Comparative Effectiveness Review
Number 39

Effective Health Care Program

First- and Second-Generation Antipsychotics for Children and Young Adults

Executive Summary

Introduction

Antipsychotic medications are widely used to treat several psychiatric disorders and are commonly categorized into two classes. First-generation antipsychotics (FGAs), also known as typical antipsychotics, were developed in the 1950s. Although they are used to treat psychotic symptoms, they are associated with various side effects including extrapyramidal symptoms, which are movement disorders characterized by repetitive, involuntary muscle movements, restlessness, or an inability to initiate movement. Other common side effects are dry mouth and sedation. Neuroleptic malignant syndrome and tardive dyskinesia are rare but serious side effects. Second-generation antipsychotics (SGAs), also known as atypical antipsychotics, emerged in the 1980s. They are generally thought to have a lower risk of motor side effects. However, SGAs are associated with a higher risk of weight gain, elevated lipid and prolactin levels, and development of type 2 diabetes.

Use of antipsychotics for children and adolescents has increased during the past 20 years.[1-5] Prescribing antipsychotics to the pediatric population is controversial because there are few high-quality and longitudinal studies on which to base clinical practice recommendations. For the majority of antipsychotic drugs, approved indications in the United States are restricted to the treatment of childhood schizophrenia and bipolar disorders. In 2006, the U.S. Food and Drug Administration (FDA) approved risperidone and aripiprazole for the treatment of irritability associated with autism. Off-label prescriptions are given to

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

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younger children for behavioral symptoms (e.g., aggression) that are related to diagnosable conditions (e.g., attention deficit hyperactivity disorder [ADHD]). In general, the choice of medication in children and adolescents is often driven by side-effect profiles that may affect growth and development, medication adherence and persistence, as well as other important domains such as school performance and health-related quality of life.[6]

This comparative effectiveness review provides a comprehensive synthesis of the evidence examining the benefits and harms associated with the use of FDA-approved FGAs and SGAs in children, adolescents, and young adults ≤24 years of age.

Key Questions

The Key Questions are as follows:

1. What is the comparative efficacy or effectiveness of FGAs and SGAs for treating disorder- or illness-specific and nonspecific symptoms in children, youth, and young adults (≤24 years) for the following disorders or illnesses?

- Pervasive developmental disorders, including autistic disorder, Rett's disorder, childhood disintegrative disorder, Asperger's disorder, and pervasive developmental disorder not otherwise specified.
- ADHD and disruptive behavior disorders, including conduct disorder, oppositional defiant disorder, and disruptive behavior disorder not otherwise specified.
- Pediatric bipolar disorder, including manic or depressive phases, rapid cycling, and mixed states.
- Schizophrenia and schizophrenia-related psychoses, including schizoaffective disorder and drug-induced psychosis.
- Obsessive-compulsive disorder.
- Post-traumatic stress disorder.
- Anorexia nervosa.
- Tourette syndrome.
- Behavioral issues, including aggression, agitation, anxiety, behavioral dyscontrol, irritability, mood lability, self-injurious behaviors, and sleep disorders.

2. Do FGAs and SGAs differ in medication-associated adverse events when used in children, youth, and young adults (≤24 years)? This includes:

- Overall adverse events.
- Specific adverse events.
- Withdrawals and time to withdrawal due to adverse events.
- Persistence and reversibility of adverse events.

3. Do FGAs and SGAs differ in other short- and long-term outcomes when used in children, youth, and young adults (≤24 years)? Short-term is defined as outcomes occurring within 6 months; long-term is defined as outcomes occurring after 6 months.

- Response rates with corresponding dose, duration of response, remission, relapse, speed of response, and time to discontinuation of medication.
- Growth and maturation.
- Cognitive and emotional development.
- Suicide-related behaviors or death by suicide.
- Medication adherence and persistence.
- School performance and attendance.
- Work-related functional capacity.
- Patient insight into illness.
- Patient-, parent-, or care provider–reported outcomes, including levels of physical activity or inactivity and diet (e.g., caloric intake, food preferences).
- Health-related quality of life.
- Legal or justice system interaction (e.g., arrests, detention).
- Health care system utilization (e.g., protective services, social services).
- "Outcomes that matter" to children, youth, young adults, and their families. These functional outcomes may reflect a developmental perspective.

4. Do the effectiveness and risks of FGAs and SGAs vary in differing subpopulations including:

- Sex?
- Age group (<6 years [preschool], 6–12 years [preadolescent], 13–18 years [adolescent], 19–24 years [young adult])?
- Race?
- Comorbidities, including substance abuse and ADHD?
- Cotreatment versus monotherapy?
- First-episode psychosis versus treatment in context of history of prior episodes (related to schizophrenia)?

- Duration of illness?
- Treatment naïve versus history of previous antipsychotics use?

Methods

Literature Search

We systematically searched the following bibliographic databases: MEDLINE, Embase, CENTRAL, PsycINFO, International Pharmaceutical Abstracts (IPA), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus, ProQuest Dissertations International, MedEffect Canada, and TOXLINE. The searches are up to date to February 2011. We limited the searches to studies published from 1987 or later to coincide with the Diagnostic and Statistical Manual of Mental Disorders III–Revised. We restricted the search results to studies published in the English language. We applied filters to restrict the results to children and young adults ≤24 years of age and to trials and cohort studies.

We hand searched proceedings of the following scientific meetings that were identified by our clinical experts: American Academy of Child and Adolescent Psychiatry (2007–2008), International College of Neuropsychopharmacology (2007–2009), and International Society for Bipolar Disorders (2007–2009). We searched clinical trial registers for ongoing studies and reference lists of relevant studies to identify additional studies. In addition, we contacted drug manufacturers to request published and unpublished study data. We reviewed FDA documents related to the eligible drugs to identify additional data.

Study Selection

Two reviewers independently screened titles and abstracts using broad inclusion criteria. We retrieved the full text of all articles identified as "include" or "unclear." Two reviewers independently assessed each article using a priori inclusion criteria and a standardized form. We resolved disagreements by consensus or third-party adjudication.

Randomized controlled trials (RCTs), nonrandomized controlled trials (NRCTs), and cohort studies that examined a condition of interest (pervasive developmental disorders, ADHD and disruptive behavior disorders, bipolar disorder, schizophrenia or schizophrenia-related psychosis, Tourette syndrome, obsessive-compulsive disorder, post-traumatic stress disorder, anorexia nervosa, or behavioral issues) in children or young adults ≤24 years of age were considered for inclusion. Eligible studies compared a FDA-approved FGA or SGA with any other antipsychotic or with placebo. Studies were required to report at least one outcome of interest including symptom improvement, other short- or long-term outcomes, or adverse events. No minimum followup duration was specified.

Quality Assessment and Grading the Body of Evidence

Two reviewers independently assessed the methodological quality of studies. We assessed RCTs and NRCTs using the Cochrane Collaboration risk of bias tool. We assessed cohort studies using a modified Newcastle-Ottawa Quality Assessment Scale. In addition, we recorded the source of funding for all studies. We developed decision rules regarding the application of the tools a priori. We resolved discrepancies through consensus or third-party adjudication.

Two independent reviewers graded the body of evidence using the Evidence-based Practice Center (EPC) GRADE approach and resolved discrepancies by consensus. Table A lists the key outcomes that were graded. We assessed the following four major domains: risk of bias (low, moderate, or high), consistency (consistent, inconsistent, or unknown), directness (direct or indirect), and precision (precise or imprecise). The overall strength of evidence was graded as high, moderate, low, or insufficient.

Data Extraction

One reviewer extracted data using a standardized form, and a second reviewer verified the data for accuracy and completeness. We extracted information on study characteristics, inclusion and exclusion criteria, participant characteristics, interventions, and outcomes. Reviewers resolved discrepancies by consensus or in consultation with a third party.

Data Analysis

We presented evidence tables and a qualitative description of results for all studies. We combined studies in a meta-analysis if the study design, population, interventions, and outcomes were sufficiently similar. Results were combined using random effects models. We quantified statistical heterogeneity using the I-squared (I^2) statistic.

Table A. Key outcomes assessed for strength of evidence			
KQ1 Outcomes		**KQ2 Adverse Events**	**KQ3 Outcomes**
Aggression	Manic symptoms	Dyslipidemia	Health-related quality of life
Anxiety	Obsessive-compulsive symptoms	Extrapyramidal symptoms	Legal and justice system interactions
Autistic symptoms	Social or occupational functioning	Insulin resistance	Medication adherence
Clinical global impressions	Positive and negative symptoms	Prolactin-related and sexual side effects	Patient-, parent- or care provider-reported outcomes
Depression	Tics	Sedation Weight	Suicide-related behaviors

KQ = Key Question

Applicability

We assessed the applicability of the body of evidence following the PICOTS (population, intervention, comparator, outcomes, timing of outcome measurement, and setting) format used to assess study characteristics. Factors that may potentially limit applicability were reported in the results.

Results

Description of Included Studies

The search strategy identified 10,745 citations. A total of 140 articles met the inclusion criteria, of which 81 were unique studies. The studies included 62 RCTs, 2 NRCTs, and 17 cohort studies (9 prospective and 8 retrospective). The number of participants in the studies ranged from 8 to 335 (median = 42). The mean age of study participants ranged from 4.0 to 21.5 years (median = 13.6). Few studies included young adults ages 19 to 24 years.

Studies examined the following conditions: pervasive developmental disorders (12 studies), ADHD and disruptive behavior disorders (8 studies), bipolar disorder (11 studies), schizophrenia and schizophrenia-related psychosis (31 studies), Tourette syndrome (7 studies), behavioral issues (4 studies), and various psychiatric and behavioral conditions (9 studies). One study provided separate data for both bipolar disorder and schizophrenia.

None of the included studies examined obsessive-compulsive disorder, post-traumatic stress disorder, or anorexia nervosa.

Overall, 38 studies provided head-to-head evidence on a total of 19 comparisons of different antipsychotics. In addition, 17 studies compared different doses of the same antipsychotic, and 26 studies compared a single antipsychotic with placebo.

Methodological Quality of Included Studies

Nearly all of the RCTs had a high risk of bias (N = 56, 90 percent); six RCTs had an unclear risk of bias. The two NRCTs had a high risk of bias. Common sources of potential bias were inadequate allocation concealment, inadequate blinding, and incomplete outcome data. Most of the trials (78 percent) received industry funding, which introduces a risk of overestimating the treatment effect.

Overall, the cohort studies were of moderate quality (median score of 5 out of a possible 8). Common weaknesses included lack of independent and blind outcome assessment and failure to adequately control for potential confounding factors.

Results of Included Studies

The results are presented by the Key Question(s) they address. Tables with the summary of findings for efficacy and safety are presented below. Comparisons and outcomes for which evidence was insufficient to draw a conclusion are not displayed in the tables.

Key Question 1: Disorder-specific and nonspecific symptoms. The findings for symptom improvement are presented for each condition in Table B. With the exception of studies examining pervasive developmental disorders and schizophrenia, the evidence comparing FGAs with SGAs and antipsychotics within each class was insufficient to draw conclusions. For most conditions, the majority of the findings focused on the comparison of SGAs with placebo. Comparisons and outcomes for which the evidence was graded as insufficient are not discussed.

A total of 11 studies examining pervasive developmental disorders reported measures of symptom improvement. No significant difference was observed between FGAs and SGAs for autistic symptoms. SGAs were favored over placebo for autistic and obsessive-compulsive symptoms, but no difference was found for on the clinical global impressions (CGI) scale. The strength of evidence for these findings was low.

Eight studies reported the effects of antipsychotics on symptoms in ADHD and disruptive behavior disorders. SGAs were superior to placebo on various measures of behavior symptoms and on the CGI (moderate strength of evidence). There was no difference between SGAs and placebo for aggression or anxiety (low strength of evidence).

Eleven bipolar studies reported symptom improvement. SGAs were favored over placebo on the CGI (moderate strength of evidence). Studies showed no significant difference for depression and a significant difference for mania favoring SGAs over placebo (low strength of evidence).

A total of 25 studies reported symptom improvement in patients with schizophrenia or schizophrenia-related psychosis. SGAs were favored over placebo for the CGI and positive and negative symptoms (moderate strength of evidence). SGAs were significantly favored over FGAs on the CGI (low strength of evidence). No significant difference was found between clozapine and olanzapine or olanzapine and risperidone for the CGI or positive and negative symptoms (low strength of evidence).

Five studies provided evidence on symptom improvement in Tourette syndrome. SGAs were favored over placebo for tics (moderate strength of evidence).

Four studies examined improvement for behavioral issues. One study found greater improvement in autistic symptoms with risperidone than placebo (low strength of evidence).

Table B. Summary of the strength of evidence for symptoms (Key Question 1)			
Outcome	**Comparison (# studies)**	**SOE**	**Summary**
Pervasive Developmental Disorder			
Autistic symptoms	FGA vs. SGA (2 RCTs)	Low	No significant difference.
	SGA vs. placebo (7 RCTs)	Low	Significant effect in favor of SGA on ABC (MD = -18.3; 95% CI: -27.1, -9.5) and CARS (MD = -4.9; 95% CI: -8.5, -1.4).
Clinical global impressions	SGA vs. placebo (3 RCTs)	Low	No significant difference.
OC symptoms	SGA vs. placebo (3 RCTs)	Low	Significant effect in favor of SGA (MD = -1.7; 95% CI: -3.2, -0.3).
ADHD and Disruptive Behavior Disorder			
Aggression	SGA vs. placebo (5 RCTs)	Low	No significant difference.
Anxiety	SGA vs. placebo (4 RCTs)	Low	No evidence of difference.
Behavior symptoms	SGA vs. placebo (7 RCTs)	Moderate	Significant effect in favor of SGA for ABC (MD = -20.97; 95% CI: -31.1, -10.8), BPI (MD = -3.8; 95% CI: -6.2, -1.4), and NCBRF (MD = -6.9; 95% CI: -10.4, -3.5).
Clinical global impressions	SGA vs. placebo (7 RCTs)	Moderate	Significant effect in favor of SGA for CGI–I (MD = -0.95; 95% CI: -1.7, -0.3) and CGI–S (MD = -1.3; 95% CI: -2.2, -0.5).
Bipolar Disorder			
Clinical global impressions	SGA vs. placebo (6 RCTs)	Moderate	Significant effect in favor of SGA (MD = -0.7; 95% CI: -0.8, -0.5).
Depression	SGA vs. placebo (4 RCTs)	Low	No significant difference.
Manic symptoms	SGA vs. placebo (8 RCTs)	Low	All except one study significantly favored SGA (studies not pooled due to high heterogeneity).
Schizophrenia			
Clinical global impressions	FGA vs. SGA (3 RCTs)	Low	Significant effect in favor of SGA (MD = -0.76; 95% CI: -1.3, -0.3).
	Clozapine vs. olanzapine (2 RCTs)	Low	No significant difference.
	Olanzapine vs. risperidone (3 RCTs)	Low	No significant difference.
	SGA vs. placebo (6 RCTs)	Moderate	Significant effect in favor of SGA (MD = -0.5; 95% CI: -0.7, -0.3).
Positive and negative symptoms	FGA vs. SGA (3 RCTs, 1 PCS)	Low	No significant difference.
	Clozapine vs. olanzapine (2 RCTs, 1 PCS)	Low	No significant difference.
	Olanzapine vs. risperidone (3 RCTs, 1 PCS)	Low	No significant difference.
	SGA vs. placebo (6 RCTs)	Moderate	Significant effect in favor of SGA (MD = -8.7; 95% CI: -11.8, -5.6).

Table B. Summary of the strength of evidence for symptoms (Key Question 1) (continued)			
Outcome	**Comparison (# studies)**	**SOE**	**Summary**
Tourette Syndrome			
Tics	SGA vs. placebo (2 RCTs)	Moderate	Significant effect in favor of SGA (MD = -6.98 (95% CI: -10.3, -3.6).
Behavioral Issues			
Autistic symptoms	Risperidone vs. placebo (2 RCTs)	Low	Significant effect in favor of risperidone in one study (MD = -27, 95% CI: NR); significance in second study NR.

ABC = Aberrant Behavior Checklist; BPI = Behavior Problem Inventory; CARS = Childhood Autism Rating Scale; CGI–I = Clinical Global Impressions–Improvement; CGI–S = Clinical Global Impressions–Severity; CI = confidence interval; FGA = first-generation antipsychotic; MD = mean difference; NCBRF = Nisonger Child Behavior Rating Scale; NR = not reported; OC = obsessive-compulsive; PCS = prospective cohort study; RCT = randomized controlled trial; SGA = second-generation antipsychotic; SOE = strength of evidence

Key Question 2: Adverse events. The results for adverse events are summarized by drug comparison across all conditions in Table C.

Twelve studies provided adverse-events data for FGAs versus SGAs. For extrapyramidal symptoms, SGAs were significantly favored over haloperidol (low strength of evidence). Haloperidol was favored over olanzapine for body composition (low strength of evidence). All other adverse events were not significant (low strength of evidence) or had insufficient evidence.

For all comparisons of different FGAs or FGA with placebo, evidence was insufficient to draw a conclusion for adverse events.

A total of 25 studies compared the adverse event profiles of various SGAs. Risperidone was favored over olanzapine for dyslipidemia (moderate strength of evidence). Olanzapine was favored over risperidone for prolactin-related events (moderate strength of evidence). Both quetiapine and risperidone were favored over olanzapine for body composition (moderate strength of evidence). Table C presents outcomes and comparisons for which the strength of evidence was low.

Adverse events were reported in 36 studies comparing SGAs with placebo. For nearly all outcomes and comparisons, the placebo group experienced significantly fewer adverse events than the group receiving SGAs. One exception to this trend was a significant effect in favor of aripiprazole for prolactin-related adverse event (moderate strength of evidence).

Key Question 3: Short- and long-term outcomes. The findings for other short- and long-term outcomes are presented separately for each condition in Table D. The evidence was rated as insufficient to draw conclusions for health-related quality of life, involvement with the legal system, and other patient-, parent-, or care provider–reported outcomes for all conditions. Comparisons and outcomes for which the evidence was graded as insufficient are not discussed.

Short- and long-term outcomes were reported in nine studies examining pervasive developmental disorders and in eight studies examining ADHD and disruptive behavior disorders. Medication adherence was not significantly different between SGAs and placebo for both conditions (low strength of evidence).

Eleven bipolar studies provided data for other outcomes. Medication adherence was significantly better for placebo than for SGAs (low strength of evidence). SGAs and placebo did not significantly differ for suicide-related behaviors (moderate strength of evidence).

Table C. Summary of the strength of evidence for adverse events (Key Question 2)

Outcome	Comparison (# studies)	SOE	Summary
FGA vs. SGA			
EPS	Haloperidol vs. olanzapine (2 RCTs, 1 PCS)	Low	Significant effect in favor of olanzapine (RR = 3.5, 95% CI: 1.1, 10.9).
	Haloperidol vs. risperidone (2 RCTs, 1 PCS)	Low	Significant effect in favor of risperidone for akathisia (RR = 6.9, 95% CI: 1.3, 38.1).
Prolactin-related and sexual AE	Haloperidol vs. olanzapine (1 RCT, 1 PCS)	Low	No significant difference.
	Haloperidol vs. risperidone (2 RCTs)	Low	No significant difference.
Sedation	Haloperidol vs. olanzapine (2 RCTs, 1 PCS)	Low	No significant difference.
	Haloperidol vs. risperidone (1 RCT, 1 PCS)	Low	No significant difference.
Weight/body composition	Haloperidol vs. olanzapine (2 RCTs, 2 PCS)	Low	Significant effect in favor of haloperidol (MD = -5.8, 95% CI: -8.6, -3.0).
	Haloperidol vs. risperidone (2 RCTs, 1 PCS)	Low	No significant difference.
SGA vs. SGA			
Dyslipidemia	Aripiprazole vs. olanzapine (1 PCS)	Low	Significant effect in favor of aripiprazole (RR = 0.25, 95% CI, 0.08, 0.8).
	Aripiprazole vs. quetiapine (1 PCS)	Low	Significant effect in favor of aripiprazole (MD = -39.4, 95% CI, -71.3, -7.4).
	Clozapine vs. olanzapine (2 RCTs)	Low	No significant difference.
	Olanzapine vs. quetiapine (2 PCSs)	Low	No significant difference.
	Olanzapine vs. risperidone (3 RCTs, 2 PCSs)	Moderate	Significant effect in favor of risperidone (triglyceride MD =17.3, 95% CI, 3.5, 31.1).
	Quetiapine vs. risperidone (1 RCT, 2 PCSs)	Low	No significant difference.
EPS	Clozapine vs. olanzapine (1 RCT, 1 PCS, 1 RCS)	Low	No significant difference.
	Clozapine vs. risperidone (1 PCS, 1 RCS)	Low	No significant difference.
	Olanzapine vs. quetiapine (2 RCTs, 1 RCS)	Low	No significant difference
	Olanzapine vs. risperidone (5 RCTs, 3 PCSs, 3 RCSs)	Low	No significant difference
	Quetiapine vs. risperidone (3 RCTs)	Low	No significant difference.
Insulin resistance	Olanzapine vs. quetiapine (2 PCSs)	Low	No significant difference.
	Olanzapine vs. risperidone (2 RCTs, 3 PCSs)	Low	No significant difference.
	Quetiapine vs. risperidone (2 PCSs)	Low	No significant difference.
Prolactin-related and sexual AE	Clozapine vs. olanzapine (1 RCT, 1 PCS, 1 RCS)	Low	Significant effect in favor of clozapine (MD = -10.8, 95% CI, -16.7, -4.8).
	Olanzapine vs. risperidone (10 RCTs, 1 PCS, 1 RCS)	Moderate	Significant effect in favor of olanzapine (RR = 0.4, 95% CI, 0.2, 0.6).
	Quetiapine vs. risperidone (3 RCTs)	Low	No significant difference.

Table C. Summary of the strength of evidence for adverse events (Key Question 2) (contined)

Outcome	Comparison (# studies)	SOE	Summary
SGA vs. SGA (continued)			
Sedation	Clozapine vs. olanzapine (1 RCT, 1 PCS, 1 RCS)	Low	No significant difference.
	Olanzapine vs. quetiapine (2 RCTs, 1 RCS)	Low	No significant difference.
	Olanzapine vs. risperidone (5 RCTs, 2 PCSs, 2 RCSs)	Low	No significant difference.
	Quetiapine vs. risperidone (3 RCTs)	Low	No significant difference.
Weight/body composition	Aripiprazole vs. olanzapine (1 PCS)	Low	Significant effect in favor of aripiprazole (MD = -4.1, 95% CI: -5.5, -2.7).
	Aripiprazole vs. quetiapine (1 PCS)	Low	Significant effect in favor of aripiprazole (MD = -1.6, 95% CI: -3.0, -0.3).
	Aripiprazole vs. risperidone (1 PCS)	Low	Significant effect in favor of aripiprazole (MD = -2.3, 95% CI: -3.9, -0.7).
	Clozapine vs. olanzapine (2 RCTs, 2 PCSs, 1 RCS)	Low	No significant difference.
	Clozapine vs. risperidone (1 RCS, 1 PCS)	Low	No significant difference.
	Olanzapine vs. quetiapine (5 RCTs, 2 PCSs)	Moderate	Significant effect in favor of quetiapine (RR = 1.5, 95% CI: 1.1, 2.0).
	Olanzapine vs. risperidone (8 RCTs, 1 NRCT, 4 PCSs, 1 RCS)	Moderate	Significant effect in favor of risperidone (MD = 2.4, 95% CI: 1.5, 3.3).
	Quetiapine vs. risperidone (3 RCTs, 2 PCSs)	Low	No significant difference.
SGA vs. placebo			
Dyslipidemia	Aripiprazole vs. placebo (2 RCTs)	Low	Significant effect in favor of placebo (RR = 2.5, 95% CI: 1.4, 4.4).
	Olanzapine vs. placebo (2 RCTs)	Low	Significant effect in favor of placebo (RR = 2.4, 95% CI: 1.2, 4.9).
	Quetiapine vs. placebo (3 RCTs)	Low	Significant effect in favor of placebo (RR = 2.4, 95% CI: 1.1, 5.4).
EPS	Aripiprazole vs. placebo (4 RCTs)	Moderate	Significant effect in favor of placebo (RR = 4.2, 95% CI: 2.4, 7.2).
	Olanzapine vs. placebo (3 RCTs)	Low	No significant difference.
	Quetiapine vs. placebo (3 RCTs)	Low	No significant difference.
	Risperidone vs. placebo (15 RCTs)	Moderate	Significant effect in favor of placebo (RR = 2.7, 95% CI: 1.4, 4.9).
	Ziprasidone vs. placebo (3 RCTs)	Low	Significant effect in favor of placebo (RR = 10.3, 95% CI: 1.4, 74.9).
Insulin resistance	Aripiprazole vs. placebo (3 RCTs) Olanzapine vs. placebo (3 RCTs)	Low Low	No significant difference. No significant difference.

Table C. Summary of the strength of evidence for adverse events (Key Question 2) (continued)			
Outcome	**Comparison (# studies)**	**SOE**	**Summary**
SGA vs. placebo (continued)			
Prolactin-related and sexual AE	Aripiprazole vs. placebo (3 RCTs)	Moderate	Significant effect in favor of aripiprazole (MD = -4.1, 95% CI: -6.3, -1.8).
	Olanzapine vs. placebo (2 RCTs)	Moderate	Significant effect in favor of placebo (MD = 11.5. 95% CI: 8.8, 14.1).
	Quetiapine vs. placebo (5 RCTs)	Low	No significant difference.
	Risperidone vs. placebo (9 RCTs)	Low	Seven studies significantly favor placebo; one study finds no difference (not pooled due to heterogeneity).
Sedation	Aripiprazole vs. placebo (4 RCTs)	Low	Significant effect in favor of placebo (RR = 2.7, 95% CI: 1.1, 6.5).
	Olanzapine vs. placebo (3 RCTs)	Low	No significant difference.
	Quetiapine vs. placebo (5 RCTs)	Low	No significant difference.
	Risperidone vs. placebo (13 RCTs)	Moderate	Significant effect in favor of placebo (RR = 2.9, 95% CI: 1.5, 5.5).
	Ziprasidone vs. placebo (3 RCTs)	Moderate	Significant effect in favor of placebo (RR = 2.98, 95% CI: 1.7, 5.2).
Weight/body composition	Aripiprazole vs. placebo (4 RCTs)	Moderate	Significant effect in favor of placebo (MD = 0.8, 95% CI: 0.4, 1.2).
	Olanzapine vs. placebo (4 RCTs)	Moderate	Significant effect in favor of placebo (MD = 4.6, 95% CI: 3.1, 6.1).
	Quetiapine vs. placebo (5 RCTs)	Moderate	Significant effect in favor of placebo (MD = 1.8, 95% CI: 1.1, 2.5).
	Risperidone vs. placebo (12 RCTs)	Moderate	Significant effect in favor of placebo (MD = 1.8; 95% CI: 1.5, 2.1).
	Ziprasidone vs. placebo (3 RCTs)	Low	No significant difference.

AE = adverse event; CI = confidence interval; EPS = extrapyramidal symptom; FGA = first-generation antipsychotic; MD = mean difference; NRCT = nonrandomized controlled trial; PCS = prospective cohort study; RCS = retrospective cohort study; RCT = randomized controlled trial; RR = relative risk; SGA = second-generation antipsychotics; SOE = strength of evidence

A total of 22 studies provided data on a variety of short- and long-term outcomes for patients with schizophrenia and related psychosis. The studies found no significant difference in medication adherence between FGAs and SGAs, olanzapine and quetiapine, olanzapine and risperidone, or SGAs and placebo (low strength of evidence). Similarly, SGAs and placebo did not differ in suicide-related behaviors (low strength of evidence).

Other outcomes were reported by four studies on Tourette syndrome and two studies on behavioral issues. The evidence was insufficient for all of the outcomes and comparisons examined in these studies.

Key Question 4: Subpopulations. A total of 36 studies compared outcomes across various patient subpopulations. Sex and age were examined most frequently. Overall, few studies identified differences in the results across subpopulations. Few associations between the patient or clinical variables and outcomes were supported by more than one study. Studies frequently had discordant conclusions in whether there was a significant association between subpopulations and outcomes and the direction of this association.

Table D. Summary of the strength of evidence for other short- and long-term outcomes (Key Question 3)

Outcome	Comparison (# studies)	SOE	Summary
Pervasive Developmental Disorder			
Medication adherence	SGA vs. placebo (2 RCTs)	Low	No significant difference.
ADHD and Disruptive Behavior Disorder			
Medication adherence	SGA vs. placebo (5 RCTs)	Low	No significant difference.
Bipolar Disorder			
Medication adherence	SGA vs. placebo (2 RCTs)	Low	Significant effect in favor of placebo (RR = 2.0; 95% CI: 1.0, 4.0).
Suicide-related behaviors	SGA vs. placebo (7 RCTs)	Moderate	No significant difference for suicide-related deaths, attempts, or ideation.
Schizophrenia			
Medication adherence	FGA vs. SGA (2 RCT, 1 PCS) Olanzapine vs. quetiapine (2 RCTs) Olanzapine vs. risperidone (4 RCTs, 1 PCS) SGA vs. placebo (2 RCTs)	Low Low Low Low	No significant difference. No significant difference. No significant difference. No significant difference.
Suicide-related behaviors	SGA vs. placebo (5 RCTs)	Low	No significant difference.

CI = confidence interval; FGA = first-generation antipsychotic; PCS = prospective cohort study; RCT = randomized controlled trial; RR = relative risk; SGA = second-generation antipsychotic; SOE = strength of evidence

Applicability

The majority of the studies in this body of evidence were small to moderate-sized RCTs that examined the efficacy of two or more intervention groups. The studies generally excluded patients with two or more psychiatric or behavioral diagnoses, comorbidities, or a history of adverse events. Several studies also excluded patients who did not meet minimum response criteria or were nonadherent during a run-in phase before the double-blind treatment phase. Patients who used adjunctive medications (e.g., mood stabilizers or antidepressants) or were previously unresponsive to the study medication were also frequently excluded. Because patients in clinical practice often have multiple diagnoses and undergo cotreatment with several drugs, these restrictions reduce the applicability of this body of evidence.

Few studies examined young adults ages 19 to 24 years; therefore, the results are often not applicable to this population. Another factor that restricts the applicability is the limited duration of followup. In particular, the median study duration of 8 weeks is insufficient to assess some long-term efficacy outcomes and harms.

Future Research

The following general recommendations for future research are based on the limitations of the current evidence:

- Studies examining long-term (at least 6 months followup) efficacy and, particularly, the safety of antipsychotics over the course of several years are needed. Future research should evaluate long-term developmental outcomes, such as growth, maturation, and cognitive and emotional development.
- Future studies should evaluate outcomes that are important to patients and parents, including health-related quality of life, school performance, and involvement with the legal system.
- Studies examining the impact of key patient subpopulations on important outcomes are needed to inform clinical practice.

- Future research should seek to minimize risk of bias by blinding study participants and outcome assessors, adequately concealing allocation, and handling and reporting missing data appropriately.
- Consensus on outcomes and outcome measures is needed to ensure consistency and comparability across future studies. Moreover, consensus on minimal clinically important differences is needed to guide the interpretation of study results.
- Study authors should explicitly disclose sources of funding and the nature and extent of industry involvement in the design, conduct, supply of materials, analysis of outcomes, and reporting of studies.
- Large-scale effectiveness studies that use inclusive patient-selection criteria and closely match typical clinical practice are needed to achieve greater applicability of the results.

Conclusions

For symptom improvement and other short- and long-term outcomes, most of the evidence examining head-to-head comparisons of different antipsychotic drugs was graded low or insufficient to draw conclusions. This was particularly true for comparisons of FGAs with SGAs and FGAs versus other FGAs. Similarly, few conclusions can be drawn regarding the comparison of adverse event profiles across different antipsychotics. Some SGAs are associated with a better adverse-event profile than other SGAs. As would be expected, SGAs consistently resulted in greater symptom improvement and greater risk for adverse events than placebo. Numerous studies reported separate outcomes for various subpopulations; however, few consistent trends were observed.

Treatment benefits and risks were examined most frequently for schizophrenia; the evidence for conditions such as pervasive developmental disorders, disruptive behavior disorders, and Tourette syndrome was sparse. No evidence was identified for obsessive compulsive disorder, post-traumatic stress disorder, or anorexia nervosa. Future high-quality research is needed in order to determine the relative effectiveness and safety among various antipsychotics in children, adolescents, and young adults.

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Full Report

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