 2 weeks of initation.[22] We believe that, in Ms. X's case, quetiapine might have masked the severity of aripiprazole withdrawal dyskinesia by causing some degree of D2 receptor blockade. It may have decreased the duration of withdrawal dyskinesia by the same effect on D2 receptors. It may have lasted longer if aripiprazole was not replaced by another antipsychotic. This is particularly evident because dyskinesia improved quickly when quetiapine was titrated to 150 mg/d. The higher quetiapine dosage of 150 mg/d is closer to 5 mg/d of aripiprazole in terms of D2 receptor occupancy and affinity. However, quetiapine is weaker than aripiprazole in terms of D2 receptor occupancy at all dosages, and therefore less likely to cause EPS.[16]

Summing up

Withdrawal dyskinesia in the absence of a history of TD is a common symptom of antipsychotic discontinuation or dosage reduction after long-term use of an antipsychotic. It is more commonly seen with antipsychotics with high D2 receptor occupancy, and has been hypothesized to be related to D2 receptor supersensitivity to ambient dopamine, resulting as a compensatory response to chronic D2 blockade by this class of medication.

Evidence suggests that reversible withdrawal dyskinesia could represent a prodrome to irreversible TD. Therefore, keeping a watchful eye for these movements during the exam, along with specific inquiry about withdrawal dyskinesias while taking a history at every follow-up visit, is important because doing so can:

- inform the clinician about partial compliance or noncompliance to these medications, which could lead to treatment failure
- help prevent development of irreversible TD syndrome.

Ms. X's case reminds clinicians (1) to be aware of this unexpected side effect occurring even with second-generation antipsychotics and (2) that they should consider

Clinical Point

Withdrawal dyskinesia has been reported with aripiprazole and is thought to be related to the drug's strong affinity for D2 receptors

Clinical Point

It is important to inform patients that different forms of dyskinesias can be potential side effects of antipsychotics

Related Resources

- Abnormal Involuntary Movement Scale. http://www.cqaimh.org/pdf/tool_aims.pdf.
- Goldberg JF, Ernst CL. Managing the side effects of psychotropic medications. Arlington, VA: American Psychiatric Publishing, Inc; 2012.
- Tarsay D. Tardive dyskinesia: prevention and treatment. http://www.uptodate.com/contents/tardive-dyskinesia-prevention-and-treatment?topicKey=NEURO%2F4908&elapsedTimeMs=3&view=print&displayedView=full#.

Drug Brand Names

Amantadine • Symmetrel	Levothyroxine • Levoxyl, Synthroid
Aripiprazole • Abilify	Metformin • Glucophage
Benztropine • Cogentin	Methylphenidate • Ritalin
Carvedilol • Coreg	Olanzapine • Zyprexa
Citalopram • Celexa	Omeprazole • Prilosec
Clonazepam • Klonopin	Pravastatin • Pravachol
Clozapine • Clozaril	Quetiapine • Seroquel
Divalproex sodium • Depakote	Risperidone • Risperdal
Donepezil • Aricept	Tetrabenazine • Xenazine
Enalapril • Vasotec	Trazodone • Desyrel, Oleptro
Haloperidol • Haldol	Ziprasidone • Geodon
Lamotrigine • Lamictal	Zonisamide • Zonegran
Levetiracetam • Keppra	

EPS in patients while they are discontinuing their drugs. Furthermore, it is important for clinical and medicolegal reasons to inform our patients that different forms of dyskinesias can be potential side effects of antipsychotics.

References

1. Bhidayasiri R1, Fahn S, Weiner WJ, et al; American Academy of Neurology. Evidence-based guideline: treatment of tardive syndromes: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2013;81(5):463-469.
2. Dolder CR, Jeste DV. Incidence of tardive dyskinesia with typical versus atypical antipsychotics in very high risk patients. Biol Psychiatry. 2003;53(12):1142-1145.
3. Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. Am J Psychiatry. 2004;161(3):414-425.
4. Gardos G, Cole JO, Tarsy D. Withdrawal syndromes associated with antipsychotic drugs. Am J Psychiatry. 1978;135(11):1321-1324.
5. Salomon C, Hamilton B. Antipsychotic discontinuation syndromes: a narrative review of the evidence and its integration into Australian mental health nursing textbooks. Int J Ment Health Nurs. 2014;23(1):69-78.
6. Moseley CN, Simpson-Khanna HA, Catalano G, et al. Covert dyskinesia associated with aripiprazole: a case report and review of the literature. Clin Neuropharmacol. 2013;36(4):128-130.
7. Anand VS, Dewan MJ. Withdrawal-emergent dyskinesia in a patient on risperidone undergoing dosage reduction. Ann Clin Psychiatry. 1996;8(3):179-182.
8. Schultz SK, Miller DD, Arndt S, et al. Withdrawal-emergent dyskinesia in patients with schizophrenia during antipsychotic discontinuation. Biol Psychiatry. 1995;38(11):713-719.
9. Degkwitz R, Bauer MP, Gruber M, et al. Time relationship between the appearance of persisting extrapyramidal hyperkineses and psychotic recurrences following sudden interruption of prolonged neuroleptic therapy of chronic schizophrenic patients [in German]. Arzneimittelforschung. 1970;20(7):890-893.
10. Sethi KD. Tardive dyskinesias. In: Adler CH, Ahlskog JE, eds. Parkinson's disease and movement disorders: diagnosis and treatment guidelines for the practicing physician. New York, NY: Humana Press; 2000:331-338.
11. Diagnostic and statistical manual of mental disorders, fifth edition. Washington, DC: American Psychiatric Association; 2013.
12. Horváth K, Aschermann Z, Komoly S, et al. Treatment of tardive syndromes [in Hungarian]. Psychiatr Hung. 2014;29(2):214-224.
13. Samaha AN, Seeman P, Stewart J, et al. "Breakthrough" dopamine supersensitivity during ongoing antipsychotic treatment leads to treatment failure over time. J Neurosci. 2007;27(11):2979-2986.
14. Thelma B, Srivastava V, Tiwari AK. Genetic underpinnings of tardive dyskinesia: passing the baton to pharmacogenetics. Pharmacogenomics. 2008;9(9):1285-1306.
15. Keith SJ, Kane JM. Partial compliance and patient consequences in schizophrenia: our patients can do better. J Clin Psychiatry. 2003;64(11):1308-1315.
16. Lieberman JA, Saltz BL, Johns CA, et al. The effects of clozapine on tardive dyskinesia. Br J Psychiatry. 1991;158:503-510.
17. Farah A. Atypicality of atypical antipsychotics. Prim Care Companion J Clin Psychiatry. 2005;7(6):268-274.
18. Rana AQ, Chaudry ZM, Blanchet PJ. New and emerging treatments for symptomatic tardive dyskinesia. Drug Des Devel Ther. 2013;7:1329-1340.
19. Shekelle PG, Woolf SH, Eccles M, et al. Developing clinical guidelines. West J Med. 1999;170(6):348-351.
20. Cloud LJ, Zutshi D, Factor SA. Tardive dyskinesia: therapeutic options for an increasingly common disorder. Neurotherapeutics. 2014;11(1):166-176.
21. Urbano M, Spiegel D, Rai A. Atypical antipsychotic withdrawal dyskinesia in 4 patients with mood disorders. J Clin Psychopharmacol. 2007;27(6):705-707.
22. Pani L, Pira L, Marchese G. Antipsychotic efficacy: relationship to optimal D2-receptor occupancy. Eur Psychiatry. 2007;22(5):267-275.

Bottom Line

Dyskinesias can result from withdrawal of both typical and atypical antipsychotics, and usually are self-limited. Withdrawal dyskinesia may represent a prodrome to tardive dyskinesia; early recognition may aid in preventing development of persistent tardive dyskinesia.