Beyond anxiety and agitation: A clinical approach to akathisia

Richardson Oghoteru Tachere, Mandana Modirrousta

Background

When patients suddenly become restless and are unable to sit or stand still, especially in general medical settings, anxiety is often the topmost differential on every clinician's mind. However, the possibility of the very subjectively distressing condition called 'akathisia' should always be considered.

Objective

The aim of this article is to discuss a clinical approach to the management of akathisia, drawing on the presentation of a patient who was admitted to a general medical ward.

Discussion

Akathisia, a subjective and very distressing feeling of restlessness, has been found to be caused by a wide range of medications used in general medical settings, such as azithromycin, antiemetics and antipsychotics. Despite its high incidence and association with an increase in suicidal thoughts, it often goes unrecognised. This paper highlights the need for its early recognition, provides a diagnostic guide and an approach to its management.

Akathisia is a 'subjective feeling of motor restlessness manifested by a compelling need to be in constant movement'.[1] The American Psychiatric Association's *Diagnostic and statistical manual of mental disorders*, 5th edition (DSM-5), describes medication-induced acute akathisia as:

> *subjective complaints of restlessness, often accompanied by observed excessive movements (eg fidgety movements of the legs, rocking from foot to foot, pacing, inability to sit or stand still), developing within a few weeks of starting or raising the dosage of a medication (such as a neuroleptic) or after reducing the dosage of a medication used to treat extrapyramidal symptoms.*

Patients with akathisia often describe feeling very tense and uncomfortable, and unable to remain still. Rocking, pacing, shifting weight while standing and an inability to remain seated are commonly observed clinically.[3]

The need for all medical practitioners to be competent in promptly identifying and managing akathisia cannot be overemphasised. As highlighted in Box 1, this is particularly important because akathisia may be caused by medications across a number of categories, including antiemetics (eg metoclopramide), antidepressants (eg selective serotonin receptor inhibitors such as paroxetine), reserpine, alpha methyldopa, buspirone, diltiazem, cinnarizine and antipsychotics (including those in the second-generation class).[4–7] Recently, akathisia caused by azithromycin (a commonly used antibiotic)[8] and pregabalin (commonly used for peripheral neuropathy and post-herpetic neuralgia)[9] were reported. It is worth emphasising that akathisia is a very distressing condition that is known to increase the risk of impulsive behaviour and suicidal ideation.[6,10]

While there are no clear data on the prevalence of akathisia in general medical settings, a recent large study among a community sample of patients with schizophrenia on several psychotropic medications found a prevalence of about 15–35%.[11] Unfortunately, akathisia often goes unrecognised.[4,12] This is due, in part, to a lack of well-defined criteria for its diagnosis, as well as many other mimicking conditions such as agitation and anxiety related to mood or psychotic disorders, restless leg syndrome, substance-related

Box 1. Key clinical points about akathisia

- Presents as a very distressing subjective feeling of restlessness and dysphoria
- Can be observed as fidgety movements of the legs, rocking from foot-to-foot, pacing, and inability to sit or stand still
- May be caused by medications across a number of categories, including antipsychotics, antidepressants and antiemetics
- Is associated with an increased rate of suicidal ideation
- Early recognition and treatment is crucial

conditions (eg withdrawal states) and movement disorders.[4,5]

Through this paper, we aim to increase awareness about akathisia, which is often not considered by medical practitioners when patients become 'anxious' or 'agitated'. We discuss its clinical management using the presentation of a patient admitted to a medical ward to illustrate the need for its urgent recognition and treatment.

Case

Ms D, aged 27 years, was admitted to a medical ward with a history of persistent abdominal pain, nausea and vomiting for about three months. Her past medical history was significant for type 1 diabetes mellitus (with several complications including retinopathy, neuropathy and gastroparesis). She also had hypertension and end-stage renal failure. Prior to admission, she was on citalopram 20 mg daily for depression (this was discontinued earlier during this admission because of gastrointestinal issues). Ms D's other regular medications included insulin, zopiclone, furosemide, ondansetron, amitriptyline, amlodipine, prochlorperazine, domperidone, rabeprazole, scopolamine, erythropoietin and pregabalin.

Given the increased difficulty in controlling her nausea, despite making medication adjustments, she was started on regular oral haloperidol 1 mg every four hours, in addition to a PRN order of oral or intramuscular haloperidol 1 mg every eight hours. An urgent psychiatric consultation was sought five days after commencing haloperidol because she was '… displaying lots of anxiety and suicidal ideations …'. When seen by the psychiatric team, Ms D indicated that she felt restless and could not stop herself from moving her legs. She reported her symptoms as 'miserable' and 'very distressing'. There was no previous history of similar symptoms, and she denied use of alcohol and other substances. Objectively, she appeared fidgety and had obvious motor restlessness in her limbs in sitting and lying positions. Ms D was unable to stand still on one spot without moving around. She did not have any tremors or other Parkinsonian signs. She confirmed that she had low mood and reported thoughts of suicide in the context of the uncontrollable restlessness she was experiencing. The clinicians determined that Ms D had acute akathisia because of her clinical features (subjective report and objective findings), and the fact that she was recently started on haloperidol. Her haloperidol was tapered off over three days, and the clinicians simultaneously converted her PRN lorazepam to a regular dose of longer acting clonazepam. She was provided ongoing, daily follow-up in the medical ward. By the third day, there was no observable restlessness and she reported that she was 'back to myself'.

Discussion

Akathisia is a 'subjective feeling of motor restlessness manifested by a compelling need to be in constant movement'.[1] Making a diagnosis of akathisia is often a challenge because of a lack of specific, well-defined criteria. In addition, as described in this article, akathisia may not be a single 'neat' entity, and patients with akathisia often present differently.[13] Hence, clinicians should give serious consideration to akathisia and review the patient's medications whenever anxiety or agitation arises as a potential side effect.

Criteria for drug-induced akathisia initially proposed by Sachdev[14] for research purposes are very applicable in clinical settings. These include the essential criterion of taking a suspect medication, in addition to a subjective report and objective findings. Subjectively, there could be one or more of the following:[14]

- feeling of restlessness or inner tension or discomfort, with special reference to the lower limbs
- an urge to constantly move the legs, and sometimes other parts of the body (eg arms, trunk)
- difficulty or inability in maintaining a posture for several minutes.

One key point worth emphasising is that clinicians should observe patients in at least two positions, preferably sitting and standing on one spot. Objectively, Sachdev[14] suggests that features highly suggestive of akathisia include one or more of the following:

- While sitting:
  - Semi-purposeful or purposeless movements in the leg, feet, hand, arm and/or trunk
  - A tendency to repeatedly shift bodily position in the chair and an inability to remain seated for several minutes, with a tendency to get up and walk or pace
- While standing on one spot:
  - Semi-purposeful or purposeless movements in the leg, feet, hand, arm and/or trunk
  - A tendency to shift weight from foot-to-foot or march on the spot
  - An inability to stand in one spot with a tendency to walk or pace.

Clinically applying these criteria will help to distinguish akathisia from other conditions such as anxiety, restless leg syndrome, agitation from other causes and drug withdrawal or intoxication states. It is important to clarify that while the above symptoms and signs are virtually bilateral, their severity may be asymmetrical and none of them is pathognomonic, though rocking from foot-to-foot while standing (in the setting of taking a suspect medication) is considered as highly characteristic.[15]

While its exact pathophysiology is still unclear, akathisia is currently attributed to a reduction in dopaminergic activity in the mesocortical pathway projecting from the ventral tegmental area to the limbic system and prefrontal cortex. This results in suppression of the usual inhibitory effects on motor function, leading to the unwanted involuntary movements.[16,17] This view is supported by animal studies.[18] However, an indirect mechanism has also been postulated; that is, an increase in serotonin and norepinephrine may contribute to akathisia by indirectly reducing dopaminergic activity in the ventral tegmental area.[19]

On the basis of the time of onset, pattern of presentation and its duration, akathisia can be classified into several types:[5,20]

- Acute akathisia – develops soon after starting an antipsychotic or increasing its dose, or switching to a high-potency medication. It usually lasts for less than six months and is characterised by intense dysphoria and restlessness.
- Chronic akathisia – lasts longer than six months after the last change in medication, and often includes mild dysphoria and restlessness, as well as some limb and orofacial dyskinesia.
- Pseudoakathisia – believed to be a late stage of the chronic type. There are some motor manifestations, but there is no subjective awareness of restlessness.
- Tardive akathisia – a delayed onset, usually more than three months since a medication or dose change, and it is often associated with tardive dyskinesia.
- Withdrawal or rebound akathisia – due to discontinuing or decreasing an anticholinergic medication, usually occurring within six weeks.

As a first step in the pharmacological management of akathisia, lowering the dose of the offending medication is recommended (Box 2). Switching to an alternative agent should also be considered. Among adjunctive medications, the evidence favours propranolol (40–80 mg po bid) and low-dose mirtazapine (15 mg po daily), with mianserin (15 mg po daily) and cyproheptadine (8–16 mg po daily) being less evidence-based alternatives.[20,21] Benzodiazepines (eg clonazepam 0.5–1 mg po bid) may be used alone or combined with propranolol. Anticholinergic medications (eg benztropine 2 mg po bid) are often helpful when other extrapyramidal features are present. Other options include clonidine (0.2–0.8 mg/day), amantadine (100 mg po tid) and diphenhydramine (50 mg po daily).[20–24]

Considering the incidence of akathisia, its association with several commonly used medications, its severely distressing nature, and associated higher risk of impulsive behaviour and suicidal ideation, it is very crucial that clinicians recognise it and offer appropriate treatment to patients promptly.

Box 2. Summary of treatment recommendations for acute akathisia[21]

Patient education (eg akathisia, causes, treatment options)

Change in medication regimen (eg reduce dose or stop and switch to an alternative medication)

Adjunctive treatment:

- beta-blockers (eg propranolol 40–80 mg po daily)
- $5HT_{2A}$ receptor antagonists (eg mirtazapine 15 mg po daily, cyproheptadine 8–16 mg po daily)
- benzodiazepines (eg clonazepam 0.5–1 mg po daily, diazepam 5–15 mg po daily)
- anticholinergics (eg benztropine 1–4 mg po daily) should be used mainly for patients who have concurrent Parkinsonism
- Other agents such as amantadine 100 mg po daily, clonidine (up to 0.15 mg po daily)

Authors

Richardson Oghoteru Tachere, MBBS, MPH, MA, Resident Physician – Postgraduate Year 5, Department of Psychiatry, Max Rady College of Medicine, University of Manitoba, Canada. tachereo@myumanitoba.ca

Mandana Modirrousta, MD, PhD, FRCPC, Assistant Professor, Department of Psychiatry, Max Rady College of Medicine, University of Manitoba, Canada; Staff Psychiatrist, St Boniface Hospital, Winnipeg, MB, Canada.

Competing interest: None.

Provenance and peer review: Not commissioned, externally peer reviewed.

Ethical clearance

In addition to obtaining informed written consent from the patient directly, the authors sought and obtained approval – Ethics Reference Number: HS20267 (H2016:410) – from the Health Research Ethics Board at the University of Manitoba, Canada.

References

1. Sadock BJ, Sadock VA, Ruiz P. Kaplan and Sadock's synopsis of psychiatry, behavioral sciences/clinical psychiatry. 11th edn. Philadelphia: Wolters Kluwer, 2015.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th edn. Washington, DC: American Psychiatric Publishing, 2013.
3. Gardner DM, Teehan MD. Antipsychotics and their side effects. Cambridge: Cambridge University Press, 2011.
4. Forcen FE. Akathisia: Is restlessness a primary condition or an adverse drug effect? Keep a discerning eye out for this adverse effect of antipsychotics and other drugs. Current Psychiatry 2015;14(1):14–18.
5. Kane JM, Fleischhacker WW, Hansen L, Perlis R, Pikalov A, Assunção-Talbott S. Akathisia: An updated review focusing on second-generation antipsychotics. J Clin Psychiatry 2009;70(5):627–43.
6. Sachdev P, Loneragan C. The present status of akathisia. J Nerv Ment Dis 1991;179(7):381–89.
7. Poyurovsky M, Fuchs C, Schneidman M, Weizman A. Treatment of neuroleptic-induced akathisia with the 5-HT, antagonist mianserin – Double-blind, placebo-controlled study. Br J Psychiatry 1999;174(3):238–42.
8. Riesselman A, El-Mallakh, RS. Akathisia with azithromycin. Ann Pharmacother 2015;49(5):609.
9. Dag E, Gokce B, Buturak SV, Tiryaki D, Erdemoglu AK. Pregabalin-induced akathisia. Ann Pharmacother 2013;47(4):592–93.
10. Iqbal N, Lambert T, Masand P. Akathisia: Problem of history or concern of today. CNS Spectr 2007;12(9S14):1–13.
11. Berna F, Misdrahi D, Boyer L. et al. Akathisia: Prevalence and risk factors in a community-dwelling sample of patients with schizophrenia. Results from the FACE-SZ dataset. Schizophrenia Research 2015;169(1–3):255–61.
12. Weiden P, Mann JJ, Haase G, Mattson M, Frances A. Clinical non-recognition of neuroleptic-induced movement disorders: A cautionary study. Am J Psychiatry 1987;144(9):1148–53.
13. Hirose, S. The causes of underdiagnosing akathisia. Schizophrenia Bulletin 2003;29(3):547–58.
14. Sachdev P. Research diagnostic criteria for drug-induced akathisia: Conceptualization, rationale and proposal. Psychopharmacology 1994;114(1):181–86.
15. Barnes TRE, Braude WM. Akathisia variants and tardive dyskinesia. Arch Gen Psychiatry 1985;42(9):874–78.
16. Kumar R, Sachdev PS. Akathisia and second-generation antipsychotic drugs. Curr Opin Psychiatry 2009;22(3):293–99.
17. Marsden CD, Jenner P. The pathophysiology of extrapyramidal side-effects of neuroleptic drugs. Psychol Med 1980;10(1):55–72.
18. Tassin JP, Stinus L, Simon H, et al. Relationship between the locomotor hyperactivity induced by A10 lesions and the destruction of the fronto-cortical dopaminergic innervation in the rat. Brain Res 1978;141(2):267–81.
19. Lane RM. SSRI-induced extrapyramidal side effects and akathisia: Implications for treatment. J Psychopharmacol 1998;12(2):192–214.
20. Sachdev P. The development of the concept of akathisia: A historical overview. Schizophrenia Research 1995;16(1):33–45.
21. Poyurovsky M. Acute antipsychotic-induced akathisia revisited. Br J Psychiatry 2010;196(2):89–91.
22. Laoutidis ZG, Luckhaus C. 5-HT2A receptor antagonists for the treatment of neuroleptic-induced akathisia: A systematic review and meta-analysis. Int J Neuropsychopharmacol. 2014;17(5):823–32.
23. Poyurovsky M, Pashinian A, Weizman R, Fuchs C, Weizman A. Low-dose mirtazapine: A new option in the treatment of antipsychotic-induced akathisia. A randomized, double-blind, placebo and propranolol controlled trial. Biol Psychiatry 2006;59(11):1071–77.
24. Miller CH, Fleischhacker WW. Managing antipsychotic-induced acute and chronic akathisia. Drug Saf 2000;22(1):73–81.