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DERP Surveillance: Second-Generation Antipsychotic Medications in Children and Adolescents

January 2022

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Objectives

The purpose of this Drug Effectiveness Review Project (DERP) surveillance report is to preview the volume and nature of new research and relevant clinical information that has emerged since the last systematic review on second-generation antipsychotic drugs (SGAs). The literature search for this report focuses on new randomized controlled trials (RCTs), along with actions taken by the US Food and Drug Administration (FDA) since the last report, including approval of new drugs, formulations, or indications, and identification of serious harms. Comprehensive searches, quality assessment, and synthesis of evidence would follow only if DERP participants commission an updated review or another research product type for this topic. Comprehensive searches might identify additional eligible studies.

Topic History and Context

This report is the first surveillance document on this topic since the completion of the systematic review in September 2020.[1] The search strategy for that systematic review was through April 17, 2020.

Table 1. Topic History and Search Dates on SGAs for Children and Adolescents

Document Type	Date Presented	Search Dates
Systematic Review	September 2020	Database inception to April 2020

Abbreviation. SGA: second-generation antipsychotic drug.

PICOS

Population

Diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria is preferred, but we accepted investigator-defined criteria for diagnosis in the absence of DSM-5 criteria.

- Adolescents (aged 12 to 17 years) with a diagnosis of schizophrenia or other psychotic disorder, such as schizophreniform disorder (< 6 months duration of schizophrenia symptoms), delusional and schizoaffective disorders, and first episode schizophrenia, as well as patients who are refractory to treatment
- Adolescents (aged 12 to 17 years), and children (under age 12) with bipolar disorder (BD; manic or depressive phases, rapid cycling, mixed states)
- Children (under age 12) or adolescents (aged 12 to 17 years) with a DSM-5 diagnosis of autism spectrum disorder (ASD)
- Children (under age 12) or adolescents (aged 12 to 17 years) with DSM-5 diagnoses of disruptive behavior, impulse control, or conduct disorder

Interventions

Table 2. Included SGA Interventions for Children and Adolescents

Generic Name	Brand Name	Form	Initial Year of FDA Approval	Approved Indications in Children or Adolescents
Aripiprazole	Abilify	Oral tablet	2002	• Schizophrenia[a] • Bipolar disorder[a,b] • ASD[a,b]
Asenipine	Saphris	Sublingual tablet	2009	• Bipolar disorder[a]
Lurasidone	Latuda	Oral tablet	2010	• Schizophrenia[a] • Bipolar disorder[a,b]
Olanzapine	Zyprexa	Oral tablet	1996	• Schizophrenia[a] • Bipolar disorder[a]
	Zyprexa Zydis	ODT	2000	
Paliperidone	Invega	ER oral tablet	2006	• Schizophrenia[a]
Quetiapine	Seroquel	Oral tablet	1997	• Schizophrenia[a] • Bipolar disorder[a,b]
	Seroquel XR	ER oral tablet	2007	
Risperidone	Risperdal	Oral tablet	1993	• Schizophrenia[a] • Bipolar disorder[a,b] • ASD[a,b]
		Oral solution	1996	
	Risperdal M-TAB	ODT	2003	

Note. Overview of populations with FDA-approved indications; [a] adolescents; [b] children.
Abbreviations. ASD: autism spectrum disorder; ER: extended release; FDA: US Food and Drug Administration; M-TAB: orally disintegrating tablet; ODT: orally disintegrating tablet; SGA: second-generation antipsychotic drug; XR: extended release.

Comparators

All populations:

- Head-to-head (a listed intervention compared to another)

Individuals with BD, ASD; or disruptive behavior, impulsive control, or conduct disorder:

- Placebo

Outcomes

Efficacy and Effectiveness Outcomes

- Quality of life (validated scales)
- Functional capacity (i.e., social, academic, activities of daily living, employment, and encounters with the legal system)
- Hospitalization (due to mental illness and all-cause), emergency department visits
- Persistence (i.e., ability to continue taking medication over time)

Children and adolescents with ASD

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

Adolescents with schizophrenia and other psychotic disorders, first episode schizophrenia, BD, 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, and time to discontinuation of medication
    - Excluded: very short-term studies that focused exclusively on treatment of acute agitation associated with schizophrenia or BD

Children and adolescents with disruptive behavior, impulse control, or conduct disorders

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

Harms Outcomes

- Overall adverse events (AEs)
- Withdrawals due to AEs, time to withdrawal due to AEs
- Specific AEs
    - 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, agranulocytosis)
    - General: Incidence of extrapyramidal adverse events, clinically important weight change, metabolic syndrome, and incidence and severity of adverse sexual events

Study Designs

- RCTs

Key Questions

KQ1. For children and adolescents with ASD:
   a. Do SGAs differ from each other in terms of benefits or harms?
   b. Do SGAs differ from placebo in terms of benefits or harms?

KQ2. For adolescents with schizophrenia (including a first episode) and other psychotic disorders:
   a. Do SGAs differ from each other in terms of benefits or harms?

KQ3. For children and adolescents with BD:
   a. Do SGAs differ from each other in terms of benefits or harms?
   b. Do SGAs differ from placebo in terms of benefits or harms?

KQ4. For children and adolescents with disruptive behavior, impulse control, or conduct disorders:
   a. Do SGAs differ from each other in terms of benefits or harms?
   b. Do SGAs differ from placebo in terms of benefits or harms?

Methods

Using the PICOS outlined above, Center for Evidence-based Policy (Center) researchers searched for eligible RCTs in ClinicalTrials.gov, the ISRCTN Registry, and the FDA website. Using relevant clinical trial numbers and other identifiers, we then searched Ovid MEDLINE ALL from April 17, 2020 to November 2, 2021. We used the Google search engine to identify studies published since the implementation of the search strategy in the previous systematic review (September 2020). We used limits for English language and human participants. We also searched the FDA website to identify newly approved drugs, formulations, indications, and new serious harms (e.g., boxed warnings) or warnings for included interventions. To identify new drugs, we used Google and searched CenterWatch, a privately owned database of clinical trials information, and IPD Analytics, a privately owned database of pharmaceutical information.

Findings

New Drugs or Formulations

No new drugs or formulations were identified since the searches in the last systematic review.

New Indications

No new indications were identified since the searches in the last systematic review.

New Serious Harms or Warnings

We identified 6 new warnings (Table 3) since the last systematic review, including 1 for lurasidone, 2 for olanzapine, 1 for paliperidone, 1 for quetiapine, and 1 for risperidone.

Table 3. New Serious Harms or Warnings of SGAs for Children and Adolescents

Drug	New Serious Harms or Warnings	Date
Lurasidone	New warning for increased risk of metabolic changes and hyperprolactinemia[2]	December 2019
Olanzapine	New warning for an increased risk of tardive dyskinesia with the Zyprexa suite of products[3]	October 2019
	New warning for an increased risk of anticholinergic effects with the Zyprexa suite of products (i.e., Zyprexa oral tablets, Zyprexa Zydis ODT)[4]	April 2020
Paliperidone	New warnings for increased risk of potential cognitive and motor impairment; leukopenia, neutropenia, or agranulocytosis; tardive dyskinesia; and neuroleptic malignant syndrome[5]	February 2021
	Warnings for an increased risk of thrombocytopenic purpura and antiemetic effects were removed[5]	
Quetiapine ER	New warning for an increased risk of anticholinergic effects with Seroquel XR[6]	September 2020
Risperidone	New warning for an increased risk of neuroleptic malignant syndrome and tardive dyskinesia with the Risperdal suite of products (i.e., Risperdal oral, oral solution, M-TAB)[7]	February 2021

Abbreviations. ER: extended release; M-TAB: orally disintegrating tablets; ODT: orally disintegrating tablet; SGA: second-generation antipsychotic drug; XR: extended release.

Randomized Controlled Trials

We identified 2 new eligible head-to-head RCTs (Table 4) assessing SGA treatment in children aged 10 to 17 years with BD-I with sample sizes ranging from 109 to 116.[8,9] We also identified 1 new eligible head-to-head RCT (Table 4) assessing SGA treatment in 546 individuals aged 15 to 65 years with schizophrenia.[10]

Table 4. Included RCTs of SGAs for Children and Adolescents

Author (Year) Trial Number Enrollment	Population Duration Treatment Groups	Eligible Outcomes
Children		
Streicher et al.[9] (2020) N = 116	Children aged 10 to 17 years with BD-I 6 weeks • Quetiapine 400 to 600 mg • Lithium targeted serum level of 1.0 to 1.2 mEq/L	• Change from baseline CPT-IP
Patino et al.[8] (2021) NCT00893581 N = 109	Children aged 10 to 17 years with BD-I 6 weeks • Quetiapine 400 to 600 mg • Lithium targeted serum level 1.0 to 1.2 mEq/L	• Change from baseline YMRS • Treatment response defined as: ≥ 50% decrease from baseline YMRS • Remission defined as YMRS ≤ 12, CDRS-R ≤ 28, and CGI-BP-S ≤ 3
Adolescents and adults		
Hou et al.[10] (2020) NCT01057849 N = 546	Individuals aged 16 to 45 years with schizophrenia 1 year, open-label • Risperidone 3 mg • Aripiprazole 15 to 30 mg • Olanzapine 10 to 20 mg	• Change from baseline PANSS • AEs • Change from baseline cognitive performance

Abbreviations. AE: adverse event; BD-I: Bipolar I Disorder; CDRS-R: Children's Depression Rating Scale, Revised; CGI-BP-S: Clinical Global Impression Bipolar Severity Scale; CPT-IP: Identical Pairs Continuous Performance Task; mEq/L: milliequivalents per liter; mg: milligram; PANSS: Positive and Negative Symptom Scale; RCT: randomized controlled trial; SGA: second-generation antipsychotic drug; YMRS: Young Mania Rating Scale.

Ongoing Studies

Since the last systematic review, we identified 3 ongoing studies (Table 5) assessing SGA treatment, including:

- 1 head-to-head study of 350 children ≤ 17 years with ASD,[11] expected to be completed in July 2025
- 1 head-to-head study of 114 individuals aged 16 to 40 years with an intellectual disability and psychosis according to DSM-5,[12] expected to be completed in February 2024

We identified 1 placebo-controlled RCT[13] of 19 individuals aged 15 to 24 years with BD or disruptive mood dysregulation disorder and substance use disorder, completed in April 2021. No publications have been identified at the time of report writing.

Table 5. Included Ongoing Studies of SGAs for Children and Adolescents

Trial Number Trial Name Estimated Completion Estimated Enrollment	Population Treatment Groups	Eligible Outcomes
NCT02845453[13] April 2021 (actual) N = 19 (actual) *No publications identified*	Individuals aged 15 to 24 years with BD or DMDD and SUD • Quetiapine • Placebo	• Change in number of days of most problematic substance use in previous month • Change in symptoms of mania • Change in number of negative urine toxicology samples • Change in craving for substance identified as most problematic • Change in depression symptoms
NCT04529226[12] CLOZ-AID February 2024 N = 114	Individuals aged 16 to 40 years with a diagnosis of intellectual disability and psychosis according to DSM-5 • Clozapine • Haloperidol, pimozide, olanzapine, risperidone, or amisulpride	• Clinical improvement on CGI-SCH • Clinical improvement on PANSS • Clinical improvement on SANS • QoL based on Euro-QoL 5D-5L • Treatment-related AEs
NCT04903353[11] July 2025 N = 350	Children ≤ 17 years old with ASD • Risperidone • Aripiprazole	• Change in weight

Abbreviations. AE: adverse event; ASD: autism spectrum disorder; BD: bipolar disorder; CGI-SCH: Clinical Global Impression-Schizophrenia; DMDD: disruptive mood dysregulation disorder; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; Euro-QoL 5D-5L: EuroQol Group 5-Level Quality of Life 5-Dimensional Questionnaire; PANSS: Positive and Negative Syndrome Scale; QoL: quality of life; SANS: Scale for the Assessment of Negative Symptoms; SGA: second-generation antipsychotic drug; SUD: substance use disorder.

Summary

Since the completion of the DERP systematic review, we identified:

- 3 new RCTs
  - 3 head-to-head trials
- 3 ongoing RCTs
  - 2 head-to-head trials
  - 1 placebo-controlled trial
- No new drugs, formulations, or serious harms
- No new indications
- 6 new warnings
  - 1 for lurasidone: metabolic changes and hyperprolactinemia
  - 2 for olanzapine oral and orally disintegrating tablet (ODT): tardive dyskinesia; anticholinergic effects
  - 1 for paliperidone: potential cognitive and motor impairment, leukopenia/neutropenia/agranulocytosis, tardive dyskinesia, and neuroleptic malignant syndrome
  - 1 for quetiapine ER: anticholinergic effects

- 1 for risperidone oral, oral solution, and ODT: neuroleptic malignant syndrome and tardive dyskinesia

Using the *Is There a There There Scale* (ITS; Table 6), we rated this topic as ***No*** (see Appendix B for ratings and definitions).

Table 6. Summary and ITS Rating

Clinical Evidence	Yes How many?	No
New Comparative Trial	☑ 3 total; 2 in children and 1 in adolescents and adults	
New Placebo-Controlled Trial (if needed)		☒
New Meaningful[a] Study		☒
Ongoing Study Likely to be Published in the Next Year	☑ 1 total in adolescents and adults	
FDA Actions	**Yes Description**	**No**
New Drug or Formulation		☒
New Indication		☒
New Serious Harm or Warning	☑ 6 new warnings	
ITS Rating: ***No***		

Note. [a] Large studies (≥ 1,000 participants), studies that have long-term follow-up (≥ 12 months), studies that compare one drug with another that is considered the standard of care or has not been reported and is clinically important, and studies that include an intervention or outcome that is not previously reported in the literature or is clinically important (e.g., mortality) and adds to the body of literature.

Abbreviations. FDA: US Food and Drug Administration; ITS: Is There a There There Scale.

References

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9. Streicher JV, Wen H, Blom TJ, et al. A preliminary study of the effects of treatment with lithium versus quetiapine on attention of adolescents with bipolar disorder. *J Child Adolesc Psychopharmacol.* 2020;30(7):465-469. doi: 10.1089/cap.2019.0169.

10. Hou Y, Xie J, Yuan Y, et al. Neurocognitive effects of atypical antipsychotics in patients with first-episode schizophrenia. *Nord J Psychiatry.* 2020;74(8):594-601. doi: 10.1080/08039488.2020.1771767.

11. ClinicalTrials.gov. Pragmatic trial comparing weight gain in children with autism taking risperidone versus aripiprazole. 2021; https://clinicaltrials.gov/ct2/show/NCT04903353. Accessed November 3, 2021.

12. ClinicalTrials.gov. Study to compare clozapine vs treatment as usual in people with intellectual disability & treatment-resistant psychosis (CLOZ-AID). 2020; https://clinicaltrials.gov/ct2/show/NCT04529226. Accessed November 3, 2021.

13. ClinicalTrials.gov. Treatment with quetiapine for youth with substance use disorders and severe mood dysregulation. 2021; https://clinicaltrials.gov/ct2/show/NCT02845453. Accessed November 1, 2021.

Appendix A. Abstracts of New Eligible Studies

Hou Y, Xie J, Yuan Y, et al. Neurocognitive effects of atypical antipsychotics in patients with first-episode schizophrenia. *Nord J Psychiatry.* 2020;74(8):594-601. doi: 10.1080/08039488.2020.1771767.

Introduction: Cognitive impairment is a core feature of schizophrenia. The effects of atypical antipsychotics on the cognitive functions of patients with first-episode schizophrenia have not been comprehensively investigated so far. This study aims to compare neurocognitive effects of risperidone, olanzapine, and aripiprazole for first-episode schizophrenia. Methods: The study was a multicenter, randomized, open-label clinical trial. 546 patients were randomly divided into three medication groups, and followed up for 1 year. Cognitive performance was evaluated with a neuropsychological test battery. The Clinical trials.gov ID of the study is NCT01057849. Results: At 6 months, treatment resulted in significant improvements in all three groups in most cognitive domains except verbal learning and memory. At 12 months, three treatment groups had further improvements in three cognitive domains, but visual learning and memory performance dropped back to baseline. Conclusion: All three atypical antipsychotics tested in the study can potentially improve cognitive performance in first-episode schizophrenia, but no significant difference in the degree of improvement was found between drugs.

Patino LR, Klein CC, Strawn JR, et al. A randomized, double-blind, controlled trial of lithium versus quetiapine for the treatment of acute mania in youth with early course bipolar disorder. *J Child Adolesc Psychopharmacol.* 2021;31(7):485-493. doi: 10.1089/cap.2021.0039.

Objective: To compare the efficacy and tolerability of lithium versus quetiapine for the treatment of manic or mixed episodes in youths with early course bipolar I disorder. Methods: Six-week, randomized, double-blind clinical trial of lithium versus quetiapine for the treatment of adolescents with acute manic/mixed episode. Target dose of quetiapine dose was adjusted to a target dose of 400-600 mg and target serum level for lithium was 1.0-1.2 mEq/L. Primary outcome measure was baseline-to-endpoint change in the Young Mania Rating Scale (YMRS). Secondary outcomes were treatment response (50% or more decrease from baseline in YMRS score) and remission (YMRS score <=12, Children's Depression Rating Scale-Revised [CDRS-R] total score <=28 and Clinical Global Impression Bipolar Severity Scale [CGI-BP-S] overall score of <=3, respectively). Results: A total of 109 patients were randomized (quetiapine = 58 and lithium = 51). Participants in the quetiapine treatment group showed a significantly greater reduction in YMRS score than those in the lithium group (-11.0 vs. -13.2; $p < 0.001$; effect size 0.39). Response rate was 72% in the quetiapine group and 49% in the lithium group ($p = 0.012$); no differences in remission rates between groups were observed. Most frequent side effects for lithium were headaches (60.8%), nausea (39.2%), somnolence (27.5%), and tremor (27.5%); for quetiapine somnolence (63.8%), headaches (55.2%), tremor (36.2%), and dizziness (36.2%) were evidenced. Participants receiving quetiapine experienced more somnolence ($p < 0.001$), dizziness ($p < 0.05$), and weight gain ($p < 0.05$). Conclusions: Treatment with both lithium and quetiapine led to clinical improvement. Most study participants in this study experienced a clinical response; however, less than half of the participants in this study achieved symptomatic remission. The head-to-head comparison of both treatment groups showed quetiapine was associated with a statistically significant greater rate of response and overall symptom reduction compared with lithium. Trial registration: clinicaltrials.gov NCT00893581.

Streicher JV, Wen H, Blom TJ, et al. A preliminary study of the effects of treatment with lithium versus quetiapine on attention of adolescents with bipolar disorder. *J Child Adolesc Psychopharmacol.* 2020;30(7):465-469. doi: 10.1089/cap.2019.0169.

Objectives: Despite attentional deficits being a prominent feature of bipolar disorder, there are limited data on the effects of common treatments for bipolar disorder on attention. Thus, we sought to compare the effects of lithium versus quetiapine on attention in adolescents with bipolar disorder. Methods: Adolescents ages 10-17 with bipolar disorder, type I, who were experiencing a manic or mixed episode, were recruited from outpatient settings and the inpatient psychiatric units at Cincinnati Children's Hospital Medical Center during their first manic episode. Healthy comparison subjects were recruited from outreach programs in the community. Patients were randomized to lithium or quetiapine, administered in a double-dummy, double-blinded manner for 6 weeks. Attentional deficits were assessed in all groups using the Identical Pairs Continuous Performance Task at baseline and at week 6. Results: Patients with bipolar disorder (n = 79) had impaired attention relative to the healthy group (n = 57) at both baseline and after 6 weeks of treatment. The lithium-treated group (n = 30) had poorer attentional performance than the healthy group at week 6. There was a difference in change in performance between lithium- and quetiapine-treated (n = 49) groups. Conclusion: Youth with bipolar disorder may have impaired attention relative to their healthy peers. Conclusions are limited by the high dropout rate in the lithium-treated group.

Appendix B. ITS Ratings and Definitions

The *Is There a There There Scale* (ITS) consists of 3 ratings: *no*, *maybe,* and *yes*. The definitions of these ratings and methods for selection are described below. Center for Evidence-based Policy (Center) researchers use these definitions to rate each surveillance topic. The assigned rating is offered as guidance and does not require Drug Effectiveness Review Project (DERP) participants to follow this recommendation. Each rating is strictly based on the identified new research and clinical information and is not comprehensive to all aspects of policy decision making, such as competing priorities, budget, contracting, or internal and external state agency needs.

No

- We did not find clinical evidence or information that would indicate a need to update the report or develop a derivative research product.
- A rating of *No* is typically given when there are few new studies and/or no new meaningful studies, and no new serious harms.

Maybe

- We found some clinical evidence or information that might suggest a need to update the report or develop a derivative research product.
- A rating of *Maybe* is typically given when there are multiple new comparative trials or at least 1 new meaningful study or serious harm.

Yes

- We found clinical evidence or information that suggests a need to update the report or develop a derivative research product.
- A rating of *Yes* is typically given when there are multiple new comparative trials and meaningful studies and/or new serious harms, drugs, formulations, or indications.

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