

Unhappy feet: One woman's severe akathisia

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Continuous leg and arm movements have left Ms. K sleepless and suicidal. A medication change stills the involuntary motion but causes sudden weight gain. What would you try next?

How would you handle this case? 

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HISTORY 'Bizarre' days

Ms. K, age 45, is brought to the ER by her brother, who reports she has been acting "bizarre and crazy" for 3 days. He says his sister—who has bipolar I disorder—has had trouble sleeping, is restless, hears voices, and is contemplating suicide. He adds she was discharged from a psychiatric hospital 2 weeks ago after a 3-month stay.

Risperidone, 2 mg nightly, was controlling Ms. K's mania until this recent episode. According to her brother, she also has developed continuous involuntary leg and arm movements and cannot sit or stand still. When she tries to sleep, her feet sway back and forth in bed for hours.

We admit Ms. K to the psychiatric inpatient unit because of her suicidality and hallucinations. She is restless and agitated during initial evaluation, pacing around the room or rocking her feet while standing or sitting. Her speech is pressured and the "voices" are urging her to kill herself.

Ms. K is dysphoric and severely distraught about her "nervousness" and continuous urges to move. She says she would rather die than live with incessantly "jittery" legs and arms, yet she wants to be discharged and denies that she is mentally ill. She believes decreased sleep is causing her symptoms and requests a "sleeping pill."

Ms. K was diagnosed with bipolar I disorder

in her late 20s. During manic episodes she goes on spending sprees, makes reckless investments, and gambles impulsively. She has long battled euphoric/irritable mood and paranoid delusions, but she habitually views her medications as useless and stops taking them.

The patient has been hospitalized at least 4 times with severe manic and psychotic symptoms. She does not use illicit drugs and is medically healthy.

The authors' observations

Ms. K's involuntary movements suggest akathisia, a common extrapyramidal side effect of antipsychotics and other psychotropics (*Table, page 90*).¹

Akathisia is characterized by strong feelings of inner restlessness that manifest as excessive walking or pacing and difficulty remaining still. Ms. K's movements met at least 2 of 5 DSM-IV-TR criteria for acute akathisia (*Box, page 93*).²

Akathisia is characterized by at least 5 subtypes:³

- **Acute akathisia** begins hours or days after starting the offending medication and lasts <3 months.
- **Tardive** is similar to acute akathisia

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Clinical Point

Patient history is crucial to diagnosing akathisia subtype; repeated medication nonadherence could signal withdrawal akathisia

Table

Drugs that can cause akathisia

• Dopamine receptor agonists (such as antiparkinsons agents)
• Carbidopa/levodopa
• Ethosuximide
• Metoclopramide
• Neuroleptics
• Reserpine
• Selective serotonin reuptake inhibitors

but can arise within 3 to 4 months of starting the offending medication and persists for years.

- **Chronic akathisia** lasts ≥ 3 months and usually has no temporal correlation with antipsychotic initiation or dosage increase.⁴
- **Withdrawal akathisia** begins within 6 weeks of discontinuing a medication or significantly reducing the dosage.
- **Pseudo akathisia** consists of objective symptoms of movement without subjective awareness or distress. This subtype usually is seen in older patients.

Patient history is critical to determining akathisia subtype. Ms. K's sudden onset of manic and movement symptoms and history of medication nonadherence strongly suggest akathisia secondary to risperidone withdrawal.⁵ Several cases of akathisia after risperidone cessation have been reported.⁵

We know risperidone is not causing acute akathisia because Ms. K responded well to the medication during her last hospitalization with no adverse effects. Also, her family confirmed that she stopped taking risperidone after her most recent discharge.

Mania also can fuel incessant movement and increase physical activity, but patients often do not realize they have a problem while in a manic phase. Also, swinging and rocking of legs is rarely seen in mania. By contrast, Ms. K was morbidly distraught over her akathisia.

How would you treat Ms. K's akathisia?

- reduce antipsychotic dosage
- add a beta blocker
- add a benzodiazepine
- add an anticholinergic

The authors' observations

Numerous treatments are available for akathisia:

Beta blockers such as propranolol are most widely used because of their rapid onset of action and overall effectiveness in akathisia.³ Researchers believe these drugs reduce extrapyramidal symptoms (EPS) by blocking the adrenergic system. Propranolol can be used at a maximum 120 mg/d in divided doses.

Beta blockers, however, can cause bradycardia, hypotension, or respiratory distress. Use beta blockers with caution, and monitor for these adverse effects.

Benzodiazepines. Clonazepam, which enhances the inhibitory effect of GABA in the brain, is commonly used for akathisia because of its effectiveness and long elimination half-life³ (30 to 40 hours), which decreases the risk of medication withdrawal.

Patients, however, can develop a tolerance to clonazepam and become addicted to it. Use clonazepam with caution in patients with past substance abuse, and watch for sedation, fatigue, and disinhibition-induced aggression in all patients.

Anticholinergics such as trihexyphenidyl are more commonly used for EPS associated with parkinsonian symptoms or side effects but can be partially effective for akathisia.³ Anticholinergics block the CNS cholinergic activity that causes parkinsonian symptoms.

Cyproheptadine, clonidine, and mianserin have shown some positive results against akathisia in clinical trials.⁶⁻⁸ Iron, nicotine patches, and amantadine have shown limited effectiveness against akathisia in research studies and case reports.^{3,9}

Restarting risperidone at a lower dosage—rather than adding a medication—might have resolved Ms. K's akathisia,

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but because she was morbidly despondent over her akathisia, we felt we had no time to experiment. We also believed Ms. K's would respond well to a neuroleptic with a lower EPS risk—such as quetiapine.^{1,10}

TREATMENT Trying trials

We perform a complete medical workup to rule out an underlying medical problem. We then start valproic acid, 500 mg bid, for Ms. K's mania; quetiapine, 50 mg bid, for psychosis and mania; and propranolol, 30 mg bid, for akathisia.

We titrate quetiapine by 100 mg/d every 2 days to 400 mg/d, but after 10 days her akathisia, irritable mood, decreased sleep, and suicidal thoughts persist. We cannot increase propranolol because her blood pressure is 90/60 mm Hg, and adding lorazepam, 0.5 mg tid, does not control her movements. Three days later, we add trihexyphenidyl, 5 mg bid.

Fifteen days after admission, Ms. K remains akathistic, dysphoric, and suicidal despite a 5-drug regimen. Her "nervousness" prevents her from attending groups or other unit activities, and her uncontrollable foot swaying still keeps her awake at night.

How would you treat Ms. K's persistent symptoms now?

- switch antipsychotics
- switch mood stabilizers
- change medications for akathisia
- all of the above

The authors' observations

Neither propranolol, clonazepam, nor trihexyphenidyl alleviated Ms. K's akathisia. Switching to another neuroleptic with a relatively low EPS risk—such as olanzapine—might help. Olanzapine reduced akathisia in 3 case reports,¹¹ and we hope its strong anticholinergic and antiserotonergic action will help resolve Ms. K's akathisia.

Patients treated with therapeutic dosages of olanzapine have shown increased

Box

DSM-IV-TR criteria for acute akathisia

- Subjective complaints of restlessness after exposure to neuroleptics
- At least 1 of the following is observed:
 - Fidgety movements or swinging of the legs
 - Rocking from foot to foot while standing
 - Pacing to relieve restlessness
 - Inability to sit or stand still for at least several minutes
- Symptoms develop within 4 weeks of starting or raising the dosage of a neuroleptic or after reducing a medication used to treat extrapyramidal symptoms
- Criterion A symptoms are not better accounted for by a mental disorder
- Criterion A symptoms are not caused by a nonneuroleptic or a general medical condition

Source: Adapted from reference 2 with permission

Clinical Point

Propranolol or clonazepam can reduce akathisia, but watch for adverse effects

muscarinic receptor occupancy compared with patients receiving therapeutic dosages of risperidone.¹² In another study, olanzapine showed anticholinergic activity at therapeutic doses but risperidone did not.¹³ Researchers believe these features reduce olanzapine's EPS risk compared with other antipsychotics.

TREATMENT Drug works, but ...

Three weeks after Ms. K's presentation, we stop all psychotropics, start olanzapine, 10 mg nightly, for psychosis and mania, and continue propranolol, 30 mg bid, for akathisia. Within 2 days, Ms. K's akathisia improves significantly.

We also start lithium, 150 mg bid, for mania, and increase it 4 days later to 300 mg bid to

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Clinical Point

Because it blocks serotonin receptors and has anticholinergic activity, olanzapine can reduce akathisia

Related Resource

• AkathisiaSupport.org. Online resource offers links to articles describing causes of and treatments for akathisia subtypes. www.akathisiastupport.org.

Drug Brand Names

Aripiprazole • Abilify	Metoclopramide • Reglan
Carbidopa/levodopa • Stalevo, Parcopa	Olanzapine • Zyprexa
Clonazepam • Klonopin	Propranolol • Inderal
Clonidine • Catapres	Quetiapine • Seroquel
Cyproheptadine • Periactin	Reserpine • various
Ethosuximide • Zarontin	Risperidone • Risperdal
Lithium • Eskalith, others	Trihexyphenidyl • Artane
Lorazepam • Ativan	Valproic acid • Depakote

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maintain serum lithium at approximately 1 mEq/L. We check serum lithium every 3 days after dosage adjustment. Although lithium can induce akathisia, we thought it would most effectively control her mania.

Six days after we started the new medications, Ms. K's mania and psychosis begin to improve and she becomes euthymic. She is able to sit calmly during group therapy and community meetings.

Ten days after we start olanzapine and lithium, Ms. K appears bloated. Weight check shows an approximate 5-lb weight gain since starting the medications, both of which can cause weight gain and other metabolic side effects.

At Ms. K's request, we stop olanzapine and start aripiprazole, 5 mg/d, to try to control her weight gain. We continue lithium and propranolol, which have been controlling her mood and akathisia. The next day—after 1 dose of aripiprazole—her akathisia returns.

What caused Ms. K's akathisia to return?

- olanzapine withdrawal
- adding aripiprazole
- both of the above

The authors' observations

Because aripiprazole was started as soon as olanzapine was discontinued, it is unclear which action aggravated Ms. K's akathisia or if both were to blame.

Akathisia's underlying cause is uncertain. Researchers believe dopamine receptor blockade in the mesocortical dopamine system might be responsible.³ Positron-emission tomography studies suggest that D2 receptor occupancy in the striatum contributes to akathisia, and noradrenergic and serotonergic systems also play a role.^{3,14}

Antipsychotics, antidepressants, and sympathomimetics all have been implicated in akathisia, but antipsychotics that are potent serotonin (5HT) receptor antagonists—such as olanzapine and clozapine—show a lower incidence compared with other psychotropic agents.³

Aripiprazole—a partial D2 and 5HT1A receptor agonist and 5HT2 receptor antagonist—could have caused Ms. K's akathisia. In 1 study, 11% of patients receiving aripiprazole, 15 to 30 mg/d, for acute mania reported akathisia symptoms.¹⁵

Olanzapine cessation could have caused Ms. K's akathisia, although no cases of akathisia secondary to olanzapine withdrawal have been reported. Alternatively, olanzapine could have interacted with lithium to block lithium's ability to induce akathisia.

TREATMENT Back to olanzapine

After we thoroughly discuss olanzapine's risks and benefits with Ms. K, she consents to switch back to olanzapine, 10 mg/d. We also instruct her to exercise daily and strictly control her diet after discharge.

Ms. K's akathisia improves dramatically within 1 to 2 days, and her psychosis and mania improve gradually. Her persistent delusions and hallucinations are less intense, although she is still concocting grandiose get-rich-quick schemes.

Ten days after this latest dosage change, we discharge Ms. K on olanzapine, 10 mg/d, and lithium, 300 mg bid. She has no akathisia symptoms, and we arrange placement in an adult home where a psychiatrist sees her

regularly. Three years later, she has been lost to follow-up.

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Bottom Line

Watch for akathisia and other extrapyramidal symptoms (EPS) in patients taking neuroleptics, even at low dosages. When stopping a neuroleptic, taper slowly when possible to avoid withdrawal akathisia. Olanzapine, which carries a lower risk of EPS than many antipsychotics, can help resolve treatment-resistant akathisia, but watch for metabolic side effects.

Clinical Point

When prescribing olanzapine, thoroughly discuss its risks and benefits; urge patients to exercise daily and watch their diets

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