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REVIEW ARTICLE

Treatment of Antipsychotic-Induced Akathisia: Role of Serotonin 5-HT_{2a} Receptor Antagonists

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Abstract

Akathisia is one of the most prevalent and distressing adverse effects associated with antipsychotic drug treatment. Propranolol, a non-selective beta-adrenergic receptor antagonist, is currently considered a first-line treatment for antipsychotic-induced akathisia (AIA). Surprisingly, the evidence for its anti-akathisia effect is modest. Propranolol's side effects (e.g. orthostatic hypotension, bradycardia), contraindications (e.g. asthma) and increased complexity in titration schedules limit its use in some patients. Anticholinergic agents and benzodiazepines merely provide symptomatic relief in patients with AIA. Effective and well-tolerated treatment remains a major unmet need in akathisia and warrants a search for new anti-akathisia agents. Accumulating evidence during the last two decades indicates that agents with marked postsynaptic serotonin 5-HT_{2a} receptor antagonism (ritanserin, cyproheptadine, trazodone, mianserin, mirtazapine) may represent a new class of potential anti-akathisia remedies. Among these agents, low-dose mirtazapine (7.5 mg or 15 mg once daily) has demonstrated the most compelling evidence for therapeutic efficacy. In this narrative review we highlight the clinical significance of AIA, outline major approaches for its management and propose a practical algorithm for its treatment.

Key Points

Akathisia remains one of the most prevalent and distressing adverse effects associated with antipsychotic drug treatment, impacting adherence and response to treatment.

Propranolol, anticholinergics and benzodiazepines are currently used for the treatment of akathisia. However, their side effects and limited efficacy warrant a search for new anti-akathisia remedies.

Agents with marked postsynaptic serotonin 5-HT_{2a} receptor antagonism (ritanserin, cyproheptadine, trazodone, mianserin, mirtazapine), primarily low-dose mirtazapine, have emerged as a new class of effective and well-tolerated anti-akathisia agents.

1 Introduction

Akathisia is characterised by typical restless movements associated with a subjective sense of inner restlessness and mental distress. Akathisia was identified in patients with Parkinson's disease and other neuro-psychiatric disorders well before the development of psychopharmacological agents. However, the introduction of antipsychotic medications for the treatment of schizophrenia brought akathisia to the forefront of clinical care. Subsequent detection of a meaningful incidence of akathisia among patients with mood and anxiety disorders treated with selective serotonin reuptake inhibitors (SSRIs) further highlights its clinical relevance. Akathisia also afflicts some patients treated with calcium channel blockers, antibiotics, anti-emetic and anti-vertigo agents, posing a diagnostic and treatment challenge in non-psychiatric populations as well [1–4].

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Diagnosis of antipsychotic-induced akathisia (AIA) is challenging owing to the existence of various forms of AIA [5]. Thus, acute akathisia usually emerges during the initiation of antipsychotic drug treatment. Chronic akathisia is defined as the persistence of symptoms for more than 3 months. Akathisia may also arise following reduction of dosage or cessation of antipsychotic medication, referred to as withdrawal akathisia. Similar to tardive dyskinesia, tardive akathisia develops late in the course of treatment, is exacerbated or provoked by antipsychotic dose reduction or withdrawal, and improves at least temporarily when the antipsychotic dose is increased. Persistent akathisia is particularly disabling and often refractory to treatment. When a patient exhibits the objective signs of akathisia in the absence of awareness of the typical subjective experience, it is sometimes called pseudo-akathisia [5].

The accurate diagnosis of AIA is also complicated by diurnal variations in its expression and common association with other extrapyramidal syndromes (EPS), such as Parkinsonism and tardive dyskinesia [6]. The complex interplay of the observable restless movements and the subjective sense of inner restlessness and distress account for the difficulties in differentiating AIA from psychotic psychomotor agitation, anxiety, agitated depression, substance intoxication/withdrawal and tardive dyskinesia [3, 4, 7].

Risk factors for the development of akathisia remain to be clarified; however, several associations have been detected. Patient's age seems to play a role. An inverse relationship between AIA and age has been reported; children and adolescents are more susceptible to the development of EPS and akathisia than adults [8, 9]. Ethnicity is a putative risk factor with Caucasians being less vulnerable to AIA than other ethnic groups; however, this association was more robust among patients with tardive dyskinesia [10, 11]. Individuals experiencing their first episode of psychosis previously untreated with antipsychotic agents are particularly vulnerable to the development of akathisia [1]. Notably, those with affective disorders, primarily bipolar depression, appeared to be more susceptible to AIA than schizophrenia patients. Non-psychiatric patients with delirium, substance abuse and those residing in palliative care settings, were also found to be sensitive to the development of AIA [1, 12, 13].

Early detection and rapid amelioration of acute akathisia are essential because of its association with several serious clinical outcomes. There is compelling evidence indicating that AIA is associated with poor treatment response, exacerbation of psychosis. AIA can be a forerunner of tardive dyskinesia. AIA is a potential contributing factor to violent and suicidal behaviour of patients with severe psychiatric illnesses. Mental distress that accompanies akathisia makes it one of the most common reasons for non-adherence to antipsychotic drug treatment [1, 2, 14, 15].

Akathisia appears to be one of the most frequent and distressing drug-induced movement disorders, occurring in around one in four patients treated with first-generation antipsychotics (FGAs). Notably, high-potency FGAs, high doses and rapid dose escalation are among the predisposing factors for development of FGA-induced akathisia [1]. Moreover, polypharmacy with two FGAs was found to be associated with a substantially higher prevalence of akathisia compared to those on monotherapy with FGAs (40% vs 21%, respectively), after controlling for confounding factors [16]. A similar pattern was found among patients treated with second-generation antipsychotics (SGAs) (polypharmacy, 34.2% vs monotherapy, 10.9%) [16].

Although low propensity to induce EPS is a defining feature of SGAs, this seems not to hold entirely true for akathisia. The landmark Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) revealed no significant differences between the intermediate-potency FGA perphenazine and four SGAs (olanzapine, quetiapine, risperidone, ziprasidone) in the percentage of chronic schizophrenia patients who developed AIA [17]. Subsequent rigorous analysis of the CATIE results using multiple criteria of AIA (Barnes Akathisia Scale (BARS) [18] score ≥ 2, administration of anti-akathisia medications, treatment discontinuation due to akathisia) estimated the 12-month akathisia rate at 26–35% for SGAs and 35% for perphenazine, with a trend towards the addition of anti-akathisia medications to more perphenazine- and risperidone-treated patients [19]. A substantial rate of AIA induced by SGAs; amisulpride (200–800 mg, 16%), olanzapine (5–20 mg, 10%), quetiapine (200–750 mg, 13%) and ziprasidone (40–160 mg, 28%) was shown in the European First Episode Schizophrenia Trial [20]. Lack of a substantial difference in moderate-to-severe akathisia (BARS score ≥ 3) between the FGA molindone (10–140 mg) and the SGAs (olanzapine, 2.5–20 mg and risperidone, 0.5–6 mg) was substantiated among adolescents in a Treatment of Early Onset Schizophrenia Spectrum Disorders study (18%, 13%, 8% respectively) [21]. Overall, akathisia has been observed with all of the "older" SGAs; however, there is a difference in incidence. Although direct comparative studies that explicitly evaluated the incidence of akathisia are lacking, it seems that risperidone, paliperidone and ziprasidone possess a higher risk than olanzapine, while quetiapine and clozapine exhibit the lowest risk [1, 22, 23].

Newly approved SGAs also differ in their potential to induce akathisia: lurasidone and asenapine are associated with dose-related and clinically meaningful rates of

akathisia, whereas iloperidone is not [23]. Thus, lurasidone-treated patients had a significantly higher incidence of akathisia compared to placebo (15% vs 3%, respectively), especially with higher doses (80–120 mg/day). Similarly, significantly higher akathisia rates were noted in clinical trials of asenapine (6% vs 3% for placebo). In contrast, patients treated with iloperidone (12–24 mg/day) had comparable (to placebo) rates of akathisia as assessed by the BARS, and their scores were substantially lower compared to patients treated with risperidone or ziprasidone [23]. Indeed, a recent systematic review and meta-analysis addressing the incidence of AIA induced by newer SGAs in patients with severe mental illnesses substantiates these findings [24]. In general, the propensity of newer SGAs to cause akathisia is more than twofold higher than placebo [odds ratio (OR) 2.43, 95% confidence interval (CI) 1.91–3.10]. The estimated incidence rate of akathisia for individual newly introduced SGAs is 3.9% (95% CI 2.4–6.3) for iloperidone, 6.8% (95% CI 5.1–9.0) for asenapine, 10.0% (95% CI 7.4–13.5) for brexpiprazole, 12.7% (95% CI 10.1–16.1) for lurasidone, and 17.2% (95% CI 13.4–22.1) for cariprazine. Overall, iloperidone is characterised by the most benign akathisia profile comparable to that of quetiapine, followed by asenapine and brexpiprazole with a risk comparable to that of olanzapine. Lurasidone and cariprazine, as well as aripiprazole, have the highest potential for akathisia among the newly approved SGAs, both comparable to that of risperidone [24, 25].

Recently, a comprehensive systematic review of 40 studies on akathisia was conducted and served as a foundation for evidence-based recommendations for the assessment and treatment of AIA [26]. In the present narrative review, we briefly address currently available options for the management of AIA, and then explicitly focus on the rationale for the use of and therapeutic efficacy of agents with marked serotonin 5-HT_{2a} antagonistic properties (ritanserin, cyproheptadine, trazodone, mianserin, and mirtazapine) as putative anti-akathisia remedies". Although 5-HT_{2a} antagonists are increasingly used by clinicians in the treatment of AIA, we believe that there is still a need for an up-to-date review summarising the current knowledge regarding therapeutic efficacy and clinical utility of this unique pharmacological group for patients with akathisia. In this narrative review we included open-label and controlled trials published in PubMed until February 2020 that explicitly evaluated anti-akathisia properties of pharmacological agents with marked 5-HT_{2a} antagonism (ritanserin, cyproheptadine, trazodone, mianserin, mirtazapine).

2 Current Management Approaches for Acute Antipsychotic-Induced Akathisia

Management of acute akathisia is challenging. Adequate adjustment of the antipsychotic drug regimen to avoid the development of akathisia is a primary clinical goal. The administration of a minimal effective dose of an antipsychotic, avoidance of rapid dose escalation and polypharmacy are essential to minimise the risk of akathisia [1, 26]. Gradual dose reduction or switch to an antipsychotic with a lower potential to induce akathisia are advised to deal with persisting akathisia. This strategy however carries a risk of psychotic deterioration due to a loosening of the therapeutic effect. Overall, high incidence and clinical significance of akathisia, limitations of preventive approaches and risks associated with switching antipsychotics to deal with existing akathisia, prompted a search for effective and safe anti-akathisia remedies.

2.1 Adrenergic Agents

Propranolol, a non-selective centrally acting lipophilic beta (β)-adrenergic receptor antagonist, is currently considered a first-line treatment for AIA. The anti-akathisia effect of β-blockers has been attributed to an interaction between hyperactive adrenergic neurons originating in the locus coeruleus and the hypoactive dopaminergic neurons in the midbrain [27]. However, this hypothesis is compromised by the fact that interactions between adrenergic and dopaminergic neurons are primarily mediated by α- and not by β-adrenoceptors [27]. Clinical experience worldwide for several decades supports efficacy of propranolol in the treatment of AIA. Surprisingly, the evidence base for its anti-akathisia effect is modest at best [28]. The majority of controlled studies that evaluated anti-akathisia properties of propranolol were conducted in the early 1990s, were of short duration (ranging from 2 to 12 days) and included small samples of predominantly schizophrenia patients [for review see 28]. Noteworthy, the beneficial effect of propranolol on AIA has been extended to other centrally acting non-selective beta-adrenergic receptor antagonists (e.g. metoprolol, nadolol) [29]. However, these agents have not been widely used in clinical practice due to limited evidence of their clinical utility. Finally, clonidine, a selective alpha-2 adrenergic presynaptic agonist, can also improve AIA; however, clonidine is not administered routinely owing to its frequent side effects of sedation and hypotension.

2.2 Anticholinergic Agents

EPS have been attributed to the dopamine/acetylcholine imbalance produced by the antipsychotic blockage of the dopamine (D_2) receptors in the nigrostriatal system. This assumption is based on the inverse relationship between the affinity of conventional antipsychotic agents for muscarinic receptors and their propensity for causing EPS. However, although anticholinergic agents have proven efficacious in the treatment of antipsychotic-induced Parkinsonism and acute dystonia, they produced equivocal results in AIA [30–32]. Indeed, a recent review showed that the evidence supporting the administration of the anticholinergic medications benztropine and biperiden for the treatment of AIA is limited and at high risk of bias, and the doses used exceeded those currently recommended [for review see 26]. Furthermore, treatment with anticholinergic agents is associated with a substantial burden of side effects (e.g. cognitive impairment, blurred vision, constipation, urinary retention). Co-administration of anticholinergics and antipsychotic agents with marked anticholinergic properties highlights this problem even more. Some data suggest that anticholinergic medications may be more helpful in patients with akathisia that co-exists with Parkinsonian symptoms leading to the suggestion of a specific Parkinsonian-related subtype of akathisia [33]. Overall, the available data pointing toward a questionable anti-akathisia effect of anticholinergics along with the risk of adverse effects make them of limited therapeutic value in AIA.

2.3 Benzodiazepines

Benzodiazepines have some clinical utility in AIA, putatively owing to their non-specific anti-dysphoric and sedative effects. Nevertheless, clinical practice indicates that these effects are not sufficient to ameliorate AIA. The evidence base is remarkably poor with only few small studies conducted in the early 1990s that addressed the anti-akathisia effects of the short-acting benzodiazepine clonazepam [34–36]. In addition, the side effects of benzodiazepines (e.g. cognitive impairment, addictive potential) limit their clinical utility in antipsychotic-treated patients.

3 Rationale for Using Serotonergic Agents for Acute Antipsychotic-Induced Akathisia

Lack of efficacy in a meaningful proportion of patients and poor tolerability of the existing anti-akathisia agents led to the search for new effective and better-tolerated treatment options. With the introduction of SGAs, the serotonergic system attracted researchers' attention. It has been suggested that the prevention of onset or mitigation of antipsychotic-induced EPS can be achieved with the preponderance of the serotonin ($5\text{-}HT_{2a}$) receptor antagonism, over the dopamine D_2 blockade [37].

Dopamine neurons in the ventral tegmental area and substantia nigra (brain regions apparently involved in the pathophysiology of EPS and AIA) receive inhibitory serotonergic input from midbrain raphe nuclei. It was hypothesised that a reduction in brain serotonergic function (e.g. $5\text{-}HT_{2a}$ antagonists, $5\text{-}HT_{1a}$ agonists, raphe lesions) may increase the basal activity of dopaminergic neurons and thereby alleviate EPS induced by D_2 receptor antagonists [38]. An additional indication of a link between EPS and the serotonergic system was provided by studies showing that SSRIs, which apparently increase serotonin neurotransmission, have a propensity to induce EPS and akathisia [39, 40]. Moreover, the SGAs, which display lower propensity to induce EPS and AIA, share at least one pharmacological property that distinguishes them from FGAs—the predominance of $5\text{-}HT_{2a}$ receptor blockade over D_2 receptor antagonism. Indeed, antipsychotics with lower $5\text{-}HT_{2a}/D_2$ receptor binding affinity ratio, indicating higher affinity for $5\text{-}HT_{2a}$ than D_2 receptors (e.g. clozapine, quetiapine), seem to have a lower potential to induce akathisia (Table 1). In contrast, antipsychotics with higher $5\text{-}HT_{2a}/D_2$ ratio, indicating predominance of D_2 over $5\text{-}HT_{2a}$ receptor blockade (e.g. haloperidol, aripiprazole, cariprazine), are associated with a higher potential to induce akathisia (Table 1). It is of note that risperidone, despite having a similar to quetiapine $5\text{-}HT_{2a}/D_2$ receptor affinity ratio, possesses a relatively high risk to induce akathisia, suggesting that additional pathophysiological mechanisms underlie AIA [41]. All these serve as a basis for the use of agents with marked $5\text{-}HT_{2a}$ antagonistic effect in the treatment of AIA.

4 Non-selective $5\text{-}HT_{2a}$ Antagonists

Although there are no selective $5\text{-}HT_{2a}$ antagonists approved for clinical use in patients with AIA, several compounds from different pharmacological classes that share pronounced $5\text{-}HT_{2a}$ antagonistic activity, ritanserin, cyproheptadine, trazodone, mianserin and mirtazapine, have been suggested as putative anti-akathisia remedies [2, 42, 43] (Table 2).

4.1 Ritanserin

Miller et al. evaluated the putative anti-akathisia properties of ritanserin, an agent with a pronounced $5\text{-}HT_{2a}$ and $5\text{-}HT_{2c}$ antagonistic activity, in an open-label study of patients with

Table 1 Serotonin (5-HT_{2a}), dopamine (D_2) and 5-HT_{2a}/D_2 receptor binding affinity ratio and the potential of antipsychotic agents to induce akathisia

Antipsychotic	Clinically effective dose (mg/day)	Ki values (nM)[a]			Potential to induce akathisia[b]
		5-HT_{2a}	D_2	$5HT_{2a}/D_2$	
Haloperidol	5–10	61.0	2.6	37.4	++++
Aripiprazole	10–15	8.7	0.66	18.42	+++/++
Cariprazine	1.5–6	18.6	0.49	37.9	+++/++
Risperidone	1–4	0.15	3.8	0.04	+++/++
Paliperidone	3–6	1.2	2.8	0.42	++
Ziprasidone	120–160	0.1	2.6	0.04	++
Lurasidone	40–80	2.03	1.68	1.2	++
Asenapine	10–20	10.15	8.9	1.14	++
Brexpiprazole	2–4	0.47	0.3	1.5	++
Chlorpromazine	300–900	0.41	11	0.04	++
Olanzapine	10–15	1.5	20	0.08	+
Iloperidone	12–24	1.94	3.5	0.55	+
Quetiapine	150–750	31	770	0.04	−/+
Clozapine	300–800	2.6	210	0.01	−/+

Ki, constant of dissociation (lower Ki values correspond to higher receptor affinity), ++++ high potential to induce akathisia, +++ high-to-moderate, ++ moderate, + low, −/+ questionable

[a]Ki values for $5HT_{2a}$ and D_2 receptors are taken from Li et al. [65]

[b]References [22–26]

akathisia induced by FGAs [42]. Ten patients received a mean dose of 13.5 mg/day (5–20 mg/day) of ritanserin for 2 to 4 days. Treatment response was assessed by the Hillside Akathisia Scale (HAS). After 3 days of treatment, HAS baseline ratings dropped from 16.4 ± 6 to 7.4 ± 5.2 ($p = 0.0069$ matched pairs signed rank test). Two patients did not respond. The effect of ritanserin was rapid and clinically significant, and no significant side effects were noted. Ritanserin was also shown to be effective in patients with AIA who failed to respond to conventional anti-akathisia agents (e.g. anticholinergics, benzodiazepines and a β-blocker), highlighting the diversity of mechanisms underlying AIA [44]. Notably, ritanserin was never marketed for clinical use.

4.2 Cyproheptadine

Cyproheptadine, a first-generation antihistamine, possesses potent 5-HT_{2a} and $5HT_{2c}$ antagonistic properties, in addition to anti-histaminergic and anti-cholinergic properties. Its anti-akathisia effect was explored in an open trial of 17 patients with acute AIA induced by FGAs [45]. The drug was administered in a fixed oral dose of 16 mg/day, in four divided doses for the duration of 4 days. The therapeutic effect of cyproheptadine was rapid and pronounced and could already be discerned by Day 2 of treatment. By Day 4, all 17 participants had improved to some degree, and 15 showed a more than 50% reduction in the BARS global score. In six patients, the AIA disappeared completely. These results were replicated in a double-blind comparison study of cyproheptadine ($n = 18$, 16 mg/day) and propranolol ($n = 12$, 80 mg/day) in patients with acute FGA-induced AIA [46]. Both drugs demonstrated significant anti-AIA activity (46% vs 42% decrease in the BARS score, respectively) within four days of treatment. Cyproheptadine was well tolerated, and side effects of mild sedation, dry mouth and blurred vision occurred only in those patients receiving concurrent anticholinergic medication.

4.3 Trazodone

Trazodone is an antidepressant acting as a potent serotonin 5-HT_{2a} receptor and α_1-adrenergic receptor antagonist, a weak serotonin reuptake inhibitor and a weak histamine H_1 receptor antagonist. Initially its anti-akathisia effect was demonstrated in an open-label study [47]. Nine female patients with a global BARS score of at least 2 and receiving a stable dose of FGAs were titrated up to 100 mg/day of trazodone over a period of 5 days. The addition of trazodone was associated with rapid improvement in symptoms of akathisia to at least some degree in all participants. These results were substantiated in a controlled cross-over design study of 13 schizophrenia inpatients with FGA-induced

Table 2 Reports on the efficacy of serotonergic agents in patients with antipsychotic-induced akathisia

Serotonergic agent Reference	Study design	*N*	Treatment duration (days)	Dose (mg/day)	Outcome measures	Results
5-HT$_{2a}$ antagonists						
Ritanserin						
Miller et al. [67]	Open trial	10	3	5–20	HAS, CGI	8/10 improved
Cyproheptadine						
Weiss et al. [45]	Open trial	17	4	16	HAS, BPRS, HRSD,AIMS	15/17 improved; 6/17 complete
Fischel et al. [46]	Double-blind trial vs propranalol	18 cyproheptadine 12 propranalol	4	Cyproheptadine 16 Propranalol 80	BARS, BPRS, SAS	Both cyproheptadine and propranolol were efficacious (46% and 42% improvement in BARS, respectively)
Mianserin						
Poyurovsky et al. [50]	Open trial	16	14	15	BARS, SAS	Improvement in all 4 BARS subscales
Poyurovsky et al. [51]	Double-blind trial vs placebo	15 mianserin 11 placebo	5	15	BARS, SAS, BPRS, mLAS, HRSD	14/15 of mianserin group improved vs 5/11 in placebo group
Trazodone						
Stryjer et al. [47]	Open trial	9	5	100	BARS, SAS, PANSS, mLAS, CGI, HRSD	Improvement in all 4 BARS subscales
Stryjer et al. [48]	Double-blind crossover trial vs placebo	8 trazadone/placebo 5 placebo/trazadone	6	100	BARS	Statistically significant improvement in BARS subscales in Trazodone vs placebo treated patients
Mirtazapine						
Poyurovsky et al. [53]	Double-blind trial vs placebo	13 mirtazapine 13 placebo	5	15	BARS, PANSS, HRSD, SAS	Improvement in global and objective BARS subscales. 7/13 (53.8%) of mirtazapine group vs 1/13 (7.7%)in placebo group responded
Poyurovsky et al. [54]	Double-blind trial vs placebo and propranalol	30 mirtazapine 30 propranolol 30 placebo	7	Mirtazapine 15 Propranolol 80	BARS, BARS, PANSS, HRSD, SAS	Significant decrease in global BARS subscales in the mirtazapine group (34%), propranolol group (29%) vs placebo group (11%)
Poyurovsky et al. [60]	Retrospective chart review	8	8.5	15	BARS	Significant decrease in the BARS subjective distress and global sub-scales. Response rate 5/8 (62.5%)
Poyurovsky and Weizman [61]	Retrospective chart review	12	10.3	7.5	BARS	Significant decrease in the BARS subjective distress and global subscales. Response rate 5/12 (41.6%)

Table 2 (continued)

Serotonergic agent Reference	Study design	*N*	Treatment duration (days)	Dose (mg/day)	Outcome measures	Results
$5HT_{1A}$ partial agonist						
Buspirone						
Poyurovsky and Weizman [39]	Open trial	10	4	10–30	BARS, SAS	2/10 improved, 6/10 unchanged, 2/10 worse
$5HT_3$ antagonist						
Granisetron						
Poyurovsky and Weizman [65]	Open trial	10	4	2	BARS, SAS, mLAS, BPRS, HRSD	3/10 dropouts, 5/10 unchanged, 2/10 improved
$5HT_{1D}$ agonist						
Zolmitriptan Avital et al. [66]	Double-blind trial vs propranolol	14 zolmitriptan 19 propranolol	3	7.5 120	BARS, HRSD, SAS, PANSS	Both zolmitriptan and propranolol efficacious (26.1% and 39.5% decrease in BARS, respectively)

AIMS Abnormal Involuntary Movement Scale, *BARS* Barnes Akathisia Scale, *BPRS* Brief Psychiatric Rating Scale, *CGI* Clinical Global Impression scale, *HAS* Hillside Akathisia Scale, *HRSD* Hamilton Rating Scale for Depression, *mLAS* Modified Leeds Anxiety Scale, *PANSS* Positive and Negative Syndrome Scale, *SAS* Simpson and Angus Scale for extrapyramidal side effects

akathisia [48]. Patients were randomly assigned to receive trazodone (100 mg/day before bedtime) for 3 days followed by placebo for 3 consecutive days (8 patients) or the reversed order placebo-trazodone (5 patients). Statistically significant and clinically meaningful improvement in most symptoms of AIA was detected with trazodone compared to placebo. Although expected, no patients complained of drowsiness or dizziness attributed to sedation and orthostatic hypotension, both relatively common side effects of trazodone. Noteworthy, there is a single case report indicating that trazodone (100 mg/day) may exert an anti-akathisia effect when other medications (e.g. propranolol, clonazepam, biperiden, tetrabenazine) fail [49].

4.4 Low-Dose Mianserin

Mianserin is a tetracyclic antidepressant that possesses marked 5-HT_{2a} and 5-HT_{2c} antagonism, as well as antihistaminergic and α_2 antagonistic activity, without marked anticholinergic properties. Mianserin in higher doses (30–90 mg/day) is used for treatment of major depressive disorder. It was suggested that the 5-HT_{2a} antagonism preponderates in a low dose of mianserin (15 mg) and contributes to its anti-akathisia properties [50]. In a preliminary open trial, 16 patients who developed FGA-induced akathisia were treated with low-dose mianserin (15 mg/day) [50]. A beneficial effect was detected in 14 patients on the third day of treatment, consisting primarily of the disappearance of the subjective sense of inner restlessness, followed by a substantial decrease in characteristic akathisia movements. The drug was well tolerated, and the only side effect, mild sedation in five patients, was transient. These promising preliminary results were confirmed in a double-blind placebo-controlled study in which patients who met the criteria for acute AIA were randomly allocated to receive either low-dose mianserin (15 mg/day; $n = 15$) or placebo ($n = 15$) once a day (at 08.00 h) for 5 days [51]. Treatment response was defined as a reduction of at least one point on the BARS global sub-scale. Results indicated that 14 of the 15 patients treated with mianserin (93.3%) responded, compared with only five of the 11 patients (45.6%) given placebo who completed the trial. When a more rigorous response criterion was applied, namely, reduction of at least two points on the BARS, the positive response rate was 40% in the mianserin group and only 9.1% in the placebo group. Complete disappearance of the AIA occurred in four patients in the mianserin group (26.6%) but in none of the placebo group. Moreover, the beneficial effect of mianserin was accompanied by a corresponding reduction in neuroleptic-induced dysphoria. By contrast, mianserin had no effect on concurrent symptoms of neuroleptic-induced Parkinsonism in AIA patients. These studies confirmed the tolerability and safety of low-dose mianserin; mild, transient sedation

and clinically irrelevant orthostatic hypotension were the only side effects. Notably, a beneficial anti-akathisia effect, as well as safety and tolerability of low-dose mianserin were substantiated in a patient who exhibited symptoms of chronic akathisia [52].

4.5 Low-Dose Mirtazapine

Mirtazapine is structurally and pharmacologically similar to mianserin. Mirtazapine is characterised by potent presynaptic alpha-2 adrenergic antagonism, which accounts for its antidepressant activity, and marked 5-HT_{2a} blockade that seems to predominate in a low dose and contribute to its anti-akathisia properties. In addition, mirtazapine is a potent anti-histaminergic compound. In a randomised double-blind design study, 26 FGA-treated schizophrenic patients with AIA received add-on mirtazapine (15 mg/day) or placebo for 5 days [53]. Low-dose mirtazapine was associated with rapid and clinically significant improvement in akathisia ratings and significantly more mirtazapine-than placebo-treated patients (53.8% vs 7.7%, respectively; $p=0.004$), met operational response criterion, a reduction of at least two points on the BARS global subscale. Mirtazapine treatment was also associated with modest improvement of psychotic symptoms. Mild sedation was the only side effect. These encouraging results were substantiated by the subsequent largest-to-date randomised placebo-controlled trial comparing low-dose mirtazapine and propranolol in 90 patients with FGA-induced akathisia [54]. Mirtazapine, given once daily (15 mg) was as effective as propranolol (40 mg twice daily) in producing a greater improvement in AIA compared to placebo [reduction in BARS global scale: 1.10 ± 1.37 points (34%) and 0.80 ± 1.11 (29%) vs 0.37 ± 0.72 (11%), respectively, $p=0.036$]. Responder analysis (BARS global scale reduction ≥ 2) yielded a similar robust anti-akathisia effect in mirtazapine and propranolol versus placebo (43.3%, 30% vs 6.7%, respectively, $p=0.005$). Low number-needed-to-treat (NNT) supports high clinical effectiveness of both mirtazapine and propranolol (3 and 4, respectively). Mirtazapine did not interfere with the antipsychotic effect of FGAs. Notably, mirtazapine and propranolol had no effect on Parkinsonian symptoms coincident with akathisia, reinforcing the hypothesis that antipsychotic-induced Parkinsonism might be related to dopamine/acetylcholine dysfunction and may preferentially respond to anticholinergic agents [33]. An imbalance between dopaminergic and noradrenergic/serotonergic systems seems to predominate in AIA that responds to β-adrenergic and 5-HT_{2a} antagonists [2, 38].

These two randomised placebo-controlled trials were meta-analysed to address therapeutic efficacy and tolerability of low-dose mirtazapine in patients ($N=86$) with FGA-induced akathisia [55]. Using the fixed-effects model, it was found that risk ratio (RR) for response and remission was 6.67 (95% CI 2.14–20.78; $p=0.001$) and 6.20 (95% CI 1.74–22.08; $p=0.005$), respectively, indicating that mirtazapine is about six times more effective than placebo in ameliorating symptoms of acute AIA. The relative clinical effectiveness was high, with one in four patients showing partial response (NNT = 4; 95% CI 2.6–8.6) and one in five patients (NNT = 5; 95% CI 2.9–11.6) showing complete remission.

This meaningful therapeutic efficacy of mirtazapine in AIA was associated with a low side-effect burden, with mild sedation as the most common adverse effect. Notably, this meta-analysis is limited by the number of studies included, short duration of treatment varying from 5 to 7 days and the fixed dose of mirtazapine (15 mg).

In addition, to address the overall class effect of agents with marked 5HT_{2a} antagonism (ritanserin, cyproheptadine, mianserin, mirtazapine and trazodone) in the treatment of FGA-induced akathisia, a systematic review and meta-analysis of six controlled studies (4 placebo-controlled, 1 propranolol-controlled; 1 propranolol- and placebo-controlled; $N=249$ patients) was conducted [56].

Using the BARS to quantify symptoms of AIA and defining response as a reduction of the BARS score by at least two points, the meta-analysis revealed that 5-$HT2_a$ antagonists are about seven times more effective than placebo in the treatment of AIA [RR = 7.10 (95% CI 3.08–16.40, $p<0.0001$)]. Remission rates were also significantly higher in the drug groups than in the placebo groups (RR = 4.95, 95% CI 2.01–12.22, $p=0.0005$). There were no significant differences between the drug and placebo groups in adverse effects and dropouts, suggesting that short-term administration of these agents is safe and well-tolerated in antipsychotic-treated patients. Notably, 5-HT_{2a} antagonists did not interfere with the antipsychotic effect of the offending drug.

4.5.1 Low-Dose Mirtazapine for Aripiprazole-Induced Akathisia

A robust anti-akathisia effect of low-dose mirtazapine comparable to propranolol has consistently been shown in patients treated with FGAs, underscoring the role of 5-HT_{2a} antagonism in the pathophysiology and treatment of acute akathisia. The clinically reasonable question is whether low-dose mirtazapine would exert a similar beneficial effect in patients who developed akathisia while being treated with SGAs. Among SGAs, aripiprazole is associated with a substantial rate of emerging akathisia; at clinically effective doses (10–30 mg/day) it exerts marked striatal D_2 receptor occupancy, and is distinguished from

the majority of SGAs by relatively low 5-HT_{2a} antagonism in schizophrenia patients [57]. We previously suggested that aripiprazole's low 5-HT_{2a}/D_2 receptor affinity ratio (Table 1), may account at least in part for its high propensity to induce akathisia, and proposed low-dose mirtazapine as a potential remedy [58]. Notably, brexpiprazole, a partial dopamine agonist similar to aripiprazole, has an approximately tenfold higher affinity for the 5-HT_{2a} receptor and is associated with a substantially lower incidence of akathisia (number-needed-to-harm for akathisia: aripiprazole, 25; brexpiprazole, 112) [59]. A beneficial effect of mirtazapine (15 mg/day for the duration of 8.5 ± 2.3 days) was indeed revealed in a retrospective analysis of computerised medical charts of 8 patients with schizophrenia or affective disorders who were treated with aripiprazole (mean 12.5 ± 3.5 mg) and who developed acute akathisia [60]. The response rate was clinically meaningful (5 of 8 patients; 62.5%). Similar to the mirtazapine trials among patients who experienced FGA-induced akathisia, the beneficial anti-akathisia effect of mirtazapine in aripiprazole-treated patients was detected early in the course of treatment, was exerted at a fixed daily dose (15 mg) and was safe and well-tolerated with mild sedation as its only detected side effect. Retrospective study design, small sample size and short duration of administration preclude definite conclusions regarding the clinical utility of mirtazapine in aripiprazole-induced akathisia.

4.5.2 Very Low-Dose Mirtazapine (7.5 mg) for SGA-Induced Akathisia

Clinical experience has indicated that although in general, mirtazapine 15 mg/day is well tolerated by patients with AIA, increased appetite, subsequent weight gain and daytime drowsiness observed in some patients prompted drug discontinuation. A retrospective chart review was undertaken to determine whether mirtazapine, in a lower dose of 7.5 mg, maintains its anti-akathisia properties while exhibiting better tolerability in patients with schizophrenia and mood disorders who developed acute SGA-induced akathisia [61]. Indeed, the results of this small study revealed that mirtazapine at a very low dose (7.5 mg) given for mean 10.3 days (Table 2) maintained its beneficial anti-akathisia effect and exhibited an excellent tolerability profile in 12 patients with acute risperidone- and aripiprazole-induced akathisia. Mirtazapine (7.5 mg) demonstrated a rapid and clinically significant anti-akathisia effect with a response rate comparable to that found in a higher mirtazapine dose (15 mg) (41.6% and 62.5%, respectively) [60, 61]. Noteworthy, comparison of the 2 mirtazapine doses (7.5 and 15 mg) for patients with aripiprazole-induced akathisia in the 2 studies yielded a remarkably similar response rate (62.5%).

5 Proposed Treatment Algorithm for Acute Antipsychotic-Induced Akathisia: Incorporating Serotonin 5-HT_{2a} Antagonists

There are two major treatment strategies for dealing with acute AIA: modification of the antipsychotic drug regimen and/or the addition of an anti-akathisia agent (Fig. 1). A dose reduction of the antipsychotic or switch to an antipsychotic with a lower potential to induce akathisia is a

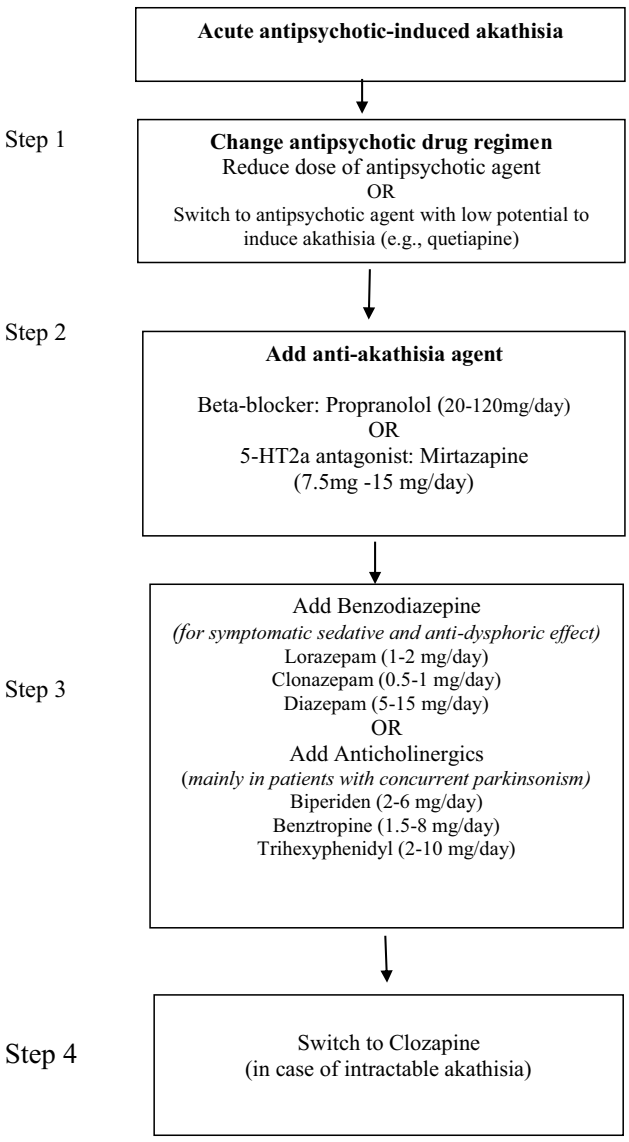

Fig. 1 Practical guidelines for treatment of acute antipsychotic-induced akathisia. *5-HT_{2a}* serotonin

reasonable first step in the management of acute AIA (Fig. 1). Close follow-up is required to ensure that an antipsychotic effect is maintained. In cases of persistent intractable akathisia, initiation of clozapine may be necessary [1, 2, 26].

When the decision is to add an anti-akathisia agent, propranolol (20–120 mg) or low-dose mirtazapine (7.5–15 mg) have the most supportive evidence. Propranolol has a long record of clinical utility in patients with AIA. However, it has not been formally approved for the treatment of AIA. Limitations of propranolol's use are its side effects (e.g. orthostatic hypotension, bradycardia), contraindications (e.g. asthma), drug–drug interactions and increased complexity in administration and titration schedules. In contrast, low-dose mirtazapine achieves 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 is also supported by the absence of significant changes in vital signs. Long-term use of mirtazapine, however, can be associated with weight gain, and very rarely with agranulocytosis. Mirtazapine is used off-label and has not yet been approved for the treatment of AIA. It is of note, that the recently published evidenced-based recommendations consider a trial of propranolol as a first-choice option, after reviewing contraindications and associated precautions on a per-patient basis [26]. When propranolol is contraindicated, ineffective or not tolerated and long-term pharmacological management of AIA is anticipated, a trial of low-dose mirtazapine may be considered [26].

Mianserin (15 mg once daily), cyproheptadine (8–16 mg/day) and trazodone (100 mg) are potential alternative options. However, large-scale trials are not yet available, and their clinical utility has yet to be determined. Mianserin is not approved for clinical use in the USA. Mianserin and especially trazodone, have marked α_1-adrenolytic properties, which can cause somnolence, impairment of cognitive functioning and orthostatic hypotension. Trazodone can cause priapism, an infrequent but clinically significant side effect. Cyproheptadine and trazodone can slow cardiac repolarisation causing QT prolongation, a clinically relevant adverse effect with antipsychotic co-administration.

Anticholinergic agents can help in achieving symptomatic improvement in some cases of AIA associated with antipsychotic-induced Parkinsonism [33]. Similarly, symptomatic anti-dysphoric and sedative effects can be achieved with benzodiazepines [34, 36]. Co-administration of benzodiazepines with propranolol may be beneficial in some patients, while co-administration of benzodiazepines with mirtazapine should be avoided owing to their shared sedative properties. In case of intractable akathisia, clozapine may be tried [2].

6 Future Directions

Akathisia remains one of the most frequent and distressing adverse effects associated with antipsychotic drug treatment. Effective, well-tolerated and easy-to-use anti-akathisia agents continue to be a major unmet need in patients with AIA that justifies a search for new treatment options. Extensive research during the last two decades indicates that non-selective 5-HT_{2a} antagonists (ritanserin, cyproheptadine, trazodone, mianserin and mirtazapine) exert a beneficial effect in patients with AIA (Table 2). Low-dose mirtazapine has the most compelling evidence of efficacy and tolerability in patients who developed akathisia treated by FGAs. Elucidation of an anti-akathisia effect of mirtazapine in patients with SGA-induced akathisia is a reasonable next step. The demonstration of a positive effect of mirtazapine on aripiprazole-induced akathisia in a small open-label study is the initial step in this direction [60]. Large-scale explicit evaluation of anti-akathisia properties of low-dose mirtazapine in SGA-induced akathisia, especially in antipsychotics with partial dopamine agonistic activity, such as aripiprazole, cariprazine, and to a lesser degree, brexpiprazole, is warranted. Identification of predictors of response to mirtazapine versus propranolol, that remains a "gold standard" of anti-akathisia treatment, is of particular clinical importance. An additional limitation of the current evidence is that it does not provide data on durability of response beyond 7–14 days of treatment. Longer prospective investigations are needed to clarify an adequate duration of treatment with mirtazapine and propranolol as anti-akathisia agents. Moreover, the effective dose range of mirtazapine should be addressed in future studies. It seems that mirtazapine in a dose as low as 7.5 mg is effective in ameliorating symptoms of AIA in some individuals. Explicit comparison of the anti-akathisia effect of mirtazapine in 2 dose regimens (7.5 mg and 15 mg) in patients treated with FGAs and SGAs is warranted. An additional clinically relevant question is whether patients with AIA who do not respond to 7.5 mg would respond to a higher dose of mirtazapine (15 mg) or would need a switch to another anti-akathisia agent, such as propranolol. Notably, even lower doses such as 1.5–4.5 mg of esmirtazapine significantly improved quantity and quality of sleep and were well tolerated in individuals with insomnia; thus, it is possible that even doses lower than 7.5 mg might exert anti-akathisia properties [62].

There is a preliminary indication that mirtazapine might cause akathisia in susceptible individuals [63]. The mechanism of this bi-directional effect of mirtazapine, akathisia ameliorating versus akathisia provoking, is yet to be elucidated. It is possible that marked 5-$HT2_a$ receptor

antagonism accounts for mirtazapine's anti-akathisia effect, while its facilitation of adrenergic neurotransmission via alpha-adrenergic receptor leads to the occurrence of akathisia [2].

Finally, since mirtazapine binds to multiple receptors, evaluation of the anti-akathisia properties of selective 5-HT_{2a} antagonists might further clarify the role of this mechanism in the pathophysiology of akathisia. In this respect, the selective inverse agonist pimavanserin that is currently approved for use in patients with Parkinson's disease psychosis is a reasonable candidate for evaluation of putative anti-akathisia properties [64]. Finally, additional receptor mechanisms within the serotonergic system may underlie an anti-akathisia effect. While the 5-HT_{1a} partial agonist buspirone and the 5-HT_3 antagonist granisetron are of limited therapeutic value [39, 65], the selective 5-HT_{1D} receptor agonist zolmitriptan revealed comparable anti-akathisia properties to propranolol. However, its clinical utility has not yet been clarified (Table 2) [66].

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