Akathisia was initially observed in patients with basal ganglia disorders, primarily Parkinson's disease. Introduction of first-generation antipsychotic (FGA) agents drew attention to antipsychotic-induced akathisia as it appeared to be one of the most frequent and distressing drug-induced movement disorders, occurring in around one in four FGA-treated patients. It is characterised by restless movements and a subjective sense of inner restlessness coupled with distress, and develops predominantly in patients treated with high-potency FGAs, at high doses and during rapid dose escalation. The identification of akathisia in a meaningful proportion of patients treated with selective serotonin reuptake inhibitors and its association with suicidal behaviour highlights its clinical significance. Akathisia also afflicts a substantial proportion of patients treated with preoperative sedatives, calcium channel blockers, and anti-emetic and anti-vertigo agents, posing a diagnostic and treatment challenge in non-psychiatric populations as well. Early detection and rapid amelioration of acute akathisia are essential since it is a risk factor for psychotic exacerbation and non-adherence to pharmacotherapy. Intercorrelation between akathisia, depressive symptoms and impulsiveness may account for suicidal and violent behaviour in patients with akathisia.

**Summary**

Akathisia remains one of the most prevalent and distressful antipsychotic-induced adverse events. Effective and well-tolerated treatment is a major unmet need in akathisia that merits a search for new remedies. Accumulating evidence indicates that agents with marked serotonin-2A receptor antagonism may represent a new class of potential anti-akathisia treatment.

**Declaration of interest**

M.P. is a member of the advisory board of Schering Plough, and served as a consultant for akathisia studies for Acadia Pharmaceuticals.

**Current treatment options for akathisia**

** Beta-adrenergic blockers **

Propranolol, a non-selective lipophilic beta-adrenergic antagonist, was used as a first-line anti-akathisia agent for decades. Surprisingly, this treatment was not supported by large-scale controlled trials. The robust anti-akathisia effect of propranolol was substantiated in the largest-to-date akathisia trial (see Poyurovsky et al.). Propranolol tolerability, however, was poor and a substantial proportion (20%, 6 of 30 patients) developed clinically meaningful orthostatic hypotension and bradycardia prompting premature drug discontinuation. Additional drawbacks of propranolol co-administration with antipsychotics are increased complexity in administration and titration schedules as well as contraindications for propranolol use (diabetes mellitus, cardiac conductance impairment, bronchial asthma).
Anticholinergic agents
Although anticholinergics have proven efficacy in antipsychotic-induced Parkinsonism and dystonia, their clinical utility in akathisia remains unclear. A recent short-term placebo-controlled trial revealed no difference between intramuscular biperiden and placebo in patients with FGA-induced akathisia. Anticholinergic-induced side-effects further limit their use in antipsychotic-treated patients. Barnes & McPhilips’ suggestion to use anticholinergics only in patients with akathisia who have associated Parkinsonian symptoms seems to hold true, although explicit evaluation is warranted.9

Benzodiazepines
Benzodiazepines have some therapeutic value in antipsychotic-induced akathisia, putatively owing to their non-specific anti-anxiety and sedative effects. Nevertheless, clinical experience shows that these effects are not sufficient to ameliorate akathisia.

Newer treatment options
In a previous editorial in this Journal we suggested agents with marked 5-HT2A receptor antagonism (mianserin, cyproheptadine) as anti-akathisia remedies based on their potential to counteract antipsychotic-induced dopamine D2 receptor blockade by increasing dopamine neurotransmission.10 Indeed, small randomised placebo-controlled trials consistently demonstrated anti-akathisia properties, safety and tolerability of mianserin and cyproheptadine in FGAtreated patients with akathisia.10 Mild sedation and non-clinically significant orthostatic hypotension were the only side-effects. Both compounds did not interfere with the antipsychotic effects of FGAs.

Low-dose mirtazapine
The most compelling evidence indicating that 5-HT2A antagonists may represent a new class of effective anti-akathisia agent comes from the largest-to-date randomised controlled trial comparing low-dose mirtazapine with propranolol in 90 patients with FGA-induced acute akathisia.7 Mirtazapine is characterised by potent presynaptic alpha-2 adrenergic antagonism, which accounts for its antidepressant activity, and marked 5-HT2A blockade that seems to preponderate in a low dose and contribute to its anti-akathisia properties. Mirtazapine, given once daily (15 mg) was as effective as propranolol (80 mg twice daily) in producing a greater improvement in akathisia compared with placebo (reduction in BARS global scale: 1.10 (s.d. = 1.37) points (34%) and 0.80 (s.d. = 1.11) points (29%) v. 0.37 (s.d. = 0.72) points (11%) respectively; \(P = 0.036\)). Responder analysis (BARS global scale reduction \(\geq 2\)) yielded a similar robust anti-akathisia effect in mirtazapine and propranolol v. placebo (43.3% and 30% v. 6.7% respectively; \(P = 0.005\)). Low numbers needed to treat (3 and 4 respectively) support high clinical efficacy of both compounds. Importantly, mirtazapine achieved an anti-akathisia effect with more convenient dosing than propranolol and better tolerability, with mild transient sedation as the only observed side-effect. The favourable mirtazapine safety profile was also evidenced by their efficacy in animal models of EPS.14

Suggested treatment guidelines for acute akathisia
Systematic evaluation of agents with marked 5-HT2A receptor antagonism in acute akathisia prompts modification of the previously suggested guidelines.10 There are two major treatment strategies: modification of the antipsychotic drug regimen and/or the addition of an anti-akathisia agent. The former includes a dose reduction of the culprit antipsychotic, switch to a low-potency FGA (e.g. chlorpromazine) or to a more commonly used SGA with low potential to induce akathisia (e.g. quetiapine), and if necessary initiation of clozapine in cases of intractable akathisia. Noteworthy, the CATIE investigators showed that patients with perphenazine-induced akathisia are particularly vulnerable to this side-effect when medication is switched to risperidone. It is plausible that this holds true when switching to other SGAs with high akathisia potential (e.g. ziprasidone, aripiprazole), although evidence is lacking.

When the decision is to add an anti-akathisia agent, propranolol (40–80 mg/day twice daily) or low-dose mirtazapine (15 mg once daily) as first-line treatment have the most supportive evidence. Mianserin (15 mg once daily) and cyproheptadine (8–16 mg/day) are alternative options; however, large-scale trials are not yet available.

In antipsychotic-induced akathisia associated with Parkinsonism, anticholinergic agents (e.g. biperiden, trihexyphenidyl, benztropine) may be considered. Non-specific anxiolytic and sedative effects of benzodiazepines alone or in combination with propranolol may be beneficial in some patients. Co-administration of benzodiazepines with mirtazapine, mianserin and cyproheptadine should be avoided owing to their shared sedative properties. Clonidine and amantadine may be tried if other options have failed (Fig. 1).

Future directions
Elucidation of an anti-akathisia effect of mirtazapine and other agents with marked 5-HT2A antagonism in patients with SGA-induced akathisia is a reasonable next stage. Among SGAs, aripiprazole is distinguished by a low affinity for the 5-HT2A receptor, hence additional 5-HT2A antagonism may be required to mitigate aripiprazole-induced akathisia.14 Since mirtazapine exhibits an antagonistic effect on multiple receptors, evaluation of the anti-akathisia properties of selective 5-HT2A antagonists might further clarify the role of this mechanism in the pathophysiology of akathisia. Notably, the selective inverse agonist pimavanserin ameliorates haloperidol-induced akathisia in healthy volunteers.15

Additional receptor mechanisms within the serotonergic system may underlie an anti-akathisia effect. Indeed, a selective 5-HT1D receptor agonist zolmitriptan (7.5 mg/day) revealed anti-akathisia properties comparable to those of propranolol, although its clinical utility is not yet clarified. Along an intriguing new line of thought beyond adrenergic/serotonergic mechanisms, adenosine-2A receptor antagonists may represent potentially active anti-akathisia agents owing to their ability to increase dopaminergic neurotransmission in the striatum, as evidenced by their efficacy in animal models of EPS.14
As noted, akathisia may be ‘forgotten, but it is indeed not gone’. Effective, safe and easy-to-use anti-akathisia agents remain a major unmet need in antipsychotic-induced akathisia that merits a search for new remedies.

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### References


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**Fig. 1** Proposed treatment guidelines for acute antipsychotic-induced akathisia.

| Acute antipsychotic-induced akathisia |
| Change antipsychotic drug regimen |
| Reduce dose of antipsychotic agent |
| Switch to low-potency FGA (e.g. chlorpromazine) |
| Switch to SGA with low potential to induce akathisia (e.g. quetiapine) |
| Add anti-akathisia agents |
| Beta-blocker: propranolol (40–80 mg/day) |
| S-HT2A receptor antagonist: mirtazapine (15 mg/day) |
| 5-HT2A receptor antagonists: mianserin (15 mg/day) or cyproheptadine (8–16 mg/day) |
| 5-HT2A receptor antagonists: mianserin (15 mg/day) or cyproheptadine (8–16 mg/day) |
| S-HT2A receptor antagonists: mianserin (15 mg/day) or cyproheptadine (8–16 mg/day) |
| Anticholinergics (mainly for patients with concurrent Parkinsonism): biperiden (2–6 mg/day), benztropine (1.5–6 mg/day) or trihexyphenidyl (2–10 mg/day) |
| Benzodiazepines: lorazepam (1–2 mg/day), clonazepam (0.5–1 mg/day) or diazepam (5–15 mg/day) |
| Amantadine (100 mg/day) or clonidine (up to 0.15 mg/day) |

FGA, first-generation antipsychotic; SGA, second-generation antipsychotic. An earlier version of these guidelines has been published.10
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