

# Akathisia: Case Presentation and Review of Newer Treatment Agents

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## ABSTRACT

Akathisia is a common and potentially debilitating adverse effect of many psychotropic agents. To a physician not specifically screening for this phenomenon, symptoms can appear similar to depression, anxiety, and/or psychosis. Further complicating matters, akathisia may also occur at different points during the treatment period with varying levels of severity in terms of patient distress. Treatment options have been limited by our somewhat poor understanding of akathisia's neurological basis, but dopamine dysregulation is theorized to play a central role. Most pharmacotherapy regimens focus on beta-adrenergic antagonists (eg, propranolol, the current gold-standard), which are thought to affect noradrenergic inputs into the dopamine pathways of the brain. However, new research suggests a role for serotonin-based pharmacotherapy, particularly those affecting 5-HT<sub>2a/c</sub> receptors (eg, mirtazapine) in regulating dopamine. [*Psychiatr Ann.* 2014; 44(8):391-396.]

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This article presents a real-world case report of akathisia and discusses emerging evidence-based treatment strategies for it.

## CASE PRESENTATION

Mr. R. is a 65-year-old man with a history of posttraumatic stress disorder, alcohol use disorder (in remission), peptic ulcer disease (status post total

gastrectomy), hepatitis C, and unspecified cognitive disorder. He was brought in by family members for bizarre behavior and increasing anxiety over the past several days. He wanted to attend a family reunion but instead presented to the hospital with the chief complaint of restlessness. He reported depressed mood, ongoing for several months, as well as hopelessness, anhedonia, and

impaired sleep, most of which appeared to coincide with the onset of restlessness. Anxiety appeared to last 1 to 2 hours, with an accompanying sensation of chest tightness and shortness of breath. He experienced these symptoms many times per day and has had them intermittently for several years. Mr. R. denied symptoms of manic episodes or psychotic symptoms but made vague, passive suicidal statements of “not wanting to live like this anymore.” Throughout the initial interview, he appeared restless—standing up and sitting down, pacing, and asking to go outside to smoke. He began taking olanzapine during an admission 2.5 years prior for irritability and verbally abusive behavior but had no history of psychotic symptoms. He had been prescribed trihexyphenidyl and hydroxyzine for his restlessness and anxiety, as well as gabapentin for neuropathy and anxiety relief. A head computed tomography was performed and showed mild, diffuse atrophy and ventricular dilatation but no acute intracranial processes. Neurological examination was benign and negative for cerebellar signs that may have been related to prior alcohol use. He was initially admitted with a provisional diagnosis of anxiety disorder, major depression, posttraumatic stress disorder, and a cognitive disorder, possibly secondary to gabapentin use.

Throughout his 1-month admission, Mr. R. continued to complain of restlessness. He had difficulty remembering the names of his recent residences. During multiple interviews, he became too restless to sit and had to terminate the interviews early. Akathisia or catatonic-like agitation was part of the initial differential diagnosis. A St. Louis University School of Medicine mental status examination was performed, and Mr. R. received a maximum score of 16 of 30 points. He denied perceptual disturbances or concrete reasons for anxiety and restlessness. A Barnes Akathisia-

Rating Scale was administered and indicated severe akathisia. At this point, the diagnostic impression was changed to major neurocognitive disorder (formerly “dementia”) and akathisia as his key problems. Gabapentin was discontinued early in treatment, but his cognitive abilities remained impaired. He initially began taking low-dose diazepam 10 mg nightly at bedtime to treat neuroleptic-induced akathisia or possible catatonia, but he did not respond to this therapy. Based on a literature review, propranolol 20 mg twice per day (BID), ropinirole 0.25 mg BID, and vitamin B6 300 mg BID were prescribed. All medications were given via oral administration. Mr. R. remained restless, became agitated, and started yelling while on the unit. At this time, olanzapine 10 mg was added back to his regimen as a nightly dose because akathisia may have also been attributable to antipsychotic withdrawal. However, behavioral problems continued and this medication was changed to haloperidol liquid 10 mg three times per day (TID), supplemented with chlorpromazine 50 mg for breakthrough agitation. The need for higher doses of medications reflects his status post total gastrectomy. Propranolol and ropinirole were discontinued due to a lack of effect and trihexyphenidyl 1 mg TID was restarted. With this combination of medications (haloperidol, chlorpromazine, trihexyphenidyl, vitamin B6), his akathisia, anxiety, and mood symptoms improved considerably. He was able to sit still for longer than 5 minutes, representing a significant reduction of target symptoms attributable to drug-withdrawal akathisia. He was then discharged to a subacute care facility.

## **BACKGROUND AND PATHOPHYSIOLOGY OF AKATHISIA**

Akathisia is a movement disorder described as the subjective sensation of inner restlessness and the objective

observation by clinicians of fidgeting movements. It is most often associated with antipsychotic drugs, which antagonize dopamine receptors.<sup>1</sup> The subjective component can be characterized by the aforementioned restlessness, as well as tension, panic, irritability, and impatience. Objective signs include increased motor activity, such as complex, repetitive movements. The urge to move appears to be a core feature, with the abnormal movements being a method used to calm this urge. Several subtypes exist, with classification based on timing, duration, and clinical presentation. Categories include the following:<sup>2</sup>

- Acute: develops soon after starting medications; lasts less than 6 months; intense dysphoria; awareness of restlessness; and complex, semi-purposeful fidgetiness
- Chronic: persists for more than 6 months; tends to have milder dysphoria; has stereotyped movements, often with presence of limb/orofacial dyskinesia
- Tardive: delayed in onset; not related to medication changes; associated with tardive dyskinesia
- Withdrawal: associated with switching/stopping antipsychotic medications; onset usually within 6 weeks of discontinuation, dosage decreases, or stoppage of anticholinergic medication

Akathisia is an important diagnosis to make early in the treatment course of psychiatric illness due to its negative effects regarding patient outcomes. It has been associated with severe distress, suicidal thoughts, impulsive/violent behavior,<sup>3,4</sup> a risk of developing tardive dyskinesia,<sup>4</sup> drug use,<sup>5</sup> medication noncompliance,<sup>5,6</sup> and poor treatment response.<sup>6</sup> For patients with schizophrenia and bipolar I disorder,<sup>6-8</sup> who are the usual target population of antipsychotic medications, this could mean very real, negative healthcare consequences.<sup>4</sup>

As a result, several rating scales and criteria have been developed to

identify akathisia. The *Diagnostic and Statistical Manual of Mental Disorders* provides a guideline for identifying akathisia but does not provide a quantifiable assessment.<sup>9</sup> The most commonly used, reliable, and validated scale is the Barnes Akathisia-Rating Scale, first published in the *British Journal of Psychiatry* in 1989.<sup>10</sup> By quantifying both objective and subjective components, the scale gives a measure of akathisia severity. It includes objective findings, subjective awareness of restlessness, subjective distress, and a global clinical assessment of akathisia.<sup>2,10</sup> Although some clinicians may forego scales in favor of clinical observation, akathisia can be confused in the clinical setting with other disorders, such as agitation related to mood or psychotic disorders, restless legs syndrome, anxiety states, drug-withdrawal states, antipsychotic dysphoria, organic medical/neurological disorders, or tardive dyskinesia.<sup>2,4,6</sup> As such, a rating scale may be useful in diagnosis and early treatment.

The pathophysiology of akathisia is poorly understood, despite its high incidence (20% to 45%) among those taking antipsychotics.<sup>1</sup> Neuroleptic use is the most common cause of akathisia, although other causes are also attributable (eg, selective serotonin reuptake inhibitors [SSRIs], anti-emetics, drug withdrawal syndromes, dementia). It is most often associated with conventional, first-generation antipsychotics.<sup>2,5</sup> Although newer, second-generation antipsychotics have a lower propensity of symptoms, the literature shows that they are not free from inducing akathisia.<sup>2,8,11-13</sup> Low dopaminergic tone continues to be the primary attributable mechanism by which we understand this problem due to its association with medications that block dopaminergic transmission. Studies point to interactions of the mesolimbic, mesocortical, and spinal dopamine/norepinephrine systems, particularly with respect to

the dopaminergic neurons of the ventral tegmental area and substantia nigra.<sup>1-3,14</sup>

However, treatment strategies that include benzodiazepines, beta-adrenergic blockers, and serotonin antagonists suggest that a more complicated relationship exists between multiple neurotransmitter systems, including

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dopamine, acetylcholine, gamma-aminobutyric acid (GABA), norepinephrine, serotonin, and neuropeptides.<sup>2,5</sup> Involvement of multiple neurotransmitter systems is further supported by the fact that drugs such as clozapine and quetiapine, which tend to weakly bind with dopamine receptors (and more potently with serotonin receptors), may cause akathisia in the absence of other extrapyramidal effects. Finally, the currently understood mechanism of extrapyramidal symptoms (EPS) suggests that dopamine antagonism results in changes to the two pathways emanating from the basal ganglia—affecting the direct pathway results in dyskinetic movements and affecting the indirect pathway results in symptoms of Parkinson's disease. Because this model does not indicate or explain a clear pathway for the development of akathisia,<sup>5</sup> it suggests that the picture is more complicated than dopamine's effects alone.

#### **COMMON TREATMENT METHODS Prevention, Psychosocial Interventions, and Regimen Modifications**

Several broad treatment regimens exist when a patient initially presents

with akathisia. Prevention of this phenomenon can be aided by using a standardized titration schedule and preferential selection of second-generation antipsychotics.<sup>15,16</sup> If akathisia does develop, psychosocial interventions are indicated, including patient education of the benefits and risks associated with treatment, establishing clear expectations, continuous open dialogue about adverse effects, and reassurance.<sup>1,2,4</sup>

Regarding medications, a common first step is lowering the antipsychotic dose, switching to low-potency antipsychotic agents (eg, chlorpromazine, thioridazine), or switching to an atypical agent. However, a conservative approach should be used when changing doses, cross-tapering, or switching medications due to adverse effects, such as precipitation of psychotic relapses or withdrawal akathisia.<sup>2</sup> Several pharmacological interventions are seen as first-line therapy for the treatment of akathisia. Beta-adrenergic antagonists, clonidine, benzodiazepines, and anticholinergics are most supported in the literature and are discussed below.

#### **Beta-blockers and Clonidine**

Lipophilic beta-adrenergic antagonists, such as propranolol, are one of the most well-tolerated and consistently effective therapeutic agents for the treatment of akathisia,<sup>1,5,15-18</sup> making it the most commonly used first agent for treatment. The exact mechanism of action is not understood well but is thought to act by blockade of the noradrenergic and serotonergic (5-hydroxytryptamine [5-HT] 1a) inputs into the dopaminergic pathways.<sup>6</sup> Although most agree that the use of propranolol is the standard initial choice, at least one large clinical trial and several studies have called its efficacy into question.<sup>4,19,20</sup> Significant side effects, such as hypotension and sleep disturbances, may necessitate changing agents.<sup>4</sup> Pro-

TABLE 1.

## Treatment Recommendations

1. Psychosocial intervention
2. Consider altering antipsychotic regimen (reduce dose, lower potency antipsychotic, or antipsychotic with low potential to cause akathisia)
3. Anti-akathisia agents:
  - a. **First line:** beta-blockers (eg, propranolol) OR 5-HT<sub>2a</sub> receptor antagonists (eg, mirtazapine, mianserin, cyproheptadine)
  - b. **Second line:** anticholinergics (eg, benztropine, trihexyphenidyl)
  - c. **Third line:** benzodiazepines
  - d. **Fourth line:** amantadine or clonidine

*Adapted from Poyurovsky.<sup>11</sup>*

propranolol can be started at lower doses, such as 10 mg TID, and titrated to 40 to 120 mg/day.<sup>1</sup>

Clonidine, a selective alpha-2 adrenergic agonist, may also be used, usually when other treatment methods have failed. Side effects include sedation and hypotension. Clonidine dosing is up to 0.15 mg/day.<sup>1</sup>

### Benzodiazepines

Benzodiazepines are a second-line treatment for akathisia, and their use is consistently mentioned in literature.<sup>1-3,5,20</sup> Alleviation of akathisia symptoms has been attributed to a GABA mechanism. Only short treatment courses of these drugs (lorazepam, clonazepam, diazepam) are indicated.<sup>20</sup> Although most clinical trials confirm improvement greater than placebo, they tend to be small studies.<sup>20</sup> Furthermore, as with beta-blockers and anticholinergic medications, this class is limited by its side effect profile (drug dependence, cognitive impairment, lethargy, personality changes), especially with long-term use. Lorazepam can be dosed at 1 to 2 mg/day, clonazepam at 0.5 to 1 mg/day, and diazepam at 5 to 15 mg/day.<sup>1</sup>

### Anticholinergics

Anticholinergic medications are typically used when there are co-occurring EPS. EPS are a result of acetylcholine/dopamine imbalance caused by antipsychotic medications' effects on the D<sub>2</sub> receptors of the nigrostriatal system.<sup>1</sup> The use of anticholinergics (eg, benztropine and trihexyphenidyl) is frequently mentioned in the literature as a common treatment method.<sup>1-3,5</sup> However, data supporting their use in lone akathisia remain equivocal. In addition, their noted side effect profile (cognitive impairment, blurred vision, constipation, urinary retention) make them relatively unsuitable for long-term use. Benztropine can be dosed at 1.5 to 8 mg/day and trihexyphenidyl at 2 to 10 mg/day.<sup>1</sup>

### New Treatment Strategies

New treatment strategies tend to belie previous suppositions about akathisia's pathophysiology from purely dopaminergic roots. Most new data are supportive of serotonin's role. However, other treatment strategies are also being explored, such as the use of vitamin B<sub>6</sub> and drugs that affect dopamine or GABA directly.

### SEROTONIN-BASED PHARMACOTHERAPY

If low dopaminergic activity of the ventral tegmental area and substantia nigra is involved in the development of akathisia and EPS, antagonism of 5-HT (which exerts inhibitory control on dopaminergic neurons) would theoretically decrease symptoms. Conversely, the use of SSRIs increases serotonin, thus inhibiting dopamine and explaining side effects, such as akathisia and EPS. Furthermore, many atypical antipsychotics block 5-HT<sub>2a/c</sub> receptors, which may be responsible for their decreased risk of akathisia and EPS.<sup>1</sup> However, this effect appears to be limited to 5-HT<sub>2a/c</sub> because drugs that in-

fluence other serotonin receptors, such as 5-HT<sub>1a</sub> (eg, buspirone) and 5-HT<sub>3</sub> (eg, granisetron), appear to have limited therapeutic value in the treatment of akathisia.<sup>1</sup>

Several medications have a pronounced 5-HT<sub>2a/c</sub> antagonistic activity, including ritanserin, cyproheptadine, mianserin, mirtazapine, and trazodone.<sup>1,2,4-6,11,15,16</sup> Initial research performed in the 1990s suggested that the use of ritanserin significantly reduced symptoms in those resistant to first-line therapies.<sup>1,21,22</sup> Cyproheptadine is another 5-HT<sub>2a</sub> antagonist but possesses further anticholinergic properties. Several studies show its beneficial effect to be on par with propranolol.<sup>23,24</sup> Mianserin works similarly but lacks anticholinergic properties,<sup>25</sup> making it better tolerated and a better choice than either ritanserin or cyproheptadine. Mianserin is dosed at 15 mg/day and cyproheptadine at 8 to 16 mg/day.<sup>1</sup>

The latest research supports an increased role for mirtazapine as the preferred treatment method due to its marked 5-HT<sub>2a/c</sub> antagonism.<sup>1,4,11</sup> In a 90-patient, double-blind, controlled trial, mirtazapine was shown to be as effective as propranolol in controlling akathisia when given at low doses (15 mg/day) over the course of 7 days and had better tolerability and more convenient dosing than propranolol.<sup>4</sup> Short-term side effects included transient sedation but did not affect blood pressure like propranolol.<sup>4,11</sup> Similar to mirtazapine, trazodone demonstrated potent anti-akathistic effects through 5-HT<sub>2a/c</sub> antagonism when titrated to a dose of 100 mg/day over a period of 5 days.<sup>6,7</sup>

Future directions of serotonin's role include the study of other receptors that may have therapeutic effects. Zolmitriptan works on the 5-HT<sub>1d</sub> receptor and, in a 33-patient, double-blind study,<sup>26</sup> was shown to be as beneficial as propranolol.

## Dopamine and GABA-Based Pharmacotherapy

Although restless legs syndrome (RLS) and akathisia are considered two separate medical entities, evidence exists that similar mechanisms may play a role in both disorders. Although their pathophysiology remains unclear, increased serotonin transmission or abnormalities of subcortical pathways resulting in dopamine deficiency may underlie or exacerbate symptoms. Further supporting their connection, several medications that cause akathisia can also worsen symptoms of RLS (neuroleptics, SSRIs, tricyclic antidepressants).<sup>27,28</sup>

Due to this common potential mechanism, medications for RLS that work on the same neurotransmitters have been hypothesized to work for akathisia. Amantadine has been used for several years as an anti-Parkinson's agent and a last-course alternative in treating akathisia.<sup>2,15</sup> As a weak antagonist of the glutamate receptor, it both increases dopamine release and works as a dopamine reuptake inhibitor.<sup>5</sup> It is typically prescribed at a dose of 100 mg/day.<sup>1</sup> Similarly, ropinirole is a potent dopamine agonist that works at the D2, D3, and D4 receptors.<sup>12</sup> Its use in Parkinson's disease and RLS is well-documented,<sup>12</sup> but a lack of substantial evidence exists for its use in akathisia. One case study found that aripiprazole-induced tardive akathisia responded to treatment with ropinirole.<sup>12</sup> Unfortunately, the use of dopamine-increasing medications is limited by side effect profiles, such as psychosis and impulsivity, which may be the target symptoms being treated by neuroleptics in the first place.

Effects on GABA have also been implicated in development of akathisia.<sup>5,14</sup> Many antipsychotic medications cause an inhibition of GABA receptors via dopamine antagonism. This mechanism may underlie side effects like akathisia,

RLS, and lowering of the seizure threshold.<sup>30</sup> Further support for GABA's role is seen in the long-standing use of benzodiazepines as a treatment regimen for akathisia. Medications that increase levels of GABA (eg, pregabalin) have been shown in double-blind, placebo-controlled studies to effectively control RLS symptoms.<sup>31</sup> One case study found that relatively high doses of gabapentin (3000 mg/day) helped effectively treat a patient with neuroleptic-induced akathisia.<sup>32</sup> Another case study found that the addition of pregabalin (150 mg/day) to a regimen of aripiprazole helped reduce tardive akathisia.<sup>13</sup> Although further research is warranted, drugs that affect GABA may be a new avenue for treatment when other therapies have failed.

## Vitamin B6

There have been reports of vitamin B6 being effective in the treatment of neuroleptic-induced movement disorders, such as Parkinson's disease and tardive dyskinesia. In two randomized, double-blind, controlled studies of patients with acute neuroleptic-induced akathisia, administration of high doses (1200 mg/day) of vitamin B6 for 5 days resulted in significant improvement in subjective and global subscales of the Barnes Akathisia Rating Scale.<sup>33,34</sup> Although a mechanism of action is unclear, vitamin B6 serves as a cofactor in the synthesis of several neurotransmitters, including dopamine, serotonin, and GABA. Its interactions with multiple neurotransmitter systems might thus explain its efficacy in treating akathisia.<sup>33</sup>

## CONCLUSION

Akathisia remains an ongoing problem, despite the greater use of second-generation antipsychotics. The exact mechanism of development remains poorly understood, although ongoing research points to a greater involvement

of other neurotransmitter systems outside of dopamine, such as acetylcholine, serotonin, and GABA. From this new theoretical foundation, treatment strategies have moved beyond long-standing regimens (eg, beta-blockers, anticholinergics, benzodiazepines) by including serotonin-based pharmacotherapy (eg, mirtazapine, mianserin). Based on akathisia's similarity to movement disorders such as RLS, new approaches under investigation include medications that increase dopamine and GABA (eg, ropinirole, gabapentin, pregabalin, vitamin B6), which are depleted with neuroleptic use. Timely diagnosis and adequate treatment are key in maintaining patient rapport, improving medication compliance, and increasing efficacy. Thus, providers need to be aware of this phenomenon and understand how to manage it effectively using the latest research-supported treatment regimens (**Table 1**).

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