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Akathisia: Is restlessness a primary condition or an adverse drug effect?

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Keep a discerning eye out for this adverse effect of antipsychotics and other drugs

Akathisia—from the Greek for "inability to sit"—is a neuropsychiatric syndrome characterized by subjective and objective psychomotor restlessness. Patients typically experience feelings of unease, inner restlessness mainly involving the legs, and a compulsion to move. Most engage in repetitive movement. They might swing or cross and uncross their legs, shift from one foot to the other, continuously pace, or persistently fidget.

In clinical settings, akathisia usually is a side effect of medication. Antipsychotics, serotonin reuptake inhibitors, and buspirone are common triggers, but akathisia also has been associated with some antiemetics, preoperative sedatives, calcium channel blockers, and antivertigo agents. It also can be caused by withdrawal from an antipsychotic or related to a substance use disorder, especially cocaine. Akathisia can be acute or chronic, occurring in a tardive form with symptoms that last >6 months.[1-3]

Much isn't known about drug-induced akathisia

Our understanding of the pathophysiology of akathisia is incomplete. Some have suggested that it results from an imbalance between the dopaminergic/cholinergic and dopaminergic/serotonergic systems[4]; others, that the cause is a mismatch between the core and the shell of the nucleus accumbens, due in part to overstimulation of the locus ceruleus.[5]

More recently, researchers established a positive association between higher scores on the Liverpool University

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Neuroleptic Side Effects Rating Scale and D2/D3 receptor occupancy in the ventral striatum (nucleus accumbens and olfactory tubercle).[6] The D2/D3 receptor occupancy model might explain withdrawal symptoms associated with cocaine,[7] as well as relative worsening of symptoms after tapering or discontinuing stimulants in attention-deficit/hyperactivity disorder (ADHD).

Elements of a clinical evaluation

When akathisia is suspected, evaluation by a clinician familiar with its phenomenology is crucial. A validated tool, such as the Barnes Akathisia Rating Scale (at out cometracker.org/library/BAS.pdf) can aid in the detection and assessment of severity.[8]

In evaluating patients, keep in mind that the inner restlessness that characterizes akathisia can affect the trunk, hands, and arms, as well as the legs, and can cause dysphoria and anxiety. Akathisia has been linked to an increased likelihood of developing suicidal ideation and behavior.[9]

Less common subjective symptoms include rage, fear, nausea, and worsening of psychotic symptoms. Because of its association with aggression and agitation, drug-induced akathisia has been cited—with little success—as the basis for an insanity defense by people who have committed a violent act.[10]

Or is akathisia another psychiatric disorder?

Akathisia might go undetected for several reasons. One key factor: Its symptoms resemble and often overlap with those of other psychiatric disorders, such as mania, psychosis, agitated depression, and ADHD. In addition, akathisia often occurs concurrently with, and is masked by, akinesia, a common extrapyramidal side effect of many antipsychotics. Such patients might have the inner feeling of restlessness and urge to move but do not exhibit characteristic limb movements. In some cases, cognitive or intellectual limitations prevent patients from communicating the inner turmoil they feel.[11]

Medication nonadherence further complicates the picture, sometimes prompting a clinician to increase the dosage of the drug that is causing akathisia (***Box 1***[12]).

Box 1

Think twice before increasing the dosage

Patients who develop symptoms of akathisia sometimes stop taking their medication; this often results in psychiatric relapse.[12] In addition, symptoms of akathisia often mimic psychiatric symptoms and can be mistaken for worsening anxiety or psychosis; in such cases, a practitioner might increase the dosage of the agent that is causing akathisia, potentially leading to further deterioration of the clinical picture. Psychiatric patients admitted to the hospital also are vulnerable.

Last, patients who do not adhere to their outpatient drug regimen can develop akathisia when they begin receiving all their scheduled medications—and could be subject to chemical or physical restraint if agitation results.

Managing drug-induced akathisia

Akathisia usually resolves when the drug causing it is discontinued; decreasing the dosage might alleviate the symptoms. Whenever akathisia is detected, careful revision of the current drug regimen—substituting an antipsychotic with a lower prevalence of akathisia, for example—should be considered (***Box 2***,[13-16] ***page 16***). Treatment of drug-induced akathisia, which should be tailored to the patient's psychopathology and comorbidities, is needed as well (***Table***,[17-25] ***page 17***).

Beta blockers, particularly propranolol, are considered first-line therapy for drug-induced akathisia, with a dosage of 20 to 40 mg twice daily used to relieve symptoms[26] The effect can be explained by adrenergic terminals in the locus ceruleus and ending in the nucleus accumbens and prefrontal cortex stimulate β adrenoreceptors.[5,27] Although multiple small studies and case reports[26,28-32] support the use of beta blockers to treat drug-induced akathisia, the quality of evidence of their efficacy is controversial.[12,21,27] Consider the risk of hypotension and bradycardia and

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Clinical Point

The inner restlessness that characterizes akathisia can affect the trunk, hands, and arms, as well as the legs, and can cause dysphoria and anxiety

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Akathisia

Clinical Point

Data are insufficient to support use of anticholinergics for akathisia, a Cochrane Review concluded

Box 2

Selecting an antipsychotic with akathisia in mind

High-potency, first-generation antipsychotics have a higher prevalence of akathisia, compared with low to intermediate potency first- and second-generation antipsychotics (SGAs). SGAs differ in terms of their propensity for akathisia as well, with higher rates reported for aripiprazole and lurasidone compared with iloperidone, quetiapine, and clozapine; the latter are no more likely than placebo to cause akathisia.[13] It's necessary to carefully consider the risk-benefit ratio before prescribing an SGA that has a greater propensity to cause akathisia.[14-16]

be aware of contraindications for patients with asthma or diabetes.

Low-dose mirtazapine (15 mg/d) was found to be as effective as propranolol, 80 mg/d, in a placebo-controlled study, and to be more effective than a beta blocker in treating akathisia induced by a first-generation antipsychotic. The authors concluded that both propranolol and mirtazapine should be first-line therapy.[23] Others have suggested that these results be interpreted with caution because mirtazapine (at a higher dosage) has been linked to akathisia.[33] Mirtazapine blocks α-adrenergic receptors, resulting in antagonism of 5-HT2 and 5-HT3 receptors and consequent enhancement of 5-HT1A serotonergic transmission.[34] In one study, it was shown to reduce binding of the D2/D3 receptor agonist quinpirole.[35]

Serotonin antagonists and agonists. Blockade of 5-HT2 receptors can attenuate D2 blockade and mitigate akathisia symptoms. Mianserin, 15 mg/d, can be helpful, and ritanserin, 5 to 20 mg/d, produced about a 50% reduction in akathisia symptoms in 10 patients taking neuroleptics.[36] Neither is available in the United States, however.

Cyproheptadine, a potent 5-HT2A and 5-HT2C antagonist with anticholinergic and antihistaminic action, improved akathisia symptoms in an open trial of 17 patients with antipsychotic-induced akathisia.[37] The recommended dose is 8 to 16 mg/d.

A study using the selective inverse agonist pimavanserin (not FDA-approved) decreased akathisia in healthy volunteers taking haloperidol.[14,24,33]

Zolmitriptan, a 5-HT1D agonist, also can be used[38]; one study found that 7.5 mg/d of zolmitriptan is as effective as propranolol.[39]

A 2010 study showed a statistically significant improvement in 8 patients taking trazodone, compared with 5 patients on placebo, all of whom met criteria for at least mild akathisia. Trazodone's antiakathitic effect is attributed to its 5-HT2A antagonism.[25]

Anticholinergics. Traditionally, benztropine, biperiden, diphenhydramine, and trihexyphenidyl have been used for prevention and treatment of extrapyramidal side effects. A Cochrane review concluded, however, that data are insufficient to support use of anticholinergics for akathisia.[40] Although multiple case reports have shown anticholinergics to be effective in treating drug-induced akathisia,[12,17,33] their association with cognitive side effects suggests a need for caution.[18]

Benzodiazepines. Through their sedative and anxiolytic properties, benzodiazepines are thought to partially alleviate akathisia symptoms. Two small trials found clonazepam helpful for akathisia symptoms[2,20]; and 1 case report revealed that a patient with akathisia improved after coadministration of clonazepam and baclofen.[41]

Anticonvulsants. Valproic acid has not been found to be useful in antipsychotic-induced tardive akathisia.[42] However, a case report described a patient with schizophrenia whose akathisia symptoms improved after the dosage of gabapentin was increased.[43] Last, carbamazepine was found to be effective in reducing akathisia symptoms in 3 patients with schizophrenia who were resistant to beta blockers, anticholinergics, antihistaminergics, and benzodiazepines.[19]

α-adrenergic agonists. In an open trial, akathisia symptoms in 6 patients improved with clonidine, 0.2 to 0.8 mg/d.[17] Speculation is that strong α_1 antagonism might help pre-

Table

Tailoring treatment to the patient with akathisia

Drug class and drug	Comments and considerations
Alpha adrenergic agonist[17] • Clonidine	Consider for patients with ADHD or impulsivity
Anticholinergics[18] • Benztropine • Biperiden • Diphenhydramine • Trihexyphenidyl	Consider for patients with parkinsonism Can produce cognitive side effects
Anticonvulsants[19] • Carbamazepine • Gabapentin	Consider for patients with schizophrenia, epilepsy, or bipolar disorder and who are resistant to other treatments
Benzodiazepine[20] • Clonazepam	Consider for patients with acute anxiety
Beta blocker[21,23] • Propranolol	First-line therapy, but carries an increased risk of hypotension and bradycardia Contraindicated in patients with asthma or diabetes
D2 agonists[22] • Cabergoline • Pramipexole • Ropinirole • Rotigotine	Consider for patients with hyperprolactinemia Contraindicated in patients with a psychotic disorder
Serotonin antagonists and agonists[23-25] • Cyproheptadine • Mianserin • Mirtazapine (low-dose) • Ritanserin • Trazodone • Zolmitriptan	Low-dose mirtazapine recommended as first-line therapy Consider for patients with depression, weight loss, or insomnia

ADHD: attention-deficit/hyperactivity disorder

Source: References 17-25

vent akathisia, which could be why this condition is not associated with iloperidone.[44]

D2 agonists. Akathisia and restless legs syndrome have similar pathophysiology,[1,2] and patients with akathisia could benefit from D2 agonists such as cabergoline, pramipexole, rotigotine, and ropinirole. One case study revealed that a patient with aripiprazole-induced akathisia improved with ropinirole.[45] D2 agonists can precipitate or worsen psychosis, however, and would be a relative contraindication in patients with psychotic disorders.[22]

Clinical Point

Carbamazepine reduced akathisia in 3 schizophrenia patients resistant to beta blockers, anticholinergics, antihistaminergics, and benzodiazepines

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continued

Akathisia

Clinical Point

Through their sedative and anxiolytic properties, benzodiazepines are thought to partially alleviate akathisia symptoms

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Drug Brand Names

Aripiprazole • Abilify
Baclofen • Lioresal
Benztropine • Cogentin
Biperiden • Akineton
Buspirone • BuSpar
Cabergoline • Dostinex
Carbamazepine • Tegretol
Clonazepam • Klonopin
Clonidine • Catapres
Clozapine • Clozaril
Cyproheptadine • Periactin
Diphenhydramine • Benadryl
Gabapentin • Neurontin
Haloperidol • Haldol
Iloperidone • Fanapt
Lurasidone • Latuda
Mirtazapine • Remeron
Pramipexole • Mirapex
Propranolol • Inderal
Quetiapine • Seroquel
Ropinirole • Requip
Rotigotine • Neupro
Trazodone • Desyrel, Oleptro
Trihexyphenidyl • Artane
Valproic acid • Depakene
Zolmitriptan • Zomig

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Bottom Line

Failure to detect drug-induced akathisia can increase morbidity and delay recovery in patients undergoing psychiatric care. Knowing what to look for and how to tailor treatment to the needs of a given patient is an essential component of good care.