Akathisia: An Updated Review Focusing on Second-Generation Antipsychotics

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Objectives: To provide a brief description of the pathophysiology of akathisia, the challenges of diagnosing and treating this condition, and potential associated clinical issues. Also, to provide a review of the literature on the incidence of drug-induced akathisia associated with the use of second-generation antipsychotics (SGAs) and first-generation antipsychotics (FGAs).

Data Sources: English-language literature with no date restrictions cited in PubMed was searched for the keywords *akathisia*, *placebo*, *neuroleptic*, or *haloperidol*, and the generic names of SGAs (*clozapine*, *risperidone*, *olanzapine*, *quetiapine*, *ziprasidone*, or *aripiprazole*).

Study Selection: Limits were set to search clinical trials, meta-analyses, or randomized controlled trials reviewing data from adult schizophrenia or bipolar disorder clinical trials. Studies including SGA comparisons with placebo and with FGAs, and also between SGAs themselves, were selected. Studies that specifically assessed akathisia (either subjectively or objectively or both) were included. Studies reporting generalized results pertaining to extrapyramidal symptoms (EPS) were excluded.

Data Extraction: The incidence of akathisia, EPS rating scores, and required medications for the management of movement disorders were reviewed.

Data Synthesis: Seventy-seven trials were included in the comparative review. Akathisia was observed with the use of all the SGAs. The akathisia incidence reported in bipolar disorder trials was generally higher compared with schizophrenia trials. The incidence reported for FGAs was consistently higher than that reported for SGAs, regardless of the patient population studied.

Conclusions: Akathisia remains a concern with the use of SGAs. More accurate and standardized evaluations are required for a better understanding of the nature and incidence of akathisia.

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Akathisia is a movement disorder characterized by restlessness that is frequently associated with the use of antipsychotic drugs that are dopamine-receptor antagonists.[1,2] Its reported incidence varies from 21% to 75% and its prevalence from 20% to 35%.[3,4] It is generally agreed that akathisia consists of both subjective and objective components.[3,5,6] The subjective component is characterized by an inner restlessness often accompanied by tension, panic, irritability, and impatience. The objective component consists of increased motor activity, described as complex, semipurposeful, repetitive movements. There is no consensus among clinicians, however, on the relative importance of the subjective and objective components in the establishment of diagnostic criteria. Some stress the urge to move as the core feature, and the abnormal movements as a nonobligate mechanism to calm down this urge.[4,7–10] Others have considered the movements themselves—with or without the urge—as sufficient to diagnose akathisia.[11] Different subtypes of antipsychotic-related akathisia have been proposed that depend on the different clinical profiles and timing of onset (Table 1). Effective and reliable assessment of akathisia requires valid quantification tools and the acumen of trained clinicians who can recognize its full spectrum of subjective and objective manifestations. Table 2 provides a description of measurement scales that have been designed to assist in the assessment of akathisia in clinical trials. Many clinicians, however, may prefer not to use scales to assess akathisia and instead rely primarily on clinical observations and phenomenology for diagnosis. Diagnosis, however, is complicated by the fact that it may

Table 1. Classification of Akathisia[a]

Classification	Characteristics/Clinical Features
Acute akathisia	Duration ≤ 6 mo Develops soon after starting antipsychotic medication or following: dose increase switch to high-potency antipsychotic withdrawal of anticholinergic Intense dysphoria Awareness of restlessness Complex and semipurposeful motor fidgetiness
Chronic akathisia	Persists for > 6 mo after last dosage increment Subjective sense of restlessness may be less marked Mild dysphoria Awareness of restlessness Motor fidgetiness with stereotyped movement Limb and orofacial dyskinesia often present
Pseudoakathisia	Motor manifestations without subjective component Predominantly in men Possibly late stage of chronic akathisia No dysphoria No awareness of restlessness Motor fidgetiness with stereotyped movement Great overlap with limb and orofacial dyskinesia
Tardive akathisia	Delayed onset (usually 3 mo) Not related to a recent change in drug or dose Significantly associated with tardive dyskinesia
Withdrawal or "rebound" akathisia	Associated with switching antipsychotic medications Onset usually within 6 wk of discontinuation or dose decrease Anticholinergic discontinuation reaction

[a]Data from Halstead et al.,[4] Barnes and Braude,[5] Chung and Chin,[12] and Miller et al.[13]

be difficult to differentiate akathisia from a multitude of other disorders,[21] including agitation secondary to psychotic symptoms or mood disorder, antipsychotic dysphoria, restless legs syndrome, anxiety, insomnia, drug withdrawal states, tardive dyskinesia, or other neurologic and medical conditions (Table 3).[12,22–26] Another barrier to specific diagnosis is the fact that the severity of movement dysfunction associated with akathisia can vary according to the situation and the person's degree of arousal.[26] Mild cases of akathisia are particularly challenging to diagnose because the condition can be easily overlooked or misdiagnosed as psychotic agitation, which may lead to an inappropriate increase of antipsychotic therapy.[26,27] Children may be particularly vulnerable to misdiagnosis for this reason.[28]

Our understanding of the pathophysiology of akathisia remains limited. Its association with medications that block dopaminergic transmission supports the notion that it may be linked to low dopaminergic tone in the brain.[29] Furthermore, drugs with therapeutic efficacy in the treatment of medication-induced akathisia (e.g., benzodiazepines, β-adrenergic blockers, and serotonin antagonists) have provided additional insight into the involvement of other transmitter systems.[22,30–32] Recently, Strous et al.[33] have proposed a role for the neurosteroid system. Given the varied clinical profile of akathisia, it seems likely that a complex interplay of several neurotransmitter systems underlies its complex pathophysiology.

Although the etiology of this disorder remains elusive, and there are difficulties associated with diagnosis, it is important for the clinician to realize that akathisia can still be prevented or effectively managed. This review will provide a brief overview of the suggested management options for akathisia based on a synthesis of published recommendations and suggestions.

Prior reviews have focused primarily on the first-generation antipsychotics (FGAs). This article compiles clinical trial data on rates of antipsychotic-induced akathisia associated with the current U.S. Food and Drug Administration–approved antipsychotic medications, including comparative studies between second-generation antipsychotics (SGAs). Although it is well known that there is generally a diminished risk of movement disorders with the use of the SGAs, studies with SGAs have shown that extrapyramidal symptoms (EPS), including akathisia, although occurring at a lower rate than that seen with FGAs, are also observed with SGAs.[13,26,34,35]

Each of the SGAs (clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and paliperidone) that is commercially available in the United States is unique in terms of its pharmacologic profile, including mechanism of action and overall receptor-binding affinity.[36] Thus, the balance between therapeutic efficacy and side-effect liability is affected by the full spectrum of the pharmacodynamic profile of a particular medication.[37,38] For example, the binding of SGAs to classes of receptors other than dopamine—such as α_1-adrenergic, histamine H_1, and muscarinic receptors—is thought to be associated with their propensity to cause a variety of adverse events (AEs) such as orthostatic hypotension, weight gain, sedation, somnolence, and anticholinergic side effects.[39–41] Thus, as with other side effects, differences in the incidence and clinical characteristics of treatment-emergent akathisia among antipsychotics may be explained by the differences in the pharmacodynamics of these drugs.

AKATHISIA RISK WITH ANTIPSYCHOTIC MEDICATIONS

An important evolution in the treatment of schizophrenia has been the introduction of the SGAs. One significant advantage that the SGAs have over the FGAs is a lower incidence of extrapyramidal side effects, including akathisia.[13,26,34,35] However, akathisia can occur with the use of newer antipsychotics and has not been discussed in a comprehensive review.

Data Source and Study Selection Criteria

In this review, the main data source was the National Center for Biotechnology Information (NCBI) PubMed

Table 2. Diagnostic Tools Available for the Assessment of Akathisia[a]

Diagnostic Tool	Description
DSM-IV	Operational definition; guideline for the identification of akathisia, not its assessment
Chouinard Extrapyramidal Symptom Rating Scale	1 subjective and 1 objective component; rates on a 0 to 6 scale (0 = absent, 6 = constant movement) Rates patient complaints from 0 = none to 3 = unable to sit down or being "restless, nervous, unable to sit still"
Hillside Akathisia Scale	2 subjective and 3 objective items Anchored rating points Assessments for sitting, standing, and lying positions and a clinical global impressions rating
Barnes Akathisia Rating Scale	Most widely used measurement scale Reported interrater reliability and validity Severe akathisia—both subjective and objective components required Rater observes characteristic motor phenomena and systematically probes the subjective experience Gives overall measure of severity: (1) objective, (2) subjective awareness, (3) subjective distress, (4) global clinical assessment of akathisia
Prince Henry Hospital Akathisia Rating Scale	Objective ratings for sitting and standing Subjective ratings Global ratings Scale 0 to 3: 0 = absent, 1 = mild, 2 = moderate, 3 = severe
Schedule for the Assessment of Drug-Induced Movement Disorders	Compilation of rating scales Measures dystonia, dyskinesia, parkinsonism, akathisia, ataxia, and several types of tremor
Drug-Induced Extrapyramidal Symptoms Scale	Multidimensional scale 9 items: 8 individual parameters and 1 global 5-point rating scale Quantifies the severity of drug-induced parkinsonism, akathisia, dystonia, and dyskinesia Measures subjective distress and degree of influence on activities of daily living

[a]Data from Fleischhacker et al.,[9] Barnes,[14] American Psychiatric Association,[15] Chouinard et al.,[16] Barnes,[17] Sachdev,[18] Loonen et al.,[19] and Inada et al.[20]

Table 3. Differential Diagnoses of Akathisia[a]

Agitation secondary to psychotic symptoms
Non-akathisia antipsychotic dysphoria
Restless legs syndrome
Anxiety
Agitation related to affective disorder
Drug-withdrawal states
Organic disorders (eg, delirium, head injury, hypoglycemia, encephalitis lethargica)
Neurologic disorders (eg, Parkinson's disease, Huntington's disease)
Tardive dyskinesia (commonly coexists with akathisia)
Insomnia

[a]Data from Sachdev,[6] Chung and Chin,[12] Miller and Fleischhacker,[22] Nelson,[23] and Sachdev.[24]

database; the search criteria included the name of an SGA (*clozapine*, *risperidone*, *olanzapine*, *quetiapine*, *ziprasidone*, or *aripiprazole*) and the keywords *akathisia*, *placebo* (limited to section below vs. placebo), *neuroleptic*, or *haloperidol* (only to section below vs. FGA). Furthermore, we limited this review to schizophrenia and bipolar disorder adult clinical trials. Finally, limits were set to search clinical trials, meta-analyses, or randomized controlled trials with no date restrictions imposed.

Seventy-seven trials were included in the comparative analyses (Table 4). In addition to the stated criteria, other studies of antipsychotic drugs that reported akathisia data were identified by reviews of bibliographies, trial registries, or personal communication with investigators when possible. Studies that specifically assessed akathisia (either subjectively or objectively or both) were included. Studies reporting more generalized results pertaining to EPS (without a separate analysis) were excluded.

A limitation of this analysis is that no meta-analytic procedure was used in this report, and thus no comparison between trials should be made.

MAIN CLINICAL FINDINGS

Before describing the results of the main findings from trials that assess akathisia, a couple of points should be taken into consideration. First, it should be emphasized that akathisia and movement disorders, in general, are not easily rated without training, and most trials (including multicenter, industry-sponsored ones) do not provide for systematic training or the establishment of interrater reliability. Second, many studies have relied on spontaneous reporting, which would tend to reflect different patterns and rates than systematic examinations. Therefore, results must be interpreted cautiously, and the relative risk rates might be more meaningful than the absolute risks.[117] Third, some studies do not always show the clinically observed drug/placebo differences in the prevalence and severity of akathisia. This may be a result of the short-term nature of these trials and reflect withdrawal akathisia or differential diagnosis. Although the majority of the studies had a washout period that should have ensured that no withdrawal akathisia was observed, the washout period may not have been sufficient. An alternative explanation

Table 4. Treatment-Emergent Akathisia: Summary of Clinical Evidence

Reference	SGA	N	Duration	Trial Design	Spontaneously Reported vs Objectively Measured Events[a]	Main Findings
Second-Generation Antipsychotics vs Placebo						
Schizophrenia Spectrum Disorders						
Potkin et al,[42] 2003	Risperidone	Risperidone = 99 Placebo = 103	4 wk	Double-blind, parallel-group, multicenter	Both	Risperidone 14% akathisia vs placebo 9%
Potkin et al,[43] 2006	Risperidone	Risperidone = 153 Placebo = 73	6 wk	Double-blind, randomized, international	Both	Akathisia incidence 12% risperidone vs 3% placebo BARS global severity score (change from baseline to endpoint): % worsened (during monotherapy phase): risperidone, 15%; placebo, 8%; % worsened (during additive therapy phase): risperidone, 17%, placebo, 4%
Beasley et al,[44] 1996	Olanzapine	Olanzapine = 52 Placebo = 50	6 wk	Fixed-dose	Both	No significant differences
Beasley et al,[45] 1996	Olanzapine	Olanzapine = 198 Placebo = 68	6 wk	Double-blind, randomized	Both	Akathisia: olanzapine 2.5–7.5 mg/d, 4.6%; olanzapine 7.5–12.5 mg/d, 6.3%; olanzapine 12.5–17.5 mg/d, 7.2%; placebo, 1.5%
Carlson et al,[46] 2003	Olanzapine	Olanzapine = 387 Placebo = 153	≤ 8 wk	Meta-analysis	Both	BARS total scores:19.2, olanzapine vs 19.0, placebo Endpoint, olanzapine significantly greater reduction in BARS from baseline (p = .007)
Small et al,[47] 1997	Quetiapine	Quetiapine = 186 Placebo = 94	6 wk	Randomized	Both	No statistically significant change from baseline to endpoint in BARS Akathisia incidence: 1% placebo to 4% in high-dose quetiapine group
Buckley,[48] 2004	Quetiapine	Quetiapine = 502 Placebo = 202	6 wk	Combined analysis, 3 trials	Spontaneously reported	Akathisia incidence 2% quetiapine vs 2.5% placebo
Potkin et al,[43] 2006	Quetiapine	Quetiapine = 156 Placebo = 73	6 wk	Double-blind, randomized, international	Both	Akathisia incidence 2% quetiapine vs 3% placebo
Keck et al,[49] 1998	Ziprasidone	Ziprasidone = 91 Placebo = 48	4 wk	Double-blind, multicenter	Both	Akathisia incidence rates < 1% all treatment groups
Daniel et al,[50] 1999	Ziprasidone	Ziprasidone = 210 Placebo = 92	6 wk	Double-blind	Both	Akathisia rate: ziprasidone groups (13%–14%) versus placebo (7%) with no close relationship No difference between groups in mean change in the BARS scores More patients in the ziprasidone groups than in the placebo group took benztropine
Keck et al,[51] 2001	Ziprasidone	Ziprasidone = 81 Placebo = 34	4–6 wk	Double-blind, multicenter (2 studies combined)	Both	Study 1: placebo, 20%; ziprasidone 40 mg/d, 5.8%; ziprasidone 120 mg/d, 5% Study 2: placebo, 0%; ziprasidone 80 mg/d, 16%; ziprasidone 160 mg/d, 16%
Kane et al,[52] 2002	Aripiprazole	Aripiprazole = 204 Placebo = 106	4 wk	Double-blind, randomized, multicenter	Both	Akathisia rates: aripiprazole 15 mg, 8%; aripiprazole 30 mg, 12%; placebo 11% No significant change in BARS vs placebo
Potkin et al,[42] 2003	Aripiprazole	Aripiprazole = 202 Placebo = 103	4 wk	Double-blind, randomized	Both	Akathisia rates: aripiprazole 20 mg, 20%; aripiprazole 30 mg, 20%; placebo, 9% No differences in the BARS vs placebo.
Pigott et al,[53] 2003	Aripiprazole	Aripiprazole = 155 Placebo = 155	26 wk	Double-blind, randomized, parallel-group, multicenter	Both	Incidence rates: 7.8% aripiprazole vs 6.5% placebo No significant differences in mean change in BARS
Marder et al,[54] 2003	Aripiprazole	Aripiprazole = 932 Placebo = 416	4–6 wk	Pooled analysis, 5 trials	Both	Akathisia incidence: aripiprazole 10.0% (all doses); placebo 6.8% Mean change from baseline (LOCF) in BARS: 15 mg aripiprazole +0.2 vs placebo 0.05 (p ≤ .01)

(continued)

Table 4 (continued). Treatment-Emergent Akathisia: Summary of Clinical Evidence

Reference	SGA	N	Duration	Trial Design	Spontaneously Reported vs Objectively Measured Events[a]	Main Findings
Second-Generation Antipsychotics vs Placebo (continued)						
Cutler et al,[55] 2006	Aripiprazole	Aripiprazole = NR Placebo = NR	6 wk	Double-blind, randomized	Both	Akathisia rates: aripiprazole 10 mg/d, 11%; aripiprazole 15mg/d, 6%; aripiprazole 20 mg/d, 5%; placebo, 4%
Andrezina et al,[56] 2006	Aripiprazole	Aripiprazole = 175 Placebo = 88	24 h	Double-blind, randomized	Both	BARS: aripiprazole, –0.15; placebo, –0.11
Tran-Johnson et al,[57] 2007	Aripiprazole	Aripiprazole = 235 Placebo = 62	24 h	Double-blind, randomized	Both	Akathisia rates: aripiprazole 1 mg, 0%, aripiprazole 5.25 mg, 2.3%, aripiprazole 9.75 mg, 5.4%, aripiprazole 15 mg, 0%, placebo, 0%
Davidson et al,[58] 2007	Paliperidone	Paliperidone = 246 Placebo = 120	6 wk	Double-blind, randomized	Objectively measured	Incidence (BARS ≥ 1): paliperidone, 3 mg 14.8%, paliperidone 9 mg, 23.8%, paliperidone 15 mg, 21.1%, placebo, 21.6% No differences between paliperidone ER arms and placebo in the mean BARS Anticholinergic use: placebo, 10%; paliperidone 23%
Kane et al,[59] 2007	Paliperidone	Paliperidone = 374 Placebo = 126	6 wk	Double-blind, randomized	Objectively measured	Incidence (BARS ≥ 1) paliperidone 6 mg, 8%; paliperidone 9 mg, 10%; paliperidone 12mg, 13%; placebo, 7% Anticholinergic use: paliperidone 6 mg, 11%; paliperidone 9 mg, 17%; paliperidone 12 mg, 22%; placebo, 6%
Bipolar Disorder						
Tohen et al,[60] 1999	Olanzapine	Olanzapine = 70 Placebo = 69	3 wk	Double-blind	Objectively measured	No significant differences
Yatham et al,[61] 2004	Quetiapine	Quetiapine = 197 Placebo = 205		Double-blind (2 studies combined)	Both	No significant differences Mean changes (baseline to endpoint) in BARS scores: quetiapine –0.2 vs placebo 0.0 Proportion of patients showing increases from baseline in BARS scores (19.9% vs 14.0%) up to day 42, p = NS
Keck et al,[62] 2003	Ziprasidone	Ziprasidone = 140 Placebo = 70	3 wk	Double-blind, randomized	Both	Reported akathisia: ziprasidone 10.7% vs 5.7% placebo No significant differences between treatment groups on SARS, BARS, AIMS
Potkin et al,[63] 2005	Ziprasidone	Ziprasidone = 139 Placebo = 66	3 wk	Double-blind	Objectively measured	Akathisia (BARS): ziprasidone 9.4%; placebo, 4.5%
Keck et al,[64] 2006	Aripiprazole	Aripiprazole = 77 Placebo = 83	26 wk	Double-blind, randomized	Objectively measured	Akathisia (BARS): aripiprazole 6.5% vs placebo 1.2%
Sachs et al,[65] 2006	Aripiprazole	Aripiprazole = 136 Placebo = 133	3 wk	Double-blind, randomized, multicenter	Both	Reported akathisia: aripiprazole 17.6% vs placebo 4.5% Mean change in BARS at endpoint: 0.05 placebo vs 0.25 aripiprazole (p = .034)
Keck et al,[66] 2003	Aripiprazole	Aripiprazole = 130 Placebo = 132	3 wk	Double-blind, randomized	Both	Akathisia: aripiprazole 11% vs placebo 2% Changes from baseline in BARS: aripiprazole mean 0.33 ± 1.17 vs placebo mean –0.11 ± 0.70 (p = .01)
Second-Generation Antipsychotics vs First-Generation Antipsychotics						
Claghorn et al,[67] 1987	Clozapine	Clozapine = NR Chlorpromazine = NR		Double-blind, randomized, multicenter	Spontaneously reported	Comparable frequency of akathisia across treatment groups
Cohen et al,[68] 1991	Clozapine	Clozapine = 23 Haloperidol = 29	3 mo	Single-blind clinician rating	Objectively measured	Mean total akathisia score and akathisia prevalence similar across treatment groups
Peacock et al,[69] 1996	Clozapine	Clozapine = 100 Control = 100	1 y	Retrospective, prospective	Objectively measured	Subjective akathisia: clozapine 14% vs FGA 40% Motor akathisia clozapine 7% vs FGA 29%
Kurz et al,[70] 1995	Clozapine	Clozapine = 92 Haloperidol = 59		Open-label, naturalistic	Objectively measured	Akathisia incidence: clozapine 5.6% vs haloperidol 31.7%; (p = .005)

(continued)

Table 4 (continued). Treatment-Emergent Akathisia: Summary of Clinical Evidence

Reference	SGA	N	Duration	Trial Design	Spontaneously Reported vs Objectively Measured Events[a]	Main Findings
Second-Generation Antipsychotics vs First-Generation Antipsychotics (continued)						
Miller et al,[13] 1998	Clozapine	Clozapine = 41 Control = 42	≥ 3 mo	Chart review from prospective prevalence study	Both	Akathisia (point-prevalence rate): clozapine 7.3% vs FGA[b] 23.8%
Ceskova and Svestka,[71] 1993	Risperidone	Risperidone = 31 Haloperidol = 31	8 wk	Double-blind, randomized, parallel-group	Spontaneously reported	Akathisia incidence: risperidone 32.2% vs haloperidol 48.3%
Rosebush and Mazurek,[72] 1999	Risperidone	Risperidone = 34 Haloperidol = 212		Prospective	Objectively measured	Akathisia incidence: risperidone 50% vs haloperidol 39%
Bouchard et al,[73] 2000	Risperidone	Risperidone = 93 Control = 91	1 y	Longitudinal, open-label, parallel-group, multicenter	Spontaneously	Worsening of akathisia less frequent in risperidone vs conventional antipsychotic (p = .02)
Miller et al,[13] 1998	Risperidone	Risperidone = 23 Control = 42	≥ 3 mo	Chart review from ongoing prospective prevalence study	Objectively measured	Point-prevalence of akathisia[c]: risperidone 13% vs FGA[d] 23.8% No between-group differences in akathisia severity
Marder et al,[74] 2003	Risperidone	Risperidone = 33 Haloperidol = 30	2 y	Double-blind, randomized	Objectively measured	Risperidone significantly greater reductions in akathisia
Wirshing et al,[75] 1999	Risperidone	Risperidone = 34 Haloperidol = 33	8 wk	Double-blind, randomized, 4-week fixed-dose/4 week flexible-dose	Spontaneously reported	Concomitant anticholinergic medication use after 4 weeks (risperidone 20% vs haloperidol 63%) Risperidone significantly less observable akathisia (24% vs 53%)
Tollefson et al,[76] 1997	Olanzapine	Olanzapine = 1336 Haloperidol = 660	6 wk	Double-blind, randomized	Both	Akathisia incidence: olanzapine 14.2%, haloperidol 35.5% BARS: olanzapine-treated patients improved and haloperidol patients worsened
Leelahanaj et al,[77] 2005	Olanzapine	Olanzapine = 29 Haloperidol = 29	4 wk	Double-blind, randomized	Objectively measured	Change to endpoint in BARS significantly different in favor of olanzapine vs haloperidol (p = .02)
Dossenbach et al,[78] 2004	Olanzapine	Olanzapine = 30 Control = 30	22 wk	Double-blind, randomized	Objectively measured	Akathisia rates significantly lower in olanzapine than in controls: 10% vs 30%, respectively (p = .053)
Rosenheck et al,[79] 2003	Olanzapine	Olanzapine = 159 Haloperidol = 150	12 mo	Double-blind, randomized, multicenter	Spontaneously reported	Reduced akathisia with olanzapine (p < .001 vs haloperidol)
Kennedy et al,[80] 2003	Olanzapine	Olanzapine = 83 Haloperidol = 34	6 wk	Double-blind	Both	Akathisia significantly more common in haloperidol group (p < .001) Greater proportion of haloperidol-treated patients required at least 1 dose of anticholinergic medication
Carlson et al,[46] 2003	Olanzapine	Total = 4611	≤ 8 wk	Retrospective, 23 clinical trials (1991 to 2001)	Both	A significantly greater % of haloperidol-treated patients experienced akathisia (p < .001 vs olanzapine) Significantly greater reductions in BARS with olanzapine vs haloperidol (p < .001)
Lieberman et al,[81] 2003	Olanzapine	Olanzapine = 131 Haloperidol = 132	12 wk acute treatment, up to 104 wk follow-up	Double-blind, randomized	Objectively measured	Akathisia: olanzapine 11.9% vs haloperidol 51.2%; p < .001

(continued)

Table 4 (continued). Treatment-Emergent Akathisia: Summary of Clinical Evidence

Reference	SGA	N	Duration	Trial Design	Spontaneously Reported vs Objectively Measured Events[a]	Main Findings
Second-Generation Antipsychotics vs First-Generation Antipsychotics (continued)						
Breier and Hamilton,[82] 1999	Olanzapine	Olanzapine = 352 Haloperidol = 174	6 wk	Post hoc subanalysis	Objectively measured	Akathisia: olanzapine 11.6% vs haloperidol 45%; p < .001
Conley et al,[83] 1998	Olanzapine	Olanzapine = 42 Control = 39	8 wk	Double-blind, randomized, fixed-dose	Objectively measured	Improvement in BARS akathisia scores regardless of medication (p < .0001)
Sanger et al,[84] 1999	Olanzapine	Olanzapine = 59 Haloperidol = 24	6 wk	Post hoc subanalysis from prospective, multicenter, double-blind	Both	Akathisia: olanzapine 11.3% vs haloperidol 38.1%; p = .02 Statistically significant improvements in BARS with olanzapine (mean change on global score, p = .005)
Beasley et al,[45] 1996	Olanzapine	Olanzapine = 198 Haloperidol = 69	6 wk	Double-blind, randomized	Both	Akathisia: olanzapine 2.5–7.5 mg/d, 4.6%; olanzapine 7.5–12.5 mg/d, 6.3%; olanzapine 12.5–17.5 mg/d, 7.2%; haloperidol, 15.9% BARS (at endpoint): numerical improvement from baseline in all olanzapine groups and numerical worsening in the haloperidol group
Beasley et al,[85] 1997	Olanzapine	Olanzapine = 350 Haloperidol = 81	6 wk	Double-blind, multicenter	Both	Akathisia: olanzapine up to 7.5 mg/d; no akathisia: olanzapine 10 ± 2.5 mg, 1.2%; olanzapine 15 ± 2.5 mg, 3.4%; haloperidol, 14.8% BARS (at endpoint) improved vs baseline in all olanzapine groups but worsened in haloperidol group (p < .001)
Nemeroff et al,[86] 1997	Olanzapine	Study 1 = 152 Study 2 = 335 Study 3 = 431 Study 4 = 1996	6 wk	Double-blind comparison of 4 trials	Objectively measured	Olanzapine 5 to 20 mg/d significantly lower mean changes in BARS vs haloperidol during acute phases in 3/4 studies (p < .01)
Wright et al,[87] 2003	Olanzapine (IM)	Olanzapine = 131 Haloperidol = 126	1 d	Double-blind	Both	Spontaneously reported akathisia: olanzapine 1.1% vs haloperidol 6.5% (p = .065) Required anticholinergic treatment: olanzapine 4.6% vs haloperidol 20.6%; p < .001 Mean change in BARS global score: –0.27 olanzapine vs 0.01 haloperidol; p < .05
Breier et al,[88] 2002	Olanzapine (IM)	Olanzapine = 171 Haloperidol = 38	1 d	Double-blind, dose-response	Spontaneously reported	Spontaneously reported akathisia IM olanzapine: 2.5, 7.5, and 10.0 mg, 0%; 5.0 mg, 4.8% vs IM haloperidol, 7.9% Anticholinergic medication received: IM haloperidol, 7.5% vs IM olanzapine 2.5 mg: 2.1% (p = NS)
McIntyre et al,[89] 2005	Quetiapine	Quetiapine = 102 Haloperidol = 99	12 wk	Double-blind, randomized, parallel-group	Spontaneously reported	Akathisia incidence: quetiapine 5.9% vs haloperidol 33.3% (p < .001)
Glick and Marder,[90] 2005	Quetiapine	Quetiapine = 16 Haloperidol = 9	48 wk	Double-blind	Both	Quetiapine significantly greater improvements in akathisia (BARS; p < .05)
Aravanitis and Miller,[91] 1997	Quetiapine	Quetiapine = 258 Haloperidol = 52	6 wk	Multicenter, fixed-dose	Spontaneously reported	Quetiapine akathisia rates across the full dosage range were 0% to 2% vs 15% with haloperidol
Hirsch et al,[92] 2002	Ziprasidone	Ziprasidone = 148 Haloperidol = 153	28 wk	Double-blind, randomized, parallel-group, flexible-dose	Both	Akathisia incidence: ziprasidone 5% vs haloperidol 16% Mean BARS increased (baseline to endpoint; week 28, LOCF) in haloperidol group; no change in ziprasidone group
Brook et al,[93] 2005	Ziprasidone (IM and oral)	Ziprasidone = 429 Haloperidol = 138	6 wk	Open-label, randomized, parallel-group, multicenter, flexible-dose	Both	Significantly higher BARS ratings with haloperidol vs ziprasidone (p < .0001) Akathisia incidence (IM and oral phases): ziprasidone 8.2% vs haloperidol 23.4%

(continued)

Table 4 (continued). Treatment-Emergent Akathisia: Summary of Clinical Evidence

Reference	SGA	N	Duration	Trial Design	Spontaneously Reported vs Objectively Measured Events[a]	Main Findings
Second-Generation Antipsychotics vs First-Generation Antipsychotics (continued)						
Marder et al,[54] 2003	Aripiprazole	Aripiprazole = 932 Haloperidol = 200	4–6 wk	Double-blind, pooled analysis from 5 trials	Spontaneously reported	Akathisia: aripiprazole 10.0% vs haloperidol 18% Akathisia-associated discontinuations: aripiprazole 0.6% vs haloperidol 1.5%
Kasper et al,[94] 2003	Aripiprazole	Aripiprazole = 859 Haloperidol = 431	52 wk	Pooled analysis of 2 trials	Both	Akathisia: aripiprazole 13% vs haloperidol 25%; $p < .001$
Kane et al,[52] 2002	Aripiprazole	Aripiprazole = 204 Haloperidol = 104	4 wk	Double-blind, randomized, multicenter	Spontaneously reported	Akathisia: aripiprazole 15 mg, 8%; 30 mg, 12%; placebo, 11%; and haloperidol, 23%
Vieta et al,[95] 2005	Aripiprazole	Aripiprazole = 175 Haloperidol = 169	12 wk	Double-blind	Spontaneously reported	Akathisia: aripiprazole 11.4% vs haloperidol 23.1%
Andrezina et al,[56] 2006	Aripiprazole	Aripiprazole = 175 Haloperidol = 185	24 h	Double-blind, randomized	Both	BARS: aripiprazole –0.15; haloperidol –0.07
Tran-Johnson et al,[57] 2007	Aripiprazole	Aripiprazole = 235 Haloperidol = 60	24 h	Double-blind, randomized	Both	Akathisia rates: aripiprazole 1 mg, 0%; aripiprazole 5.25 mg, 2.3%; aripiprazole 9.75 mg, 5.4%; aripiprazole 15 mg, 0%; haloperidol, 10.5%
Andrezina et al,[56] 2006	Aripiprazole (IM)	Aripiprazole = 125 Haloperidol = 135 Placebo = 65 (all IM)	24 h	Subpopulation analysis from randomized, double-blind	Spontaneously reported	IM aripiprazole (9.75 mg): no EPS-related adverse events IM haloperidol (6.5 mg): 6 (4.5%) experienced akathisia
Potkin et al,[42] 2003	Aripiprazole	Aripiprazole = 202 Placebo = 103	4 wk	Double-blind, randomized	Both	Akathisia rates: aripiprazole 20 mg, 20%; aripiprazole 30 mg, 20%; placebo, 9%; risperidone, 14%
Kane et al,[120] 2007	Aripiprazole	Aripiprazole = 154 Perphenazine = 146	6 wk	Double-blind, randomized	Both	Akathisia: aripiprazole 4% vs perphenazine 9% BARS: no difference between groups Anticholinergic use for EPS: aripiprazole 18% vs perphenazine 28%
Jones et al,[96] 2006	First-generation antipsychotic Second-generation antipsychotic	First-generation antipsychotic = NR Second-generation antipsychotic = NR	56 wk	Randomized	Objectively measured	Both SGA and FGA groups showed a decrease from baseline to endpoint in the BARS, with no difference between groups
Comparative Studies of Second-Generation Antipsychotics						
Miller et al,[13] 1998	Risperidone Clozapine	Risperidone = 23 Clozapine = 41	3 mo	Prospective	Spontaneously reported	Akathisia (point prevalence): clozapine 7.3% vs risperidone 13%
Meltzer et al,[97] 2003	Clozapine Olanzapine	Clozapine = 479 Olanzapine = 477			Spontaneously reported	Akathisia: olanzapine 8.2% vs clozapine 4.4%, $p = .02$
Bitter et al,[98] 2004	Clozapine Olanzapine	Clozapine = 72 Olanzapine = 75	18 wk	Double-blind, randomized, parallel-group	Spontaneously reported	Akathisia: clozapine 0.0% vs olanzapine 5.3%, $p = .072$
Carlson et al,[46] 2003	Clozapine Olanzapine	Clozapine = 225 Olanzapine = 231	≤ 8 wk	Retrospective, 23 clinical trials	Both	No significant differences in akathisia rates
Kelly et al,[99] 2003	Clozapine Olanzapine	Clozapine = 10 Olanzapine = 10	16 wk	Randomized, crossover, fixed-dose, 8-wk, double-blind	Spontaneously reported	Neither olanzapine nor clozapine was associated with significant akathisia

(continued)

Table 4 (continued). Treatment-Emergent Akathisia: Summary of Clinical Evidence

Reference	SGA	N	Duration	Trial Design	Spontaneously Reported vs Objectively Measured Events[a]	Main Findings
Comparative Studies of Second-Generation Antipsychotics (continued)						
Tran et al,[100] 1997	Olanzapine Risperidone	Olanzapine = 72 Risperidone = 67	28 wk	Prospective, multicenter, double-blind, parallel-group	Spontaneously reported	Akathisia in males: significantly lower in olanzapine 11.0% vs risperidone 21.2%, p = .04 No significant difference in females Overall akathisia rate: olanzapine 9.9% vs risperidone 10.8%; p = .79
Ho et al,[101] 1999	Olanzapine Risperidone	Olanzapine = 21 Risperidone = 21	4 wk	Open-label	Both	Risperidone more likely to induce akathisia following acute treatment
Alvarez et al,[102] 2006	Olanzapine Risperidone	Olanzapine = 124 Risperidone = 123	1 y	Randomized, 1-y follow-up	Spontaneously reported	Akathisia (spontaneous reports): olanzapine 1.6% vs risperidone 8.9%, p < .01 Akathisia incidence: risperidone 18.2% vs olanzapine 7.4%, p = .02
Gureje et al,[103] 2003	Olanzapine Risperidone	Olanzapine = 32 Risperidone = 33	30 wk	Multicenter, double-blind, randomized	Both	No significant differences
Carlson et al,[46] 2003	Olanzapine Risperidone	Olanzapine = 400 Risperidone = 279	Variable	Double-blind	Spontaneously reported	No significant differences
Van Bruggen et al,[104] 2003	Olanzapine Risperidone	Olanzapine = 18 Risperidone = 24	6–10 wk	Randomized	Both	No significant differences
Mozes et al,[105] 2006	Olanzapine Risperidone	Olanzapine = 12 Risperidone = 13	12 wk	Prospective, open-label, randomized	Objectively measured	No significant differences
Mintzer et al,[106] 2004	Quetiapine Risperidone	Quetiapine = 67 Risperidone = 27	4 mo	Post hoc randomized, multicenter, open-label	Spontaneously reported	Quetiapine less likely to cause akathisia in elderly subpopulation vs risperidone
Potkin et al,[43] 2006	Risperidone Quetiapine	Risperidone = 153 Quetiapine = 156	6 wk	International, randomized, double-blind	Both	Akathisia incidence: risperidone 12% vs quetiapine 2% % worsened (BARS): risperidone 15% vs quetiapine 7% Received anticholinergic drugs: risperidone 28% vs quetiapine 17%; p < .05
Addington et al,[107] 2004	Ziprasidone Risperidone	Ziprasidone = 149 Risperidone = 147	8 wk	Double-blind, multicenter	Both	Akathisia: risperidone 20.4% vs ziprasidone 12.8% BARS scores at the last observation: ziprasidone 0.28 [0.22] vs risperidone + 0.28 [0.21]; p = .04 Required medication for the management of movement disorders: ziprasidone 27.5% vs risperidone 37.4%
Simpson et al,[108] 2004	Ziprasidone Olanzapine	Ziprasidone = 136 Olanzapine = 133	6 wk	Parallel-group, multicenter, double-blind, flexible-dose	Objectively measured	No significant differences in BARS mean scores at endpoint
Breier et al,[109] 2005	Ziprasidone Olanzapine	Ziprasidone = 271 Olanzapine = 277	28 wk	Double-blind, randomized, multicenter, parallel-group	Objectively measured	Greater improvement in mean baseline-to-endpoint change on BARS in olanzapine group (p = .03)
Potkin et al,[42] 2003	Aripiprazole Risperidone	Aripiprazole = 201 Risperidone = 99	4 wk	Double-blind, randomized	Both	Akathisia incidence: aripiprazole 20% vs risperidone 18%
McQuade et al,[110] 2004	Aripiprazole Olanzapine	Aripiprazole = 156 Olanzapine = 161	26 wk	Double-blind, randomized	Both	EPS: aripiprazole 17% vs olanzapine 16% Akathisia: aripiprazole 6% vs olanzapine 3%
Chrzanowski et al,[111] 2006	Aripiprazole Olanzapine	Aripiprazole = 105 Olanzapine = 110	52 wk	Double-blind, randomized	Both	EPS: aripiprazole 10% vs olanzapine 18% Akathisia: aripiprazole 5% vs olanzapine 6% BARS: aripiprazole: –0.06 vs olanzapine: –0.13 (p = NS) Anticholinergic use for EPS: aripiprazole 22% vs olanzapine 26%

(continued)

Table 4 (continued). Treatment-Emergent Akathisia: Summary of Clinical Evidence

Reference	SGA	N	Duration	Trial Design	Spontaneously Reported vs Objectively Measured Events[a]	Main Findings
Comparative Studies of Second-Generation Antipsychotics (continued)						
Zimbroff et al,[112] 2007	Aripiprazole Ziprasidone	Aripiprazole = 128 Ziprasidone = 125	4 wk	Double-blind, randomized	Both	Akathisia incidence: aripiprazole 9% vs ziprasidone 7% BARS: aripiprazole –0.1 vs ziprasidone +0.1 (p = NS)
Davidson et al,[58] 2007	Paliperidone Olanzapine	Paliperidone = 246 Olanzapine = 126	6 wk	Double-blind, randomized	Objectively measured	Incidence (BARS = 1): paliperidone 3 mg, 14.8%; paliperidone 9 mg, 23.8%; paliperidone 15 mg, 21.1%; olanzapine, 13.6%
Kane et al,[59] 2007	Paliperidone Olanzapine	Paliperidone = 374 Olanzapine = 128	6 wk	Double-blind, randomized	Objectively measured	Incidence (BARS = 1) paliperidone 6 mg, 8%; paliperidone 9 mg, 10%; paliperidone 12 mg, 13%; olanzapine, 7% Anticholinergic use: paliperidone 6 mg, 11%; paliperidone 9 mg, 17%; paliperidone 12 mg, 22%; olanzapine 10 mg, 8%
Lieberman et al,[113] 2005	 Risperidone Olanzapine Quetiapine Ziprasidone	Perphenazine = NR Risperidone = NR Olanzapine = NR Quetiapine = NR Ziprasidone = NR	18 mo	Double-blind, randomized	Both	Perphenazine: 7% BARS global score ≥ 3 Risperidone: 7% BARS global score ≥ 3 Olanzapine: 5% BARS global score ≥ 3 Quetiapine: 5% BARS global score ≥ 3 Ziprasidone: 9% BARS global score ≥ 3
McEvoy et al,[114] 2006	Clozapine Risperidone Olanzapine Quetiapine	Clozapine = 41 Risperidone = 13 Olanzapine = 17 Quetiapine = 13	18 mo	Double-blind, randomized	Both	Clozapine: 5% Barnes Global Clinical Assessment score ≥ 3 Risperidone: 0% Barnes Global Clinical Assessment score ≥ 3 Quetiapine: 23% Barnes Global Clinical Assessment score ≥ 3 Olanzapine: 0% Barnes Global Clinical Assessment score ≥ 3
Stroup et al,[115] 2006	Risperidone Olanzapine Quetiapine Ziprasidone	Risperidone = NR Olanzapine = NR Quetiapine = NR Ziprasidone = NR	18 mo	Double-blind, randomized	Both	Risperidone: 3% Barnes Global Clinical Assessment score ≥ 3 Olanzapine: 6% Barnes Global Clinical Assessment score ≥ 3 Quetiapine: 6% Barnes Global Clinical Assessment score ≥ 3 Ziprasidone: 5% Barnes Global Clinical Assessment score ≥ 3
McEvoy et al,[116] 2007	Risperidone Olanzapine Quetiapine	Risperidone = 133 Olanzapine = 133 Quetiapine = 134	52 wk	Double-blind, randomized	Both	Risperidone: akathisia rate 22.6% Olanzapine: akathisia rate 20.3% Quetiapine: akathisia rate 18.7%

[a]Spontaneously reported events vs. incidence by objectively measured events.
[b]Fluphenazine, haloperidol, trifluoperazine, thiothixene, loxapine, thioridazine, molindone, perphenazine, or chlorpromazine.
[c]In patients with mixed diagnoses: schizophrenia, schizoaffective disorder, and personality disorder.
[d]Fluphenazine, haloperidol, trifluoperazine, thiothixene, molindone, perphenazine, or chlorpromazine.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BARS = Barnes Akathisia Rating Scale, EPS = extrapyramidal symptoms, FGA = first-generation antipsychotic, IM = intramuscular, LOCF = last observation carried forward, NR = not reported, NS = not significant, SARS = Simpson-Angus Rating Scale, SGA = second-generation antipsychotic.

is that what is observed is not truly akathisia. Fourth, apart from incidence rates of treatment-emergent akathisia and mean changes in Barnes Akathisia Rating Scale (BARS) scores,[14] there is a lack of information on additional clinical characteristics of akathisia, such as severity, time of onset, duration of akathisia, or discontinuation rates due to this AE. Fifth, strategies for management of this AE are not usually specified in clinical protocols and will vary based on investigators' discretion. Most studies allow the use of anticholinergic drugs to treat EPS symptoms, including akathisia, and in some cases benzodiazepines or propranolol to treat akathisia or restlessness. Finally, although most studies used an objective measurement of akathisia (e.g., BARS), the majority failed to report any data regarding severe akathisia. Data on these topics are warranted for both FGAs and SGAs in order to better inform clinicians on risks and management of a more severe form of akathisia.

However, despite the limitations mentioned above and the fact that no meta-analytic procedure was used in this review, certain trends in the incidence of akathisia appeared to emerge. For example, despite the differences in incidence, akathisia was a treatment-emergent AE observed with all of the SGAs (Table 4). These findings corroborate those in the literature that this condition, although usually less frequent when compared with FGAs, is not absent with the use of SGAs. Overall, the akathisia incidence reported in the bipolar disorder clinical trials was generally higher than that reported in schizophrenia ones. Although the reasons for this phenomenon are unclear, some hypotheses have been raised. One explanation is that akathisia would be expected to occur in disorders for which several drugs are taken chronically, such as bipolar disorder. Alternatively, the onset of akathisia may result from the low dosage or dose reductions of neuroleptics that can lead to demasking effects due to diminishing parkinsonian symptoms.[118] The akathisia incidence reported for FGAs was consistently higher than that reported for SGAs, regardless of the patient population studied (schizophrenia or bipolar disorder).

Table 4 summarizes the data on SGA-related akathisia; these data are presented in the order that these drugs were introduced to the U.S. market. Also, data from placebo-controlled studies with active controls are described in the Second-Generation Antipsychotics vs. Placebo section or in the Second-Generation Antipsychotics vs. First-Generation Antipsychotics section of Table 4.

Clozapine

Clozapine was the first antipsychotic with the "atypical" characteristic of showing, contrary to the knowledge at the time, efficacy in treatment of psychotic symptoms with lower risk for causing movement disorders.[119] To our knowledge, there are no placebo-controlled trials of clozapine in which akathisia rates were specifically assessed. In studies comparing clozapine with FGAs, most studies report lower rates of akathisia for clozapine versus FGAs.[13,67–70] However, 2 studies described comparable rates between clozapine and FGAs.[67,68] Comparative studies between clozapine and other SGAs have reported equivocal results, with some studies showing no difference between clozapine and other SGAs,[46,99] whereas others showed a lower incidence of akathisia in the clozapine-treated group.[13,97,98]

Risperidone

In risperidone placebo-controlled trials, the placebo rates for akathisia are usually lower than that of risperidone.[42,43] Most studies comparing risperidone with an FGA show a lower incidence of akathisia in the risperidone group versus conventionals,[13,71,73–75] with 1 study showing higher rates of akathisia with risperidone than with haloperidol.[72] However, despite differences in incidence, the severity of akathisia was similar between risperidone and conventional drugs.[13] Results are conflicting in comparative studies versus other SGAs. The incidence of akathisia in patients treated with risperidone appears to be higher than that reported with the use of clozapine[13] and quetiapine[63,106] in schizophrenia spectrum patients. When compared with olanzapine, some studies showed lower rates for olanzapine,[101,102] whereas others have failed to find any significant differences between these 2 SGAs with regard to the frequency of akathisia.[46,100,103–105] One study of risperidone versus aripiprazole showed lower rates of akathisia in the risperidone arm.[42]

Olanzapine

Most published data from placebo-controlled clinical studies have shown similar rates of akathisia between olanzapine and placebo in both schizophrenia and bipolar disorder.[44,46,60] However, in one study, olanzapine-treated patients experienced higher rates when compared with placebo.[45] In comparison to FGAs, studies have shown lower akathisia rates associated with olanzapine treatment when compared with conventional drugs.[46,76–86] Placebo-controlled studies with an intramuscular formulation of olanzapine, which included haloperidol as an active control, showed no significant differences in rates of akathisia between olanzapine and this FGA.[87,88] Two studies comparing olanzapine with ziprasidone showed conflicting results; one study reported no differences in the BARS scores at endpoint,[108] whereas the other showed a significant improvement favoring olanzapine.[109] In 2 studies versus aripiprazole, the incidence of akathisia varied from 3% to 6% in the olanzapine group versus 6% and 5% in the aripiprazole arm.[110,111] One of the trials reported that both drugs were associated with improvement in the BARS scores and that there was no difference in anticholinergic use.[111] Olanzapine was included as an active control arm in 2 paliperidone placebo-controlled studies, and

akathisia rates were lower for olanzapine when compared with the higher doses of paliperidone.[58,120] Comparative data between olanzapine and either clozapine or risperidone were described earlier in the article in the clozapine and risperidone sections above, respectively.

Quetiapine

Placebo-controlled studies show similar rates of akathisia between placebo and quetiapine in both patients with schizophrenia and those with bipolar disorder.[43,47,48,61] One study showed an akathisia incidence of 1% in the placebo group versus 4% in the high-dose quetiapine arm.[47] Consistent with data on other SGAs, quetiapine-related akathisia has been reported at a lower rate when compared with FGAs.[89–91] Available data comparing quetiapine with risperidone were discussed in the risperidone section earlier in this article.

Ziprasidone

In placebo-controlled trials in both schizophrenia spectrum and bipolar disorder, the rates of akathisia were usually higher in the ziprasidone arm than in the placebo one,[50,62,63] with the exception of 1 study that showed similar rates for the active and placebo arms.[49] Compared with conventional antipsychotics, both the oral and intramuscular formulations of ziprasidone were associated with lower rates of akathisia than the FGA haloperidol.[92,93] Comparison data with aripiprazole[112] and risperidone[107] showed similar incidences for ziprasidone and aripiprazole but higher rates of akathisia for risperidone when compared with ziprasidone. Available data comparing ziprasidone with risperidone were discussed in the risperidone section earlier in this article.

Aripiprazole

In studies comparing aripiprazole with placebo, akathisia rates in the aripiprazole arm were similar in some studies[52,53] and higher in others.[42,64–66] As with other SGAs, akathisia rates with aripiprazole were lower than those of FGAs.[52,54,94,95,120] Comparisons between aripiprazole and risperidone, olanzapine, or ziprasidone are described in the risperidone, olanzapine, and ziprasidone sections, respectively.

Paliperidone

In 2 placebo-controlled studies, akathisia rates appeared to be dose-dependent for paliperidone, and the use of anticholinergics were usually higher in the active arm when compared with placebo.[58,59] These studies included olanzapine as an active control arm and results are described in the olanzapine section.

Multiple Drugs Comparison Studies

There are few studies comparing multiple antipsychotics.[96,113–116] Lieberman et al.[113] compared 4 SGAs (risperidone, olanzapine, quetiapine, and ziprasidone) with perphenazine, an FGA usually considered to have a lower risk of causing EPS than other FGAs. They found similar akathisia rates between SGAs and perphenazine. Similar results were seen by Jones et al.[96] Two other studies comparing multiple SGAs found no difference among drugs,[115,116] whereas McEvoy et al.,[114] in the second phase of the Clinical Antipsychotic Trials of Intervention Effectiveness (Lieberman et al.,[113] discussed above), found higher rates of akathisia with quetiapine (23%) versus clozapine (5%), and risperidone and olanzapine (0% for both).[114] None of these studies included aripiprazole or paliperidone; at the time of their initiation, these drugs were not available.

AKATHISIA-ASSOCIATED BEHAVIOR ISSUES

As described earlier, akathisia may be associated with subjective distress, and some case reports have described that akathisia may precipitate aggressive, violent, or suicidal behaviors.[121,122] It is well known that patients with schizophrenia spectrum and bipolar disorders are at a high risk of suicide.[123,124] In addition, suicidal behavior has been described in patients with akathisia in case reports, both in patients receiving antipsychotic medication[122] and in patients receiving selective serotonin reuptake inhibitors (SSRIs).[125] The dysphoric effects and behavioral toxicity of FGA medications have further supported the notion that this group of medications may cause or increase suicidal impulses.[121] Hansen[125] notes in his critical review of the relationship between suicidality and akathisia that it is not possible to conclude, based on the present evidence, whether or not akathisia is unequivocally linked to suicidal behavior, but the possibility certainly cannot be excluded. Two small studies have been carried out exploring the issue further.[121,126] Despite equivocal results, these studies collectively indicate that further work must be done to study possible differences in toxicity between different subgroups of patients with akathisia (chronic, acute, and of varying intensity) as well as whether subjective complaints of akathisia are predictive of suicidal intentions.

MANAGEMENT AND TREATMENT OF AKATHISIA

Despite the fact that akathisia might be caused by many different factors, including psychiatric pathology itself, discontinuation of specific drugs, and introduction of a new drug, it can still be effectively managed. Based on the literature,[1,2,22,24,127–139] there are 2 main options for effective management—pharmacologic and psychosocial (Table 5). As, however, there are different levels of evidence for some of these therapy options, each case should be considered individually. It is prudent for clinicians to use every preventative and therapeutic measure available

Table 5. Management Options in the Treatment of Akathisia

Pharmacotherapy	Psychosocial
Lowering medication dose	Patient education on benefit and risks associated with antipsychotic treatment
Short term adjunctive therapies:	Establish clear expectations[b]
β-adrenergic agonists	Open and frank dialogue about potential adverse events
Benzodiazepines[a]	Provide reassurance
Anticholinergic[c]	Discuss risks
Clonidine	
Amantadine	
Diphenhydramine	
Other[d]	
Consider switching to antipsychotic with lower liability for akathisia	

[a]Especially if concomitant anxiety.
[b]Discuss clinical characteristics of importance to patients such as time at onset, duration, potentially manageable side effects, other options, need to talk to physician.
[c]Especially if concomitant parkinsonism.
[d]E.g., serotonin antagonists and mirtazapine.

in the management of this side effect, as studies have shown that it may impact treatment adherence.[140–144]

Psychosocial Intervention

Patient education is an integral part of effective management. The clinician should focus on open and frank discussions with the patient, providing reassurance and forewarning of any possible side effects. By establishing clear expectations, the clinician can help to minimize patient anxiety. Open discussions will promote mutual trust and respect between clinician and patient and may improve medication adherence.[145–147]

Pharmacologic Treatment of Akathisia

Taylor et al.[127] recommend lowering the dose of the antipsychotic medication as an initial response to drug-induced akathisia; however, exposure to subtherapeutic doses must always be carefully considered in the context of relapse risk. A conservative approach on the part of the clinician when planning a medication switch or dosage adjustment may be an effective preemptive strategy to minimize the risk of akathisia. Observed cases of akathisia concurrent with an abrupt medication dosage decrease, withdrawal, or switch have been documented.[148–150] The clinician should always consider previous exposure to antipsychotics when looking at the diagnosis and management of akathisia during medication changes and adjustments.

A number of adjunctive pharmacologic interventions appear to have anti-akathisia effects, although the levels of evidence for each agent vary and should be considered along with dosage decrease or switching medications (for a review, see Miller and Fleischhacker[22]). Among these are β-adrenergic antagonists (e.g., propranolol, with recommendations to initiate therapy at low dosages, 10 mg tid, which can be increased every few days to a maximum of 90–120 mg/day),[6,151] and benzodiazepines (e.g., lorazepam 1.5–3 mg/day in divided doses or clonazepam 0.5 mg/day).[152–155] Anticholinergics (e.g., benztropine 2 mg) appear to demonstrate their best efficacy when other EPS are present.[156] Other alternatives include serotonin antagonists (e.g., cyproheptadine 16 mg/day)[157,158]; clonidine (0.2–0.8 mg/day)[159,160]; mirtazapine (suggested low dose of 15 mg)[161,162]; diphenhydramine (50 mg)[163]; and amantadine (100 mg t.i.d.).[164]

CONCLUSIONS AND FUTURE DIRECTIONS

Akathisia produces unnecessary suffering and adds to the health burden of disease. Therefore, its prompt recognition and treatment are critical to an optimum outcome. Although SGAs are generally associated with a lower propensity for movement disorders compared with their FGA counterparts, an emerging body of comparative literature shows that second-generation medications are not completely free from inducing akathisia. Currently, there is significant discrepancy among studies of the same antipsychotic with respect to akathisia incidence rates. These discrepancies may arise from differences in diagnostic approach, the timing of the assessment, the measurement parameters and scales utilized, prior medications, or even the time at which a new antipsychotic is introduced to the clinicians' armamentarium.

The comparative incidence of akathisia among the newer antipsychotic agents remains poorly characterized. Randomized, controlled trials that systematically and specifically assess these potential differences are limited. Moreover, many of the published direct comparative studies are performed in relatively homogenous and chronic populations that may not accurately represent all patients seen in clinical practice. Consistent with this notion, a recent naturalistic study evaluating patients with bipolar I disorder in a real-world setting reported much higher rates of akathisia associated with SGAs than those reported in randomized clinical trials.[117] This discrepancy highlights the need for more data systematically collected in a way that specifically assesses the incidence and severity of akathisia. Achieving consensus on an operational definition of akathisia will promote more accurate assessments and, at the same time, bolster efforts for effective management. Furthermore, a stronger theoretical and practical understanding of the pathophysiology of akathisia will also improve patient care and therapeutic outcome.

Drug names: amantadine (Symmetrel and others), aripiprazole (Abilify), benztropine (Cogentin and others), chlorpromazine (Thorazine, Sonazine, and others), clonazepam (Klonopin and others), clonidine (Catapres, Duraclon, and others), clozapine (FazaClo, Clozaril, and others), diphenhydramine (Benadryl and others), haloperidol (Haldol and others), lorazepam (Ativan and others), mirtazapine (Remeron and others), molindone (Moban), olanzapine (Zyprexa), paliperidone (Invega), propranolol (Inderal and others), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane and others), trifluoperazine (Stelazine and others), ziprasidone (Geodon).

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