

# Akathisia and Newer Second-Generation Antipsychotic Drugs: A Review of Current Evidence

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Akathisia continues to present a significant challenge in clinical practice. As a class, so-called atypical, or second-generation, antipsychotics (SGAs) are the mainstay of treatment for schizophrenia and are commonly used to treat mood disorders. These medications have traditionally been distinguished from first-generation antipsychotics by their lowered risk of extrapyramidal side effects (EPS) such as dystonia, dyskinesia, akathisia, and pseudoparkinsonism. However, the occurrence of EPS, particularly akathisia, has been demonstrated to some degree in all commercially available SGAs. This review examines the incidence of akathisia in nine newer SGAs in patients with schizophrenia, bipolar disorder, and major depressive disorder (MDD). We performed a search of PubMed, ClinicalTrials.gov, Cochrane Central Register, and Google Scholar, as well as manufacturer websites and product labeling for published and unpublished clinical trials, meta-analyses, and systematic reviews. Studies evaluating adult patients with schizophrenia, bipolar disorder, or MDD were eligible for inclusion. Data on treatment-emergent akathisia rates were gathered from each study, and potential dose-response relationships were explored. A total of 177 studies were included in this review, comprising 58,069 patients across 414 treatment arms. Compared with placebo with a composite 3.7% incidence of akathisia, individual SGAs produced akathisia at total composite rates ranging from 2.9–13.0% across the included studies. High doses of an SGA were generally associated with an increased risk of akathisia. Clinicians should consider the risk of akathisia when choosing a treatment option and monitor for akathisia in patients beginning therapy with an SGA or following a dose increase of the SGA.

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Akathisia is a movement disorder characterized by distressing feelings of restlessness or inner tension generally associated with the use of so-called typical, or first-generation, antipsychotics (FGAs). Despite being recognized as the most common movement-related adverse effect of antipsychotics, historically akathisia has been both under- and

misdiagnosed in clinical practice, likely due to its subjective nature.<sup>1–3</sup> The unrelenting urge to move often manifests as increased motor activity consisting of complex, repetitive movements, although in some patients it remains internalized. Akathisia has been identified as a principal cause of medication nonadherence in patients with schizophrenia, and it is associated with treatment-emergent suicidality.<sup>4, 5</sup> This adverse effect presents a substantial treatment challenge in patients with schizophrenia and mood disorders such as bipolar disorder and major depressive disorder (MDD). For these reasons, the likelihood of akathisia is an important consideration in the choice of an antipsychotic agent.<sup>6, 7</sup>

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Different classifications of drug-induced akathisia have been proposed based on the timing of onset and clinical profile; these include acute, chronic, withdrawal, and even tardive akathisia. Acute akathisia typically develops within a few days to 2 weeks following initiation, dose escalation, or switch to a high-potency antipsychotic agent.<sup>3, 6</sup> If symptoms of akathisia develop after this time frame, or are consistently present for numerous months, it is classified as chronic akathisia.<sup>6</sup> After the discontinuation or dose reduction of an antipsychotic medication, a patient may experience withdrawal akathisia.<sup>7</sup> However, if symptoms do not resolve within 6 weeks, or a patient experiences a delayed onset of symptoms (1–3 mo after treatment initiation), it would be considered tardive akathisia.<sup>7</sup> The Barnes Akathisia Rating Scale (BARS) is currently the most widely used diagnostic tool for identifying and measuring akathisia in clinical trials.<sup>2,8</sup>

As a class, so-called atypical, or second-generation, antipsychotics (SGAs) are the mainstay of treatment for schizophrenia and commonly used to treat mood disorders.<sup>6, 9, 10</sup> These medications have traditionally been distinguished from FGAs by their lower risk of extrapyramidal side effects (EPS) such as dystonia, dyskinesia, akathisia, and pseudoparkinsonism.<sup>11, 12</sup> However, EPS, particularly akathisia, occurs, to some degree, with all commercially available SGAs.<sup>12–17</sup> Evidence from clinical trials on the risk of akathisia in individual SGAs has been largely inconsistent with questionable applicability to real-world practice due to issues with carryover effects and the study of nonequivalent doses.<sup>16</sup> Furthermore, previous meta-analyses and systematic reviews comparing the safety and tolerability of FGAs and SGAs have found little evidence to support the notion that as a class, SGAs pose a reduced risk for EPS compared with FGAs.<sup>7, 9, 13–15</sup> However, high-potency FGAs do tend to pose the greatest risk for EPS.<sup>13</sup>

Rates of akathisia with older SGAs, such as clozapine, olanzapine, and quetiapine, were reviewed comprehensively and published.<sup>3</sup> Although it is generally accepted that clozapine and quetiapine have the lowest rates of akathisia, studies included in that review reported rates of akathisia from 0–10% for clozapine, olanzapine, and quetiapine.<sup>3</sup> This review examines the literature on the use of nine newer SGAs (Table 1) with regard to the incidence of akathisia in patients with schizophrenia, bipolar disorder, and depression based on clinical trials involving

**Table 1. Dosage Recommendations and Indications for Included Second-Generation Antipsychotics**

Drug	Target dose, <sup>a</sup> mg/day	Max dose, <sup>a</sup> mg/day	FDA-approved indication(s) for all available drug products
Aripiprazole <sup>18,19</sup>	10–30	30	Schizophrenia; Bipolar disorder; MDD (adjunct); Irritability with autistic disorder; Tourette's disorder
Asenapine <sup>20</sup>	10–20	20	Schizophrenia; Bipolar disorder
Brexipiprazole <sup>21</sup>	2–4	4	Schizophrenia; MDD (adjunct)
Cariprazine <sup>22</sup>	1.5–6	6	Schizophrenia; Bipolar disorder
Iloperidone <sup>23</sup>	12–24	24	Schizophrenia
Lurasidone <sup>24</sup>	40–160	160	Schizophrenia; Bipolar disorder
Paliperidone <sup>25,26</sup>	3–12	12	Schizophrenia
Risperidone <sup>27,28</sup>	4–8	16	Schizophrenia; Bipolar disorder; Irritability with autistic disorder
Ziprasidone <sup>29</sup>	40–160	200	Schizophrenia; Bipolar disorder

FDA = Food and Drug Administration; MDD = major depressive disorder.

<sup>a</sup>Reference dosage from product labeling of oral formulation for schizophrenia.

indications approved by the Food and Drug Administration (FDA) respective to each agent.

## Methods

A review of the literature was conducted to identify studies evaluating adult patients receiving maintenance treatment for schizophrenia, bipolar disorder, or MDD with one of the nine antipsychotics listed in Table 1. Both open-label and double-blind randomized controlled trials that compared doses of at least one of the previously mentioned SGAs with another SGA, placebo, or an FGA were included. All flexible-dose studies were included; fixed-dose studies evaluating target doses up to the maximum approved by the FDA and established by the international consensus study of antipsychotic dosing were also included.<sup>30</sup> Each study was evaluated for data on treatment-emergent akathisia rates in study participants.

We searched PubMed, ClinicalTrials.gov, Cochrane Central Register, and Google Scholar, as well as manufacturer websites and product labeling for published and unpublished clinical

trials, meta-analyses, and systematic reviews using search terms consisting of the generic names of SGAs along with the terms “schizophrenia,” “bipolar,” or “major depressive disorder.” Additionally, the reference lists of all studies identified in the search were inspected for more trials. Studies were excluded if they involved patients younger than 18 years of age.

Studies that specifically assessed akathisia, with a Global Clinical Assessment item score of 2 or greater on the BARS, were included, whereas those that only reported generalized results for EPS were excluded. Studies evaluating akathisia largely rely on the BARS, a four-item scale that accounts for both the objective (i.e., observable) features and the subjective experience of akathisia. The objective item assesses the type and frequency of fidgety, restless movements, whereas the subjective items evaluate the intensity of the feelings of restlessness as well as the level of associated distress. Together, this allows for an overall measure of severity to be made using the Global item, composed of clinically relevant severity classifications scored on a 5-point scale: 0 = absent; 1 = questionable; 2 = mild akathisia; 3 = moderate akathisia; 4 = marked akathisia; and 5 = severe akathisia. A Global item score of 2 or greater on the BARS meets the diagnostic threshold for akathisia.<sup>2, 31</sup>

An analysis of potential dose-response relationships was explored based on expert opinion from an international consensus study of antipsychotic dosing and using low- and high-dosage cutoffs (Table 2) to detect inequalities in dosing in the multiple-treatments meta-analysis study comparing efficacy and tolerability of 15 antipsychotics.<sup>13, 30</sup>

## Results

A total of 177 studies with 58,069 participants across 414 treatment arms were included in the

Table 2. Definitions of Low and High Doses of Oral Second-Generation Antipsychotic Drugs<sup>13,30</sup>

Drug	Low dose, mg/day	High dose, mg/day
Aripiprazole	< 10	> 25
Asenapine	< 10	> 18
Brexpiprazole	< 2	> 3
Cariprazine	< 2	> 5
Iloperidone	< 12	> 22
Lurasidone	< 40	> 120
Paliperidone ER	< 6	> 9
Risperidone	< 4	> 6
Ziprasidone	< 120	> 150

ER = extended release.

comparative analysis (Appendix S1).<sup>32–111</sup> Of these, the breakdown for numbers of studies including each medication are aripiprazole (88), asenapine (10), brexpiprazole (8), cariprazine (10), iloperidone (6), lurasidone (14), paliperidone (9), risperidone (25), and ziprasidone (11). Less than half (63) of the studies were placebo controlled. Most of the included studies evaluated patients with schizophrenia (162), were short term in duration (12 wks or less; 130), and used flexible dosing (122). Some studies reported using the Simpson-Angus Scale and/or the Abnormal Involuntary Movement Scale to measure movement disorders; however, all but one study used the BARS to assess akathisia specifically. Studies were excluded due to lack of usable data (4) or when only a single-dose administration was being assessed (2).

Included studies had the following SGA dosage ranges: aripiprazole 2–40 mg/day, aripiprazole long-acting injectable (LAI) 50–400 mg/month, aripiprazole lauroxil 441–882 mg/month, asenapine 10–20 mg/day, brexpiprazole 0.25–6 mg/day, cariprazine 0.75–12 mg/day, iloperidone 4–24 mg/day, lurasidone 20–160 mg/day, paliperidone extended release (ER) 3–15 mg/day, paliperidone palmitate 39–234 mg/month, quetiapine 50–800 mg/day, risperidone 0.5–12 mg/day, risperidone LAI 25–50 mg/2 weeks, and ziprasidone 10–200 mg/day.

All of the SGAs produced treatment-emergent akathisia at varying rates (Table 3). Total composite rates of akathisia for SGAs ranged from 2.94–13.04% across included studies compared with an overall incidence of 3.69% for placebo. Of the nine newer SGAs, iloperidone had the lowest incidence of akathisia (2.9%), followed by paliperidone palmitate (4.4%), aripiprazole lauroxil (4.5%), brexpiprazole (6.3%), and asenapine (6.3%). Middle-range medications included paliperidone ER (6.6%), aripiprazole LAI (8.3%), aripiprazole (8.7%), risperidone LAI (8.9%), and ziprasidone (9.0%). Finally, lurasidone (11.2%), cariprazine (13.0%), and risperidone (13.0%) had the highest incidences of akathisia. Doses classified as “high” in fixed-dose studies were generally associated with an increased risk of akathisia when compared with lower doses of the same drug.

No identifiable trends in akathisia rate were found between the diagnoses of schizophrenia, bipolar disorder, and MDD in the studies we examined in this review (Table 4). The composite rates of akathisia in patients treated for schizophrenia for all SGAs in this review ranged from 2.94–13.03% compared with 4.03% for

Table 3. Overall Incidence of Akathisia in Individual SGAs and Placebo<sup>32-111</sup>

Diagnosis	Dosing strategy	Dose classification	No. of studies	Patients, N	Akathisia incidence, n	Rate, %
<b>Aripiprazole</b>						
Schizophrenia	Fixed	High	2	228	33	14.47
		Target	7	1232	104	8.44
	Flexible	Target	78	5427	463	8.53
		Total	86	6887	600	8.71
Aripiprazole total			86	6887	600	8.71
<b>Aripiprazole LAI</b>						
Schizophrenia	Fixed	Low	1	131	11	8.40
		Target	2	534	44	8.24
	Total	3	665	55	8.27	
Aripiprazole LAI total			3	665	55	8.27
<b>Aripiprazole lauroxil</b>						
Schizophrenia	Fixed	Target	2	893	40	4.48
	Total	2	893	40	4.48	
Aripiprazole lauroxil total			2	893	40	4.48
<b>Asenapine</b>						
Bipolar	Fixed	High	1	119	18	15.13
		Target	1	122	5	4.10
	Flexible	Target	3	884	56	6.33
		Total	4	1125	79	7.02
Schizophrenia	Fixed	High	3	1208	83	6.87
		Target	3	595	25	4.20
	Flexible	Target	1	572	34	5.94
Asenapine total			9	3500	221	6.31
<b>Brexpiprazole</b>						
MDD	Fixed	Low	1	226	10	4.42
		Target	2	417	45	10.79
	Total	2	643	55	8.55	
Schizophrenia	Fixed	High	2	364	25	6.87
		Low	3	252	6	2.38
		Target	2	368	17	4.62
	Flexible	High	1	93	14	15.05
		Low	1	89	6	6.74
		Target	4	1710	97	5.67
	Brexpiprazole total			6	2876	165
Cariprazine			8	3519	220	6.25
<b>Cariprazine</b>						
Bipolar	Fixed	Low	1	287	11	3.83
		Target	1	146	21	14.38
	Flexible	Target	2	494	101	20.45
MDD	Flexible	Low	3	927	133	14.35
		Target	1	273	18	6.59
Schizophrenia	Total	Target	1	273	61	22.34
		Low	1	546	79	14.47
	Fixed	High	1	157	23	14.65
		Low	1	145	13	8.97
	Flexible	Target	3	678	55	8.11
		High	2	281	37	13.17
Cariprazine total			6	2125	257	12.09
Cariprazine total			10	3598	469	13.04
<b>Iloperidone</b>						
Schizophrenia	Fixed	High	2	473	7	1.48
	Flexible	Target	4	3299	104	3.15
		Total	6	3772	111	2.94
Iloperidone total			6	3772	111	2.94

(continued)

Table 3. (continued)

Diagnosis	Dosing strategy	Dose classification	No. of studies	Patients, N	Akathisia incidence, n	Rate, %
Lurasidone						
Bipolar	Flexible	Target	2	1293	111	8.58
	Total		2	1293	111	8.58
Schizophrenia	Fixed	High	3	285	21	7.37
		Low	1	71	4	5.63
		Target	8	1439	190	13.20
	Flexible	Target	4	1122	144	12.83
	Total		12	2917	359	12.31
Lurasidone total			14	4210	470	11.16
Paliperidone ER						
Schizophrenia	Fixed	High	2	468	43	9.19
		Low	2	254	13	5.12
		Target	2	605	39	6.45
	Flexible	Target	1	164	3	1.83
	Total		3	1491	98	6.57
Paliperidone ER total			3	1491	98	6.57
Paliperidone palmitate						
Schizophrenia	Fixed	Target	5	1491	65	4.36
	Flexible	Target	2	985	44	4.47
	Total		7	2476	109	4.40
Paliperidone palmitate total			7	2476	109	4.40
Risperidone						
Schizophrenia	Fixed	Target	10	1069	99	9.26
		High	1	113	12	10.62
	Flexible	Target	58	4097	577	14.08
	Total		68	5279	688	13.03
Risperidone total			68	5279	688	13.03
Risperidone LAI						
Schizophrenia	Fixed	Target	1	223	44	19.73
	Flexible	Target	3	1155	79	6.84
	Total		4	1378	123	8.93
Risperidone LAI total			4	1378	123	8.93
Ziprasidone						
Bipolar	Flexible	Target	5	1493	156	10.45
	Total		5	1493	156	10.45
Schizophrenia	Fixed	High	2	254	24	9.45
		Low	2	150	18	12.00
		Target	2	749	60	8.01
	Flexible	Target	9	1107	81	7.32
	Total		13	2260	183	8.10
Ziprasidone total			18	3753	339	9.03
Placebo						
Bipolar	NA	NA	13	1696	51	3.01
MDD	NA	NA	3	677	13	1.92
Schizophrenia	NA	NA	47	6872	277	4.03
Placebo total			63	9245	341	3.69

Target doses summarized in Table 1; high and low doses summarized in Table 2.

ER = extended-release; LAI = long-acting injectable; MDD = major depressive disorder; NA, not available; SGA = second-generation antipsychotic.

placebo. Composite incidence of akathisia in patients with bipolar disorder with the use of asenapine, cariprazine, lurasidone, and ziprasidone were 7.02%, 14.35%, 8.58%, and 10.45%, respectively. Moreover, in comparison with a 1.92% incidence of akathisia for placebo, patients being treated for MDD experienced a

composite akathisia rate of 8.55% with brexpiprazole and 14.47% for cariprazine. Cariprazine was the only SGA with studies that reported akathisia rates in all three diagnoses examined in this review (with composite rates of 12.1%, 14.4%, and 14.5% for schizophrenia, bipolar disorder, and MDD, respectively).

## Discussion

Akathisia poses a major treatment challenge in schizophrenia and mood disorders, and it adds to the health burden of these diseases. Quetiapine and clozapine are SGAs known to have a very low risk of inducing akathisia with rates of 0–10% when compared with placebo or other SGAs.<sup>3, 112–117</sup> Because the rates of akathisia in these older SGAs have been studied extensively, the focus of this review was to assess and compare the incidence of akathisia with nine newer SGAs in patients with schizophrenia, bipolar disorder, and MDD.

Results from this review show that discrepancies in the incidence of akathisia exist even among studies of the same antipsychotic, and they indicate that further work must be done to better quantify and qualify akathisia risk in these medications. These discrepancies can stem from a number of causes including differences in diagnostic approach, measurement parameters and scales used, timing of assessment, prior therapies tried, or even when in the course of the disease that a patient is enrolled into the trial. Although mood disorders were considered to be a risk factor for akathisia in previous studies,<sup>12, 111</sup> antipsychotic doses were generally similar in mood disorder studies when compared with schizophrenia studies.

In this review, asenapine, cariprazine, lurasidone, and ziprasidone were the only SGAs with studies that examined akathisia rates in patients with bipolar disorder. Although the rates of akathisia for asenapine and ziprasidone were higher in patients treated for bipolar disorder compared with schizophrenia (7.0% vs 6.0% for asenapine, and 10.5% vs 8.1% for ziprasidone

in bipolar disorder vs schizophrenia, respectively), the same trend did not occur in patients taking lurasidone (8.6% vs 12.3%). Moreover, a higher composite akathisia rate was determined in patients taking brexpiprazole for MDD compared with patients being treated for schizophrenia (8.6% vs 5.7%). These results also support the growing understanding that SGAs are not benign, and clinicians should be monitoring for akathisia more regularly in patients taking SGAs.

Notably, the overall incidence of akathisia observed with aripiprazole was much lower than expected when compared with other SGAs included in this review, at ~8% for both the oral and LAI formulations and less than 5% for the lauroxil formulation. Oral and parenteral risperidone produced rates of akathisia that were among the highest in this group of SGAs at 13% and 9%, respectively. In contrast, akathisia was observed half as often with oral and parenteral paliperidone as with risperidone, although this finding may be attributed to the target and that maximum doses of risperidone were much higher relative to paliperidone.

Dosing of SGAs can impact akathisia development in patients. A dose-response relationship was evident in many of the SGAs with studies evaluating a fixed dose above or below the target dosing range. Oral aripiprazole given at higher doses in patients with schizophrenia had a much higher incidence of akathisia compared with doses less than 25 mg/day (14.5% vs 8.5%). There was a disparity in akathisia incidence between asenapine at high versus target dose in patients with bipolar disorder (15.1% vs 4.1%) and a smaller disparity between asenapine at high versus target dose in patients with

Table 4. Composite Akathisia Rates by Diagnosis in Individual SGAs and Placebo

	Schizophrenia, %	Bipolar disorder, %	MDD, %	Total composite, %
Aripiprazole	8.71	–	–	8.71
Aripiprazole LAI	8.27	–	–	8.27
Aripiprazole lauroxil	4.48	–	–	4.48
Asenapine	5.98	7.02	–	6.31
Brexpiprazole	5.74	–	8.55	6.25
Cariprazine	12.09	14.35	14.47	13.04
Iloperidone	2.94	–	–	2.94
Lurasidone	12.31	8.58	–	11.16
Paliperidone ER	6.57	–	–	6.57
Paliperidone palmitate	4.40	–	–	4.40
Risperidone	13.03	–	–	13.03
Risperidone LAI	8.93	–	–	8.93
Ziprasidone	8.10	10.45	–	9.03
Placebo	4.03	3.01	1.92	3.69

ER = extended release; LAI = long-acting injectable; MDD = major depressive disorder; SGA = second-generation antipsychotic.

schizophrenia (6.9% vs 4.2%). In fixed-dose studies for brexpiprazole, high doses were associated with higher incidences of akathisia than target doses (6.9% vs 4.6%), and low doses were likewise associated with the lowest incidence of akathisia (2.4%) in patients with schizophrenia.

In patients with MDD, target doses of brexpiprazole showed higher incidence of akathisia than low doses (10.8% vs 4.4%). Cariprazine showed a similar dose-related response, with low doses associated with a lower incidence of akathisia than doses in the target dose range for patients with bipolar disorder (3.8% vs 14.4%), and low and target doses showing lower rates of akathisia compared with high doses in patients with schizophrenia (8.1–9.0% vs 14.7%). Oral paliperidone at high versus target versus low doses likewise showed a dose-related effect on the incidence of akathisia (9.2% vs 6.5% vs 5.1%) in patients with schizophrenia. Lurasidone was the only SGA where a dose-related effect on akathisia was not observed, with target doses showing much higher incidence of akathisia than high doses (13.2% vs 7.4%).

Limitations of this review included a lack of continuity and consensus in assessment and reporting of akathisia between the included studies. Some studies used a diagnostic threshold of 3 or higher on the BARS Global item to assess akathisia, and many others did not explicitly state their methodology for measuring akathisia beyond noting the rating scale that was used. Additionally, most trials do not verify systematic training or the establishment of inter-rater reliability for akathisia in published results. Without this, scores may be discrepant due to the subjective nature of rating akathisia. Similarly, because akathisia ratings are subjective, of note less than 10% of the studies included in this review were open-label studies. Moreover, the concomitant use of antidepressants, antipsychotic polytherapy, or pharmacotherapy for akathisia treatment were not consistently reported in the studies we examined. Some trials resulted in multiple publications for post hoc and subanalyses that can lead to biased composite results. Every effort was made to exclude such post hoc analyses; however, it is possible that the same subjects were included more than once in results (e.g., with open-label follow-up studies).

Finally, although our intent was to focus on a comparison of newer agents, another limitation was the exclusion of studies examining akathisia rates in patients taking aripiprazole for bipolar

disorder or MDD, aripiprazole LAI or risperidone LAI for bipolar disorder, and the exclusion of other SGAs from this review. Although both aripiprazole LAI and risperidone LAI are indicated for the treatment of bipolar disorder, published data are lacking on the rates of akathisia for these formulations and indications specifically.

## Conclusion

Second-generation antipsychotics as a class are associated with akathisia. This disorder is often difficult to identify and distinguish from other conditions, and available information continues to be lacking on the clinical severity, timing of onset, and duration of akathisia. Further analysis on the risk of akathisia in individual SGAs is needed. Future studies may also evaluate the incidence of akathisia in patients based on established cutoff values or mean change in BARS scores, the use of anti-akathisia treatment agents, discontinuation rate due to akathisia, and rate of associated adverse reactions such as agitation, tremors, anxiety, or other movement disorders. Risk of akathisia must be considered when choosing a treatment option because certain SGAs appear to have lower potential for causing akathisia than others, and SGA dosage was found to be associated with the rate of akathisia. Clinicians should monitor for akathisia in all patients beginning therapy with any of these agents or following a dose increase of the SGA.

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## Supporting Information

The following supporting information is available in the online version of this paper:

Appendix S1. Characteristics of included studies.