REVIEW ARTICLE

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Struggling to find Effective Pharmacologic Options for Akathisia? B-CALM!

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ABSTRACT *~ Akathisia is a movement disorder affecting the trunk and limbs, characterized by subjective and objective restlessness. Key signs include continual, repetitive rocking, leg shuffling, and fidgeting. Antipsychotic-induced akathisia is optimally managed by reducing the medication dose or switching to a second generation antipsychotic that is less prone to inducing akathisia. However, since medication changes are often not feasible, we review the available classes of rescue agents for akathisia symptoms. The fitting acronym, "B-CALM", which stands for Beta-blockers, Clonazepam, Anticholinergics, cLonidine and Mirtazapine, will assist prescribers in facile recall of evidence-based treatment options for akathisia. Pharmacological agents such as mianserin, trazodone, Vit B6, amantadine, gabapentin, and pregabalin have also been examined as treatment options for antipsychotic-induced akathisia. Although initial exploratory reports on these agents have been promising, the current evidence is insufficient. Akathisia has a good prognosis when managed early in the course of treatment. A variety of safe rescue agents are available for the management of this condition, however, current evidence best supports the use of propranolol and mirtazapine.* Psychopharmacology Bulletin. *2021;51(3):72–78.*

Introduction

Akathisia, the Greek term for "inability to sit", is a movement disorder affecting the trunk and limbs, characterized by subjective and objective restlessness. Key objective signs include continual, repetitive rocking, inability to sit still, fidgeting, leg shuffling, and pacing. The akathisia syndrome spans the boundary between subjective symptoms, such as inner restlessness, anxiety, and discomfort, and objective signs of restlessness that are observable to the clinician on examination. For milder forms of akathisia, the subjective symptoms of inner restlessness can

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occur in the absence of an objective component. Recognising and treating the condition is crucial, as severe untreated akathisia can increase the risk of suicidality, aggression, and violence, and lead to poor medication adherence.[1,2] The Barnes Akathisia Rating Scale is a four-item rating scale which assesses both the subjective symptoms and the objective signs of akathisia. The scale can be used to rate the initial severity of presenting symptoms of akathisia and to follow their progress and response to treatment changes over time.[3]

Akathisia has a number of causes, though drug-induced akathisia is the most common. The akathisia syndrome is classified into several subcategories, that are most applicable to the drug-induced forms of the disorder. These subcategories refer to the timing and conditions at the onset of the symptoms, with the exception of psuedoakathisia. The subtypes include: Acute, subacute, and chronic onset akathisia (acute occurs within a few days, chronic within a few weeks of initiating an antipsychotic or increasing the dose); withdrawal akathisia (occurs upon antipsychotic dose reduction or discontinuation, usually within 2–6 weeks); tardive akathisia (occurs late, usually after 3 months into the course of the antipsychotic treatment and persists for years even in the absence of antipsychotic medications) and pseudoakathisia (objective signs of akathisia noticed in the absence of a subjective component). Bing-Sicard akathisia, occurs in the context of parkinsonian disorders such as parkinson's disease, multiple system atrophy, post-encephalitic parkinsonism and cortico-basal ganglionic degeneration.[1]

Akathisia results most commonly as a side effect of medications. Common offenders are first-generation high-potency antipsychotics, Selective serotonin reupdate-Inhibitors (SSRIs), and antiemetics. The risk of akathisia from first generation antipsychotics varies from 8–76%, and is generally higher than the risk from the second generation antipsychotics. The prevalence of akathisia varies widely between the second generation antipsychotics: aripiprazole (23–42%), risperidone (7–50%), olanzapine (3–16%) and quetapine (2–13%).[1] Interestingly, the risk of akathisia from iloperidone is minimal. This agent is well suited for patients who are sensitive to develop antipsychotic-induced akathisia.[4,5] Although acute antipsychotic-induced akathisia is usually associated with schizophrenia, it should be noted that patients with bipolar disorder are also at a higher risk of drug induced akathisia. Other risk factors for drug-induced akathisia include rapid medication dose increase, traumatic brain injury, cancer, and iron deficiency.

Akathisia occurs not only as a result of withdrawal from antipsychotics, but also in association with illicit substance intoxication and withdrawal states. The syndrome is most notable with use of cocaine, methamphetamine, MDMA, ecstasy and GHB. Alcohol and opiate

withdrawal syndromes can produce anxious, restless states that mimic akathisia.

Medical and psychiatric conditions can produce restless states that masquerade as akathisia, complicating accurate diagnosis. Organic anxiety states produced by hyperthyroidism syndromes, respiratory alkalosis, septicemia, meningitis can mimic akathisia. Excessive motor movement is also seen in the agitation, excitement and psychomotor agitation of bipolar mania, schizophrenia, depression and post-traumatic stress disorder, as well as Tic and Tourettes Disorder, antipsychotic-induced movement disorders (dystonia, parkinsonianism and tardive dyskinesia), restless leg syndrome and periodic leg movement disorder. As the diagnosis of akathisia is made solely by clinical assessment, a careful medical, psychiatric, and medication history that includes timelines of medication trials in relation to symptom-onset, and a detailed physical examination with attention to excessive bodily movements, are key components for accurate diagnosis.

Medication-induced akathisia is optimally managed by reducing the antipsychotic dose or switching to a second generation antipsychotic less likely to cause akathisia.[1,2] According to the *Maudsley Prescribing Guidelines in Psychiatry*, qualify aripiprazole, ziprasidone and lurasidone are classified as having a "very low" risk of inducing akathisia.[6] Iloperidone, with its negligible propensity to cause akathisia may be the agent with the lowest risk. However, not infrequently, antipsychotic regimen changes are not feasible for reasons related to medication efficacy, tolerance or cost, and the akathisia symptoms must be treated separately. We discuss below and display in Table 1, the available classes of rescue agents to address medication-induced akathisia. The fitting acronym "B-CALM" will assist prescribers in facile recall of evidence-based treatment options for akathisia.[1]

Beta-Blockers

Antipsychotic medications can induce a hypo-dopaminergic state that leads to a compensatory increase in noradrenergic activity, which predisposes toward the development of akathisia. Beta-blockers, act primarily by modulating noradrenergic activity and are believed to provide their benefit in the management of akathisia by downregulating this hyper-noradrenergic pathophysiologic state. Propranolol, a non-selective, centrally-acting beta-blocker, is the most highly investigated rescue medication for antipsychotic-induced akathisia. Six of seven clinical trials (n = 194) comparing propranolol (20–120mg) vs. placebo in the treatment of akathisia in patients with schizophrenia (2–12 days) reported improvement in akathisia symptoms from propranolol. Smaller studies

TABLE 1

Pharmacological Options for Akathisia[2,7]

CLASS	DRUG	MECHANISM OF ACTION	DOSE (MG/D)	CLINICAL RECOMMENDATIONS FOR ANTIPSYCHOTIC-INDUCED AKATHISIA
Beta-Blockers	Propranolol	non-selective beta blockade	20–120	First-line adjunctive medication treatment
Benzodiazepine	**C**lonazepam	agonist action at GABA-A receptors	0.5–2	Consider for short term treatment
Anti-cholinergics	Benztropine/ Biperiden	antagonizes acetylcholine	Benztropine (1.5–8) Biperiden (2–6)	May help mild subjective symptoms with concurrent parkinsonian symptoms; not routinely recommended
Central alpha agonist	C**l**onidine	stimulates alpha-2 adrenergic receptors	0.2–0.8	Limited evidence supports treatment
Tricycyclic/ Tetracyclic antidepressant	**M**irtazapine	antagonizes alpha-2 adrenergic and serotonin 5HT2A receptors	15	Considered as first-line treatment when propranolol is contraindicated, ineffective, intolerable

Other pharmacological options[2]: Mianserin, trazodone, cyproheptadine, Vit B6, amantadine, gabapentin, and pregabalin have been examined with insufficient evidence.

have also provided evidence that even cardioselective beta-blockers such as metoprolol and nadolol provide benefit in the treatment of akathisia. Nonetheless, propranolol is generally considered the first-line adjunctive medication treatment for antipsychotic-induced akathisia.[2]

Clonazepam

This benzodiazepine agent reduces the overall central nervous system excitatory state by agonist action at the GABA-A receptors and by indirectly increasing dopamine levels and likely addressing the hypodopaminergic state). Two trials (n = 27) comparing clonazepam (0.5–2.5mg/d) vs. placebo for the treatment (7–14 days) of antipsychotic-induced akathisia in patients with psychosis, reported significant

improvement in akathisia symptoms when compared to placebo. Due to the risk of tolerance, dependence, and cognitive effects, clonazepam is generally considered for short-term treatment of antipsychotic induced akathisia. Dosing is started low and slowly up-titrated with the intent to use the lowest effective dose.[2] In addition to clonazepam, lorazepam (1–2mg/d) and diazepam (5–15mg/d) have been utilized in the management of antipsychotic induced akathisia with insufficient evidence.[7] Once the symptoms stabilize, a gradual taper of the benzodiazepine is generally recommended.

Anticholinergics

Benztropine effectively mitigates many neurologic side effects of antipsychotics. Two trials with a specific focus on akathisia symptoms investigated benztropine vs. placebo and two other trials examined benztropine vs. propranolol and benztropine vs. amantadine. The results of these studies showed a subjective decrease in akathisia ratings from benztropine, whereas the objective ratings did not show improvement. Similarly, two trials investigating PO and IM biperiden vs. placebo showed limited evidence for the treatment of antipsychotic-induced akathisia. In addition to this lack of objective evidence of efficacy, clinicians should minimize their use of anticholinergics as a treatment option for akathisia due to the following side effects: confusion, drowsiness, dizziness, dry mouth, and memory impairment. Amongst potential side effects, cognitive impairment is the most concerning when long term management of symptoms is required.[2] These agents are most likely to be helpful when mild subjective akathisia and other parkinsonian side effects are concurrent.

CLonidine

This agent acts as an agonist at central nervous system (CNS) alpha-2-adrenergic receptors. Clonidine modulates the hyperadrenergic state observed in akathisia through presynaptic negative feedback at the central nervous system (CNS) alpha-2-adrenergic receptor. Two studies, one an open trial (n = 6) of clonidine (0.2–0.8mg) and another a single-blind trial (n = 6), showed improvement in neuroleptic-induced akathisia symptoms in all 12 patients. In the open trial, patients showed maximal benefit to dosage adjustments within 24–48 hours. Controlled studies with larger sample sizes are needed. Even though these studies are promising, the current evidence for clonidine as treatment for akathisia is insufficient. Clinicians should consider hypotension risk prior to prescribing clonidine.[8,9]

Mirtazapine

Mirtazapine is a tetracyclic antidepressant that modulates noradrenergic and serotonergic neurotransmission primarily via blockade of presynaptic central α2-adrenergic autoreceptors, which medicates the enhancement of serotonergic (5HT-1) transmission. Mirtazapine also blocks 5-HT2 and 5-HT3 receptors.[10] Due to its potent antagonistic activity at the 5HT2A receptor, mirtazapine has been studied as an akathisia reducing agent. In two randomized double-blind studies (n = 116) comparing mirtazapine (15mg/d) vs placebo, and mirtazapine (15mg/d) vs. placebo and propranolol (80mg/d), mirtazapine demonstrated significant improvement in the global subscale of the Barnes akathisia rating scale. Sedation was the most common side effect associated with mirtazapine. The authors concluded that mirtazapine should be considered as first-line treatment in antipsychotic-induced akathisia when propranolol is contraindicated, ineffective, or intolerable.[2]

Other Pharmacological Agents

Mianserin, trazodone, cyproheptadine, Vit B6, amantadine, gabapentin, and pregabalin have been examined as possible treatments for antipsychotic-induced akathisia. Other medications such as amantadine, apomorphine, zolmitriptan and gabapentin have also been suggested in the literature. Although a few reports on these agents have been promising, the current evidence is insufficient.[1,2]

B-CALM

Akathisia is a troublesome movement disorder that adds risk and complexity to the care of patients who must take antipsychotics to control their psychiatric conditions. When managed early, the condition has a good prognosis. The initial step in the management of akathisia is to consider antipsychotic dose reduction, or switch to a low risk antipsychotic agent. When medication adjustment strategies are ineffective or impractical, a variety of safe rescue agents are available. The current evidence best supports the use of propranolol and mirtazapine. Use the B-CALM acronym to quickly recall the wider range of adjunct medication choices when other options are needed. Further large scale, randomized controlled trials are required to examine possible treatments for antipsychotic-induced akathisia and enhance the data base for psychopharmacological options. ✤

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