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DERP VI Update Scan 2: Second-Generation Antipsychotic Drugs

November 2018



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Objectives

The purpose of this literature scan is to preview the volume and nature of new research that has emerged since the last update report on second-generation antipsychotic drugs. The literature search for this scan focuses on new randomized controlled trials (RCTs) and systematic reviews (with and without a meta-analysis), and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Comprehensive searches, quality assessment, and synthesis of evidence would follow only if Drug Effectiveness Review Project (DERP) participating organizations agreed to proceed with an update of the report or other research product.

Topic History

Scan #1: April 2017

Update #5: October 2016, searches through July 2016

Update #4: November 2013

Update #3: July 2010

Update #1: April 2006

Original Report: January 2005

Background and Context

Second-generation antipsychotic (SGA) agents, also called atypical antipsychotics, are a newer group of antipsychotic drugs that differ from older, conventional first-generation antipsychotics (FGAs or typical antipsychotics).¹ FGAs have been classified according to their chemical structure (i.e., serotonin-dopamine antagonists and multi-acting receptor-targeted antipsychotics), whereas SGAs have been categorized according to their pharmacological properties as dopamine partial agonists.² SGAs have been shown to have a lower incidence than FGAs of extrapyramidal side effects such as parkinsonism, dystonia, dyskinesia, and akathisia.³ Clozapine, the first available SGA, was introduced in 1989.¹ Since then, 11 other SGAs have been approved by the FDA: risperidone (1993), olanzapine (1996), quetiapine (1997), ziprasidone (2001), aripiprazole (2002), extended-release paliperidone (2006), asenapine (2009), iloperidone (2009), lurasidone (2010), brexpiprazole (2015), and cariprazine (2015).¹ SGAs differ from each other in receptor interaction, selection, and affinity, and these differences are thought to lead to variations in symptom response and adverse effects.¹

Key Questions

1. For adults and adolescents with schizophrenia (including a first episode) and other psychotic disorders, do SGAs differ from each other in benefits (efficacy, effectiveness) or harms?

2. For adults with major depressive disorder, do SGAs differ from each other in benefits (efficacy, effectiveness) or harms?
3. For adults with bipolar disorder, do SGAs differ from each other in benefits (efficacy, effectiveness) or harms?
4. For children and adolescents with bipolar disorder
 - a. Do SGAs differ from placebo in benefits (efficacy, effectiveness) or harms?
 - b. Do SGAs differ from each other in benefits (efficacy, effectiveness) or harms?
5. For children and adolescents with autism spectrum disorder
 - a. Do SGAs differ from placebo in benefits (efficacy, effectiveness) or harms?
 - b. Do SGAs differ from each other in benefits (efficacy, effectiveness) or harms?
6. For children and adolescents with disruptive, impulse control, and conduct disorders
 - a. Do SGAs differ from placebo in benefits (efficacy, effectiveness) or harms?
 - b. Do SGAs differ from each other in benefits (efficacy, effectiveness) or harms?
7. Are there subgroups of patients based on demographics, socioeconomic status, other medications, or comorbidities for which a particular SGA is more effective or associated with fewer harms?

Inclusion Criteria

Using the PICO outlined below, we screened our search results for eligible systematic reviews (with or without meta-analyses) and RCTs published since the implementation of the search strategy in the most recent scan, which occurred on March 2017.

Populations

Diagnosis based on Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (any version) is preferred, but we accepted investigator-defined criteria for diagnosis in the absence of DSM criteria.

- Adults (age 18 years or older) and adolescents (age 12 to 17 years) with a diagnosis of schizophrenia, including other psychotic disorders such as schizophreniform (< 6 months of schizophrenia symptoms),⁴ delusional and schizoaffective disorders, and including first-episode schizophrenia and patients refractory to treatment
- Adults (age 18 years or older), adolescents (age 12 to 17 years), and children (under age 12 years) with bipolar disorder (manic or depressive phases, rapid cycling, mixed states)
- Adults with major depressive disorder
- Children (under age 12 years) or adolescents (age 12 to 17 years) with a DSM-V diagnosis for autism spectrum disorder or a DSM-III-R or DSM-IV diagnosis for a pervasive developmental disorder, including autistic disorder, Rett's disorder, childhood disintegrative disorder, Asperger's disorder, and pervasive developmental disorder not otherwise specified
- Children (under age 12 years) or adolescents (age 12 to 17 years) with a DSM-V diagnosis of disruptive, impulse control, or conduct disorders or a DSM-III-R or DSM-IV diagnosis of a disruptive behavior disorder, including conduct disorders, oppositional defiant disorder, and disruptive behavior disorder not otherwise specified

Interventions

Table 1. Included Interventions

Generic Name	Brand Name and Form	Form	Populations*
Aripiprazole	Abilify	Oral tablet	Schizophrenia ^{a,b} Bipolar disorder ^{a,b,c} Autism spectrum disorder ^{b,c} Major depressive disorder ^a
	Abilify Maintena Kit	ER IM injection	Schizophrenia ^a Bipolar disorder ^a
Aripiprazole Lauroxil	Aristada	ER IM injection	Schizophrenia ^a
Asenapine	Saphris	Sublingual tablet	Schizophrenia ^a Bipolar disorder ^{a,b}
Brexiprazole	Rexulti	Oral tablet	Schizophrenia ^a Major depressive disorder ^a
Cariprazine	Vraylar	Oral capsule	Schizophrenia ^a Bipolar disorder ^a
Clozapine	Clozaril	Oral tablet	Schizophrenia ^a
	Fazaclo	ODT	
	Versacloz	Oral suspension	
Iloperidone	Fanapt	Oral tablet	Schizophrenia ^a
Lurasidone	Latuda	Oral tablet	Schizophrenia ^{a,b} Bipolar disorder ^{a,b,c}
Olanzapine	Zyprexa	Oral tablet, IM injection	Schizophrenia ^{a,b} Bipolar disorder ^{a,b}
	Zyprexa Zydis	ODT	
Olanzapine Pamoate	Zyprexa Relprevv	ER IM injection	Schizophrenia ^a
Paliperidone	Invega	ER oral tablet	Schizophrenia ^{a,b} Schizoaffective disorder ^a
Paliperidone Palmitate	Invega Sustenna	ER IM injection	Schizophrenia ^a Schizoaffective disorder ^a
	Invega Trinza	ER IM injection	Schizophrenia ^a
Quetiapine	Seroquel	Oral tablet	Schizophrenia ^{a,b} Bipolar disorder ^{a,b,c}

Generic Name	Brand Name and Form	Form	Populations*
	Seroquel XR	ER oral tablet	Schizophrenia ^{a,b} Bipolar disorder ^{a,b,c} Major depressive disorder ^a
Risperidone	Risperdal	Oral tablet, oral solution	Schizophrenia ^{a,b} Bipolar disorder ^{a,b,c}
	Risperdal M-TAB	ODT	Autism spectrum disorder ^{b,c}
	Risperdal Consta	Long-acting IM injection	Schizophrenia ^a Bipolar disorder ^a
Ziprasidone	Geodon	Oral capsule, IM injection	Schizophrenia ^a Bipolar disorder ^a

Note. * Overview of populations with FDA-approved indications; full details available in product labels. Abbreviations. ER: extended-release; IM: intramuscular; Max: maximum; MDD: major depressive disorder; ODT: orally disintegrating tablet; XR: extended-release. ^a Adults, ^b Adolescents, ^c Children.

Comparators

- Head-to-head
 - All populations
- Placebo
 - Children and adolescents with bipolar disorder, autism spectrum disorder, or disruptive, impulse control, or conduct disorders
 - Adults with major depressive disorder (add-on or background therapy)

Outcomes

Effectiveness and Efficacy (all populations)

- Quality of life (validated scales)
- Functional capacity (e.g., social, academic, activities of daily living, employment, and encounters with legal system)
- Hospitalization (because of mental illness and all-cause), emergency department visits
- Persistence; ability to continue taking medication over time
- Excluded: very short-term studies that focused exclusively on treatment of acute agitation associated with schizophrenia or bipolar disorder

Effectiveness and Efficacy (population-specific)

Adults and adolescents with schizophrenia and other psychotic disorders, first-episode schizophrenia, bipolar disorder, and major depressive disorder:

- Mortality

- Symptom response (e.g., global state, mental state, positive and negative symptoms), response rates, duration of response, remission, relapse, speed of response, time to discontinuation of medication

Children and adolescents with autism spectrum disorder:

- Symptom response (e.g., global state, irritability, aggressiveness, and self-injurious behavior) response rates, duration of response, remission, relapse, speed of response, time to discontinuation of medication

Children and adolescents with disruptive, impulse control, and conduct disorders:

- Symptom response (e.g., global state, irritability, noncompliance, aggressive conduct, property damage, theft)
- Disciplinary consequences (e.g., detention, suspension, encounters with legal system)

Harms

- Overall adverse events
- Withdrawals due to adverse events, time to withdrawal due to adverse events
- Specific adverse event
 - Major: those that are life-threatening, result in long-term morbidity, or require medical intervention to treat (e.g., mortality, cardiovascular and cerebrovascular disease-related events, development of diabetes mellitus, diabetic ketoacidosis, neuroleptic malignant syndrome, seizures, tardive dyskinesia, cardiomyopathies and cardiac arrhythmias, and agranulocytosis)
 - General: incidence of extrapyramidal adverse events, clinically important weight change, and metabolic syndrome and incidence and severity of sexual adverse events

Methods

We searched the FDA website to identify newly approved drugs/formulations, new indications, and new serious harms (e.g., boxed warnings) for included interventions. To identify new drugs, we also searched CenterWatch, a privately owned database of clinical trials information and conducted an internet search using Google. To identify relevant literature, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from March 2017 through September 2018 using terms for included drugs and limits for English language and humans. We also conducted an internet search using Google and Google Scholar with key words for included drugs.

Findings

New Drugs and Formulations

We identified no newly approved SGA drugs since the last scan. However, we did identify 3 newly approved formulations of SGA drugs since the last scan (Table 2). These new formulations are aimed at addressing issues of medication compliance and continuity of care as patients transition from inpatient to outpatient care.⁵

The Abilify MyCite Kit (aripiprazole oral tablet) is a drug-device combination product (“digital medicine system”) consisting of aripiprazole tablets embedded with an Ingestible Event Marker (IEM) sensor intended to track drug ingestion. The kit includes the drug (Abilify MyCite), the MyCite patch (wearable sensor), the MyCite app (smartphone application), and web-based portals for healthcare providers and caregivers.⁶ This new formulation is approved for daily dosing in adults with schizophrenia, bipolar disorder, or major depressive disorder.

The Aristada Initio Kit (aripiprazole lauroxil extended-release intramuscular injection) is approved for the initiation of Aristada (aripiprazole) for adults with schizophrenia.⁵ Aristada Initio and Aristada both contain aripiprazole, but the 2 medications are not interchangeable because of differing pharmacokinetic profiles.⁵ The new Aristada Initio formulation allows for faster dissolution and quicker dose achievement of aripiprazole.⁵

The Perseris Kit (risperidone extended-release subcutaneous suspension) is approved for the treatment of schizophrenia in adults.⁷ This formulation is administered monthly and is constituted by combining the liquid and powder components via syringe.⁷

Table 2. Newly Approved Formulations

Generic Name	Brand Name	Date of FDA Approval	Formulation	Frequency of administration	Indication
Aripiprazole	Abilify MyCite Kit	11/13/2017	Oral tablet	1 dose daily	Adults with schizophrenia, bipolar disorder, or MDD
Aripiprazole Lauroxil	Aristada Initio Kit	6/28/2018	ER IM injection	Single dose in conjunction with first dose or oral aripiprazole	Adults with schizophrenia
Risperidone	Perseris ^a Kit	7/27/2018	ER SC suspension	1 dose per month	Adults with schizophrenia

Abbreviations. ER: extended release; IM: intramuscular; MDD: major depressive disorder; SC: subcutaneous. Note. ^a Manufacturer identifier RBP-7000.

New Indications

Since the last scan on this topic, we have identified 2 new indications for SGA drugs. On July 27, 2017, the Abilify Maintena Kit (aripiprazole extended-release intramuscular injection) received an expanded indication for maintenance monotherapy treatment of bipolar disorder in adults.⁸ On March 5, 2018, Latuda (lurasidone oral tablet) received an expanded indication for monotherapy treatment of bipolar disorder in pediatric patients ages 10 to 17 years.⁹

New Serious Harms

We identified no new boxed warnings for SGA drugs.

Systematic Reviews

Since the last update of the report, we have identified 4 new systematic reviews, 1 of which was identified in the prior scan.¹⁰ Of the 3 systematic reviews that were identified in this scan (Table 3),¹¹⁻¹³ 2 reviews pertain to treatment of adults with either bipolar disorder¹¹ or schizophrenia¹³ and 1 review pertains to treatment of children with disruptive behavior disorders.¹²

Table 3. Characteristics of Systematic Reviews

Author, Year Organization	Population	Interventions	Outcomes
Butler et al., 2018 ¹¹ AHRQ	Adults with bipolar disorder	Aripiprazole, asenapine, cariprazine, olanzapine, quetiapine, risperidone, ziprasidone (vs. placebo or active comparator)	Functional capacity, quality of life, symptom response, adverse events
Loy et al., 2017 ¹² Cochrane	Children with disruptive behavior disorders	Risperidone, quetiapine, ziprasidone (vs. placebo)	Symptom response, adverse events, functional capacity
McDonagh et al., 2017 ¹³ AHRQ	Adults with schizophrenia	SGAs compared with SGAs	Functional capacity, symptom response, quality of life, adverse events

Randomized Controlled Trials

Since the last update of the report on this topic, we identified 5 new head-to-head trials,¹⁴⁻¹⁸ 4 new secondary analyses of head-to-head trials,¹⁹⁻²² and 5 new placebo-controlled trials.²³⁻²⁷ Of these, we identified 4 new head-to-head trials,¹⁴⁻¹⁷ 4 new placebo-controlled trials,²³⁻²⁶ and 2 new secondary analyses^{19,20} in this scan (Tables 4 to 6). Of the new head-to-head trials, all assessed the treatment of schizophrenia; 3 compared olanzapine to paliperidone palmitate,¹⁴ risperidone,¹⁶ and ziprasidone¹⁷; and the other eligible head-to-head trial compared risperidone and cariprazine.¹⁵ Both secondary analyses reported additional outcomes of the QUALIFY trial in adults with schizophrenia. Two of the 4 placebo-controlled trials involved aripiprazole in the treatment of children and adolescents with bipolar disorder²⁴ or autism spectrum disorder.²⁵ The other 2 placebo-controlled trials involved lurasidone for children and adolescents with bipolar depression²³ and a combination of risperidone and methylphenidate for children with comorbid oppositional defiant disorder and attention deficit hyperactivity disorder (ADHD).²⁶

Table 4. Characteristics of New Head-to-Head Trials

Author, Year	N Duration	Population	Intervention	Comparator	Outcomes
Huang et al., 2018 ¹⁴	57 13 weeks	Adolescents and adults with first-episode schizophrenia	Olanzapine	Paliperidone palmitate	Symptom response, weight change
Noordsy et al., 2017 ¹⁶	107 18 months	Adults with schizophrenia	Olanzapine	Risperidone	Hospitalization, persistence on medication
Wang et al., 2017 ¹⁷	148 12 weeks	Adolescents and adults with schizophrenia	Olanzapine ^a	Ziprasidone ^a	Symptom response, weight change, adverse events
Nemeth et al., 2017 ¹⁵	461 26 weeks	Adults with schizophrenia	Risperidone	Cariprazine	Symptom response, adverse events

Abbreviation. NR: not reported. Note. ^a Trial involved switching from olanzapine to ziprasidone and compared each arm to combination of olanzapine + ziprasidone.

Table 5. Characteristics of New Secondary Analyses of Head-to-Head Trials

Author, Year	N Population Duration	Primary Trial	Comparison	Outcomes
Potkin et al., 2017a ²⁰	295 Adults with schizophrenia 28 weeks	QUALIFY	Aripiprazole once-monthly vs. paliperidone palmitate	Sexual dysfunction
Potkin et al., 2017b ¹⁹	295 Adults with schizophrenia 28 weeks	QUALIFY	Aripiprazole once-monthly vs. paliperidone palmitate	Work-related function, symptom response, quality of life

Table 6. Characteristics of New Placebo-Controlled Trials

Author, Year	N Duration	Population	Intervention	Outcomes
Findling et al., 2017 ²⁴	59 12 weeks	Children and adolescents symptomatic and at high risk for bipolar disorder	Aripiprazole	Symptom response, adverse events
Ichikawa et al., 2017 ²⁵	92 8 weeks	Japanese children and adolescents with autism spectrum disorder	Aripiprazole	Symptom response, adverse events
DelBello et al., 2017 ²³	347 6 weeks	Children and adolescents with bipolar depression	Lurasidone	Symptom response, adverse events
Jahangard et al., 2017 ²⁶	84 8 weeks	Children with oppositional defiant disorder and ADHD	Risperidone + methylphenidate	Symptom response, weight change

Summary

- We identified no newly approved SGAs since the last update of the report. However, we have identified 3 newly approved formulations of SGAs, all of which were identified in this scan:
 - Abilify MyCite Kit (aripiprazole oral tablet)
 - Aristada Initio Kit (aripiprazole lauroxil extended-release intramuscular injection)
 - Perseris Kit (risperidone extended-release subcutaneous suspension)
- We identified 2 new indications for SGAs, both of which were identified in this scan:
 - Expanded indication for Abilify Maintena Kit for maintenance monotherapy treatment of bipolar disorder in adults
 - Expanded indication for Latuda (lurasidone oral tablet) for monotherapy treatment of bipolar disorder in pediatric patients ages 10 to 17 years
- We identified no new boxed warnings since the last update of the report.
- We identified 4 new systematic reviews since the last update of the report, 3 of which were identified in this scan:
 - 2 AHRQ reviews (adults with bipolar disorder or schizophrenia) and 1 Cochrane review (children with disruptive behavior disorders)

- We identified 5 new head-to-head trials, 4 new secondary analyses of head-to-head trials, and 5 new placebo-controlled trials, of which 4 head-to-head trials, 2 secondary analyses of head-to-head trials, and 4 placebo-controlled trials were identified in this scan:
 - All new head-to-head trials assessed the treatment of schizophrenia; 3 compared olanzapine to paliperidone palmitate, risperidone, and ziprasidone, and the other eligible head-to-head trial compared risperidone and cariprazine
 - Both secondary analyses reported additional outcomes of the QUALIFY trial in adults with schizophrenia
 - Two of the 4 placebo-controlled trials involved aripiprazole in the treatment of children and adolescents with bipolar disorder or autism spectrum disorder; the other 2 placebo-controlled trials involved lurasidone for children and adolescents with bipolar depression and a combination of risperidone and methylphenidate for children with comorbid oppositional defiant disorder and ADHD

References

1. McDonagh M, Selph S, Blazina I, et al. *Drug class review: second-generation antipsychotic drugs: draft for final approval update 5 report*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2016.
2. Abou-Setta A, Mousavi S, Spooner C, et al. First-generation versus second-generation antipsychotics in adults: comparative effectiveness. Comparative Effectiveness Review No. 63. (Prepared by the University of Alberta Evidence-based Practice Center under Contract No. 290-2007-10021.) AHRQ Publication No. 12-EHC054-EF. Rockville, MD: Agency for Healthcare Research and Quality. 2012; www.effectivehealthcare.ahrq.gov/reports/final.cfm.
3. 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.
4. Fischer BA, Buchanan RW. Schizophrenia in adults: clinical manifestations, course, assessment, and diagnosis. 2018; https://www.uptodate.com/contents/schizophrenia-in-adults-clinical-manifestations-course-assessment-and-diagnosis?search=schizophreniform&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed October 12, 2018.
5. PR Newswire. FDA approves ARISTADA INITIO™ for the initiation of ARISTADA® for schizophrenia. 2018; <https://www.prnewswire.com/news-releases/fda-approves-aristada-initio-for-the-initiation-of-aristada-for-schizophrenia-300675138.html>. Accessed September 25, 2018.
6. Proteus Digital Health. Otsuka and Proteus® announce the first U.S. FDA approval of a digital medicine system: Abilify MyCite® (aripiprazole tablets with sensor). 2017; <https://www.proteus.com/press-releases/otsuka-and-proteus-announce-the-first-us-fda-approval-of-a-digital-medicine-system-abilify-mycite/>. Accessed September 25, 2018.
7. U.S. Food and Drug Administration. Perseris (risperidone) product label. 2018; https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210655s000lbl.pdf. Accessed September 25, 2018.
8. U.S. Food and Drug Administration. Abilify Maintena (aripiprazole) product label. 2017; https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/202971s010lbl.pdf. Accessed September 25, 2018.

9. U.S. Food and Drug Administration. Latuda (lurasidone) product label. 2018; https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/200603s029lbl.pdf. Accessed September 25, 2018.
10. Pillay J, Boylan K, Carrey N, et al. First- and second-generation antipsychotics in children and young adults: systematic review update. Comparative Effectiveness Review No. 184. (Prepared by the University of Alberta Evidence-based Practice Center under Contract No. 290-2015-00001-I.) AHRQ Publication No. 17-EHC001-EF. Rockville, MD: Agency for Healthcare Research and Quality. 2017; www.effectivehealthcare.ahrq.gov/reports/final/cfm.
11. Butler M, Urosevic S, Desai P, et al. Treatment for bipolar disorder in adults: a systematic review. Comparative Effectiveness Review No. 208. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2012-00016-I.) AHRQ Publication No. 18-EHC012-EF. Rockville, MD: Agency for Healthcare Research and Quality. 2018. doi: <https://doi.org/10.23970/AHRQEPCCER208>.
12. Loy JH, Merry SN, Hetrick SE, Stasiak K. Atypical antipsychotics for disruptive behaviour disorders in children and youths. *Cochrane Database Syst Rev*. 2017;8:CD008559. doi: <https://dx.doi.org/10.1002/14651858.CD008559.pub3>.
13. McDonagh M, Dana T, Selph S, et al. Treatments for schizophrenia in adults: a systematic review. Comparative Effectiveness Review No. 198. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290- 2015-00009-I.) AHRQ Publication No. 17(18)-EHC031-EF. Rockville, MD: Agency for Healthcare Research and Quality. 2017. doi: <https://doi.org/10.23970/AHRQEPCCER198>.
14. Huang M, Yu L, Pan F, et al. A randomized, 13-week study assessing the efficacy and metabolic effects of paliperidone palmitate injection and olanzapine in first-episode schizophrenia patients. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;81:122-130. doi: <https://dx.doi.org/10.1016/j.pnpbp.2017.10.021>.
15. Nemeth 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. *Lancet*. 2017;389(10074):1103-1113. doi: [https://dx.doi.org/10.1016/S0140-6736\(17\)30060-0](https://dx.doi.org/10.1016/S0140-6736(17)30060-0).
16. Noordsy DL, Glynn SM, Sugar CA, O'Keefe CD, Marder SR. Risperidone versus olanzapine among patients with schizophrenia participating in supported employment: eighteen-month outcomes. *J Psychiatr Res*. 2017;95:299-307. doi: <https://dx.doi.org/10.1016/j.jpsychires.2017.09.008>.

17. Wang HH, Cai M, Wang HN, et al. An assessor-blinded, randomized comparison of efficacy and tolerability of switching from olanzapine to ziprasidone and the combination of both in schizophrenia spectrum disorders. *J Psychiatr Res*. 2017;85:59-65. doi: <https://dx.doi.org/10.1016/j.jpsychires.2016.11.002>.
18. Lamberti M, Siracusano R, Italiano D, et al. Head-to-head comparison of aripiprazole and risperidone in the treatment of ADHD symptoms in children with autistic spectrum disorder and ADHD: a pilot, open-label, randomized controlled study. *Paediatr Drugs*. 2016;18(4):319-329. doi: 10.1007/s40272-016-0183-3.
19. Potkin SG, Loze JY, Forray C, et al. Multidimensional assessment of functional outcomes in schizophrenia: results from QUALIFY, a head-to-head trial of aripiprazole once-monthly and paliperidone palmitate. *Int J Neuropsychopharmacol*. 2017b;20(1):40-49. doi: <https://dx.doi.org/10.1093/ijnp/pyw093>.
20. Potkin SG, Loze JY, Forray C, et al. Reduced sexual dysfunction with aripiprazole once-monthly versus paliperidone palmitate: results from QUALIFY. *Int Clin Psychopharmacol*. 2017a;32(3):147-154. doi: <https://dx.doi.org/10.1097/YIC.000000000000168>.
21. Ceskova E, Prikryl R, Libiger J, Svancara J, Jarkovsky J. Gender differences in the treatment of first-episode schizophrenia: results from the European First Episode Schizophrenia Trial. *Schizophr Res*. 2015;169(1-3):303-307. doi: 10.1016/j.schres.2015.10.013.
22. Volavka J, Czobor P, Citrome L, Van Dorn RA. Effectiveness of antipsychotic drugs against hostility in patients with schizophrenia in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. *CNS Spectr*. 2014;19(5):374-381. doi: 10.1017/s1092852913000849.
23. DelBello MP, Goldman R, Phillips D, Deng L, Cucchiaro J, Loebel A. Efficacy and safety of lurasidone in children and adolescents with bipolar I depression: a double-blind, placebo-controlled study. *J Am Acad Child Adolesc Psychiatry*. 2017;56(12):1015-1025. doi: <https://dx.doi.org/10.1016/j.jaac.2017.10.006>.
24. Findling RL, Youngstrom EA, Rowles BM, et al. A double-blind and placebo-controlled trial of aripiprazole in symptomatic youths at genetic high risk for bipolar disorder. *J Child Adolesc Psychopharmacol*. 2017;27(10):864-874. doi: <https://dx.doi.org/10.1089/cap.2016.0160>.
25. Ichikawa H, Mikami K, Okada T, et al. Aripiprazole in the treatment of irritability in children and adolescents with autism spectrum disorder in Japan: a randomized, double-blind, placebo-controlled study. *Child Psychiatry Hum Dev*. 2017;48(5):796-806. doi: <https://dx.doi.org/10.1007/s10578-016-0704-x>.

26. Jahangard L, Akbarian S, Haghghi M, et al. Children with ADHD and symptoms of oppositional defiant disorder improved in behavior when treated with methylphenidate and adjuvant risperidone, though weight gain was also observed--results from a randomized, double-blind, placebo-controlled clinical trial. *Psychiatry Res.* 2017;251:182-191. doi: <https://dx.doi.org/10.1016/j.psychres.2016.12.010>.
27. Findling RL, Landbloom RL, Mackle M, et al. Long-term safety of asenapine in pediatric patients diagnosed with bipolar I disorder: a 50-week open-label, flexible-dose trial. *Paediatr Drugs.* 2016;18(5):367-378. doi: 10.1007/s40272-016-0184-2.

Appendix A. Abstracts of Relevant Randomized Controlled Trials

Head-to-Head Trials

Huang M, Yu L, Pan F, et al. A randomized, 13-week study assessing the efficacy and metabolic effects of paliperidone palmitate injection and olanzapine in first-episode schizophrenia patients. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;81:122-130. doi: <https://dx.doi.org/10.1016/j.pnpbp.2017.10.021>.

BACKGROUND: This study was conducted to evaluate the efficacy and metabolic effects of paliperidone palmitate (PP) injections against oral olanzapine in first-episode schizophrenia (FES) patients. **METHODS:** Eligible patients were randomized to receive PP or olanzapine. Efficacy assessments and weight-related parameters were assessed at baseline, weeks 1, 5, 9, and endpoint or at early withdrawal. Lipid, glucose, insulin and prolactin were evaluated at baseline and endpoint or at early withdrawal. **RESULTS:** The Positive And Negative Syndrome Scale (PANSS) scores declined significantly after treatment in both groups. Significant increases in weight-related parameters from baseline to endpoint were shown in both groups. Although there was no significant difference in PANSS scores and weight-related parameters between the two groups through the whole 13-week study. The increased level of triglyceride and HOMA-IR at endpoint from baseline in the olanzapine group was higher than the PP group. There was a stronger elevation of prolactin level in the PP group. **CONCLUSIONS:** In summary, PP and olanzapine showed similar improvement in the treatment of FES patients. This study also reinforced the necessity for regular monitoring of metabolic parameters in schizophrenia patients prescribed atypical antipsychotics. Clinical trial registration numbers: ChiCTR-IOR-14005304. Date of registration: 2014-10-11.

Lamberti M, Siracusano R, Italiano D, et al. Head-to-head comparison of aripiprazole and risperidone in the treatment of ADHD symptoms in children with autistic spectrum disorder and ADHD: a pilot, open-label, randomized controlled study. *Paediatr Drugs*. 2016;18(4):319-329. doi: 10.1007/s40272-016-0183-3.

BACKGROUND: Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are frequently overlapping neurodevelopmental disorders. Individuals in whom the disorders are comorbid show more severe impairment because of deficits in the processing of social situations, adaptive functioning, and executive control than individuals with either disorder alone. **OBJECTIVE:** This open-label pilot study aimed to evaluate and compare the efficacy and tolerability of risperidone and aripiprazole for treating ADHD symptoms in patients with both ASD and ADHD over the course of 24 weeks of treatment. **METHODS:** Patients (n = 44) were randomly assigned to start treatment with risperidone (22 patients) or aripiprazole (22 patients). Children were evaluated before starting treatment (T0), and after 12 weeks (T1) and 24 weeks (T2) of treatment. At each visit, specific psychiatric clinical scales were administered to assess the efficacy of the two drugs. **RESULTS:** The mean age was 8.4 +/- 2.9 years in the aripiprazole group and 7.8 +/- 2.3 years in the risperidone group. A total of 37 children (29 boys and 8 girls) completed the study (18 in the aripiprazole group and 19 in the risperidone group). Aripiprazole and risperidone appeared to have similar benefits in

terms of efficacy and tolerability, although there were slight differences between the two drugs. Both groups showed a significant improvement in ADHD symptoms after 24 weeks of treatment (ADHD Rating Scale, Conners Parent Rating Scale-Hyperactivity, and Clinical Global Improvement-Severity Scale). No significant difference between the two drugs on any parameters at 24 weeks were found. Prolactin levels were decreased in the aripiprazole group. Both drugs were well tolerated, with no serious adverse events detected. CONCLUSIONS: Our study confirms the efficacy of both aripiprazole and risperidone in ameliorating ADHD symptoms of children also presenting with ASD.

Nemeth 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. *Lancet*. 2017;389(10074):1103-1113. doi: [https://dx.doi.org/10.1016/S0140-6736\(17\)30060-0](https://dx.doi.org/10.1016/S0140-6736(17)30060-0).

BACKGROUND: Although predominant negative symptoms of schizophrenia can be severe enough to cause persistent impairment, effective treatment options are lacking. We aimed to assess the new generation antipsychotic cariprazine in adult patients with predominant negative symptoms. METHODS: In this randomised, double-blind, phase 3b trial, we enrolled adults aged 18-65 years with long-term (>2 year), stable schizophrenia and predominant negative symptoms (>6 months) at 66 study centres (mainly hospitals and university clinics, with a small number of private practices) in 11 European countries. Patients were randomly assigned (1:1) by an interactive web response system to 26 weeks of monotherapy with fixed-dose oral cariprazine (3 mg, 4.5 mg [target dose], or 6 mg per day) or risperidone (3 mg, 4 mg [target dose], or 6 mg per day); previous medication was discontinued over 2 weeks. The primary outcome was change from baseline to week 26 or end of treatment on the Positive and Negative Syndrome Scale factor score for negative symptoms (PANSS-FSNS) analysed in a modified intention-to-treat population of patients who had follow-up assessments within 5 days after last receipt of study drugs with a mixed-effects model for repeated measures. Safety was assessed in all patients who received at least one dose of study drug. This study is registered with EudraCT, number 2012-005485-36. FINDINGS: Between May 27, 2013, and Nov 17, 2014, 533 patients were screened and 461 (86%) patients were randomised to treatment (230 for cariprazine and 231 for risperidone); 460 were included in the safety population (one patient discontinued before study drug intake). 227 (99%) of 230 patients in the cariprazine group and 229 (99%) of 230 patients in the risperidone group were included in the modified intention-to-treat population (178 [77%] in each group completed 26 weeks of treatment). Mean daily doses were 4.2 mg (SD 0.6) for cariprazine and 3.8 mg (0.4) for risperidone. Treatment-emergent adverse events (eg, insomnia, akathisia, worsening of schizophrenia, headache, anxiety) were reported in 123 (54%) patients treated with cariprazine and 131 (57%) patients treated with risperidone. Use of cariprazine led to a greater least squares mean change in PANSS-FSNS from baseline to week 26 than did risperidone (-8.90 points for cariprazine vs -7.44 points for risperidone; least squares mean difference -1.46, 95% CI -2.39 to -0.53; p=0.0022; effect size 0.31). One patient in the risperidone group died of a cause regarded as unrelated to treatment.

INTERPRETATION: Our results support the efficacy of cariprazine in the treatment of predominant negative symptoms of schizophrenia. FUNDING: Gedeon Richter Plc.

Noordsy DL, Glynn SM, Sugar CA, O'Keefe CD, Marder SR. Risperidone versus olanzapine among patients with schizophrenia participating in supported employment: eighteen-month outcomes. *J Psychiatr Res.* 2017;95:299-307. doi: <https://dx.doi.org/10.1016/j.jpsychires.2017.09.008>.

This study compares the efficacy and tolerability of olanzapine versus risperidone among patients with schizophrenia who are established in outpatient psychiatric care and entering supported employment. A multicenter, randomized, double-blind trial was conducted among 107 outpatients with schizophrenia, who were cross-titrated to flexible dose risperidone or olanzapine over 2 weeks. Clinical endpoints included time to hospitalization and persistence on assigned medication. Weight, laboratory tests, psychopathology, neurologic side effects, social adjustment and role functioning were assessed at 3-6 month intervals. Data were analyzed first by randomized treatment, and then reassessed controlling for prior medication treatment. The proportion of patients on assigned medication at 18 months was 30.9% for risperidone and 37.3% for olanzapine. Mean doses were 6.4 +/- 3.2 mg daily for risperidone, and 17.0 +/- 5.0 mg daily for olanzapine. The groups did not differ significantly in time to medication discontinuation, first hospitalization or first employment. There were few differences in psychopathology, laboratory, or neurological assessments between groups at 18 months. Patients randomized to olanzapine gained modestly more weight. Controlling for pre-randomization medication suggested improvement in some aspects of psychopathology from switching medications; however, switching from olanzapine to risperidone was associated with more hospitalizations. Risperidone and olanzapine have similar efficacy and tolerability in patients with schizophrenia who are participating in supported employment. Randomization to olanzapine was associated with more weight gain, but randomization from olanzapine to risperidone appeared to be associated with a greater likelihood of hospitalization. Careful monitoring of metabolic effects and participation in supported employment may have contributed to minimal weight gain and metabolic effects.

Wang HH, Cai M, Wang HN, et al. An assessor-blinded, randomized comparison of efficacy and tolerability of switching from olanzapine to ziprasidone and the combination of both in schizophrenia spectrum disorders. *J Psychiatr Res.* 2017;85:59-65. doi: <https://dx.doi.org/10.1016/j.jpsychires.2016.11.002>.

BACKGROUND: Ziprasidone (ZIP) is often used with olanzapine (OLZ) in 'switch' and combination therapy but empirical evidence to support these strategies is limited.

OBJECTIVE: This study was therefore designed to compare the efficacy and tolerability of switching from OLZ to ZIP, the combination of both medications, and OLZ and ZIP monotherapy, in patients with schizophrenia spectrum disorders (SSD). METHODS: In this 12 week open-label, assessor-blinded randomized trial, 148 patients with SSD who had not used antipsychotics for at least 3 months were assigned to ZIP (n = 49) or OLZ monotherapy (n = 31); OLZ for 4 weeks then a switch to ZIP (OLZ/ZIP, n = 35); or

combination therapy (OLZ + ZIP, n = 33). The severity of psychosis and abnormal involuntary movements was evaluated at baseline, 1, 2, 4, 8, and 12 weeks using standard instruments. Baseline-to-endpoint changes in weight gain and metabolic measures were compared. RESULTS: The efficacy of both OLZ/ZIP and OLZ + ZIP was comparable to OLZ monotherapy and better than ZIP monotherapy in reducing overall psychotic and negative symptoms at most 8 and 12 week measurement points. Changes in weight gain, glucose, and lipid measures did not differ between OLZ/ZIP and OLZ + ZIP, but were markedly higher following OLZ monotherapy. The OLZ + ZIP group had the lowest overall incidence of adverse events and extrapyramidal symptoms of all the treatment regimens. CONCLUSIONS: We conclude that combining ZIP and OLZ at the outset of treatment is superior to switching from OLZ to ZIP in terms of improving psychotic symptoms and limiting movement side effects without increasing the risk of metabolic syndrome.

Secondary Analyses

Ceskova E, Prikryl R, Libiger J, Svancara J, Jarkovsky J. Gender differences in the treatment of first-episode schizophrenia: results from the European First Episode Schizophrenia Trial. *Schizophr Res*. 2015;169(1-3):303-307.

Gender differences in the response to antipsychotic treatment have been detected in the past, but not studied in great detail. The results of the European First-Episode Schizophrenia Trial (EUFEST) were analyzed with a focus on gender differences in the response to randomized treatment of first-episode schizophrenia. A total of 498 patients (298 men and 200 women) were randomly assigned by a web-based online system to open-label treatment with haloperidol, amisulpride, olanzapine, quetiapine, and ziprasidone. Treatment response was evaluated using the positive and negative syndrome scale (PANSS). Data were collected at baseline and then prospectively for one year. Baseline characteristics (age and proportion of patients assigned to individual antipsychotics) were the same between the male and female patients with the exception of ziprasidone: significantly fewer men, proportionately, were prescribed ziprasidone. There was no significant difference between genders between the initial total PANSS and subscale scores. A significant interaction between time and gender was found, with more robust PPANSS and TPANSS score improvement in women during the course of treatment. Of all of the antipsychotics used, only olanzapine led to significantly greater improvement in the total PANSS score in women during the follow-up period. Gender differences should be given more attention in research and clinical practice. Their causes require clarification, and future strategies for dealing with them may be considered in early intervention programs and guidelines.

Potkin SG, Loze JY, Forray C, et al. Multidimensional assessment of functional outcomes in schizophrenia: results from QUALIFY, a head-to-head trial of aripiprazole once-monthly and paliperidone palmitate. *Int J Neuropsychopharmacol*. 2017b;20(1):40-49. doi: <https://dx.doi.org/10.1093/ijnp/pyw093>.

Background: QUALIFY was a 28-week, randomized, open-label, head-to-head trial that assessed improvements across multiple measures in stable patients with schizophrenia

with aripiprazole once-monthly 400 mg vs paliperidone palmitate. Methods: Secondary effectiveness assessments included physician-rated readiness for work using the Work Readiness Questionnaire, the Clinical Global Impression-Severity and Clinical Global Impression-Improvement scales, and quality of life with the rater-blinded Heinrichs-Carpenter Quality of Life Scale. Patients assessed their treatment satisfaction and quality of life with Subjective Well-Being under Neuroleptic Treatment-short version and Tolerability and Quality of Life questionnaires. Results: Odds of being ready for work at week 28 were significantly higher with aripiprazole once-monthly 400 mg vs paliperidone palmitate (adjusted odds ratio, 2.67; 95% CI, 1.39-5.14; P=.003). Aripiprazole once-monthly 400 mg produced numerically or significantly greater improvements from baseline vs paliperidone palmitate in all Quality of Life Scale items. With aripiprazole once-monthly 400 mg vs paliperidone palmitate at week 28, there were significantly more Clinical Global Impression-Severity and Clinical Global Impression-Improvement responders (adjusted odds ratio, 2.26; P=.010, and 2.51; P=.0032) and significantly better Clinical Global Impression-Improvement scores (least squares mean treatment difference, -0.326; 95% CI, -0.60 to -0.05; P=.020). Numerically larger improvements with aripiprazole once-monthly 400 mg vs paliperidone palmitate were observed for patient-rated scales Subjective Well-Being under Neuroleptic Treatment-short version and Tolerability and Quality of Life. Partial correlations were strongest among clinician-rated and among patient-rated scales but poorest between clinician and patient-rated scales. Conclusions: Consistently greater improvements were observed with aripiprazole once-monthly 400 mg vs paliperidone palmitate across all measures. Partial correlations between scales demonstrate the multidimensionality of various measures of improvement. More patients on aripiprazole once-monthly 400 mg were deemed ready to work by the study end. Trial registry: National Institutes of Health registry, NCT01795547, <https://clinicaltrials.gov/ct2/results?id=NCT01795547>).

Potkin SG, Loze JY, Forray C, et al. Reduced sexual dysfunction with aripiprazole once-monthly versus paliperidone palmitate: results from QUALIFY. *Int Clin Psychopharmacol*. 2017a;32(3):147-154. doi: <https://dx.doi.org/10.1097/YIC.000000000000168>. Sexual dysfunction, a common side effect of antipsychotic medications, may be partly caused by dopamine antagonism and elevation of prolactin. In QUALIFY, a randomized study, aripiprazole once-monthly 400mg (AOM 400), a dopamine D2 receptor partial agonist, showed noninferiority and subsequent superiority versus paliperidone palmitate (PP), a dopamine D2 receptor antagonist, on the Heinrichs-Carpenter Quality-of-Life Scale (QLS) in patients with schizophrenia aged 18-60 years. Sexual dysfunction (Arizona Sexual Experience Scale) and serum prolactin levels were also assessed. Odds for sexual dysfunction were lower with AOM 400 versus PP [week 28 adjusted odds ratio (95% confidence interval), 0.29 (0.14-0.61); P=0.0012] in men [0.33 (0.13-0.86); P=0.023], women [0.14 (0.03-0.62); P=0.0099], and patients aged 18-35 years [0.04 (<0.01-0.34); P=0.003]. Among patients shifting from sexual dysfunction at baseline to none at week 28, there was a trend toward greater improvement in the QLS total score. The mean (SD) prolactin concentrations decreased with AOM 400 [-150.6 (274.4)mIU/l] and increased with PP [464.7 (867.5)mIU/l] in both men and women. Six PP-treated patients

experienced prolactin-related adverse events. In addition to greater improvement on QLS, patients had a lower risk for sexual dysfunction and prolactin elevation with AOM 400 versus PP in QUALIFY.

Volavka J, Czobor P, Citrome L, Van Dorn RA. Effectiveness of antipsychotic drugs against hostility in patients with schizophrenia in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. *CNS Spectr*. 2014;19(5):374-381.

INTRODUCTION: Aggressive behavior can be a dangerous complication of schizophrenia. Hostility is related to aggression. This study aimed to compare the effects of olanzapine, perphenazine, risperidone, quetiapine, and ziprasidone on hostility in schizophrenia. METHODS: We used the data that were acquired in the 18-month Phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. We analyzed the scores of the Positive and Negative Syndrome Scale (PANSS) hostility item in a subset of 614 patients who showed at least minimal hostility (a score ≥ 2) at baseline. RESULTS: The primary analysis of hostility indicated an effect of difference between treatments ($F(4,1487) = 7.78, P < 0.0001$). Olanzapine was significantly superior to perphenazine and quetiapine at months 1, 3, 6, and 9. It was also significantly superior to ziprasidone at months 1, 3, and 6, and to risperidone at months 3 and 6. DISCUSSION: Our results are consistent with those of a similar post-hoc analysis of hostility in first-episode subjects with schizophrenia enrolled in the European First-Episode Schizophrenia Trial (EUFEST) trial, where olanzapine demonstrated advantages compared with haloperidol, quetiapine, and amisulpride. CONCLUSION: Olanzapine demonstrated advantages in terms of a specific antihostility effect over the other antipsychotics tested in Phase 1 of the CATIE trial.

Placebo-Controlled Trials

DelBello MP, Goldman R, Phillips D, Deng L, Cucchiaro J, Loebel A. Efficacy and safety of lurasidone in children and adolescents with bipolar I depression: a double-blind, placebo-controlled study. *J Am Acad Child Adolesc Psychiatry*. 2017;56(12):1015-1025. doi: <https://dx.doi.org/10.1016/j.jaac.2017.10.006>.

OBJECTIVE: To evaluate the efficacy and safety of lurasidone in children and adolescents with bipolar depression. METHOD: Patients 10 to 17 years old with a DSM-5 diagnosis of bipolar I depression were randomized to 6 weeks of double-blind treatment with flexible doses of lurasidone 20 to 80 mg/day. The primary endpoint was change from baseline to week 6 in the Children's Depression Rating Scale-Revised (CDRS-R) total score, evaluated by a mixed-model repeated-measures analysis. RESULTS: A total of 347 patients were randomized and received at least 1 dose of lurasidone ($n = 175$; mean age 14.2 years; mean dose 33.6 mg/day) or placebo ($n = 172$; mean age 14.3 years). At week 6, treatment with lurasidone was associated with statistically significant improvement compared with placebo in CDRS-R total score (-21.0 versus -15.3; $p < .0001$; effect size 0.45). Lurasidone also was associated with statistically significant improvement in the Clinical Global Impression-Bipolar Severity depression score (key secondary measure) and in measures of anxiety, quality of life, and global functioning. Study completion rates were 92.0% in the lurasidone group and 89.7% in the placebo group; discontinuation

rates due to adverse events were the same for the 2 groups (1.7%). The 2 most common adverse events on lurasidone were nausea and somnolence. Treatment with lurasidone was associated with few effects on weight and metabolic parameters. CONCLUSION: In this placebo-controlled study, monotherapy with lurasidone, in the dose range of 20 to 80 mg/day, significantly decreased depressive symptoms in children and adolescents with bipolar depression. Lurasidone was well tolerated, with minimal effects on weight and metabolic parameters. Clinical trial registration information-Lurasidone Pediatric Bipolar Study; <http://Clinicaltrials.gov>; NCT02046369.

Findling RL, Landbloom RL, Mackle M, et al. Long-term safety of asenapine in pediatric patients diagnosed with bipolar I disorder: a 50-week open-label, flexible-dose trial. *Paediatr Drugs*. 2016;18(5):367-378. doi: 10.1007/s40272-016-0184-2.

BACKGROUND: Sublingually administered asenapine was approved in March 2015 by the United States Food and Drug Administration for patients aged 10-17 years with an acute manic or mixed episode associated with bipolar I disorder (BP-1). This is the first long-term safety and tolerability study of asenapine in this population. METHODS: Following the 3-week randomized, double-blind, placebo-controlled trial of patients aged 10-17 years with an acute manic or mixed episode associated with BP-1, patients could enroll in this flexible-dose (2.5-10 mg twice daily) open-label extension (OLE) study for an additional 50 weeks, conducted from August 2011 to September 2014 in the United States and Russia. Treatment-emergent adverse events (TEAEs) were assessed and predefined TEAEs of interest reported in addition to metabolic and anthropometric parameters. The Young Mania Rating Scale (YMRS) and Clinical Global Impressions scale in bipolar illness (CGI-BP) were used to assess effectiveness. RESULTS: A total of 321 patients (lead-in study treatment: placebo, n = 80; asenapine, n = 241) were included; 267 (83.2 %) reported one or more TEAE and 181 (56.4 %) discontinued early, 48 (15.0 %) due to TEAEs. Of the predefined TEAEs of interest, combined somnolence/sedation/hypersomnia occurred most frequently (42.4 %) followed by oral hypoesthesia/dysgeusia (7.5 %). In total, 109 (34.8 %) patients experienced clinically significant weight gain (≥ 7 % increase). No clinically meaningful changes were noted for laboratory parameters measured. Eighteen patients met the criteria for new-onset metabolic syndrome (MBS) post-baseline during the extension study, whereas 10 patients who met MBS criteria at baseline did not meet MBS criteria at endpoint. A total of 12 patients met MBS at baseline and endpoint. Mean change in YMRS total score from OLE baseline was -9.2 points at week 50, and change in CGI-BP severity overall score was similar among all treatment groups (those who initially received asenapine and those who initially received placebo). After 26 weeks of treatment in the OLE, 79.2 % of patients were classified as YMRS 50 % responders relative to acute trial baseline. CONCLUSIONS: Asenapine was generally well tolerated in pediatric patients with BP-1 during ≤ 50 weeks of open-label treatment; among predefined TEAEs of interest, the combination of somnolence/sedation/hypersomnia was the most common. Trial registration ClinicalTrials.gov: NCT01349907.

Findling RL, Youngstrom EA, Rowles BM, et al. A double-blind and placebo-controlled trial of aripiprazole in symptomatic youths at genetic high risk for bipolar disorder. *J Child Adolesc Psychopharmacol*. 2017;27(10):864-874. doi: <https://dx.doi.org/10.1089/cap.2016.0160>.

OBJECTIVE: To determine if acute treatment with aripiprazole (APZ) would be superior to treatment with placebo in reducing dysfunctional symptoms of elevated mood and/or irritability in symptomatic children and adolescents at familial high risk for bipolar disorder (BPD) whose mood episodes occur spontaneously. These are patients we have previously referred to as suffering from "cyclothaxia." METHODS: This was single-site, randomized, double-blind, placebo-controlled outpatient clinical trial in which youths aged 5-17 years who met diagnostic criteria for either cyclothymic disorder (CYC) or BPD not otherwise specified (BP-NOS) were randomly assigned to receive either APZ or placebo. Eligible participants had at least one parent with BPD, another first- or second-degree relative afflicted with a mood disorder, and also had not responded to psychotherapy. Treatment with APZ was initiated at a dose of approximately 0.1mg/kg/day and could be increased by approximately 0.05mg/kg/day at each study visit. Patients were seen weekly for 4 weeks and then every other week thereafter for 12 weeks. The primary outcome measure was mean change from baseline on Young Mania Rating Scale (YMRS) total score. RESULTS: A total of 59 patients (30 APZ, 29 placebo) aged 11.8 (SD=2.7) years were randomized and returned for at least one postbaseline assessment. The mean total daily doses of active APZ and placebo were 7.1mg (SD=3.7) and 7.4mg (SD=4.2), respectively. At the 12-week time point, APZ was superior to placebo on the primary outcome measure ($p<0.005$). Most adverse events were mild and transient in nature. There was a significant difference in weight gain from baseline between patients who received APZ (2.3kg [SD=3.3]) and those who received placebo (0.7kg [SD=1.8]). CONCLUSION: This double-blind trial found that APZ was significantly more efficacious than placebo in reducing symptoms of mania in children and adolescents with cyclothaxia.

Ichikawa H, Mikami K, Okada T, et al. Aripiprazole in the treatment of irritability in children and adolescents with autism spectrum disorder in Japan: a randomized, double-blind, placebo-controlled study. *Child Psychiatry Hum Dev*. 2017;48(5):796-806. doi: <https://dx.doi.org/10.1007/s10578-016-0704-x>.

We evaluated the efficacy and safety of aripiprazole in the treatment of irritability in children and adolescents (6-17 years) with autism spectrum disorder (ASD) in a randomized, double-blind, placebo-controlled 8-week study in Japan. Patients received flexibly dosed aripiprazole (1-15 mg/day) or placebo. Ninety-two patients were randomized to placebo (n=45) or aripiprazole (n=47). Aripiprazole produced a significant improvement in the mean parent/caregiver-rated Aberrant Behavior Checklist Japanese Version irritability subscale score relative to placebo from week 3 through week 8. Administration of aripiprazole provided significantly greater improvement in the mean clinician-rated Clinical Global Impression-Improvement scores than placebo from week 2 through week 8. All patients randomized to aripiprazole completed the study, and no serious adverse events were reported. Three patients in placebo group discontinued.

Aripiprazole was effective and generally safe and well-tolerated in the treatment of irritability associated with ASD in Japanese children and adolescents.

Jahangard L, Akbarian S, Haghighi M, et al. Children with ADHD and symptoms of oppositional defiant disorder improved in behavior when treated with methylphenidate and adjuvant risperidone, though weight gain was also observed--results from a randomized, double-blind, placebo-controlled clinical trial. *Psychiatry Res.* 2017;251:182-191. doi: <https://dx.doi.org/10.1016/j.psychres.2016.12.010>..

Children with ADHD often show symptoms of oppositional defiant disorders (ODD). We investigated the impact of adjuvant risperidone (RISP) to a standard treatment with methylphenidate (MPH) in children with ADHD and symptoms of ODD. Eighty-four children with ADHD and ODD (age: M=8.55; range: 7.28-9.95 years; 73.8% males) took part in a double-blind, randomized, placebo-controlled, clinical trial lasting eight weeks. Participants were randomly assigned either to the MPH+RISP (1mg/kg/d+0.5mg/d) or to the MPH+PLCO (1mg/kg/d+placebo) condition. Symptoms of ADHD, weight, height, and blood pressure were assessed at baseline, and at weeks 2, 4, 6 and 8. Symptoms of ADHD decreased over time, but more so in the MPH+RISP than in the MPH only condition. In the MPH+RISP condition weight, waist circumference and prolactine levels increased over time. Data suggest that adjuvant RISP improved symptoms in children with ADHD and ODD, but weight gain and higher prolactine levels were also observed, which are two alarming side effects. This may become an issue, once children become adolescents, a period of life in which body shape and body self-image are closely linked to self-confidence and peer acceptance. Health care professionals should carefully balance the short-term and long-term costs and benefits of administration of RISP.