

# Pathophysiology and management of Akathisia 70 years after the introduction of the chlorpromazine, the first antipsychotic

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**Abstract.** – **OBJECTIVE:** Akathisia is among the most troubling effects of psychiatric drugs as it is associated with significant distress on behalf of the patients, and it limits treatment adherence. Though it most commonly presents during treatment with antipsychotic drugs which block dopamine D2 receptors, Akathisia has also been reported during treatment with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), stimulants, mirtazapine, tetrabenazine and other drugs.

**MATERIALS AND METHODS:** This article was designed as a narrative review on akathisia with a focus on its clinical presentation, pathophysiology and management. A PubMed search for akathisia was conducted which returned 8481 articles.

**RESULTS:** Akathisia is experienced as severe restlessness commonly accompanied by dysphoria and purposeless movement which relieves subjective tension. It has been attributed to an imbalance between dopaminergic and noradrenergic neurotransmission in the basal ganglia. Acute akathisia commonly resolves upon treatment discontinuation but tardive and chronic akathisia may persist after the causative agent is withdrawn and prove resistant to pharmacological treatment. Even drugs which induce no other extrapyramidal side effects (such as clozapine, quetiapine, aripiprazole and cariprazine) may induce akathisia. A high index of suspicion should be maintained in patients with motor disabilities, drug-induced parkinsonism and those under mechanical restraint. Propranolol and low-dose mirtazapine are the most thoroughly studied pharmacological interventions for akathisia, though benzodiazepines, voltage-gated calcium channel blockers (gabapentin, pregabalin) and opioids may be effective.

**CONCLUSIONS:** Pharmacological management may pose a challenge in chronic akathisia. Rotation between different pharmacological management strategies may be optimal in resistant cases. Discontinuation of the causative drug and use of b-blockers, mirtazapine, benzodiazepines or gabapentinoids for symptomatic relief is the basis of management.

*Key Words:*

Aripiprazole, Extrapyramidal symptoms, Haloperidol, Locus coeruleus, Propranolol.

## Introduction

Akathisia is a common adverse effect of treatment with antipsychotic drugs, with incidence rates ranging from 5-50% depending on the duration of treatment and the drug used<sup>1</sup>. It is a common cause of treatment non-adherence and has been associated with violence and suicide<sup>2,3</sup>. Though most commonly observed with dopamine D2 receptor antagonists, it may also complicate treatment with other psychiatric drugs which do not interact with dopamine receptors directly, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) tricyclic antidepressants, mirtazapine and vesicular monoamine transporter 2 (VMAT2) inhibitors which deplete dopamine and other monoamine neurotransmitters<sup>4</sup>. Drugs of this class include reserpine (used as an antipsychotic in the 1950s, now prescribed only rarely in low doses as an antihypertensive), tetrabenazine (indicated for the treatment of Huntington's dis-

ease) and valbenazine, the only drug indicated for the treatment of antipsychotic-induced tardive dyskinesia<sup>5</sup>.

It is difficult to comprehend the concept of akathisia as it is not a normal component of human experience. It is typically encountered as a side effect of psychiatric drugs but may also occur during opioid or stimulant withdrawal and rarely as a result of traumatic brain injury<sup>6</sup>. It can be described as an intense sensation of inner restlessness accompanied by an urge to remain constantly in motion. It is typically accompanied by intense dysphoria which worsens when willingly remaining still. It was initially classified as part of the extrapyramidal syndrome (EPS) induced by antipsychotic drugs, but some evidence suggests that akathisia is fundamentally distinct from other EPS manifestations<sup>7</sup>. The underlying mechanism is the inhibition of dopaminergic neurotransmission in the nigostriatal pathway for acute events, whereas tardive dyskinesia has been attributed to D2 receptor upregulation and subsequent hypersensitivity to dopamine following prolonged exposure to D2 antagonists<sup>5</sup>. Patients are characteristically indifferent to EPS and the presentation is far more distressing to observers of the movement disorders than to those actually experiencing them<sup>8</sup>.

Akathisia by definition has a strong subjective component and may cause significant distress in patients even in the absence of typical motor symptoms (pacing, adjusting position constantly in bed). This is indicative of cortical involvement in the pathogenesis of the condition, whereas the indifference typical of EPS suggests that only subcortical structures are involved<sup>1</sup>. The controversial entity of pseudoakathisia is defined as the presence of behavior typical of akathisia in the absence of the subjective component. This may be encountered in chronic schizophrenic patients with prominent negative symptoms<sup>9</sup>. Akathisia is considered acute if its duration is less than 3 months, chronic if its duration is greater than 3 months and tardive if it presents after long-term treatment. Historically it was assumed that it presents some time (2 weeks or more) after initiation of neuroleptic treatment or dose increase, but recent evidence<sup>10</sup> suggests that this is accurate only for drugs with a long half-life (aripirazole, cariprazine) which require weeks to reach their therapeutic steady state concentration. Drugs which attain therapeutic concentrations following administration of a single dose (haloperidol, risperidone) can induce akathisia within hours of

treatment initiation or dose adjustment<sup>11</sup>. Acute akathisia after a single dose of haloperidol has also been described by physicians who took the drug to understand its action<sup>12</sup>.

Objective of this article is to review the presentation, pathophysiology and management of akathisia. A comprehensive review would be valuable for clinicians and researchers alike due to its distressing nature, high prevalence and lack of high-quality clinical trials regarding its management.

## Materials and Methods

A review of the literature was conducted on PubMed using akathisia as a search term. The search returned 8481 articles. This work was conceived as a narrative review with added emphasis placed on uncommon presentations of akathisia and management options. All articles were however screened for relevance (by title and abstract) and the full text of those considered likely to be relevant was retrieved. A hand search of the references of these articles was also conducted. All recommendations regarding management of akathisia were made based on the available empirical evidence (clinical trials and naturalistic studies) and on the pharmacological properties of the drugs if no other evidence was available. A meta-analysis of clinical trials regarding the management of akathisia may not be feasible as relatively few studies have been conducted which are characterized by high heterogeneity and small sample sizes. As this work is a narrative review we did not strictly adhere to a systematic review methodology as dictated by the PRISMA guidelines.

## Results

### *Presentation and Differential Diagnosis of Akathisia*

The presentation of akathisia is distinct from restless leg syndrome (RLS), though the pathophysiological underpinnings may be similar. Patients with RLS complain of an uncomfortable sensation in the legs and an insurmountable urge to move them<sup>13,14</sup>. It is worse during the night and the discomfort associated with it is primarily due to its disruptive effect on sleep. Patients may have a history of substance abuse, as RLS is commonly present in the post-acute

withdrawal syndrome of many illicit drugs. It is also associated with iron deficiency<sup>15</sup>. Akathisia on the other hand affects the entire body, is associated with intense dysphoria and symptoms are constant throughout the day. It may dissipate entirely when the patient is asleep, though it is not uncommon for patients to experience frequent awakenings (every 15-30 minutes) in order to pace for a few moments prior to going back to bed<sup>16</sup>. This is especially common when neuroleptics with a high propensity for causing akathisia (aripiprazole, haloperidol, lurasidone) are prescribed as monotherapy in high doses<sup>17</sup>. It is important to differentiate RLS from akathisia as the first line treatment is different.

Akathisia may rarely present after traumatic brain injury or as a consequence of a cerebrovascular event<sup>18,19</sup>. In elderly patients with multiple cardiovascular risk factors imaging studies (CT or MRI of the brain) are recommended to rule out focal lesions as a cause of akathisia.

A common clinical pitfall is the misdiagnosis of akathisia as agitation due to the underlying psychiatric condition (schizophrenia, manic and mixed episodes of bipolar disorder) for which a drug was initially prescribed. The dysphoria which accompanies akathisia is similar to that encountered in mixed episodes of bipolar disorder, but the recommended management strategies are clearly distinct: acute akathisia usually resolves upon antipsychotic discontinuation or dose reduction, whereas a mixed state may respond to an increase in the dose of the antipsychotic<sup>9</sup>.

The physical manifestations of akathisia (constant movement) in patients chronically exposed to neuroleptics may be masked by EPS (rigidity and bradykinesia due to Parkinsonism)<sup>20</sup> so it is important to maintain a high index of suspicion and inquire about the subjective component<sup>21</sup>. An atypical presentation of akathisia can be observed in patients who experience intense restlessness while being physically unable to move (because of a pre-existing disability or as a consequence of mechanical restraint)<sup>22</sup>. Restrained patients may ask to be released and tend to negotiate removal of the restraints from 1 or 2 limbs if the initial request is refused. The experience of akathisia while restrained has been described as a state of unfathomable torment and is typically encountered when a high potency typical antipsychotic (usually haloperidol) is administered as monotherapy for the management of acute agitation<sup>23</sup>. The propensity

of haloperidol to reliably induce akathisia even in restrained individuals may explain why it was used as a pharmacological torture agent<sup>24</sup>. Restrained patients should be frequently evaluated for akathisia. It is recommended to inquire directly about the nature of the patient's discomfort (whether he feels as if he needs to move, if it is localised to a particular limb, whether it started after a drug was administered) and offer benzodiazepines to provide symptomatic relief if the diagnosis is confirmed.

It should be noted that all neuroleptics and any other substance which acts as a D2 receptor antagonist can cause akathisia. That said, some are more likely to cause it than others. Haloperidol causes akathisia alongside the full spectrum of EPS, a property it shares with most high potency typical antipsychotics (fluphenazine, trifluoperazine, flupentixol, benperidol, pimozide), whereas low potency typical antipsychotics are far more likely to cause akathisia than other EPS when used at low doses<sup>2,21</sup>; this is particularly important for levomepromazine, which is used almost exclusively in low doses (12.5-50 mg) as a sedative. It is also preferred in the palliative care setting for the potentiation of opioid analgesics and to prevent opioid-induced nausea and vomiting. Despite its potent anticholinergic, antiadrenergic and antisertotnergic properties it frequently causes akathisia which may be misdiagnosed as delirium<sup>25</sup>. It is important for clinicians who routinely use levomepromazine in their practice to be aware of this, as haloperidol and mechanical restraint (commonly used for the management of delirium) may cause unnecessary suffering and contribute to deterioration of the patient's condition. Even clozapine and quetiapine, the two antipsychotic drugs considered to have an EPS liability low enough so as to be used safely in Parkinson's disease can cause akathisia, though the risk is lower compared to other drugs<sup>26</sup>. Interestingly, the antipsychotic least likely to induce akathisia is iloperidone, which has an extremely high affinity for  $\alpha_1$  adrenergic receptors, approximately 50 times higher than its affinity for D2 and 5-HT<sub>2A</sub> receptors<sup>27</sup>. The development of akathisia appears to be independent of other EPS and it does not predict the occurrence of parkinsonism during the first few months of treatment. Likewise, the emergence of acute akathisia early in the course of treatment has not been identified as a risk factor for the development of tardive dyskinesia or other tardive syndromes<sup>2,5,6</sup>.

### ***Not Just a Dopamine Deficiency: Remarks on the Pathophysiology of Akathisia***

The mechanisms underlying akathisia are more complex than the simple inhibition of D2 mediated nigostriatal signaling that has been implicated in the other forms of EPS. The cell bodies of the dopaminergic neurons involved are located in the ventral tegmental area, not the substantia nigra<sup>8</sup>. Focal lesions of this nucleus give rise to a syndrome reminiscent of akathisia in rodents, and pontine infarcts in man have also led to the development of akathisia and RLS which has responded to treatment with dopamine agonists<sup>19</sup>. The ventral tegmental area projects to the limbic system via the nucleus accumbens, the core of the brain's reward circuit.

Animal models of akathisia had been proposed during the 1990s, although their validity and clinical relevance may not be ideal. The most common model is that of emotional defecation in rats. In this model rats habituated to a particular environment tend to defecate more frequently if exposed to dopamine antagonists. Increased frequency of defecation is widely recognized as a sign of dysphoria in rodents<sup>28</sup>. This response is attenuated by  $\beta$ -blockers such as propranolol, supporting the hypothesis that antipsychotics induce an imbalance between noradrenergic and dopaminergic neurotransmission<sup>29</sup>. Overactivation of noradrenergic neurons leads to  $\beta_1$  adrenergic receptor mediated activation of the amygdala and the nucleus accumbens shell, resulting in purposeless movements and intense dysphoria. Under normal conditions both the shell and the core of the nucleus accumbens are innervated by the dopaminergic neurons of the ventral tegmental area to control goal directed behavior by inhibiting inhibitory gabaergic neurons which project to the limbic system and the cortex, but in the presence of antipsychotics the shell becomes hyperactive due to its noradrenergic innervation<sup>30</sup>. This response can be attenuated by either  $\beta_1$  antagonists or  $\alpha_2$  agonists such as clonidine, which reduce norepinephrine release by activating the inhibitory autoreceptors present in locus coeruleus neurons<sup>31</sup>. The mechanism discussed above explains the efficacy of sympatholytic drugs such as beta blockers and clonidine in the treatment of akathisia. The fact that the response to sympatholytics is often partial suggests however that additional pathways are involved. The neurons of the ventral tegmental area receive inhibitory serotonergic inputs from the dorsal raphe nucleus,

which explains why 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> antagonists induce dopamine release in the mesocorticolimbic pathway. This may be the mechanism underlying akathisia induced by serotonergic drugs such as SSRIs, which may be distinct from the akathisia induced by D2 antagonists<sup>1,32</sup>. In a preclinical study in rodents in which fluoxetine was compared with amphetamine it was observed that the behavioral effects of the 2 drugs were distinct. Specifically, fluoxetine induced directionless movement whereas amphetamine caused the subjects to forward along a straight line, in accordance with the tendency of stimulants to promote goal-directed behavior<sup>33</sup>.

These findings of an underlying mechanism for akathisia are also supported by clinical studies in healthy volunteers, neuroleptic naive psychotic patients and even psychiatrists themselves: akathisia may be ubiquitous during acute neuroleptic exposure; it is in fact the principal subjective effect of the drugs. In one study in healthy volunteers almost all subjects developed akathisia after exposure to haloperidol 3 mg per day and aripiprazole 15 mg per day by mouth<sup>34</sup>. Haloperidol even at this low dose had a higher rate of discontinuation. Reserpine which is a monoamine depleting agent did not have such a high incidence of akathisia, but symptoms of depression were more common. Though the incidence of acute akathisia appears to be ubiquitous with certain drugs, the intensity of the symptoms appears to lessen over time as the condition becomes chronic. This may also explain the relatively low incidence of akathisia in crossover studies, as patients with constant exposure to antipsychotics may have stable chronic akathisia which is not significantly affected by switching to another drug<sup>35,36</sup>. These insights may be useful for clinicians to better understand the pharmacological treatment of akathisia and to re-evaluate the use of antipsychotic drugs, especially for off label indications.

### ***Clinical Management of Akathisia***

The first step in the management of akathisia should always be to identify the causative agent and if possible, discontinue treatment immediately. This should not come as a surprise as individualized treatment is the norm in psychiatry and akathisia is a syndrome diametrically opposed to the stated goals of treatment for any psychiatric condition<sup>2,32</sup>. A drug which causes akathisia in a particular patient is ill suited to treat major depression, anxiety disorders, somatoform dis-

order, PTSD or OCD and it would be difficult to imagine how it could serve as a long-term mood stabilizer. First, do no harm: one should bear in mind that akathisia especially as an adverse effect of antidepressant treatment is associated with suicidality and aggression<sup>37</sup>. The epidemiological association between antidepressants and suicide is stronger in the pediatric population and young adults, as reported in the black box warning of all drugs in this class marketed in the US. Apart from SSRIs and SNRIs, akathisia may also occur with tricyclic agents and mirtazapine in doses higher than 30 mg per day<sup>38,39</sup>. Any antipsychotic prescribed off label to augment antidepressant treatment should be discontinued and short-term pharmacological treatment for akathisia should be offered.

In cases where neuroleptic treatment is absolutely indicated (manic or mixed states in bipolar disorder, exacerbations of schizophrenia with prominent positive symptoms) it is recommended to prescribe antipsychotics at the lowest dose which adequately controls symptoms. High doses of neuroleptics may cause or exacerbate akathisia in virtually anyone but certain risk factors have been identified. The most notable of these are use of high potency typical agents, rapid dose titration, young age and no previous exposure to antipsychotic drugs<sup>40,41</sup>. Clozapine, quetiapine and iloperidone may be less likely to cause akathisia than other drugs, but it still occurs in a substantial proportion of patients.

The first line treatment for akathisia is propranolol, the prototypical non-selective beta blocker. Though it does not appear particularly more efficacious or well tolerated than other drugs, it is the one which has been more thoroughly evaluated in clinical studies<sup>30,38</sup>. It is a lipophilic compound which readily crosses the blood brain barrier and is devoid of intrinsic sympathetic activity (meaning that it is not a partial agonist). It is typically prescribed at 40-120 mg per day in 3 divided doses for the management of akathisia. The evidence for other beta blockers is not as robust, though especially those with intrinsic sympathetic activity (such as pindolol which is also a 5-HT<sub>1A</sub> antagonist occasionally used off-label to augment antidepressant treatment) should be avoided<sup>42,43</sup>. Beta blockers were the first recognized treatment for akathisia and remain up to this day the most extensively evaluated in clinical trials. Their action against akathisia does not appear to be dose-dependent as a maximal response may be obtained at the low end of the dosage range of

propranolol. It has been noted that the response is often partial, in which case either further reduction in dosage of the causative agent or addition of another drug for akathisia may be required<sup>42,43</sup>. We would not recommend clonidine as a first or even second line treatment for akathisia due to its substantial side effects (hypotension, sedation) and lack of clear evidence for efficacy<sup>30,31,43</sup>.

Anticholinergic drugs including biperiden, trihexyphenidyl, benztropine and diphenhydramine are commonly used alongside antipsychotics to minimize their side effects and improve treatment adherence. They are the first line treatment for EPS and are routinely co-prescribed when agents with a high probability of inducing EPS (haloperidol, fluphenazine) are used in high doses<sup>44</sup>. They are more useful for the treatment of acute dystonia than parkinsonism. As they are associated with delirium, cognitive impairment and increased risk of falls in the elderly it is recommended to avoid prolonged treatment especially in geriatric patients<sup>45</sup>. They are extremely effective for acute dystonia but less so for neuroleptic-induced Parkinsonism. It is not clear whether they are of any benefit in akathisia and should only be prescribed for other manifestations of EPS.

Serotonergic antagonists, specifically mirtazapine in low doses (7.5-15 mg per day) and trazodone (50-100 mg per day) have also been evaluated in clinical trials for akathisia. They may be particularly effective for akathisia induced by typical antipsychotics with negligible affinity for 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors<sup>38</sup>. Antagonism of these receptors may attenuate akathisia by promoting dopamine release in the mesocorticolimbic pathway. Mirtazapine is a 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> antagonist but its affinity for H<sub>1</sub> receptors is approximately 20 times higher, suggesting that it is significantly more potent as an antihistamine. At higher doses (more commonly employed when it is used as an antidepressant) it induces norepinephrine release by blocking  $\alpha_2$  autoreceptors and may cause or worsen akathisia. Trazodone is a potent  $\alpha_1$  adrenergic receptor antagonist which may explain its notorious association with priapism. Like mirtazapine it is a 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> antagonist, but its affinity for  $\alpha_1$  receptors is much higher. Doses in excess of 100 mg per day affect additional serotonergic receptors while also inhibiting serotonin reuptake. Trazodone has an active metabolite, meta-chloro-phenyl-piperazine (mCPP), a non-selective serotonin agonist and releasing agent which induces dys-

phoria and hallucinations. Its contribution to the action of trazodone throughout its dosage range remains unclear, though at low doses it is not likely to be significant<sup>46</sup>. Both trazodone and mirtazapine cause significant sedation. 5-HT<sub>2</sub> antagonism is not however a particularly convincing explanation for their efficacy against akathisia. Many antipsychotics also function as 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> antagonists and although it has been hypothesized that an inverse correlation exists between a drug's affinity for these receptors and its propensity to cause akathisia, this has not been definitively proven and it is not supported by routine clinical experience. Akathisia is commonly observed with antipsychotics which saturate 5-HT<sub>2</sub> receptors throughout their clinical dosage range, including risperidone, ziprasidone and olanzapine<sup>27,47</sup>.

Benzodiazepines are the final first line treatment for akathisia, as they provide significant symptomatic relief. This is attributed to their general sedative and anxiolytic action rather than an effect which specifically addresses the pathogenesis of akathisia. They may be especially useful for patients with severe symptoms which adversely affect sleep by causing frequent awakenings<sup>48</sup>. In practice they are commonly initiated alongside antipsychotics for acute psychosis, thus they confer some protection from akathisia and neuroleptic-induced dysphoria. It should be noted that there is a risk of paradoxical disinhibition as a consequence of benzodiazepine treatment especially in young adults and geriatric patients, though it is reduced significantly by use of an antipsychotic. In rare occasions they have been known to induce akathisia, with case reports of patients experiencing akathisia on one benzodiazepine while tolerating equivalent doses of another well<sup>49</sup>. Concerns regarding physical dependence, cognitive impairment and delirium necessitate using the lowest dose which adequately treats symptoms for the shortest possible time span.

Recent case reports<sup>50-53</sup> and a pilot study suggest gabapentin and its analog gabapentin enacarbil may be effective for the management of akathisia. This should not come as a surprise, as gabapentinoids are a first line treatment for RLS, which apart from a similar clinical presentation may overlap in terms of pathogenesis as well. Theoretically pregabalin could be effective as well, though at least one case of pregabalin causing akathisia has been reported<sup>54</sup>. If there was a stronger evidence base to support their efficacy they would be recommended as a first line treat-

ment as they are safer than propranolol and benzodiazepines. Unlike propranolol, they have no organic contraindications whereas propranolol is not recommended in patients with bronchial asthma, COPD and diabetes. Physical dependence to and withdrawal reactions are mild in comparison to benzodiazepines, they are not associated with paradoxical disinhibition and their abuse potential is limited as tolerance develops rapidly to the effects recreational users find desirable. As they are safer for long term use, they are particularly attractive for the treatment of tardive akathisia, though prolonged treatment with high doses may be required<sup>55</sup>.

Amantadine, an NMDA antagonist indicated for the early stages of Parkinson's disease is a second line treatment which clinicians should be aware of as a possible adjunctive treatment<sup>6</sup>. It has been successfully used in such cases, though concerns regarding physical toxicity and psychotomimetic effects necessitate caution. The use of dopamine agonists is generally not indicated as they may exacerbate psychosis, with the risk being significantly greater for patients who have been maintained on antipsychotics for many years. D<sub>2</sub> receptors tend to upregulate after long-term exposure to antipsychotics and other D<sub>2</sub> antagonists and this compensatory mechanism accounts both for the emergence of tardive dyskinesia and for the increased sensitivity of this population to the psychotomimetic effects of dopamine agonists. This option may be considered if the offending neuroleptic has been discontinued and akathisia persists despite treatment with first-line drugs, despite the substantial risk of supersensitivity psychosis<sup>56</sup>.

Mu opioid receptor agonists may be regarded as the last resort in the pharmacological management of akathisia. Only two articles<sup>57,58</sup> regarding this use of opioids have been identified, noting a substantial response in acute akathisia but more modest therapeutic effects in the tardive syndrome. This is an option to be considered in inpatients either in acute care wards or in long term care facilities who failed to adequately respond to other treatments. They typically have a long history of neuroleptic exposure and may have concurrent tardive dyskinesia. Since the prognosis of such patients in terms of functional rehabilitation is poor, the use of opioids if informed consent is provided may offer substantial relief from dysphoria and despair, even if only a partial response is attained. This should not be a controversial position, as the care of such patients is essentially palliative<sup>59</sup>. Table I provides an overview of the

pharmacological treatment of akathisia. Clinical algorithms for the management of both acute and chronic akathisia are provided in Table II.

### Conclusions

Akathisia is among the most common adverse effects of antipsychotic drugs and the one most

likely to be implicated in treatment discontinuation and adverse clinical outcomes including aggressive behavior and suicidality. Though it may be managed with the use of other drugs, the best course of action is usually to discontinue the offending agent as the emergence of akathisia is not compatible with the stated purpose of treatment. Further research is warranted particularly for the evaluation of gabapentinoids and opioids in the

**Table I.** Overview of drug classes used in the pharmacological management of Akathisia.

Drug class	Dosage	Common adverse effects	Contraindications	Comments
Propranolol	40-120 mg per day in 2 doses	Bradycardia, malaise Considered marginally psychoactive but may precipitate depression or psychotic symptomatology	Asthma, chronic obstructive pulmonary disease, diabetes mellitus under insulin treatment, acute decompensated heart failure	Consider first line in patients with a concomitant medical indication for beta blocker therapy. May cause hypertensive crisis with concomitant stimulant use or pheochromocytoma due to unopposed a adrenergic receptor mediated vasoconstriction
Anticholinergics	Benztropine: 1-4 mg per day Trihexyphenidyl: 5-15 mg per day Biperiden: 4-12 mg per day	Tachycardia, xerostomia, sedation, hallucinations, mydriasis, constipation, urinary retention May precipitate delirium in the elderly	Glaucoma, urinary tract obstruction	Not particularly effective for akathisia but commonly routinely used for parkinsonism and dystonia. Consider prophylactic treatment in patients receiving high potency first generation agents (haloperidol, luphenazine)
5-HT <sub>2A</sub> antagonists	Mirtazapine: 7.5-15 mg per day Trazodone: 50-100 mg per day	Sedation, weight gain, vivid dreams May worsen akathisia in higher doses	Previous adverse reaction to the drug	Consider first line in patients on high potency first generation drugs and benzamides. Most other antipsychotics block 5-HT <sub>2A-2C</sub> receptors to a significant degree at clinically relevant doses
Benzodiazepines	15-30 mg diazepam equivalent per day in divided doses	Sedation, respiratory repression when combined with other sedatives, paradoxical disinhibition, euphoria May precipitate delirium in the elderly	Myasthenia gravis, obstructive sleep apnea	Consider first line in inpatients with a history of alcohol abuse. Treatment duration should be limited due to the development of tolerance and dependence

*Continued*

**Table I (Continued).** Overview of drug classes used in the pharmacological management of akathisia.

Drug class	Dosage	Common adverse effects	Contraindications	Comments
A2δ voltage gated calcium channel blockers	Gabapentin: 1200-3600 mg per day Pregabalin: 300-600 mg per day Gabapentin enacarbil: 300-600 mg per day	Sedation, euphoria, ataxia, weight gain	Dose must be adjusted in renal failure	As they are well tolerated may be considered first line drugs for akathisia. In patients on long-term treatment rotation with agents of a different class may help prevent the development of tolerance
Opioids	Highly individualized. Less than 30 mg per day of oral morphine equivalent may be sufficient in opiate-naive patients	Sedation, euphoria, miosis respiratory depression, nausea and vomiting, constipation, pruritus, allergic reactions	Monoamine oxidase inhibitor therapy for tramadol, pethidine, methadone, tapentadol Paralytic ileus	Particularly effective for acute akathisia (in the emergency setting and in restrained patients) due to immediate onset of therapeutic benefit If long term treatment for chronic or tardive akathisia is required rotation with agents of a different class may help prevent the development of tolerance and dependence
Dopamine agonists and amantadine	Amantadine: 100-200 mg per day Ropinirole: 4-12 mg per day	Sedation, unexpected sleep attacks, hallucinations, impulse control disorders, dopamine agonist withdrawal syndrome with prolonged treatment	Hypersensitivity to the drugs, renal failure for amantadine	Not recommended

**Table II.** Management algorithms for Akathisia.

<b>Acute akathisia</b>
<p>Discontinue the causative agent if it is not an antipsychotic; prior to discontinuation of antipsychotic treatment a dose adjustment may be considered. Switching from a high potency first generation drug to a low potency first generation or a second generation drug may resolve symptoms. A final option is switching to clozapine or quetiapine which do not cause akathisia as often as other drugs.</p> <p>Symptomatic treatment of akathisia with a benzodiazepine, calcium channel blocker or opioid drug is recommended due to the intense dysphoria associated with the condition. Long term prophylactic treatment with an anti-akathisia drug is not recommended; the mainstay of management is reducing or removing the causative agent. Treatment may have to be continued for a few weeks to months if the akathisia is due to a drug with a particularly long half-life (fluspirilene, pimozone) or if it occurred due to use of a long-acting injectable formulation). In this case see principles mentioned below in the management of chronic akathisia.</p>
<b>Chronic or Tardive Akathisia</b>
<p>Reducing neuroleptic burden should be a priority but must be done gradually to minimize the risk of rebound psychosis or relapse. The same principles outlined above apply here as well: Switching from a high potency first generation drug to a low potency first generation or a second generation drug may resolve symptoms. A final option is switching to clozapine or quetiapine which do not cause akathisia as often as other drugs. Treatment with a single agent (propranolol, gabapentinoid, benzodiazepine or opioid) should be attempted first. In patients treated with medication for opioid use disorder switching to methadone or increasing methadone dose should be considered. If there is no response to a single agent at an adequate dose a combination may be tried. In patients who relapse despite discontinuation of neuroleptic therapy but respond adequately to pharmacological treatment a rotation between opioids, gabapentinoids and benzodiazepines may be attempted to reduce tolerance and prevent dependence.</p>

treatment of chronic and tardive akathisia associated with long-term antipsychotic treatment. The management of this clinical entity is particularly challenging as it may persist after antipsychotics are discontinued, requiring prolonged treatment to attain symptomatic relief. Furthermore, in long term patients abrupt or even gradual antipsychotic discontinuation presents significant risks because of D2 receptor upregulation and the risk of rebound psychosis.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

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