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

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Abstract

INTRODUCTION: Akathisia continues to present a significant challenge in clinical practice. As a class, “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.
OBJECTIVE: This review examines the incidence of akathisia in nine newer SGAs in patients with schizophrenia, bipolar disorder, and major depressive disorder (MDD).

METHODS: We performed a search of PubMed, ClinicalTrials.gov, Cochrane Central Register, Google Scholar, as well as manufacturer websites and product labeling for published and unpublished clinical trials, meta-analyses, and systematic reviews.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 was explored.
RESULTS: A total of 177 studies were included in this review, comprising 58,069 patients across 414 treatment arms. Compared to placebo with a composite 3.7% incidence of akathisia, individual SGAs produced akathisia at total composite rates ranging from 2.9% to 13.0% across the included studies. High doses of an SGA were generally associated with an increased risk of akathisia.
CONCLUSION: Clinicians should consider 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.
KEY WORDS: akathisia, antipsychotics, schizophrenia, bipolar disorder, major depressive disorder

Introduction

Akathisia is a movement disorder characterized by distressing feelings of restlessness or inner tension generally associated with the use of “typical” or first-generation antipsychotics (FGAs). Despite its recognition for being the most common movement-related adverse effect of antipsychotics, historically akathisia has been both under- and mis-diagnosed in clinical practice – likely due to its subjective nature.[1–3] The unrelenting urge to move often manifests as increased motor activity consisting of complex, repetitive movements, though in some patients it remains internalized. Akathisia has been identified as a principal cause of medication non-adherence in patients with schizophrenia, and is associated with treatment emergent suicidality.[4,5] 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.[6,7]

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

As a class, “atypical” or second-generation antipsychotics (SGAs) are the mainstay of treatment for schizophrenia and are commonly used to treat mood disorders.[6,9,10] These medications have traditionally been distinguished from FGAs by their lower risk of extrapyramidal side effects (EPS) such as dystonia, dyskinesia, akathisia, and pseudoparkinsonism.[11,12] However EPS, particularly akathisia, occurs, to some degree, with all commercially available SGAs.[12–17] 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 non-equivalent doses being studied.[16] 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 to FGAs.[7,9,13–15] However, high potency first-generation antipsychotics tend to pose the greatest risk for EPS.[13]

Rates of akathisia with older SGAs, such as clozapine, olanzapine and quetiapine, have been comprehensively reviewed and published.[3] 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% to 10% for clozapine, olanzapine and quetiapine.[3] This review examines the literature on the use of nine newer SGAs (Table 1) with regard to incidence of akathisia in patients with schizophrenia, bipolar disorder, and depression based on clinical trials involving FDA approved indications 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 (RCTs) which compared doses of at least one of the aforementioned 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 Food and Drug Administration (FDA) and established by the international consensus study of antipsychotic dosing were also included.[18] Each study was evaluated for data on treatment emergent akathisia rates in study participants.

The authors searched PubMed, ClinicalTrials.gov, Cochrane Central Register, 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 under 18 years of age.

Studies that specifically assessed akathisia, with a Global 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. The BARS is 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 Clinical Assessment item, comprised of clinically relevant severity classifications scored on a five-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 diagnostic threshold for akathisia.[2,19]

An analysis of potential dose-response relationships was explored based on expert opinion from an international consensus study of antipsychotic dosing and using the 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.[13,18]

Results

A total of 177 studies with 58,069 participants across 414 treatment arms were included in the comparative analysis (Appendix S1).[32-111] Of these, the breakdown for numbers of studies including each medication are as follows: aripiprazole (n=88), asenapine (n=10), brexpiprazole n=(8), cariprazine (n=10), iloperidone (n=6), lurasidone (n=14), paliperidone (n=9), risperidone (n=25), and ziprasidone (n=11). Less than half (n=63) of the studies were placebo-controlled. Most of the included studies evaluated patients with schizophrenia (n=162), were short-term in duration (12 weeks or less) (n=130), and employed flexible dosing (n=122). Some studies reported using the Simpson-Angus Scale (SAS), and/or Abnormal Involuntary Movement Scale (AIMS) 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 (n=4) or when only a single-dose administration was being assessed (n=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% to 13.04% across included studies compared to 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 extended-release (6.6%), aripiprazole long-acting injectable (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.

There were no identifiable trends in akathisia rate between the diagnoses of schizophrenia, bipolar disorder, and MDD in the studies that were examined in this review (Table 4). The composite rates of akathisia in patients being treated for schizophrenia for all SGAs in this review ranged from 2.94% to 13.03% compared to 4.03% for 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 to 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 adds to the health burden of these diseases. Quetiapine and clozapine are second generation antipsychotics known to have a very low risk of inducing akathisia with rates of 0 to 10% when compared to placebo or other SGAs.[3,112-117] Since the rates of akathisia in these older SGAs have been extensively studied, 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 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. While mood disorders have been considered to be a risk factor for akathisia in previous studies,[12,111] antipsychotic doses were generally similar in mood disorder studies when compared to 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 to schizophrenia (7.0% versus 6.0% for asenapine, and 10.5% versus 8.1% for ziprasidone in bipolar disorder versus schizophrenia, respectively), the same trend did not occur in patients taking lurasidone (8.6% versus 12.3%). Moreover, a higher composite akathisia rate was determined in patients taking brexpiprazole for MDD compared to patients being treated for schizophrenia (8.6% versus 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 approximately 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, though this may be attributed to the target and maximum doses of risperidone being 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% versus 8.5%). There was a disparity in akathisia incidence between asenapine at high versus target dose in patients with bipolar disorder (15.1% versus 4.1%), and a smaller disparity between asenapine at high versus target dose in patients with schizophrenia (6.9% versus 4.2%). In fixed-dose studies for brexpiprazole, high doses were associated with higher incidences of akathisia than target doses (6.9% versus 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% versus 4.4%). Cariprazine showed a similar dose-related response, with low doses associated with lower incidence of akathisia than doses in the target dose range for patients with bipolar disorder (3.8% versus 14.4%), and low and target doses showing lower rates of akathisia compared to high doses in patients with schizophrenia (8.1-9.0% versus 14.7%). Oral paliperidone at high versus target versus low doses likewise showed a dose-related effect on incidence of akathisia (9.2% versus 6.5% versus 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% versus 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 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 interrater reliability for akathisia in published results. Without this, there may be discrepancies in scores due to the subjective nature of rating akathisia. Similarly, since akathisia ratings are subjective, it should be noted that 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 that were examined. Some trials resulted in multiple publications for post-hoc and sub-analyses which 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 (eg, with open-label follow-up studies). Finally, while 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, there is a lack of published data on the rates of akathisia for these formulations and indications specifically.

Conclusion

SGAs as a class are associated with akathisia. This disorder is often difficult to identify and distinguish from other conditions, and there continues to be a lack of information available 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, as certain SGAs appear to have lower potential for causing akathisia than others and SGA dosage has been found to be associated with 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.

References

1. Hirose S. The causes of underdiagnosing akathisia. *Schizophr Bull*. 2003;29(3):547-558.

2. Barnes TRE. The Barnes Akathisia Rating Scale–Revisited. *J Psychopharmacol (Oxf)*. 2003;17(4):365-370. doi:10.1177/0269881103174013

3. Kane JM, Fleischhacker WW, Hansen L, Perlis R, Pikalov A, Assunção-Talbott S. Akathisia: an updated review focusing on second-generation antipsychotics. *J Clin Psychiatry*. 2009;70(5):627-643. doi:10.4088/JCP.08r04210

4. Putten TV. Why Do Schizophrenic Patients Refuse to Take Their Drugs? *Arch Gen Psychiatry*. 1974;31(1):67-72. doi:10.1001/archpsyc.1974.01760130049008

5. Seemüller F, Lewitzka U, Bauer M, et al. The Relationship of Akathisia with Treatment Emergent Suicidality among Patients with First-Episode Schizophrenia Treated with Haloperidol or Risperidone. *Pharmacopsychiatry*. 2012;45(07):292-296. doi:10.1055/s-0032-1309004

6. Sachdev PS. Neuroleptic-induced Movement Disorders: An Overview. *Psychiatr Clin North Am*. 2005;28(1):255-274. doi:10.1016/j.psc.2004.10.004

7. Salem H, Nagpal C, Pigott T, Teixeira AL. Revisiting Antipsychotic-induced Akathisia: Current Issues and Prospective Challenges. *Curr Neuropharmacol*. 2017;15(5):789-798. doi:10.2174/1570159X14666161208153644

8. APPENDIX 5, VALIDITY OF OUTCOME MEASURES. In: *Aripiprazole Prolonged Release Suspension for Injection (Abilify Maintena) (300 Mg and 400 Mg Vial)*. CADTH Common Drug Reviews. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2017. https://www.ncbi.nlm.nih.gov/books/NBK447744/. Accessed April 27, 2019.

9. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet Lond Engl*. 2009;373(9657):31-41. doi:10.1016/S0140-6736(08)61764-X

10. Lindström L, Lindström E, Nilsson M, Höistad M. Maintenance therapy with second generation antipsychotics for bipolar disorder – A systematic review and meta-analysis. *J Affect Disord*. 2017;213:138-150. doi:10.1016/j.jad.2017.02.012

11. Meltzer HY. What's atypical about atypical antipsychotic drugs? *Curr Opin Pharmacol*. 2004;4(1):53-57. doi:10.1016/j.coph.2003.09.010

12. Kumar R, Sachdev PS. Akathisia and second-generation antipsychotic drugs: *Curr Opin Psychiatry*. 2009;22(3):293-299. doi:10.1097/YCO.0b013e32832a16da

13. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *The Lancet*. 2013;382(9896):951-962. doi:10.1016/S0140-6736(13)60733-3

14. Citrome L. Activating and Sedating Adverse Effects of Second-generation Antipsychotics in the Treatment of Schizophrenia and Major Depressive Disorder: Absolute Risk Increase and Number Needed to Harm. *J Clin Psychopharmacol*. 2017;37(2):138-147. doi:10.1097/JCP.0000000000000665

15. Peluso MJ, Lewis SW, Barnes TRE, Jones PB. Extrapyramidal motor side-effects of first- and second-generation antipsychotic drugs. *Br J Psychiatry*. 2012;200(5):387-392. doi:10.1192/bjp.bp.111.101485

16. Rummel-Kluge C, Komossa K, Schwarz S, et al. Second-Generation Antipsychotic Drugs and Extrapyramidal Side Effects: A Systematic Review and Meta-analysis of Head-to-Head Comparisons. *Schizophr Bull*. 2012;38(1):167-177. doi:10.1093/schbul/sbq042

17. Weiden PJ. Eps Profiles: The Atypical Antipsychotics: Are Not All the Same. *J Psychiatr Pract*. 2007;13(1):13-24.

18. Gardner DM, Murphy AL, O'Donnell H, Pharm B, Centorrino F, Baldessarini RJ. International Consensus Study of Antipsychotic Dosing. *Am J Psychiatry*. 2010:8.

19. Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry*. 1989;154:672–676.

20. *Abilify (Aripiprazole) [Package Insert]. Rockville, MD: Otsuka America Pharmaceutical Inc.; June 2018.*

21. *Abilify Maintena (Aripiprazole) [Package Insert]. Rockville, MD: Otsuka Pharmaceutical Co.; February 2019.*

22. Saphris (asenapine) [package insert]. Irvine, CA: Allergan Inc.; February 2017.

23. Rexulti (brexpiprazole) [package insert]. Rockville, MD: Otsuka Pharmaceutical Co.; February 2018.

24. Vraylar (cariprazine) [package insert]. Madison, NJ: Allergan USA, Inc.; November 2018.

25. Iloperidone [package insert]. Morgantown, WV: Mylan Pharmaceuticals, Inc.; February 2019.

26. Latuda (lurasidone) [package insert]. Marlborough, MA: Sunovion Pharmaceuticals Inc.; March 2018.

27. Paliperidone [package insert]. Memphis, TN: NorthStar Rx LLC; October 2018.

28. *Invega Sustenna (Paliperidone Palmitate) [Package Insert].Titusville, NJ: Janssen Pharmaceuticals, Inc.; June 2017.*

29. Risperidone [package insert]. Horsham, PA: Janssen Pharmaceutical, Inc.; February 2019.

30. *Risperdal Consta (Risperdone LAI) [Package Insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2007*.

31. Geodon (ziprasidone) [package insert]. New York, NY: Pfizer Inc.; November 2018.

32. El-Sayeh HG, Morganti C. Aripiprazole for schizophrenia. Cochrane Database Syst Rev. 2006;(2):CD004578. doi:10.1002/14651858.CD004578.pub3

33. Fleischhacker WW, McQuade RD, Marcus RN, Archibald D, Swanink R, Carson WH. A Double-Blind, Randomized Comparative Study of Aripiprazole and Olanzapine in Patients with Schizophrenia. Biol Psychiatry. 2009;65(6):510-517. doi:10.1016/j.biopsych.2008.07.033

34. McEvoy JP, Daniel DG, Carson WH, McQuade RD, Marcus RN. A randomized, double-blind, placebo-controlled, study of the efficacy and safety of aripiprazole 10, 15 or 20 mg/day for the treatment of patients with acute exacerbations of schizophrenia. J Psychiatr Res. 2007;41(11):895-905. doi:10.1016/j.jpsychires.2007.05.002

35. Pigott TA, Carson WH, Saha AR, et al. Aripiprazole for the prevention of relapse in stabilized patients with chronic schizophrenia: a placebo-controlled 26-week study. J Clin Psychiatry. 2003;64(9):1048-1056.

36. Marder SR, McQuade RD, Stock E, et al. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. Schizophr Res. 2003;61(2):123-136. doi:10.1016/S0920-9964(03)00050-1

37. Center for Drug Evaluation and Research. Drug Approval Package: Abilify (Aripiprazole) NDA #21-436. Medical Review(s). November 2002. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-436_Abilify.cfm. Accessed May 3, 2019.

38. Potkin SG, Saha AR, Kujawa MJ, et al. Aripiprazole, an Antipsychotic With a Novel Mechanism of Action, and Risperidone vs Placebo in Patients With Schizophrenia and Schizoaffective Disorder. Arch Gen Psychiatry. 2003;60(7):681-690. doi:10.1001/archpsyc.60.7.681

39. Kane JM, Sanchez R, Perry PP, et al. Aripiprazole Intramuscular Depot as Maintenance Treatment in Patients With Schizophrenia: A 52-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study. J Clin Psychiatry. 2012;73(5):617-624. doi:10.4088/JCP.11m07530

40. Fleischhacker WW, Sanchez R, Perry PP, et al. Aripiprazole once-monthly for treatment of schizophrenia: double-blind, randomised, non-inferiority study. Br J Psychiatry J Ment Sci. 2014;205(2):135-144. doi:10.1192/bjp.bp.113.134213

41. Khanna P, Suo T, Komossa K, et al. Aripiprazole versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2014;(1):CD006569. doi:10.1002/14651858.CD006569.pub5

42. Zimbroff D, Warrington L, Loebel A, Yang R, Siu C. Comparison of ziprasidone and aripiprazole in acutely ill patients with schizophrenia or schizoaffective disorder: a randomized, double-blind, 4-week study: Int Clin Psychopharmacol. 2007;22(6):363-370. doi:10.1097/YIC.0b013e32816f7779

43. Nasrallah HA, Newcomer JW, Risinger R, et al. Effect of Aripiprazole Lauroxil on Metabolic and Endocrine Profiles and Related Safety Considerations Among Patients With Acute Schizophrenia. J Clin Psychiatry. 2016;77(11):1519-1525. doi:10.4088/JCP.15m10467

44. Chrzanowski WK, Marcus RN, Torbeyns A, Nyilas M, McQuade RD. Effectiveness of long-term aripiprazole therapy in patients with acutely relapsing or chronic, stable schizophrenia: a 52-week, open-label comparison with olanzapine. Psychopharmacology (Berl). 2006;189(2):259-266. doi:10.1007/s00213-006-0564-3

45. Chan H-Y, Lin W-W, Lin S-K, et al. Efficacy and safety of aripiprazole in the acute treatment of schizophrenia in Chinese patients with risperidone as an active control: a randomized trial. J Clin Psychiatry. 2007;68(1):29-36.

46. Nasrallah HA, Aquila R, Du Y, Stanford AD, Claxton A, Weiden PJ. Long-term safety and tolerability of aripiprazole lauroxil in patients with schizophrenia. CNS Spectr. August 2018:1-9. doi:10.1017/S1092852918001104

47. Saphris (asenapine) [package insert]. Irvine, CA: Allergan Inc.; February 2017.

48. Kane JM, Mackle M, Snow-Adami L, Zhao J, Szegedi A, Panagides J. A Randomized Placebo-Controlled Trial of Asenapine for the Prevention of Relapse of Schizophrenia After Long-Term Treatment. J Clin Psychiatry. 2011;72(3):349-355. doi:10.4088/JCP.10m06306

49. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. Asenapine for long-term treatment of bipolar disorder: A double-blind 40-week extension study. J Affect Disord. 2010;126(3):358-365. doi:10.1016/j.jad.2010.04.005

50. Landbloom R, Mackle M, Wu X, et al. Asenapine for the treatment of adults with an acute exacerbation of schizophrenia: results from a randomized, double-blind, fixed-dose, placebo-controlled trial with olanzapine as an active control. CNS Spectr. 2017;22(4):333-341. doi:10.1017/S1092852916000377

51. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. Asenapine in the treatment of acute mania in bipolar I disorder: A randomized, double-blind, placebo-controlled trial. J Affect Disord. 2010;122(1):27-38. doi:10.1016/j.jad.2009.12.028

52. Landbloom RL, Mackle M, Wu X, et al. Asenapine: Efficacy and safety of 5 and 10mg bid in a 3-week, randomized, double-blind, placebo-controlled trial in adults with a manic or mixed episode associated with bipolar I disorder. J Affect Disord. 2016;190:103-110. doi:10.1016/j.jad.2015.06.059

53. Kane JM, Cohen M, Zhao J, Alphs L, Panagides J. Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. J Clin Psychopharmacol. 2010;30(2):106-115. doi:10.1097/JCP.0b013e3181d35d6b

54. Kane JM, Skuban A, Ouyang J, et al. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. Schizophr Res. 2015;164(1-3):127-135. doi:10.1016/j.schres.2015.01.038

55. Fleischhacker WW, Hobart M, Ouyang J, et al. Efficacy and Safety of Brexpiprazole (OPC-34712) as Maintenance Treatment in Adults with Schizophrenia: a Randomized, Double-Blind, Placebo-Controlled Study. Int J Neuropsychopharmacol. 2017;20(1):11-21. doi:10.1093/ijnp/pyw076

56. Thase ME, Youakim JM, Skuban A, et al. Adjunctive Brexpiprazole 1 and 3 mg for Patients With Major Depressive Disorder Following Inadequate Response to Antidepressants: A Phase 3, Randomized, Double-Blind Study. J Clin Psychiatry. 2015;76(9):1232-1240. doi:10.4088/JCP.14m09689

57. Thase ME, Youakim JM, Skuban A, et al. Efficacy and Safety of Adjunctive Brexpiprazole 2 mg in Major Depressive Disorder: A Phase 3, Randomized, Placebo-Controlled Study in Patients With Inadequate Response to Antidepressants. J Clin Psychiatry. 2015;76(9):1224-1231. doi:10.4088/JCP.14m09688

58. Study to Evaluate the Efficacy, Safety, and Tolerability of Oral OPC-34712 and Aripiprazole for Treatment of Acute Schizophrenia - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT00905307. Accessed April 28, 2019.

59. Otsuka Pharmaceutical Development & Commercialization, Inc. Multicenter, Open-label, Safety and Tolerability Study (STEP 210). From: https://clinicaltrials.gov/ct2/show/NCT01649557. Identifier: NCT01649557. Accessed May 30, 2019.

60. Correll CU, Skuban A, Ouyang J, et al. Efficacy and Safety of Brexpiprazole for the Treatment of Acute Schizophrenia: A 6-Week Randomized, Double-Blind, Placebo-Controlled Trial. Am J Psychiatry. 2015;172(9):870-880. doi:10.1176/appi.ajp.2015.14101275

61. Forbes A, Hobart M, Ouyang J, Shi L, Pfister S, Hakala M. A Long-Term, Open-Label Study to Evaluate the Safety and Tolerability of Brexpiprazole as Maintenance Treatment in Adults with Schizophrenia. Int J Neuropsychopharmacol. 2018;21(5):433-441. doi:10.1093/ijnp/pyy002

62. Durgam S, Earley W, Lipschitz A, et al. An 8-Week Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Cariprazine in Patients With Bipolar I Depression. Am J Psychiatry. 2016;173(3):271-281. doi:10.1176/appi.ajp.2015.15020164

63. Durgam S, Starace A, Li D, et al. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: a phase II, randomized clinical trial. Schizophr Res. 2014;152(2-3):450-457. doi:10.1016/j.schres.2013.11.041

64. Durgam S, Cutler AJ, Lu K, et al. Cariprazine in acute exacerbation of schizophrenia: a fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. J Clin Psychiatry. 2015;76(12):e1574-1582. doi:10.4088/JCP.15m09997

65. Sachs GS, Greenberg WM, Starace A, et al. Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, phase III trial. J Affect Disord. 2015;174:296-302. doi:10.1016/j.jad.2014.11.018

66. Durgam S, Litman RE, Papadakis K, Li D, Németh G, Laszlovszky I. Cariprazine in the treatment of schizophrenia: a proof-of-concept trial. Int Clin Psychopharmacol. 2016;31(2):61-68. doi:10.1097/YIC.0000000000000110

67. Németh G, Laszlovszky I, Czobor P, et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. The Lancet. 2017;389(10074):1103-1113. doi:10.1016/S0140-6736(17)30060-0

68. Durgam S, Earley W, Guo H, et al. Efficacy and Safety of Adjunctive Cariprazine in Inadequate Responders to Antidepressants: A Randomized, Double-Blind, Placebo-Controlled Study in Adult Patients With Major Depressive Disorder. J Clin Psychiatry. 2016;77(3):371-378. doi:10.4088/JCP.15m10070

69. Kane JM, Zukin S, Wang Y, et al. Efficacy and Safety of Cariprazine in Acute Exacerbation of Schizophrenia: Results From an International, Phase III Clinical Trial. J Clin Psychopharmacol. 2015;35(4):367-373. doi:10.1097/JCP.0000000000000346

70. Calabrese JR, Keck PE, Starace A, et al. Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated with bipolar I disorder: a double-blind, placebo-controlled study. J Clin Psychiatry. 2015;76(3):284-292. doi:10.4088/JCP.14m09081

71. Cutler AJ, Durgam S, Wang Y, et al. Evaluation of the long-term safety and tolerability of cariprazine in patients with schizophrenia: results from a 1-year open-label study. CNS Spectr. 2018;23(1):39-50. doi:10.1017/S1092852917000220

72. Weiden PJ, Citrome L, Alva G, et al. A trial evaluating gradual- or immediate-switch strategies from risperidone, olanzapine, or aripiprazole to iloperidone in patients with schizophrenia. Schizophr Res. 2014;153(1-3):160-168. doi:10.1016/j.schres.2013.11.042

73. Weiden PJ, Cutler AJ, Polymeropoulos MH, Wolfgang CD. Safety profile of iloperidone: a pooled analysis of 6-week acute-phase pivotal trials. J Clin Psychopharmacol. 2008;28(2 Suppl 1):S12-19. doi:10.1097/JCP.0b013e3181694f5a

74. Cutler AJ, Kalali AH, Weiden PJ, Hamilton J, Wolfgang CD. Four-Week, Double-Blind, Placebo- and Ziprasidone-Controlled Trial of Iloperidone in Patients With Acute Exacerbations of Schizophrenia: J Clin Psychopharmacol. 2008;28(Suppl. 1):S20-S28. doi:10.1097/JCP.0b013e318169d4ce

75. Kane JM, Lauriello J, Laska E, Di Marino M, Wolfgang CD. Long-Term Efficacy and Safety of Iloperidone: Results From 3 Clinical Trials for the Treatment of Schizophrenia. J Clin Psychopharmacol. 2008;28(Suppl. 1):S29-S35. doi:10.1097/JCP.0b013e318169cca7

76. Cutler AJ, Kalali AH, Mattingly GW, Kunovac J, Meng X. Long-term safety and tolerability of iloperidone: results from a 25-week, open-label extension trial. CNS Spectr. 2013;18(1):43-54. doi:10.1017/S1092852912000764

77. Weiden PJ, Manning R, Wolfgang CD, et al. A Randomized Trial of Iloperidone for Prevention of Relapse in Schizophrenia: The REPRIEVE Study. CNS Drugs. 2016;30(8):735-747. doi:10.1007/s40263-016-0345-4

78. Potkin SG, Kimura T, Guarino J. A 6-week, double-blind, placebo- and haloperidol-controlled, phase II study of lurasidone in patients with acute schizophrenia. Ther Adv Psychopharmacol. 2015;5(6):322-331. doi:10.1177/2045125315606027

79. Loebel AD, Siu CO, Cucchiaro JB, Pikalov AA, Harvey PD. Daytime sleepiness associated with lurasidone and quetiapine XR: results from a randomized double-blind, placebo-controlled trial in patients with schizophrenia. CNS Spectr. 2014;19(2):197-205. doi:10.1017/S1092852913000904

80. Stahl SM, Cucchiaro J, Simonelli D, Hsu J, Pikalov A, Loebel A. Effectiveness of lurasidone for patients with schizophrenia following 6 weeks of acute treatment with lurasidone, olanzapine, or placebo: a 6-month, open-label, extension study. J Clin Psychiatry. 2013;74(5):507-515. doi:10.4088/JCP.12m08084

81. Loebel A, Cucchiaro J, Xu J, Sarma K, Pikalov A, Kane JM. Effectiveness of lurasidone vs. quetiapine XR for relapse prevention in schizophrenia: a 12-month, double-blind, noninferiority study. Schizophr Res. 2013;147(1):95-102. doi:10.1016/j.schres.2013.03.013

82. Loebel A, Cucchiaro J, Sarma K, et al. Efficacy and safety of lurasidone 80 mg/day and 160 mg/day in the treatment of schizophrenia: a randomized, double-blind, placebo- and active-controlled trial. Schizophr Res. 2013;145(1-3):101-109. doi:10.1016/j.schres.2013.01.009

83. Correll CU, Cucchiaro J, Silva R, Hsu J, Pikalov A, Loebel A. Long-term safety and effectiveness of lurasidone in schizophrenia: a 22-month, open-label extension study. CNS Spectr. 2016;21(5):393-402. doi:10.1017/S1092852915000917

84. Citrome L, Cucchiaro J, Sarma K, et al. Long-term safety and tolerability of lurasidone in schizophrenia: a 12-month, double-blind, active-controlled study. Int Clin Psychopharmacol. 2012;27(3):165-176. doi:10.1097/YIC.0b013e32835281ef

85. Loebel A, Silva R, Goldman R, et al. Lurasidone Dose Escalation in Early Nonresponding Patients With Schizophrenia: A Randomized, Placebo-Controlled Study. J Clin Psychiatry. 2016;77(12):1672-1680. doi:10.4088/JCP.16m10698

86. Nasrallah HA, Silva R, Phillips D, et al. Lurasidone for the treatment of acutely psychotic patients with schizophrenia: a 6-week, randomized, placebo-controlled study. J Psychiatr Res. 2013;47(5):670-677. doi:10.1016/j.jpsychires.2013.01.020

87. Calabrese JR, Pikalov A, Streicher C, Cucchiaro J, Mao Y, Loebel A. Lurasidone in combination with lithium or valproate for the maintenance treatment of bipolar I disorder. Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol. 2017;27(9):865-876. doi:10.1016/j.euroneuro.2017.06.013

88. Nakamura M, Ogasa M, Guarino J, et al. Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. J Clin Psychiatry. 2009;70(6):829-836. doi:10.4088/JCP.08m04905

89. Ogasa M, Kimura T, Nakamura M, Guarino J. Lurasidone in the treatment of schizophrenia: a 6-week, placebo-controlled study. Psychopharmacology (Berl). 2013;225(3):519-530. doi:10.1007/s00213-012-2838-2

90. Meltzer HY, Cucchiaro J, Silva R, et al. Lurasidone in the Treatment of Schizophrenia: A Randomized, Double-Blind, Placebo- and Olanzapine-Controlled Study. Am J Psychiatry. 2011;168(9):957-967. doi:10.1176/appi.ajp.2011.10060907

91. Loebel A, Cucchiaro J, Silva R, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. Am J Psychiatry. 2014;171(2):160-168. doi:10.1176/appi.ajp.2013.13070984

92. Fleischhacker WW, Gopal S, Lane R, et al. A randomized trial of paliperidone palmitate and risperidone long-acting injectable in schizophrenia. Int J Neuropsychopharmacol. 2012;15(1):107-118. doi:10.1017/S1461145711001076

93. Gopal S, Hough DW, Xu H, et al. Efficacy and safety of paliperidone palmitate in adult patients with acutely symptomatic schizophrenia: a randomized, double-blind, placebo-controlled, dose-response study. Int Clin Psychopharmacol. 2010;25(5):247-256. doi:10.1097/YIC.0b013e32833948fa

94. Meltzer HY, Bobo WV, Nuamah IF, et al. Efficacy and tolerability of oral paliperidone extended-release tablets in the treatment of acute schizophrenia: pooled data from three 6-week, placebo-controlled studies. J Clin Psychiatry. 2008;69(5):817-829.

95. Davidson M, Emsley R, Kramer M, et al. Efficacy, safety and early response of paliperidone extended-release tablets (paliperidone ER): Results of a 6-week, randomized, placebo-controlled study. Schizophr Res. 2007;93(1):117-130. doi:10.1016/j.schres.2007.03.003

96. Kramer M, Litman R, Hough D, et al. Paliperidone palmitate, a potential long-acting treatment for patients with schizophrenia. Results of a randomized, double-blind, placebo-controlled efficacy and safety study. Int J Neuropsychopharmacol. 2010;13(5):635-647. doi:10.1017/S1461145709990988

97. Nussbaum AM, Stroup TS. Paliperidone palmitate for schizophrenia. Cochrane Database Syst Rev. 2012;(6). doi:10.1002/14651858.CD008296.pub2

98. Tzimos A, Samokhvalov V, Kramer M, et al. Safety and Tolerability of Oral Paliperidone Extended-Release Tablets in Elderly Patients With Schizophrenia: A Double-Blind, Placebo-Controlled Study With Six-Month Open-Label Extension. Am J Geriatr Psychiatry. 2008;16(1):31-43. doi:10.1097/JGP.0b013e31815a3e7a

99.Komossa K, Rummel-Kluge C, Schwarz S, et al. Risperidone versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2011;(1). doi:10.1002/14651858.CD006626.pub2

100.Rattehalli RD, Zhao S, Li BG, Jayaram MB, Xia J, Sampson S. Risperidone versus placebo for schizophrenia. Cochrane Database Syst Rev. 2016;(12). doi:10.1002/14651858.CD006918.pub3

101.Sampson S, Hosalli P, Furtado VA, Davis JM. Risperidone (depot) for schizophrenia. Cochrane Database Syst Rev. 2016;(4). doi:10.1002/14651858.CD004161.pub2

102.Sachs GS, Ice KS, Chappell PB, et al. Efficacy and safety of adjunctive oral ziprasidone for acute treatment of depression in patients with bipolar I disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2011;72(10):1413-1422. doi:10.4088/JCP.09m05934

103.Komossa K, Rummel-Kluge C, Hunger H, et al. Ziprasidone versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2009;(4). doi:10.1002/14651858.CD006627.pub2

104.Study Evaluating The Safety, Tolerability, And Efficacy Of Switching From Quetiapine To Ziprasidone - Study Results - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/results/NCT00406315. Accessed April 26, 2019.

105.Keck P, Buffenstein A, Ferguson J, et al. Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. Psychopharmacology (Berl). 1998;140(2):173-184. doi:https://doi-org.proxy.lib.umich.edu/10.1007/s002130050755

106.Daniel D, Zimbroff D, Potkin S, Reeves K, Harrigan E, Lakshmirarayanan M. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. https://www-ncbi-nlm-nih-gov.proxy.lib.umich.edu/pubmed/10192829. Accessed April 29, 2019.

107.Keck PE, Versiani M, Potkin S, West SA, Giller E, Ice K. Ziprasidone in the Treatment of Acute Bipolar Mania: A Three-Week, Placebo-Controlled, Double-Blind, Randomized Trial. Am J Psychiatry. 2003;160(4):741-748. doi:10.1176/appi.ajp.160.4.741

108.Vieta E, Ramey T, Keller D, English P, Loebel A, Miceli J. Ziprasidone in the treatment of acute mania: a 12-week, placebo-controlled, haloperidol-referenced study. J Psychopharmacol (Oxf). 2008;24(4):547-558. doi:10.1177/0269881108099418

109.Bowden CL, Vieta E, Ice KS, Schwartz JH, Wang PP, Versavel M. Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. J Clin Psychiatry. 2010;71(2):130-137. doi:10.4088/JCP.09m05482yel

110.Carnahan RM, Lund BC, Perry PJ. Ziprasidone, a new atypical antipsychotic drug. Pharmacotherapy. 2001;21(6):717-730.

111.Gao K, Kemp DE, Ganocy SJ, Gajwani P, Xia G, Calabrese JR. Antipsychotic-induced extrapyramidal side effects in bipolar disorder and schizophrenia: a systematic review. *J Clin Psychopharmacol*. 2008;28(2):203-209.

112. Poyurovsky M. Acute antipsychotic-induced akathisia revisited. *Br J Psychiatry*. 2010;196(2):89-91. doi:10.1192/bjp.bp.109.070540

113. Buckley PF. Efficacy of quetiapine for the treatment of schizophrenia: a combined analysis of three placebo-controlled trials. *Current Medical Research and Opinion*. 2004;20(9):1357-1363. doi:10.1185/030079904125004510

114. Potkin SG, Gharabawi GM, Greenspan AJ, et al. A double-blind comparison of risperidone, quetiapine and placebo in patients with schizophrenia experiencing an acute exacerbation requiring hospitalization. *Schizophrenia Research*. 2006;85(1):254-265. doi:10.1016/j.schres.2006.03.027

115. Nasrallah HA, Brecher M, Paulsson B. Placebo-level incidence of extrapyramidal symptoms (EPS) with quetiapine in controlled studies of patients with bipolar mania. *Bipolar Disorders*. 2006;8(5p1):467-474. doi:10.1111/j.1399-5618.2006.00350.x

116. Arvanitis LA, Miller BG. Multiple fixed doses of “Seroquel” (quetiapine) in patients with acute exacerbation of schizophrenia: A comparison with haloperidol and placebo. *Biological Psychiatry*. 1997;42(4):233-246. doi:10.1016/S0006-3223(97)00190-X

117. Miller CH, Mohr F, Umbricht D, Woerner M, Fleischhacker WW, Lieberman J. 756 - The prevalence of acute extrapyramidal signs and symptoms in patients treated with clozapine, risperidone and conventional antipsychotics. :2.

Tables

Table 1. Dosage recommendations and indications for included second-generation antipsychotics

Drug	Target dose† (mg/day)	Max dose† (mg/day)	FDA approved indication(s) for all available drug products
aripiprazole[20,21]	10-30	30	Schizophrenia; Bipolar disorder; MDD (adjunct); Irritability with autistic disorder; Tourette's disorder
asenapine[22]	10-20	20	Schizophrenia; Bipolar disorder
brexpiprazole[23]	2-4	4	Schizophrenia; MDD (adjunct)
cariprazine[24]	1.5-6	6	Schizophrenia; Bipolar disorder
iloperidone[25]	12-24	24	Schizophrenia
lurasidone[26]	40-160	160	Schizophrenia; Bipolar disorder
paliperidone[27,28]	3-12	12	Schizophrenia
risperidone[29,30]	4-8	16	Schizophrenia; Bipolar disorder; Irritability with autistic disorder
ziprasidone[31]	40-160	200	Schizophrenia; Bipolar disorder

†Reference dosage from product labeling of oral formulation for schizophrenia.

Table 2. Definitions of low and high doses of oral second-generation antipsychotic drugs[13,18]

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

Table 3. Overall incidence of akathisia in individual SGAs and placebo[32-111]

Diagnosis	Dosing Strategy	Dose Classification	No. of Studies	Patients (N)	Akathisia Incidence (n)	Rate (%)
aripiprazole						
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%**
aripiprazole LAI						
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%**
aripiprazole lauroxil						
Schizophrenia	Fixed	Target	2	893	40	4.48%
	Total		2	893	40	4.48%
aripiprazole lauroxil Total			**2**	**893**	**40**	**4.48%**
asenapine						
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%
	Total		5	2375	142	5.98%
asenapine Total			**9**	**3500**	**221**	**6.31%**
brexpiprazole						
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%
	Total		6	2876	165	5.74%
brexpiprazole Total			**8**	**3519**	**220**	**6.25%**
cariprazine						
Bipolar	Fixed	Low	1	287	11	3.83%
		Target	1	146	21	14.38%
	Flexible	Target	2	494	101	20.45%
	Total		3	927	133	14.35%
MDD	Flexible	Low	1	273	18	6.59%
		Target	1	273	61	22.34%
	Total		1	546	79	14.47%
Schizophrenia	Fixed	High	1	157	23	14.65%
		Low	1	145	13	8.97%
		Target	3	678	55	8.11%
	Flexible	High	2	281	37	13.17%
		Target	3	864	129	14.93%
	Total		6	2125	257	12.09%
cariprazine Total			**10**	**3598**	**469**	**13.04%**
iloperidone						
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%**
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	N/A	N/A	13	1696	51	3.01%
MDD	N/A	N/A	3	677	13	1.92%
Schizophrenia	N/A	N/A	47	6872	277	4.03%
placebo Total			**63**	**9245**	**341**	**3.69%**

Abbreviations: LAI, long-acting injectable; MDD, major depressive disorder, ER, extended-release.Target doses summarized in Table 1, high and low doses summarized in Table 2.

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%

Abbreviations: MDD, major depressive disorder.