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OHSU Drug Effectiveness Review Project Summary Report – Second Generation Antipsychotic Medications in Children and Adolescents

Date of Review: April 2021

Date of Last Review: August 2020 (Adults/Pediatrics)
Literature Search: 01/01/1946-04/14/2020

Current Status of PDL Class:
See **Appendix 1**.

Research Questions:

1. What are the benefits and harms of using second generation antipsychotics (SGAs) to treat adolescents with schizophrenia and other psychotic disorders, first episode schizophrenia, and bipolar disorder?
2. What are the benefits and harms of using SGAs to treat children and adolescents with agitation associated with autism spectrum disorder (ASD)?
3. What are the benefits and harms of using SGAs to treat children and adolescents with disruptive behavior disorders, impulse control disorders, and conduct disorders?

Conclusions:

- Irritability Associated with Autism Spectrum Disorder
  - Fourteen randomized controlled trials (RCTs) were included in the analysis.
  - Agents studied included: aripiprazole, lurasidone, and risperidone.
  - Risperidone and aripiprazole demonstrated efficacy using the Aberrant Behavior Checklist and Clinical Global Impressions-Improvement subscale, lurasidone did not.
  - Most Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) outcome ratings were moderate given larger sample sizes than seen in other therapeutic areas.
  - Most studies were placebo-controlled.
- Schizophrenia and First Episode Psychosis
  - Sixteen RCTs were included in the analysis.
  - Agents studied included: aripiprazole, asenapine, haloperidol (not SGA), lurasidone, molindone (not available in United States), olanzapine, paliperidone extended release (ER), quetiapine, and risperidone.
  - No head-to-head studies showed statistical improvement of one therapy over another, though all drugs did show benefit over placebo for symptomatic and functional improvement using various assessment scales.
  - Most studies had moderate or high risk of bias, and many studies had high placebo response rates.

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- Most GRADE outcome ratings were low to very low.
- Patients with first episode psychosis may be more sensitive to adverse events (AEs), particularly weight gain, than patients who have used antipsychotics in the past.

- Bipolar Disorder
  - Ten RCTs were included in the analysis.
  - Agents studied included: aripiprazole, asenapine, lurasidone, olanzapine, quetiapine, quetiapine extended release (XR), and risperidone.
  - Six of the 10 RCTs were 4 weeks or less, which may be inadequate to determining full response to treatment.
  - All trials were placebo controlled except for one head-to-head study of risperidone vs. quetiapine in bipolar II depression.
  - SGAs lowered patient scores on mania assessments versus placebo. A Young Mania Rating Scale and/or Clinical Global Impressions-Improvement score indicating moderate to severe disease were common patient inclusion criteria.
  - SGAs did not provide greater benefit than placebo in patients with bipolar depression (bipolar I or bipolar II) based on Children's Depression Rating Scale and Clinical Global Impressions-Bipolar Disorder assessment.
  - GRADE ratings were low to very low, with improvement on the Young Mania Rating Scale for asenapine over placebo rated as moderate.
- Disruptive Behavior Disorders
  - Eight RCTs were included in the analysis.
  - Agents studied included: aripiprazole, quetiapine, and risperidone.
  - Head-to-head studies of risperidone versus aripiprazole showed no statistical improvement of one therapy over another.
  - Risperidone consistently showed functional and symptomatic outcome improvements when given according to typical clinical dosage.
  - Risperidone demonstrated efficacy soon after treatment initiation (2 weeks).
  - GRADE ratings ranged from moderate to very low. All efficacy outcomes for quetiapine were considered very low because of small sample size.
- Harms
  - Weight gain is a common AE with SGAs, and typically increases with longer treatment exposure.
  - Prolactin levels often increase with risperidone and paliperidone ER, and may decrease with aripiprazole.
  - Electrocardiogram (ECG) changes were not routinely reported.
  - Akathisia and extrapyramidal symptoms (EPS) are increased with all SGAs compared to placebo. Risperidone, aripiprazole, paliperidone ER, lurasidone, and asenapine may have highest risk.
  - Other metabolic parameters (total cholesterol, low-density lipoprotein [LDL], triglycerides, and fasting glucose) should be monitored for all SGAs, particularly olanzapine and quetiapine.
  - Elevations in liver enzymes resulted in study discontinuation in multiple patients with schizophrenia taking olanzapine in a single study.
  - Grade ratings were not included for harms outcomes in this review, consider evidence insufficient.
- There is lack of evidence testing for the effectiveness of SGAs in improving school progress.
- Hospitalizations, need for acute symptom treatment, and progress in different social settings (such as school) were not discussed in these studies in relation to ASD and disruptive behavior disorder.

Recommendations:

- No changes to current preferred drug list (PDL).
- Identifying provider education opportunities to more broadly address off-label use of antipsychotics in kids and pursue strategies to notify prescribers.
- After review costs in executive session, no PDL changes were made.

Summary of Prior Reviews and Current Policy

In the Oregon Health Plan, antipsychotic drugs (APD) are exempt from traditional preferred drug list (PDL) and prior authorization (PA) requirements. However, clinical PA criteria that address safety concerns or medically inappropriate use may be implemented. Currently, safety edits are implemented for low dose quetiapine to prevent off-label use. The PA criteria for the quetiapine safety edit is outlined in **Appendix 2**. Injectable formulations of aripiprazole, chlorpromazine, fluphenazine, haloperidol, paliperidone palmitate, and risperidone are on the PDL. Oral SGAs on the PDL are listed in **Appendix 1**. Most APD use in the Oregon Medicaid population is for oral SGAs, including aripiprazole, quetiapine, risperidone, and olanzapine. Approximately 4% of APD claims are for parenteral formulations. Paliperidone and aripiprazole are the most frequently prescribed injectable APDs in this class. Overall, oral and parenteral SGAs represent some of the highest gross expenditure on the PDL. Previous reviews have found insufficient evidence of clinically meaningful differences between antipsychotic agents in efficacy, effectiveness, or harms between antipsychotic agents for schizophrenia, bipolar mania, or major depressive disorder (MDD). There is insufficient evidence from randomized controlled trials or high-quality systematic reviews to determine if new formulations of long-acting injectable aripiprazole and paliperidone offer improved safety or efficacy over other formulations of aripiprazole and paliperidone, or to other APDs.

Methods:

The September 2020 drug class report on Second Generation Antipsychotic Medications in Children and Adolescents by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

PICOS

The population for this report included individuals with diagnosis as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (preferred) or investigator-defined criteria for diagnosis in the absence of DSM-5 criteria. These included:

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

The medications with FDA approval for use in children and adolescents and included in this review are available in **Appendix 3**. The review searched for head-to-head comparisons and placebo comparisons for all populations. Study designs were limited to RCTs. Quality of life, functional capacity, hospitalization, persistence (ability to continue medication over time) and symptom response were the efficacy and effectiveness outcomes, while harms included overall AEs, withdrawals due to AEs, and specific adverse events. There were 22 different rating scales included in outcomes throughout the report, with the most common being the Aberrant Behavior Checklist (ABC), Clinical Global Impressions (CGI with Severity and Improvement subscales), Nisonger Child Behavior Rating Form (NCBRF), Positive and Negative Symptoms Scale (PANSS), Brief Psychiatric Rating Scale-Child (BPRS-C), Children's Global Assessment Scale (CGAS), Young Mania Rating Scale (YMRS), Children's Depression Rating Scale-Revised Version (CDRS-R), and Conners Parent Rating Scale (CPRS).

A total of 60 publications, representing 48 RCTs, met criteria and were included in the data synthesis.

Summary Findings:
This report did not include a pooled meta-analysis of study outcomes given small number of trials with similar endpoints and comparison groups. Therefore, an overall quantitative assessment with magnitude of effect is not available.

Irritability in ASD

There were 14 RCTs analyzed which included an intervention for irritability in patients with ASD or developmental disorders. Most of the studies focused on participants aged 5 to 17, while 1 study focused specifically on preschool aged children. Patients generally had a baseline Aberrant Behavior Checklist-Irritability (ABC-I) of 18 or more, indicating moderate to severe agitation. The studies were rated as low risk of bias (RoB) (5 studies), moderate RoB (6 studies), and high RoB (3 studies), with the most common limitations being small sample sizes (range 23 to 316 participants), high attrition rates, and significant involvement of industry beyond study funding. Details of efficacy outcomes are provided in **Table 1.** Most studies lasted 8 to 16 weeks.

Table 1: Efficacy outcomes for Irritability Associated with ASD

Outcome	Comparison	Quality of Evidence (GRADE)	Evidence conclusion*
ABC-I	Risperidone vs. placebo 3 RCTs; N=331	Moderate Downgraded 1 level for risk of bias	Risperidone superior to placebo
	Risperidone vs. aripiprazole 2 RCTs; N=120	Moderate Downgraded 1 level for risk of bias	Risperidone was similar to aripiprazole
	Aripiprazole vs. placebo 4 RCTs; N=493	Moderate Downgraded 1 level each for risk of bias and inconsistency Upgraded 1 level for aripiprazole dose-response relationship	Aripiprazole was superior to placebo
	Lurasidone vs. placebo 1 RCT; N=150	Moderate Downgraded 1 level for imprecision	Lurasidone was not efficacious compared to placebo
CGI-I	Risperidone vs. placebo 2 RCTs; N=197	Moderate Downgraded 1 level for risk of bias	High-dose risperidone may have better efficacy than placebo
	Risperidone vs. aripiprazole 2 RCTs; N=120	Moderate Downgraded 1 level for risk of bias	Risperidone was similar to aripiprazole
	Aripiprazole vs. placebo 4 RCTs; N=493	Moderate Downgraded 1 level for risk of bias Upgraded 1 level for aripiprazole dose-response relationship	Aripiprazole was superior to placebo
	Lurasidone vs. placebo 1 RCT; N=150	Moderate Downgraded 1 level for inconsistency	Uncertain relationship between lurasidone and placebo Low dose showed significant improvement while high dose did not
CGI-S	Risperidone vs. placebo 3 RCTs; N=258	Moderate Downgraded 1 level for risk of bias	No significant difference between risperidone and placebo
	Aripiprazole vs. placebo 3 RCTs; N=408	Moderate Downgraded 1 level for risk of bias	Aripiprazole was superior to placebo
	Lurasidone vs. placebo 1 RCT; N=150	Moderate No downgrading or upgrading for this outcome	Lurasidone was similar to placebo
NCBRF-Conduct Problem	Risperidone vs. placebo 2 RCTs; N=134	Moderate Downgraded 1 level for risk of bias	Risperidone was superior to placebo

Abbreviations: ABC-I = Aberrant Behavior Checklist-Irritability domain; CGI-I = Clinical Global Impressions-Improvement; CGI-S = Clinical Global Impressions-Severity; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; N = number; NCBRF = Nisonger Child Behavior Rating Form; RCTs = randomized controlled trials.
*Conclusions relate to statistical significance. Minimum clinically important difference may not be defined for all outcomes.

Schizophrenia and First Episode Psychosis

There were 16 RCTs analyzed for schizophrenia and first episode psychosis. The studies were rated as low RoB (1 study), moderate RoB (7 studies), and high RoB (8 studies). Details of efficacy outcomes are provided in **Table 2.** Studies had 22 to 326 participants with most frequent duration of 6 to 12 weeks, and a range of 6 to 52 weeks for schizophrenia and 6 weeks to 6 months for first episode psychosis.

Table 2: Efficacy Outcomes for Schizophrenia

Outcome	Comparison	Quality of Evidence (GRADE)	Evidence conclusion*
Schizophrenia			
PANSS Total score	Risperidone vs. olanzapine: 3 RCTs; N = 171	Low Downgraded 1 level for risk of bias and 1 level for indirectness	No significant difference was observed between risperidone and olanzapine.
	Risperidone vs. quetiapine: 1 RCT; N = 30	Low Downgraded 1 level for risk of bias and 1 level for imprecision	Risperidone was superior to quetiapine.
	Risperidone vs. placebo: 1 RCT; N = 160	Low Downgraded 2 levels for risk of bias	Risperidone was superior to placebo.
	Aripiprazole vs. placebo: 1 RCT; N = 294	Low Downgraded 2 levels for risk of bias	High-dose aripiprazole was more efficacious than placebo.
	Olanzapine vs. placebo: 1 RCT; N = 107	Low Downgraded 2 levels for risk of bias	Olanzapine was superior to placebo.
	Paliperidone vs. placebo: 1 RCT; N = 200	Very low Downgraded 2 levels for risk of bias and 1 level for inconsistency	Uncertain relationship between paliperidone and placebo.
	Quetiapine vs. placebo: 1 RCT; N = 222	Low Downgraded 2 levels for risk of bias	Quetiapine was superior to placebo.
	Paliperidone vs. aripiprazole: 1 RCT; N = 228	Low Downgraded 2 levels for risk of bias	No difference between paliperidone and aripiprazole.
	Asenapine vs. placebo: 1 RCT; N = 306	Moderate Downgraded 1 level for risk of bias	No difference between asenapine and placebo.
	Lurasidone vs. placebo: 1 RCT; N = 326	Low Downgraded 2 levels for risk of bias	Lurasidone was superior to placebo.
CGI-S Score	Risperidone vs. olanzapine: 3 RCTs; N = 106	Low Downgraded 1 level for risk of bias and 1 level for indirectness	No significant differences were observed between risperidone and olanzapine.
	Risperidone vs. quetiapine: 1 RCT; N = 30	Very low	No significant differences between risperidone and quetiapine.

		Downgraded 1 level for risk of bias, 1 level for indirectness, and 1 level for imprecision	
	Aripiprazole vs. placebo: 1 RCT; N = 294	Low Downgraded 2 levels for risk of bias	Both low and high doses of aripiprazole were statistically significantly superior to placebo.
	Risperidone vs. placebo: 1 RCT; N = 160	Low Downgraded 2 levels for risk of bias	Risperidone was superior to placebo.
	Olanzapine vs. placebo: 1 RCT; N = 107	Low Downgraded 2 levels for risk of bias	Olanzapine was superior to placebo.
	Paliperidone vs. placebo: 1 RCT; N = 200	Low Downgraded 2 levels for risk of bias	Both medium and high paliperidone doses were more effective compared to placebo.
	Quetiapine vs. placebo: 1 RCT; N = 222	Low Downgraded 2 levels for risk of bias	High-dose quetiapine was statistically significantly superior to placebo.
	Paliperidone vs. aripiprazole: 1 RCT; N = 228	Low Downgraded 2 levels for risk of bias	No difference between paliperidone and aripiprazole.
	Lurasidone vs. placebo: 1 RCT; N = 326	Low Downgraded 2 levels for risk of bias	Lurasidone was superior to placebo.
CGAS Score	Risperidone vs. olanzapine: 2 RCTs; N = 55	Very low Downgraded 1 level for risk of bias, 1 level for imprecision, and 1 level for indirectness	No significant difference between risperidone and olanzapine.
	Risperidone vs. quetiapine: 1 RCT; N = 30	Very low Downgraded 1 level for risk of bias, 1 level for imprecision, and 1 level for indirectness	No significant difference between risperidone and quetiapine.
	Aripiprazole vs. placebo: 1 RCT; N = 294	Low Downgraded 2 levels for risk of bias	Both low and high doses of aripiprazole were statistically significantly superior to placebo.
	Risperidone vs. placebo: 1 RCT; N = 160	Low Downgraded 2 levels for risk of bias	Risperidone was superior to placebo.
	Olanzapine vs. placebo: 1 RCT; N = 107	Low Downgraded 2 levels for risk of bias	Olanzapine was superior to placebo.
	Paliperidone vs. placebo: 1 RCT; N = 200	Low Downgraded 2 levels for risk of bias	Uncertain relationship between paliperidone and placebo; mixed results.
	Quetiapine vs. placebo: 1 RCT; N = 222	Very low Downgraded 2 levels for risk of bias and 1 level for imprecision	High-dose quetiapine was statistically superior to placebo.
	Lurasidone vs. placebo: 1 RCT; N = 326	Low Downgraded 2 levels for risk of bias	Lurasidone was superior to placebo.
	Risperidone vs. olanzapine vs. molindone:	Moderate Downgraded 1 level for risk of bias	Both risperidone and olanzapine had better efficacy than placebo.

	1 RCT; N = 116		
	Olanzapine vs. placebo: 1 RCT; N = 107	Low Downgraded 2 levels for risk of bias	Olanzapine was superior to placebo.
BPRS-C	Quetiapine vs. placebo: 1 RCT; N = 222	Very low Downgraded 2 levels for risk of bias and 1 level for imprecision	High-dose quetiapine was statistically superior to placebo.
	Quetiapine vs. placebo: 1 RCT; N = 222	Very low Downgraded 2 levels for risk of bias and 1 level for imprecision	High-dose quetiapine was statistically superior to placebo.
First Episode Psychosis			
PANSS	Quetiapine vs. olanzapine: 1 RCT; N = 50	Moderate Downgraded 1 level for risk of bias	No difference between quetiapine and olanzapine.
	Quetiapine vs. risperidone: 1 RCT; N = 22	Very low Downgraded 1 level for risk of bias, 1 level for imprecision, and 1 level for indirectness	No difference between quetiapine and risperidone.
	Quetiapine vs. aripiprazole: 1 RCT; N = 113	Moderate Downgraded 1 level for risk of bias	No difference between quetiapine and aripiprazole.
CGI-S Score	Quetiapine vs. olanzapine: 1 RCT; N = 50	Moderate Downgraded 1 level for risk of bias	No difference between quetiapine and olanzapine.
	Quetiapine vs. risperidone: 1 RCT; N = 22	Very low Downgraded 1 level for risk of bias, 1 level for imprecision, and 1 level for indirectness	No difference between quetiapine and risperidone.
CGAS Score	Quetiapine vs. olanzapine: 1 RCT; N = 50	Moderate Downgraded 1 level for risk of bias	No difference between quetiapine and olanzapine.

Abbreviations: BPRS-C = Brief Psychiatric Rating Scale-Child; CGAS = Children's Global Assessment; CGI-S = Clinical Global Impressions Scale- Severity; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; PANSS = Positive and Negative Syndrome Scale; N = number; RCT = Randomized controlled trial.
*Conclusions relate to statistical significance. Minimum clinically important difference may not be defined for all outcomes.

Bipolar Disorder

There were 10 RCTs analyzed for bipolar affective disorder included in this review. The studies were rated as low RoB (1 study), moderate RoB (3 studies), and high RoB (6 studies). Details of efficacy outcomes are provided in **Table 3.** Studies had 22 to 403 participants with most frequent duration of 3 to 8 weeks, and a range of 3 to 72 weeks. Only one study included head-to-head comparison of two drugs (quetiapine vs. risperidone); this 12-week, open-label trial was the smallest of the analysis.

Table 3: Efficacy Outcomes for Bipolar Disorder

Outcome	Comparison	Quality of Evidence (GRADE)	Evidence conclusion*
YMRS	Olanzapine vs. placebo: 1 RCT; N = 161	Low Downgraded 2 levels for risk of bias	Olanzapine was statistically superior to placebo.
	Risperidone vs. placebo: 1 RCT; N = 169	Very low Downgraded 2 levels for risk of bias and 1 level for imprecision	Risperidone was statistically superior to placebo.
	Quetiapine vs. risperidone: 1 RCT; N = 22	Very low Downgraded 1 level for risk of bias, 1 level for indirectness, and 1 level for imprecision	No significant difference between quetiapine and risperidone.
	Quetiapine vs. placebo: 1 RCT; N = 316	Low Downgraded 2 levels for risk of bias	No significant difference between quetiapine and placebo.
	Aripiprazole vs. placebo: 1 RCT; N = 296	Low Downgraded 2 levels for risk of bias	Aripiprazole was statistically superior to placebo.
	Asenapine vs. placebo: 1 RCT; N = 403	Moderate Downgraded 1 level of risk of bias	Asenapine was statistically superior compared to placebo.
CDRS-R	Quetiapine vs. placebo: 3 RCTs; N = 509	Very low Downgraded 2 levels for risk of bias and 1 level for inconsistency	No significant difference was observed between quetiapine and placebo. High-dose quetiapine may have some efficacy over placebo.
	Aripiprazole vs. placebo: 2 RCTs; N = 356	Low Downgraded 2 levels for risk of bias	No difference between aripiprazole and placebo.
	Asenapine vs. placebo: 1 RCT; N = 403	Moderate Downgraded 1 level for risk of bias	No difference between asenapine and placebo.
	Lurasidone vs. placebo: 1 RCT; N = 347	Moderate Downgraded 1 level for risk of bias	Lurasidone was statistically superior to placebo.
CGAS Score	Quetiapine vs. risperidone: 1 RCT; N = 22	Very low Downgraded 1 level for risk of bias, 1 level for imprecision, and 1 level for indirectness	No significant difference between quetiapine and risperidone.
	Quetiapine vs. placebo: 1 RCT; N = 284	Low Downgraded 2 levels for risk of bias	Both quetiapine doses were statistically superior to placebo.
	Aripiprazole vs. placebo: 1 RCT; N = 296	Low Downgraded 2 levels for risk of bias	Aripiprazole was statistically superior to placebo.
	Asenapine vs. placebo: 1 RCT; N = 403	Moderate Downgraded 1 level for risk of bias	Asenapine was statistically superior to placebo.

Abbreviations: CDRS-S = Children's Depression Rating Scale-Revised Version; CGAS = Children's Global Assessment Scale; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; N = number; RCT = randomized controlled trial; YMRS = Young Mania Rating Scale.

*Conclusions relate to statistical significance. Minimum clinically important difference may not be defined for all outcomes.

Disruptive Behavior, Impulse Control, and Conduct Disorders

Eight RCTs were identified and analyzed for disruptive behavior, impulse control, and conduct disorders in this review. The studies were rated as moderate RoB (4 studies) and high RoB (4 studies). Details of efficacy outcomes are provided in **Table 4**. One study assessing risperidone versus placebo was significantly larger (N=335) and longer (6 months) than the other trials, which included 13 to 118 participants and had durations of 4 to 10 weeks. Most studies allowed or required sub-average intelligence quotient for study enrollment.

Table 4: Efficacy Outcomes for Disruptive Behavior, Impulse Control, and Conduct Disorders

Outcome	**Comparison**	**Quality of Evidence (GRADE)**	**Evidence conclusion***
N-CBRF Conduct Subscale	Risperidone vs. placebo: 4 RCTs; N = 640	Moderate Downgraded 1 level for risk of bias	Statistically significant improvement in risperidone group compared to placebo.
VAS	Risperidone vs. placebo: 5 RCTs; N = 653	Moderate Downgraded 1 levels for risk of bias	Risperidone was superior to placebo.
CGI-I	Risperidone vs. placebo: 3 RCTs; N = 248	Low Downgraded 2 levels for risk of bias	Risperidone was superior to placebo.
	Risperidone vs. aripiprazole: 1 RCT; N = 40	Low Downgraded 2 levels for risk of bias	No difference between risperidone and aripiprazole.
CGI-S	Risperidone vs. placebo: 2 RCTs; N = 355	Low Downgraded 2 levels for risk of bias	The relationship between risperidone and placebo was uncertain. One trial demonstrated significance and one did not.
	Risperidone vs. aripiprazole: 1 RCT; N = 40	Very low Downgraded 2 levels for risk of bias and 1 for imprecision	No difference between risperidone and aripiprazole.
	Quetiapine vs. placebo: 1 RCT; N = 19	Very low Downgraded 2 levels for risk of bias and 1 for imprecision	Quetiapine was statistically significant over placebo by week 5 (total 7 week duration)
ABC-I	Risperidone vs. placebo: 3 RCTs; N = 241	Low Downgraded 2 levels for risk of bias	Statistically significant improvement in risperidone group compared to placebo.
CPRS	Risperidone vs. placebo: 1 RCT; N = 20	Very low Downgraded 2 levels for risk of bias and 1 level for imprecision	Risperidone had some efficacy over placebo.
	Risperidone vs. aripiprazole: 1 RCT; N = 40	Very low Downgraded 2 levels for risk of bias and 1 level for imprecision	No difference between risperidone and aripiprazole.
	Quetiapine vs. placebo: 1 RCT; N = 19	Very low Downgraded 2 levels for risk of bias and 1 level for imprecision	Unable to detect differences between the experimental and control group for CPRS-CP due to small sample size.

Abbreviations: ABC = Aberrant Behavior Checklist-irritability subscale; CGI-I = Clinical Global Impressions-improvement; CGI-S = Clinical Global Impressions-severity; CPRS = Conners Parent Rating Scale; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; N = number; N-CBRF = Nisonger Child Behavior Rating Form; RCT = randomized controlled trial; VAS = Visual Analog Scale.
*Conclusions relate to statistical significance. Minimum clinically important difference may not be defined for all outcomes.

Harms

Harms data varied in assessment and may be affected by length of intervention, with longer studies more likely to reveal certain side effects. Harms were not pooled between studies in this report and there are no GRADE ratings.

ASD

In general, weight gain (2.7 to 5.7 kg), drowsiness/somnolence, increased prolactin, and fatigue were all more common in risperidone treated patients, while no change was noted in ECG measures. No significant differences were noted in lipid measures, fasting plasma glucose, or abnormal involuntary movement scale (AIMS) measures, though maximum trial duration of 16 weeks may have limited these outcomes. An increased appetite and EPS were noted in some studies.

Aripiprazole was also associated with weight gain (1.3 to 11 kg), somnolence, fatigue, EPS, and drooling. Weight differences were not always statistically significant versus placebo. Changes in appetite and ECG were not noted. Decreased prolactin was noted in more than one study.

Lurasidone patients had higher rates of vomiting and somnolence, as well as weight gain (0.5 to 1.2 kg, dose dependent) than placebo.

Adverse event rates of interest, such as movement-related AEs and metabolic parameters were not reported in all studies.

Schizophrenia and First Episode Psychosis

Olanzapine was associated with significant, non-time limited weight gain. Olanzapine and quetiapine increased other metabolic parameters, including: total cholesterol, LDL, triglycerides, and fasting blood glucose. Prolactin was increased with risperidone and paliperidone ER, but decreased with aripiprazole. All SGAs tested in this population were associated with increased akathisia and EPS compared to placebo, with risperidone, aripiprazole, paliperidone ER, lurasidone, and asenapine being associated with the highest risk.

Bipolar Disorder

Six of the 10 trials involving patients with bipolar disorder were 4 weeks or less in duration, making assessment of long-term side effects more difficult. Olanzapine, then quetiapine and risperidone caused the greatest weight gain. Similar to patients with schizophrenia, risperidone increased prolactin while aripiprazole decreased the prolactin level. Weight gain for asenapine versus placebo varied by trial.

Disruptive Behavior, Impulse Control, and Conduct Disorders

Description of AEs in patients with these diagnoses were difficult. High rates of AEs in both active and placebo groups were reported, and differentiation of AEs from symptoms associated with underlying condition was challenging. Weight gain was noted and tended to increase with longer exposure. Clinical effects of

increased prolactin concentrations with risperidone use were not seen in these short-term studies. Extrapyramidal symptoms and abnormal movements were not commonly reported.

Ongoing Trials

There are two ongoing trials, both for ASD, that fit within the scope of this review. A single phase 2 RCT is evaluating risperidone vs. placebo in 8 to 16-year-olds, while a phase 3 RCT compares aripiprazole vs. placebo in 6 to 17-year-olds. Data completion is estimated for December 1, 2016 for 41 patients for the phase 2 trial, and April 1, 2020 with an enrollment of 100 patients in the aripiprazole study.

References:

1. Drug Effectiveness Review Project (DERP). Second Generation Antipsychotic Medications in Children and Adolescents: Systematic Review Update. September 2020

Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
aripiprazole	ABILIFY	ORAL	TABLET	Y
aripiprazole	ARIPIPRAZOLE	ORAL	TABLET	Y
asenapine maleate	ASENAPINE MALEATE	SUBLINGUAL	TAB SUBL	Y
asenapine maleate	SAPHRIS	SUBLINGUAL	TAB SUBL	Y
cariprazine HCl	VRAYLAR	ORAL	CAP DS PK	Y
cariprazine HCl	VRAYLAR	ORAL	CAPSULE	Y
clozapine	CLOZAPINE	ORAL	TABLET	Y
clozapine	CLOZARIL	ORAL	TABLET	Y
lurasidone HCl	LATUDA	ORAL	TABLET	Y
olanzapine	OLANZAPINE	ORAL	TABLET	Y
olanzapine	ZYPREXA	ORAL	TABLET	Y
quetiapine fumarate	QUETIAPINE FUMARATE	ORAL	TABLET	Y
quetiapine fumarate	SEROQUEL	ORAL	TABLET	Y
risperidone	RISPERDAL	ORAL	SOLUTION	Y
risperidone	RISPERIDONE	ORAL	SOLUTION	Y
risperidone	RISPERDAL	ORAL	TABLET	Y
risperidone	RISPERIDONE	ORAL	TABLET	Y
ziprasidone HCl	GEODON	ORAL	CAPSULE	Y
ziprasidone HCl	ZIPRASIDONE HCL	ORAL	CAPSULE	Y
aripiprazole	ARIPIPRAZOLE	ORAL	SOLUTION	V
aripiprazole	ARIPIPRAZOLE ODT	ORAL	TAB RAPDIS	V
aripiprazole	ABILIFY MYCITE	ORAL	TAB SENSPT	V
asenapine	SECUADO	TRANSDERM	PATCH TD24	V
brexpiprazole	REXULTI	ORAL	TABLET	V
clozapine	VERSACLOZ	ORAL	ORAL SUSP	V
clozapine	CLOZAPINE ODT	ORAL	TAB RAPDIS	V
clozapine	FAZACLO	ORAL	TAB RAPDIS	V
iloperidone	FANAPT	ORAL	TAB DS PK	V
iloperidone	FANAPT	ORAL	TABLET	V
lumateperone tosylate	CAPLYTA	ORAL	CAPSULE	V
olanzapine	OLANZAPINE ODT	ORAL	TAB RAPDIS	V
olanzapine	ZYPREXA ZYDIS	ORAL	TAB RAPDIS	V
paliperidone	INVEGA	ORAL	TAB ER 24	V

paliperidone	PALIPERIDONE ER	ORAL	TAB ER 24	V
pimavanserin tartrate	NUPLAZID	ORAL	CAPSULE	V
pimavanserin tartrate	NUPLAZID	ORAL	TABLET	V
quetiapine fumarate	QUETIAPINE FUMARATE ER	ORAL	TAB ER 24H	V
quetiapine fumarate	SEROQUEL XR	ORAL	TAB ER 24H	V
quetiapine fumarate	SEROQUEL XR	ORAL	TAB24HDSPK	V
risperidone	RISPERIDONE ODT	ORAL	TAB RAPDIS	V

Low Dose Quetiapine

Goal(s):
- To promote and ensure use of quetiapine that is supported by the medical literature.
- To discourage off-label use for insomnia.
- Promote the use of non-pharmacologic alternatives for chronic insomnia.

Initiative:
- Low dose quetiapine (Seroquel® and Seroquel XR®)

Length of Authorization:
- Up to 12 months (criteria-specific)

Requires PA:
- Quetiapine (HSN = 14015) doses ≤50 mg/day
- Auto PA approvals for :
  - Patients with a claim for a second generation antipsychotic in the last 6 months
  - Patients with prior claims evidence of schizophrenia or bipolar disorder
  - Prescriptions identified as being written by a mental health provider

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org/drugs/
- Zolpidem is available for short-term use (15 doses/30 days) without PA.

Table 1. Adult (age ≥18 years) FDA-approved Indications for Quetiapine

Bipolar Disorder	
Major Depressive Disorder (MDD)	Adjunctive therapy with antidepressants for MDD
Schizophrenia	
Bipolar Mania	
Bipolar Depression	

Table 2. Pediatric FDA-approved indications

Schizophrenia	Adolescents (13-17 years)	

Bipolar Mania	Children and Adolescents (10 to 17 years)	Monotherapy

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code. Do not proceed and deny if diagnosis is not listed in Table 1 or Table 2 above (medical appropriateness)	
2. Is the prescription for quetiapine less than or equal to 50 mg/day? (verify days' supply is accurate)	**Yes**: Go to #3	**No:** Trouble-shoot claim processing with the pharmacy.
3. Is planned duration of therapy longer than 90 days?	**Yes:** Go to #4	**No:** Approve for titration up to maintenance dose (60 days).
4. Is reason for dose ≤50 mg/day due to any of the following: • low dose needed due to debilitation from a medical condition or age; • unable to tolerate higher doses; • stable on current dose; or • impaired drug clearance? • any diagnosis in table 1 or 2 above?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny for medical appropriateness. Note: may approve up to 6 months to allow taper.

P&T/DUR Review: *4/21(SF); 8/20 (SF); 3/19 (DM); 9/18; 11/17; 9/15; 9/10; 5/10*
Implementation: *1/1/18; 10/15; 1/1/11*

Appendix 3: Medications Included

Generic Name	Brand Name	Form	Initial Year Approved	Approved Indications in Children[b] or Adolescents[a]
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	

Abbreviations. ASD: autism spectrum disorder; ER: extended release; ODT: orally disintegrating tablet; XR: extended release.