Effective Health Care Program

Comparative Effectiveness Review
Number 39

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

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see

www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly. We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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

Structured Abstract

Objectives. To review and synthesize the evidence on first-generation antipsychotics (FGA) and second-generation antipsychotics (SGA) for the treatment of various psychiatric and behavioral conditions in children, adolescents, and young adults (ages ≤ 24 years).

Data Sources. We conducted comprehensive searches in 10 electronic databases from 1987 to February 2011. We searched the grey literature, trial registries, and reference lists.

Methods. Two reviewers conducted study selection and quality assessment independently and resolved discrepancies by consensus. One reviewer extracted data, and a second reviewer verified the data. We conducted a descriptive analysis for all studies and performed meta-analyses when appropriate.

Results. Eighty-one studies (64 trials and 17 cohort studies) examined the following conditions: pervasive developmental disorders (12 studies); attention deficit hyperactivity disorder (ADHD) or disruptive behavior disorders (8 studies); bipolar disorder (11 studies); schizophrenia and related psychosis (31 studies); Tourette syndrome (7 studies); behavioral issues (4 studies); and multiple conditions (9 studies). One study reported data on both bipolar disorder and schizophrenia.

The majority of the trials had a high risk of bias. The methodological quality of the cohort studies was moderate. Results are presented by outcome below.

Symptoms: The strength of evidence for all head-to-head comparisons of FGAs and SGAs was low or insufficient to draw conclusions. SGAs were favored over placebo for behavior symptoms (ADHD and disruptive behavior disorders), the Clinical Global Impressions scale (ADHD and disruptive behavior disorders, bipolar disorder, and schizophrenia), positive and negative symptoms (schizophrenia), and tics (Tourette syndrome) (moderate strength of evidence).

Other short- and long-term outcomes: All head-to-head comparisons had low or insufficient strength of evidence. There was no significant difference between SGAs and placebo for suicide-related behaviors (moderate strength of evidence). 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.

Adverse events: All outcomes comparing FGAs with SGAs had low or insufficient strength of evidence. Outcomes comparing FGAs versus FGAs and FGAs versus placebo had insufficient evidence. Risperidone was favored over olanzapine for dyslipidemia; olanzapine was favored over risperidone for prolactin-related events; and both quetiapine and risperidone were favored over olanzapine for weight gain (moderate strength of evidence). For nearly all outcomes and comparisons, placebo resulted in significantly fewer adverse events than SGAs.

Subpopulations: Thirty-six studies examined the association between various patient subpopulations and outcomes. Most concluded that the results did not differ by subpopulations, or findings were discordant across studies.

Conclusion. Evidence comparing FGAs with SGAs, various FGAs, and FGAs with placebo was very limited. Some SGAs appear to have a better side-effect profile than other SGAs. Compared with placebo, SGAs have better symptom improvement but more adverse events. Future high-quality research examining head-to-head antipsychotic comparisons is needed.

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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 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.

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	Suicide-related behaviors
		Weight	

KQ = Key Question

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 an evidence table 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.

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).
Tourette Syndrome			
Tics	SGA vs. placebo (2 RCTs)	Moderate	Significant effect in favor of SGA (MD = -6.98 (95% CI: -10.3, -3.6).

Table B. Summary of the strength of evidence for symptoms (Key Question 1) (continued)

Outcome	Comparison (# Studies)	SOE	Summary
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).

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.

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

Outcome	Comparison (# studies)	SOE	Summary
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.
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.

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

Outcome	Comparison (# studies)	SOE	Summary
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)	Low	No significant difference.
	Olanzapine vs. placebo (3 RCTs)	Low	No significant difference.
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

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).

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.

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)	Low	No significant difference.
	Olanzapine vs. quetiapine (2 RCTs)	Low	No significant difference.
	Olanzapine vs. risperidone (4 RCTs, 1 PCS)	Low	No significant difference.
	SGA vs. placebo (2 RCTs)	Low	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

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.

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.

Introduction

Antipsychotics are widely used to treat several psychiatric disorders in pediatric and adult populations, including schizophrenia, bipolar mania, and psychotic depression. Antipsychotics are commonly categorized into two drug classes, first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs), marking two waves of historical development. FGAs were developed in the 1950s. Although FGAs provide treatment for psychotic symptoms, use of these drugs can result in extrapyramidal symptoms, which are various 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. SGAs emerged in the 1980s. They generally have lower risk of motor side effects, but are associated with significant weight gain, lipid and prolactin elevation, and the development of type 2 diabetes.

Studies have shown that prescriptions for psychotropics, including antipsychotics, have increased during the last 20 years in children and youth.[1-5] Use of antipsychotics in the pediatric population is controversial mainly due to a lack of high-quality or longitudinal data on which to base conclusive clinical practice recommendations, especially with regard to safety.

In children and youth, antipsychotics vary in their use depending on the country and psychiatric condition. For the majority of antipsychotic drugs, approved indications are restricted to the treatment of childhood schizophrenia and bipolar disorders in the United States. 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 younger children for behavioral symptoms (e.g., aggression) that are related to diagnosable conditions (e.g., attention deficit hyperactivity disorder [ADHD]). In some instances, antipsychotics may be used off-label for behaviors that are also part of a child's normal developmental trajectory or may reflect an adaptive response to an environmental stressor (e.g., parental divorce).

In general, the choice of medication for children and youth is often driven by side-effect profiles that may affect growth and development, medication adherence and persistence, and other important domains such as school performance and health-related quality of life.[6] Therefore, close clinical monitoring is recommended.[7]

This comparative effectiveness review provides a comprehensive synthesis of the evidence on the benefits and harms associated with the use of FDA-approved FGAs and SGAs in pediatric and young adult populations (≤24 years of age). Young adults were included alongside pediatric patients in this review because age 18 is an arbitrary cutoff and falls within the peak age for the onset of schizophrenia and psychosis. Furthermore, young adults with behavioral or psychiatric conditions face unique challenges, as they often become ineligible for continued access of services once they become legal adults at age 18. The report is intended for a broad audience consisting of professional societies developing clinical practice guidelines, patients and their care providers, and researchers conducting studies in this field.

Antipsychotic Drugs

A list of FDA-approved FGAs and SGAs and their indications is presented in Table 1 and Table 2, respectively. There is no consensus on the terminology used to describe antipsychotic medications (e.g., FGA and SGA versus typical and atypical antipsychotics). For the purposes of this review, the terms "first-generation" and "second-generation" will be used. This terminology

can more easily accommodate the categorization of drug classes developed in the future (i.e., third-generation antipsychotics).

Table 1. Food and Drug Administration-approved first-generation antipsychotics

Generic Name	Indications	Age Group for Which Approved
Chlorpromazine	Schizophrenia	Adults and children (1–12 years)
	Bipolar disorder (mania)	
	Hyperactivity	
	Severe behavioral problems	
Droperidol	Agitation	Adults and children
Fluphenazine	Psychotic disorders	Adults
Haloperidol	Schizophrenia	Adults
	Tourette syndrome	
	Hyperactivity	
	Severe childhood behavioral problems	
Loxapine	Schizophrenia	Adults and children ≥12 years
Perphenazine	Schizophrenia	Adults and children ≥12 years
Pimozide	Tourette syndrome	Adults and children ≥12 years
Prochlorperazine	Schizophrenia	Adults and children >2 years and >20 pounds
	Generalized nonpsychotic anxiety	Adults
Thiothixene	Schizophrenia	Adults and children ≥12 years
Thioridazine	Schizophrenia	Adults and children
Trifluoperazine	Schizophrenia	Adults and children ≥6 years
	Generalized nonpsychotic anxiety	Adults

Table 2. Food and Drug Administration-approved second-generation antipsychotics

Generic Name	Indications	Age Group for Which Approved
Aripiprazole	Schizophrenia	Adults and adolescents (13–17 years)
	Bipolar disorder (manic/mixed) monotherapy or adjunctive to lithium or valproate	Adults and children (10–17 years)
	Adjunctive treatment of major depressive disorder	Adults
	Irritability associated with autistic disorder	Children (6–17 years)
	Acute treatment of agitation	Adults
Asenapine	Acute schizophrenia	Adults
	Bipolar disorder type 1 (manic/mixed)	
Clozapine	Treatment resistant schizophrenia	Adults
	Reduce risk of suicidal behavior in younger patients with schizophrenia	
Iloperidone	Acute schizophrenia	Adults
Olanzapine	Schizophrenia Bipolar disorder (manic/mixed)	Adults and adolescents (13–17 years)
	Bipolar disorder (depressive episode)	Adults
	Treatment-resistant depression	
	Agitation associated with schizophrenia and bipolar I mania	

Table 2. Food and Drug Administration-approved second-generation antipsychotics (continued)

Generic Name	Indications	Age Group for Which Approved
Paliperidone	Schizophrenia Schizoaffective disorder	Adults
Quetiapine	Schizophrenia	Adults and adolescents (13–17 years)
	Bipolar disorder (acute manic)	Adults, children and adolescents (10–17 years)
	Bipolar disorder (depression)	Adults
	Bipolar disorder (maintenance)	
	Major depressive disorder	
Risperidone	Schizophrenia	Adults and adolescents (13–17 years)
	Bipolar disorder (manic/mixed)	Adults, children and adolescents (10–17 years)
	Irritability associated with autism	Children (5–16 years)
Ziprasidone	Schizophrenia	Adults
	Bipolar disorder (manic/mixed)	
	Bipolar disorder (maintenance)	
	Acute agitation in patients with schizophrenia	

Conditions and Prevalence

The University of Alberta Evidence-based Practice Center was commissioned to examine the use of FGAs and SGA for the following conditions: pervasive developmental disorders, ADHD, disruptive behavior disorders, bipolar disorder, schizophrenia and schizophrenia-related psychosis, Tourette syndrome, obsessive-compulsive disorder, post-traumatic stress disorder, and behavioral issues (e.g., aggression, agitation, anxiety, behavioral dyscontrol, irritability, mood lability, self-injurious behaviors, and sleep disorders).

Pervasive Developmental Disorders

Pervasive developmental disorders are characterized by impairments in reciprocal social interaction that are present before age 3 and persist to varying degrees across the lifespan. The prevalence of childhood autism is 39 per 10,000, and that of other autism spectrum disorders (e.g., Asperger's disorder, pervasive developmental disorders not otherwise specified) is 77 per 10,000.[8] There has been a rising trend in prevalence rates, which may be due to broadening diagnostic criteria, better ascertainment, or increased incidence.[8]

The child's age, developmental level, and intellectual level strongly affect the presentation of pervasive developmental disorders. Key features are the inability to use language effectively for communication, an absence of symbolic play, stereotyped or repetitive behaviors (which may be harmful to the child), and focused, restricted patterns of interest or obsessions. Children with pervasive developmental disorders have varying degrees of problems using or interpreting language and nonverbal cues for communication.

Psychotropic medications are used as part of the management of pervasive developmental disorder-related symptoms. Antipsychotics may be used to manage aggressive outbursts in the context of emotional reactivity, reduce hyperactivity or repetitive behaviors, promote sleep onset and continuity, and treat other psychiatric comorbid symptoms. The increasing prevalence of pervasive developmental disorders raises concerns about the increased use of pharmacological interventions such as antipsychotics in young children.

ADHD and Disruptive Behavior Disorders

ADHD and disruptive behavior disorders (including oppositional defiant disorder and conduct disorder) are common childhood disorders and are so named because the core symptoms disrupt the daily functioning of children and their families. These disorders are the most common reason for presentation to child psychiatry clinics.

The prevalence of ADHD ranges between 6 and 12 percent. Similar prevalence estimates are given for oppositional defiant disorder; the prevalence of conduct disorder may be slightly lower.[9] The rates of disorder vary by age and sex, but the most marked difference is the 6 to 1 ratio of boys to girls with ADHD prior to puberty. In general, sex differences are less for children with oppositional defiant disorder and conduct disorder and diminish with increasing age.

There are common causes posited for these conditions, which commonly co-occur in childhood. These causes relate to inadequate or delayed development of the prefrontal cortex, which is a key region of the brain involved in the executive control of behaviors and emotions. Because of their deficits in executive functioning, children with disruptive behaviors are particularly sensitive to their environmental context. A core ingredient of therapeutic interventions is parent and teacher education and training about how to help shape a child's behavior at home and school. When children are 6 years of age and older (latency stage), child-focused interventions that involve group- and individual-level training may be used to promote the use of the prefrontal cortex. Group-level training teaches skills in social problem solving, emotional regulation (specifically frustration tolerance), and selection of nonaggressive responses to frustration.

Many children with disruptive behaviors, particularly those with multiple disorders, require treatment with medication. Psychostimulant medications are used to treat symptoms of hyperactivity and distractibility, and may have some benefit for oppositional behaviors associated with inflexibility. Antipsychotic medications are used predominantly to manage impulsive aggression and to help regulate negative emotions (sadness, anger, and anxiety) that, left untreated, may also worsen impulsivity. Antipsychotic medications are also used in small doses to promote somnolence (an intended side effect), as many children with ADHD have sleep disturbance.

Bipolar Disorder

Bipolar disorder is a disorder characterized by unstable mood. There are several types of bipolar disorder that affect children and adolescents: bipolar type 1 (manic episodes and depressive episodes occur independently of each other), bipolar type 2 (hypomanic episodes and depressive episodes occur independently of each other), and bipolar disorder not otherwise specified (brief mood shifts between positive or agitated and negative mood states, not meeting criteria for mania or hypomanic episodes in duration). The latter disorder appears to be the most prevalent (3 percent of children in the community) and is a focus of much research and controversy because many of these children are treated with antipsychotics approved by the FDA as mood stabilizers.[10] Bipolar I and bipolar II disorders are less common (approximately 1 percent and 0.5 percent prevalence, respectively) but are associated with higher morbidity.[10] Children with bipolar disorders of any type often have multiple co-occurring mental health problems.

Treatment for bipolar disorder includes the use of traditional mood stabilizers (i.e., anticonvulsants, such as valproic acid or carbemazepine) and antipsychotics. Antipsychotics may be used as the first-line medication in children and adolescents even when psychosis is not present. This is due to the difficulty of clinically diagnosing an episode of mania in a child and because many children and families have concerns with monitoring mood stabilizer levels with blood testing. Both kinds of medication appear to be effective in promoting emotional stability and sleep hygiene and at reducing impulsivity, psychotic symptoms, self harm, hostility, and aggression.

Schizophrenia and Schizophrenia-Related Psychosis

Schizophrenia and schizophrenia-related psychosis are grouped together because psychotic symptoms are prominent features of both conditions. Psychotic symptoms are also associated with comorbid psychiatric disorders, most particularly substance-use disorders and depressive disorders. Schizophrenia and related psychoses are uncommon in preadolescent children; prevalence estimates in this population are not known. In adolescents, the prevalence is estimated to be 0.1 percent, and about twice as many boys are affected as girls.[11] The onset of the condition is usually insidious, with symptoms gradually becoming apparent over an extended period of time. Typically, psychotic symptoms are classed as either being positive (e.g., hallucinations or delusions) or negative (e.g., anhedonia or lack of motivation). People are typically affected by both types of symptoms. Depending on the degree of impairment, patients may have little or no insight into their symptoms. However, patient insight is difficult to assess, particularly in young children or those with developmental delays. The duration of an episode of psychosis and course of illness are also highly variable across individuals.

Treatment of psychotic disorders or psychotic features includes the use of antipsychotic medications. Whether these medications are beneficial for the treatment of substance abuse and mood difficulties is not well known. A variety of psychosocial interventions are also used to target the maintenance of social engagement, cognitive development, academic achievement, and avoidance of substance use.

Tourette Syndrome

Tourette syndrome is a tic disorder. Tics are involuntary motor movements or vocalizations. Although some individuals have only motor or verbal tics, a diagnosis of Tourette syndrome requires that both types of tics occur many times a day, nearly every day, or intermittently over a period of 1 year. The prevalence is 0.04 to 0.05 percent, and three times as many boys are affected as girls.[12] For a diagnosis of Tourette syndrome, the onset of symptoms must occur before age 18; the average age of onset is 7 years. Children with Tourette syndrome commonly have ADHD (up to 50 percent) or obsessive-compulsive disorder (up to 40 percent).

Abnormalities in many neurotransmitter systems are involved in the disorder; however, most evidence suggests dysfunction in the regulation of the release and reuptake of dopamine in the basal ganglia (a deep brain structure partly responsible for motor control). Medications that inhibit dopamine reuptake, such as antipsychotics, generally help to reduce tics, but may induce tics in some cases (i.e., tardive Tourette disorder). Antipsychotics may also have a beneficial impact on comorbid conditions.

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder is an anxiety disorder characterized by developmentally inappropriate and persistent anxiety with associated behavioral disturbances. Behaviors include obsessions and/or compulsions that are severe enough to be time consuming (more than 1 hour per day) and significantly interfere with daily activities. Obsessions are recurrent, persistent, and unwanted thoughts, images, or impulses that are intrusive and inappropriate and that cause a great deal of anxiety, distress, fear, or worry. They often center on aggressive, sexual, or religious topics that the affected person recognizes as a product of their own mind.

Compulsions are deliberate, repetitive behaviors (e.g., hand washing, cleaning, checking, or hoarding) or mental acts (e.g., preoccupation with praying, counting, or word repetition) and may involve performing rituals according to strict rules. Compulsions are aimed at reducing the anxiety caused by the obsessions with the hope of preventing obsessive thoughts or making them go away. Performing these behaviors temporarily reduces the anxiety; not performing them increases anxiety. Core diagnostic criteria present differently depending on age. For example, young children may present with physical complaints or temper tantrums rather than anxieties and worries that may be seen in adolescents. There can also be fluctuation in symptom severity over time.[13,14]

Community studies of children and adolescents in many different cultures have estimated a lifetime prevalence of 1 to 2.3 percent.[15] Age of onset is seen across childhood and adolescence.

Post-traumatic Stress Disorder

Post-traumatic stress disorder is an anxiety disorder that develops following a reaction of intense fear, helplessness, or horror resulting from a traumatic event. Events may involve actual or threatened death or serious injury to oneself or others. Characteristic symptoms of post-traumatic stress disorder include a persistent re-experience of the traumatic event (e.g., images, thoughts, dreams, or flashbacks), persistent avoidance of stimuli associated with the trauma, numbing of general responsiveness, and persistent symptoms of increased arousal (e.g., difficulty sleeping, irritability, or outbursts of anger). Symptoms may appear soon after the event or several years later, but are present for more than 1 month and cause clinically significant distress or impairment in social, occupational, or other areas of functioning.

The prevalence of post-traumatic stress disorder is 6 to 8 percent in children and adolescents under 18 years of age.[16] Studies of at-risk individuals (i.e., groups exposed to specific traumatic incidents) indicate variation in rates across risk groups. The highest rates range from one-third to more than half among victims of rape and survivors of military combat, captivity, ethnically or politically motivated internment, and genocide.

Anorexia Nervosa

Anorexia nervosa is an eating disorder in which a fear of weight gain coupled with a distorted body image leads to refusal to maintain a minimally acceptable body weight.[15] The cardinal psychological feature of the disorder is a pervasive fear of weight gain and unrealistic evaluation of physical shape despite a starved appearance. Self-employed strategies to achieve this state can include lengthy periods of starvation, excessive exercise, extreme food restriction, and purgatives (e.g., laxatives, diuretics). Because of the extreme weight loss in this disorder, physiological dysfunction occurs including amenorrhea (loss of menstruation for at least 3

consecutive months) due to abnormally low levels of estrogen, which is included as a diagnostic criterion.

This eating disorder includes two subtypes that are defined by behavioral indicators: restricting, and binge-eating and purging. The individual with the restricting subtype predominantly limits caloric intake and may engage in excessive pharmacologic (i.e., diuretics) or exercise-induced measures to lose weight. In contrast, the individual with the binge and purge subtype may engage in recurrent eating of a substantially large amount of food in a discrete period of time, followed by compensatory purging activities to expel the food (i.e., self-induced vomiting or the misuse of laxatives, enemas, or diuretics).

Though some individuals may acknowledge being thin, their illness precludes them from being able to recognize the serious medical implications of their malnourished state. The individual is often brought to professional attention by family members. Medications such as antidepressants, antipsychotics, and mood stabilizers may help treat anorexia nervosa and comorbid conditions when given as part of a complete psychological treatment program.

The prevalence of anorexia is more predominant in females, with approximately 0.13 percent of females ages 15 to 20 years having the disorder. In males, it is approximately one-tenth of that. The incidence of anorexia nervosa appears to have increased in recent decades.[15]

Outcome Measures

A wide variety of checklists and scales are used to assess symptomatology and side effects in patients with psychiatric and behavioral disorders. Measures vary and can be generic or disease-specific, patient-, parent-, or clinician-rated, and general or child-specific. An overview of the domains, scoring, and psychometric properties of the most common scales evaluating outcomes and extrapyramidal side effects is provided in Table 3 and Table 4, respectively. These tables provide information for the scales that were most frequently used in the studies included in this review but do not describe every outcome measure.

Table 3. Common outcome measures

Outcome Measure/ Assessor	Objective	Domains/Items	Scaling	Psychometric Properties
Aberrant Behavior Checklist (ABC)[17] Health care staff	To assess drug and other treatment effects on profoundly mentally retarded residents	(1) Irritability, agitation, crying (15 items) (2) Lethargy, social withdrawal (16 items) (3) Stereotypic behavior (7 items) (4) hyperactivity, noncompliance (16 items) (5) Inappropriate speech (4 items)	58 items are rated on a 4-point scale (0 = "not a problem" to 3 = "problem is severe"); the greater the score the greater the severity of behavior	Coefficient α of all domains: 0.91 (mean), 0.86–0.94 (range); Cohen's κ for all domains, 0.63 (mean); test-retest reliability of all domains, 0.98 (mean), 0.96–0.99 (range)
Brief Psychiatric Rating Scale–Children (BPRS–C)[18,19] Clinician	To assess childhood psychiatric disorder symptomatology and to evaluate response to treatment	(1) Behavioral problems (2) Depression (3) Thinking (4) Disturbance (5) Psychomotor excitation (6) Withdrawal retardation (7) Anxiety and organicity	21 items are rated on a 7-point scale (0 = "not present" to 6 = "extremely severe"); the greater the score the greater the severity of symptoms	Coefficient α of all domains: 0.79; Pearson's correlation: 0.83 (anchored version), 0.73 (nonanchored); concurrent validity with other scales (change score) CGI: r = 0.75, CGAS: r = -0.75, CDRS: r = 0.7
Children's Depression Rating Scale (CDRS)[20] Clinician	To assess the severity of depression in children ages 6–12	(1) Mood (i.e., depressed feelings) (2) Somatic (i.e., appetite) (3) Subjective (i.e., self-esteem) (4) Behavior (i.e., social withdrawal)	17 items are rated on a 7-point scale (0 = "unable to rate" to 7 = "severe"); score totaled out of 113; the greater the score, the greater the severity of depression	Cohen's κ for correlations between 0 and 2 week ratings, 0.86, and 2 and 6 week ratings, 0.81; correlation between CDRS and Global Rating of Depression: r = 0.87
Children's Global Assessment Scale (CGAS)[21] Clinician	To measure the overall severity of disturbance in children; a global measure of social and psychiatric functioning for children ages 4–16 years	The single numerical score represents the severity of disturbance	1 (most impaired) to 100- (superior level of functioning) point scale. Scores >70 are considered normal; scores ≤10 indicate children need constant supervision	Reliability (tested in both research and clinical settings): 0.83–0.91 (range); reliability (clinical settings): 0.53–0.66 (range) (3/4 of rates agreed within 10 points); test-retest reliability (research settings): 0.85
Clinical Global Impressions (CGI)[22,23] Clinician	To provide a global rating of illness severity, improvement, and response to treatment	(1) Severity of illness (i.e., how mentally ill is the patient) (2) Global improvement (i.e., total improvement whether or not it is likely to be due to drug treatment) (3) Efficacy index (i.e., based on drug effect only)	*Domains 1 and 2*: are rated on a 7-point scale (1 = "normal/very much improved" to 7 = "most severe/very much worse"); *Domain 3*: is rated on 4-point scale (1 = "marked improvement and no side effects" to 4 = "unchanged/worse/side effects outweigh the therapeutic effect")	Test-retest reliability (severity): 0.66 (physician), 0.41 (nurses); Significant association with anticipatory anxiety and depression ratings on Hamilton Rating Scale for Depression

Table 3. Common outcome measures (continued)

Outcome Measure/ Assessor	Objective	Domains/Items	Scaling	Psychometric Properties
Nisonger Child Behavior Rating Form (NCBRF)[24] Parent/Teacher	To be evaluate childhood problems including stereotypic behavior and self-injury because of mental retardation	*Problem Behaviors:* (1) Conduct problem (2) Insecure/anxious (3) Hyperactive (4) Self-injury/stereotypic (5) Self-isolated/ritualistic (6) Overly sensitive/irritable *Social Competence:* (1) Compliant/calm (2) Adaptive social	Domains are rated on a 4-point scale (0 = "behavior did not occur/was not a problem" to 3 = "behavior occurred a lot/was a severe problem"); the greater the score, the greater the severity of the problem behaviors	Median coefficient α on the *Problem Behavior* subscales: 0.85 (parents), 0.88 (teachers); median coefficient α on the *Social Competence* subscales: 0.78 (parents), 0.84 (teachers); Median Pearson correlation for *Problem Behavior* subscales (excluding item 6): 0.51, *Conduct Behavior* subscales: 0.31; median correlation of the NCBRF with the ABC: 0.72 (parents), 0.69 (teachers)
Overt Aggression Scale (OAS)[25] Family/Health care staff	To document and quantify verbal and physical overt aggressive behaviors	(1) Verbal aggression (2) Physical aggression against objects (3) Physical aggression against self (4) Physical aggression against others	Each domain is rated on a 4-point scale (0 = "absence of behavior" to 3 = "presence of all behaviors"); level of intervention used in response to violent behaviors were factored into ratings of aggressive episodes; the greater the score, the greater the severity of the aggressive behavior	11 items (52%) showed ICC >0.75, 9 items (43%) showed ICC 0.50–0.75, 1 item (5%) showed ICC<0.50; correlation coefficient for total aggression score: 0.87; Pearson's r for children 0.07 (Domain 1), 0.41 (Domain 2), 0.15 (Domain 3), 0.17 (Domain 4)
Positive and Negative Syndrome Scale (PANSS)[26] Clinician	To measure the prevalence of positive and negative syndromes in schizophrenia	(1) Positive scale (PS) (2) Negative scale (NS) (3) General psychopathology scale (GPS)	30 items are rated on a 7-point scale (1 = "absent" to 7 = "extreme"); scored by summing ratings across items; potential ratings of 7–49 for PS and NS, and 16–112 for the GPS; composite scale derived by subtracting the negative from the positive score yielding a bipolar index that ranges from -42 to + 42	Coefficient α: 0.73 (total PS), 0.83 (total NS), 0.79 (GPS); test-retest Pearson's r: 0.80 (PS), 0.68 (NS), 0.66 (GPS), 0.60 (composite score)
Young Mania Rating Scale (YMRS)[27] Clinician	To measure the severity of mania, but not for use in diagnosis	(1) Elevated mood (2) Increased motor activity-energy (3) Sexual interest (4) Sleep (5) Irritability (6) Sleep (rate and amount) (7) Language-thought disorder (8) Content (9) Disruptive-aggressive behavior (10) Appearance (11) Insight	11 domains are rated on a 5-point severity scale (0 = "normal/absent" to 4 = "greatest severity of condition"); domains 5, 6, 8, and 9 are given twice the weight of the others; the greater the score, the greater the severity of mania	Reliability between the total scores: 0.9, 0.66–0.95(range); validity with the Global Rating: 0.88, Petterson Scale: 0.89, Beigel Scale: 0.71; predictive validity (no. days in hospital): 0.66; sensitivity, the YMRS differentiated between the pre and post treatment at the 0.005 level

ICC = interclass correlation coefficient

Table 4. Extrapyramidal symptom measures

Outcome Measure/ Assessor	Objective	Domains/Items	Scaling	Psychometric Properties
Abnormal Involuntary Movements Scale (AIMS)[28] Clinician	To provide a quantitative assessment of tardive dyskinesia	(1) Facial and oral movements (4 items) (2) Extremity movements (2 items) (3) Trunk movements (1) (4) Global judgments (3 items) (5) Dental status (2 items)	7 items are rated on a 5-point scale (0 = "no movements" to 4 = "severe movements"); upper extremities are rated separately by the right and left side; the larger or common value is used for the score; the greater the score the greater the severity of abnormal movements	ICC: 0.64 (mean), 0.50–0.79 (range); Pearson's r: 0.67 (mean), 0.46–0.81 (range)
Barnes Akathisia Scale (BAS)[29] Clinician	To rate drug-induced akathisia	(1) Objective measures *Subjective measures:* (2a) Awareness of restlessness (2b) Distress related to restlessness (3) Global clinical assessment of akathisia	*Domains 1 and 2*: 3 items are rated on a 4-point scale (0 = "Normal/No distress/Absent" to 3 = "Severe/Constant movement"); *Domain 3*: is rated on 6-point scale (0 = "Absent" to 5 = "severe")	Cohen's κ: 0.738 (Domain 1), 0.827 (Domain 2a), 0.901 (Domain 2b), 0.955 (Domain 3)
Extrapyramidal Symptom Rating Scale (ESRS)[30,31] Clinician	To measure extrapyramidal symptoms in patients on neuroleptic drug treatments	(1) Parkinsonism symptoms questionnaire (2) Physician examination: [i]Parkinsonism and Akathisia, [ii] Dystonia, [iii] Dyskinetic Movements (3) Global impression for severity of dyskinesia, parkinsonism, dystonia, akathisia	*Domain 1*: 7 items are rated on a 4-point scale (0 = "absent' to 3 = "severe"); *Domain 2*: sections [i] and [iii] contain 7 items rated on a 7-point scale (0 = "Absent" to 6 = "extremely severe"), [ii] contains 1 item rated on a 7-point scale (0 = "absent" to 6 = "extremely severe"); *Domain 3*: is rated on a 9-point scale (0 = "absent" to 8 = "extremely severe")	Cohen's κ for each item of the scale ranged from 0.80—0.97 (mean ranges); Cohen's κ for each division of the scale: Domain 1, 0.97, Domain 2 [i], 0.88, [ii], 0.88, and [iii], 0.96
Simpson-Angus Scale (SAS)[32] Clinician	To measure extrapyramidal side effects related to neuroleptic drug treatments	(1) Gait (2) Arm dropping (3) Shoulder shaking (4) Elbow rigidity (5) Wrist rigidity (6) Leg pendulousness, (7) Head dropping (8) Glabella tap (9) Tremor (10) Salivation	Domains are rated on a 5-point scale (0 = "absence of condition" to 4 = "condition present in extreme form"); the scale score is obtained by adding the items and dividing by 10; the greater the score, the greater the severity of extrapyramidal symptoms	Correlation coefficient: total score, 0.87 (mean), and 0.71–0.96 (range)

ICC = interclass correlation coefficient

Scope and Key Questions

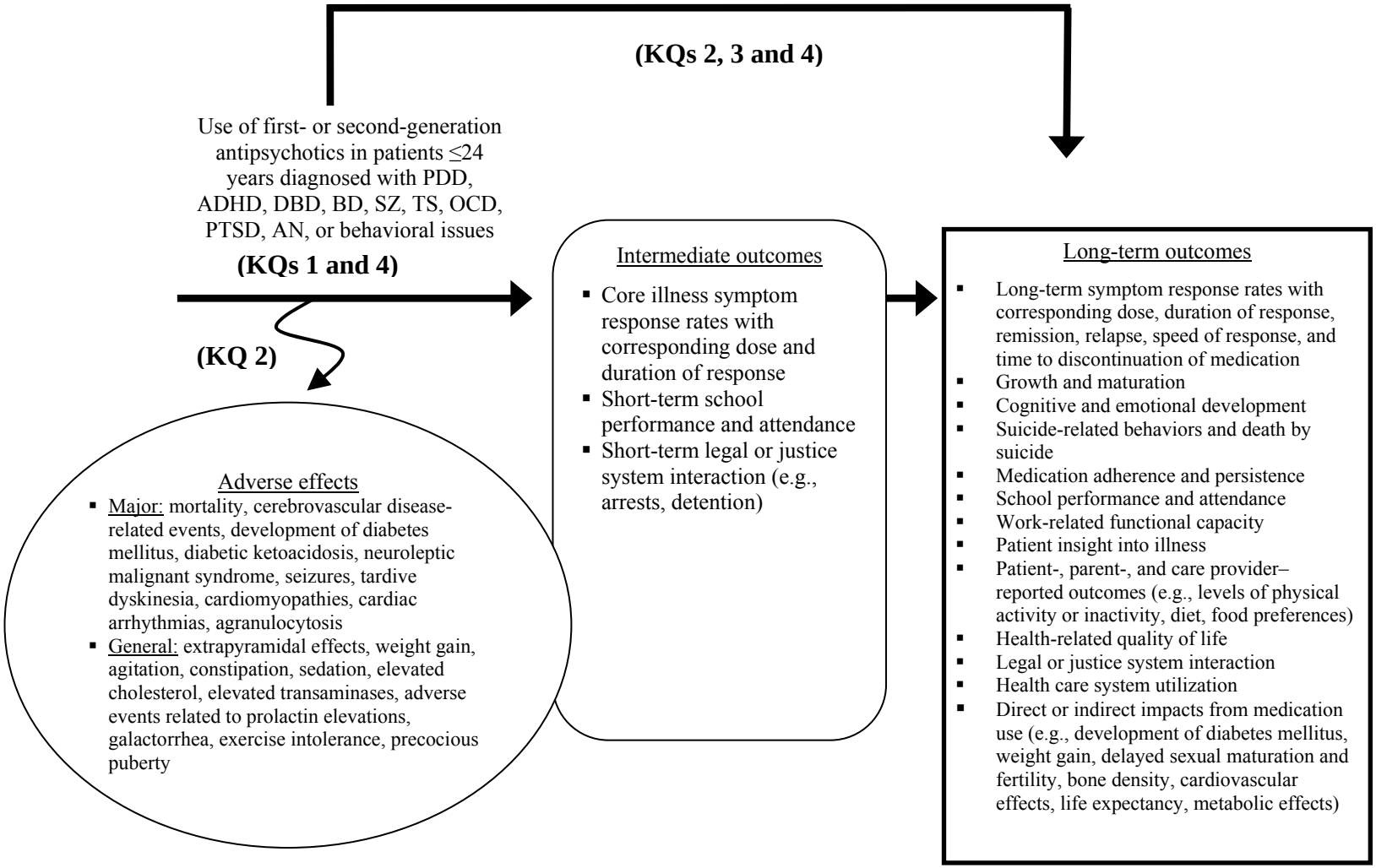
The Key Questions are as follows:

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?

Figure 1 is an analytic framework that portrays the clinical concepts and mechanism by which treatment with antipsychotics may improve outcomes. In particular, this figure illustrates the relationship between intermediate and long-term outcomes. We have labeled each link in this pathway with the key question that addresses the various outcomes (i.e., intermediate, long-term, and adverse event outcomes).

Figure 1. Analytic framework for first- and second-generation antipsychotics in children and young adults (≤24 years)



ADHD = attention deficit hyperactivity disorder; AN = anorexia nervosa; BD = bipolar disorder; DBD = disruptive behavior disorder; KQ = key question; OCD = obsessive-compulsive disorder; PDD = pervasive developmental disorder; PTSD = post-traumatic stress disorder; SZ = schizophrenia or other related psychosis; TS = Tourette syndrome

Methods

In this chapter, we describe the topic refinement process and our a priori methods for reviewing, assessing, and synthesizing the evidence on first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) for the treatment of children and young adults.

Topic Refinement and Technical Expert Panel

The University of Alberta Evidence-based Practice Center (EPC) was commissioned to conduct a preliminary literature review to gauge the availability of evidence and to draft key research questions for a comparative effectiveness review. Investigators from our EPC developed the key questions in consultations with the Agency for Healthcare Research and Quality (AHRQ), the Scientific Resource Center, and a panel of key informants. AHRQ posted the key questions on their website for public comment for a period of 1 month. Our EPC revised the Key Questions based on the public feedback we received, and AHRQ approved the final Key Questions.

We assembled a technical expert panel to provide content and methodological expertise throughout the development of the comparative effectiveness review. The technical experts are identified in the front matter of this report.

Literature Search Strategy

Our research librarian systematically searched the following bibliographic databases for studies published from 1987 to May 2010: MEDLINE, Embase, CENTRAL, PsycINFO, International Pharmaceutical Abstracts (IPA), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus, and ProQuest Dissertations International. In February 2011, we performed an update search in MEDLINE, Embase, CENTRAL, and PsycINFO. We restricted the searches to studies published in 1987 and later to coincide with the Diagnostic and Statistical Manual of Mental Disorders (DSM) III–Revised. We searched MedEffect Canada and TOXLINE to identify additional data on adverse events. We restricted the search results to studies published in English and to children and young adults ≤24 years of age. We applied filters for randomized controlled trials (RCTs) and cohort studies (see Appendix A for the detailed search strategies).

We selected search terms by scanning search strategies of systematic reviews on similar topics and examining index terms of potentially relevant studies. We adapted a combination of patient headings and text words for each electronic resource. Text words related to the conditions of interest: child development disorders, Asperger syndrome, autism, Rett syndrome, childhood schizophrenia, aggression, psychomotor agitation, sleep disorders, mood disorders, personality disorders, affective dysregulation, mood lability, irritability, self-injurious behavior, attention deficit hyperactivity disorder, conduct disorder, oppositional defiant disorder, psychotic disorders, bipolar disorder, depressive disorder, obsessive-compulsive disorder, anorexia nervosa, Tourette syndrome, and post-traumatic stress disorder. We included terms for the Food and Drug Administration (FDA)-approved FGAs and SGAs (see Table 5 for a listing of drugs). A second research librarian independently peer reviewed the search strategy.

We screened the reference lists to identify additional studies and searched online trial registries (World Health Organization and ClinicalTrials.gov) to identify unpublished and ongoing trials. We hand searched conference 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). These proceedings were selected because of their close match to the content of this report. We reviewed FDA documents related to the drugs of interest for additional data. In addition, the Scientific Resource Center contacted drug manufacturers to request published and unpublished study data.

We used a Reference Manager for Windows version 11.0 (2004–2005 Thomson ResearchSoft) bibliographic database to manage the results of our literature searches.

Criteria for Study Selection

The eligibility criteria were developed in consultation with the technical expert panel and are provided in Table 5. Our population of interest was children, adolescents, and young adults ≤24 years of age with psychiatric disorders or behavioral disturbances. Studies that enrolled adults were included only when at least 80 percent of patients were ≤24 years of age or when subgroup analyses or individual data for patients within the eligible age range were provided. Studies that enrolled patients with different conditions (e.g., pervasive developmental disorder and schizophrenia) were included only if they reported efficacy data separately by condition. However, we included studies that aggregated adverse event data across patients with various conditions.

Molindone was removed from the list of FDA-approved drugs due to its discontinuation in January 2010. Patients were not excluded for polypharmacy. However, studies in which cotreatments were systematically given to only one treatment group (e.g., olanzapine and citalopram vs. ziprasidone) were excluded.

Table 5. Eligibility criteria for the review

Category	Criteria
Publication type	Primary research published in 1987 or later (coincides with DSM–III–R), published in English
Study design	Clinical trials (RCTs and NRCTs) and cohort studies (prospective or retrospective)
Population	Children, adolescents, and young adults (≤24 years) with one or more of the following conditions: PDD, ADHD, DBD, bipolar disorder, schizophrenia or related psychosis, Tourette syndrome, OCD, PTSD, anorexia nervosa, or other behavioral issues
Intervention	Any FDA-approved FGA (chlorpromazine, droperidol, fluphenazine, haloperidol, loxapine, perphenazine, pimozide, prochlorperazine, thiothixene, thioridazine, trifluoperazine) Any FDA-approved SGA (aripiprazole, asenapine, clozapine, iloperidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone)
Comparator	Any other FGA or SGA (active comparator), placebo, or a different dose of the same antipsychotic.
Outcomes of interest	At least one of the following: symptoms, response, remission, growth, maturation, cognitive and emotional development, suicide-related behaviors, medication adherence, school performance, work-related functional capacity, patient insight into illness, patient-, parent-, or care provider-reported outcomes, health-related quality of life, legal system interaction, health care system utilization, and adverse events. No minimum followup duration was specified.

ADHD = attention deficit hyperactivity disorder; DBD = disruptive behavior disorder; DSM = Diagnostic and Statistical Manual of Mental Disorders; FDA = Food and Drug Administration; FGA = first-generation antipsychotic; NRCT = nonrandomized controlled trial; OCD = obsessive-compulsive disorder; PDD = pervasive developmental disorder; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; SGA = second-generation antipsychotic

We screened the eligibility of articles in two phases. In the first phase, two reviewers independently screened the titles, keywords, and abstracts (when available) to determine if an article met broad screening criteria. We rated each article as "include," "exclude," or "unclear." We retrieved the full text article for any study that was classified as "include" or "unclear" by at least one reviewer. Once the article was retrieved, two reviewers independently assessed each study using a detailed form (Appendix B1). We resolved disagreements by consensus or third-party adjudication.

A single reviewer screened FDA reports for relevance. Based on an a priori decision, studies were considered for inclusion only if patients were 18 years of age or younger, due to the complexities of determining the age of study participants referenced in the FDA reports.

Assessment of Methodological Quality

Two reviewers independently assessed the methodological quality of the studies and resolved discrepancies through consensus. We pilot tested each quality assessment tool on a sample of studies and developed guidelines for assessing the remaining studies.

Quality Assessment of Trials

We assessed the internal validity of RCTs and nonrandomized controlled trials using the Cochrane Collaboration risk of bias tool (Appendix B2).[33] This tool consists of six domains of potential bias (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and "other" sources of bias) and a categorization of the overall risk of bias. Each separate domain was rated as having "low," "unclear," or "high" risk of bias. We assessed blinding and incomplete outcome data separately for subjective outcomes (e.g., health-related quality of life) and objective clinical outcomes (e.g., laboratory measures). For "other" sources of bias, we assessed baseline imbalances between groups, early stopping for benefit, and funding source. Industry funding was considered as a source of potential bias because studies have shown that sponsorship influences published results.[34]

The overall assessment was based on the responses to individual domains. If one or more of the individual domains had a high risk of bias, we rated the overall score as high risk of bias. We rated the overall risk of bias as low only if all components were assessed as having a low risk of bias. The overall risk of bias was unclear for all other studies.

Quality Assessment of Cohort Studies

We used a modified version of the Newcastle-Ottawa Quality Assessment Scale (Appendix B2)[35] to assess cohort studies. The scale comprises seven items that evaluate three domains of quality: sample selection, comparability of cohorts, and assessment of outcomes. Each item that is adequately addressed is awarded one star, except for the "comparability of cohorts" item, for which a maximum of two stars can be given. The overall score is calculated by tallying the stars. We considered a total score of 6 to 8 stars to indicate high quality, 4 or 5 stars to indicate moderate quality, and 3 or fewer stars to indicate poor quality. In addition, we extracted the source of funding for each study.[36]

Data Extraction

We extracted data using a structured, electronic form and imported the data into a Microsoft Excel 2007 spreadsheet (Microsoft Corp., Redmond, WA) (Appendix B3). One reviewer

extracted data, and a second reviewer checked the data for accuracy and completeness. Reviewers resolved discrepancies by consensus or in consultation with a third party. We extracted the following data: study and participant characteristics (including inclusion and exclusion criteria, age, sex, ethnicity, and diagnosis), intervention and co-intervention characteristics (including dose, frequency, and duration), and outcomes.

We reported outcomes only if quantitative data were reported or could be derived from graphs. We did not include outcomes that were only described qualitatively (e.g., "there was no difference between the groups") or reported only as a p-value in the data analysis. We classified studies that directly compared one antipsychotic with another antipsychotic as "head-to-head" studies and studies that compared an antipsychotic with placebo as "placebo" studies. Studies with three of more treatment groups could provide data both for "head-to-head" and "placebo" comparisons.

When more than one publication reported the results of a single study, we considered the earliest published report of the main outcome data to be the primary publication. We extracted data from the primary publication first and then added outcome data reported in the secondary publications. We reference the primary publication throughout the evidence report. A list of the references for the companion articles is provided at the end of this report.

We made decisions regarding which outcome measures to extract for Key Question 1 in consultation with clinical experts. A list of the outcome measures that we extracted for each condition is provided in Table 6. We extracted the total score for each outcome measure; when the total score was not provided, we extracted all of the reported subscores. For each study arm, we extracted the mean baseline and endpoint or change scores, standard deviations, and sample size. We did not extract either outcome data from studies that did not provide a followup change or endpoint mean or data that could be used to calculated followup scores.

Table 6. Outcome measures extracted in the comparative effectiveness review

Outcome Measure	PDD	ADHD/ DBD	Bipolar	Schizophrenia	Tourette	Other*
Aberrant Behavior Checklist	X	X		X		X
Behavior Problems Inventory		X				
Brief Psychiatric Rating Scale			X	X		X
Childhood Autism Rating Scale	X					
Child Behavior Checklist	X	X		X		
Child Mania Rating Scale			X			
Children's Aggression Scale		X				
Children's Depression Rating Scale			X			
Children's Global Assessment Scale	X	X	X	X	X	
Clinical Global Impressions Scale	X	X	X	X	X	X
Children's Psychiatric Rating Scale	X			X		
Children's Yale-Brown Obsessive-Compulsive Scale	X				X	
Conners Parent/Teacher Rating Scale		X		X		
Gilliam Autism Rating Scale	X					
General Behavior Inventory			X			
Global Assessment of Functioning				X	X	X
Hamilton Anxiety Rating Scale			X			
Hamilton Depression Rating Scale			X			
Nisonger Child Behavior Rating Scale	X	X				
Overt Aggression Scale	X	X	X	X		X
Rating of Aggression Against People and/or Property Scale		X				

Table 6. Outcome measures extracted in the comparative effectiveness review (continued)

Outcome Measure	PDD	ADHD/ DBD	Bipolar	Schizophrenia	Tourette	Other*
Personal Assessment Checklist						X
Positive and Negative Symptom Scale			X	X		
Ritvo-Freeman Real Life Rating Scale	X					
Scale for the Assessment of Negative Symptoms				X		
Scale for the Assessment of Positive Symptoms				X		
Social and Occupational Functioning Assessment Scale				X		
Strength and Difficulties Questionnaire				X		
Tic Symptom Self-Report					X	
Total Child Symptom Inventory		X				
Vineland Adaptive Behavior Scales	X	X		X		
Yale Global Tics Severity Score					X	
Young Mania Rating Scale			X	X		X

ADHD = attention deficit hyperactivity disorder; DBD = disruptive behavior disorder; PDD = pervasive developmental disorder
* Outcome measures that were used in studies that enrolled patients with behavioral issues or multiple conditions

Using the adverse event monitoring guidelines proposed by Correll et al.,[37] the lead investigators decided on adverse event data that would be extracted for each of the categories specified in Key Question 2 (see Table 7). We reported adverse events as they were reported in by the authors of the study. For each adverse event, we recorded the number of patients in each treatment or placebo group and the number of patients with an adverse event. We counted each event as if it corresponded to a unique individual. Because an individual patient may have experienced more than one event during the course of the study, this assumption may have overestimated the number of patients that experienced an adverse event. We extracted only quantitative adverse event data describing the number of patients who experienced an event; that is, studies that reported only p-values or reported one arm to have fewer events than another were not included in the analysis. For continuous adverse event measures (e.g., weight or prolactin levels), we extracted the mean change or endpoint score, standard deviation, and sample size.

Table 7. Adverse event outcome data extracted in the comparative effectiveness review

Adverse Event Categories	Specific Outcome Data Extracted
Mortality	ND
Cerebrovascular events	ND
Weight and body composition	Weight, weight status (e.g., % normal, overweight, etc.), BMI, BMI percentiles, fat mass, waist circumference
Dyslipidemia	Incidence of dyslipidemia, total cholesterol, LDL and HDL cholesterol, triglycerides, ratio of triglycerides to HDL cholesterol
Insulin resistance and diabetes	New-onset diabetes, exacerbation of previous diabetes, diabetic ketoacidosis, metabolic syndrome, HbA1c, glucose, insulin, HOMA–IR
Prolactin-related and sexual	Amenorrhea, oligomenorrhea, erectile dysfunction, decrease libido, hirsutism, breast symptom, galactorrhea, prolactin levels
Neuromotor	EPS scales, akathisia, tardive and withdrawal dyskinesia, dystonia
Cardiac	MI, cardiomyopathies, myocarditis, arrhythmias, abnormal ECG, QTc interval, hypertension, hypotension, orthostasis, postural hypotension, blood pressure, pulse, heart rate
Sedation	Sedation, somnolence, fatigue, tiredness
Liver toxicity	Liver damage, liver function test, liver enzyme levels (AST, ALT, GGT)
Neutropenia and agranulocytosis	Incidence of neutropenia, incidence of agranulocytosis, WBC counts

Table 7. Adverse event outcome data extracted in the comparative effectiveness review (continued)

Adverse Event Categories	Specific Outcome Data Extracted
Thyroid dysfunction	Serum total thyroxine, serum free thyroxine, TSH
Seizures	ND
Neuroleptic malignant syndrome	ND
Constipation	ND
Exercise intolerance	ND
Precocious puberty	ND
Behavioral side effects	ND
Dermatological	ND

ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; ECG = electrocardiogram; EPS = extrapyramidal symptoms; GGT = gamma-glutamyl transpeptidase; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; HOMA–IR = homeostasis model assessment of insulin resistance; LDL = low-density lipoprotein; MI = myocardial infarction; ND = not described (denotes categories that were not further subcategorized); QTc = QT interval corrected for heart rate; TSH = thyroid stimulating hormone; WBC = white blood cell

For other short- and long-term efficacy outcomes (Key Question 3), we reported treatment response and remission rates as defined by the study authors. For outcomes measured using scales (e.g., health-related quality of life or cognitive outcomes), we extracted the total score. When the total score was not provided, we extracted all the subscores. We did not calculate total scores based on the subscore data provided by studies.

To assess whether the efficacy of antipsychotics varied in different subpopulations (Key Question 4), we extracted information on the subpopulations (independent variables), the type of analysis (e.g., subgroup or regression analysis), the outcomes assessed (dependent variables), and the authors' conclusions. Age categories were defined as <6 years (preschool), 6 to 12 years (preadolescent), 13 to 18 years (adolescent), and ≥19 years (young adult). Age 12 was chosen as the cutoff between childhood and adolescence because this age is traditionally considered to be the onset of puberty.

Applicability

Applicability of evidence distinguishes between effectiveness studies conducted in primary care settings that use less stringent eligibility criteria, assess health outcomes, and have longer followup periods than most efficacy studies.[38] The results of effectiveness studies are more applicable to the spectrum of patients in the community than efficacy studies, which usually involve highly selected populations. The applicability of the body of evidence was assessed following the PICOTS (population, intervention, comparator, outcomes, timing of outcome measurement, and setting) format used to assess study characteristics. Factors that may potentially weaken the applicability of studies were reported in the results.

Grading the Strength of a Body of Evidence

Two independent reviewers graded the strength of the evidence for major outcomes and comparisons using the EPC GRADE approach[39] and resolved discrepancies by consensus. A list of the outcomes that were assessed is provided in Table 8.

For each outcome, we assessed four major domains: risk of bias (rated as low, moderate, or high), consistency (rated as consistent, inconsistent, or unknown), directness (rated as direct or indirect), and precision (rated as precise or imprecise). No additional domains were used.

Based on the individual domains, we assigned the following overall evidence grades for each outcome for each comparison of interest: high, moderate, or low confidence that the evidence reflects the true effect. When no studies were available or an outcome or the evidence did not permit estimation of an effect, we rated the strength of evidence as insufficient.

To determine the overall strength of evidence score, we first considered the risk of bias domain. RCTs with a low risk of bias were initially considered to have a "high" strength of evidence, whereas RCTs with high risk of bias and well-conducted cohort studies received an initial grade of "moderate" strength of evidence. Low-quality cohort studies received an initial grade of "low" strength of evidence. The strength of evidence was then upgraded or downgraded depending on the assessments of that body of evidence on the consistency, directness, and precision domains.

Some outcomes, such as autistic symptoms, were assessed using a variety of outcome measures (e.g., Aberrant Behavior Checklist, Childhood Autism Rating Scale) across the studies. We graded these outcomes taking into account the findings of each of these relevant measures and their meta-analyses.

Table 8. 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	Suicide-related behaviors
		Weight	

KQ = key question

Data Analysis

We made the following assumptions and performed the following imputations to transform reported data into the form required for analysis. We extracted data from graphs using the measurement tool of Adobe Acrobat 9 Pro (Adobe Systems Inc., California, U.S.) when data were not reported in text or tables. If necessary, we approximated means by medians and used 95 percent confidence intervals (CI) to calculate approximate standard deviations. We calculated p-values when they were not reported.

For all studies, we present qualitative data in the results section and in the evidence table in Appendix D. When appropriate, we performed meta-analyses to synthesize the available data on the efficacy of antipsychotic medications. We considered it appropriate to pool studies that were sufficiently similar in terms of their study design, population (i.e., condition and patient ages), interventions being compared, and outcomes.

We summarized the evidence for efficacy separately for each condition. Within each condition category, we present data both by individual drug comparison and across the drug class (e.g., all SGAs). We summarized adverse event data separately for each drug across all conditions.

We used Review Manager Version 5.0 (The Cochrane Collaboration, Copenhagen, Denmark) to perform meta-analyses. For continuous variables, we calculated mean differences (MD) for individual studies. For dichotomous outcomes, we computed relative risks (RR) to

estimate between-group differences. If no event was reported in one treatment arm, a correction factor of 0.5 was added to each cell of the two by two table in order to obtain estimates of the RR. All results are reported with 95% CIs.

All meta-analyses used a random effects model. We quantified statistical heterogeneity using the I-squared (I^2) statistic. A priori, we considered an I^2 value of 80 percent or greater to represent considerable heterogeneity, thereby precluding the pooling of studies.[40,41]

Results

This chapter reports on the results of our literature review and synthesis. First, we describe the results of our literature search and selection process. Description of the characteristics and methodological quality of the studies follow. We present our analysis of the study results by Key Question. We present the results for symptoms (Key Question 1) and other short- and long-term outcomes (Key Question 3) first, followed by adverse events (Key Question 2) and subpopulations (Key Question 4). Key Questions 1, 3, and 4 are organized by condition; Key Question 2 is organized by drug class comparison. Metagraphs and tables reporting the strength of evidence for key outcomes are available within each applicable section. Within each metagraph, the studies that provided data are indexed by the name of the first author. Information on the domains, scoring, and psychometric properties of common scales evaluating outcomes and extrapyramidal side effects is provided in Table 3 and Table 4 above. A list of abbreviations is provided at the end of the report.

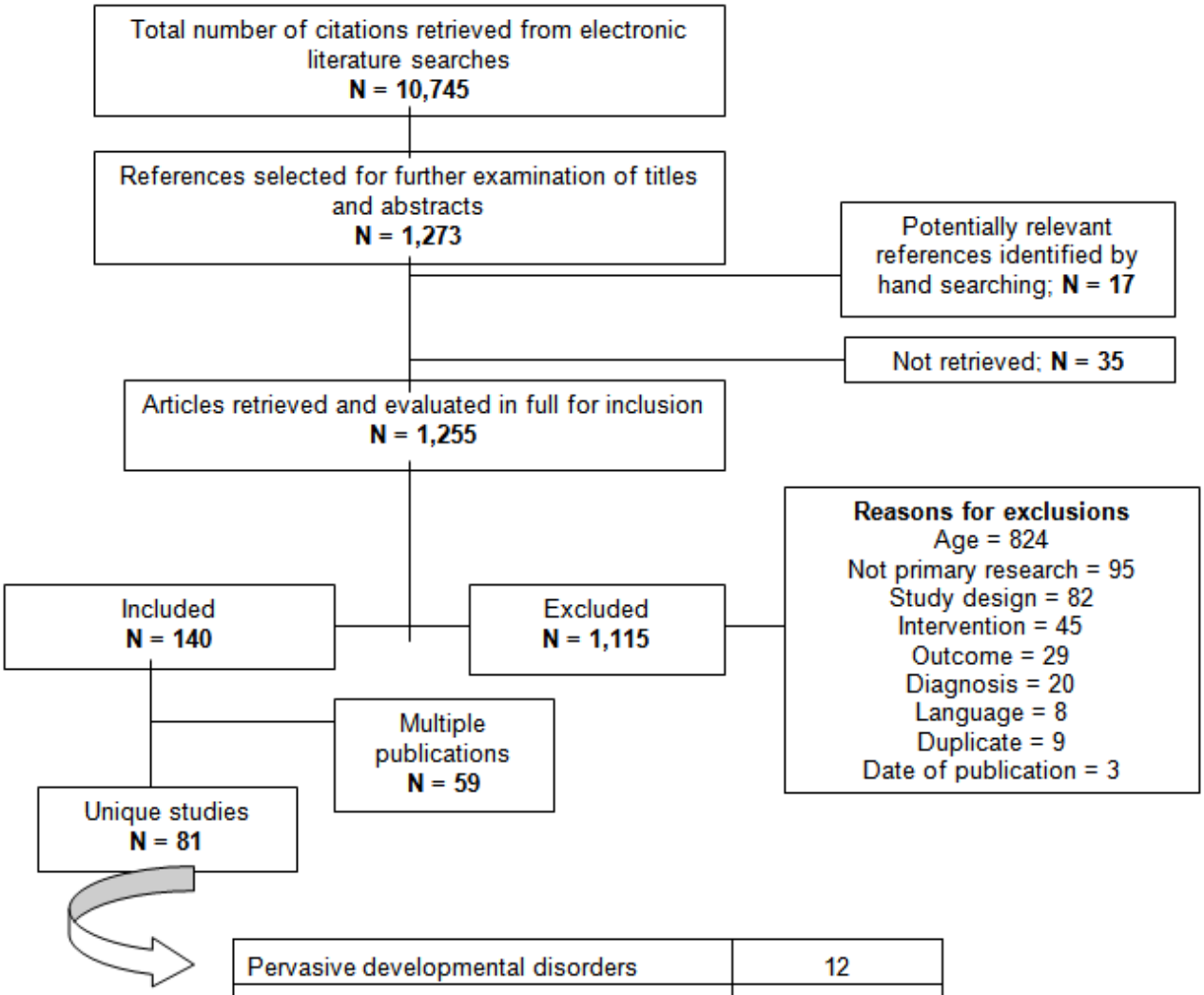
Several appendixes provide supporting information to the findings presented in this section. Appendix C provides the quality assessment ratings by domain for each study. Appendix D contains a detailed evidence table describing the study, participant, and treatment characteristics, outcomes, and conclusions for each study. A list of citations for the excluded and unobtained studies is available in Appendix E. Appendixes are available at the Agency for Healthcare Research and Quality Web site at www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Literature Search

The search strategy identified 10,745 citations from electronic databases. Screening based on titles and abstracts identified 1,273 potentially relevant studies. We identified 17 additional studies by hand searching the reference lists from included studies, conference proceedings, and clinical trial registries. The full text of 35 studies could not be retrieved through the university interlibrary loan service (Appendix E). Therefore, the full texts of 1,255 potentially relevant reports were retrieved and evaluated for inclusion in the review. Using the detailed selection criteria, 140 studies were included, and 1,115 were excluded. Of the 140 included studies, 59 were identified as companion publications; therefore, we included 81 unique studies (Figure 2). A list of companion articles is provided in a reference list at the end of this report.

The most frequent reasons for exclusion were: (1) ineligible age of study participants (N = 824); (2) the article did not report on primary research (N = 95); (3) ineligible study design (N = 82); (4) the study did not compare two antipsychotic drugs or an antipsychotic drug with placebo (N = 45); (5) no outcome data of interest (N = 29); and (6) study participants were not diagnosed with any of the conditions of interest (N = 20). Twenty studies were excluded for other reasons (Figure 2). A complete list of excluded studies and reasons for exclusion is provided in Appendix E.

Figure 2. Flow diagram of study retrieval and selection



Pervasive developmental disorders	12
ADHD and disruptive behavior disorders	8
Pediatric bipolar disorder	11*
Schizophrenia and related psychosis	31*
Tourette syndrome	7
Behavioral issues	4
Multiple conditions	9
Obsessive-compulsive disorder, post-traumatic stress disorder, and anorexia nervosa	0
TOTAL	**81**

ADHD = attention deficit hyperactivity disorder
* One study provided separate data for both bipolar disorder and schizophrenia.

Description of Included Studies

A total of 81 unique studies met the eligibility criteria for this review. The evidence table describes the characteristics of the studies (Appendix D). The studies were published between 1989 and 2010 (median = 2006 [interquartile range (IQR), 2002 to 2008]). Most of the studies (89 percent) were published in peer-reviewed publications. Studies were conducted in the U.S. (52 percent), Europe (18 percent), Israel (4 percent), Canada (2 percent), other regions (10 percent), or in multiple countries (14 percent).

A total of 63 studies (78 percent) and 55 studies (68 percent) examined the effectiveness of antipsychotics for treating symptoms (Key Question 1) or other short- and long-term outcomes (Key Question 3), respectively. Adverse events (Key Question 2) were reported in 78 studies (96 percent). In addition, 37 studies (46 percent) reported whether outcomes differed across subpopulations (Key Question 4).

Of the 81 studies, 62 (77 percent) were randomized controlled trials (RCTs) and 2 were nonrandomized controlled trials (NRCTs) (2 percent). Most of the trials had a parallel design and two treatment arms. Five trials used a crossover design; 15 trials had three or four arms. A total of 17 cohort studies (9 prospective and 8 retrospective) were included.

The studies examined the following conditions: pervasive developmental disorders (12 studies); attention deficit hyperactivity disorder (ADHD) or disruptive behavior disorders (8 studies); bipolar disorder (11 studies); schizophrenia or schizophrenia-related psychosis (31 studies); Tourette syndrome (7 studies); behavioral issues (4 studies); and patients diagnosed with various psychiatric and behavioral conditions (9 studies). One study provided separate data for both pediatric bipolar disorder and schizophrenia.[42]

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

The number of enrolled participants ranged from 8 to 335 (median = 42 [IQR, 25 to 100]). The mean age of study participants ranged from 4.0 to 21.5 years (median = 13.6 years [IQR, 10.6 to 15.2 years]). The mean age was lower than 12 years in 31 studies (38 percent).

Overall, 38 studies provided one or more head-to-head comparisons of different first- (FGAs) or second-generation antipsychotics (SGAs) (Table 9). A total of 17 studies compared different doses of the same antipsychotic, and 26 studies compared one antipsychotic with placebo.

Table 9. Head-to-head comparisons examined in the review

Comparison	Number of Studies	Comparison	Number of Studies
FGAs vs. SGAs		***SGAs vs. SGAs***	
Haloperidol vs. clozapine	2	Aripiprazole vs. olanzapine	1
Haloperidol vs. olanzapine	6	Aripiprazole vs. quetiapine	1
Haloperidol vs. risperidone	4	Aripiprazole vs. risperidone	1
Pimozide vs. risperidone	2	Aripiprazole vs. ziprasidone	1
Various FGAs vs. various SGAs	3	Clozapine vs. olanzapine	6
		Clozapine vs. quetiapine	1
FGA vs. FGAs		Clozapine vs. risperidone	2
Haloperidol vs. pimozide	2	Olanzapine vs. quetiapine	7
		Olanzapine vs. risperidone	16
		Olanzapine vs. ziprasidone	2
		Quetiapine vs. risperidone	6
		Quetiapine vs. ziprasidone	1
		Risperidone vs. ziprasidone	1

FGA = first-generation antipsychotic; SGA = second-generation antipsychotic

Methodological Quality of Included Studies

The methodological quality of each study was assessed by two independent reviewers. Our approach to assessing study quality is described in the methods section. The consensus ratings for each study and domain are presented in Appendix C, Tables C1 and C2.

Randomized and Nonrandomized Controlled Trials

The risk of bias assessments for the 62 RCTs and 2 NRCTs are presented in Appendix C, Table C1. The majority of the RCTs were considered to have a high risk of bias for both subjective and objective outcomes (N = 56, 90 percent). Sequence generation was adequate in 33 trials (53 percent), and allocation concealment was adequate in 23 studies (37 percent). Blinding was considered adequate for subjective outcomes in 31 studies (50 percent) and for objective outcomes in 43 studies (69 percent). Half of the studies either had no missing outcome data or adequately addressed missing data (31 studies reporting subjective outcomes and 30 reporting objective outcomes). Fifty studies (81 percent) were free of selective outcome reporting. Seven studies (11 percent) were considered free of other potential sources of bias, including industry funding and baseline imbalances between groups.

The two NRCTs were both considered at high risk of bias. Sequence generation and allocation concealment were inadequate in both studies, blinding was adequate in one study, and incomplete outcome data was adequate in another. Both studies were free of selective outcome reporting and were rated unclear for other sources of bias.

The most common source of funding was industry (50 trials, 78 percent), followed by government (15 trials, 23 percent). Other sources of funding were academic institutions (three trials, 5 percent), foundations (seven trials, 11 percent), and other private sources (four trials, 6 percent). One trial reported receiving no funding, and funding was not described in seven trials. Eighteen trials received funding from multiple sources.

Cohort Studies

The detailed results of the quality assessment of the 17 cohort studies using the Newcastle-Ottawa scale are presented in Appendix C, Table C2. Data were prospectively collected in nine studies and retrospectively collected in eight. Overall, the methodological quality of the cohort studies was moderate (median score = 5/8 stars; IQR, 4 to 6).

More than half of the studies enrolled patients that were rated to be truly or somewhat representative of average patients in the community (11 studies, 65 percent). The nonexposed cohort was drawn from the same community as the exposed cohort in 13 studies (76 percent). In all studies, the exposure status was based on data from a secure source, most commonly from medical records. Six studies controlled for potential confounding variables in their design or analysis. Half of the studies (nine studies, 53 percent) used independent blind assessment or record linkage to determine outcomes. All except one study had sufficient followup duration for outcomes to occur. The rate of followup was considered unlikely to introduce bias in the majority of studies (12 studies, 71 percent).

Several cohort studies received funding from government (six studies, 35 percent). Two studies (12 percent) reported receiving funding from each of the following sources: industry, academic institutions, foundations, or other private sponsors. Seven studies (41 percent) did not report their source of funding.

Key Questions 1 and 3: Disorder-Specific and Nonspecific Symptoms and Other Short- and Long-Term Outcomes

This section reviews the evidence of the effect of antipsychotics on symptoms (Key Question 1) and other short- and long-term outcomes (Key Question 3). For each condition of interest, we describe the studies that provided data for this review and present the results of studies individually and collectively. Throughout this report, a "significant" result refers to a finding that is statistically significant. We do not infer that statistically significant results are necessarily clinically meaningful.

Pervasive Developmental Disorders: Overview

Eleven RCTs[43-53] and one retrospective cohort study[54] examined the effectiveness of FGAs and SGAs in treating patients with pervasive developmental disorders. The majority of the studies reported both symptom improvement and other short- and long-term outcomes, with four exceptions: three RCTs[44,48,50] reported only symptom improvement, and one retrospective cohort study[54] reported only other outcomes.

Table 10 provides selected information on the characteristics of the individual studies. The studies are grouped according to the drug class comparisons. Studies that include both head-to-head and placebo comparisons are listed under the head-to-head category. Within each comparison, studies are listed alphabetically by the specific drugs compared. A detailed evidence table is available in Appendix D.

Overall, the average age of patients was 8.3 years. Patients were predominantly male (average 79 percent) and white. A diagnosis of pervasive developmental disorder was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM, either third edition [DSM–III], fourth edition [DSM–IV], or text revised fourth edition [DSM–IV–TR]). All studies included patients with autistic disorder. Five studies also included patients with other pervasive developmental disorders, including Asperger syndrome, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified. In four studies, all enrolled patients had behavioral issues, such as tantrums, aggression, or self-injury.[46,47,53,54] Mental retardation was present in 24 percent of all patients across the studies.

Three studies[45,48,54] provided head-to-head evidence for comparisons of a FGA (haloperidol) with SGAs (olanzapine or risperidone). One RCT[51] compared the effectiveness of continuous versus discontinuous administration of haloperidol. Most of the studies (N = 8, 67 percent) compared a SGA, usually risperidone, with placebo.

The duration of followup varied widely across studies (range, 6 weeks to 17 months). On average, studies were 4.5 months in duration. Most of the RCTs had a high risk of bias due to industry sponsorship. Six studies also had unclear allocation concealment (55 percent). The one cohort study[54] was of high quality (6 out of 8 stars).

Table 10. Characteristics of studies examining pervasive developmental disorders

Author, Year, Study Design, Duration, KQ	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
FGAs vs. SGAs			
Malone et al., 2001[45] RCT, 6 wk *KQ1, KQ3*	**G1:** Haloperidol (6), 1.4±0.7 mg/day **G2:** Olanzapine (6), 7.9±2.5 mg/day	**G1:** 7.3±1.9 yr / Male: 67% / White: 67% **G2:** 8.5±2.4 yr / Male: 67% / White: 50% Comorbidities: MR (mild (1), moderate (5), severe (5))	autistic disorder (11), PDD NOS (1) High ROB
Miral et al., 2008[48] RCT, 12 wk (12 wk extension) *KQ1*	**G1:** Haloperidol (15), 2.6±1.3 mg/day **G2:** Risperidone (15), 2.6±0.8 mg/day	**G1:** 10.9±2.9 yr / Male: 87% / White: NR **G2:** 10.0±2.7 yr / Male: 73% / White: NR Comorbidities: NR	autistic disorder (all) High ROB
Novaes et al., 2008[54] Retrospective cohort, 17 mo *KQ3*	**G1:** FGA (1), NR **G2:** Risperidone or Risperidone and FGA (13 and 5), NR **G3:** SGA (except risperidone) (4), NR **G4:** FGA and SGA (3), NR	**All groups:** 4–21 yr / Male: 89 / White: NR Comorbidities: aggression/ agitation (all), MR (20)	autistic disorder (all) 6/8 stars
FGAs vs. FGAs			
Perry et al., 1989[51] RCT, 6 mo *KQ1, KQ3*	**G1:** Haloperidol (continuous) (34), 1.2 mg/day **G2:** Haloperidol (discontinuous) (36), 1 mg/day	**G1 and G2:** 2.3–7.9 yr / Male: 69 / White: NR Comorbidities: NR	autistic disorder (all) High ROB
SGAs vs. SGAs			
Marcus et al., 2009[46] RCT, 8 wk *KQ1, KQ3*	**G1:** Aripiprazole (low) (53), target: 5 mg/day **G2:** Aripiprazole (medium) (59), target: 10 mg/day **G3:** Aripiprazole (high) (54), target: 15 mg/day **G4:** Placebo (52)	**G1:** 9.0±2.8 yr / Male: 89% / White: 70% **G2:** 10.0±3.2 yr / Male: 85% / White: 70% **G3:** 9.5±3.1 yr / Male: 93% / White: 78% **G4:** 10.2±3.1 yr / Male: 92% / 67% Comorbidities: behavior issues (e.g., tantrums, aggression, self-injury; all)	autistic disorder (all) High ROB
NCT00576732, 2010[50] RCT, 6 wk (26 wk extension) *KQ1*	**G1:** Risperidone (low) (30), 0.125–0.175 mg/day **G2:** Risperidone (high) (31), 1.25–1.75 mg/day **G3:** Placebo (35)	**All groups:** NR / Male: 88% **G1:** White: 70% **G2:** White: 81% **G2:** White: 57% Comorbidities: NR	autistic disorder (all) High ROB
SGA vs. Placebo			
Hollander et al., 2006[43] RCT, 8 wk *KQ1, KQ3*	**G1:** Olanzapine (6), 10±2 mg/day **G2:** Placebo (5)	**G1:** 9.3±2.9 yr / Male: all / White: 50% **G2:** 8.9±2.1 yr / Male: 60% / White: 80% Comorbidities: MR [mild (5), severe (2)]	Asperger syndrome (1), autism (6), PDD NOS (4) High ROB

Table 10. Characteristics of studies examining pervasive developmental disorders (continued)

Author, YearStudy design, Duration, KQ	Intervention (N Enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / White (%)Comorbidities	Diagnosis Breakdown (n) Quality Rating
SGAs vs. Placebo (continued)			
Luby et al., 2006[44] RCT, 6 mo *KQ1*	**G1:** Risperidone (12), 1.1±0.3 mg/day **G2:** Placebo (12)	**G1:** 4.1±0.9 yr / Male: 75% / White: 91% **G2:** 4.0±1.1 yr / Male: 67% / White: 92% Comorbidities: NR	autistic disorder (NR), PDD NOS (NR) High ROB
McCracken et al., 2002[47] RCT, 8 wk (4 mo extension) *KQ1, KQ3*	**G1:** Risperidone (49), 1.8±0.7 mg/day **G2:** Placebo (52)	**G1:** NR / Male: 80% / White: NR **G2:** NR / Male: 83% / White: NR Comorbidities: MR (borderline (12), mild or moderate (43), severe (31)), serious behavior issues (all)	autistic disorder (all) Unclear ROB
Nagaraj et al., 2006[49] RCT, 6 mo *KQ1, KQ3*	**G1:** Risperidone (19), 1 mg/day **G2:** Placebo (21)	**G1:** 4.8±1.7 yr / Male: 84% / White: NR **G2:** 5.3±1.7 yr / Male: 90% / White: NR Comorbidities: Aggression (20), irritability (36), self-injurious behavior (12), seizures (8)	autistic disorder (all) Unclear ROB
Shea et al., 2004[52] RCT, 8 wk *KQ1, KQ3*	**G1:** Risperidone (41), 1.2 mg/day **G2:** Placebo (39)	**G1:** 7.6 yr / Male: 73% / White: NR **G2:** 7.3 yr / Male: 82% / White: NR Comorbidities: MR (27)	Asperger syndrome (12), autistic disorder (55), childhood disintegrative disorder (1), PDD NOS (11) High ROB
Troost et al., 2005[53] RCT, 6 mo *KQ1, KQ3*	**G1:** Risperidone (12), 1.9±0.7 mg/day **G2:** Placebo (12)	**G1:** 9.4±3.4 yr / Male: 92% / White: 100% **G2:** 8.7±1.2 yr / Male: 92% / White: 83% Comorbidities: behavior issues (e.g., tantrums, aggression, or self-injury; all), MR (2)	Asperger syndrome (2), autistic disorder (6), PDD NOS (16) High ROB

FGA = first-generation antipsychotic; G = group; KQ = key question; Mg = milligram; mo = month; MR = mental retardation; N = number; NOS = not otherwise specified; NR = not reported; PDD = pervasive developmental disorder; RCT = randomized controlled trial; ROB = risk of bias; SD = standard deviation; SGA = second-generation antipsychotic; wk = week; yr = year

Pervasive Developmental Disorders: Disorder-Specific and Nonspecific Symptoms (Key Question 1)

Eleven RCTs compared the effectiveness of FGAs and SGAs for treating disorder-specific and nonspecific symptoms in patients with pervasive developmental disorders. A summary of the results by comparison is presented below. Table 11 provides the strength of evidence grades for all key outcomes that were reported by at least one study.

- Haloperidol versus olanzapine (one RCT[45]): Patients treated with olanzapine had a significantly greater reduction in anger and hyperactivity than patients on haloperidol ($p \leq 0.05$).
- Haloperidol versus risperidone (one RCT[48]): Patients on risperidone had a significantly greater reduction in the Aberrant Behavior Checklist (ABC) at 12 weeks ($p = 0.006$) and greater improvement on the Clinical Global Impressions (CGI) scale ($p = 0.02$) and language ($p = 0.04$) at 24 weeks than patients on haloperidol.

- Haloperidol–continuous versus discontinuous (5 days on haloperidol with 2 days on placebo) administration (one RCT[51]): There was no significant difference in Clinical Global Impressions of Improvement (CGI–I) between the administration schedules.
- Aripiprazole–dosing (one RCT[46]): High-dose (15 mg/day) aripiprazole resulted in significantly greater improvement in the ABC lethargy/social withdrawal subscale (p = 0.05) than medium-dose (10 mg/day) aripiprazole.
- SGAs versus placebo (eight RCTs[43,44,46,47,49,50,52,53]): Meta-analysis found SGAs to be superior to placebo for aberrant behavior on the ABC (mean difference [MD] = -18.29; 95% confidence interval [CI], -27.08 to -9.51), autism symptoms on the Childhood Autism Rating Scale (CARS) (MD = -4.94; 95% CI, -8.52 to -1.36), obsessive-compulsive symptoms on the Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS) (MD = -1.71; 95% CI, -3.17 to -0.25), but not for the CGI–I.
- Single studies found significant improvement favoring risperidone over placebo for the ABC–I (irritability subscale),[50] Ritvo-Freeman Real Life Rating Score and maladaptive behavior,[47] Children's Global Assessment Score (CGAS),[49] behavior subscales (parent-rated Nisonger Child Behavior Rating Form [NCBRF]), and improvement of the most troublesome symptom.[52]

Table 11. Strength of evidence for pervasive developmental disorders (Key Question 1)

Comparison	Outcome (N Studies; N Patients)	Strength of Evidence Domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
FGA vs. SGA	Autistic symptoms (2; 40)	Moderate	Consistent	Direct	Not pooled	Low
	Clinical global impressions (2; 40)	Moderate	Inconsistent	Direct	Not pooled	Insufficient
Haloperidol–continuous vs. discontinuous	Clinical global impressions (1; 70)	Moderate	Unknown	Direct	Imprecise	Insufficient
Aripiprazole–low- vs. medium- vs. high-dose	Autistic symptoms (1; 218)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Clinical global impressions (1; 218)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Obsessive compulsive (1; 218)	Moderate	Unknown	Direct	Imprecise	Insufficient
SGA vs. placebo	Anxiety (1; 80)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Autistic symptoms (7; 583)	Moderate	Consistent	Direct	Precise	Low
	Clinical global impressions (3; 330)	Moderate	Consistent	Direct	Imprecise	Low
	Obsessive compulsive (3; 330)	Moderate	Inconsistent	Direct	Precise	Low

FGA = first-generation antipsychotic; N = number; ROB = risk of bias; SGA = second-generation antipsychotic

We provide a detailed analysis of the results below. This section is organized by comparison, beginning with head-to-head evidence (FGAs vs. SGAs, FGAs vs. FGAs, and SGAs vs. SGAs) and followed by placebo comparisons for FGAs and SGAs.

FGAs Versus SGAs

Two RCTs compared FGAs versus SGAs.[45,48]

Haloperidol Versus Olanzapine

A 6-week RCT (N = 12) compared haloperidol (mean dose, 1.4±0.7 mg/day) with olanzapine (mean dose, 7.9±2.5 mg/day) in children ages 5 to 17 years.[45] Patients on olanzapine showed significantly greater improvement on the Children's Psychiatric Rating Scale (CPRS) anger and hyperactivity subscales ($p = 0.05$ and $p = 0.01$, respectively). Clinical Global Impressions of Severity (CGI–S) and other CPRS subscales did not significantly differ between groups.

Haloperidol Versus Risperidone

A 12-week RCT (N = 30) with a 12-week extension assessed the comparative effectiveness of haloperidol (mean dose, 2.6±0.8 mg/day) and risperidone (mean dose, 2.6±1.3 mg/day) in children ages 8 to 18 years.[48] Risperidone led to significantly greater improvement in ABC scores at 12 weeks ($p = 0.006$), CGI scores at 24 weeks ($p = 0.02$), and the language subscale of the Ritvo-Freeman Real Life Rating Score at 24 weeks ($p = 0.04$).

FGAs Versus FGAs

Haloperidol–Continuous Versus Discontinuous Administration

A 6-month RCT (N = 70) randomized patients ages 2.3 to 7.9 years to continuous or discontinuous drug administration of haloperidol.51 The discontinuous drug schedule consisted of 5 days on haloperidol with 2 days on placebo. The prescribed dose of haloperidol was similar between the groups (1.2 mg/day in the continuous group, and 1.0 mg/day in the discontinuous group). CGI scores were not significantly different between groups at endpoint.

SGAs Versus SGAs

Aripiprazole–Low- Versus Medium- Versus High-Dose

An 8-month, placebo-controlled RCT (N = 218) evaluated the effect of daily fixed-dose regimens of aripiprazole at 5 mg, 10 mg, and 15 mg on irritability associated with autistic disorder.[46] Patients were children ages 6 to 17 years with behaviors such as tantrums, agitation, or self-injury. The high-dose aripiprazole group had significantly greater improvement in the ABC lethargy/social withdrawal subscale than the medium-dose group ($p = 0.05$). No differences were found on the other ABC subscales, the CYBOCS, or CGI.

Risperidone–Low- Versus Medium- Versus High-Dose

A 6-week, placebo-controlled RCT (N = 96) compared low-dose (0.125–0.175 mg/day) and high-dose (1.25–1.75 mg/day) risperidone.[50] Patients were assessed using the ABC–I; however, the article provided no numeric data for this dosing comparison.

SGAs Versus Placebo

Eight studies compared SGAs with placebo.[43,44,46,47,49,50,52,53]

Aripiprazole Versus Placebo

An 8-week RCT (N = 218) compared three doses of aripiprazole (5 mg, 10 mg, and 15 mg) with placebo in patients ages 6 to 17 years.[46] Aripiprazole led to significantly greater improvement in the irritability ($p<0.05$), stereotypy ($p\leq0.01$), and hyperactivity ($p\leq0.01$) ABC subscales, the CGI–I ($p<0.005$), and CYBOCS ($p = 0.03$, for high-dose aripiprazole only).

Groups were not significantly different on the ABC lethargy/social withdrawal or inappropriate speech subscales.

Olanzapine Versus Placebo

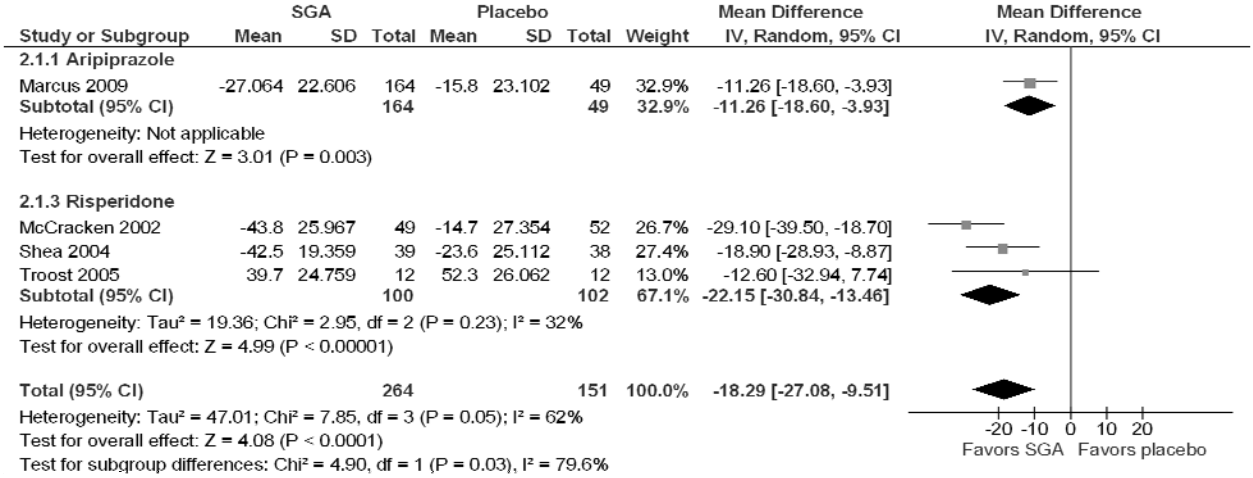
An 8-week RCT (N = 11) randomized children ages 6 to 14 years to olanzapine (mean dose, 10±2.04 mg/day) and placebo.[43] Patients treated with olanzapine had significantly greater improvement on the CGI–I (p = 0.01).

Risperidone Versus Placebo

Six RCTs compared risperidone and placebo.[44,47,49,50,52,53] The duration of studies ranged from 6 weeks to 6 months. A total of 365 children ages 2 to 17 years were enrolled in the trials. Three studies included patients with mental retardation,[47,52,53] and two studies enrolled only patients with various behavioral issues.[47,53] Symptoms were assessed using the ABC, CARS, CGAS, CGI–I, CYBOCS, NCBRF–P, Ritvo-Freeman Real Life Rating Score, Vineland Adaptive Behavior Scale, and visual analogue scale (VAS) of the most troublesome symptom.

A meta-analysis of three studies[47,52,53] found that risperidone was superior to placebo for improvement in ABC scores (MD = -22.15; 95% CI, -30.84 to -13.46) (Figure 3). Heterogeneity was moderate (p = 0.23, I2 = 32%) and may be attributable to differences in the proportion of patients with intellectual disabilities who were enrolled in the studies.

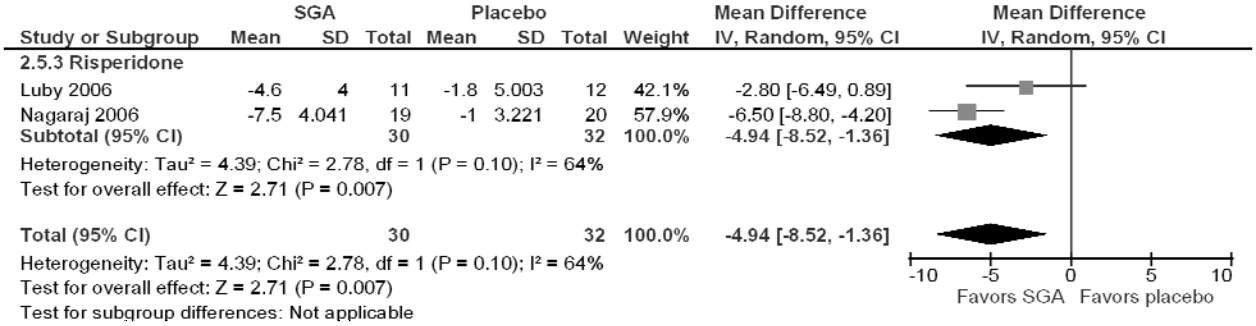
Figure 3. SGAs versus placebo on ABC in pervasive developmental disorders



ABC = Aberrant Behavior Checklist; CI = confidence interval; df = degrees of freedom; IV = inverse variance; SD = standard deviation; SGA = second-generation antipsychotic

A meta-analysis of two RCTs[44,49] examining autistic behaviors on the CARS compared risperidone with placebo (Figure 4). The pooled estimate indicated significantly greater improvement of autism symptoms in the risperidone groups than placebo (MD = -4.94; 95% CI, -8.52 to -1.36). There was substantial heterogeneity (p = 0.10, I^2 = 64%). The study by Nagaraj et al.[49] included patients who were slightly older and had a higher proportion of male participants than Luby et al.[44]

Figure 4. Risperidone versus placebo on CARS in pervasive developmental disorders



CARS = Childhood Autism Rating Scale; CI = confidence interval; df = degrees of freedom; IV = inverse variance; SD = standard deviation; SGA = second-generation antipsychotic

Individual studies found that risperidone improved symptoms more than placebo for the following measures: CGAS ($p<0.001$),[49] CGI–I ($p<0.001$),[47] CYBOCS ($p = 0.005$),[47] the conduct problem, hyperactive, insecure, and overly sensitive subscales of the NCBRF parent version ($p<0.05$),[52] Ritvo-Freeman Real Life Rating Score ($p<0.001$),[47] Vineland Adaptive Behavior Scale–maladaptive subscale (<0.001),[47] and VAS of the most troublesome symptom ($p\leq0.05$).[52] One RCT[50] found a significant reduction in irritability on the ABC–I subscale for patients who received high-dose, but not low-dose, risperidone compared with placebo.

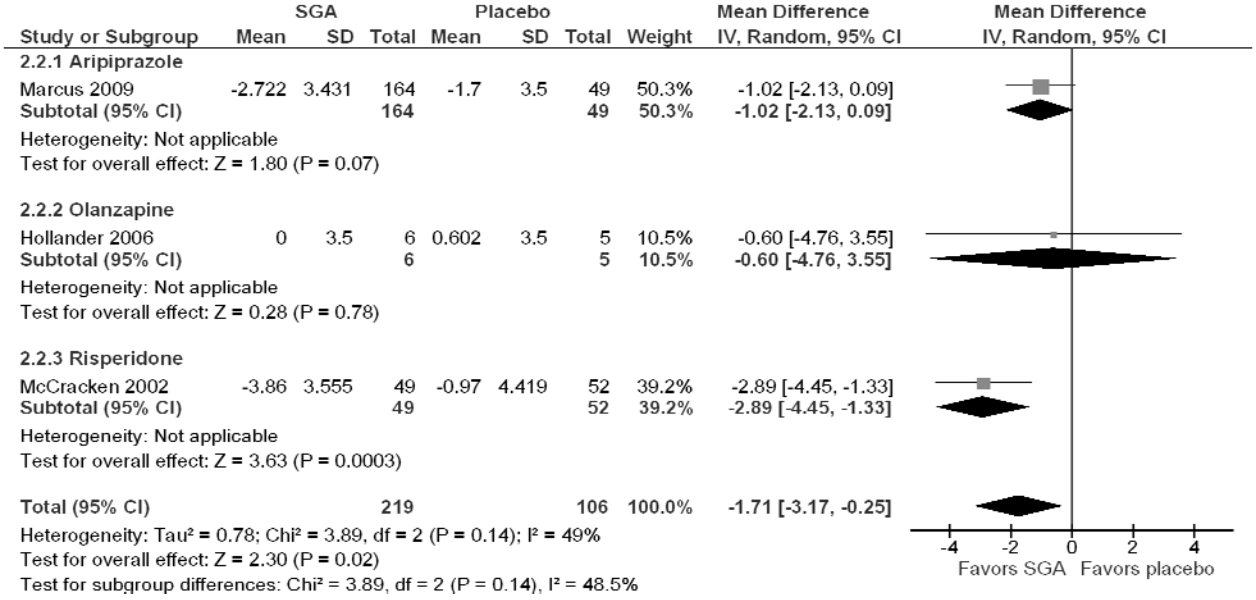
Meta-analyses Comparing Various SGAs With Placebo

Meta-analyses were conducted to compare various SGAs with placebo for the ABC, CGI–I, and CYBOCS.

Four RCTs[46,47,52,53] contributed data to a meta-analysis comparing SGAs with placebo on ABC scores (see Figure 3 above). The pooled estimate favored SGAs over placebo (MD = -18.29; 95% CI, -27.08 to -9.51). Heterogeneity was substantial ($p = 0.05$, $I^2 = 62\%$) and may be a result of differences in the SGA used as the comparator.

Three RCTs[43,46,47] were combined in a meta-analysis comparing SGAs and placebo for obsessive-compulsive behaviors on the CYBOCS (Figure 5). The effect estimate showed a significantly greater decrease in obsessive-compulsive symptoms with use of SGAs than with placebo (MD = -1.71; 95% CI, -3.17 to -0.25). Heterogeneity was high ($p = 0.14$, $I^2 = 49\%$) and may be attributable to differences in the SGAs.

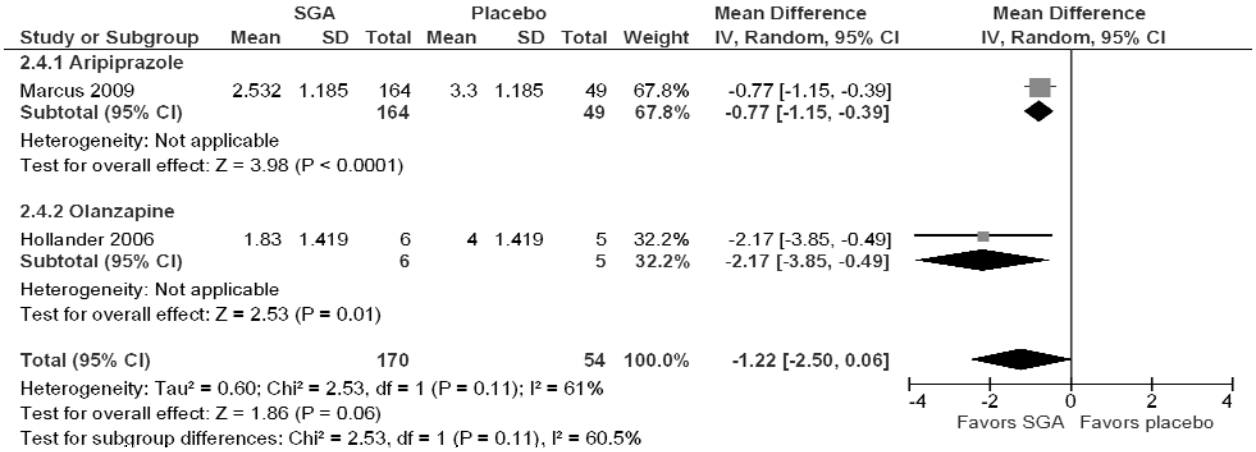
Figure 5. SGAs versus placebo on CYBOCS in pervasive developmental disorders



CI = confidence interval; CYBOCS = Children's Yale-Brown Obsessive-Compulsive Scale; df = degrees of freedom; IV = inverse variance; SD = standard deviation; SGA = second-generation antipsychotic

Two RCTs[43,46] provided data for a meta-analysis comparing SGAs with placebo on CGI–I rating (Figure 6). Although the combined estimate favored SGAs, the result was not statistically significant (MD = -1.22; 95% CI, -2.50 to 0.06). There was substantial heterogeneity (p = 0.11, I^2 = 61%). Nearly all of the patients in the study by Hollander[43] had mild to severe mental retardation, which may account for some of the observed heterogeneity.

Figure 6. SGAs versus placebo on CGI–I in pervasive developmental disorders



CGI–I = Clinical Global Impressions–Improvement; CI = confidence interval; df = degrees of freedom; IV = inverse variance; SD = standard deviation; SGA = second-generation antipsychotic

Pervasive Developmental Disorders: Short- and Long-Term Outcomes (Key Question 3)

Nine studies provided data on a variety of short- and long-term outcomes for patients with pervasive developmental disorders. A summary of the results is presented by outcome below. Table 12 provides the strength of evidence grades for all key outcomes that were reported by at least one study.

- Response and relapse: Response rate did not differ between haloperidol and olanzapine in one RCT[45] or between continuous and discontinuous administration of haloperidol in another.[51] A meta-analysis of five RCTs[43,46,47,49,52] comparing SGAs with placebo found a significantly higher response rate in patients receiving SGAs (relative risk [RR] = 2.69; 95% CI, 1.52 to 4.74). The relapse rate was significantly lower for risperidone than placebo in two RCTs (RR = 0.31; 95% CI, 0.13 to 0.73), as was the time to relapse (p = 0.01).[47,53]
- Cognitive and emotional development: Two RCTs[47,53] comparing risperidone and placebo reported patients' performance on various cognitive tasks. Risperidone was superior to placebo on a visuospatial ("dot") task; no differences were found between groups for cancellation tasks, word recognition, and hand-eye coordination.[47] Similarly, reaction time did not differ between groups.[53]
- Suicide-related behaviors: In an RCT[46] comparing three doses of aripiprazole with placebo, three patients in the placebo group experienced suicide-related behaviors compared to no patients in the aripiprazole groups. This finding was statistically significant (p = 0.04).
- Medication adherence: Two RCTs[46,47] reporting medication adherence found no difference between SGAs and placebo.
- Patient-, parent-, or care provider–reported outcomes: One RCT[47] found no significant difference between risperidone and placebo for sleep duration. There was a significant increase in vitamin K intake after 2 months of risperidone treatment compared with placebo (p<0.05).
- Other outcomes: No studies provided data for the following outcome categories: growth and maturation, school performance, work-related functional capacity, patient insight into illness, health-related quality of life, legal system interaction, or health care system utilization.

Table 12. Strength of evidence for pervasive developmental disorders (Key Question 3)

Comparison	Outcome (N Studies; N Patients)	Strength of Evidence Domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Aripiprazole–low- vs. medium- vs. high-dose	Medication adherence (1; 218)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Suicide (1; 218)	Moderate	Unknown	Indirect	Imprecise	Insufficient
SGA vs. placebo	Medication adherence (2; 319)	Moderate	Consistent	Direct	Imprecise	Low
	Patient-, parent-, or care provider-reported outcomes: sleep, food frequency (1; 101)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Suicide (1; 218)	Moderate	Unknown	Indirect	Precise	Insufficient

N = number; ROB = risk of bias; SGA = second-generation antipsychotic

A detailed analysis of the results is provided below. This section is organized by comparison, beginning with head-to-head evidence (FGAs vs. SGAs, FGAs vs. FGAs, and SGAs vs. SGAs) and followed by placebo comparisons for FGAs and SGAs.

FGAs Versus SGAs

Two studies compared FGAs with SGAs.[45,54] However, one study[54] was not included in the analysis because only one patient received a FGA alone. All other patients in this study either received a SGA or combination treatment of a FGA and a SGA.

Haloperidol Versus Olanzapine

A 6-week RCT (N = 12) examined the comparative effectiveness of haloperidol (mean dose, 1.4±0.7 mg/day) and olanzapine (mean dose, 7.9±2.5 mg/day) in children ages 5 to 17 years.[45] Response rates did not differ between groups.

FGAs Versus FGAs

Haloperidol–Continuous Versus Discontinuous Administration

A 6-month RCT (N = 70) compared continuous and discontinuous (i.e., 5 days haloperidol and 2 days placebo) administration of haloperidol in children ages 2.3 to 7.9 years.[51] Treatment response, defined as CGI–I≤2 and CGI–S≤2, was not significantly different between groups.

SGAs Versus SGAs

Aripiprazole–Low- Versus Medium- Versus High-Dose

An 8-week RCT (N = 218) examined the comparative effectiveness of three doses of aripiprazole (5 mg, 10 mg, and 15 mg) in children ages 6 to 17 years with irritability associated with autism.[46] There was no significant difference between the aripiprazole doses for treatment response, suicide-related behaviors, or adherence rate.

Risperidone Versus Other SGAs

A 17-month retrospective cohort study (N = 26) compared the effect of risperidone versus other SGAs in children and young adults ages 4 to 21 years. Eight patients received combination treatment with a FGA (five in the risperidone group, three in the other SGA group). Response rate (defined as CGI–I≤2) was not significantly different between patients treated with risperidone (with or without a FGA) and patients treated with SGAs other than risperidone (with or without a FGA).

SGAs Versus Placebo

Six RCTs compared SGAs with placebo.[43,46,47,49,52,53]

Aripiprazole Versus Placebo

An 8-week RCT (N = 218) compared three doses of aripiprazole with placebo.[46] Treatment response rate (defined as ≥25 percent reduction in ABC–I and CGI–I≤2) was significantly greater with 5 mg/day aripiprazole than placebo (p = 0.04), but there was no difference between the 10 mg/day and 15 mg/day groups versus placebo. Suicide-related behaviors were reported by three patients in the placebo group and no patients in the aripiprazole groups; this result

significantly favored the aripiprazole groups (p = 0.04). Medication adherence did not differ between the groups.

Olanzapine Versus Placebo

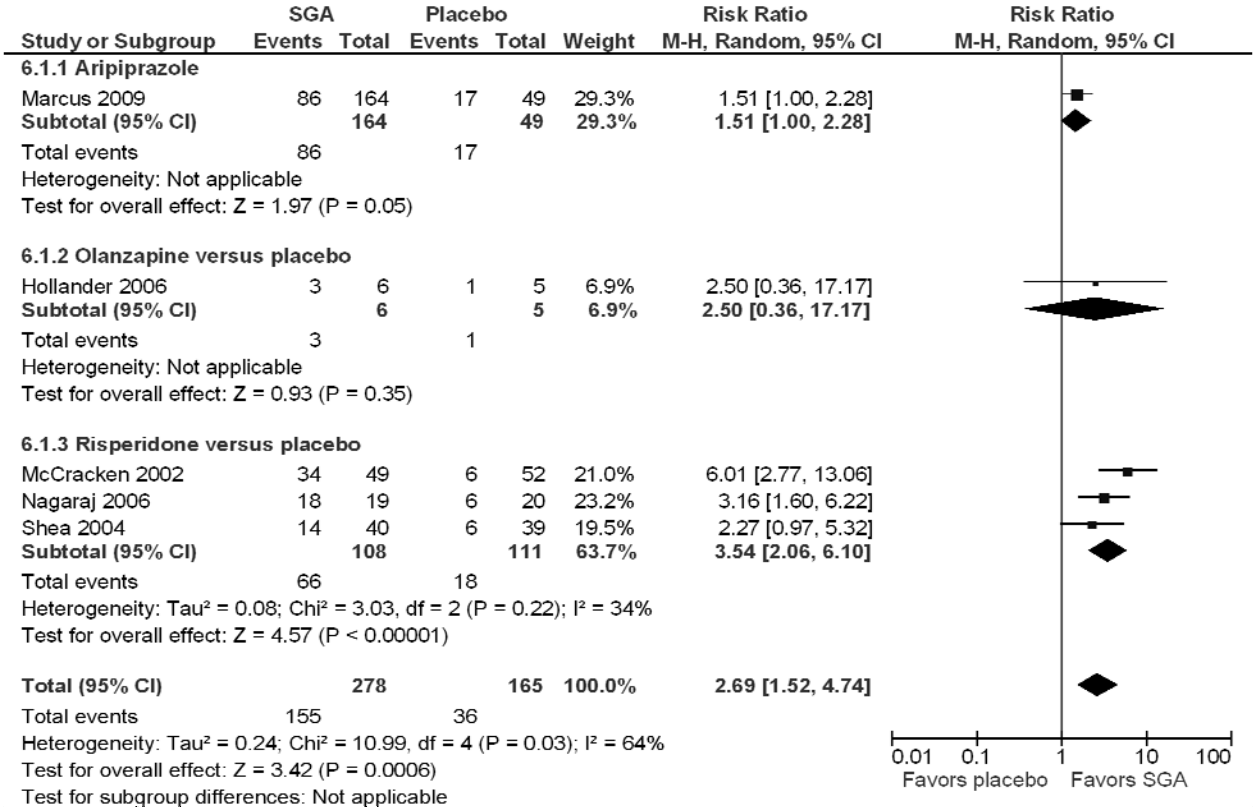
An 8-week RCT (N = 11) assessed the effectiveness of olanzapine (mean dose, 10±2 mg/day) versus placebo in children ages 6 to 14 years.[43] Response rate, based on CGI–I and CPRS ratings, was not significantly different between groups.

Risperidone Versus Placebo

Four placebo-controlled RCTs examined the effectiveness of risperidone.[47,49,52,53] Study duration ranged from 8 weeks to 6 months. Overall, 245 children were enrolled in the studies. All of the studies included school-aged children, one included preschoolers,[49] and two included adolescents.[47,53] Three studies enrolled patients with mental retardation,[47,52,53] and two examined children with behavior problems (i.e., aggression, irritability, tantrums, or self-injurious behaviors).[47,53] Mean daily risperidone doses ranged from 1 to 1.9 mg/day. Outcomes included response, relapse, time to relapse, various cognitive tasks (cancellation task, classroom analogue task, Purdue pegboard task, dot test, verbal learning task, and focused attention reaction time), medication adherence, Food Frequency Questionnaire, and sleep duration.

Three RCTs reporting response rate were pooled (Figure 7, analysis 6.1.3).[47,49,52] Patients on risperidone showed significantly higher response rates than placebo (RR = 3.54; 95% CI, 2.06 to 6.10). Heterogeneity was moderate (p = 0.22, I^2 = 34%).

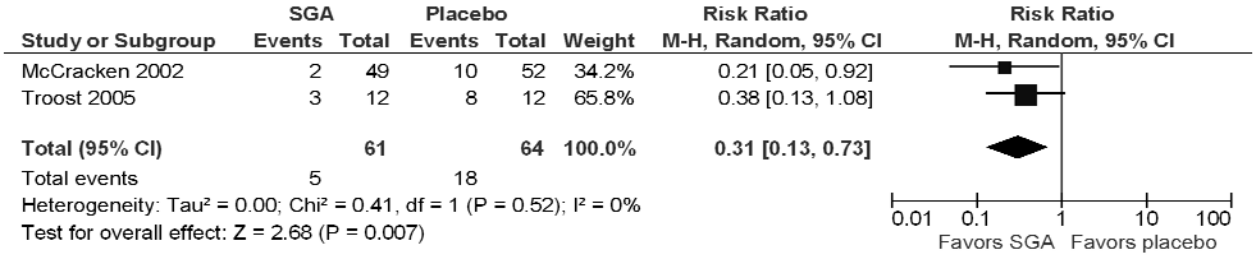
Figure 7. SGAs versus placebo on response rate in pervasive developmental disorders



CI = confidence interval; df = degrees of freedom; M–H = Mantel–Haenszel; SGA = second-generation antipsychotic

Two RCTs comparing risperidone with placebo provided data for a meta-analysis on relapse rate (Figure 8).[47,53] The pooled estimate showed significantly lower rate of relapse in the risperidone group (RR = 0.31; 95% CI, 0.13 to 0.73). There was no evidence of heterogeneity (p = 0.52, I^2 = 0%).

Figure 8. Risperidone versus placebo on relapse rate in pervasive developmental disorders



CI = confidence interval; df = degrees of freedom; M–H = Mantel–Haenszel; SGA = second-generation antipsychotic

One study found no difference between groups for medication adherence.[47] Two studies found a longer mean time to relapse for patients treated with risperidone than those receiving placebo; the result was significant in one study (p = 0.01)[53] and could not be calculated in the second study (34 days for placebo versus 57 days for risperidone; standard deviations not reported).[47] Cognitive effects were evaluated in a subset of patients in one study.[47] Compared with placebo, no significant declines were noted in the risperidone group for attention, hand-eye coordination, or short-term verbal memory. There was an increase in vitamin K intake after 2 months of risperidone treatment compared with placebo (p<0.05).[47] No significant differences in sleep time increases between the risperidone and placebo groups were found.[47]

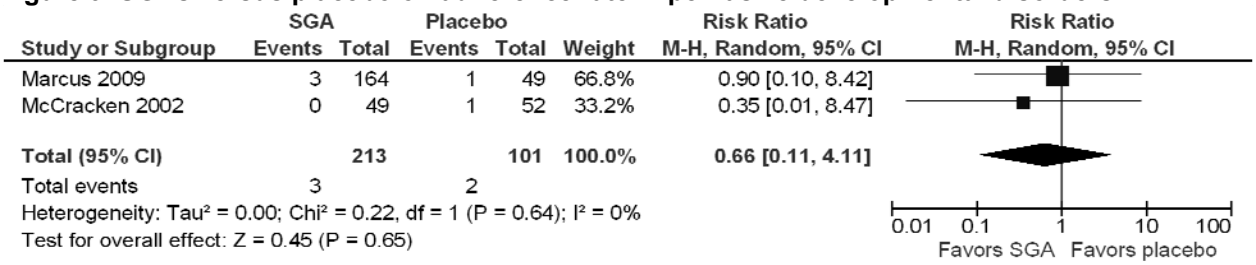
Meta-analyses Comparing Various SGAs With Placebo

Meta-analyses were conducted to compare various SGAs with placebo for response rate and adherence rate.

Five RCTs contributed data on response rate (Figure 7 above). SGAs included aripiprazole,[46] olanzapine,[43] and risperidone.[47,49,52] The combined estimate showed a significantly higher response rate in patients receiving SGAs than placebo (RR = 2.69; 95% CI, 1.52 to 4.74). There was substantial heterogeneity (p = 0.03, I^2 = 64%), which may be attributable to differences in drug comparator and dosing, as well as differences in patient ages.

Two RCTs comparing aripiprazole[46] and risperidone[47] with placebo were combined in a meta-analysis for adherence rate (Figure 9). No significant difference in adherence to study medication was found (RR = 0.66; 95% CI, 0.11 to 4.11) with no evidence of heterogeneity (p = 0.64, I^2 = 0%).

Figure 9. SGAs versus placebo on adherence rate in pervasive developmental disorders



CI = confidence interval; df = degrees of freedom; M–H = Mantel–Haenszel; SGA = second-generation antipsychotic

ADHD and Disruptive Behavior Disorders: Overview

Eight RCTs examined the effectiveness of antipsychotics for treating symptoms and other short- and long-term outcomes in patients with ADHD with aggression[55] and disruptive behavior disorders.[56-62] Table 13 provides selected information on the characteristics of the individual studies. Studies are organized alphabetically by drug, then by author. There were no head-to-head drug comparisons. All of the studies compared a SGA, usually risperidone, with placebo. A detailed evidence table is available in Appendix D.

Patients had an average age of 10.2 years and were predominantly male (84 percent). Among the studies that reported race, the majority of patients were white. Diagnosis of disruptive behavior disorders and ADHD were confirmed using the DSM–IV in all but one RCT, which used the Kiddie Schedule for Affective Disorders and Schizophrenia (K–SADS). Across the trials, patients most frequently had a primary diagnosis of oppositional defiant disorder (51 percent) or conduct disorder (41 percent). Patients were required to have aggression to be included in four of the trials.[55,58-60] Common comorbidities included ADHD in patients with a primary diagnosis of a disruptive behavior disorder, mental retardation, and anxiety disorders.

The duration of followup ranged from 4 weeks to 6 months. On average, the studies were 8.5±7.3 weeks. Two studies had a 48-week open-label extension of risperidone.[57,62] All of the trials had a high risk of bias. Five trials had incomplete outcome data, and all had potential bias due to involvement of industry.

Table 13. Characteristics of studies examining ADHD and disruptive behavior disorders

Author, Year, Study Design, Duration, KQ	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, mMean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
SGAs vs. Placebo			
Connor et al., 2008[59] RCT, 6 wk *KQ1, KQ3*	G1: Quetiapine (9), 294±78 mg/day G2: Placebo (10)	G1: 13.1±1.2 yr / Male: 78% / White: 78% G2: 15±1.4 yr / Male: 70% / White: 70% Comorbidities: ADHD (15), depression (4), dysthymia (5), GAD (3), OCD (3), ODD (18), panic disorder (1), PTSD (3), SA (6), separation anxiety (3), social phobia (3)	CD with moderate to severe aggression (all) High ROB
Aman et al., 2009[56] RCT (crossover), 4 wk *KQ1, KQ3*	G1: Risperidone (16),* 1.7±1.3 mg/day G2: Placebo (16)*	All groups: 8.6±2.6 yr / Male : 88% / White: 81% Comorbidities: MR [borderline (10), mild (4), moderate (1)]	ADHD with CD (2), ADHD with ODD (6), ADHD only (1), ASD (3), CD (1), ODD (3) High ROB
Aman et al., 2002[57] RCT, 6 wk (48 wk extension) *KQ1, KQ3*	G1: Risperidone (55), 1.2±0.6 mg/day G2: Placebo (63)	G1: 8.7±2.1 yr / Male: 85% / White: 51% G2: 8.1±2.3 yr / Male: 79% / White: 62% Comorbidities: ADHD (70), MR [all; borderline (60), mild (38), moderate (20)]	CD (47), DBD (8), ODD (63) High ROB
Armenteros et al., 2007[55] RCT, 4 wk *KQ1, KQ3*	G1: Risperidone (12), 1.1±0.6 mg/day G2: Placebo (13)	G1: 7.3±3.7 yr / Male: 83% / White: 50% G2: 8.8±3.1yr / Male: 92% / White: 46% Comorbidities: GAD (1), ODD (13), separation anxiety disorder (3)	ADHD with aggression (all) High ROB

Table 13. Characteristics of studies examining ADHD and disruptive behavior disorders (continued)

Author, Year Study Design, Duration, KQ	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
Buitelaar et al., 2001[58] RCT, 6 wk *KQ1, KQ3*	G1: Risperidone (19), 2.9 mg/day G2: Placebo (19)	G1: 14.0±1.5 yr / Male: 90% / White: NR G2: 13.7±2 yr / Male: 84% / White: NR Comorbidities: ADHD (26), anxiety disorder (3), MR (14)	CD (30), DBD NOS (2), ODD (6), aggression (all) High ROB
Findling et al., 2000[60] RCT, 10 wk *KQ1, KQ3*	G1: Risperidone (10), 0.028±0.004 mg/kg/day G2: Placebo (10)	G1: 10.7±3.4 yr / Male: NR / White: NR G2: 8.2±1.9 yr / Male: NR / White: NR Comorbidities: NR	CD with aggression (all) High ROB
Reyes et al., 2006[61] RCT, 6 mo *KQ1, KQ3*	G1: Risperidone (172), 0.81±0.34 mg/day (<50 kg), 1.22±0.36 mg/day (≥50 kg) G2: Placebo (163)	G1: 10.9±2.9 yr / Male: 82% / White: NR G2: 10.8±2.9 yr / Male: 91% / White: NR Comorbidities: ADHD (227)	CD (123), DBD NOS (8), ODD (204) High ROB
SGAs vs. Placebo			
Snyder et al, 2002[62] RCT, 6 wk (48 wk extension) *KQ1, KQ3*	G1: Risperidone (53), 1±0.73 mg/day G2: Placebo (57)	G1: 8.6±0.3 yr / Male: 77% / White: 79% G2: 8.8±0.3 yr / Male: 74% / White: 74% Comorbidities: ADHD (84), MR (all; borderline (53), mild (42), moderate (15))	CD (41), ODD (69) High ROB

ADHD = attention deficit hyperactivity disorder; ASD = autism spectrum disorder; CD = conduct disorder; DBD = disruptive behavior disorder; G = group; GAD = general anxiety disorder; KQ = key question; mg = milligrams; mo = month; MR = mental retardation; N = number; NOS = not otherwise specified; NR = not reported; OCD = obsessive-compulsive disorder; ODD = oppositional defiant disorder; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; ROB = risk of bias; SA = substance abuse; SD = standard deviation; wk = week *All patients experienced each of the treatment arms in this crossover study

ADHD and Disruptive Behavior Disorders: Disorder-Specific and Nonspecific Symptoms (Key Question 1)

Eight placebo-controlled RCTs evaluated the efficacy of SGAs in treating symptoms of patients with ADHD and disruptive behavior disorders. A summary of the results by outcome is presented below. Table 14 provides the strength of evidence grades for all key outcomes that were reported by at least one study.

- Behavior symptoms: Patients treated with risperidone had a significantly greater reduction in behavior problems than patients on placebo. Three meta-analyses supported this finding using various measures: ABC in four RCTs[56-58,62] (MD = -20.97; 95% CI, -31.11 to -10.83), Behavior Problem Inventory in two RCTs[57,62] (MD = -3.77; -6.16 to -1.39), and NCBRF in four RCTs[56,57,61,62] (MD = -6.93; -10.38 to -3.49). One RCT[60] found a significant reduction in delinquent behavior for patients treated with risperidone versus placebo.
- Conners Parent Rating Scale: SGAs (risperidone[60] and quetiapine[59]) were significantly favored over placebo for parent rating scores in two RCTs examining patients with conduct disorder (studies were not pooled due to heterogeneity). The effect was greater in patients treated with risperidone.[60]

- Clinical global impressions: Patients treated with SGAs versus placebo had significantly better scores on the CGI–S (MD = -1.33; 95% CI, -2.15 to -0.50) in a meta-analysis of five studies[55,58-61]) and CGI–I (MD = -0.95; 95% CI, -1.66 to -0.25) in a meta-analysis of three studies[55,60,61]).
- VAS: Three RCTs[57,61,62] found significantly greater improvement in clinical symptoms on a VAS for risperidone compared with placebo (studies were not pooled due to heterogeneity).
- Aggression: A meta-analysis of two RCTs (risperidone[58] and quetiapine[59]) found no difference between either of these two SGAs and placebo for aggression (MD= -15.81, 95% CI, -51.56 to 19.94).

Table 14. Strength of evidence for ADHD and disruptive behavior disorders (Key Question 1)

Comparison	Outcome (N Studies; N Patients)	Strength of Evidence Domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
SGA vs. placebo	Aggression (5; 302)	Moderate	Consistent	Direct	Imprecise	Low
	Anxiety (4; 580)	Moderate	Inconsistent	Direct	Not pooled	Low
	Behavior symptoms (7; 669)	Moderate	Consistent	Direct	Precise	Moderate
	Clinical global impressions (7; 662)	Moderate	Consistent	Direct	Precise	Moderate

N = number; ROB = risk of bias; SGA = second-generation antipsychotic

A detailed analysis for the comparative effectiveness of SGAs versus placebo is presented below.

SGAs Versus Placebo

Quetiapine Versus Placebo

A 6-week, placebo-controlled RCT (N = 19) assessed the effectiveness of quetiapine (mean dose, 294±78 mg/day) for treating adolescents ages 12 to 17 years with conduct disorder and aggression.[59] Quetiapine significantly improved on the CGI compared with placebo (CGI–I scores, $p<0.001$; CGI–S, $p<0.01$). No significant differences were observed in the Overt Aggression Scale (OAS) and Conners Parent Rating Scale.

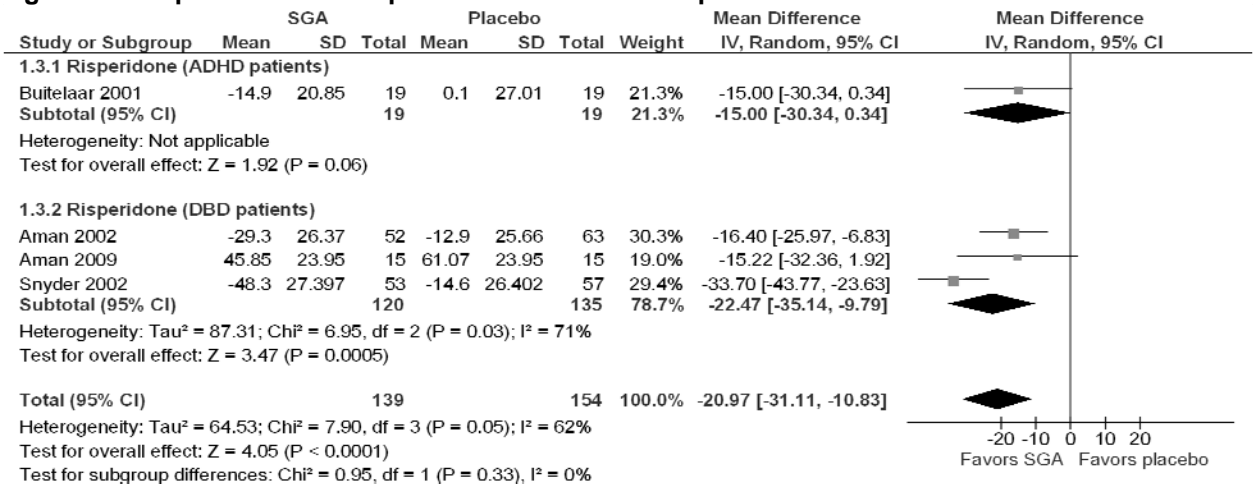
Risperidone Versus Placebo

Seven RCTs compared risperidone and placebo in patients with ADHD and aggression[55] and disruptive behavior disorders.[56-58,60-62] The duration of studies ranged from 4 weeks to 6 months. Overall, 662 children ranging from age 4 to 17 years participated in the trials. The average age of participants was between 8 and 10 years, with the exception of one study with an average age around 14 years.[58] Mean daily risperidone doses ranged from 0.8 to 2.9 mg/day. Symptoms were assessed using the following scales: ABC, Behavior Problem Inventory, Child Behavior Checklist, CGAS, CGI–I, CGI–S, Conners Parent Rating Scale, NCBRF, OAS, Rating of Aggression Against People and/or Property scale, and VAS.

Four RCTs[56-58,62] comparing risperidone with placebo for ABC scores were pooled (Figure 10). The study by Buitelaar[58] that included only patients with ADHD and aggression was presented separately from the remaining studies that examined participants with disruptive behavior disorders. In all studies, risperidone was favored over placebo. The combined analysis

showed a significantly greater reduction in aberrant behavior for patients treated with risperidone (MD = -20.97; 95% CI, -31.11 to -10.83). Heterogeneity was substantial (p = 0.05, I^2 = 62%). Studies were similar in terms of design, followup duration, and comorbidities. Patients in the study by Buitelaar[58] were older than those enrolled in the other studies.

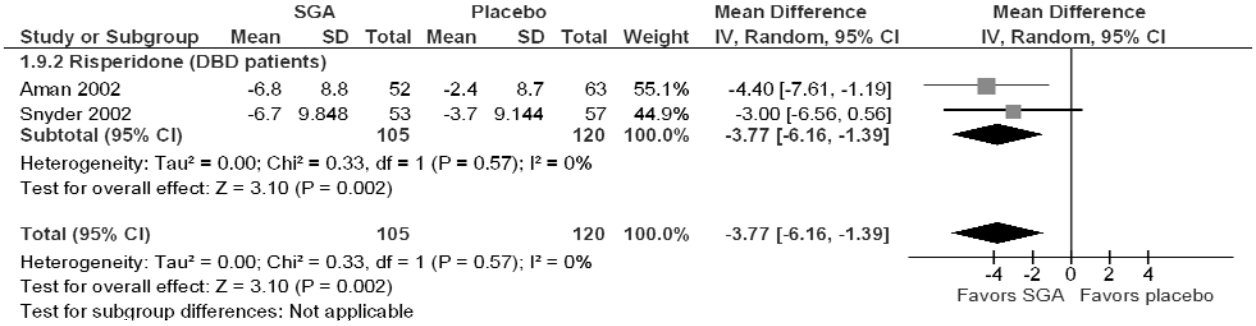
Figure 10. Risperidone versus placebo on ABC in disruptive behavior disorders



ABC = Aberrant Behavior Checklist; ADHD = attention deficit hyperactivity disorder; CI = confidence interval; DBD = disruptive behavior disorder; df = degrees of freedom; IV = inverse variance; SD = standard deviation; SGA = second-generation antipsychotic

Two RCTs[57,62] were pooled in a meta-analysis examining risperidone versus placebo on the Behavior Problem Inventory (Figure 11). The combined estimate showed a significant difference favoring risperidone for behavior problems (MD = -3.77; -6.16 to -1.39) with no evidence of heterogeneity (p = 0.57, I^2 = 0%).

Figure 11. Risperidone versus placebo on BPI in disruptive behavior disorders

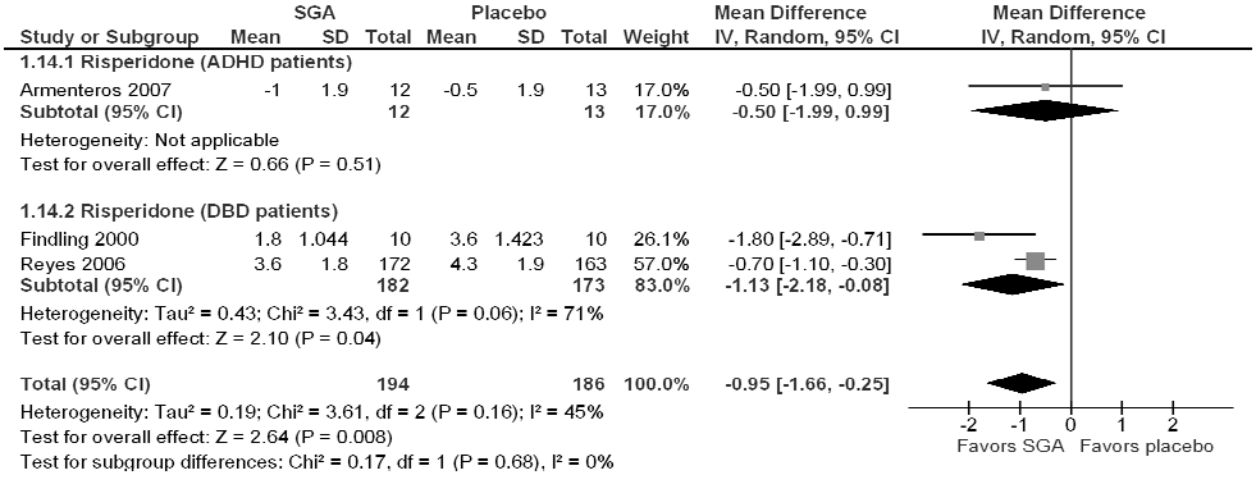


BPI = Behavior Problems Inventory; CI = confidence interval; DBD = disruptive behavior disorder; df = degrees of freedom; IV = inverse variance; SD = standard deviation; SGA = second-generation antipsychotic

Three RCTs[55,60,61] provided data for a meta-analysis comparing CGI–I scores in patients receiving treatment with risperidone versus placebo (Figure 12). The pooled estimate showed a significant difference between groups favoring risperidone (MD = -0.95; 95% CI, -1.66 to -0.25); however, considerable heterogeneity was evident (p = 0.16, I^2 = 45%). The studies differed in patients' diagnoses (one study[55] enrolled patients with ADHD and aggression, the others examined disruptive behavior disorders) and followup duration, which ranged from 4 weeks to 6 months.

A significantly greater proportion of patients treated with risperidone had a rating of "very much improved" or "much improved" (CGI–I≤2) than placebo in three trials.[57,59,62]

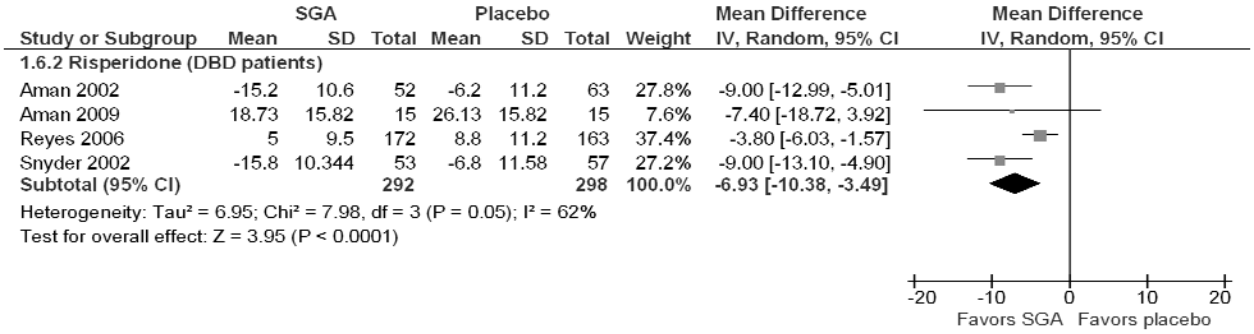
Figure 12. Risperidone versus placebo on CGI–I in disruptive behavior disorders



ADHD = attention deficit hyperactivity disorder; CGI–I = Clinical Global Impressions–Improvement; CI = confidence interval; DBD = disruptive behavior disorder; df = degrees of freedom; IV = inverse variance; SD = standard deviation; SGA = second-generation antipsychotic

Four RCTs[56,57,61,62] provided data comparing risperidone with placebo for behavior scores on the NCBRF (Figure 13). The pooled estimate showed a significantly greater reduction in problem behaviors for the risperidone group (MD = -6.93; 95% CI, -10.38 to -3.49). There was substantial heterogeneity (p = 0.05, I^2 = 62%). The study with the largest sample size[61] showed the most precision, and the confidence intervals of the smaller studies overlapped with the effect estimate of this study.

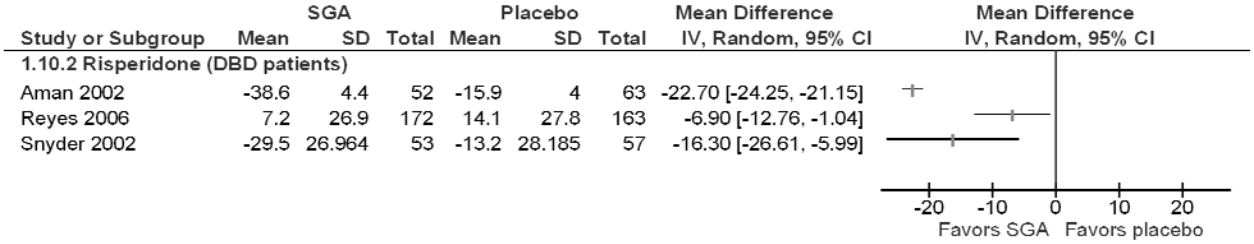
Figure 13. Risperidone versus placebo on NCBRF in disruptive behavior disorders



CI = confidence interval; DBD = disruptive behavior disorders; df = degrees of freedom; IV = inverse variance; NCBRF = Nisonger Child Behavior Rating Form; SD = standard deviation; SGA = second-generation antipsychotic

Three RCTs[57,61,62] compared risperidone with placebo on a VAS for symptom improvement (Figure 14). There was considerable heterogeneity; therefore, we did not pool the studies. All trials showed a significantly greater improvement in symptoms with risperidone than placebo.

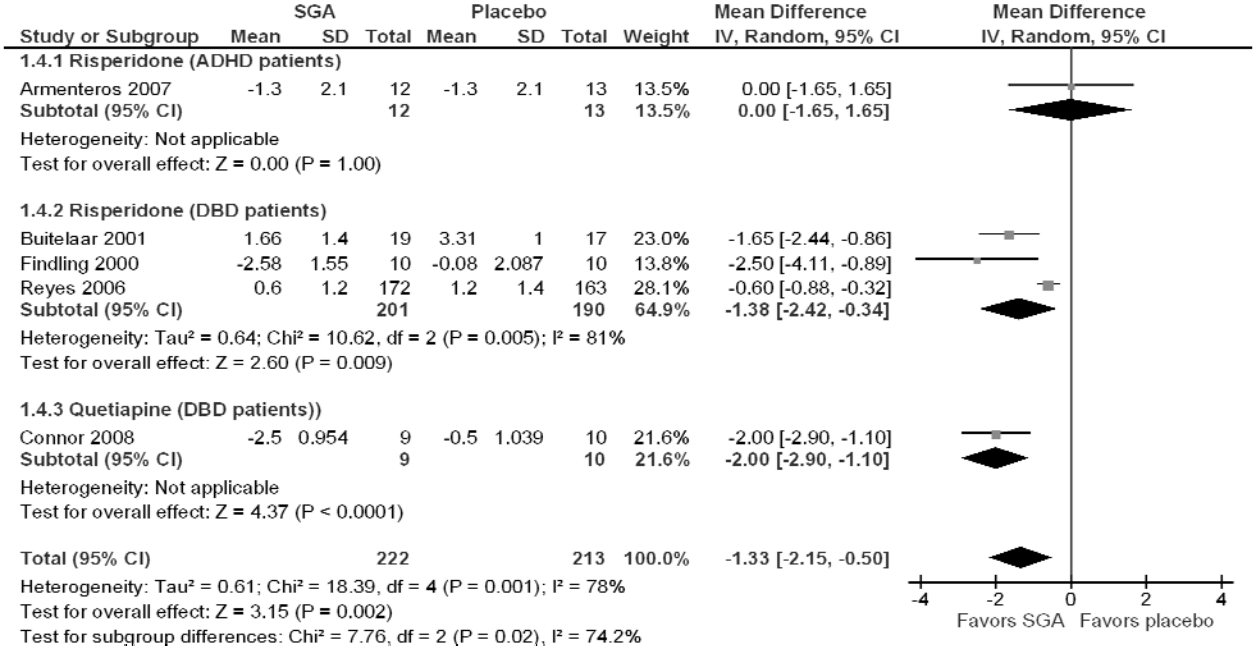
Figure 14. Risperidone versus placebo on VAS in disruptive behavior disorders



CI = confidence interval; DBD = disruptive behavior disorders; IV = inverse variance; SD = standard deviation; SGA = second-generation antipsychotic; VAS = visual analogue scale

Four RCTs[55,58,60,61] provided data for a comparison of CGI–S scores (Figure 15; analysis 1.4.1 and 1.4.2). No difference was found between the groups in one study examining patients with ADHD and aggression.[55] Risperidone was favored over placebo in three studies examining patients with disruptive behavior disorders. There was considerable heterogeneity, which may be due to the lower dosing of risperidone used and longer followup period in Reyes et al.[61]

Figure 15. SGAs versus placebo on CGI–S in disruptive behavior disorders



ADHD = attention deficit hyperactivity disorder; CGI–S = Clinical Global Impressions–Severity; CI = confidence interval; DBD = disruptive behavior disorder; df = degrees of freedom; IV = inverse variance; SD = standard deviation; SGA = second-generation antipsychotic

Single studies found a significant difference favoring risperidone over placebo for the Child Behavior Checklist (CBCL) delinquent behavior subscale ($p = 0.04$),[60] the Rating of Aggression Against People and/or Property scale ($p = 0.03$),[60] and the CGAS ($p<0.001$).[61]

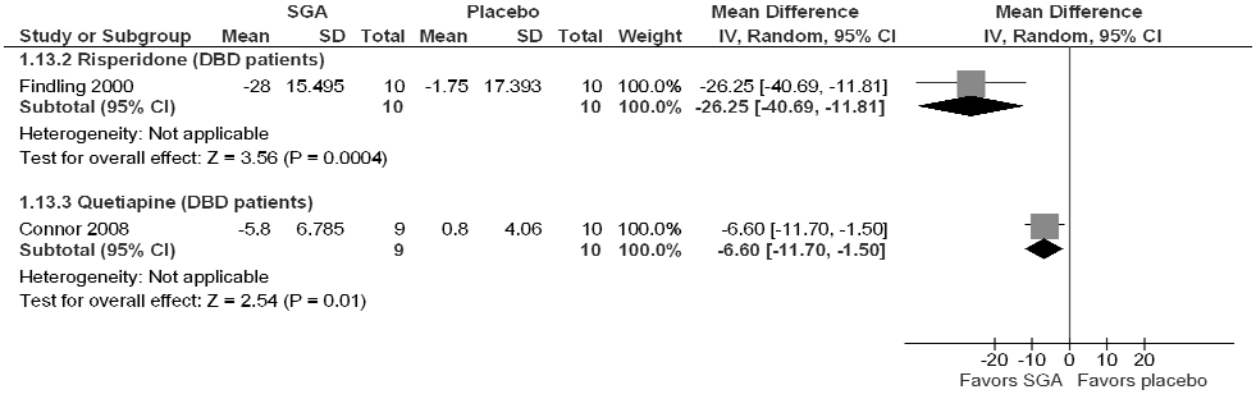
Meta-analyses Comparing Various SGAs With Placebo

Meta-analyses were conducted to compare various SGAs with placebo for the CGI–S, Conners Parent Rating Scale, and OAS.

Five RCTs[55,58-61] provided data for a comparison of CGI–S scores (Figure 15 above). All but one study[55] favored SGAs. The combined estimate showed a significant difference in symptom severity between the groups favoring SGAs (MD = -1.33; 95% CI, -2.15 to -0.50); however, there was substantial heterogeneity between the studies (p = 0.001, I^2 = 78%). Reyes et al.[61] indicated a smaller difference between risperidone and placebo than the other studies. This difference may be due to the lower dose of risperidone used or the longer followup time (6 months vs. 10 weeks); it is possible that the medication effects were reduced over time. In addition, differences in the conditions being treated may have contributed to the difference in effect: Armenteros et al.[55] examined patients with ADHD and aggression, whereas the remaining four studies examined patients with disruptive behavior disorders with or without ADHD comorbidity.

Two RCTs[59,60] examining risperidone and quetiapine evaluated patients on Conners Parent Rating Scale (Figure 16). The studies were not pooled due to considerable heterogeneity (p = 0.01, I^2 = 84%). Patients in the study by Findling et al.[60] were predominantly treatment naïve and were younger than those in the study by Connor et al.[59] Both studies significantly favored the SGA; however, the effect was greater in patients treated with risperidone.[60]

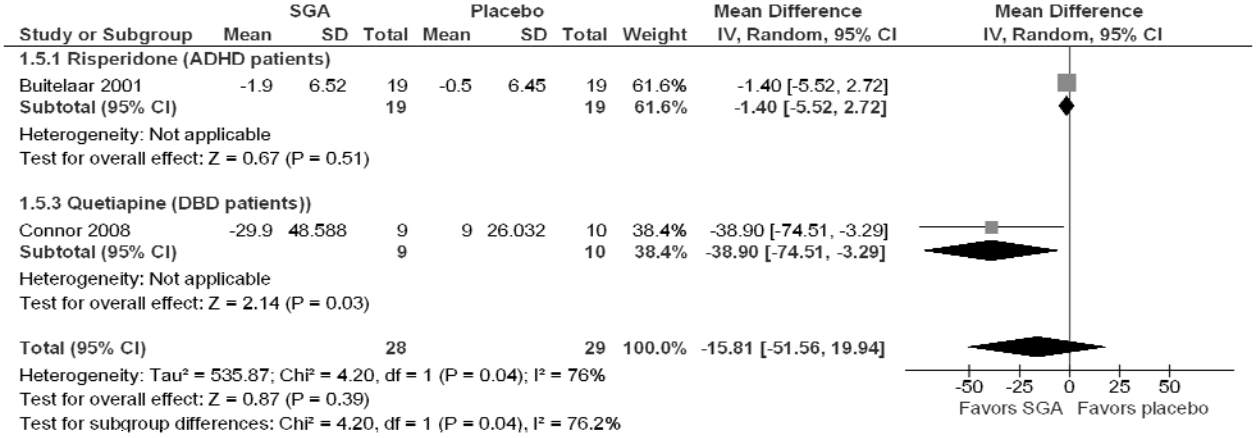
Figure 16. SGAs versus placebo on Conners Parent Rating Scale in disruptive behavior disorders



CI = confidence interval; DBD = disruptive behavior disorder; IV = inverse variance; SD = standard deviation; SGA = second-generation antipsychotic

Two RCTs compared a SGA, risperidone[58] or quetiapine,[59] with placebo for aggression on the OAS (Figure 17). The pooled estimate showed no difference (MD = -15.81, 95% CI, -51.56 to 19.94), and there was substantial heterogeneity (p = 0.04, I^2 = 76%). The studies were similar in length of followup, patient age, and comorbidities; the heterogeneity may be explained by differences between the SGAs used in the studies.

Figure 17. SGAs versus placebo on OAS in disruptive behavior disorders



ADHD = attention deficit hyperactivity disorder; CI = confidence interval; DBD = disruptive behavior disorders; df = degrees of freedom; IV = inverse variance; OAS = Overt Aggression Scale; SD = standard deviation; SGA = second-generation antipsychotic

ADHD and Disruptive Behavior Disorders: Short- and Long-Term Outcomes (Key Question 3)

Eight studies provided data on a variety of short- and long-term outcomes for patients with ADHD and disruptive behavior disorders. A summary of the results is presented by outcome below. Table 15 provides the strength of evidence grades for all key outcomes that were reported by at least one study.

- Response and relapse: Two RCTs comparing risperidone and placebo reported treatment response rate. One study[57] found a significant difference in response favoring risperidone ($p<0.001$), whereas another study[55] found no significant difference between the groups. One RCT[61] found risperidone to be significantly superior to placebo for relapse, symptom recurrence, and time-to-symptom recurrence ($p\leq0.002$).
- Growth and maturation: One RCT[61] compared changes in Tanner stages from baseline for patients treated with risperidone or placebo. No group differences in the distribution of stages were observed.
- Cognitive and emotional development: Two RCTs compared risperidone and placebo for performance on cognitive tasks. Risperidone resulted in faster response time, fewer seat movements on a short-term memory task, and fewer contacts (less tremor) on a graduated holes task ($p\leq0.05$).[56] Reyes et al.[61] found no difference between groups on verbal learning and continuous performance tasks.
- Medication adherence: A meta-analysis of four studies[55,57,60,62] comparing risperidone with placebo showed no significant difference between the study groups (RR = 1.43; 95% CI, 0.35 to 5.83) for adherence rate.
- School performance: School refusal was assessed in one RCT[59] comparing quetiapine and placebo; no significant difference was found between groups.
- Patient-, parent-, or care provider-reported outcomes: Social withdrawal was assessed in an RCT[59] comparing quetiapine and placebo; no difference was found between treatment arms.

- Health-related quality of life: One RCT[59] assessed patients on the Quality of Life Enjoyment and Satisfaction Questionnaire and found a significant difference favoring treatment with quetiapine over placebo (p = 0.005).
- Other outcomes: No studies provided data for the following outcome categories: suicide-related behaviors, work-related functional capacity, patient insight into illness, legal system interaction, or health care system utilization.

Table 15. Strength of evidence for ADHD and disruptive behavior disorders (Key Question 3)

Comparison	Outcome (N Studies; N Patients)	Strength of Evidence Domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
SGA vs. placebo	HRQL (1; 19)	Moderate	Unknown	Direct	Precise	Insufficient
	Medication adherence (5; 311)	Moderate	Inconsistent	Direct	Imprecise	Low

ADHD = attention deficit hyperactivity disorder; HRQL = health-related quality of life; N = number; ROB = risk of bias; SGA = second-generation antipsychotic

A detailed analysis comparing SGAs and placebo is provided below.

SGA Versus Placebo

Quetiapine Versus Placebo

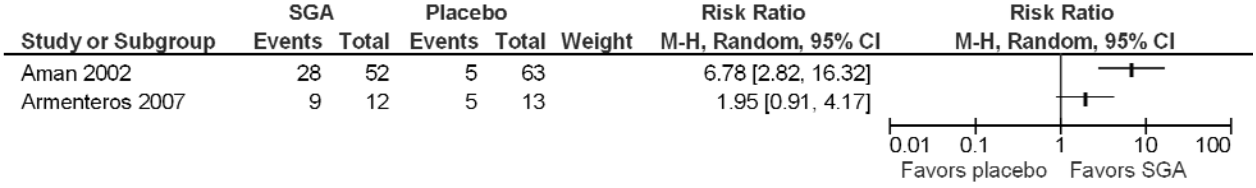
A 6-week RCT (N = 19) compared the effectiveness of quetiapine (mean dose, 294±78 mg/day) versus placebo in adolescents ages 12 to 17 with conduct disorder and aggression. Scores on the Quality of Life Enjoyment and Satisfaction Questionnaire improved significantly in the quetiapine group compared with the placebo group (p = 0.005); however, no significant differences between groups were found for school refusal or social withdrawal.

Risperidone Versus Placebo

Seven placebo-controlled RCTs evaluated the effects of risperidone on other short- and long-term outcomes in patients with ADHD with aggression[55] and disruptive behavior disorders.[56-58,60-62] The characteristics of these studies are described in Key Question 1 above. The studies reported the following outcomes: response, relapse, symptom recurrence, adherence, maturation (i.e., Tanner staging), and cognitive tasks (i.e., match to sample, short-tIn Ierm memory recognition, graduated holes, and continuous performance tasks).

Two studies[55,57] comparing risperidone versus placebo-reported treatment response rates (Figure 18). The results of two studies were not pooled due to considerable heterogeneity (p = 0.02, I^2 = 81%). All patients in one study[57] had mental retardation, and mental retardation was an exclusion criteria in the second study.[55] This may account for the difference in response rates. Aman et al.[57] found a significant difference in favor of risperidone.

Figure 18. Risperidone versus placebo on response rate in disruptive behavior disorders

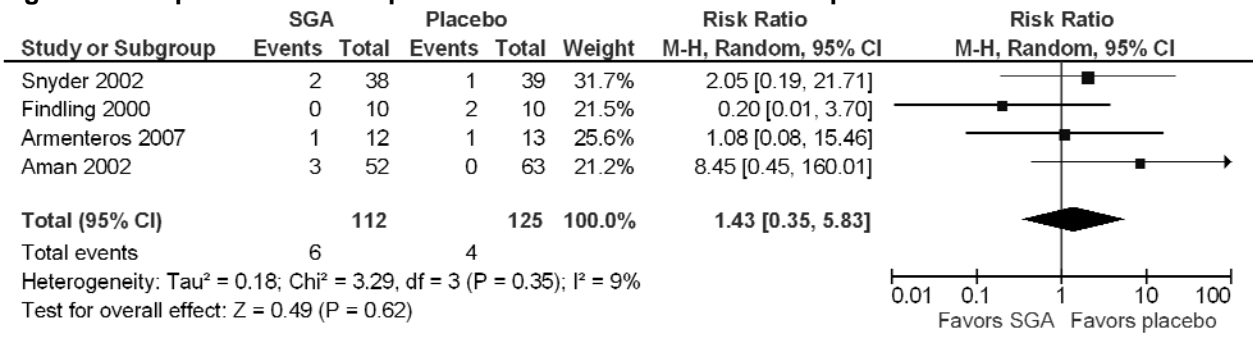


CI = confidence interval; M–H = Mantel–Haenszel; SGA = second-generation antipsychotic

Four studies[55,57,60,62] contributed data for a meta-analysis comparing adherence rate for patients receiving risperidone and placebo (Figure 19). There was no significant difference between the study groups (RR = 1.43; 95% CI, 0.35 to 5.83) and little evidence of heterogeneity ($p = 0.35$, $I^2 = 9\%$).

One study[58] reported treatment adherence using plasma samples. The mean plasma concentration of risperidone in the treatment group was 18±24 ng/mL; no risperidone was detected in patients in the placebo group.

Figure 19. Risperidone versus placebo on adherence rate in disruptive behavior disorders



CI = confidence interval; df = degrees of freedom; M–H = Mantel–Haenszel; SGA = second-generation antipsychotic

Two trials reported performance on various cognitive tasks. Seat movements and response time on the short-term recognition memory task and contacts on the graduated holes task favored the risperidone group ($p \leq 0.05$ for both) in one study.[56] The following outcomes were not significantly different between groups: match to sample task,[56] the continuous performance task,[56,61] and the Modified California Verbal Learning Questionnaire.[61]

One RCT[61] found risperidone to be significantly superior to placebo for symptom recurrence, time to symptom recurrence, 6-month recurrence, and relapse ($p \leq 0.002$). Tanner stages showed no significant difference.

Bipolar Disorder: Overview

Eleven RCTs evaluated the effectiveness of SGA with other drugs of the same class or placebo for treating symptoms and other short- and long-term outcomes in children and adolescents with bipolar disorder.[42,63-72] Table 16 provides selected information on the characteristics of the individual studies. Studies that include both head-to-head and placebo comparisons are listed under the head-to-head category. Head-to-head drug comparison were made in two studies.[63,64] Different doses of the same SGA were compared in four trials.[42,67,68,73] The majority of the studies were placebo controlled. A detailed evidence table is available in Appendix D.

The average age of patients was 12.6 years. Both sexes were equally represented across the studies (55 percent male). The majority of patients were of white race. Diagnosis of bipolar disorder was established using the DSM–IV or DSM–IV–TR. Nearly all of the patients enrolled in the studies were classified as having bipolar I disorder; one study included eight patients with bipolar II disorder,[72] and another study included four patients with bipolar disorder not-otherwise-specified.[63] As noted earlier, the diagnosis of bipolar disorder in children is controversial, particularly in young children (e.g., preschoolers in Biederman et al.[63]). The

majority of children had secondary diagnoses, including ADHD, disruptive behavior disorders, anxiety, and psychosis.

The studies had short followup periods, ranging from 3 to 8 weeks. Two trials had extension phases of 24 weeks[42] and 6 months.[71] All of the trials had a high risk of bias. The most common sources of potential bias were involvement of industry and incomplete outcome data.

Table 16. Characteristics of studies examining bipolar disorder

Author, Year, Study Design, Duration, KQ	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
SGAs vs. SGAs			
Findling et al, 2009[67] RCT, 4 wk *KQ1, KQ3*	G1: Aripiprazole (low) (98), range: 2–10 mg/day G2: Aripiprazole (high) (99), range: 2–30 mg/day G3: Placebo (99)	G1: 13.7±2.2 yr / Male: 53% / White: 66% G2: 13.3±2.3 yr / Male: 52% / White: 69% G3: 13.3±2.1 yr / Male: 57% / White: 61% Comorbidities: ADHD (153), DBD (93), psychosis (14)	Bipolar I (all), mania (119), mixed (125), unknown (52) High ROB
Biederman, 2004[64] RCT, 8 wk *KQ1, KQ3*	G1: Olanzapine (19), 8.5±3.2 mg/day G2: Quetiapine (19), 213.1±150.5 mg/day G3: Risperidone (42), 1.36±0.7 mg/day G4: Ziprasidone (21), 56.2±34.3	All groups: 10.2±2.7 yr / Male: 67% / White: NR Comorbidities: NR	mania (all) High ROB
Biederman et al, 2005[63] RCT, 8 wk *KQ1, KQ3*	G1: Olanzapine (15), 6.3±2.3 mg/day G2: Risperidone (16), 1.4±0.5 mg/day	G1: 5.0±0.8 yr / Male: 67% / White: 100% G2: 5.3±0.8 yr / Male: 75% / White: 94% Comorbidities: ADHD (19), CD (13), MDD (22)	Bipolar I (27), bipolar NOS (4), mania (all) High ROB
NCT00090311, 2008[73] RCT, 3 wk *KQ1, KQ3*	G1: Quetiapine, low dose (93), 400 mg/day G2: Quetiapine, high dose (95), 600 mg/day G3: Placebo (89)	G1: 13.1±2.2 yr / Male: 51% / White: 79% G2: 13.2±2.2 yr / Male: 58% / White: 77% G3: 13.3±2.1 yr / Male: 61% / White: 75% Comorbidities: ADHD (124)	Manic (272), Mixed (5) High ROB
Haas et al, 2009[68] RCT, 3 wk *KQ1, KQ3*	G1: Risperidone (low) (50), range: 0.5–2.5 mg/day G2: Risperidone (high) (61), range: 3–6 mg/day G3: Placebo (58)	G1: NR / Male: 56% / White: 70% G2: NR / Male: 43% / White: 82% G3: NR / Male: 48% / White: 78% Comorbidities: ADHD (85), DBD (101)	Bipolar I (all), manic episode (60), mixed episode (109) High ROB
DelBello et al, 2008[42] RCT, 3 wk (24 wk extension) *KQ1, KQ3*	G1: Ziprasidone (low) (15), target: 80 mg/day G2: Ziprasidone (high) (31), target: 160 mg/day	G1: 13.2±2.1 yr / Male: 47% / White: NR G2: 13.8±2.4 yr / Male: 77% / White: NR Comorbidities: NR	Bipolar I (all) High ROB

Table 16. Characteristics of studies examining bipolar disorder (continued)

Author, Year, Study Design, Duration, KQ	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
SGA vs. Placebo			
Tramontina et al, 2009[72] RCT, 6 wk *KQ1, KQ3*	G1: Aripiprazole (18), 13.6±5.4 mg/day G2: Placebo (25)	G1: 11.7±2.7 yr / Male: 33% / White: 83% G2: 12.2±2.8 yr / Male: 56% / White: 96% Comorbidities: ADHD (all), anxiety disorders (21), DBD (35), psychosis (16)	Bipolar I (35), bipolar II (8) High ROB
Tohen et al, 2007[71] RCT, 3 wk (6 mo extension) *KQ1, KQ3*	G1: Olanzapine (107), 8.9 mg/day G2: Placebo (54)	G1: 15.1±1.3 yr / Male: 57% / White: 66% G2: 15.4±1.2 yr / Male: 44% / White: 76% Comorbidities: ADHD (58), DBD (49)	Bipolar I (all), mixed (86), psychotic features (29), rapid cycling (30) High ROB
DelBello et al, 2009[65] RCT, 8 wk *KQ1, KQ3*	G1: Quetiapine (17), 403±133 mg/day G2: Placebo (15)	G1: 16.0±2 yr / Male: 29% / White: 82% G2: 15±2 yr / Male: 33% / White: 80% Comorbidities: ADHD (4), anxiety disorder (8), DBD (8), psychosis (3)	Bipolar I with depressive episode (all) High ROB
DelBello et al, 2002[66] RCT, 6 wk *KQ1, KQ3*	G1: Quetiapine (15), 432 mg/day G2: Placebo (15)	G1: 14.1±2 yr / Male: 53% / White: 80% G2: 14.5±2 yr / Male: 53% / White: 87% Comorbidities: ADHD (18), psychosis (14)	Bipolar I (all), mixed episode (23) High ROB
NCT00257166, 2008[70] RCT, 4 wk *KQ1, KQ3*	G1: Ziprasidone (149), target: 60–80 mg/day (<45 kg), 120–160 mg/day (>45 kg) G2: Placebo (88)	G1: 13.6 yr / Male: NR / White: NR G2: 13.7 yr / Male: NR / White: NR Comorbidities: NR	Bipolar I (all) High ROB

ADHD = attention deficit hyperactivity disorder; CD = conduct disorder; DBD = disruptive behavior disorder; G = group; KQ = key question; MDD = major depressive disorder; mg = milligrams; mo = month; N = number; NOS = not otherwise specified; NR = not reported; RCT = randomized controlled trial; ROB = risk of bias; SD = standard deviation; SGA = second-generation antipsychotic; wk = week; yr = year

Bipolar Disorder: Disorder-Specific and Nonspecific Symptoms (Key Question 1)

Eleven RCTs compared the efficacy of SGAs for the treatment of disorder-specific and nonspecific symptoms in children with bipolar disorder. A summary of the results by comparison is presented below. Table 17 provides the strength of evidence grades for all key outcomes that were reported by at least one study.

- Olanzapine versus risperidone (two RCT[63,64]): Patients treated with risperidone had significantly fewer mania symptoms on the Young Mania Rating Scale (YMRS) than patients treated with olanzapine (MD = 6.83; 95% CI, 1.97 to 11.69).
- Olanzapine versus quetiapine versus risperidone versus ziprasidone (one RCT[64]): Risperidone was superior to ziprasidone for change in YMRS scores. All other comparisons of SGAs showed no significant differences.

- SGAs dosing (four RCTs comparing low- versus high-dose aripiprazole,[67] quetiapine,[73] risperidone,[68] and ziprasidone[42]): No significant differences were found between the dosing regimens for any of the antipsychotics.
- SGAs versus placebo (eight RCTs[65-68,70-73]): All but one study examining quetiapine[65] found a significant difference in favor of the SGAs on the YMRS (studies not pooled due to heterogeneity). SGAs were significantly favored over placebo for the CGI (MD = -0.67; 95% CI, -0.84 to -0.51). Four studies found no significant difference between SGAs and placebo for improving depression on the Children's Depression Rating Scale (CDRS) (studies not pooled due to clinical heterogeneity).

Table 17. Strength of evidence for bipolar disorder (Key Question 1)

Comparison	Outcome (N Studies; N Patients)	Strength of Evidence Domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Olanzapine vs. quetiapine	Manic symptoms (1; 38)	Moderate	Unknown	Direct	Imprecise	Insufficient
Olanzapine vs. risperidone	Depression (1; 31)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Manic symptoms (2; 92)	Moderate	Unknown	Direct	Imprecise	Insufficient
Olanzapine vs. ziprasidone	Manic symptoms (1; 40)	Moderate	Unknown	Direct	Imprecise	Insufficient
Quetiapine vs. risperidone	Manic symptoms (1; 61)	Moderate	Unknown	Direct	Imprecise	Insufficient
Quetiapine vs. ziprasidone	Manic symptoms (1; 40)	Moderate	Unknown	Direct	Imprecise	Insufficient
Risperidone vs. ziprasidone	Manic symptoms (1; 63)	Moderate	Unknown	Direct	Precise	Insufficient
Aripiprazole–low- vs. high-dose	Clinical global impressions (1; 296)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Depression (1; 296)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Manic symptoms (1; 296)	Moderate	Unknown	Direct	Imprecise	Insufficient
Quetiapine–low- vs. high-dose	Manic symptoms (1; 188)	Moderate	Unknown	Direct	Imprecise	Insufficient
Risperidone–low- vs. high-dose	Clinical global impressions (1; 169)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Manic symptoms (1; 169)	Moderate	Unknown	Direct	Imprecise	Insufficient
Ziprasidone–low- vs. high-dose	Clinical global impressions (1; 46)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Manic symptoms (1; 46)	Moderate	Unknown	Direct	Imprecise	Insufficient
SGA vs. placebo	Aggression (1; 161)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Clinical global impressions (6; 978)	Moderate	Consistent	Direct	Precise	Moderate
	Depression (4; 532)	Moderate	Inconsistent	Direct	Imprecise	Low
	Manic symptoms (8; 1245)	Moderate	Inconsistent	Direct	Not pooled	Low

N = number; ROB = risk of bias; SGA = second-generation antipsychotic

A detailed analysis for the comparative effectiveness of SGAs and placebo is presented below. The section is organized by comparison (SGAs head-to-head, dosing, and placebo comparisons).

SGAs Versus SGAs

Olanzapine Versus Risperidone

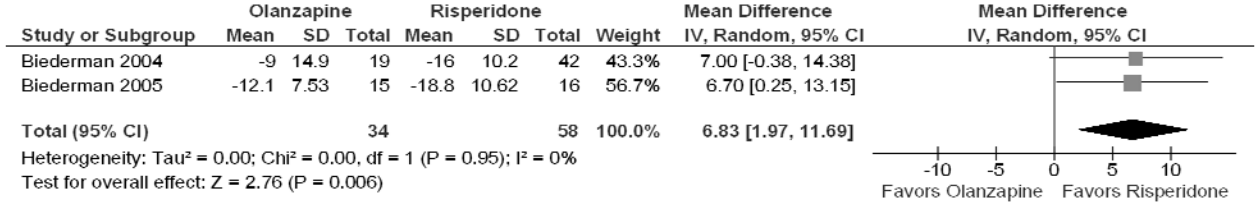
An 8-week RCT (N = 31) compared olanzapine (6.3±2.3 mg/day) with risperidone (1.4±0.5 mg/day) in children ages 4 to 6.[63] No significant differences were found between the groups on the Brief Psychiatric Rating Scale (BPRS), CDRS, or YMRS.

Olanzapine Versus Quetiapine Versus Risperidone Versus Ziprasidone

An 8-week open-label RCT compared four SGAs [olanzapine (N = 19), quetiapine (N = 19), risperidone (N = 42), and ziprasidone (N =42)] for the treatment of mania in children and youth with bipolar disorder. Change in YMRS scores differed significantly between the risperidone and ziprasidone groups (p = 0.03), favoring risperidone. All other SGAs comparisons were not significantly different on the YMRS.

Two RCTs provided data for a meta-analysis of the efficacy of olanzapine versus risperidone on YMRS (Figure 20). The combined estimate favored risperidone (MD = 6.83; 95% CI, 1.97 to 11.69). There was no evidence of heterogeneity (p = 0.95, I^2 = 0%).

Figure 20. Olanzapine versus risperidone on YMRS in bipolar disorder



CI = confidence interval; df = degrees of freedom; IV = inverse variance; SD = standard deviation; YMRS = Young Mania Rating Scale

Aripiprazole–Low- Versus High-Dose

A 4-week RCT (N = 296) randomized children ages 10 to 17 to two doses of aripiprazole (10 mg/day and 30 mg/day) and placebo.[67] No significant differences were observed between the two aripiprazole doses on the CDRS, CGAS, CGI–BP, General Behavior Inventory, or YMRS.

Quetiapine–Low- Versus High-Dose

A 3-week placebo-controlled RCT compared the efficacy of low-dose (400 mg/day) and high-dose (600 mg/day) quetiapine in the treatment of children and adolescents ages 10 to 17 with bipolar I mania.[73] No significant differences were observed between the two quetiapine dose regimens for CGAS, CGI–BP, or YMRS.

Risperidone–Low- Versus High-Dose

A 3-week placebo-controlled RCT (N = 169) compared the effectiveness of low-dose (0.5–2.5 mg/day) and high-dose (3–6 mg/day) risperidone in children ages 10 to 17.[68] The following outcomes showed no significant differences between the low- and high-dose groups: YMRS, CGI–BP, or BPRS for Children (BPRS–C) change scores.

Ziprasidone–Low- Versus High-Dose

Children ages 10 to 17 years with bipolar disorder or schizophrenia were randomized to low-dose (80 mg/day) and high-dose (160 mg/day) ziprasidone in a 3-week RCT.[42] Separate analyses

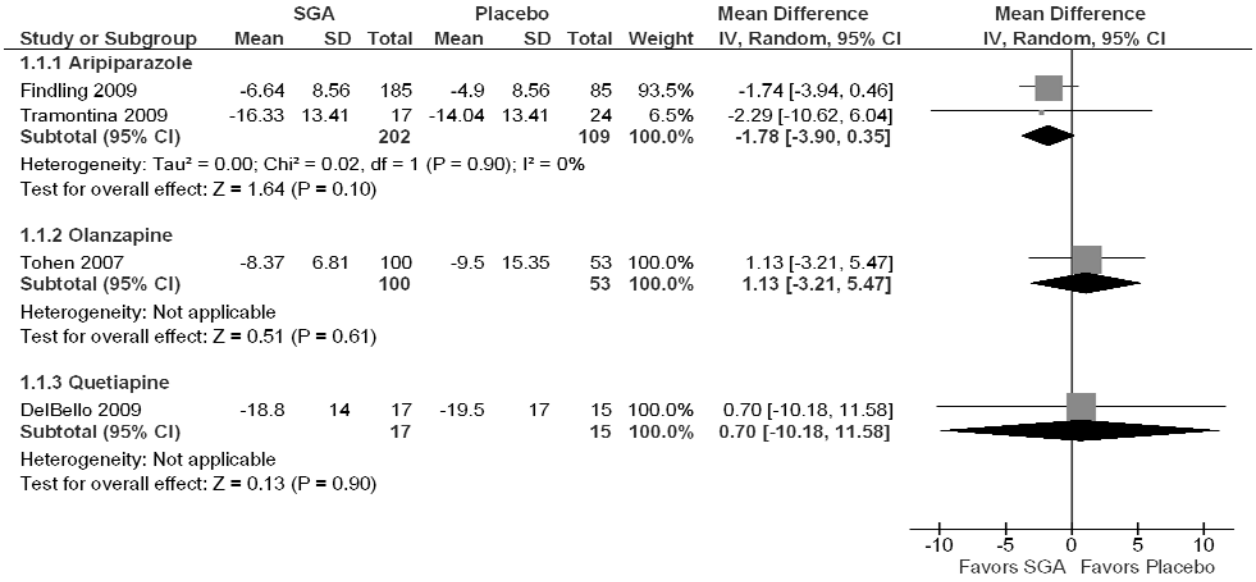
were provided for patients with bipolar disorder (N = 46). No significant differences were found between the two groups on the CGI–S or YMRS scores.

SGAs Versus Placebo

Eight RCTs compared various SGAs with placebo for alleviating bipolar symptoms: aripiprazole,[67,72] olanzapine,[71] quetiapine,[65,66,73] risperidone,[68] and ziprasidone.[70] Study duration ranged from 3 to 8 weeks. A total of 1,253 patients between the ages of 10 and 18 years were enrolled in the trials. All patients had a diagnosis of bipolar I disorder with the exception of eight patients in one trial.[72] Symptoms were assessed using the BPRS–C, CDRS, CGAS, CGI–BP, Child Mania Rating Scale, General Behavior Inventory, Hamilton Anxiety Rating Scale, OAS, and YMRS.

Four RCTs[65,67,71,72] compared various SGAs versus placebo on the CDRS (Figure 21). The studies were not pooled due to clinical heterogeneity: Delbello et al.[65] included only patients with a depressive episode, whereas the other studies enrolled predominantly patients with mania or mixed episodes. None of the studies found a statistically significant difference between SGA and placebo.

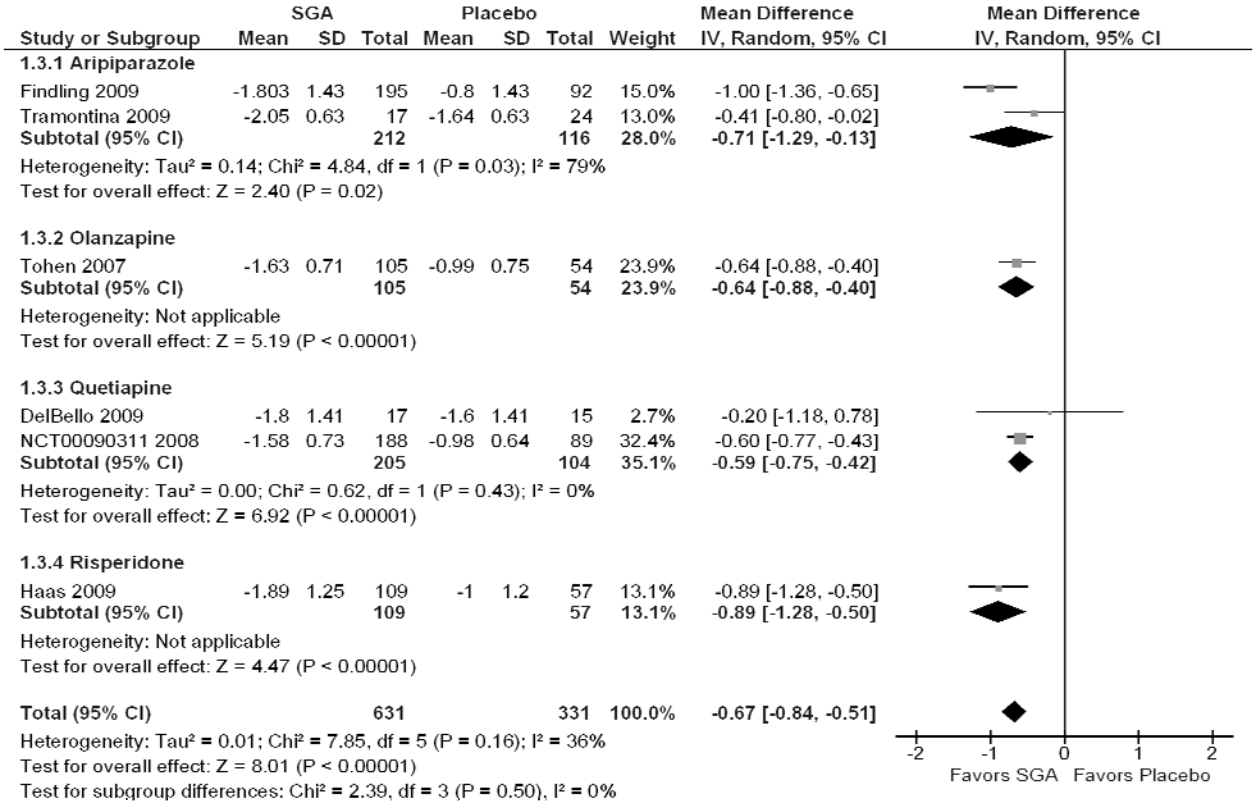
Figure 21. SGAs versus placebo on CDRS in bipolar disorder



CDRS = Children's Depression Rating Scale; CI = confidence interval; df = degrees of freedom; IV = inverse variance; SD = standard deviation; SGA = second-generation antipsychotic

Six RCTs[65,67,68,71-73] provided data for a meta-analysis of the efficacy of SGAs versus placebo for CGI (Figure 22). One study used the CGI–S,[72] and five studies used the CGI–BP. Two studies[67,72] comparing aripiprazole versus placebo showed a pooled estimate that significantly favored aripiprazole (MD = -0.71; 95% CI, -1.29 to -0.13); there was substantial heterogeneity (p = 0.03, I2 = 79%). The heterogeneity may be related to variability in the followup duration (4 weeks[67] versus 6 weeks[72]) and the proportion of patients with comorbid ADHD. Two studies[65,73] comparing quetiapine versus placebo had a pooled estimate that significantly favored quetiapine (MD = -0.59; 95% CI, -0.75 to -0.42), with no evidence of heterogeneity (p = 0.43, I2 = 0%). The combined estimate favored SGAs (MD = -0.67; 95% CI, -0.84 to -0.51). There was moderate heterogeneity (p = 0.16, I2 = 36%).

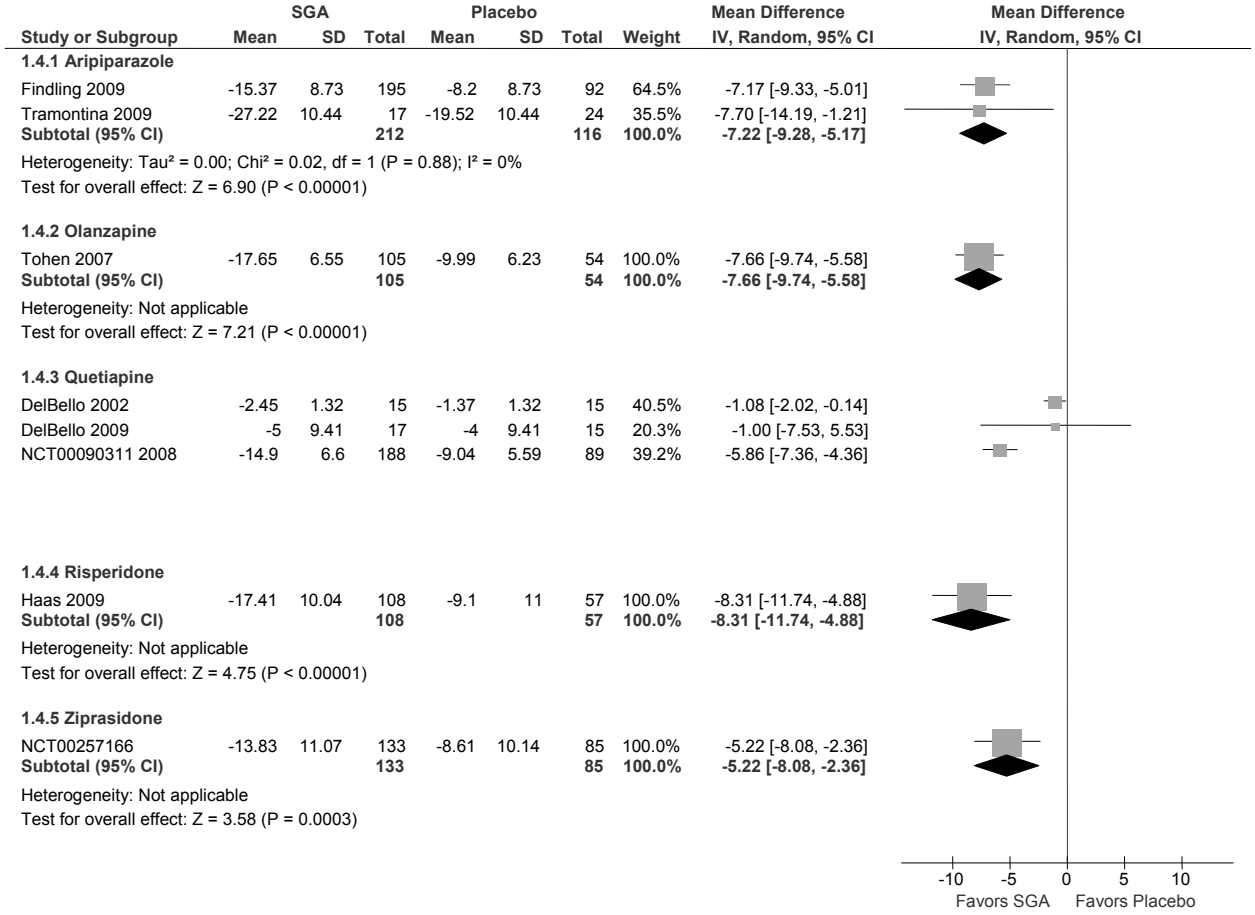
Figure 22. SGAs versus placebo on CGI in bipolar disorder



CGI = Clinical Global Impressions; CI = confidence interval; df = degrees of freedom; IV = inverse variance; SD = standard deviation; SGA = second-generation antipsychotic

Eight RCTs[65-68,70-73] evaluated the efficacy of SGAs versus placebo for manic symptoms, as measured by the YMRS (Figure 23). A meta-analysis of two studies[67,72] comparing aripiprazole with placebo showed a significant difference favoring aripiprazole (MD = -7.22; 95% CI, -9.28 to -5.17); there was no evidence of heterogeneity ($p = 0.88$, $I^2 = 0\%$). Three studies[65,66,73] compared quetiapine with placebo; the studies were not pooled due to considerable heterogeneity ($p<0.001$, $I^2 = 93\%$). One study examined patients experiencing a depressive episode.[65] Patients with bipolar depression can switch to mania or a mixed episode. All other SGAs were significantly favored over placebo. We did not pool the seven studies due to the considerable heterogeneity ($I^2>80\%$), which may be attributed to the quetiapine studies.[65,66,73]

Figure 23. SGAs versus placebo on YMRS in bipolar disorder



CI = confidence interval; df = degrees of freedom; IV = inverse variance; SD = standard deviation; SGA = second-generation antipsychotic; YMRS = Young Mania Rating Scale

Single studies favored aripiprazole over placebo on the CGAS,[67] Child Mania Rating Scale,[72] and General Behavior Inventory.[67] Patients using olanzapine showed significantly greater improvement in aggression on the OAS than patients on placebo.[71] Risperidone was favored over placebo on the BPRS.[68] Quetiapine was superior to placebo on CGAS in one study,[73] but there was no significant difference between quetiapine and placebo on the Hamilton Anxiety Rating Scale in another study.[65]

Bipolar Disorder: Short- and Long-Term Outcomes (Key Question 3)

Eleven studies provided data on a variety of short- and long-term outcomes for patients with bipolar disorder receiving treatment with SGAs. A summary of the results is presented by outcome below. Table 18 provides the strength of evidence grades for all key outcomes that were reported by at least one study.

- Response rate: Response rate was reported in nine studies. High-dose aripiprazole was favored over low-dose aripiprazole.[67] No significant differences in response rates were observed between olanzapine and risperidone in a meta-analysis of two studies[63,64] (RR = 0.72; 95% CI, 0.50 to 1.03) or low- and high-dose risperidone.[68] A meta-analysis of

seven studies[65-68,71-73] that compared a SGA with placebo showed a significant difference favoring SGAs (RR = 1.76; 95% CI, 1.46 to 2.13).

- Remission rate: The remission rate was significantly higher for high-dose aripiprazole than low-dose aripiprazole.[67] No differences were observed in a study comparing low- and high-dose risperidone.[68] A meta-analysis of five placebo-controlled studies[65,67,68,71-73] examining SGAs showed a significant difference favoring SGAs (RR = 2.40; 95% CI, 1.50 to 3.83) for remission rate.
- Cognitive and emotional development: One RCT[70] found a lower speed of processing score in patients receiving ziprasidone than placebo; however, the level of significance was not reported.
- Suicide-related behaviors: Three RCTs found no deaths by suicide.[67,68,70] No differences were found in suicidal ideation[42,67,68,70-73] and suicide attempts[65,68,70,71] between SGAs.
- Medication adherence: One RCT comparing two doses of risperidone found no difference in adherence rate between groups.[68] A meta-analysis of three RCTs[66,68,72] found a significant difference between groups favoring placebo over SGAs.
- Patient-, parent-, or care provider–reported outcomes: One RCT found no difference between olanzapine and placebo in the incidence of switch to depression during the trial.[71] A second RCT[73] found no difference between low- and high-dose quetiapine or quetiapine and placebo on the Caregiver Strain Questionnaire (CSQ).
- Other outcomes: No studies provided data for the following outcome categories: growth and maturation, school performance, work-related functional capacity, patient insight into illness, health-related quality of life, legal system interactions, or health care system utilization.

Table 18. Strength of evidence for bipolar disorder (Key Question 3)

Comparison	Outcome (N Studies; N Patients)	Strength of Evidence Domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Aripiprazole–low- vs. high-dose	Suicide (1; 296)	Moderate	Unknown	Direct	Imprecise	Insufficient
Risperidone–low- vs. high-dose	Medication adherence (1; 169)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Suicide (1; 169)	Moderate	Unknown	Direct	Imprecise	Insufficient
Ziprasidone–low- vs. high-dose	Suicide (1; 46)	Moderate	Unknown	Indirect	Imprecise	Insufficient
SGA vs. placebo	Medication adherence (2; 73)	Moderate	Consistent	Direct	Imprecise	Low
	Patient-reported outcome: Switch to depression (1; 161)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Care provider-reported outcomes: CGSQ (1; 277)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Suicide (7; 1245)	Moderate	Consistent	Direct	Imprecise	Moderate

CGSQ = Caregiver Strain Questionnaire; N = number; ROB = risk of bias; SGA = second-generation antipsychotic

Data on the effectiveness of SGAs and placebo on short- and long-term outcomes are presented in detail below.

SGAs Versus SGAs

Olanzapine Versus Risperidone

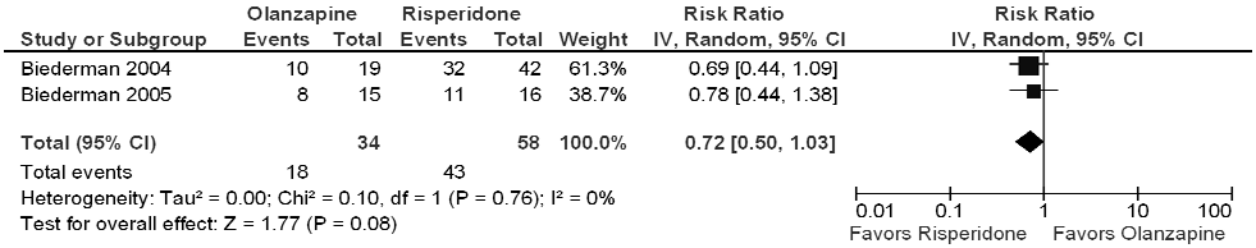
A 4-week RCT (N = 31) compared the effectiveness of olanzapine (6.3±2.3 mg/day) and risperidone (1.4±0.5 mg/day) in children ages 4 to 6 years with bipolar I disorder.[63] As noted earlier, bipolar I is a controversial diagnosis in young children. No significant difference was found between groups in response rate, defined as a greater than 30 percent reduction in YMRS or CGI–I≤2.

Olanzapine Versus Quetiapine Versus Risperidone Versus Ziprasidone

An 8-week open-label RCT evaluated the relative effectiveness of four SGA monotherapy regimens on children and adolescents with bipolar disorder.[64] No significant differences in response rates was found among the SGAs.

Two studies[63,64] provided data for a meta-analysis of olanzapine versus risperidone on response rate (Figure 24). The combined estimate favored risperidone but was not significant (RR = 0.72; 95% CI, 0.50 to 1.03). There was no evidence of heterogeneity (p = 0.76, I^2 = 0%).

Figure 24. Olanzapine versus risperidone on response rate in bipolar disorder



CI = confidence interval; df = degrees of freedom; IV = inverse variance

Aripiprazole–Low- Versus High-Dose

Findling et al. compared two doses of aripiprazole (10 mg/day and 30 mg/day) and placebo in a 4-week RCT (N = 296) of children ages 10 to 17.[67] Treatment response was defined as a 50 percent or greater reduction in YMRS score. Remission was defined as YMRS≤12 points and CGI–BP≤2 points at endpoint. Response and remission rates were significantly higher in high-dose aripiprazole than low-dose aripiprazole (p = 0.01 and p = 0.002, respectively). No deaths by suicide occurred during the study; however, one patient in the low-dose aripiprazole group reported suicidal ideation.

Quetiapine–Low- Versus High-Dose

A 3-week placebo-controlled RCT compared the efficacy of low-dose (400 mg/day) and high-dose (600 mg/day) quetiapine in the treatment of children and adolescents ages 10 to 17 with bipolar I mania.[73] No significant differences were observed between the dosing groups for response rate, remission rate, or the CSQ.

Risperidone–Low- Versus High-Dose

Low-dose (0.5–2.5 mg/day) and high-dose (3–6 mg/day) risperidone were compared in a 3-week placebo-controlled RCT (N = 169) of children ages 10 to 17 years.[68] No significant differences were observed between the risperidone groups for response (defined as a ≥50 percent reduction in YMRS) and remission (defined as YMRS≤12 and CGI–BP ≤2). No deaths by

suicide occurred during the study. Rates of suicide attempt and suicidal ideation were not significantly different between groups.

Ziprasidone–Low- Versus High-Dose

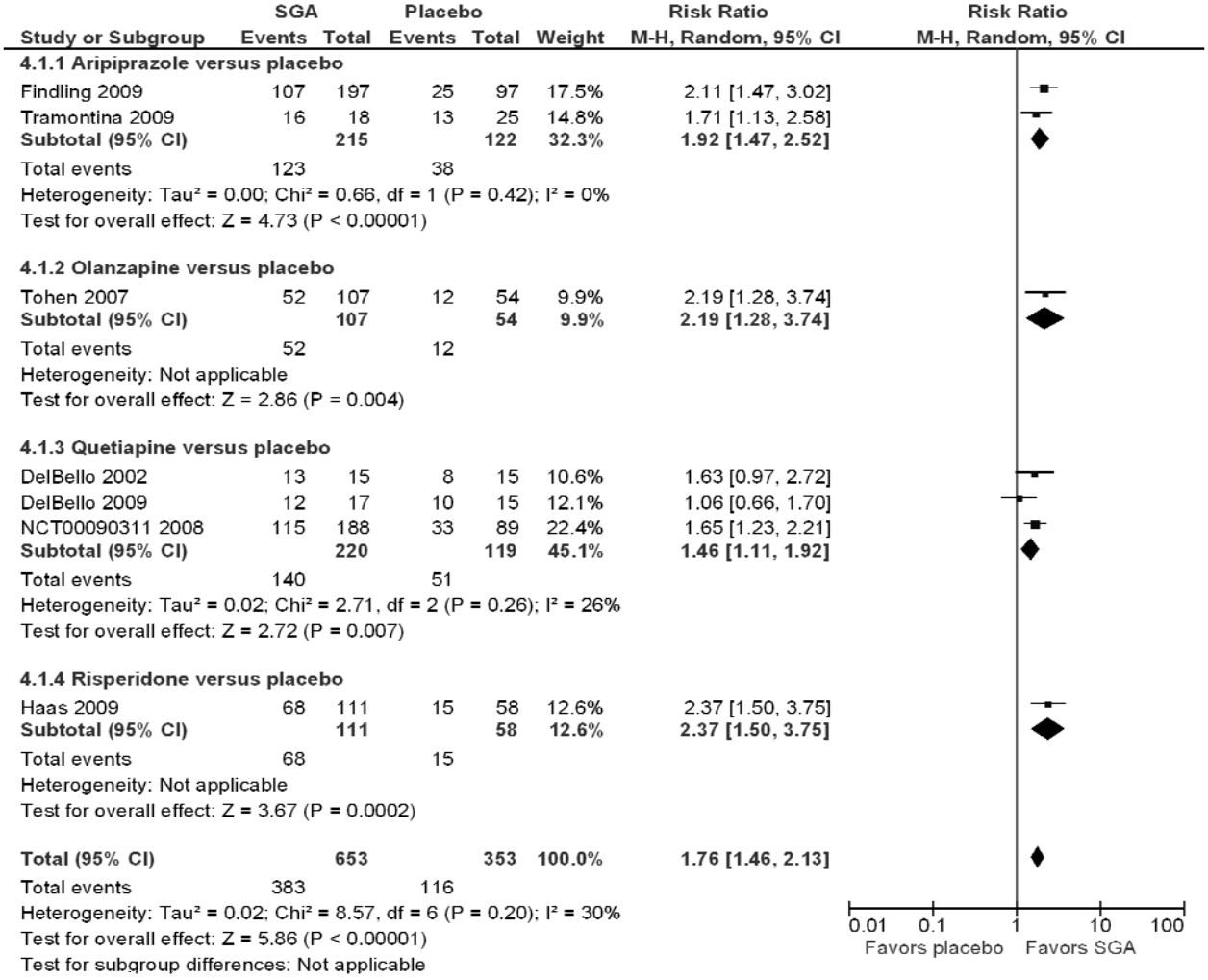
A 3-week RCT (N = 46) randomized children ages 10 to 17 with bipolar disorder or with schizophrenia or schizoaffective disorder to low-dose (80 mg/day) and high-dose (160 mg/day) ziprasidone.42 One patient in the high-dose group reported suicidal ideation; it was unclear whether this patient had bipolar disorder or schizophrenia.

SGAs Versus Placebo

Eight RCTs provided data on five comparisons with placebo: aripiprazole,[67,72] olanzapine,[71] quetiapine,[65,66,73] risperidone,[68] and ziprasidone.[70] A summary of the characteristics of these studies is presented in Key Question 1 above. The following outcomes were examined by the studies: response, remission, medication adherence, suicide-related behaviors, self-injurious behavior, speed of processing, switch to depression, and caregiver strain.

Seven RCTs[65-68,71-73] provided data for a meta-analysis comparing SGAs with placebo for treatment response rate (Figure 25). The combined estimate showed a significant difference between treatments favoring SGAs (RR = 1.76; 95% CI, 1.46 to 2.13). There was moderate heterogeneity ($p = 0.20$, $I^2 = 30\%$). The heterogeneity may be attributable to one study[65] that enrolled patients who were older and were experiencing a depressive episode during the study.

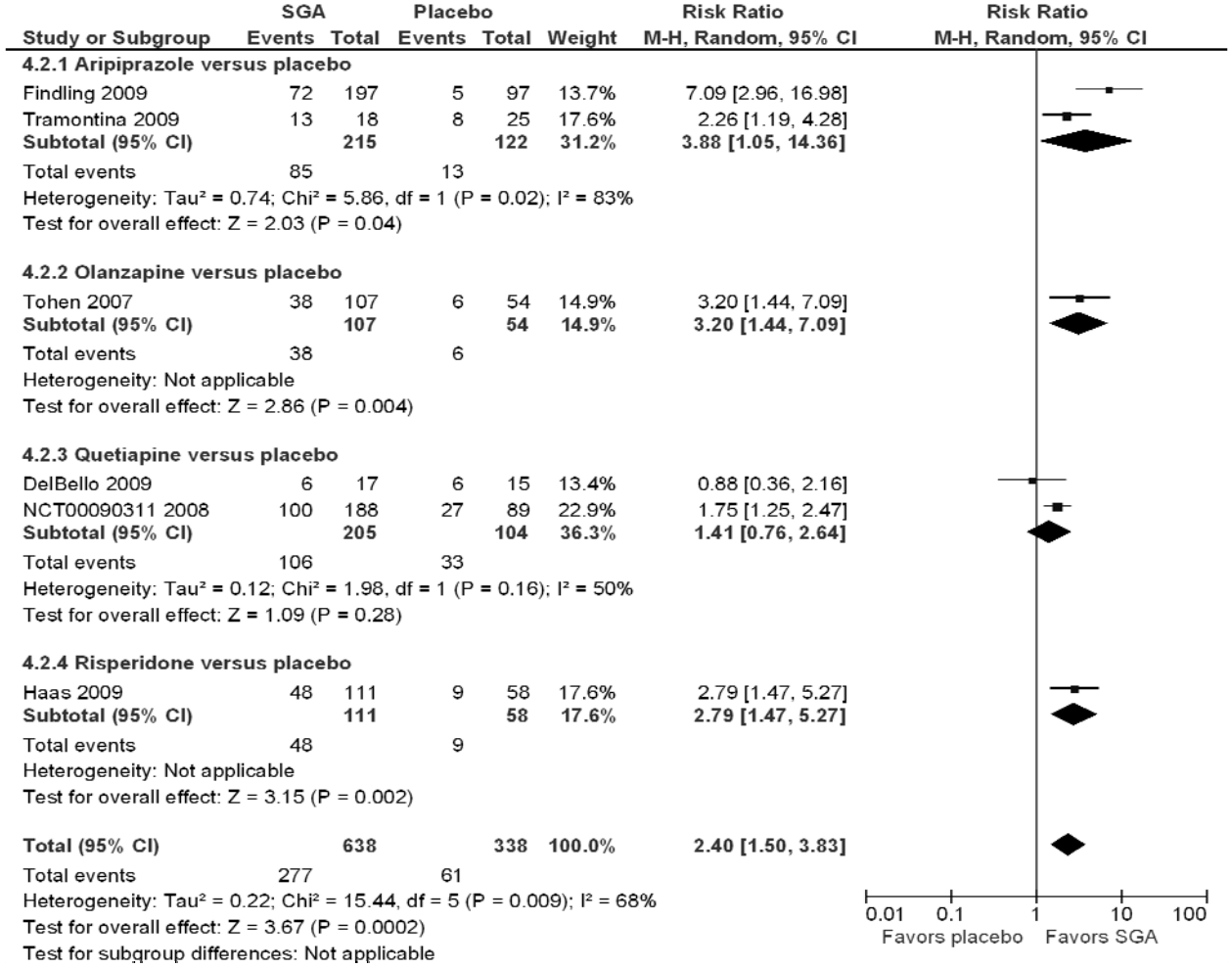
Figure 25. SGAs versus placebo on response rate in bipolar disorder



CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; SGA = second-generation antipsychotic

Six RCTs[65,67,68,71-73] provided data for a meta-analysis comparing SGAs with placebo for remission rate (Figure 26). The pooled estimate showed a significant difference between treatments favoring SGAs (RR = 2.40; 95% CI, 1.50 to 3.83). There was substantial heterogeneity ($p = 0.009$, $I^2 = 68$ percent), which was mostly a result of one study[65] that included only patients experiencing a depressive episode.

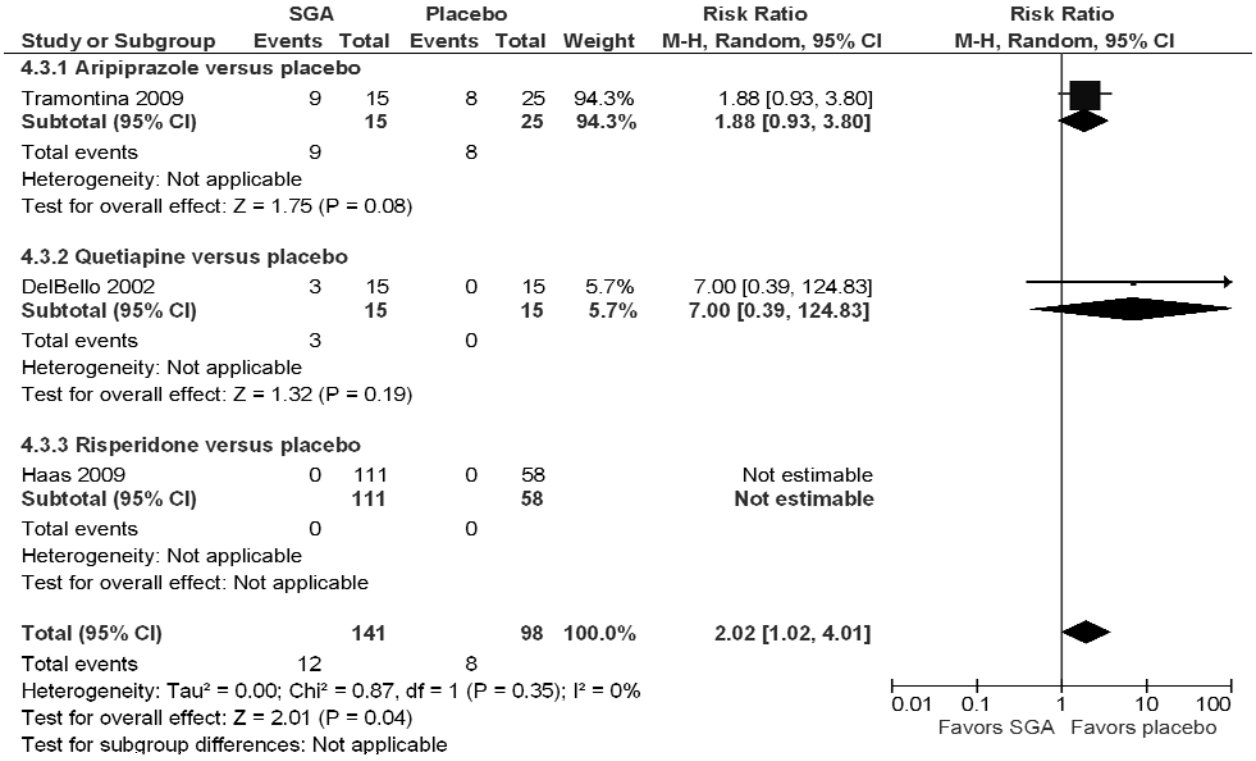
Figure 26. SGAs versus placebo on remission rate in bipolar disorder



CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; SGA = second-generation antipsychotic

Three RCTs[66,68,72] contributed to a meta-analysis comparing adherence rate for SGAs versus placebo (Figure 27). The pooled risk ratio showed a significant difference favoring placebo (RR = 2.02; 95% CI, 1.02 to 4.01). There was no evidence of heterogeneity ($p = 0.35$, $I^2 = 0\%$).

Figure 27. SGAs versus placebo on adherence rate in bipolar disorder

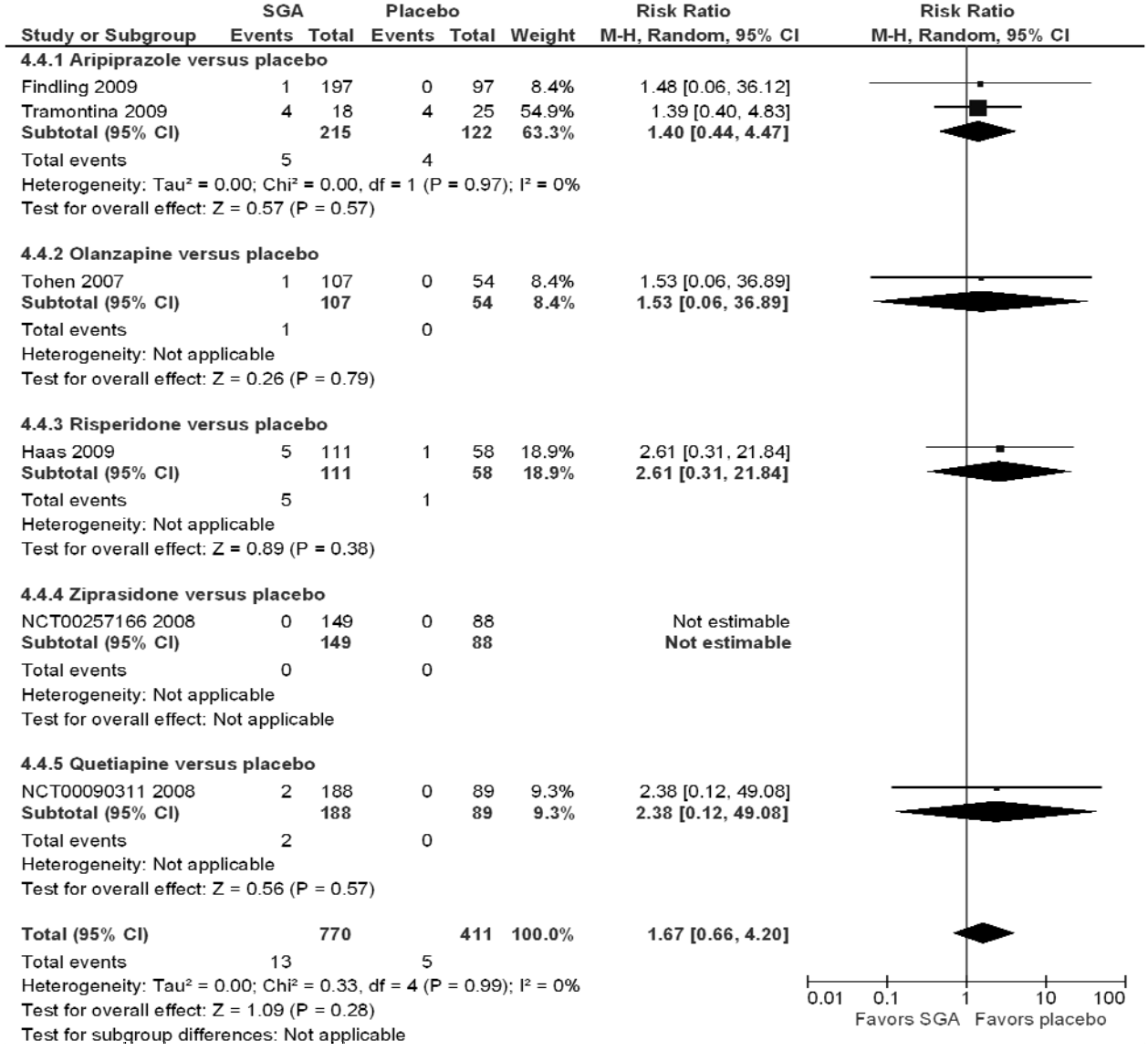


CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; SGA = second-generation antipsychotic

Three RCTs[67,68,70] reported suicide rates for SGAs versus placebo comparisons. No deaths by suicide occurred in either of the groups across all studies; therefore, a meta-analysis could not be conducted.

Six RCTs[67,68,70-73] comparing SGAs with placebo reported rate of suicidal ideation (Figure 28). The pooled estimate showed no significant difference between the groups (RR = 1.67; 95% CI, 0.66 to 4.20). There was no evidence of heterogeneity ($p = 0.99$, $I^2 = 0\%$).

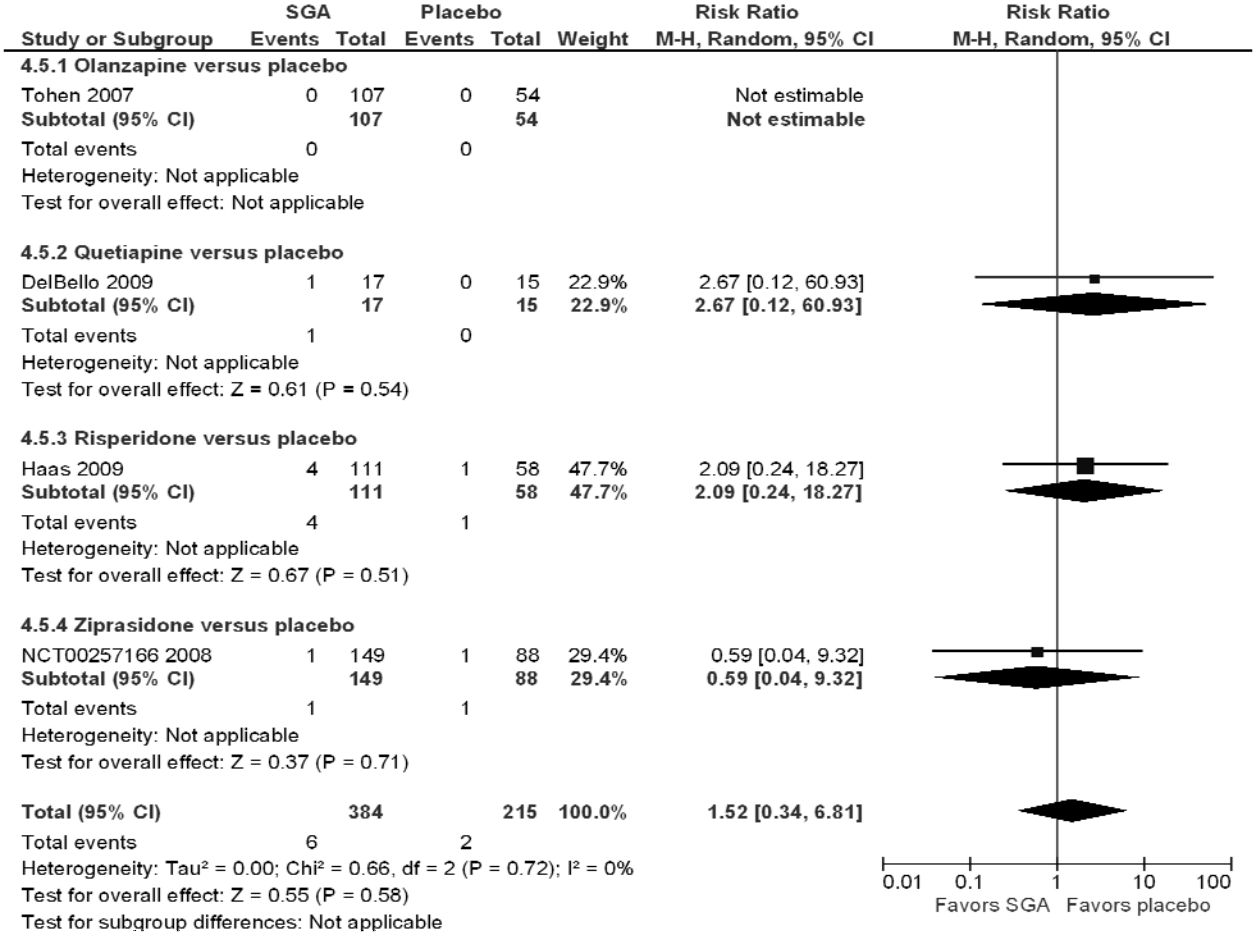
Figure 28. SGAs versus placebo on suicidal ideation in bipolar disorder



CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; SGA = second-generation antipsychotic

The suicide attempt rate was pooled for four RCTs[65,68,70,71] comparing SGAs with placebo (Figure 29). There was no significant difference between the groups (RR = 1.52; 95% CI, 0.34 to 6.81) and no evidence of heterogeneity (p = 0.72, I^2 = 0%).

Figure 29. SGAs versus placebo on suicide attempts in bipolar disorder



CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel; SGA = second-generation antipsychotic

One study found no difference between ziprasidone and placebo on self-injurious behavior.[70] Speed of processing score was lower in patients treated with ziprasidone than with placebo; however, the level of significance was not reported.[70] The incidence of switch to depression (CGI depression score ≤3 at baseline and ≥4 points at any time during the double-blind phase) did not differ significantly between olanzapine and placebo.[71] One study found no significant difference between quetiapine and placebo in relieving caregiver burden, as assessed by the CSQ.[73]

Schizophrenia and Related Psychosis: Overview

Twenty-five studies (23 RCTs[42,69,74-94] and 2 prospective cohort studies[95,96]) examined the efficacy of FGAs and SGAs for treating symptoms in patients with schizophrenia and schizophrenia-related psychosis. All studies reported on symptom improvement measures, and all except for three studies[82,90,94] reported on other short- and long-term outcomes.

Table 19 highlights key characteristics of the studies. Individual studies are presented in order of drug comparison, with head-to-head evidence preceding placebo comparisons, and then alphabetically by drug name. Several studies included both head-to-head comparisons and a placebo control; these studies are classified under the head-to-head category. A detailed evidence table is available in Appendix D.

The average age of patients across the studies was 15.7 years. Sexes were equally represented across the studies (54 percent male). Among the studies that reported race, the majority of patients were white, with the exception of one study of African Americans.[81] Diagnoses were established using the DSM–IV in the majority of studies (N = 19, 76 percent). Three studies enrolled only patients experiencing a first episode of psychosis,[74,75,91] and one study enrolled patients with psychosis related to bipolar disorder and schizophrenia (results were not presented separately for these conditions).[89] All other patients had a disorder along the schizophrenia spectrum. The most common comorbidities included substance abuse (89 patients), ADHD (32 patients), and anxiety disorder (28 patients); however, each of these were reported in less than 5 percent of the total number of patients.

Haloperidol was compared with various SGAs (clozapine, olanzapine, and risperidone) in five studies. Sixteen studies compared SGAs. Of these, nine studies compared different SGAs (clozapine vs. olanzapine, olanzapine vs. quetiapine, olanzapine vs. risperidone, and quetiapine vs. risperidone), and seven compared two doses of the same SGA. Haloperidol was compared with placebo in one study. SGAs were compared with placebo in seven studies.

The studies were generally of short duration, ranging from 3 weeks to 6 months (average of 7.7 weeks). The majority of the trials had a high risk of bias. The most common sources of potential bias were incomplete outcome data and industry sponsorship. Three trials had an unclear risk of bias.[87,88,90] The two prospective cohort studies had low[96] and moderate quality.[95]

Table 19. Characteristics of studies examining schizophrenia and related psychosis

Author, Year, Study Design, Duration, KQ	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
FGAs vs. SGAs			
Kumra et al, 1996[82] RCT, 6 wk *KQ1*	G1: Haloperidol (11), 16±8 mg/day G2: Clozapine (10), 176±149 mg/day	G1: 13.7±1.6 yr / Male: 55% / White: NR G2: 14.4±2.9 yr / Male: 50% / White: NR Comorbidities: NR	disorganized (10), paranoid (1), undifferentiated (10) High ROB
de Haan et al, 2003[76] RCT, 6 wk *KQ1, KQ3*	G1: Haloperidol (12), 2.5 mg/day G2: Olanzapine (12), 7.5 mg/day	G1: 21.0±2.8 yr / Male: NR / White: NR G2: 21±2.3 yr / Male: NR / White: NR Comorbidities: NR	disorganized (6), paranoid (13), undifferentiated (5) High ROB
Ratzoni et al, 2002[96] Prospective cohort, 12 wk *KQ1, KQ3*	G1: Haloperidol (8), 7.6±4 mg/day G2: Olanzapine (21), 12.7±3.1 mg/day G3: Risperidone (21), 3.2±1.1 mg/day	G1: 17.3±1.3 yr / Male: 63% / White: NR G2: 17±1.6 yr / Male: 67% / White: NR G3: 17.1±2.1 yr / Male: 57% / White: NR Comorbidities: NR	CD (2), schizoaffective disorder (2), schizophrenia (46) 3/8 stars
Sikich et al, 2004[89] RCT, 8 wk (12 wk extension) *KQ1, KQ3*	G1: Haloperidol (15), 5±2 mg/day G2: Olanzapine (16), 12.3±3.5 mg/day G3: Risperidone (19), 4±1.2 mg/day	G1: 15.4±2.2 yr / Male: 53% / White: 73% G2: 14.6±3.1 yr / Male: 56% / White: 63% G3: 14.6±2.9 yr / Male: 68% / White: 47% Comorbidities: NR	affective disorders (24), schizophrenia spectrum (26) High ROB
Yen et al, 2004[94] RCT, 12 wk *KQ1*	G1: Haloperidol (2), 11.2±6.9 mg/day G2: Risperidone (6), 4.4±2.6 mg/day	G1: 24 yr / Male: 0 / White: NR G2: 20.7 yr / Male: 67% / White: NR Comorbidities: NR	NR High ROB

Table 19. Characteristics of studies examining schizophrenia and related psychosis (continued)

Author, Year, Study Design, Duration, KQ	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
SGAs vs. SGAs			
Findling et al, 2008[77] RCT, 6 wk *KQ1, KQ3*	G1: Aripiprazole (low) (100), 9.8 mg/day G2: Aripiprazole (high) (102), 28.9 mg/day G3: Placebo (100)	G1: 15.6±1.3 yr / Male: 45% / White: 54% G2: 15.4±1.4 yr / Male: 64% / White: 61% G3: 15.4 ±1.4 yr / Male: 61% / White: 64% Comorbidities: NR	NR High ROB
Kumra et al, 2008[81] RCT, 12 wk (12 wk extension) *KQ1, KQ3*	G1: Clozapine (18), 403.1±201.8 mg/day G2: Olanzapine (21), 26.2±6.5 mg/day	G1: 15.8±2.2 yr / Male: 44% / White: 11% G2: 15.5±2.1 yr / Male: 62% / White: 29% Comorbidities: NR	schizoaffective disorder (14), schizophrenia (25) High ROB
Kumra et al, 1998[95] Prospective cohort, G1: 6 wk, G2: 8 wk *KQ1, KQ3*	G1: Clozapine (15), 317±147 mg/day G2: Olanzapine (8), 17.5±2.3 mg/day	G1: 13.6±1.5 yr / Male: 53% / White: NR G2: 15.3±2.3 yr / Male: 50% / White: NR Comorbidities: NR	disorganized (11), paranoid (3), undifferentiated (9) 5/8 stars
Shaw et al, 2006[87] RCT, 8 wk (2 yr extension) *KQ1, KQ3*	G1: Clozapine (12), 327±113 mg/day G2: Olanzapine (13), 18.1±4.3 mg/day	G1: 11.7±2.3 yr / Male: 67% / White: 58% G2: 12.8±2.4 yr / Male: 54% / White: 54% Comorbidities: ADHD/ODD/CD (7), anxiety disorders (7)	NR Unclear ROB
Arango et al, 2009[74] RCT, 6 mo *KQ1, KQ3*	G1: Olanzapine (26), 9.7±6.6 mg/day G2: Quetiapine (24), 532.8±459.6 mg/day	G1: 15.7±1.4 yr / Male: 76% / White: 77% G2: 16.3±1.1 yr / Male: 79% / White: 88% Comorbidities: NR	BD (13), schizophrenia (17), other psychoses (20) High ROB
Jensen et al, 2008[79] RCT, 12 wk *KQ1, KQ3*	G1: Olanzapine (10), 14±4.6 mg/day G2: Quetiapine (10), 611±253.4 mg/day G3: Risperidone (10), 3.4±1.5 mg/day	G1: 15.3±1.5 yr / Male: 50% / White: 50% G2: 14.8±2.3 yr / Male: 70% / White: 60% G3: 15.6±2.5 yr / Male: 80% / White: 70% Comorbidities: NR	psychotic disorder NOS (9), schizophrenia/ schizoaffective disorder (16), schizophreniform disorder (5) High ROB
Mozes et al, 2006[83] RCT, 12 wk *KQ1, KQ3*	G1: Olanzapine (12), 8.2±4.4 mg/day G2: Risperidone (13), 1.6±1 mg/day	G1: 11.5±1.6 yr / Male: 42% / White: NR G2: 10.7±1.4 yr / Male: 39% / White: NR Comorbidities: ADHD (3), epilepsy (2), familial mediterranean fever (1), neurofibromatosis (1), OCD (3), tic disorder (1)	disorganized schizophrenia (7), paranoid schizophrenia (6), schizophreniform disorder (10), unspecified schizoprehenia (2) High ROB
Sikich et al, 2008[88] RCT, 8 wk (44 wk extension) *KQ1, KQ3*	G1: Olanzapine (36), 11.4±5 mg/day G2: Rispiradone (42), 2.8±1.4 mg/day	G1: NR / Male: 71% / White: 60% G2: NR / Male: 66% / White: 61% Comorbidities: ADHD (22), affective disorder (19), anxiety disorder (21), ASD (5), DBD (16), learning disability (3), psychosis (10), SA (4)	schizoaffective disorder (26), schizophrenia (50) Unclear ROB

Table 19. Characteristics of studies examining schizophrenia and related psychosis (continued)

Author, Year, Study Design, Duration, KQ	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
van Bruggen et al, 2003[92] RCT, olanzapine 9.8 wk, risperidone 6.7 wk *KQ1, KQ3*	G1: Olanzapine (18), 15.6±4 mg/day G2: Risperidone (26), 4.4±1.5 mg/day	G1: 21±2.8 yr / Male: 72% / White: NR G2: 20.6±3 yr / Male: 85% / White: NR Comorbidities: NR	NR High ROB
Robb et al, 2009[86] RCT, 6 wk *KQ1, KQ3*	G1: Paliperidone ER (low) (54), NR G2: Paliperidone ER (medium) (48), NR G3: Paliperidone ER (high) (48), NR G4: Placebo (51)	All groups: NR / Male: NR / White: NR Comorbidities: NR	paranoid schizophrenia (143), other (58) High ROB
Berger et al, 2008[75] RCT, 4 wk (8 wk extension) *KQ1, KQ3*	G1: Quetiapine (low) (69), 200 mg/day G2: Quetiapine (high) (72), 400 mg/day	G1: 19.7±2.6 yr / Male: 71% / White: NR G2: 19±2.9 yr / Male: 64% / White: NR Comorbidities: SA (58)	nonaffective psychosis (95), affective psychosis (31) High ROB
NCT00090324, 2008[84] RCT, 6 wk *KQ1, KQ3*	G1: Quetiapine (low) (73), 400 mg/day G2: Quetiapine (high) (74), 800 mg/day G3: Placebo (75)	G1: 15.5±1.3 yr / Male: 59% / White: 62% G2: 15.5±1.3 yr / Male: 60% / White: 60% G3: 15.3±1.4 yr / Male: 58% / White: 63% Comorbidities: NR	disorganized (16), paranoid (155), residual (1), undifferentiated (48) High ROB
Swadi et al, 2010[91] RCT, 6 wk *KQ1, KQ3*	G1: Quetiapine (11), 607 mg/day G2: Risperidone (11), 2.9 mg/day	G1: NR / Male: 55% / White: NR G2: NR / Male: 64% / White: NR Comorbidities: NR	NR High ROB
Haas et al, 2009[78] RCT, 8 wk *KQ1, KQ3*	G1: Risperidone (low) (132), 0.4 mg/day G2: Risperidone (high) (125), 4 mg/day	G1: 15.6±1.3 (13–17) yr / Male: 61% / White: 85% G2: 15.7±1.3 (13–17) yr / Male: 52% / White: 85% Comorbidities: NR	catatonic (7), disorganized (19), paranoid (175), residual (7), undifferentiated (49) High ROB
Haas, 2009[69] RCT, 6 wk *KQ1, KQ3*	G1: Risperidone, 1–3 mg/day (54) G2: Risperidone, 4–6 mg/day (50) G3: Placebo (54)	G1: 15.7±1.3 yr / Male: 55% / White: 60% G2: 15.6±1.3 yr / Male: 73% / White: 47% G3: 15.5±1.4 yr / Male: 65% / White: 50% Comorbidities: NR	paranoid (110), undifferentiated (33), disorganized (15), catatonic (1), residual (1) High ROB
DelBello et al, 2008[42] RCT, 3 wk (24 wk extension) *KQ1, KQ3*	G1: Ziprasidone (low) (8), target: 80 mg/day G2: Ziprasidone (high) (9), target: 160 mg/day	G1: 14.4±2.3 yr / Male: 52% / White: NR G2: 14.7±2.0 yr / Male: 75% / White: NR Comorbidities: NR	bipolar I disorder (46), schizophrenia or schizoaffective disorder (17) High ROB
FGAs vs. Placebo			
Spencer et al, 1994[90] RCT (crossover), 8 wk *KQ1*	G1: Haloperidol (16),* 2 mg/day G2: Placebo (16)*	All groups: NR / Male: NR / White: NR Comorbidities: Prior diagnoses: atypical PDD (5), atypical psychosis (3), borderline personality disorder (1), CD (1), pica (1)	NR Unclear ROB

Table 19. Characteristics of studies examining schizophrenia and related psychosis (continued)

Author, Year, Study Design, Duration, KQ	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
SGA vs. Placebo			
Kryzhanovskaya et al, 2009[80] RCT, 6 wk (6 mo extension) *KQ1, KQ3*	G1: Olanzapine (72), 11.1 mg/day G2: Placebo (35)	G1: 16.1±1.3 yr / Male: 71% / White: 72% G2: 16.3±1.6 yr / Male: 69% / White: 71% Comorbidities: NR	NR High ROB
Woods et al, 2003[93] RCT, 8 wk (12 mo extension) *KQ1, KQ3*	G1: Olanzapine (31), 8±3.1 mg/day G2: Placebo (29)	G1: 18.2±5.5 yr / Male: 68% / White: 74% G2: 17.2±4 yr / Male: 62% / White: 59% Comorbidities: SA [marijuana (16), other (11)]	NR High ROB
NCT00257192, 2010[85] RCT, 6 wk *KQ1, KQ3*	G1: Ziprasidone (NR), target: 60–80 mg/day (<45 kg), 120–160 mg/day (≥45 kg) G2: Placebo (NR)	G1: 15.3 yr / Male: NR / White: NR G2: 15.4 yr / Male: NR / White: NR Comorbidities: NR	paranoid (184) High ROB

ADHD = attention deficit hyperactivity disorder; ASD = autism spectrum disorder; BD = bipolar disorder; CD = conduct disorder; DBD = disruptive behavior disorder; ER = extended release; G = group; FGA = first-generation antipsychotic; KQ = key question; mg = milligram; mo = month; N = number; NOS = not otherwise specified; NR = not reported; OCD = obsessive-compulsive disorder; ODD = oppositional defiant disorder; PDD = pervasive developmental disorder; RCT = randomized controlled trial; ROB = risk of bias; SA = substance abuse; SD = standard deviation; SGA = second-generation antipsychotic; wk = week; yr = year

*All patients received each of the treatments in this crossover study.

Schizophrenia and Related Psychosis: Disorder-Specific and Nonspecific Symptoms (Key Question 1)

Twenty-five studies compared the efficacy of FGAs and SGAs for the treatment of symptoms in patients with schizophrenia and related psychosis. A summary of the results by comparison is presented below. Table 20 provides the strength of evidence grades for all key outcomes that were reported by at least one study.

- FGAs versus SGAs (four RCTs[76,82,89,94] and one prospective cohort study[96]): Haloperidol was compared with clozapine,[82] olanzapine,[76,89,96] and risperidone.[89,94,96] SGAs were significantly favored in meta-analyses of the BPRS (MD = -11.44; 95% CI, -19.35 to -3.52) and CGI–I (MD = -0.76; 95% CI, -1.25 to -0.26). There was no significant difference between the drug classes on the Positive and Negative Syndrome Scale (PANSS).
- Clozapine versus olanzapine (two RCTs[81,87] and one prospective cohort study [95]): Meta-analyses showed no significant differences between these SGAs on the BPRS, CGI–S, or Scale for the Assessment of Negative Symptoms (SANS).
- Olanzapine versus quetiapine (two RCTs[74,79]): There was a significant difference favoring olanzapine for Strengths and Difficulties Questionnaire as rated by patients in one study (p = 0.03).[74]
- Olanzapine versus risperidone (five RCTs[79,83,88,89,92] and one prospective cohort study[96]): Meta-analyses showed no significant differences between olanzapine and risperidone on the BPRS, CGI–S, or PANSS.
- Quetiapine versus risperidone (one RCT[91]): There was no significant difference between groups in positive and negative symptoms.

- SGAs–Dosing (seven RCTs; aripiprazole,[77] paliperidone,[86] quetiapine,[75,84] risperidone,[69,78] and ziprasidone.[42]): The high-dose (4.0 mg/day) risperidone group showed greater symptom improvement than the low-dose (0.4 mg/day) group on the CGI–I, CGI–S, and PANSS in one study.[78] A second study found no significant differences between low- (1–3 mg/day) and high-dose (4–6 mg/day) risperidone on the CGAS, CGI–I, CGI–S, or PANSS.[69] No other significant differences were found between doses.
- Haloperidol versus placebo (one crossover RCT[90]): Positive and negative syndrome scores on the CPRS improved significantly in the haloperidol group compared with placebo ($p<0.01$).
- SGAs versus placebo (seven RCTs; aripiprazole,[77] olanzapine,[80,93] paliperidone,[86] quetiapine,[84] risperidone,[69] and ziprasidone[85]): A significant difference was found favoring SGAs on the CGAS, CGI–I, CGI–S, and PANSS. No difference was found for BPRS.

Table 20. Strength of evidence for schizophrenia and related psychosis (Key Question 1)

Comparison	Outcome (N Studies; N Patients)	Strength of evidence domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
FGAs vs. SGAs	Clinical global impressions (3; 95)	Moderate	Consistent	Direct	Imprecise	Low
	Positive and negative symptoms (4; 103)	Moderate	Inconsistent	Direct	Imprecise	Low
Clozapine vs. olanzapine	Clinical global impressions (2; 65)	Moderate	Consistent	Direct	Imprecise	Low
	Positive and negative symptoms (3; 88)	Moderate	Consistent	Direct	Imprecise	Low
Olanzapine vs. quetiapine	Clinical global impressions (2; 80)	Moderate	Inconsistent	Direct	Imprecise	Insufficient
	Positive and negative symptoms (1; 50)	Moderate	Unknown	Direct	Imprecise	Insufficient
Olanzapine vs. risperidone	Clinical global impressions (3; 143)	Moderate	Consistent	Direct	Not pooled	Low
	Positive and negative symptoms (4; 197)	Moderate	Consistent	Direct	Imprecise	Low
Quetiapine vs. risperidone	Positive and negative symptoms (1; 22)	Moderate	Unknown	Direct	Imprecise	Insufficient
Low- vs. high-dose aripiprazole	Clinical global impressions (1; 302)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Positive and negative symptoms (1; 302)	Moderate	Unknown	Direct	Imprecise	Insufficient
Low- vs. high-dose paliperidone	Clinical global impressions (1; 201)	Moderate	Unknown	Direct	Precise	Insufficient
	Positive and negative symptoms (1; 201)	Moderate	Unknown	Direct	Imprecise	Insufficient

Table 20. Strength of evidence for schizophrenia and related psychosis (Key Question 1) (continued)

Comparison	Outcome (N Studies; N Patients)	Strength of evidence domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Low- vs. high-dose quetiapine	Clinical global impressions (2; 363)	Moderate	Inconsistent	Direct	Not pooled	Insufficient
	Manic symptoms (1; 141)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Positive and negative symptoms (2; 363)	Moderate	Consistent	Direct	Not pooled	Insufficient
	Social and occupational functioning (1; 141)	Moderate	Unknown	Direct	Imprecise	Insufficient
Low- vs. high-dose risperidone	Clinical global impressions (2; 361)	Moderate	Inconsistent	Direct	Not pooled	Insufficient
	Positive and negative symptoms (2; 361)	Moderate	Inconsistent	Direct	Not pooled	Insufficient
Low- vs. high-dose ziprasidone	Clinical global impressions (1; 17)	Moderate	Unknown	Direct	Imprecise	Insufficient
Haloperidol vs. placebo	Clinical global impressions (1; 32)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Positive and negative symptoms (1; 32)	Moderate	Unknown	Direct	Imprecise	Insufficient
SGA vs. placebo	Aggression (1; 107)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Clinical global impressions (6; 1050)	Moderate	Consistent	Direct	Precise	Moderate
	Manic symptoms (1; 60)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Positive and negative symptoms (6; 1068)	Moderate	Consistent	Direct	Precise	Moderate

FGA = first-generation antipsychotic; N = number; ROB = risk of bias; SGA = second-generation antipsychotic

A detailed analysis is presented by comparison below.

FGAs Versus SGAs

Five studies provided data on the following FGAs versus SGAs comparisons: haloperidol versus clozapine,[82] haloperidol versus olanzapine,[76,89,96] and haloperidol versus risperidone.[89,94,96]

Haloperidol Versus Clozapine

A 6-week RCT (N = 21) compared the efficacy of haloperidol (16±8 mg/day) and clozapine (176±149 mg/day) in patients ages 6 to 18 with schizophrenia.[82] Patients were assessed using the BPRS–C, CGAS, CGI–I, SANS, and the Scale for the Assessment of Positive Symptoms. Symptoms improved to a greater extent in the clozapine group than the haloperidol group across all outcome measures ($p<0.05$).

Haloperidol Versus Olanzapine

Three studies compared the effect of haloperidol versus olanzapine on schizophrenia symptoms. A 6-week RCT (N = 24) examined adolescents and young adults ages 17 to 26.[76] The mean drug dose was 2.5 mg/day and 7.5 mg/day for haloperidol and olanzapine, respectively. Patients were assessed using the CGI–I and PANSS. Symptoms improved from baseline to endpoint in both groups; however, there were no significant differences between the groups.

A 12-week prospective cohort study compared the efficacy of haloperidol (7.6±4 mg/day), olanzapine (12.7±3.1 mg/day), and risperidone (3.2±1.1 mg/day) in adolescents ages 14 to 20

with schizophrenia (n = 46), schizoaffective disorder (n = 2), and conduct disorder (n = 2).[96] Changes in the PANSS did not differ significantly between groups from baseline to endpoint.

An 8-week RCT (N = 50) compared the efficacy of haloperidol (5±2 mg/day) with olanzapine (12.3±3.5 mg/day) and risperidone (4±1.2 mg/day) in children with psychosis (24 with affective disorders and 26 with schizophrenia spectrum).[89] There was no significant difference between the groups for the CGI–I. However, olanzapine was significantly favored over haloperidol on the BPRS (p = 0.02).

Haloperidol Versus Risperidone

Three studies compared haloperidol with risperidone. Two of the studies are described above. Ratzoni et al. found no significant difference between haloperidol and risperidone on the PANSS.[96] Sikich et al. found a significant difference favoring risperidone over haloperidol for the CGI–S and CPRS (p = 0.03 for both outcomes), but no difference on the CGI–I.[89]

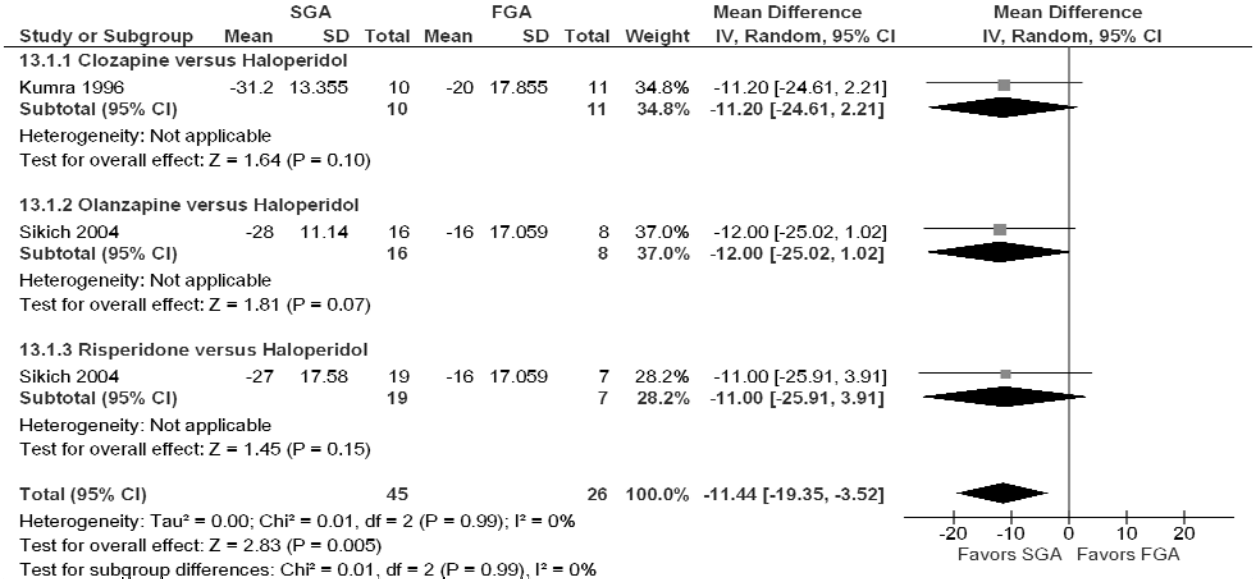
A 12-week RCT compared the efficacy of haloperidol (11.2±6.9 mg/day) and risperidone (4.4±2.6 mg/day) in adult patients with schizophrenia.[94] Data for eight patients ages ≤24 were presented separately. Patients were assessed using the PANSS. The risperidone group demonstrated significantly greater improvement in the PANSS score than the haloperidol group (p = 0.03).

Meta-analyses Comparing FGAs Versus SGAs

Meta-analyses were conducted to compare FGAs and SGAs for the BPRS, CGI–I, and PANSS.

A meta-analysis of two studies[82,89] found a significant difference favoring SGAs over haloperidol on the BPRS (MD = -11.44; 95% CI, -19.35 to -3.52) (Figure 30). There was no evidence of heterogeneity (p = 0.99, I^2 = 0%).

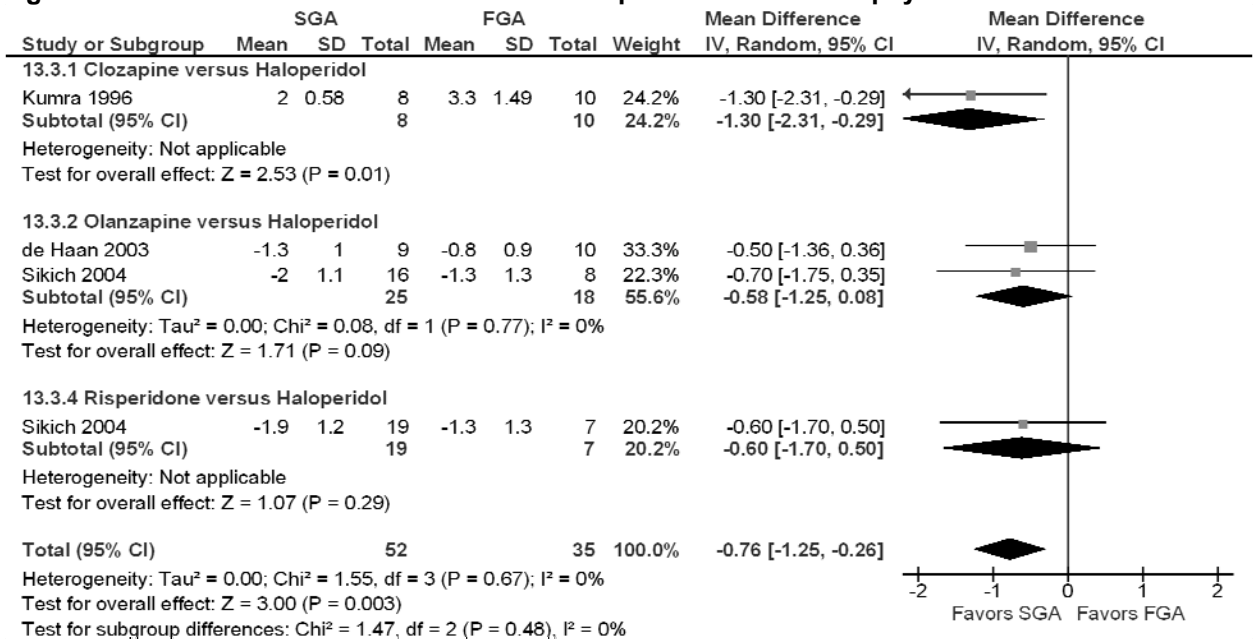
Figure 30. FGAs versus SGAs on BPRS in schizophrenia and related psychosis



BPRS = Brief Psychiatric Rating Scale; CI = confidence interval; df = degrees of freedom; FGA = first-generation antipsychotics; IV = inverse variance; SD = standard deviation; SGA = second-generation antipsychotic

Three RCTs[76,82,89] provided data for a meta-analysis on the efficacy of FGAs versus SGAs on CGI–I (Figure 31). A pooled estimate of the change scores was significant, favoring SGAs over haloperidol (MD = -0.76; 95% CI, -1.25 to -0.26). There was no evidence of heterogeneity (p = 0.67, I^2 = 0%).

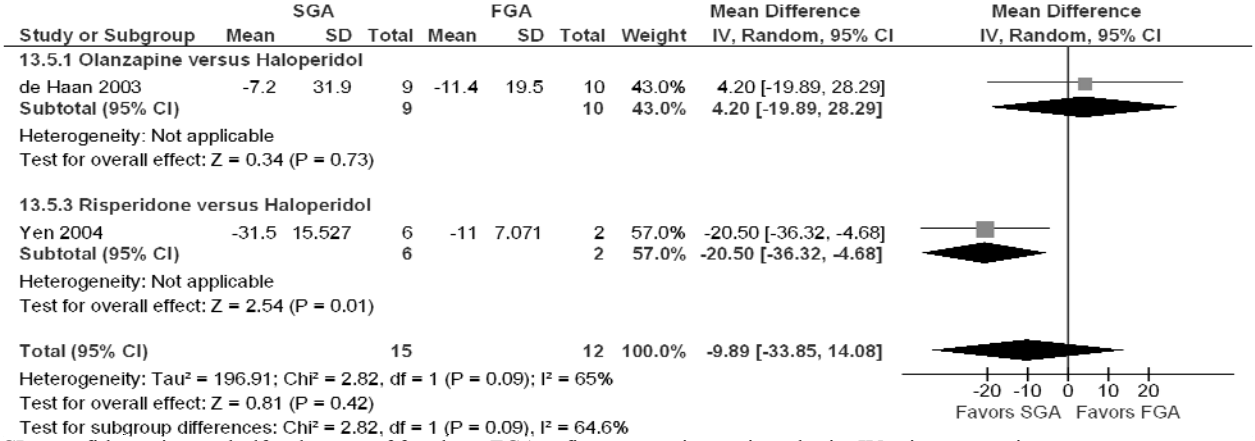
Figure 31. FGAs versus SGAs on CGI–I in schizophrenia and related psychosis



CGI–I = Clinical Global Impressions–Improvement; CI = confidence interval; df = degrees of freedom; FGA = first-generation antipsychotics; IV = inverse variance; SD = standard deviation; SGA = second-generation antipsychotic

Two RCTs[76,94] provided data for a meta-analysis on the efficacy of FGAs versus SGAs on positive and negative symptoms as measured by the PANSS (Figure 32). There was no significant difference between groups (MD = -9.89; 95% CI, -33.85 to 14.08); however, there was substantial heterogeneity (p = 0.09, I^2 = 65%), which may be attributable to the use of different SGAs. A higher dose of the FGA in one study[94] may also have contributed to the heterogeneity.

Figure 32. FGAs versus SGAs on PANSS in schizophrenia and related psychosis



CI = confidence interval; df = degrees of freedom; FGA = first-generation antipsychotic; IV = inverse variance; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; SGA = second-generation antipsychotic

SGAs Versus SGAs

Eighteen studies examined the efficacy of SGAs. Eleven of these studies provided head-to-head comparisons of different SGAs, and seven studies compared different doses of the same SGA.

Clozapine Versus Olanzapine

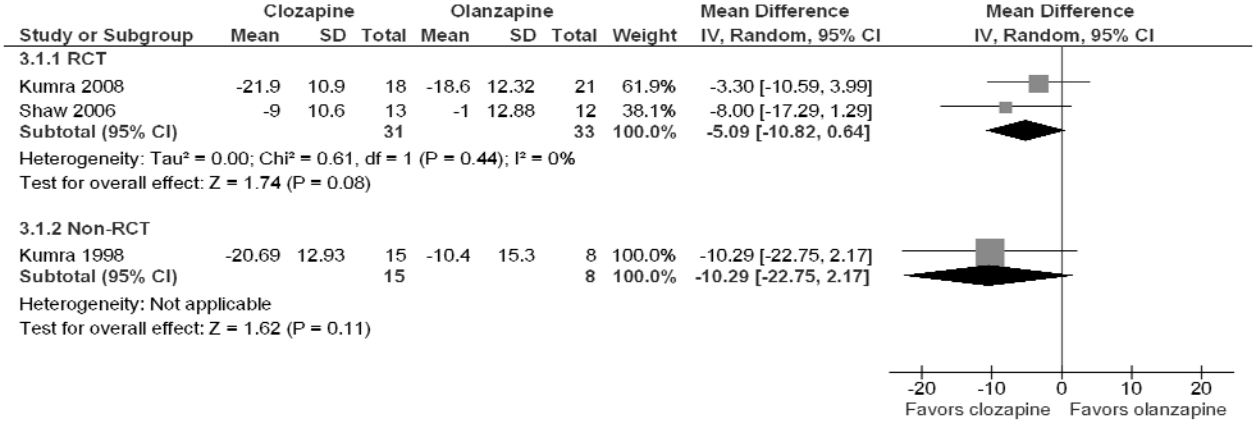
Three studies compared clozapine with olanzapine.[81,87,95] A 12-week RCT (N = 40) with a 12-week extension examined children ages 10 to 18 with schizophrenia or schizoaffective disorder.[81] The mean dosage was 403.1±201.8 mg/day and 26.2±6.5 mg/day for the clozapine and olanzapine groups, respectively. Negative symptoms as measured by the SANS showed significantly greater improvement in the clozapine group than in the olanzapine group at 12 weeks (p = 0.02) and at 24 weeks (p = 0.06). There was significantly greater improvement in CGI–I with olanzapine than with clozapine at 24 weeks (p = 0.007). No significant differences were observed between the groups for the BPRS, CGAS, or CGI–S.

An 8-week prospective cohort study (N = 23) compared the efficacy of clozapine (317±147 mg/day) and olanzapine (17.5±2.3 mg/day) in children ages 6 to 18 with schizophrenia.[95] Patients were assessed using the BPRS, SANS, and Scale for the Assessment of Positive Symptoms. The clozapine group showed a greater change from baseline on all outcome scales; however, statistical comparisons between the groups were not reported.

Twenty-five children ages 7 to 16 with schizophrenia were randomized to receive clozapine (327±113 mg/day) or olanzapine (18.1±4.3 mg/day) in an 8-week RCT with a 2-year extension.[87] The clozapine group showed significantly greater improvement on the CGI–S (p = 0.04) and SANS (p = 0.003) than the olanzapine group. There was no difference between groups in the BPRS–24 or Scale for the Assessment of Positive Symptoms.

Three studies (two RCTs[81,87] and one prospective cohort study[95]) provided data for a meta-analysis comparing clozapine with olanzapine on the BPRS (Figure 33). The pooled mean difference of the trials and the cohort study showed no significant difference between the drugs.

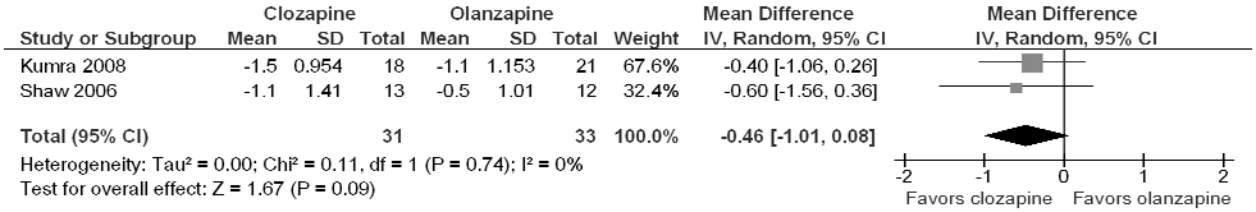
Figure 33. Clozapine versus olanzapine on BPRS in schizophrenia and related psychosis



BPRS = Brief Psychiatric Rating Scale; CI = confidence interval; df = degrees of freedom; IV = inverse variance; RCT = randomized controlled trial; SD = standard deviation

The two trials[81,87] comparing clozapine with olanzapine were pooled for CGI–S (Figure 34). The pooled estimate favored clozapine for reduction in symptom severity; however, the finding was not significant (MD = -0.46; 95% CI, -1.01 to 0.08). There was no evidence of heterogeneity ($p = 0.74$, $I^2 = 0\%$).

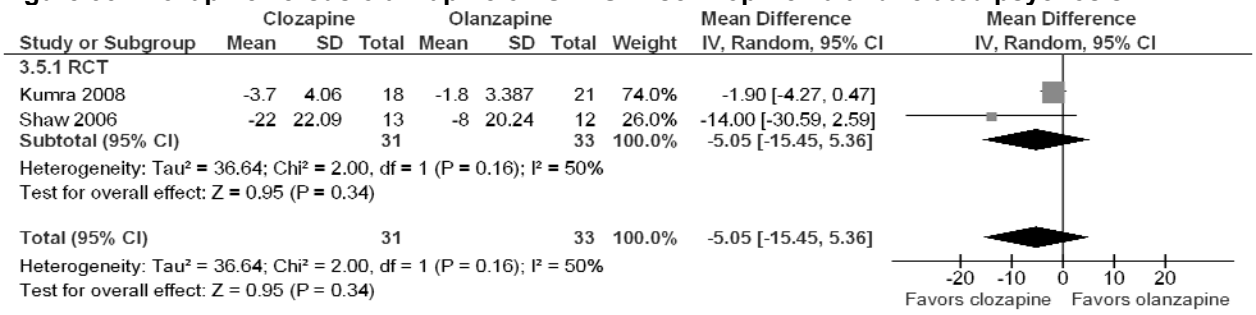
Figure 34. Clozapine versus olanzapine on CGI–S in schizophrenia and related psychosis



CGI–S = Clinical Global Impressions–Severity; CI = confidence interval; df = degrees of freedom; IV = inverse variance; SD = standard deviation

The same trials[81,87] also provided data for a meta-analysis of negative symptoms, as measured by the SANS (Figure 35). The pooled analysis showed no significant difference between the two SGAs on improvement in negative symptoms (MD = -5.05, 95% CI, -15.45 to 5.36). There was substantial heterogeneity between the two trials ($p = 0.16$, $I^2 = 50\%$), which may be attributable to the higher mean dose of olanzapine in the study by Kumra et al.[81]

Figure 35. Clozapine versus olanzapine on SANS in schizophrenia and related psychosis



CI = confidence interval; df = degrees of freedom; IV = inverse variance; RCT = randomized controlled trial; SANS = Scale for the Assessment of Negative Symptoms; SD = standard deviation

Olanzapine Versus Quetiapine

Two studies compared olanzapine with quetiapine.[74,79] A 6-month RCT (N = 50) enrolled adolescents experiencing a first episode of psychosis.[74] Patients had a variety of diagnoses, including bipolar disorder, schizophrenia, major depressive episode with psychotic features, schizoaffective disorder, schizophreniform disorder, and psychosis not otherwise specified. The mean dosage of the drugs was 9.7±6.6 mg/day and 532.8±459.6 mg/day for olanzapine and quetiapine, respectively. There was a significant difference between the groups for Strengths and Difficulties Questionnaire as rated by patients favoring olanzapine (p = 0.03). No differences were found for the CGAS, CGI–S, PANSS, or YMRS.

A 12-week RCT (N = 30) compared the efficacy of olanzapine (14±4.6 mg/day), quetiapine (611±253.4 mg/day), and risperidone (3.4±1.5 mg/day) in children ages 10 to 18 with schizophrenia-related conditions.[79] Patients had schizophrenia, schizoaffective disorder, schizophreniform disorder, and psychotic disorder not otherwise specified. Patients were assessed using the CGI–S, and no difference was found among groups.

Olanzapine Versus Risperidone

Olanzapine was compared with risperidone in six studies.[79,83,88,89,92,96] One 12-week RCT (N = 30) described above compared the efficacy of olanzapine, quetiapine, and risperidone in children ages 10 to 18 with schizophrenia-related conditions.[79] There was no difference between the groups in CGI–S scores at endpoint.

A 12-week RCT (N = 25) compared the efficacy of olanzapine (8.2±4.4 mg/day) and risperidone (1.6±1 mg/day) in children ages 8 to 14 with schizophrenia.[83] No significant differences were found between groups on the BPRS, CGAS, or PANSS.

Ratzoni et al.[96] conducted a 12-week, three-arm prospective cohort study (N = 50) comparing olanzapine (12.7±3.1 mg/day), risperidone (3.2±1.1 mg/day), and haloperidol (7.6±4 mg/day) (described previously). Changes in positive and negative symptoms did not differ significantly between olanzapine and risperidone on the PANSS.

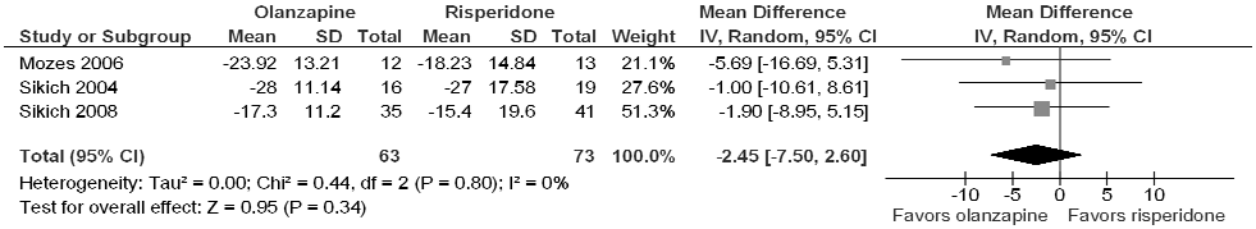
An 8-week RCT (N = 78) with a 44-week extension compared olanzapine (11.4±5 mg/day) and risperidone (2.8±1.4 mg/day) in children and adolescents ages 8 to 19 with schizophrenia-related disorders.[88] Patients had a variety of comorbidities, including ADHD (n = 22), anxiety disorder (n = 21), affective disorder (n = 19), and disruptive behavior disorders (n = 16). No significant differences were observed between the groups for the BPRS–C, CGI–I, CGI–S, or PANSS.

An 8-week RCT (N = 50) described previously compared olanzapine (12.3±3.5 mg/day), risperidone (4±1.2 mg/day), and haloperidol (5±2 mg/day) in children with psychosis.[89] No significant differences were observed between olanzapine and risperidone for the BPRS–C, CPRS, CGI–I, or CGI–S.

An RCT (N = 44) by van Bruggen et al.[92] compared the efficacy of olanzapine (15.6±4 mg/day) and risperidone (4.4±1.5 mg/day) in patients ages 16 to 28 with schizophrenia, schizophreniform disorder, or schizoaffective disorder who were experiencing a first or second psychotic episode. Change in positive and negative symptoms on the PANSS was not significantly different between the groups.

Three studies[83,88,89] comparing olanzapine with risperidone reported data for the BPRS (Figure 36). The meta-analysis showed no significant difference between the two SGAs (MD = -2.45; 95% CI, -7.50 to 2.60). There was no evidence of heterogeneity (p = 0.80, I^2 = 0%).

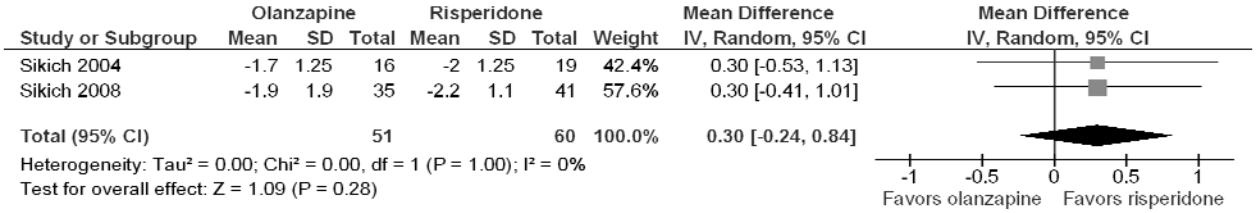
Figure 36. Olanzapine versus risperidone on BPRS in schizophrenia and related psychosis



BPRS = Brief Psychiatric Rating Scale; CI = confidence interval; df = degrees of freedom; IV = inverse variance; SD = standard deviation

Two RCTs[88,89] provided data for a meta-analysis of CGI–S scores (Figure 37). A study by Jensen et al.[79] could not be included in this analysis because it reported the proportion of patients who attained a certain CGI–S threshold instead of the change scores. No significant difference between olanzapine and risperidone was found (MD = 0.30; 95% CI, -0.24 to 0.84). There was no evidence of heterogeneity (p = 1.00, I^2 = 0%).

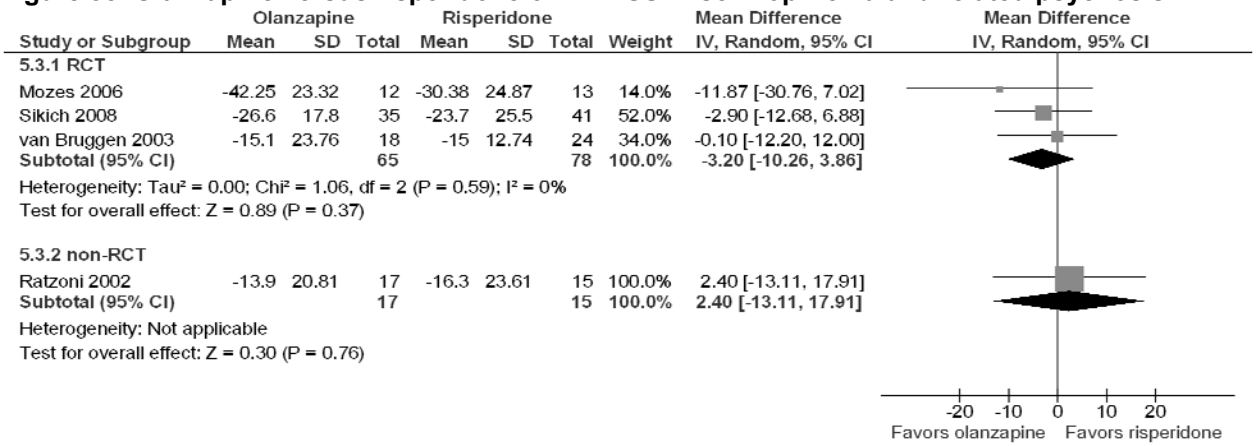
Figure 37. Olanzapine versus risperidone on CGI–S in schizophrenia and related psychosis



CGI–S = Clinical Global Impressions–Severity; CI = confidence interval; df = degrees of freedom; IV = inverse variance; SD = standard deviation

Four studies (three RCTs[83,88,92] and one prospective cohort study[96]) compared olanzapine and risperidone for treating positive and negative symptoms (Figure 38). The pooled results of the three trials showed no significant difference between the SGAs (MD = -3.20; 95% CI, -10.26, 3.86) and no evidence of heterogeneity (p = 0.59, I^2 = 0%). A similar nonsignificant finding was observed in the cohort study.

Figure 38. Olanzapine versus risperidone on PANSS in schizophrenia and related psychosis



CI = confidence interval; df = degrees of freedom; IV = inverse variance; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SD = standard deviation

Quetiapine Versus Risperidone

A 6-week RCT (N = 22) compared quetiapine (607 mg/day) and risperidone (2.9 mg/day) in adolescents 19 and younger experiencing a first episode of psychosis.[91] No significant difference between the risperidone and quetiapine groups for improvement in total positive and negative symptoms was found.

Aripiprazole–Low- Versus High-Dose

A total of 302 adolescents with schizophrenia ages 13 to 17 were randomized to low- or high-dose aripiprazole or placebo in a 6-week RCT.[77] The mean dose of the drugs was 9.8 mg/day and 28.9 mg/day for the low- and high-dose aripiprazole groups, respectively. No significant differences occurred between the low- and high-dose aripiprazole groups on the CGAS, CGI–I, CGI–S, or PANSS.

Paliperidone–Low- Versus Medium- Versus High-Dose

Robb et al.[86] compared three doses of extended-release paliperidone and placebo in a 6-week RCT (N = 201) of adolescents ages 12 to 17 with schizophrenia. Patients weighing less than 51 kg received 1.5, 3, or 6 mg, whereas patients weighing at least 51 pounds received 1.5, 6, or 12 mg in the low-, medium-, and high-dose groups, respectively. No significant differences occurred between the drug doses on the CGAS, CGI–S, PANSS, or VAS for sleep**.**

Quetiapine–Low- Versus High-Dose

Two RCTs compared two doses of quetiapine. Berger et al.[75] examined 141 patients ages 15 to 25 with first-episode psychosis in a 4-week RCT. The mean drug dose was 200 mg/day and 400 mg/day for low- and high-dose quetiapine, respectively. Symptom severity decreased in both the low- and high-dose groups following the 8-week extension period, but the reduction was significantly greater in the high-dose quetiapine group (CGI–S, $p = 0.03$). No significant differences between groups occurred for the BPRS, Global Assessment of Functioning, SANS, Social and Occupational Functioning Assessment Scale, or YMRS.

A 6-week placebo-controlled RCT (N = 222) examined the efficacy of low- (400 mg/day) and high-dose (800 mg/day) quetiapine in adolescents ages 13 to 17 with schizophrenia.[84] No significant differences between the dosing groups occurred on the CGAS, CGI–I, CGI–S, or PANSS.

Risperidone–Low- Versus High-Dose

An 8-week RCT (N = 275) compared the efficacy of low- (0.4 mg/day) and high-dose (4 mg/day) risperidone in adolescents ages 13 to 17.[78] Patients were assessed using the CGI–I, CGI–S, and PANSS. The high-dose risperidone group showed greater symptom improvement than the low-dose group on all three scales ($p<0.001$).

A 6-week placebo-controlled RCT (N = 158) compared the efficacy of low- (1–3 mg/day) and high-dose (4–6 mg/day) risperidone in adolescents ages 13 to 17.[69] Patients were assessed using the CGAS, CGI–I, CGI–S, and PANSS. No significant differences were observed between the two dosing groups for any of the outcomes.

We did not pool the results of these two studies in a meta-analysis because the doses used in the studies were not equivalent.

Ziprasidone–Low- Versus High-Dose

DelBello et al.[42] conducted a 3-week RCT comparing the efficacy of low- (80 mg/day) and high-dose (160 mg/day) ziprasidone for treating children ages 10 to 17 with bipolar mania, schizophrenia, and schizoaffective disorder. Separate analyses were provided for the 17 patients with schizophrenia. Patients were assessed using the BPRS and CGI–S. No significant differences were found between the groups.

FGAs Versus Placebo

An 8-week crossover RCT (N = 16) compared haloperidol (2 mg/day) with placebo in children ages 5 to 11 with schizophrenia.[90] Patients were assessed using the BPRS–C, CGI–I, CGI–S, and CPRS. Both the positive and negative syndrome scores on the CPRS improved significantly in the haloperidol group compared with the placebo group ($p<0.01$). Statistical comparisons between the two groups were not reported for the remaining outcome measures.

SGAs Versus Placebo

Seven studies compared a SGA with placebo: aripiprazole,[77] olanzapine,[80,93] paliperidone,[86] quetiapine,[84] risperidone,[69] and ziprasidone.[85]

Aripiprazole Versus Placebo

Findling et al.[77] conducted an RCT (N = 302) to compare the efficacy of low- and high-dose aripiprazole with placebo (described previously). Patients were assessed using the CGAS, CGI–I, CGI–S, and PANSS. Both the low- and high-dose aripiprazole groups were significantly more effective in improving symptoms than placebo for all outcomes ($p\leq0.05$).

Olanzapine Versus Placebo

A 6-week placebo-controlled RCT (N = 107) with a 6-month extension phase examined the efficacy of olanzapine (11.1 mg/day) in adolescents ages 13 to 18 years with schizophrenia.[80] The olanzapine group showed significant improvements over placebo for the BPRS–C, CGI–I, CGI–S, OAS, and PANSS ($p\leq0.05$).

A second RCT (N = 60) compared olanzapine (8±3.1 mg/day) with placebo in patients (ages 12 to 45 years, mean age of 17.7 years) with prodromal syndrome.[93] The study endpoint was 1 year, with a 1-year extension. No significant differences were found between the groups on the CGI–S, Global Assessment of Functioning, PANSS, or YMRS.

Paliperidone Versus Placebo

A 6-week RCT (N = 201) compared the efficacy of three doses of extended-release paliperidone and placebo in adolescents ages 12 to 17.[86] One hundred forty-three patients had a diagnosis of paranoid schizophrenia, and 58 had other schizophrenia spectrum diagnoses. The medium-dose paliperidone group showed statistical superiority compared with the placebo group on the CGAS ($p<0.001$). There were no significant differences on the CGI–S, PANSS, or VAS sleep.

Quetiapine Versus Placebo

A 6-week RCT (N = 222) compared the efficacy of low- and high-dose quetiapine and placebo (described previously).[84] Patients were assessed using the CGAS, CGI–I, CGI–S, and PANSS. Compared with the placebo group, both low- and high-dose quetiapine showed

significantly greater improvement for the CGI–I and PANSS ($p<0.05$). The high-dose group was superior to placebo for the CGAS ($p = 0.02$) and CGI–S ($p = 0.02$).

Risperidone Versus Placebo

A 6-week RCT (N = 158) compared the efficacy of low- (1–3 mg/day) and high-dose (4–6 mg/day) risperidone with placebo (described previously).[69] Patients receiving risperidone had significantly greater improvement on the CGAS, CGI–I, CGI–S, and PANSS than patients receiving placebo.

Ziprasidone Versus Placebo

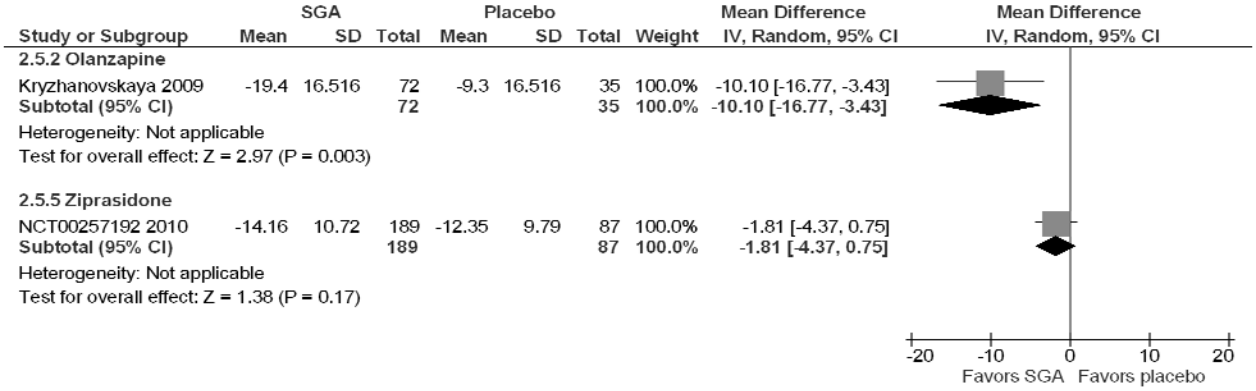
A 6-week placebo-controlled RCT examined treatment with ziprasidone in 284 adolescents ages 13 to 17 years with schizophrenia.[85] The target dose was 60 to 80 mg/day for patients <45 kg and 120 to 160 mg/day for patients ≥45 kg. There was no difference in symptom change on the BPRS–anchored version between the groups.

Meta-analyses Comparing Various SGAs With Placebo

Meta-analyses were conducted to compare various SGAs with placebo for the BPRS, CGAS, CGI–I, CGI–S, and PANSS.

Two RCTs compared two SGAs (olanzapine[80] and ziprasidone[85]) with placebo using BPRS scores (Figure 39). Results were not pooled because of considerable heterogeneity ($p = 0.02$, $I^2 = 81\%$). The heterogeneity is possibly attributable to the use of different SGAs.

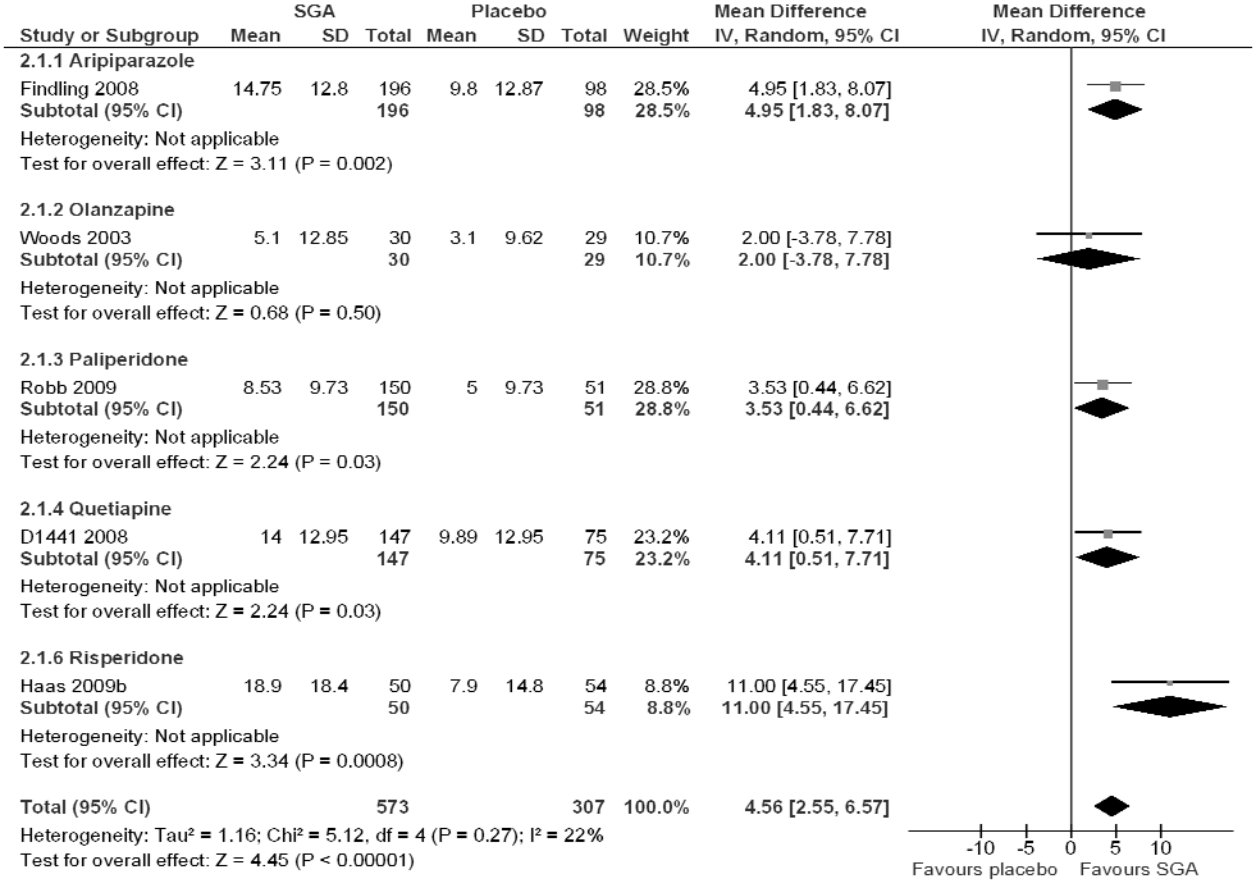
Figure 39. SGAs versus placebo on BPRS in schizophrenia and related psychosis



BPRS = Brief Psychiatric Rating Scale; CI = confidence interval; IV = inverse variance; SD = standard deviation; SGA = second-generation antipsychotic

Five RCTs[69,77,84,86,93] contributed data to a meta-analysis comparing SGAs with placebo on the CGAS (Figure 40). With the exception of one study examining olanzapine,[93] all trials significantly favored the SGAs. The pooled estimate showed a significant improvement in CGAS scores for SGAs compared with placebo (MD = 4.56; 95% CI, 2.55 to 6.57). Heterogeneity was minimal ($p = 0.27$, $I^2 = 22\%$).

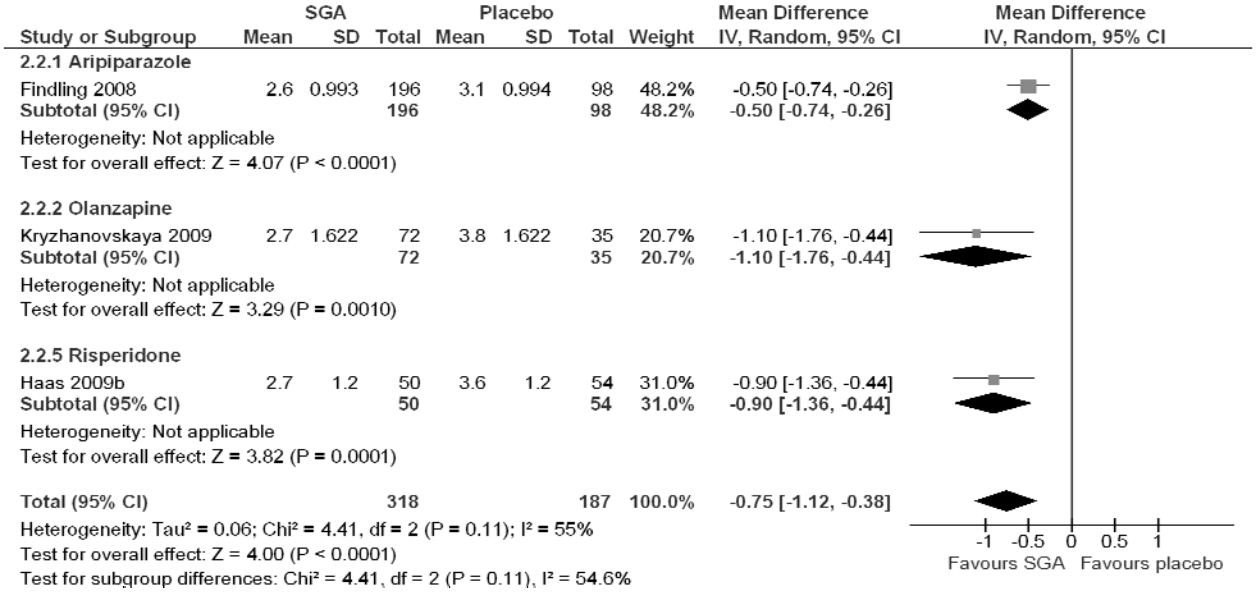
Figure 40. SGAs versus placebo on CGAS in schizophrenia and related psychosis



CI = confidence interval; CGAS = Children's Global Assessment Scale; df = degrees of freedom; IV = inverse variance; SD = standard deviation; SGA = second-generation antipsychotic

Three RCTs comparing aripiprazole,[77] olanzapine,[80] and risperidone[69] with placebo reported CGI–I scores (Figure 41). The pooled estimate significantly favored SGAs over placebo (MD = -0.75; 95% CI, -1.12 to -0.38). There was substantial heterogeneity between the studies (p = 0.11, I^2 = 55%), which was driven by differences between the SGA comparators.

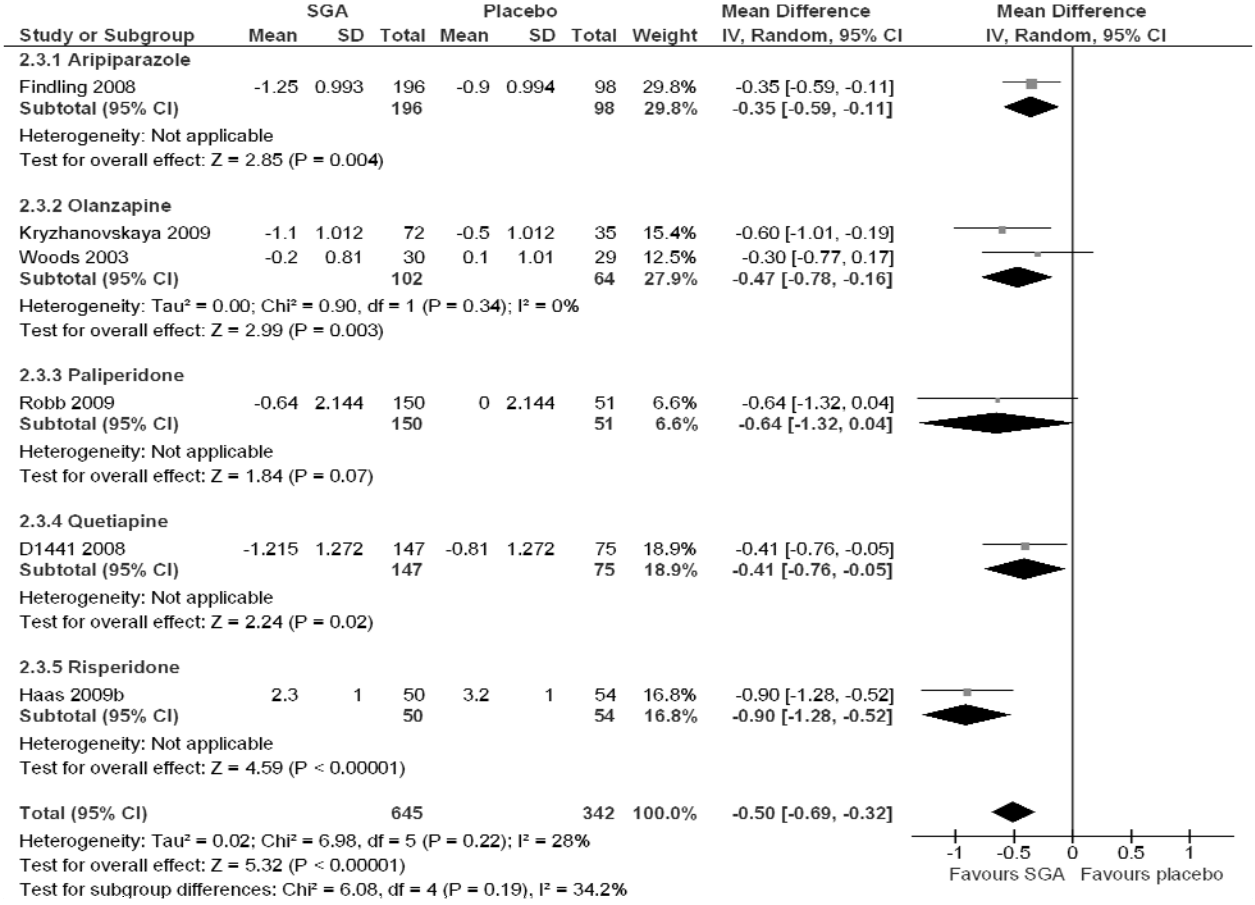
Figure 41. SGAs versus placebo on CGI–I in schizophrenia and related psychosis



CGI–I = Clinical Global Impressions–Improvement; CI = confidence interval; df = degrees of freedom; IV = inverse variance; SD = standard deviation; SGA = second-generation antipsychotic

Six RCTs[69,77,80,84,86,93] provided data for a meta-analysis comparing SGAs with placebo for global impression of severity (Figure 42). Patients treated with SGAs had a statistically greater reduction in symptom severity than those receiving placebo (MD = -0.50; 95% CI, -0.69 to -0.32). There was evidence of moderate heterogeneity due to differences in the SGAs ($p = 0.22$, $I^2 = 28\%$).

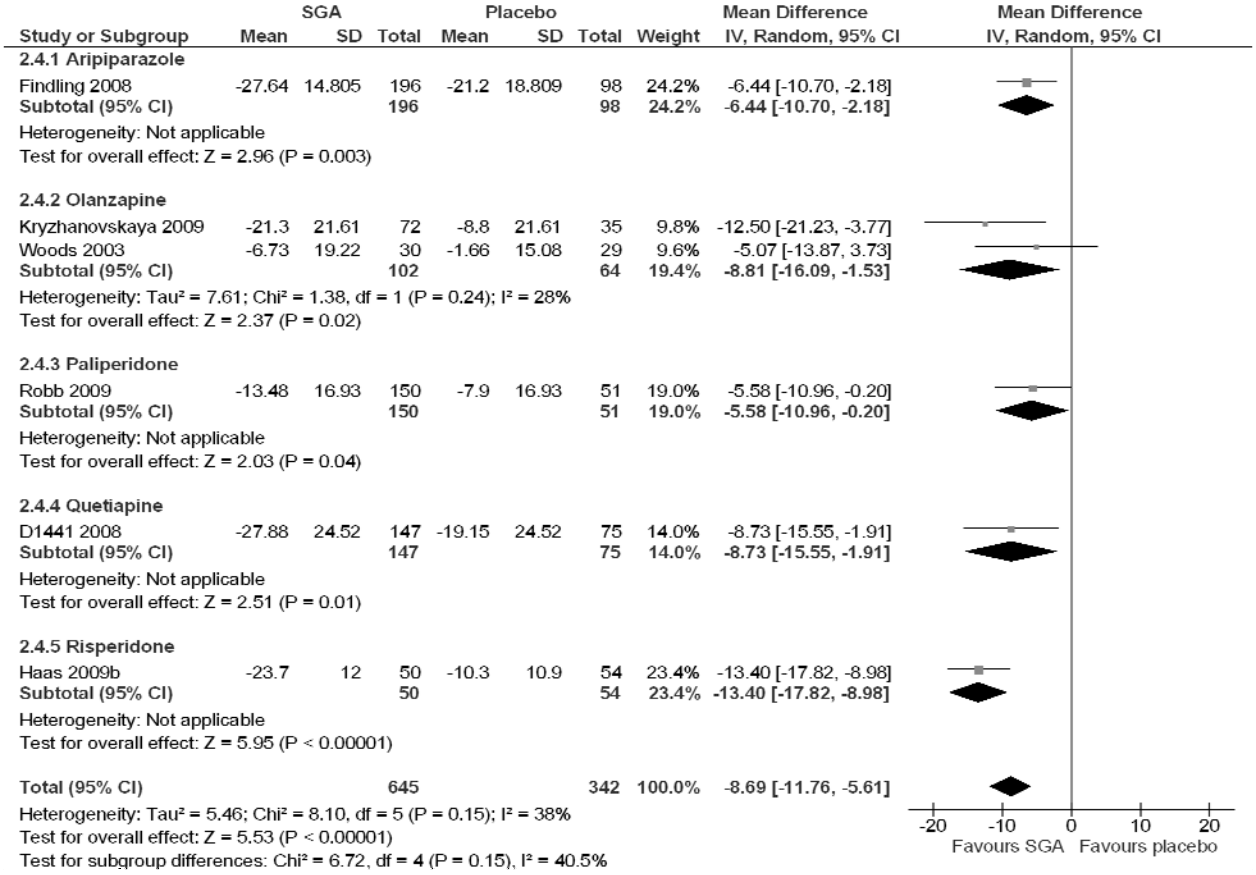
Figure 42. SGAs versus placebo on CGI–S in schizophrenia and related psychosis



CGI–S = Clinical Global Impressions–Severity; CI = confidence interval; df = degrees of freedom; SD = standard deviation; SGA = second-generation antipsychotic

The results of six RCTs[69,77,80,84,86,93] reporting positive and negative symptoms of schizophrenia using the PANSS were combined in a meta-analysis (Figure 43). The pooled estimate found SGAs to be superior to placebo in reducing positive and negative symptoms (MD= -8.69; 95% CI, -11.76 to -5.61). There was evidence of moderate heterogeneity due to the different SGAs ($p = 0.15$, $I^2 = 38\%$).

Figure 43. SGAs versus placebo on PANSS in schizophrenia and related psychosis



CI = confidence interval; df = degrees of freedom; IV = inverse variance; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; SGA = second-generation antipsychotic

Schizophrenia and Related Psychosis: Short- and Long-Term Outcomes (Key Question 3)

Twenty-two studies provided data on a variety of short- and long-term outcomes for patients with schizophrenia and related psychosis. A summary of the results is presented by outcome below. Table 21 provides the strength of evidence grades for all key outcomes that were reported by at least one study.

- Response and remission: Treatment response was reported in 14 studies and defined variably across the studies.[69,75,78-81,83,84,87-89,91,92,95] Two RCTs[69,78] compared low- and high-dose risperidone. One study[78] found a significantly greater response rate in patients receiving high-dose risperidone (p<0.001); however, the second study[69] found no difference between the dosing groups. A meta-analysis of two studies found a significant difference favoring SGAs over placebo (RR = 1.64; 95% CI, 1.26 to 2.13). One study[77] found a significantly higher remission rate in patients treated with aripiprazole than placebo.
- Cognitive and emotional development: An RCT[74] comparing olanzapine and quetiapine reported no significant differences between groups on cognitive functioning, including attention, working memory, learning, memory, and executive functions.

- Suicide-related behaviors: Four studies[69,75,77,88] reported suicide rates. One death by suicide occurred in each of two studies.[75,88] Three studies[78,80,86] examining SGAs reported that no suicide-related behaviors occurred. Suicidal ideation was also rare in four studies[42,78,85,88] and did not differ between groups.
- Medication adherence and persistence: Eleven studies[74-76,78-80,88,89,92,93,96] reported patient adherence to medication. All studies found no significant difference between groups for adherence rate.
- Legal or justice system interaction: One RCT[75] comparing low- and high-dose quetiapine reported incarceration, which occurred in one patient in the high-dose group. The difference between the groups was not significant.
- Patient-, parent-, or care provider–reported outcomes: One RCT[84] found a significant improvement on CSQ favoring low-dose quetiapine over placebo. No significant difference was observed between high-dose quetiapine and placebo.
- Health-related quality of life: One small RCT[76] comparing haloperidol with olanzapine found no significant differences between groups on the Subjective Wellbeing under Neuroleptics scale. A second RCT comparing two doses of aripiprazole and placebo found no difference between groups on the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire.[77]
- Health care system utilization: One RCT[75] reported the hospital admission rate and number of days in hospital for patients treated with low- or high-dose quetiapine. The hospital admission rate was significantly higher in the low-dose quetiapine group ($p = 0.005$). The duration of hospital stay did not differ significantly between groups.
- Other outcomes: No studies provided data for the following outcome categories: growth and maturation, school performance, work-related functional capacity, or patient insight into illness.

Table 21. Strength of evidence for schizophrenia and related psychosis (Key Question 3)

Comparison	Outcome (N Studies; N Patients)	Strength of Evidence Domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
FGAs vs. SGAs	HRQL (1; 24)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Medication adherence (3; 124)	Moderate	Consistent	Direct	Imprecise	Low
Olanzapine vs. quetiapine	Medication adherence (2; 80)	Moderate	Consistent	Direct	Imprecise	Low
Olanzapine vs. risperidone	Medication adherence (5; 237)	Moderate	Consistent	Direct	Imprecise	Low
	Suicide (1; 78)	Moderate	Unknown	Direct	Imprecise	Insufficient
Low- vs. high-dose aripiprazole	HRQL (1; 302)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Suicide (1; 302)	Moderate	Unknown	Direct	Imprecise	Insufficient
Low- vs. high-dose paliperidone	Suicide (1; 201)	Moderate	Unknown	Indirect	Imprecise	Insufficient

Table 21. Strength of evidence for schizophrenia and related psychosis (Key Question 3) (continued)

Comparison	Outcome (N Studies; N Patients)	Strength of Evidence Domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Low- vs. high-dose quetiapine	Legal system interactions (1; 141)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Medication adherence (1; 141)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Patient-, parent-, or care provider–reported outcomes (1; 222)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Suicide (1; 141)	Moderate	Unknown	Direct	Imprecise	Insufficient
Low- vs. high-dose risperidone	Medication adherence (1; 257)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Suicide (2; 361)	Moderate	Consistent	Direct	Not pooled	Insufficient
Low- vs. high-dose ziprasidone	Suicide (1; 17)	Moderate	Unknown	Indirect	Imprecise	Insufficient
SGA vs. placebo	HRQL (1; 302)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Medication adherence (2; 167)	Moderate	Consistent	Direct	Imprecise	Low
	Patient-, parent-, or care provider–reported outcomes: Caregiver strain (1; 222)	Moderate	Unknown	Direct	Precise	Insufficient
	Suicide (5; 990)	Moderate	Consistent	Direct	Not pooled	Low

FGA = first-generation antipsychotic; HRQL = health-related quality of life; N = number; ROB = risk of bias; SGA = second-generation antipsychotic

A detailed analysis of the results is provided below. Data from head-to-head comparisons are presented, followed by placebo comparisons.

FGAs Versus SGAs

Three studies (two RCTs[76,89] and one prospective cohort study[96]) compared FGAs and SGAs. Haloperidol was compared with olanzapine[76,89,96] and risperidone.[89,96]

Haloperidol Versus Olanzapine

A 6-week RCT (N = 24) compared the efficacy of haloperidol (2.5 mg/day) and olanzapine (7.5 mg/day) in adolescents and young adults ages 17 to 26 years with schizophrenia.[76] No significant differences between groups were found for the Subjective Well-being Under Neuroleptics scale or medication adherence.

Haloperidol Versus Olanzapine Versus Risperidone

A 12-week prospective cohort study (N = 50) compared the effectiveness of haloperidol (7.6±4 mg/day), olanzapine (12.7±3.1 mg/day), and risperidone (3.2±1.1 mg/day) in adolescents ages 13 to 20 years.[96] Nonadherence did not differ significantly among the three groups.

Patients ages 8 to 19 years with affective disorders (n = 24) and schizophrenia spectrum disorder (n = 26) were randomized to haloperidol (5±2 mg/day), olanzapine (12.3±3.5 mg/day), and risperidone (4±1.2 mg/day) in an 8-week RCT.[89] Patients were assessed for treatment response (CGI–I≤2 and a reduction of ≥20 percent on the BPRS–C total score) and nonadherence. No significant differences between the groups were observed.

SGAs Versus SGAs

A total of 18 studies evaluated SGAs, of which 11 examined head-to-head comparisons of different SGAs, and 7 compared doses of the same SGA.

Clozapine Versus Olanzapine

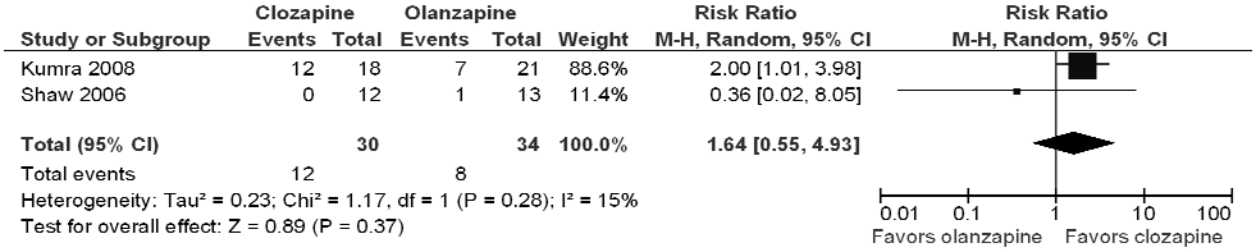
Three studies compared the effect of clozapine and olanzapine on short- and long-term outcomes. A 12-week RCT (N = 40) with a 12-week extension phase compared the efficacy of clozapine (403.1±201.8 mg/day) and olanzapine (26.2±6.5 mg/day) in children ages 10 to 18 years with schizophrenia or schizoaffective disorder.[81] Treatment response was defined as a reduction greater than 30 percent in BPRS score and CGI–I<2 points at endpoint. Significantly more patients responded to treatment in the clozapine group than in the olanzapine group (p = 0.038).

A prospective cohort study compared the efficacy of clozapine (317±147 mg/day) and olanzapine (17.5±2.3 mg/day) in 23 patients ages 6 to 18 years with schizophrenia.[95] The duration of followup was 6 weeks in the clozapine group and 8 weeks in the olanzapine group. Rates of response, partial response at 6 weeks, and full or partial response at 8 weeks did not significantly differ between groups.

Shaw et al.[87] compared the efficacy of clozapine (327±113 mg/day) and olanzapine (18.1±4.3 mg/day) for the treatment of children ages 7 to 16 years in an 8-week RCT with a 2-year extension phase (N = 25). Treatment response was assessed as either full response (20 percent reduction in BPRS–24 score and CGI–S<3 or BPRS total score<35) or partial response (20 percent reduction in BPRS–24 score) and did not differ significantly between groups.

Two RCTs[81,87] provided data for a meta-analysis comparing clozapine and olanzapine for treatment response rate (Figure 44). The pooled estimate of the trials showed no significant difference between the two SGAs (RR = 1.64; 95% CI, 0.55 to 4.93). Heterogeneity was minimal (p = 0.28, I^2 = 15%).

Figure 44. Clozapine versus olanzapine on response rate in schizophrenia and related psychosis



CI = confidence interval; df = degrees of freedom; M–H = Mantel–Haenszel

Olanzapine Versus Quetiapine

Two RCT compared olanzapine and quetiapine. An RCT conducted by Arango et al.[74] examined 50 adolescents ages 12 to 18 with psychosis for 6 months. Diagnoses included bipolar disorder (n = 13), schizophrenia (n = 17), and other psychoses. The mean dose of the drugs was 9.7±6.6 mg/day and 532.8±459.6 mg/day for the olanzapine and quetiapine groups, respectively. Adherence and performance on various cognitive domains (attention, working memory, learning and memory, and executive functions) were compared. No significant differences between the olanzapine and quetiapine groups were found for any of the outcomes.

Jensen et al.[79] randomized 30 patients ages 10 to 18 with schizophrenia-related disorders to olanzapine (14±4.6 mg/day), quetiapine (611±253.4 mg/day), and risperidone (3.4±1.5 mg/day).

The study endpoint was 12 weeks. Response (>40 percent reduction in PANSS scores) and medication adherence did not differ significantly among the groups.

Olanzapine Versus Risperidone

Olanzapine was compared with risperidone in six studies.[79,83,88,89,92,96] One study described above found no difference in response (>40 percent reduction in PANSS scores) or medication adherence between groups.[79]

A 12-week RCT (N = 25) compared olanzapine (8.2±4.4 mg/day) and risperidone (1.6±1 mg/day) in children ages 8 to 14 years with schizophrenia.[83] Patients were assessed using a symptom reduction of 50 percent on both the PANSS and BPRS; neither outcome was significantly different between groups.

Olanzapine (7.6±4 mg/day), risperidone (12.7±3.1 mg/day), and haloperidol (3.2±1.1 mg/day) were compared in a 12-week prospective cohort study (N = 50) of adolescents ages 14 to 20.[96] Nonadherence did not differ among groups.

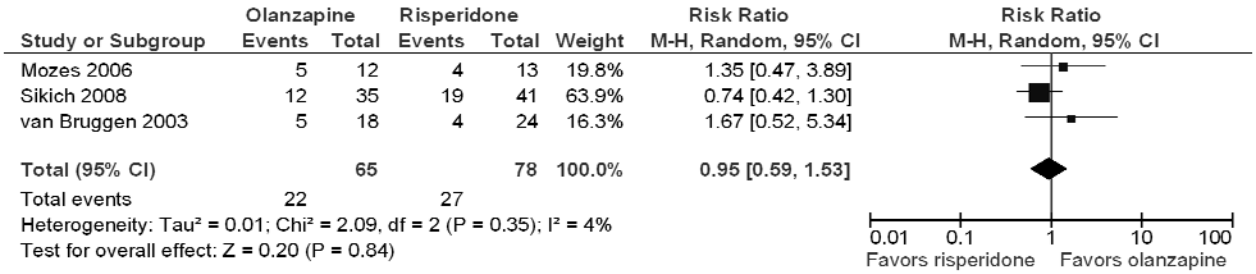
An 8-week RCT (N = 78) with a 44-week extension phase examined the efficacy of olanzapine (11.4±5 mg/day) and risperidone (2.8±1.4 mg/day) in children and adolescents ages 8 to 19 with schizophrenia-related disorders.[88] Rate of treatment response (CGI–I<2 and >20 percent reduction in PANSS score after 8 weeks of treatment) and nonadherence did not differ significantly between groups. Other criteria for response based on the CGI–I, Hamilton Rating Scale for Depression, and YMRS similarly showed no difference between groups. In the risperidone group, one patient reported suicidal ideation, and one patient died by suicide.

Sikich et al.[89] conducted an RCT to compare the efficacy of olanzapine, risperidone, and haloperidol (described previously). Olanzapine and risperidone were not significant different for response or medication adherence.

An RCT (N = 44) conducted by van Bruggen et al.[92] compared the efficacy of olanzapine (15.6±4 mg/day) and risperidone (4.4±1.5 mg/day) in patients ages 16 to 28 with schizophrenia, schizophreniform disorder, or schizoaffective disorder. The mean followup period was 9.8 weeks in the olanzapine group and 6.7 weeks in the risperidone group. Treatment response was defined as a PANSS score of less than mild at endpoint. No significant differences were found between the groups for response, time to response, or medication adherence.

Three RCTs[83,88,92] compared olanzapine and risperidone for treatment response rate (Figure 45). The pooled result showed no difference between the SGAs (RR = 0.95; 95% CI, 0.59 to 1.53). Heterogeneity was negligible (p = 0.35, I^2 = 4%).

Figure 45. Olanzapine versus risperidone on response rate in schizophrenia and related psychosis



CI = confidence interval; df = degrees of freedom; IV = inverse variance; M–H = Mantel–Haenszel

Quetiapine Versus Risperidone

An RCT (N = 22) evaluated the efficacy of quetiapine (607 mg/day) and risperidone (2.9 mg/day) in adolescents under 19 years old with first onset psychosis.[91] Patients were assessed for response using a 30 percent reduction criterion on each of following scales at 3 and 6 weeks: PANSS, BPRS, CGI–S, Hamilton Rating Scale for Depression, and YMRS. No significant difference was found between the groups for treatment response or medication adherence.

Aripiprazole–Low- Versus High-Dose

A 6-week RCT (N = 302) compared low- (9.8 mg/day) and high-dose (28.9 mg/day) aripiprazole and placebo in adolescents ages 13 to 17 with schizophrenia.[77] The two doses of aripiprazole were not significantly different for remission rate (PANSS<3 for specific items) or quality of life. No patients died by suicide.

Paliperidone–Low- Versus Medium- Versus High-Dose

Low-, medium-, and high-dose extended release paliperidone were compared in a placebo-controlled 6-week RCT (N = 201) of adolescents ages 12 to 17 with schizophrenia.[86] No patients exhibited suicidal behavior.

Quetiapine–Low-Versus High-Dose

Two RCTs compared two doses of quetiapine. Doses of 400 mg/day and 800 mg/day were compared in a 6-week RCT (N = 222) of adolescents ages 13 to 17 with schizophrenia.[84] Treatment response (reduction >30 percent from baseline in PANSS total score) did not differ significantly between the groups. There was also no difference between the groups on the CSQ scores.

A 4-week RCT (N = 141) compared 200 mg/day and 400 mg/day doses of quetiapine in patients ages 15 to 25 years experiencing a first episode of psychosis.[75] Treatment response (BPRS psychotic subscales<3 and CGI–I<2) and remission (BPRS psychotic subscales<3, CGI–S<3, and CGI–I<2) did not differ between groups. Hospital admission rate was significantly lower in the high-dose group ($p = 0.005$). Deaths by suicide, imprisonments, days in hospital, and medication adherence did not differ significantly between groups.

Risperidone–Low- Versus High-Dose

An 8-week RCT (N = 275) compared the efficacy of low- (0.4 mg/day) and high-dose (4 mg/day) risperidone in adolescents ages 13 to 17 years with schizophrenia.[78] Sustained response (time until >20 percent change in PANSS score) was significantly higher in the high-dose risperidone group. No patients had a suicide attempt; however, two patients in the low-dose risperidone group reported suicidal ideation. One patient receiving high-dose risperidone was nonadherent.

A 6-week placebo-controlled RCT (N = 158) compared the efficacy of low- (1–3 mg/day) and high-dose (4–6 mg/day) risperidone in adolescents ages 13 to 17 years.[69] The treatment response rate was not significantly different between the dosing groups. No deaths by suicide occurred.

Ziprasidone–Low- Versus High-Dose

A 3-week RCT compared the efficacy of low- (80 mg/day) and high-dose (160 mg/day) ziprasidone in treating children and adolescents ages 10 to 17 years with bipolar mania,

schizophrenia, and schizoaffective disorder.[42] Separate analyses were provided for patients with schizophrenia. One patient in the high-dose group reported suicidal ideation; however, it is unclear whether this patient had bipolar disorder or schizophrenia.

SGAs Versus Placebo

Seven placebo-controlled studies evaluated the efficacy of SGAs on short- and long-term outcome in patients with schizophrenia. The studies evaluated aripiprazole,[77] olanzapine,[80,93] paliperidone,[86] quetiapine,[84] risperidone,[69] and ziprasidone.[85]

Aripiprazole Versus Placebo

Findling et al.[77] conducted a RCT to compare the efficacy of low- and high-dose aripiprazole and placebo in adolescents ages 13 to 17 years with schizophrenia (described previously). Remission rate (PANSS<3 for specific items) was significantly higher in both the low- and high-dose aripiprazole groups than placebo ($p = 0.02$ and $p = 0.003$, respectively). There was no significant difference between aripiprazole and placebo for time to discontinuation or quality of life.

Olanzapine Versus Placebo

A 6-week RCT (N = 107) with a 6-month extension compared olanzapine (11.1 mg/day) with placebo in adolescents ages 13 to 18 years with schizophrenia.[80] Treatment response (reduction >30 percent in BPRS from baseline and CGI–S<3) and time to response did not differ significantly between the groups. No suicide-related behaviors occurred in either group. Nonadherence did not differ between the groups.

Paliperidone Versus Placebo

Robb et al.[86] conducted an RCT to compare the efficacy of low-, medium- and high-dose extended release paliperidone and placebo in adolescents ages 12 to 17 with schizophrenia (described previously). None of the patients exhibited suicide-related behaviors.

Quetiapine Versus Placebo

One RCT[84] compared the efficacy of low- and high-dose quetiapine and placebo in adolescents ages 13 to 17 with schizophrenia (described previously). Compared with the placebo group, scores on the CSQ showed significantly greater improvement in the low-dose quetiapine group ($p = 0.01$). The groups did not differ significantly on rate of treatment response.

Risperidone Versus Placebo

In a 6-week placebo-controlled RCT (N = 158) of adolescents ages 13 to 17 years (described previously), both low- (1–3 mg/day) and high-dose (4–6 mg/day) risperidone had significantly higher response rates than placebo.[69] No deaths by suicide occurred in any of the study groups.

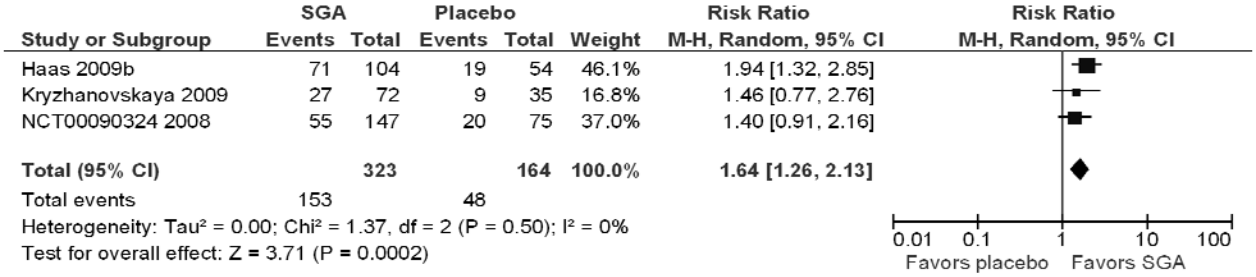
Ziprasidone Versus Placebo

A 6-week RCT[85] (N = 284) evaluated the efficacy of ziprasidone compared with placebo in adolescents ages 13 to 17 years with schizophrenia. The target dose was 60 to 80 mg/day for patients <45 kg and 120 to 160 mg/day for patients ≥45 kg. Three patients reported suicidal ideation in the ziprasidone group, and no patients reported suicide ideation in the placebo group; however, this difference was not significant.

An 8-week placebo-controlled RCT (N = 60) examined the efficacy of olanzapine (8±3.1 mg/day) in patients ages 12 to 45 (mean age of 17.7 years) with prodromal syndrome.[93] Rate of conversion to psychosis and medication adherence were not significantly different between groups.

Three RCTs reported response rate for SGAs versus placebo (Figure 46).[69,80,84] The studies examined olanzapine,[80] quetiapine,[84] and risperidone.[69] The pooled result was significant in favor of SGAs (RR = 1.64; 95% CI, 1.26 to 2.13), and there was no evidence of heterogeneity (p = 0.50, I^2 = 0%).

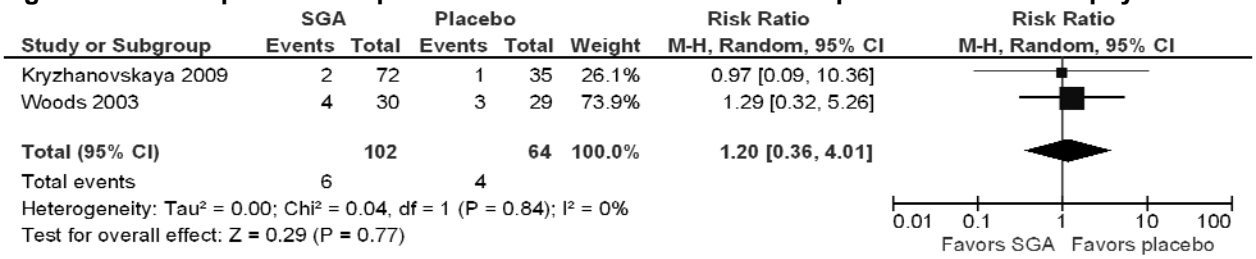
Figure 46. SGAs versus placebo on response rate in schizophrenia and related psychosis



CI = confidence interval; df = degrees of freedom; M–H = Mantel–Haenszel; SGA = second-generation antipsychotic

Two RCTs reported medication adherence rate for olanzapine versus placebo (Figure 47).[80,93] No significant difference in the proportion of patients who were nonadherent was found between the groups (RR = 1.20; 95% CI, 0.36 to 4.01), and there was no evidence of heterogeneity (p = 0.84, I^2 = 0%).

Figure 47. Olanzapine versus placebo on adherence rate in schizophrenia and related psychosis



CI = confidence interval; df = degrees of freedom; M–H = Mantel–Haenszel; SGA = second-generation antipsychotic

Three RCTs provided data on the rate of suicide-related behavior comparing SGAs and placebo.[69,80,86] No events occurred in any of the studies; therefore, meta-analysis was not possible.

Tourette Syndrome: Overview

Six RCTs[97-102] assessed the effectiveness of antipsychotics for treating children with Tourette syndrome. Half of the studies reported both symptom improvement and other short- and long-term outcomes.[99-101] Two studies reported only symptom improvement (Key Question 1),[97,98] and one study reported only other short- and long-term outcomes (Key Question 3).[102]

Table 22 provides selected information on the characteristics of the individual studies. The studies are grouped according to the drug class comparisons. Studies that included both head-to-head and placebo comparisons are listed under the head-to-head category. Within each

comparison, studies are listed alphabetically by the specific drugs compared. A detailed evidence table is available in Appendix D.

Patients enrolled in the study had an average age of 10.6 years and were predominantly male (86 percent). The distribution of patient race was not reported in any of the trials. The diagnosis of Tourette syndrome was based on the DSM–III–TR, DSM–IV, and DSM–IV–TR criteria. Patients had a variety of comorbidities, including ADHD (40 percent), obsessive-compulsive disorder (14 percent), disruptive behavior disorders (5 percent), and learning disorders (3 percent).

One trial compared a FGA (pimozide) with a SGA (risperidone).[97] Two studies[99,100] provided data on the comparative effectiveness of two FGAs, haloperidol and pimozide, one of which included a placebo comparator.[99] A placebo withdrawal study compared short-term and long-term outcomes of treatment of pimozide.[102] Two trials compared SGAs risperidone[101] and ziprasidone[98] with placebo.

Two of the RCTs had a crossover design.[97,99] The duration of treatment ranged from 6 weeks to 8 months. All trials had a high risk of bias, with the exception of one study that had an unclear risk of bias.[99] Sources of possible bias included industry sponsorship, selective outcome reporting, and incomplete outcome data.

Table 22. Characteristics of studies examining Tourette syndrome

Author, Year, Study Design, Duration, KQ	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
FGAs vs. SGAs			
Gilbert et al, 2004[97] RCT (crossover*), 8 wk *KQ1*	G1: Pimozide (7), 2.4 mg/day G2: Risperidone (12), 2.5 mg/day	All groups: NR / Male: NR / White: NR Comorbidities: ADHD (7), CD (1), learning disorder (3), OCD (2), ODD (2)	Chronic tic disorder (3), Tourette syndrome (16) High ROB
FGAs vs. FGAs			
Sallee et al, 1997[99] RCT (crossover), 24 wk *KQ1, KQ3*	G1: Haloperidol (22)*, 3.5±2.2 mg/day G2: Pimozide (22)*, 3.4±1.6 mg/day G3: Placebo (22)*	All groups: NR / Male: NR / White: NR Comorbidities: ADHD (13), OCD (5)	NR Unclear ROB
Sallee et al, 1994[100] RCT, 6 wk (3 wk extension) *KQ1, KQ3*	G1: Haloperidol (17), 1.5±0.6 mg/day G2: Pimozide (24), 3.7±1.4 mg/day	G1: 10.4 yr / Male: NR / White: NR G2: 10.8 yr / Male: NR / White: NR Comorbidities: ADHD (13)	NR High ROB
Sehgal et al, 1999[102] RCT, 8 mo *KQ3*	G1: Pimozide (short-term) (4), 3.8 mg/day G2: Pimozide (long-term) (6), 3.5 mg/day	All groups: NR / Male: NR / White: NR Comorbidities: NR	NR High ROB

Table 22. Characteristics of studies examining Tourette syndrome (continued)

Author, Year, Study Design, Duration, KQ	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
SGAs vs. Placebo			
Scahill et al, 2003[101] RCT, 8 wk *KQ1, KQ3*	G1: Risperidone (12), 2.5±0.9 mg/day G2: Placebo (14)	All groups: NR / Male: NR / White: NR Comorbidities: ADHD (11), OCD (4)	NR High ROB
Sallee et al, 2000[98] RCT, 8 wk *KQ1*	G1: Ziprasidone (16), 28.2±9.6 mg/day G2: Placebo (12)	G1: 11.3 yr / Male: 87.5% / White: NR G2: 11.8 yr / Male: 66.7% / White: NR Comorbidities: ADHD (15), DBD (5), learning disability (2), OCD (10)	NR High ROB

ADHD = attention deficit hyperactivity disorder; CD = conduct disorder; DBD = disruptive behavior disorder; FGA = first-generation antipsychotic; G = group; mg = milligrams; KQ = key question; mo = month; N = number; NR = not reported; OCD = obsessive-compulsive disorder; ODD = oppositional defiant disorder; RCT = randomized controlled trial; ROB = risk of bias; SD = standard deviation; SGA = second-generation antipsychotic; wk = week

*All patients experienced each of the treatment arms in this crossover study; 11 patients had haloperidol before pimozide, whereas another 11 patients had pimozide before haloperidol

Tourette Syndrome: Disorder-Specific and Nonspecific Symptoms (Key Question 1)

Five RCTs reported the effects of FGAs and SGAs on treating disorder-specific and nonspecific symptoms of children with Tourette syndrome. A summary of the results by comparison is presented below. Strength of evidence grades for all key outcomes that were reported by at least one study are provided in Table 23.

- Pimozide versus risperidone (one RCT[97]): Risperidone was shown to be significantly more effective in reducing tic severity than pimozide.
- Haloperidol versus pimozide (two RCTs[99,100]): One study[100] found greater improvement favoring pimozide for the Child Behavior Checklist working hard subscale. A second study found no difference between groups on the CGI or Tic Symptom Self-Report.[99]
- FGAs (haloperidol and pimozide) versus placebo (one RCT[99]): Patients treated with FGAs showed significantly greater improvement in symptom severity and in global assessment compared with placebo.
- SGAs versus placebo (two RCTs examining risperidone[101] and ziprasidone[98]): Treatment with SGAs resulted in greater improvement in tic symptoms than placebo.[98,101] Significant differences were also found in favor of SGAs for global impression of improvement[101] and obsessive-compulsive symptoms.[98] There was no difference between groups for global impressions of severity.

Table 23. Strength of evidence for Tourette syndrome (Key Question 1)

Comparison	Outcome (N Studies; **N Patients**)	Strength of Evidence Domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Pimozide vs. risperidone	Clinical global impressions (1; 19)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Tics (1; 19)	Moderate	Unknown	Direct	Imprecise	Insufficient
Haloperidol vs. pimozide	Clinical global impressions (1; 22)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Social/occupational functioning (1; 41)	Moderate	Unknown	Direct	Imprecise	Insufficient
FGAs vs. placebo	Clinical global impressions (1; 22)	Moderate	Unknown	Direct	Precise	Insufficient
SGA vs. placebo	Clinical global impressions (2; 54)	Moderate	Inconsistent	Direct	Not pooled	Insufficient
	Obsessive compulsive (1; 27)	Moderate	Unknown	Direct	Precise	Insufficient
	Tics (2; 54)	Moderate	Consistent	Direct	Precise	Moderate

FGA = first-generation antipsychotic; N = number; ROB = risk of bias; SGA = second-generation antipsychotic

A detailed analysis of the data on symptom improvement is provided by study below. This section is organized by comparison, with head-to-head data preceding placebo comparisons.

FGAs Versus SGAs

Pimozide Versus Risperidone

A crossover RCT (N = 19) compared the effectiveness of pimozide (2.4 mg/day) and risperidone (2.5 mg/day) in children ages 7 to 17 years with Tourette syndrome.[97] The study duration was 8 weeks, and patients received each drug for 4 weeks. Risperidone was significantly more effective than pimozide at reducing tic severity on the Yale Global Tic Severity Score (YGTSS) ($p = 0.05$). No significant differences between the groups were observed for the CGI or Tic Symptom Self-Report.

FGAs Versus FGAs

Haloperidol Versus Pimozide

Two RCTs compared the effect of haloperidol and pimozide on symptoms in children ages 7 to 16 with Tourette syndrome. Sallee et al.[99] conducted a placebo-controlled crossover RCT (N = 22) to compare the effectiveness of haloperidol (3.5±2.2 mg/day) and pimozide (3.4±1.6 mg/day). Patients initially underwent 2 weeks of placebo treatment and subsequently received 6 weeks of each active treatment in the sequence to which they were assigned. No significant differences were found between groups on the CGAS or CGI–S.

A second RCT (N = 41) by Sallee et al.[100] randomized patients to haloperidol (1.5±0.6 mg/day) or pimozide (3.7±1.4 mg/day) for 8 weeks. Patients were assessed using the school performance, working hard, learning, and function subscales of the Child Behavior Checklist. The pimozide group showed significantly greater improvement on the working hard subscale compared with the haloperidol group ($p<0.05$). No significant differences were found between the groups for any of the other subscales.

FGAs Versus Placebo

A crossover RCT compared the efficacy of both haloperidol and pimozide with placebo (described previously).[99] Symptoms significantly improved from baseline to endpoint in both the haloperidol and pimozide groups compared with the placebo group (CGAS, $p<0.05$; CGI–S, $p = 0.01$).

SGAs Versus Placebo

Two placebo-controlled RCTs evaluated SGAs.[98,101]

Risperidone Versus Placebo

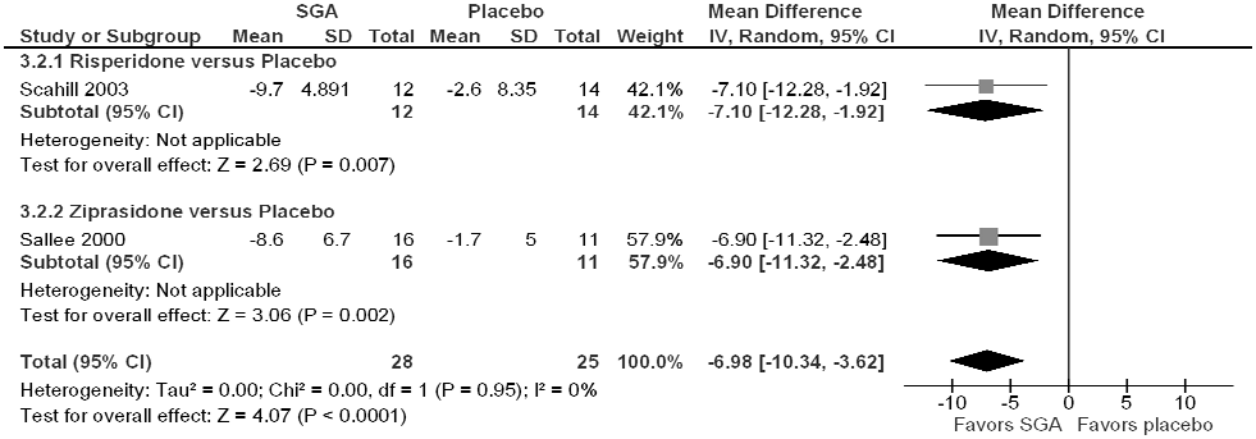
An 8-week RCT compared risperidone (2.5±0.9 mg/day) with placebo in children and adults ages 7 to 65 years with Tourette syndrome.[101] Data were provided separately for a subgroup of 26 pediatric patients (mean age of 11.1±2.2 years). The study found a significant improvement in symptoms in the risperidone group compared with placebo for the CGI–I ($p = 0.003$) and YGTSS ($p = 0.002$).

Ziprasidone Versus Placebo

An 8-week RCT (N = 28) evaluated the efficacy of ziprasidone (28.2±9.6 mg/day) compared with placebo in children ages 7 to 17 years with Tourette syndrome or chronic tic disorder.[98] Tic symptoms and obsessive-compulsive symptoms improved significantly in the ziprasidone group compared with placebo (YGTSS total tic score, $p = 0.008$; YGTSS global severity score, $p = 0.016$; CYBOCS, $p = 0.0003$). There was no significant difference between groups on the CGI–Tourette Syndrome score.

The results of the two RCTs[98,101] comparing SGAs with placebo were pooled for the YGTSS (Figure 48). The combined estimate of change from baseline in tic score shows a significant difference favoring SGAs (MD = -6.98; 95% CI, -10.34 to -3.62). There was no evidence of heterogeneity ($p = 0.95$, $I^2 = 0\%$).

Figure 48. SGAs versus placebo on YGTSS in Tourette syndrome



CI = confidence interval; df = degrees of freedom; IV = inverse variance; SD = standard deviation; SGA = second-generation antipsychotic; YGTSS = Yale Global Tic Severity Scale

Tourette Syndrome: Short- and Long-Term Outcomes (Key Question 3)

Four RCTs assessed the efficacy of antipsychotics for treating a variety of short- and long-term outcomes in patients with Tourette syndrome. Below is a summary of the results by outcome. Table 24 summarizes the strength of evidence for all key outcomes that were reported by at least one study. Evidence was insufficient to draw conclusions for any comparisons or outcomes.

- Response and remission: Treatment response rate was reported in two RCTs. One[99] found no significant difference in response rate between haloperidol and pimozide; the second[101] found a significantly higher response rate in patients treated with risperidone than placebo. One RCT[102] comparing short- and long-term treatment with pimozide found that patients receiving long-term treatment had a longer time until dose increases were required to treat tic exacerbation.
- Cognitive and emotional development: One RCT comparing haloperidol with pimozide found significantly fewer commission and omission errors on a continuous performance task in the pimozide group.[100] Reaction time did not significantly differ between groups.
- Medication adherence: Adherence was assessed in one RCT[99] comparing haloperidol, pimozide, and placebo. Treatment adherence was high in all groups, with no significant difference.
- Other outcomes: No studies provided data for the following outcome categories: growth and maturation, suicide-related behaviors, school performance, work-related functional capacity, patient insight into illness, patient-, parent-, or care provider–reported outcomes, health-related quality of life, legal system interactions, or health care system utilization.

Table 24. Strength of evidence for Tourette syndrome (Key Question 3)

Comparison	Outcome (N Studies; N Patients)	Strength of Evidence Domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Haloperidol vs. pimozide	Medication adherence (1; 22)	Moderate	Unknown	Direct	Imprecise	Insufficient
Short- vs. long-term pimozide	Patient-, parent-, or care provider–reported outcomes (1; 10)	Moderate	Unknown	Direct	Imprecise	Insufficient
FGA vs. placebo	Medication adherence (1; 22)	Moderate	Unknown	Direct	Imprecise	Insufficient

FGA = first-generation antipsychotic; N = number; ROB = risk of bias

A detailed analysis by comparisons is presented below.

FGAs Versus FGAs

Three studies provided data on the comparison of FGAs for short- and long-term outcomes.

Haloperidol Versus Pimozide

A 24-month, placebo-controlled crossover RCT (N = 22) compared haloperidol (3.5±2.2 mg/day) and pimozide (3.4±1.6 mg/day) in children ages 7 to 16.[99] The rate of treatment response (≥50 percent reduction in Tourette Syndrome Global Scale scores) was not significantly different between the groups. All patients adhered to treatment.

A 6-week RCT (N = 41) evaluated the relative effects of haloperidol (1.5±0.6 mg/day) versus pimozide (3.7±1.4 mg/day) on cognition in children ages 7 to 16.[100] Mean omission and commission errors on continuous performance task were significantly lower in patients treated with pimozide than those treated with haloperidol ($p<0.05$ for both). Mean reaction times at the highest memory load on a memory search task did not differ between groups.

Short- Versus Long-Term Pimozide

A placebo-withdrawal study (N = 10) compared the efficacy of short- and long-term treatment with pimozide in patients ages 7 to 13.[102] Patients were randomly assigned to remain on pimozide or gradual placebo withdrawal for 8 months or until a dose increase was required. The mean doses were 3.8 mg/day and 3.5 mg/day for the short- and long-term pimozide groups, respectively. Time to dose increase due to tic exacerbation was significantly longer in patients treated with long-term, continuous pimozide than short-term pimozide ($p = 0.02$).

FGAs Versus Placebo

One RCT compared haloperidol, pimozide, and placebo for response rate and adherence (described previously).[99] Response rate was significantly higher in both the haloperidol and pimozide groups than placebo ($p = 0.003$ and $p = 0.002$, respectively). Patients in all groups adhered to treatment protocol.

SGAs Versus Placebo

An 8-week, placebo-controlled RCT evaluated the efficacy of risperidone (2.5±0.9 mg/day) in patients ages 7 to 65 years.[101] Data were provided separately for 26 pediatric patients. The treatment response rate (defined as CGI–I≤2) was significantly higher with risperidone than with placebo ($p<0.003$).

Behavioral Issues: Overview

Four studies (two RCTs[103,104] and two retrospective cohort studies[105,106]) examined the effect of antipsychotics for treating behavioral disturbances in children and adolescents. All studies reported symptoms, and two studies[103,106] also reported other short- or long-term outcomes.

Table 25 provides selected information on the characteristics of the individual studies. The studies are grouped according to the drug class comparisons: SGAs versus SGAs and SGAs versus placebo. Within each comparison, studies are listed alphabetically by the specific drugs compared. Studies that include both head-to-head and placebo comparisons are listed under the head-to-head category. A detailed evidence table is available in Appendix D.

Based on three studies that reported age, the average patient age was 13.3 years. Overall, 58 percent of patients were male. In the one study that reported race, 64 percent of patients were white. To be enrolled in the studies, patients were required to exhibit behavioral disturbances including aggression,[103,105,106] agitation,[106] self-injury,[105] or property destruction[105] (one study did not specify the types of behavioral symptoms included[104]). Diagnoses were based on the DSM–IV in two studies[103,105] and not reported in the remaining two. All patients in two studies had mental retardation.[104,105] Other comorbidities included post-traumatic stress disorder and substance abuse.

Two studies provided head-to-head comparisons of different SGAs: aripiprazole versus ziprasidone[103] and olanzapine versus ziprasidone.[106] Risperidone was compared with placebo in two studies,[104,105] one of which also compared two doses of risperidone.[105]

The durations of study followup ranged from 4 to 22 weeks. The RCTs had a high risk of bias due to incomplete outcome data and industry funding. The quality of the retrospective cohort studies was moderate to high.

Table 25. Characteristics of studies examining behavioral issues

Author, Year, Study Design, Duration, KQ	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
SGAs vs. SGAs			
Bastiaens et al, 2009[103] Retrospective cohort, 2 mo *KQ1, KQ3*	G1: Aripiprazole (24), 4.5±2.3 mg/day G2: Ziprasidone (22), 42.9±18 mg/day	G1: 11.7±2.4 yr / Male: 83% / White: NR G2: 12.1±2.9 yr / Male: 91% / White: NR Comorbidities: NR	Bipolar (12), CD (14), depressive disorder (6), mood disorder NOS (8), PDD (2), psychotic disorder (4) 4/8 stars
Khan et al, 2006[106] Retrospective cohort, 1 mo *KQ1, KQ3*	G1: Olanzapine (50), 8.2±2.4 mg/day G2: Ziprasidone (50), 19.1±2.6 mg/day	G1: 13.7±2.4 yr / Male: 68% / White: 60% G2: 14.6±2.1 yr / Male: 32% / White: 68% Comorbidities: PTSD (18), SA (27)	Psychosis (34) 6/8 stars
Hellings et al, 2006[105] RCT (crossover), 22 wk (24 wk extension) *KQ1*	G1: Risperidone (low) (26),* 1 mg/day G2: Risperidone (high) (26),* 2 mg/day G3: Placebo (26)*	All groups: NR / Male: NR / White: NR Comorbidities: ASD (NR), MR (all) [mild (8), moderate (6), severe (8), profound (4)]	NR High ROB
SGAs vs. Placebo			
van Bellinghen et al, 2001[104] RCT, 4 wk *KQ1*	G1: Risperidone (6), 1.2 mg/day G2: Placebo (7)	G1: NR / Male: 33% / White: NR G2: NR / Male: 43% / White: NR Comorbidities: MR (all)	NR High ROB

ASD = autism spectrum disorder; CD = conduct disorder; G = group; KQ = key question; mg = milligrams; mo = month; MR = mental retardation; N = number; NOS = not otherwise specified; NR = not reported; PDD = pervasive developmental disorder; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; ROB = risk of bias; SA = substance abuse; SD = standard deviation; SGA = second-generation antipsychotic; wk = week

*All patients experienced each of the treatment arms in this crossover study

Behavioral Issues: Disorder-Specific and Nonspecific Symptoms (Key Question 1)

Four studies provided data on symptom improvement in patients with behavioral issues. Below is a summary of the results by comparison. For key outcomes that were reported by at least one study, strength of evidence grades are provided in Table 26.

- Aripiprazole versus ziprasidone (one RCT[103]): Global impressions of functioning and improvement, aggression, and manic symptoms did not differ significantly between groups.
- Olanzapine versus ziprasidone (one retrospective cohort study[106]): The number of aggressive episodes did not significantly differ between groups.
- Risperidone–dosing (one crossover RCT[105]): There was no difference in aberrant behavior scores between the two dosing groups.
- Risperidone versus placebo (two RCTs[104,105]): One RCT showed a significant difference favoring risperidone for improving symptoms on the ABC, CGI, VAS, and the social

relationship and occupational attitude subscales of the Personal Assessment Checklist ($p<0.05$).[104]

Table 26. Strength of evidence for behavioral issues (Key Question 1)

Comparison	Outcome (N Studies; N Patients)	Strength of Evidence Domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Aripiprazole vs. ziprasidone	Aggression (1; 46)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Clinical global impressions (1; 46)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Manic symptoms (1; 46)	Moderate	Unknown	Direct	Imprecise	Insufficient
Olanzapine vs. ziprasidone	Aggression (1; 100)	Low	Unknown	Direct	Imprecise	Insufficient
Risperidone–low- vs. high-dose	Autistic symptoms (1; 26)	Moderate	Unknown	Direct	Imprecise	Insufficient
Risperidone vs. placebo	Autistic symptoms (2; 39)	Moderate	Consistent	Direct	Not pooled	Low
	Clinical global impressions (1; 13)	Moderate	Unknown	Direct	Imprecise	Insufficient

N = number; ROB = risk of bias

The findings of individual comparisons and studies are provided below.

SGAs Versus SGAs

Two studies provided data on the comparative effectiveness of two SGAs in the treatment of behavioral issues.

Aripiprazole Versus Ziprasidone

A 2-month retrospective cohort study (N = 46) evaluated the effectiveness of aripiprazole (4.5±2.3 mg/day) and ziprasidone (42.9±18 mg/day) in treating children ages 6 to 17 years with aggressive behavior.[103] There was no significant difference between the drugs for the CGI–I, Global Assessment of Functioning, OAS, or YMRS–P.

Olanzapine Versus Ziprasidone

A retrospective cohort study (N = 100) compared the effectiveness of olanzapine and ziprasidone for treating agitation and aggression in children and youth under 18 years of age.[106] Length of stay in hospital averaged 26 days in the olanzapine group and 34 days in the ziprasidone group. During this time, patients received an average of 3±4 and 5±8 intramuscular injections of olanzapine and ziprasidone, respectively. The mean study dose was 8.2±2.4 mg for olanzapine and 19.1±2.6 mg for ziprasidone. No significant difference was found in the number of aggressive episodes between the two groups.

Risperidone–Low- Versus High-Dose

A crossover RCT investigated the efficacy of low- (1 mg) versus high-dose (2 mg) risperidone for treating aggression, self-injury, and destructive behaviors in children and adults ages 8 to 56 years with mental retardation.[105] Data were available for 26 pediatric patients. Patients received each dose for 4 weeks. Dosage was tapered between risperidone doses for a 2-week period. All patients were given placebo for 3 to 5 weeks after receiving the two doses of risperidone. Low- and high-dose groups did not significantly differ on endpoint scores of the ABC subscales.

SGAs Versus Placebo

A crossover RCT compared two doses of risperidone with placebo (described above).[105] All ABC subscales were lower in the risperidone groups than placebo (p-values were not reported and could not be calculated).

A 4-week RCT (N = 13) compared risperidone (1.2 mg/day) with placebo in treating behavioral disturbances in patients ages 6 to 18 years with mental retardation.[104] Risperidone was significantly favored for improvement on ABC ($p<0.001$), CGI ($p<0.05$), VAS ($p<0.001$), and the social relationship and occupational attitude subscales of the Personal Assessment Checklist ($p<0.05$).

Behavioral Issues: Short- and Long-Term Outcomes (Key Question 3)

Two retrospective cohort studies examined the relative effectiveness of different SGAs for treating patients with behavioral disturbances on various short- and long-term outcomes. A study[103] comparing aripiprazole with ziprasidone found no difference between the treatment groups for quality of life at 2 months. Similarly, no difference was found between olanzapine and ziprasidone for length of hospital stay, number of physical restraints needed, and duration of restraints when antipsychotics were used to treat patients with acute aggression.[106] Strength of evidence was evaluated for health-related quality of life (Table 27).

Table 27. Strength of evidence for behavioral issues (Key Question 3)

Comparison	Outcome (N Studies; N Patients)	Strength of Evidence Domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Aripiprazole vs. ziprasidone	HRQL (1; 46)	Moderate	Unknown	Direct	Imprecise	Insufficient

HRQL = health-related quality of life; N = number; ROB = risk of bias

SGAs Versus SGAs

Aripiprazole Versus Ziprasidone

The efficacy of aripiprazole (4.5±2.3 mg/day) and ziprasidone (42.9±18 mg/day) was compared in 46 children ages 6 to 17 with aggressive behavior.[103] Quality of life improved in both groups; however, there was no significant difference.

Olanzapine Versus Ziprasidone

A retrospective cohort study (N = 100) compared the effectiveness of olanzapine and ziprasidone for treating aggression in patients younger than 18 years of age. Patients received an average of 3±4 and 5±8 injections of olanzapine and risperidone, respectively. The mean study dose was 8.2±2.4 mg for olanzapine and 19.1±2.6 mg for ziprasidone. No significant differences between the groups were noted for length of hospital stay, number of physical restraints, and duration of restraints after use of medication.

Key Question 2: Adverse Events

This section reviews the evidence on comparative harms of FGAs and SGAs. The results are organized by drug class comparison, with head-to-head comparisons (FGAs vs. SGAs, FGAs vs. FGAs, SGAs vs. SGAs) preceding placebo comparisons. Data are not presented separately for

each of the conditions of interest because adverse events associated with an antipsychotic are likely to be consistent regardless of the indication for which a drug is being taken.

For each comparison, we report data on 19 adverse event categories: mortality, cerebrovascular events, weight gain and body composition, dyslipidemia, insulin resistance and diabetes, prolactin-related and sexual events, neuromotor events including tardive dyskinesia, cardiac events, sedation, liver toxicity, neutropenia and agranulocytosis, thyroid dysfunction, seizures, neuroleptic malignant syndrome, constipation, exercise intolerance, precocious puberty, behavioral effects (e.g., aggression, agitation), and dermatological effects. Data on cardiomyopathies was not available in any of the included studies.

FGAs Versus SGAs

Twelve studies compared the adverse event profile of FGAs and SGAs. Comparisons included various FGAs versus various SGAs,[107] various FGAs versus clozapine,[108] haloperidol versus clozapine,[82,109] haloperidol versus olanzapine,[45,76,89,96,109,110] haloperidol versus risperidone,[48,89,96] and pimozide versus risperidone.[97,111] The findings for each adverse event are provided below. No data were available for the following adverse events: mortality, cerebrovascular events, thyroid dysfunction, exercise intolerance, and precocious puberty. The effect estimates and 95 percent confidence intervals of results that showed a significant difference between FGAs and SGAs are presented in Table 28.

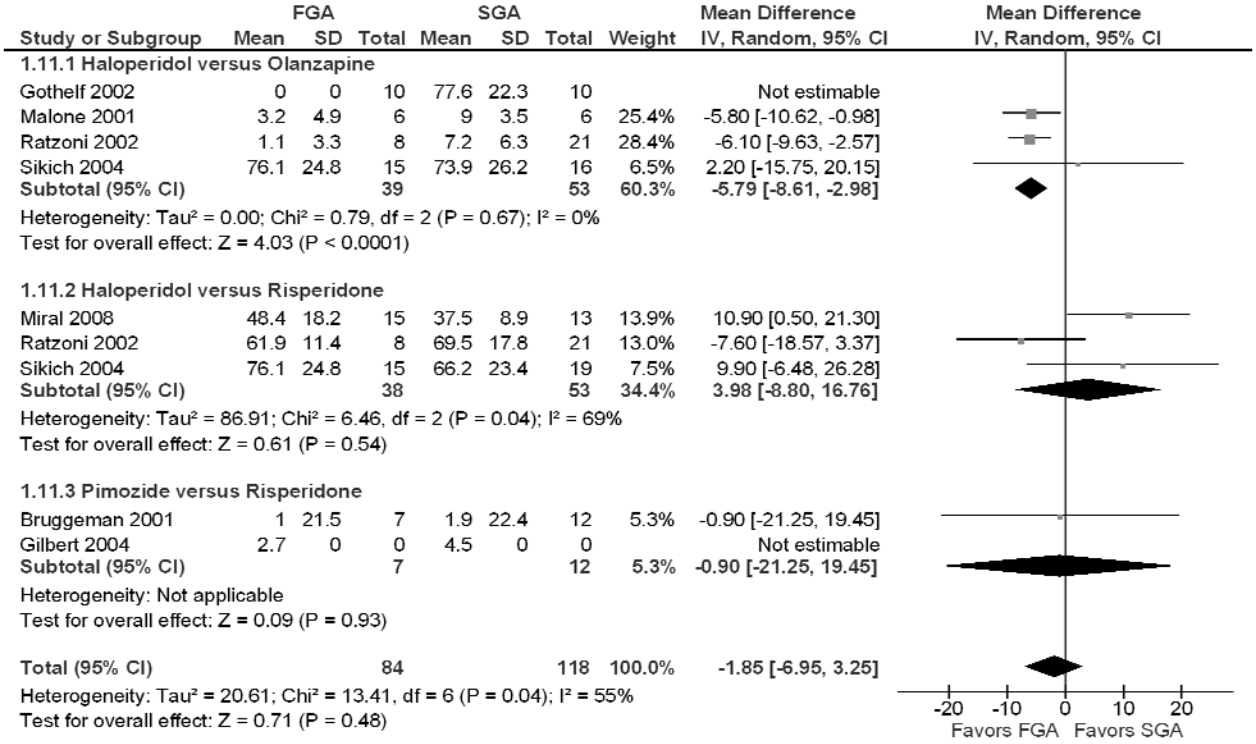
Total Adverse Events

One study reported that no severe adverse events occurred for either haloperidol or risperidone.[48]

Weight Gain/Body Composition

In a study comparing haloperidol and olanzapine, weight gain greater than seven percent occurred significantly more frequently in the olanzapine group.[45] A meta-analysis of four studies[45,89,96,110] comparing haloperidol with olanzapine found significantly less weight gain in patients receiving haloperidol (MD = -5.79 kg; 95% CI, -8.61 to -2.98 kg) (Figure 49). No significant difference between the other FGAs and SGAs was found.

Figure 49. FGAs versus SGAs for mean weight gain (kg)



CI = confidence interval; df = degrees of freedom; IV = inverse variance; kg = kilogram; FGA = first-generation antipsychotic; SD = standard deviation; SGA = second-generation antipsychotic

Dyslipidemia

One study found no significant differences between haloperidol and olanzapine or risperidone in low-density lipoprotein, high-density lipoprotein, or triglyceride levels.[89]

Insulin Resistance and Diabetes

One study found significantly higher glucose levels for olanzapine than for haloperidol.[89]

Prolactin-Related and Sexual Adverse Events

Prolactin levels were significantly higher in patients receiving various FGAs than those receiving clozapine in one study.[108] A second study[109] found prolactin levels to be higher for haloperidol than clozapine.

Neuromotor Adverse Events

None of the studies reported rates of tardive dyskinesia. Significantly more patients experienced dystonia[89,96] and any extrapyramidal side effects[45,96] in the haloperidol group than olanzapine. Similarly, one study[89] found extrapyramidal symptoms as measured by the Simpson Angus Scale to be significantly more severe for patients treated with haloperidol than for those treated with olanzapine. Akathisia occurred significantly more frequently among patients treated with haloperidol than those treated with risperidone in a meta-analysis of two studies.[89,96] Similarly, extrapyramidal symptoms as measured by the Extrapyramidal Symptom Rating Scale and the Simpson Angus Scale were significantly more severe in patients treated with haloperidol than for those treated with risperidone in two studies.[48,89]

Cardiac Adverse Events

No significant differences were found between haloperidol and olanzapine[45,96] or risperidone[96] for tachycardia, and between haloperidol and risperidone for pulse.[48] Similarly, QTc intervals did not significantly differ between haloperidol and olanzapine or risperidone[89] and between pimozide and risperidone.[97]

Sedation

A significantly greater proportion of patients receiving clozapine reported drowsiness than those receiving haloperidol in one study.[82] A single study found the rate of fatigue was significantly greater in patients receiving haloperidol than those receiving risperidone.[96]

Liver Toxicity

Aspartate amino transferase levels were significantly higher for patients treated with olanzapine and risperidone than those receiving haloperidol in one study.[89]

Neutropenia and Agranulocytosis

One study found no significant differences between haloperidol and clozapine in neutrophil counts and incidence of agranulocytosis.[82]

Seizures

No seizures occurred in a study comparing haloperidol with olanzapine and risperidone.[96] In a study comparing haloperidol and clozapine, one seizure occurred in a patient treated with clozapine; the difference between groups was not significant.[82]

Neuroleptic Malignant Syndrome

One study found no significant difference in the incidence of neuroleptic malignant syndrome between haloperidol (one event) and clozapine (no events).[82]

Constipation

Two meta-analyses comparing haloperidol with olanzapine[89,96] and haloperidol with risperidone[48,89,96] found no significant differences between groups in constipation.

Behavioral Side Effects

The rate of depression as measured on the Udvalg for Kliniske Undersogelser Side Effect Rating Scale was found to be significantly higher in patients receiving haloperidol than in those receiving olanzapine or risperidone in one study.[96]

Dermatological Adverse Events

The incidence of itching was not significantly different between haloperidol and olanzapine or risperidone.[89,96] The incidence of rash did not differ between haloperidol and olanzapine[45,89] or haloperidol and risperidone.[89]

Table 28. Significant findings for adverse events: FGAs versus SGAs

Adverse Event	# Studies	N (Drug 1)	N (Drug 2)	Effect Estimate	95% CI	Favors*
FGA (Drug 1) Versus Clozapine (Drug 2)						
Prolactin	1	20	20	MD = 15.5	(8.0, 23.0)	FGA
Haloperidol (Drug 1) Versus Clozapine (Drug 2)						
Drowsiness	1	11	10	RR = 0.30	(0.1, 0.8)	Haloperidol
Prolactin (ng/mL)	1	10	15	MD = 36.6	(17.5, 55.7)	Clozapine
Haloperidol (Drug 1) Versus Olanzapine (Drug 2)						
Weight (kg)	4	39	53	MD = -5.79	(-8.6, -3.0)	Haloperidol
Weight–gain ≥7%	1	8	21	RR = 0.14	(0.02, 0.9)	Haloperidol
Glucose (mg/dL)	1	15	16	MD = -9.7	(-19.3, -0.1)	Haloperidol
Dystonia	2	22	35	RR = 8.19	(1.0, 65.5)	Olanzapine
EPS	2	13	25	RR = 3.53	(1.1, 10.9)	Olanzapine
EPS (SAS)	1	15	16	MD = 3.3	(0.3, 6.31)	Olanzapine
AST (U/L)	1	15	16	MD = -11.7	(-22.7, -0.7)	Olanzapine
Depression	1	7	19	RR = 2.71	(1.1, 6.6)	Olanzapine
Haloperidol (Drug 1) Versus Risperidone (Drug 2)						
Akathisia	2	22	36	RR = 6.93	(1.3, 38.1)	Risperidone
Fatigue	1	7	17	RR = 6.07	(1.5, 24.2)	Risperidone
EPS (ESRS)	1	15	15	MD = 1.12	(0.21, 2.03)	Risperidone
EPS (SAS)	1	15	19	MD = 3.1	(0.003, 6.2)	Risperidone
AST (U/L)	1	15	19	MD = -7.4	(-13.8, -1.01)	Risperidone
Depression	1	7	17	RR = 6.07	(1.5, 24.2)	Risperidone

AST = aspartate aminotransferase; CI = confidence interval; dL = deciliter; EPS = extrapyramidal symptom; ESRS = extrapyramidal symptom rating scale; FGA = first-generation antipsychotic; kg = kilogram; MD = mean difference; mg = milligram; mL = milliliter; N = number; ng = nanogram; RR = relative risk; SAS = Simpson Angus Scale; SGA = second-generation antipsychotic; U/L = international units per liter

* Denotes the drug with the better adverse event profile.

Strength of evidence grades for key adverse events that were reported by at least one study are provided in Table 29. For all key adverse events, the strength of evidence for FGAs versus SGAs was low or insufficient.

Table 29. Strength of evidence for adverse events: FGAs versus SGAs (Key Question 2)

Comparison	Outcome (N Studies; N Patients)	Strength of Evidence Domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
FGAs vs. SGAs	Weight (1; 109)	Moderate	Unknown	Direct	Imprecise	Insufficient
FGAs vs. clozapine	Prolactin-related / sexual AE (1; 40)	High	Unknown	Direct	Precise	Insufficient
Haloperidol vs. clozapine	EPS (1; 21)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Prolactin-related / sexual AE (1; 47)	Moderate	Unknown	Direct	Precise	Insufficient
	Sedation (1; 21)	Moderate	Unknown	Indirect	Precise	Insufficient
	Weight (1; 21)	Moderate	Unknown	Direct	Imprecise	Insufficient
Haloperidol vs. olanzapine	Dyslipidemia (1; 50)	Moderate	Unknown	Direct	Imprecise	Insufficient
	EPS (3; 62)	High	Inconsistent	Direct	Precise	Low
	Insulin resistance (1; 50)	Moderate	Unknown	Direct	Precise	Insufficient
	Prolactin-related / sexual AE (2; 97)	Moderate	Inconsistent	Direct	Imprecise	Low
	Sedation (3; 112)	High	Consistent	Direct	Imprecise	Low
	Weight (4; 132)	High	Inconsistent	Direct	Precise	Low

Table 29. Strength of evidence for adverse events: FGAs versus SGAs (Key Question 2) (continued)

Comparison	Outcome (N studies; N patients)	Strength of Evidence Domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Haloperidol vs. risperidone	Dyslipidemia (1; 50)	Moderate	Unknown	Direct	Imprecise	Insufficient
	EPS (3; 130)	High	Consistent	Direct	Imprecise	Low
	Insulin resistance (1; 50)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Prolactin-related / sexual AE (2; 80)	Moderate	Consistent	Direct	Imprecise	Low
	Sedation (2; 100)	High	Inconsistent	Direct	Imprecise	Low
	Weight (3; 130)	High	Consistent	Direct	Imprecise	Low
Pimozide vs. risperidone	EPS (1; 19)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Weight (1; 19)	Moderate	Unknown	Direct	Imprecise	Insufficient
Haloperidol vs. pimozide	EPS (1; 22)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Prolactin-related / sexual AE (1; 22)	Moderate	Unknown	Direct	Precise	Insufficient
	Weight (1; 22)	Moderate	Unknown	Direct	Imprecise	Insufficient

AE = adverse event; EPS = extrapyramidal symptom; FGA = first-generation antipsychotic; N = number; ROB = risk of bias; SGA = second-generation antipsychotic

FGAs Versus FGAs

Three studies reported on the relative rates of adverse events between different FGAs. Comparisons included haloperidol versus haloperidol,[51] haloperidol versus pimozide,[99] and pimozide versus pimozide.[102] The findings for each adverse event are provided below. The following adverse event categories were not reported: mortality, cerebrovascular events, dyslipidemia, insulin resistance and diabetes, liver toxicity, neutropenia and agranulocytosis, thyroid dysfunction, seizures, neuroleptic malignant syndrome, constipation, exercise intolerance, precocious puberty, and dermatological adverse events. Effect estimates and 95 percent confidence intervals for the significant findings are presented in Table 30.

Total Adverse Events

One study found no significant differences between haloperidol and pimozide in treatment-limiting side effects or withdrawal due to adverse events.[99]

Weight Gain/Body Composition

One study found no difference in weight gain between haloperidol and pimozide.[99]

Prolactin-Related and Sexual Adverse Events

Prolactin levels were significantly higher in patients receiving pimozide than patients receiving haloperidol.[99]

Neuromotor Adverse Events

One study reported no tardive dyskinesia events in either the short- and long-term pimozide groups.[107] A significantly higher rate of withdrawal dyskinesia was reported in patients receiving discontinuous haloperidol versus continuous haloperidol.[51]

Cardiac Adverse Events

No significant differences were found between haloperidol and pimozide in heart rate, rhythm, and waveform in one study.[99]

Sedation

No patients reported experiencing sedation in a study comparing continuous versus discontinuous administration of haloperidol.[51]

Behavioral Side Effects

No significant differences in the proportion of patients who experienced treatment-emergent anxiety or depression were observed between haloperidol and pimozide in one study.[99]

Table 30. Significant findings for adverse events: FGAs versus FGAs

Adverse Event	# Studies	N (Drug 1)	N (Drug 2)	Effect Estimate	95% CI	Favors*
Haloperidol (Continuous) (Drug 1) Versus Haloperidol (discontinuous) (Drug 2)						
Dyskinesias	1	30	22	RR = 0.24	(0.07, 0.8)	Continuous Haloperidol
Haloperidol (Drug 1) Versus Pimozide (Drug 2)						
Prolactin	1	19	25	MD = -8.7	(-17.2, -0.2)	Haloperidol

CI = confidence interval; FGA = first-generation antipsychotic; MD = mean difference; N = number; RR = relative risk
* Denotes the drug with the better adverse event profile.

Strength of evidence grades for key adverse events that were reported by at least one study are provided in Table 31. The strength of evidence was insufficient for all key adverse events.

Table 31. Strength of evidence for adverse events: FGAs versus FGAs (Key Question 2)

Comparison	Outcome (N Studies; N Patients)	Strength of Evidence Domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Haloperidol vs. pimozide	EPS (1; 22)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Prolactin-related / sexual AE (1; 22)	Moderate	Unknown	Direct	Precise	Insufficient
	Weight (1; 22)	Moderate	Unknown	Direct	Imprecise	Insufficient

AE = adverse event; EPS = extrapyramidal symptom; FGA = first-generation antipsychotic; N = number; ROB = risk of bias

SGAs Versus SGAs: Comparison of Different Drugs

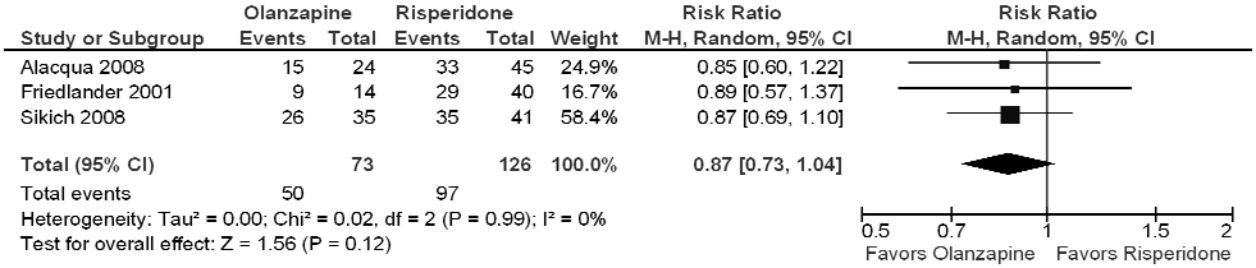
A total of 25 studies compared adverse event rates among different SGAs. The following comparisons were made (presented alphabetically by drug name): aripiprazole versus olanzapine,[112] aripiprazole versus quetiapine,[112] aripiprazole versus risperidone,[112] aripiprazole versus ziprasidone,[103] clozapine versus olanzapine,[81,87,95,109,113,114] clozapine versus quetiapine,[113] clozapine versus risperidone,[113,114] olanzapine versus quetiapine,[64,74,79,112,113,115,116] olanzapine versus risperidone,[63,64,79,83,88,89,92,96,112-120] olanzapine versus ziprasidone,[64,106] quetiapine versus risperidone,[64,79,91,112,113,115,116] quetiapine versus ziprasidone,[64] and risperidone versus ziprasidone.[64] The findings for each adverse event are provided below.

The following adverse event categories were not reported in any of the studies: mortality, cerebrovascular events, neuroleptic malignant syndrome, and exercise intolerance. The effect estimates and 95 percent confidence intervals of results that showed a significant difference between various SGAs are presented in Table 32.

Total Adverse Events

Withdrawal due to adverse events was more common for patients treated with ziprasidone than for those treated with aripiprazole in one study.[103] A meta-analysis of three studies[88,113,118] found no significant difference between olanzapine and risperidone (Figure 50).

Figure 50. Olanzapine versus risperidone for total adverse events



CI = confidence interval; df = degrees of freedom; M–H = Mantel–Haenszel

Weight Gain/Body Composition

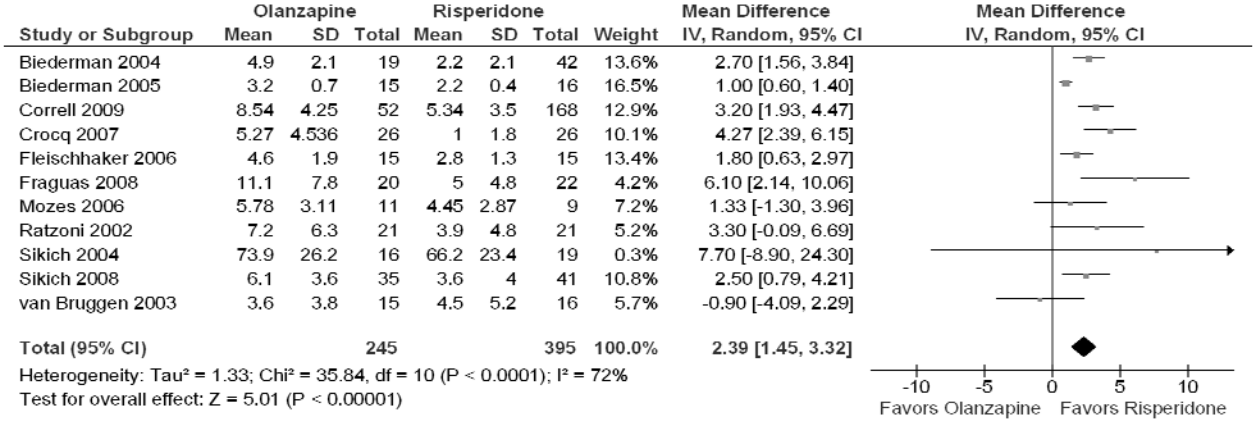
Weight gain greater than 7 percent and body mass index (BMI) increase greater than 10 percent occurred significantly more frequently in patients receiving olanzapine than those receiving aripiprazole in one study.[112] Similarly, olanzapine resulted in significantly greater mean increase in weight, percent change from baseline weight, fat mass, BMI, and waist circumference than aripiprazole.[112] Transition from normal weight to overweight or obese categories occurred in a significantly greater proportion of patients in the quetiapine group than the aripiprazole group.[112] In addition, increase in mean weight was significantly greater for quetiapine than for aripiprazole. Percent weight change from baseline was significantly greater for risperidone than with aripiprazole.[112]

Weight gain greater than 7 percent,[79,112] BMI increase greater than 10 percent,[112] and BMI greater than the 85th percentile[115] occurred in a greater proportion of patients in the olanzapine group than the quetiapine group. Similarly, the olanzapine group experienced significantly greater increase in fat mass[112] and waist circumference than quetiapine.[112] Patients on olanzapine consistently experienced significantly less mean weight gain[64,74,112,115] and increase in BMI;[74,112,115] however, the studies could not be pooled due to heterogeneity.

Significantly more patients receiving olanzapine experienced any weight gain[88,113,114,118] and BMI increase greater than 10 percent[112] than those receiving risperidone. Similarly, a meta-analysis of 11 studies[63,64,83,88,89,92,96,112,114,115,117] (Figure 51) found a greater increase in mean weight for olanzapine than risperidone (MD = 2.39; 95% CI, 1.45 to 3.32). Studies also found a greater increase for olanzapine than risperidone in weight,[63,112,117] fat mass,[112] BMI,[88,89,96,112,114,115,117] BMI percentile,[88,112] and waist circumference.[112] Fewer patients treated with risperidone had a transition from normal weight to overweight to obese than those treated with quetiapine.[112]

One study found a significantly greater mean increase in weight for olanzapine than ziprasidone.[64]

Figure 51. Olanzapine versus risperidone for mean weight gain (kg)



CI = confidence interval; df = degrees of freedom; IV = inverse variance; kg = kilogram; SD = standard deviation

Dyslipidemia

The proportion of patients with elevated total cholesterol, incidence of dyslipidemia, as well as the increase in mean total cholesterol, mean triglycerides, and ratio of triglycerides to high-density lipoprotein cholesterol were significantly greater in patients receiving olanzapine than those receiving aripiprazole in one study.[112] There was a significantly greater increase in mean triglycerides and in the ratio of triglycerides to high-density lipoprotein cholesterol for quetiapine than aripiprazole.[112] Olanzapine-treated patients experienced significantly more dyslipidemia than quetiapine-treated patients in one study.[112] Abnormal lipid profile favored risperidone over quetiapine in one small study.[91] Mean total cholesterol and mean triglycerides were found to be significantly higher for patients treated with olanzapine than risperidone in a meta-analysis of four studies[63,88,112,115] and five studies,[63,88,89,112,115] respectively. Ratio of triglycerides to high-density lipoprotein cholesterol was also significantly higher for quetiapine than risperidone in one study.[115]

Insulin Resistance and Diabetes

One study[112] reported high insulin levels in a significantly greater proportion of patients receiving olanzapine than those receiving risperidone.

Prolactin-Related and Sexual Adverse Events

Increase in mean prolactin level was significantly higher for patients treated with olanzapine than those treated with clozapine in a meta-analysis of two studies.[81,109] Patients treated with olanzapine had significantly higher prolactin levels than patients treated with quetiapine[64,116] or ziprasidone.[64] Prolactin levels were high in a greater proportion of patients[83,92,113,116] treated with risperidone than in patients treated with olanzapine. The proportion of patients with high prolactin levels[91,113,116] and mean prolactin levels[64,116] were higher with risperidone than quetiapine.

Neuromotor Adverse Events

Tardive dyskinesia was not significantly different between clozapine and olanzapine,[114] clozapine and risperidone,[114] or olanzapine and risperidone.[88,92,114,119] Dyskinesia was experienced in a significantly greater proportion of patients treated with quetiapine than olanzapine or risperidone in one small study.[113]

Cardiac Adverse Events

Hypertension was significantly more common in the clozapine group than in the olanzapine group in two studies.[87,114]

Sedation

One study[92] found somnolence to occur significantly more frequently for patients receiving risperidone than for those receiving olanzapine.

Liver Toxicity

Mean alanine transaminase and aspartate amino transferase levels were significantly higher for patients treated with olanzapine than for those treated with risperidone in meta-analyses of two studies.[88,89]

Neutropenia and Agranulocytosis

A meta-analysis of three studies found no difference between clozapine and olanzapine for neutropenia.[81,87,95] No difference was found between clozapine, olanzapine, or risperidone for leucopenia in one study.[114] White blood cell counts were not significantly different between olanzapine and risperidone.[89]

Thyroid Dysfunction

Thyroid stimulating hormone levels were significantly higher in patients receiving quetiapine than in patients receiving risperidone based on one study.[115]

Seizures

Two studies found no significant difference in the rates of seizures for clozapine and olanzapine.[87,95] Similarly, no difference was found in seizure rates for olanzapine and risperidone.[92,96]

Constipation

No difference was found in constipation rates for the following comparisons: clozapine and olanzapine,[81,87,95,114] clozapine and risperidone,[114] olanzapine and quetiapine,[74] or olanzapine and risperidone.[88,89,96,114]

Behavioral Side Effects

No significant differences in behavioral side effects were found in the following comparisons: aripiprazole versus ziprasidone,[103] clozapine versus olanzapine,[87,95,113,114] clozapine versus quetiapine,[113] clozapine versus risperidone,[113,114] olanzapine versus quetiapine,[74,79,113] olanzapine versus risperidone,[63,79,88,96,113,114] or quetiapine versus risperidone.[79,113] Agitation, anxiety, depression, irritability, and worsening psychosis were examined.

Table 32. Significant findings for adverse events: SGAs versus SGAs

Adverse Event	# Studies	N (Drug 1)	N (Drug 2)	Effect estimate	95% CI	Favors*
Aripiprazole (Drug 1) Versus Olanzapine (Drug 2)						
Weight (kg)	1	47	52	MD = -4.1	(-5.5, -2.7)	Aripiprazole
Weight–gain ≥7%	1	41	45	RR = 0.69	(0.5, 0.9)	Aripiprazole
Weight, % change from baseline	1	47	52	MD = -7.06	(-9.4, -4.7)	Aripiprazole
Fat mass (kg)	1	47	52	MD = -1.69	(-2.7, -0.7)	Aripiprazole
BMI	1	47	52	MD = -1.34	(-1.9, -0.8)	Aripiprazole
BMI>10%	1	41	45	RR = 0.33	(0.2, 0.6)	Aripiprazole
Waist circumference (cm)	1	47	52	MD = -3.15	(-5.9, -0.4)	Aripiprazole
Total cholesterol (mg/dL)	1	47	52	MD = -11.9	(-23.4, -0.3)	Aripiprazole
Cholesterol, high	1	41	45	RR = 0.27	(0.08, 0.9)	Aripiprazole
Dyslipidemia	1	41	45	RR = 0.25	(0.08, 0.8)	Aripiprazole
Triglycerides (mg/dL)	1	47	52	MD = -26.74	(-49.4, -4.1)	Aripiprazole
Ratio of triglycerides to HDL (mg/dL)	1	47	52	MD = -0.78	(-1.4, -0.2)	Aripiprazole
Aripiprazole (Drug 1) Versus Quetiapine (Drug 2)						
Weight (kg)	1	47	45	MD = -1.62	(-3.0, -0.3)	Aripiprazole
Transition to overweight or obese category	1	19	25	RR = 0.27	(0.1, 0.8)	Aripiprazole
Triglycerides (mg/dL)	1	47	45	MD = -39.4	(-71.3, -7.4)	Aripiprazole
Ratio of triglycerides to HDL (mg/dL)	1	47	45	MD = -1.41	(-2.3, -0.5)	Aripiprazole
Aripiprazole (Drug 1) Versus Risperidone (Drug 2)						
Weight, % change from baseline	1	47	168	MD = -2.26	(-3.9, -0.7)	Aripiprazole
Aripiprazole (Drug 1) Versus Ziprasidone (Drug 2)						
WAE	1	20	14	RR = 0.23	(0.05, 0.99)	Aripiprazole
Clozapine (Drug 1) Versus Olanzapine (Drug 2)						
Hypertension	2	27	27	RR = 6.34	(1.3, 31.8)	Olanzapine
Prolactin (ng/mL)	2	29	25	MD = -10.8	(-16.7, -4.8)	Clozapine
Olanzapine ODT (Drug 1) Versus Olanzapine SOT (Drug 2)						
Weight (kg)	1	16	10	MD = -5.9	(-9.2, -2.6)	Olanzapine ODT
BMI	1	16	10	MD = -0.8	(-1.3, -0.3)	Olanzapine ODT
Olanzapine (Drug 1) Versus Quetiapine (Drug 2)						
Weight–gain ≥7%	2	55	46	RR = 1.47	(1.1, 2.0)	Quetiapine
BMI>10% increase	1	45	36	RR = 1.71	(1.1, 2.7)	Quetiapine
BMI≥85th percentile	1	45	36	RR = 2.88	(1.2, 6.8)	Quetiapine
Fat mass (kg)	1	52	45	MD = 1.3	(0.1, 2.5)	Quetiapine
Waist circumference (cm)	1	52	45	MD = 3.28	(1.6, 4.9)	Quetiapine
Dyslipidemia	1	45	36	RR = 3.47	(1.1, 11.2)	Quetiapine
Dyskinesia	1	24	2	RR = 0.04	(0.0, 0.8)	Olanzapine
Prolactin (ng/mL)	2	32	25	MD = 4.33	(1.9, 6.8)	Quetiapine
Olanzapine (Drug 1) Versus Risperidone (Drug 2)						
Total AE	3	73	126	RR = 0.87	(0.7, 1.0)	Olanzapine
Weight (kg)	11	245	395	MD = 2.39	(1.5, 3.3)	Risperidone
Weight–% change	3	93	210	MD = 5.02	(3.5, 6.6)	Risperidone
Weight gain	4	89	145	RR = 1.86	(1.0, 3.4)	Risperidone
Fat mass	1	52	168	MD = 1.67	(0.8, 2.6)	Risperidone
BMI	7	175	312	MD = 0.95	(0.7, 1.2)	Risperidone
BMI percentile change	2	87	209	MD = 5.93	(1.9, 9.9)	Risperidone

Table 32. Significant findings for adverse events: SGAs versus SGAs (continued)

Adverse Event	# Studies	N (Drug 1)	N (Drug 2)	Effect estimate	95% CI	Favors*
BMI>10% increase	1	45	135	RR = 1.88	(1.4, 2.6)	Risperidone
Waist circumference (cm)	1	52	168	MD = 3.45	(2.2, 4.7)	Risperidone
Total cholesterol (mg/dL)	4	100	227	MD = 10.2	(3.1, 17.2)	Risperidone
Triglycerides (mg/dL)	5	116	246	MD = 17.3	(3.5, 31.1)	Risperidone
Insulin, high	1	45	135	RR = 2.67	(1.1, 6.5)	Risperidone
Prolactin, high	4	64	91	RR = 0.38	(0.2, 0.6)	Olanzapine
ALT (U/L)	2	51	60	MD = 12.4	(3.2, 21.5)	Risperidone
AST (U/L)	2	51	60	MD = 7.17	(3.5, 10.8)	Risperidone
Somnolence	1	12	19	RR = 0.37	(0.1, 1.0)	Olanzapine
Aripiprazole (Drug 1) Versus Quetiapine (Drug 2)						
Weight (kg)	1	47	45	MD = -1.62	(-3.0, -0.3)	Aripiprazole
Transition to overweight or obese category	1	19	25	RR = 0.27	(0.1, 0.8)	Aripiprazole
Triglycerides (mg/dL)	1	47	45	MD = -39.4	(-71.3, -7.4)	Aripiprazole
Ratio of triglycerides to HDL (mg/dL)	1	47	45	MD = -1.41	(-2.3, -0.5)	Aripiprazole
Aripiprazole (Drug 1) Versus Risperidone (Drug 2)						
Weight, % change from baseline	1	47	168	MD = -2.26	(-3.9, -0.7)	Aripiprazole
Aripiprazole (Drug 1) Versus Ziprasidone (Drug 2)						
WAE	1	20	14	RR = 0.23	(0.05, 0.99)	Aripiprazole
Clozapine (Drug 1) Versus Olanzapine (Drug 2)						
Hypertension	2	27	27	RR = 6.34	(1.3, 31.8)	Olanzapine
Prolactin (ng/mL)	2	29	25	MD = -10.8	(-16.7, -4.8)	Clozapine
Olanzapine ODT (Drug 1) Versus Olanzapine SOT (Drug 2)						
Weight (kg)	1	16	10	MD = -5.9	(-9.2, -2.6)	Olanzapine ODT
BMI	1	16	10	MD = -0.8	(-1.3, -0.3)	Olanzapine ODT
Olanzapine (Drug 1) Versus Quetiapine (Drug 2)						
Weight–gain ≥7%	2	55	46	RR = 1.47	(1.1, 2.0)	Quetiapine
BMI>10% increase	1	45	36	RR = 1.71	(1.1, 2.7)	Quetiapine
BMI≥85th percentile	1	45	36	RR = 2.88	(1.2, 6.8)	Quetiapine
Fat mass (kg)	1	52	45	MD = 1.3	(0.1, 2.5)	Quetiapine
Waist circumference (cm)	1	52	45	MD = 3.28	(1.6, 4.9)	Quetiapine
Dyslipidemia	1	45	36	RR = 3.47	(1.1, 11.2)	Quetiapine
Dyskinesia	1	24	2	RR = 0.04	(0.0, 0.8)	Olanzapine
Prolactin (ng/mL)	2	32	25	MD = 4.33	(1.9, 6.8)	Quetiapine
Olanzapine (Drug 1) Versus Risperidone (Drug 2)						
Total AE	3	73	126	RR = 0.87	(0.7, 1.0)	Olanzapine
Weight (kg)	11	245	395	MD = 2.39	(1.5, 3.3)	Risperidone
Weight–% change	3	93	210	MD = 5.02	(3.5, 6.6)	Risperidone
Weight gain	4	89	145	RR = 1.86	(1.0, 3.4)	Risperidone
Fat mass	1	52	168	MD = 1.67	(0.8, 2.6)	Risperidone
BMI	7	175	312	MD = 0.95	(0.7, 1.2)	Risperidone
BMI percentile change	2	87	209	MD = 5.93	(1.9, 9.9)	Risperidone
BMI>10% increase	1	45	135	RR = 1.88	(1.4, 2.6)	Risperidone

Table 32. Significant findings for adverse events: SGAs versus SGAs (continued)

Adverse Event	# Studies	N (Drug 1)	N (Drug 2)	Effect estimate	95% CI	Favors*
Waist circumference (cm)	1	52	168	MD = 3.45	(2.2, 4.7)	Risperidone
Total cholesterol (mg/dL)	4	100	227	MD = 10.2	(3.1, 17.2)	Risperidone
Triglycerides (mg/dL)	5	116	246	MD = 17.3	(3.5, 31.1)	Risperidone
Insulin, high	1	45	135	RR = 2.67	(1.1, 6.5)	Risperidone
Prolactin, high	4	64	91	RR = 0.38	(0.2, 0.6)	Olanzapine
ALT (U/L)	2	51	60	MD = 12.4	(3.2, 21.5)	Risperidone
AST (U/L)	2	51	60	MD = 7.17	(3.5, 10.8)	Risperidone
Somnolence	1	12	19	RR = 0.37	(0.1, 1.0)	Olanzapine
Olanzapine (Drug 1) Versus Ziprasidone (Drug 2)						
Weight (kg)	1	19	21	MD = 4.3	(3.0, 5.6)	Ziprasidone
Prolactin (ng/dL)	1	19	21	MD = -2.1	(-2.5, -6.7)	Ziprasidone
Quetiapine (Drug 1) Versus Risperidone (Drug 2)						
Transition to overweight or obese	1	36	135	RR = 2.57	(1.4, 4.7)	Risperidone
Ratio of triglycerides to HDL (mg/dL)	1	45	168	MD = 1.02	(0.2, 1.8)	Risperidone
Prolactin, high	3	19	77	RR = 0.21	(0.07, 0.7)	Quetiapine
Prolactin (ng/dL)	2	25	63	MD = -31.2	(-37.0, -25.3)	Quetiapine
Dyskinesia	1	2	45	RR = 46.0	(2.4, 905.6)	Risperidone
TSH (mIU/L)	1	24	22	MD = 0.9	(0.2, 1.6)	Risperidone

AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; BMI = body mass index; CI = confidence interval; cm = centimeter; dL = deciliter; HDL = high density lipoproteins; kg = kilogram; MD = mean difference; mg = milligram; mL = milliliter; N = number; ng = nanogram; ODT = orally disintegrating tablet; RR = relative risk; SGA = second-generation antipsychotic; SOT = standard oral tablet; TSH = thyroid stimulating hormone; WAE = withdrawal due to adverse event; U/L = international units per liter

* Denotes the drug with the better adverse event profile.

Strength of evidence for key adverse events that were reported by at least one study are provided in Table 33. The strength of evidence was moderate for the following outcomes: weight for olanzapine versus quetiapine, and dyslipidemia, prolactin-related and sexual adverse events, and weight for olanzapine versus risperidone. For all other key adverse events, the strength of evidence for SGAs versus SGAs was low or insufficient.

Table 33. Strength of evidence for adverse events: SGAs versus SGAs (Key Question 2)

Comparison	Outcome (N Studies; N Patients)	Strength of Evidence Domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Aripiprazole vs. olanzapine	Dyslipidemia (1; 312)	Moderate	Unknown	Direct	Precise	Low
	Insulin resistance (1; 312)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Weight (1; 312)	Moderate	Unknown	Direct	Precise	Low
Aripiprazole vs. quetiapine	Dyslipidemia (1; 312)	Moderate	Unknown	Direct	Precise	Low
	Insulin resistance (1; 312)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Weight (1; 312)	Moderate	Unknown	Direct	Precise	Low
Aripiprazole vs. risperidone	Dyslipidemia (1; 312)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Insulin resistance (1; 312)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Weight (1; 312)	Moderate	Unknown	Direct	Precise	Low

Table 33. Strength of evidence for adverse events: SGAs versus SGAs (Key Question 2) (continued)

Comparison	Outcome (N Studies; N Patients)	Strength of Evidence Domains				Strength of Evidence Domains
		ROB	Consistency	Direct	Precision	
Aripiprazole vs. ziprasidone	EPS (1; 46)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Sedation (1; 46)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Weight (1; 46)	Moderate	Unknown	Direct	Imprecise	Insufficient
Clozapine vs. olanzapine	Dyslipidemia (2; 65)	Moderate	Inconsistent	Direct	Imprecise	Low
	EPS (3; 98)	High	Inconsistent	Direct	Imprecise	Low
	Insulin resistance (1; 40)	Moderate	Consistent	Direct	Imprecise	Insufficient
	Prolactin-related / sexual AE (3; 113)	Moderate	Consistent	Direct	Precise	Low
	Sedation (3; 74)	Moderate	Consistent	Direct	Imprecise	Low
	Weight (5; 146)	Moderate	Inconsistent	Direct	Imprecise	Low
Clozapine vs. quetiapine	EPS (1; 26)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Prolactin-related / sexual AE (1; 26)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Sedation (1; 26)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Weight (1; 26)	Moderate	Unknown	Direct	Imprecise	Insufficient
Clozapine vs. risperidone	EPS (2; 58)	High	Consistent	Direct	Imprecise	Low
	Prolactin-related / sexual AE (1; 26)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Sedation (1; 26)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Weight (2; 58)	High	Consistent	Direct	Imprecise	Low
Olanzapine vs. quetiapine	Dyslipidemia (2; 366)	Moderate	Inconsistent	Direct	Imprecise	Low
	EPS (3; 96)	Moderate	Inconsistent	Direct	Imprecise	Low
	Insulin resistance (2; 366)	Moderate	Consistent	Direct	Imprecise	Low
	Prolactin-related / sexual AE (4; 130)	Moderate	Inconsistent	Direct	Imprecise	Insufficient
	Sedation (3; 96)	Moderate	Consistent	Direct	Imprecise	Low
	Weight (5; 259)	Moderate	Consistent	Direct	Precise	Moderate
Olanzapine vs. risperidone	Dyslipidemia (5; 418)	Moderate	Consistent	Direct	Precise	Moderate
	EPS (11; 533)	Moderate	Consistent	Direct	Imprecise	Low
	Insulin resistance (5; 418)	Moderate	Consistent	Direct	Imprecise	Low
	Prolactin-related / sexual AE (12; 609)	Moderate	Consistent	Direct	Precise	Moderate
	Sedation (9; 473)	Moderate	Inconsistent	Direct	Imprecise	Low
	Weight (14; 901)	Moderate	Consistent	Direct	Precise	Moderate
Olanzapine vs. ziprasidone	EPS (1; 100)	High	Unknown	Direct	Imprecise	Insufficient
	Sedation (1; 100)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Prolactin-related / sexual AE (1; 40)	Moderate	Unknown	Direct	Precise	Insufficient
	Weight (1; 40)	Moderate	Unknown	Direct	Precise	Insufficient
Quetiapine vs. risperidone	Dyslipidemia (3; 302)	Moderate	Consistent	Direct	Imprecise	Low
	EPS (3; 87)	Moderate	Inconsistent	Direct	Imprecise	Low
	Insulin resistance (2; 280)	Moderate	Consistent	Direct	Imprecise	Low
	Prolactin-related / sexual AE (5; 175)	Moderate	Consistent	Direct	Precise	Low
	Sedation (3; 87)	Moderate	Inconsistent	Direct	Imprecise	Low
	Weight (5; 369)	Moderate	Inconsistent	Direct	Imprecise	Low

AE = adverse event; EPS = extrapyramidal symptom; N = number; ROB = risk of bias; SGA = second-generation antipsychotic

SGAs Versus SGAs: Comparison of Doses and Formulations

Adverse event data were provided for dosing comparisons of the following drugs: aripiprazole,[46,67,77,121] paliperidone,[86,122] quetiapine,[73,75,84] risperidone,[50,68,69,78] and ziprasidone.[42] In addition, one study[117] compared orally disintegrating versus standard oral olanzapine tablets.

Four studies provided data on adverse events for comparisons of aripiprazole dosing.[46,67,77,121] One study[46] found a greater proportion of patients experiencing weight gain in the moderate-dose (10 mg/day) than low-dose (5 mg/day) aripiprazole group. Extrapyramidal side effects were found to be significantly more frequent in patients receiving higher aripiprazole doses (30 mg) than those receiving lower aripiprazole doses (10 mg) in two studies.[67,77] In addition, QTc intervals showed a significant decrease in the high-dose aripiprazole (30 mg/day) group compared with low-dose (10 mg/day) group ($p = 0.045$); however, the authors concluded that this difference was not clinically relevant.[77] One study[46] found higher incidence of fatigue in patients receiving moderate- or high-dose aripiprazole (15 mg/day) than low-dose (5 mg/day) aripiprazole. No other significant differences were found.

Two studies[86,122] compared three doses of paliperidone. Total adverse events were significantly more common for the high-dose group versus the low/medium-dose group in one study[86] but not in the other.[122] No other significant differences were found.

Two drug formulations for olanzapine were compared in one study.[117] Weight and BMI increased significantly more in patients receiving the standard oral tablet than in patients receiving the orally disintegrating tablet.

Three studies[73,75,84] reported adverse events comparing low- and high-dose quetiapine. No significant differences were found.

Four studies[50,68,69,78] compared low- and high-dose risperidone. In one RCT,[78] weight gain occurred significantly more frequently in patients receiving high-dose risperidone (1.5–6.0 mg/day) than in those receiving low-dose risperidone (0.15–0.6 mg/day). Another study found no significant difference in the frequency of weight gain in patients given risperidone at daily doses of 0.5–2.5 mg and 3–6 mg.[68] Prolactin elevation was greater for patients receiving the higher dose in two studies.[69,78] Two studies reported no incidence of tardive dyskinesia in either dosing groups.[68,78] Three studies[68,69,78] reported that extrapyramidal symptoms occurred significantly more frequently in patients given higher doses of risperidone than those given lower doses. Significantly more patients experienced somnolence when receiving higher doses of risperidone than lower doses in all three studies.

One study[42] compared two doses of ziprasidone. The only significant difference in adverse events between the groups was in the proportion of patients withdrawing due to adverse events, which occurred more in the high-dose ziprasidone (160 mg/day) group than the low-dose (80 mg/day) group.

Persistence of Adverse Events

Overall, resolution of adverse events was investigated in three studies.[59,96,98] In two studies, mean time to adverse event resolution was reported for akathisia[59,98] and somnolence.[98] Akathisia resolved in 48 hours for quetiapine-treated patients[59] in one study and ziprasidone-treated patients in another study.[98] In ziprasidone-treated patients, somnolence resolved in 20 days.[98] In one study comparing haloperidol, olanzapine, and risperidone, the relative rates of adverse events resolution were compared at the end of the study (8 weeks) for fatigability, constipation, depression, palpitations, pruritus, and sedation. No significant differences were found.[96]

FGAs Versus Placebo

Two studies reported the relative rates of adverse events between FGAs and placebo: haloperidol in two studies[90,99] and pimozide in one study.[99] Data were not reported for the following adverse event categories: mortality, cerebrovascular events, dyslipidemia, insulin resistance and diabetes, liver toxicity, neutropenia and agranulocytosis, thyroid dysfunction, seizures, neuroleptic malignant syndrome, constipation, exercise intolerance, precocious puberty, and dermatological adverse events. Effect estimates and 95 percent confidence intervals for the significant findings are presented in Table 34.

Total Adverse Events

Treatment-limiting adverse events occurred in a significantly greater proportion of patients treated with haloperidol than placebo.[99]

Weight Gain/Body Composition

One study showed no significant difference between placebo and haloperidol or pimozide for weight gain.[99]

Prolactin-Related and Sexual Adverse Events

Prolactin levels were significantly higher in patients treated with haloperidol and pimozide than placebo.[99]

Neuromotor Adverse Events

Tardive dyskinesia was not reported in studies. No significant difference was found in extrapyramidal events between haloperidol versus placebo[90,99] and pimozide versus placebo.[99]

Cardiac Adverse Events

One study showed no significant difference in electrocardiovascular measures between haloperidol or pimozide and placebo.[99]

Sedation

One study[99] found a significantly greater rate of drowsiness in the haloperidol group than placebo.

Behavioral Side Effects

There was no significant difference in anxiety or depression between haloperidol and placebo or pimozide and placebo in one study.[99]

Table 34. Significant findings for adverse events: FGAs versus placebo

Adverse Event	# Studies	N (Drug 1)	N (Drug 2)	Effect Estimate	95% CI	Favors*
Haloperidol (Drug 1) Versus Placebo (Drug 2)						
Treatment-limiting SE	1	22	22	RR = 19.00	(1.2, 307.6)	Placebo
Prolactin	1	19	25	MD = 6.1	(2.2, 10.0)	Placebo
Drowsiness	1	22	22	RR = 17.00	(1.0, 277.6)	Placebo
Pimozide (Drug 1) Versus Placebo (Drug 2)						
Prolactin	1	25	25	MD = 14.8	(7.1, 22.5)	Placebo

CI = confidence interval; FGA = first-generation antipsychotic; MD = mean difference; N = number; RR = relative risk; SE = side effect

* Denotes the drug with the better adverse event profile.

Strength of evidence grades for key adverse events that were reported by at least one study are provided in Table 35. The strength of evidence was insufficient for all key adverse events.

Table 35. Strength of evidence for adverse events: FGAs versus placebo (Key Question 2)

Comparison	Outcome (N Studies; N Patients)	Strength of Evidence Domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
FGA vs. placebo	EPS (2; 38)	Moderate	Consistent	Direct	Imprecise	Insufficient
	Prolactin-related / sexual AE (1; 22)	Moderate	Unknown	Direct	Precise	Insufficient
	Sedation (1; 16)	Moderate	Unknown	Indirect	Precise	Insufficient
	Weight (1; 22)	Moderate	Unknown	Direct	Imprecise	Insufficient

AE = adverse event; EPS = extrapyramidal symptom; FGA = first-generation antipsychotic; N = number; ROB = risk of bias

SGAs Versus Placebo

A total of 36 studies reported the relative rates of adverse events between SGAs and placebo. SGA comparisons included aripiprazole,[46,67,72,77] olanzapine,[43,71,80,93,123] paliperidone,[86] quetiapine,[59,65,66,73,84] risperidone,[44,47,49,50,52,53,55-58,60-62,68,69,101,104,105] and ziprasidone.[70,85,98] The findings for each adverse event are provided below. The following adverse events were not reported: cerebrovascular events, exercise intolerance, and precocious puberty. Effect estimates and 95 percent confidence intervals for the significant findings are presented in Table 36.

Total Adverse Events

Total adverse events were significantly higher for patients treated with aripiprazole than placebo in a meta-analysis of two studies.[46,67] A significantly greater number of patients receiving quetiapine experienced any adverse event[73,84] or withdrawal due to an adverse event than placebo.[59,65,66,73,84] Eight of 10 studies[52,55,57,58,60-62,68,69,104] showed that a significantly greater number of patients in the risperidone group experienced an adverse event than the placebo group; however, the studies could not be pooled due to heterogeneity. Treatment with ziprasidone resulted in significantly more patients with adverse events than placebo in a meta-analysis of three studies.[70,85,98]

Mortality

Studies found no difference in mortality for the following placebo comparisons: aripiprazole,[46,67,77] olanzapine,[71,80] paliperidone,[86] quetiapine,[73,84] risperidone,[44,68,69] or ziprasidone.[70,85]

Weight Gain/Body Composition

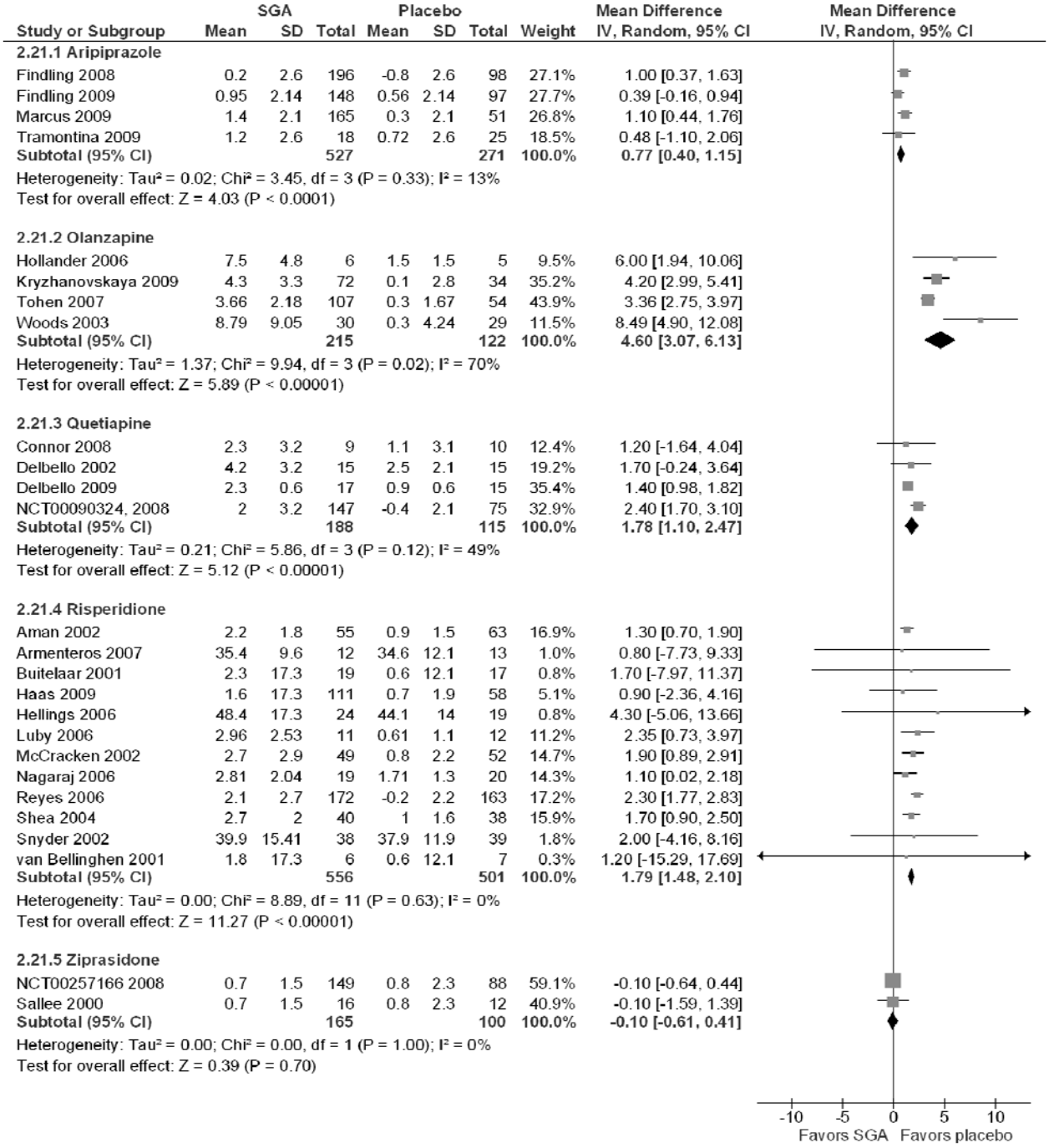
A meta-analysis of two studies[46,77] found that weight gain occurred in a significantly greater proportion of patients treated with aripiprazole than placebo. Similarly, meta-analyses favored placebo over aripiprazole for mean weight gain[46,67,72,77] (Figure 52) and change in BMI.[46,67,77] Mean weight gain (Figure 52) and weight gain of greater than 7 percent occurred significantly more frequently in olanzapine-treated patients than placebo in a meta-analysis of four studies.[43,71,80,93] Similarly, change in BMI favored placebo over olanzapine.

Placebo was favored over quetiapine for the proportion of patients experiencing weight gain, mean weight, and mean BMI.[59,73]

Risperidone-treated patients showed a significantly greater increase in mean weight in a meta-analysis of 12 studies[44,47,49,52,55,57,58,61,62,68,104,105] (MD = 1.79; 95% CI, 1.48 to 2.10) (Figure 52) and BMI in a meta-analysis of five studies.[47,55,61,62,68]

The studies were not pooled across all SGAs due to heterogeneity. Overall, olanzapine showed a greater magnitude of the effect for weight gain over placebo than the other SGAs. This finding is consistent with direct comparisons of SGAs above, in which olanzapine showed a significantly greater increase on weight and body composition measures than other SGAs.

Figure 52. SGAs versus placebo for mean weight gain (kg)



CI = confidence interval; df = degrees of freedom; IV = inverse variance; kg = kilogram; SD = standard deviation; SGA = second-generation antipsychotic

Dyslipidemia

Total cholesterol levels were elevated in a significantly greater proportion of patients treated with aripiprazole than those receiving placebo.[67] Two meta-analyses found elevated triglycerides[71,80] and abnormal cholesterol[71] to be significantly more frequent with olanzapine than placebo. Mean triglycerides levels were higher for olanzapine in one study[80] and for quetiapine in two studies.[65,84]

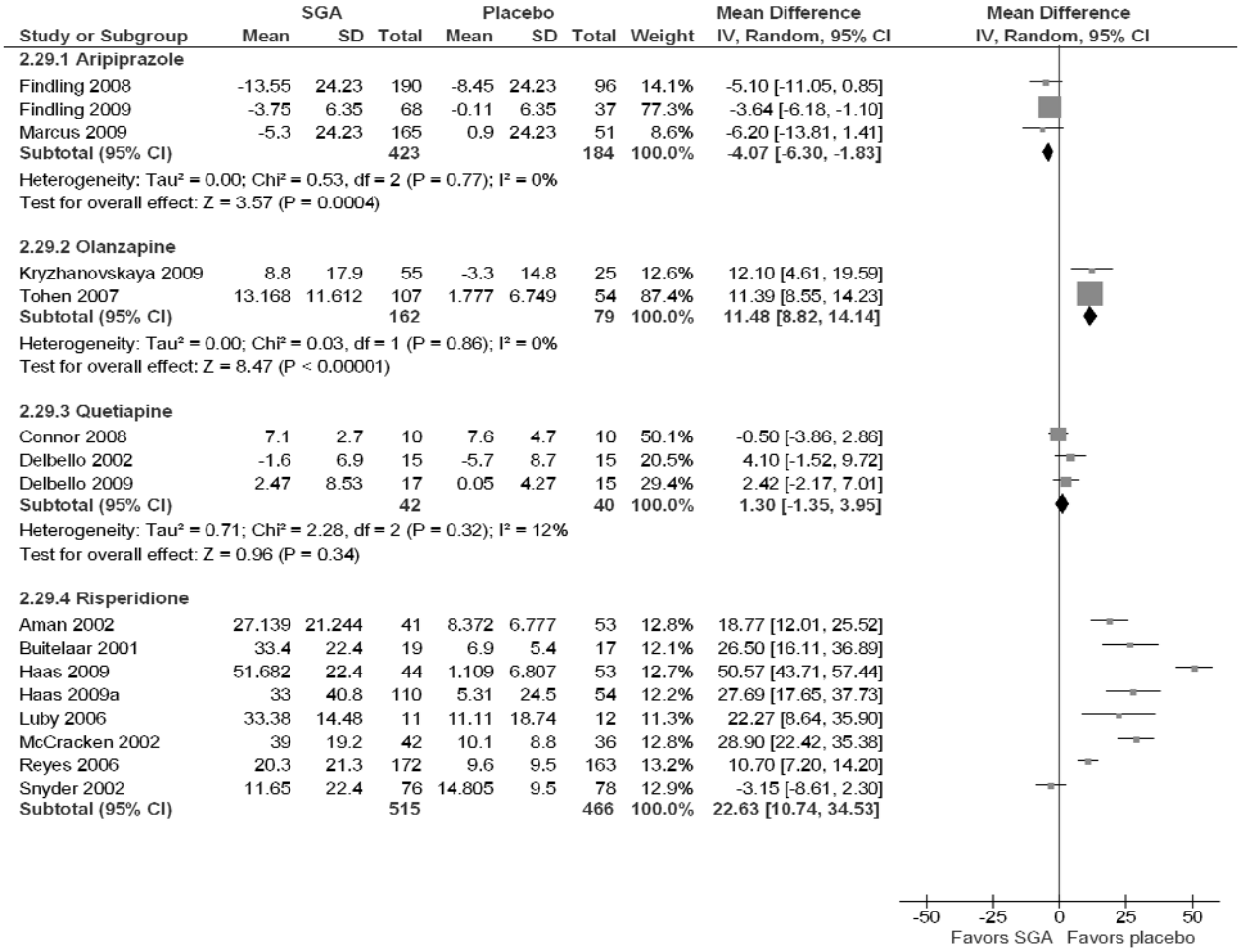
Insulin Resistance and Diabetes

No difference was found between paliperidone and placebo for insulin resistance[86] or between quetiapine and placebo for development of diabetes.[65] In addition, there was no significant difference in glucose levels between placebo and the following SGAs: aripiprazole,[46,67,77] olanzapine,[71,80,93] paliperidone,[86] quetiapine,[65] or risperidone.[68] All studies ranged between 3 and 8 weeks in duration; therefore, the studies were likely too short to detect changes in insulin resistance or risk of diabetes.

Prolactin-Related and Sexual Adverse Events

Figure 53 provides a meta-graph of the changes in prolactin levels comparing SGAs and placebo. Mean prolactin levels showed greater decrease with aripiprazole than with placebo in a meta-analysis of three studies.[46,67,77] The proportion of patients with high prolactin as well as mean prolactin levels were significantly greater for olanzapine versus placebo in a meta-analysis of two studies.[71,80] No significant difference was seen for prolactin levels between quetiapine and placebo. Placebo was significantly favored over risperidone for change in prolactin levels in seven of eight studies;[44,47,57,58,61,62,68,69] however, studies could not be pooled due to heterogeneity.

Figure 53. SGAs versus placebo for change in prolactin levels (ng/L)



CI = confidence interval; df = degrees of freedom; IV = inverse variance; ng/L = nanogram per liter; SD = standard deviation; SGA = second-generation antipsychotic

Neuromotor Adverse Events

Tardive dyskinesia was rare and not significantly different between risperidone and placebo in six studies.[52,61,62,68,78,105,] Extrapyramidal side effects, including Parkinsonism and myoclonus, occurred significantly more frequently with aripiprazole than with placebo in a meta-analysis of four studies.[46,67,72,77] Extrapyramidal symptoms were significantly more common among risperidone-treated patients than patients receiving placebo in a meta-analysis of eight studies.[47,52,57,60-62,68,101] One study[85] showed a significantly higher rate of extrapyramidal symptoms with ziprasidone versus placebo.

Cardiac Adverse Events

A significantly greater rate of tachycardia occurred with quetiapine treatment[65,73,84] than placebo. Supine systolic blood pressure[71] and pulse[71,93] were significantly lower for placebo than for olanzapine. Blood pressure and pulse were significantly higher with quetiapine than with placebo in one study.[65] A meta-analysis of four studies[52,56,62,104] showed a greater increase in pulse with risperidone than placebo.

Sedation

Sedation[46] and somnolence[46,67,72,77] occurred significantly more frequently in the aripiprazole group than in the placebo group. Rate of fatigue[93] was significantly higher with olanzapine than with placebo. Somnolence was significantly more common among patients treated with quetiapine than placebo in two studies.[73,84] Two meta-analyses showed rates of sedation[44,49,57,60,68] and fatigue[47,52,58,61,62,68] occurred significantly more frequently for risperidone than for placebo. Ziprasidone resulted in significantly greater rates of somnolence[70,85,98] and fatigue[70,85] than placebo.

Liver Toxicity

Patients treated with olanzapine experienced elevated alanine transaminase and aspartate amino transferase significantly more frequently than patients who received placebo in one study.[71] Mean alanine transaminase, aspartate amino transferase, and gamma-glutamyl transpeptidase levels were significantly higher with olanzapine than with placebo.[71,80]

Neutropenia and Agranulocytosis

White blood cell count was significantly lower in patients treated with quetiapine than in those receiving placebo.[66]

Thyroid Dysfunction

There was no significant difference between quetiapine and placebo for incidence of hypothyroidism or measures of thyroid dysfunction.[66,84]

Seizures

No difference was found in seizure rates between placebo and aripiprazole,[46,72] paliperidone,[86] or risperidone[47]

Neuroleptic Malignant Syndrome

Two studies reported no incidence of neuroleptic malignant syndrome in either the paliperidone and placebo[86] or risperidone and placebo.[105]

Constipation

A meta-analysis of three studies[44,47,52] showed that constipation occurred significantly more frequently among patients treated with risperidone than those receiving placebo.

Behavioral Adverse Events

The studies assessed a variety of adverse events, including agitation, aggression, and anxiety. No significant differences between the SGA drugs and placebo were observed.

Dermatological Events

No significant differences in dermatological adverse events, such as rashes, itching, or dry skin, were reported between placebo and aripiprazole,[46,72] risperidone,[47,60,68] or ziprasidone.[70,85]

Table 36. Significant findings for adverse events: SGAs versus placebo

Adverse Event	# Studies	N (Drug 1)	N (Drug 2)	Effect estimate	95% CI	Favors*
Aripiprazole (Drug 1) Versus Placebo (Drug 2)						
Total AE	2	362	148	RR = 1.24	(1.1, 1.4)	Placebo
Weight (kg)	4	527	271	MD = 0.77	(0.4, 1.2)	Placebo
Weight gain	2	361	149	RR = 3.81	(1.2, 12.4)	Placebo
BMI	3	508	214	MD = 0.23	(0.1, 0.4)	Placebo
Total cholesterol, elevated	1	55	65	RR = 2.50	(1.4, 4.4)	Placebo
Prolactin (ng/ml)	3	423	184	MD = -4.1	(-6.3, -1.8)	Aripiprazole
EPS	4	582	273	RR = 4.16	(2.4, 7.2)	Placebo
Parkinsonism	2	399	197	RR = 3.89	(2.1, 7.1)	Placebo
Myoclonus	2	399	197	RR = 3.98	(2.2, 7.1)	Placebo
Sedation	1	165	51	RR = 4.02	(1.3, 12.5)	Placebo
Somnolence	4	582	273	RR = 2.67	(1.1, 6.5)	Placebo
Olanzapine (Drug 1) Versus Placebo (Drug 2)						
Weight (kg)	4	215	122	MD = 4.60	(3.1, 6.1)	Placebo
Weight gain	3	109	69	RR = 3.63	(1.9, 6.8)	Placebo
Weight–gain ≥7%	4	215	122	RR = 6.57	(2.1, 20.5)	Placebo
BMI	2	179	88	MD = 1.28	(0.96, 1.6)	Placebo
Triglycerides (mg/dL)	1	55	25	MD = 37.2	(8.9, 65.5)	Placebo
Triglycerides, abnormal/high (endpoint)	2	179	89	RR = 2.42	(1.2, 4.9)	Placebo
Cholesterol, abnormal	1	107	54	RR = 10.1	(1.4, 73.2)	Placebo
Cholesterol, increase	1	75	34	RR = 7.25	(1.0, 52.5)	Placebo
Prolactin (ng/ml), change	2	162	79	MD = 11.5	(8.8, 14.1)	Placebo
Prolactin, high	2	179	89	RR = 8.88	(1.5, 52.5)	Placebo
SBP, supine	1	107	54	MD = 5.89	(2.3, 9.5)	Placebo
Pulse, sitting	1	29	29	MD = 9.27	(1.5, 17.1)	Placebo
Pulse, standing	2	135	83	MD = 9.52	(5.1, 14.0)	Placebo
Pulse, supine	1	107	54	MD = 10.18	(5.9, 14.5)	Placebo
Fatigue	1	31	29	RR = 8.42	(1.1, 62.4)	Placebo
ALT (U/L)	2	177	88	MD = 22.5	(14.3, 30.7)	Placebo
AST (U/L)	2	177	88	MD = 8.98	(5.2, 12.8)	Placebo
GGT (U/L)	1	70	34	MD = 8.6	(2.7, 14.5)	Placebo
ALT high	1	107	54	RR = 18.17	(2.6, 129.0)	Placebo
AST high	1	107	54	RR = 12.11	(1.7, 87.2)	Placebo

Table 36. Significant findings for adverse events: SGAs versus placebo (continued)

Adverse Event	# Studies	N (Drug 1)	N (Drug 2)	Effect estimate	95% CI	Favors*
Quetiapine (Drug 1) Versus Placebo (Drug 2)						
Total AE	2	340	165	RR = 1.26	(1.1, 1.4)	Placebo
WAE	5	381	205	RR = 2.53	(1.2, 5.4)	Placebo
Weight (kg)	4	188	115	MD = 1.78	(1.1, 2.5)	Placebo
Weight gain	2	202	100	RR = 5.19	(1.0, 27.6)	Placebo
BMI	1	17	15	MD = 0.6	(0.4, 0.8)	Placebo
Triglyceride (mg/dL)	2	164	90	MD = 29.1	(7.3, 50.9)	Placebo
Triglyceride, high	3	357	180	RR = 2.36	(1.1, 5.4)	Placebo
SBP, standing	1	17	15	MD = 13	(1.2, 24.8)	Placebo
SBP, supine	1	17	15	MD = 12	(5.8, 18.3)	Placebo
DBP	1	17	15	MD = 11	(3.0, 19.0)	Placebo
Pulse, change	1	17	15	MD = 14	(5.7, 22.3)	Placebo
Tachycardia	3	357	180	RR = 9.54	(1.9, 49.1)	Placebo
WBC (10^3/µL)	1	15	15	MD = -1.5	(-2.0, -1.0)	Placebo
Somnolence	2	340	165	RR = 3.41	(2.0, 5.8)	Placebo
Risperidone (Drug 1) Versus Placebo (Drug 2)						
Weight (kg)	12	556	501	MD = 1.79	(1.5, 2.1)	Placebo
BMI	5	397	343	MD = 0.57	(0.4, 0.8)	Placebo
EPS	8	431	380	RR = 2.65	(1.4, 4.9)	Placebo
EPS-related AE	1	106	54	RR = 2.42	(1.2, 4.8)	Placebo
Pulse	4	114	117	MD = 6.42	(3.5, 9.4)	Placebo
Sedation	5	206	163	RR = 2.90	(1.5, 5.5)	Placebo
Fatigue/Tiredness	6	444	385	RR = 4.58	(1.5, 14.0)	Placebo
Constipation	3	100	102	RR = 2.72	(1.3, 5.9)	Placebo
Ziprasidone (Drug 1) Versus Placebo (Drug 2)						
Total AE	3	358	190	RR = 1.40	(1.2, 1.6)	Placebo
EPS	1	193	90	RR = 10.26	(1.4, 74.9)	Placebo
Somnolence	3	358	190	RR = 2.98	(1.7, 5.2)	Placebo
Fatigue	2	342	178	RR = 1.97	(1.0, 3.9)	Placebo

AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; BMI = body mass index; CI = confidence interval; DBP = diastolic blood pressure; dl = deciliter; EPS = extrapyramidal symptom; GGT = gamma-glutamyl transpeptidase; kg = kilogram; MD = mean difference; mg = milligram; ml = milliliter; N = number; ng = nanogram; RR = relative risk; SBP = systolic blood pressure; SGA = second-generation antipsychotic; U/L = units per liter; WBC = white blood cell; WAE = withdrawal due to adverse event

***** Denotes the drug with the better adverse event profile.

Strength of evidence grades for key adverse events that were reported by at least one study are provided in Table 37. The strength of evidence was moderate for numerous outcomes: weight gain (aripiprazole, olanzapine, quetiapine, and risperidone), dyslipidemia (quetiapine), extrapyramidal symptoms (aripiprazole and risperidone), prolactin-related events (aripiprazole and olanzapine), and sedation (risperidone and ziprasidone). All of these outcomes favored placebo, except prolactin levels, which were lower with aripiprazole than placebo.

Table 37. Strength of evidence for adverse events: SGAs versus placebo (Key Question 2)

Comparison	Outcome (N studies; N patients)	Strength of Evidence Domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Aripiprazole vs. placebo	Dyslipidemia (2; 514)	Moderate	Inconsistent	Direct	Precise	Low
	EPS (4; 859)	Moderate	Consistent	Direct	Precise	Moderate
	Insulin resistance (3; 816)	Moderate	Consistent	Direct	Imprecise	Low
	Prolactin-related / sexual AE (3;816)	Moderate	Consistent	Direct	Precise	Moderate
	Sedation (4; 859)	Moderate	Consistent	Direct	Precise	Low
	Weight (4; 859)	Moderate	Consistent	Direct	Precise	Moderate
Olanzapine vs. placebo	Dyslipidemia (2; 268)	Moderate	Inconsistent	Direct	Precise	Low
	EPS (3; 232)	Moderate	Inconsistent	Direct	Imprecise	Low
	Insulin resistance (3; 328)	Moderate	Consistent	Direct	Imprecise	Low
	Prolactin-related / sexual AE (2; 268)	Moderate	Consistent	Direct	Precise	Moderate
	Sedation (3; 178)	Moderate	Consistent	Direct	Imprecise	Low
	Weight (4; 339)	Moderate	Consistent	Direct	Precise	Moderate
Paliperidone vs. placebo	Insulin resistance (1; 201)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Weight (1; 201)	Moderate	Unknown	Direct	Imprecise	Insufficient
Quetiapine vs. placebo	Dyslipidemia (3; 538)	Moderate	Consistent	Direct	Imprecise	Low
	EPS (3; 271)	Moderate	Inconsistent	Direct	Imprecise	Low
	Insulin resistance (2; 316)	Moderate	Inconsistent	Direct	Imprecise	Insufficient
	Prolactin-related / sexual AE (5; 587)	Moderate	Consistent	Direct	Imprecise	Low
	Sedation (5; 587)	Moderate	Inconsistent	Direct	Imprecise	Low
	Weight (5; 587)	Moderate	Consistent	Direct	Precise	Moderate
Risperidone vs. placebo	Dyslipidemia (1; 170)	Moderate	Unknown	Direct	Imprecise	Insufficient
	EPS (15; 1289)	Moderate	Consistent	Direct	Precise	Moderate
	Insulin resistance (2; 330)	Moderate	Consistent	Direct	Imprecise	Insufficient
	Prolactin-related / sexual AE (9; 1180)	Moderate	Inconsistent	Direct	Precise	Low
	Sedation (13; 1235)	Moderate	Consistent	Direct	Precise	Moderate
	Weight (12; 1081)	Moderate	Consistent	Direct	Precise	Moderate
Ziprasidone vs. placebo	EPS (3; 550)	Moderate	Consistent	Direct	Precise	Low
	Prolactin-related / sexual AE (1; 28)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Sedation (3; 488)	Moderate	Consistent	Direct	Precise	Moderate
	Weight (3; 488)	Moderate	Consistent	Direct	Imprecise	Low

AE = adverse event; EPS = extrapyramidal symptom; N = number; ROB = risk of bias; SGA = second-generation antipsychotic

Key Question 4: Subpopulations

Overall, 36 of the 81 studies analyzed outcomes by various patient and disease characteristics. Nine relevant subgroups were identified a priori: sex, age, race, comorbidities, cotreatment, history of psychosis, duration of illness, duration of treatment, and treatment history. Data on subpopulations are presented separately for each condition and are organized by outcome (i.e., efficacy or harm). Most of the significant correlations were based on single studies. Table 38 through Table 44 outline the type of analysis used, patient and disease variables examined, outcomes, and author conclusions for each study.

Pervasive Developmental Disorders

Three studies of pervasive developmental disorders conducted an analysis of outcomes in different subpopulations (Table 38).[47,51,54]

Three studies found no significant effect of age on response[54] or relapse[47,51] after treatment with a variety of FGAs and SGAs, including risperidone and haloperidol. One retrospective cohort study[54] examined the impact of mental retardation and nonpharmacological cotreatment on response rate. A significantly higher response rate was found in patients with no mental retardation and in patients who received at least one nonpharmacological intervention in addition to the antipsychotic therapies given (various FGAs, various SGAs, risperidone, or a combination of FGAs and SGA).

One RCT[47] found no impact of sex or age on weight gain in patients given risperidone.

Table 38. Differences between pervasive development disorder subpopulations on outcomes

Author, Year Comparison	Type of Analysis	Outcome	Authors' Conclusions
McCracken, 2002[47] *Risperidone vs. placebo*	Regression analysis for age, IQ, baseline ABC irritability	Relapse	There was no significant difference in age, IQ and baseline ABC irritability scores between relapsing and non-relapsing patients.
	Regression analysis for age, dose, sex, IQ, site, Tanner stage, and the following at baseline: ABC, Child Symptom Inventory, YBOCS, heart rate, BP, weight, initial leptin change	Weight	None of the variables or combinations of the variables listed were predictors of weight gain.
	Regression analysis for age, baseline BMI, caloric intake	BMI	There was no significant effect of age, baseline BMI or caloric intake on BMI z-score.
Novaes, 2008[54] *FGA vs. risperidone vs. other SGA vs. FGA+SGA*	Subgroup analysis by age, comorbidity (MR), cotreatment (nonpharmacological), duration of treatment, health care setting	Response (CGI–I≤2)	Patients with no MR had a significant greater response than patients with MR. Patients treated with at least one nonpharmacological intervention in addition to the principle treatment had greater clinical improvement than patients with no additional treatment. No significant improvements were observed as a function of age, health care clinic, or duration of treatment.
Perry, 1989[51] *Continuous haloperidol vs. discontinuous haloperidol*	Subgroup analysis by age, developmental quotient, baseline rating scores	Severe deterioration (CGI–I difference)	Patients with high baseline CPRS Conduct Problem Factor scores and patients with significant improvement before the antipsychotic withdrawal regimen showed significant deterioration than patients without these variables. All other variables did not predict deterioration.

ABC = Aberrant Behavior Checklist; BMI = body mass index; BP = blood pressure; CGI–I = Clinical Global Impressions–Improvement; CPRS = Children's Psychiatric Rating Scale; FGA = first-generation antipsychotic; IQ = intelligence quotient; MR = mental retardation; SGA = second-generation antipsychotic; YBOCS = Yale-Brown Obsessive Compulsive Scale

ADHD and Disruptive Behavior Disorders

Five studies of ADHD and disruptive behavior disorders conducted an analysis of outcomes in different subpopulations (Table 39).[57,58,60-62] All studies compared risperidone and placebo.

Two studies found no effect of age on the Rating of Aggression Against People and/or Property scale,[60] CPRS,[60] rate of study completion,[60] and risk of symptom recurrence.[61] In one

study, race was not significantly different in patients who completed the study than those who did not.[60] Snyder et al.[62] found no impact of comorbidities (including mental retardation, ADHD, and secondary diagnosis of disruptive behavior disorders) or cotreatment with psychostimulants on NCBRF conduct problem subscale. Two studies examined the effect of previous treatment on ABC,[58] CGI–S,[58] and NCBRF conduct problem subscale.[62] Risperidone-naïve patients had lower NCBRF conduct problem scores in one study,[62] whereas prior treatment had no impact on symptom severity (ABC, CGI–S) in another study.[58]

Two studies assessed the impact of sex on prolactin levels while on risperidone. Females experienced a greater increase in prolactin levels than males in one study.[61] A second study found that males but not females experienced a significant increase in prolactin levels.[57] Reyes et al. found no effect of age on total adverse events.[61] However, weight gain was more frequent in children younger than 12 years than children older than 12 years (nonsignificant).[61] Snyder et al.[62] found no impact of cotreatment with psychostimulants or history of previous treatment on weight gain. Risperidone-naïve patients had lower prolactin levels and reported sedation more frequently than patients who were previously treated with risperidone.[62]

Table 39. Differences between ADHD and disruptive behavior disorder subpopulations on outcomes

Author, Year Comparison	Type of Analysis	Outcome	Authors' Conclusions
Aman, 2002[57] *Risperidone vs. placebo*	Subgroup analysis by sex	Prolactin	Males had a significantly greater increase in prolactin levels on risperidone than placebo, whereas increase in mean prolactin levels was not significant for females.
Buitelaar, 2001[58] *Risperidone vs. placebo*	Subgroup analysis by IQ and use of prior medication	CGI–S, ABC (school)	No significant difference in rating scale change scores between IQ strata (60–69, 70–79, 80–90) or previous use of medication.
Findling, 2000[60] *Risperidone vs. placebo*	Regression analysis by age, race, and baseline RAAPP and CGI–S scores	Completion of study	Age, race, baseline RAAPP score, and baseline CGI–S score was not significantly different between completers and noncompleters.
		RAAPP, CPRS	When an adjustment for age was made, no alteration in rating scales scores were observed
Reyes, 2006[61] *Risperidone vs. placebo*	Subgroup analysis by sex, age, diagnosis, disease severity	Risk for symptom recurrence	Sex, age, diagnosis and baseline disruptive behavior severity did not affect risk for symptom recurrence.
	Subgroup analysis by age	Weight, AE	Weight gain was reported more frequently in children <12 years of age than those ≥12 years; however this trend was not significant. Other AEs were comparable between age groups.
	Subgroup analysis by sex	Prolactin	Females experienced greater increase in prolactin levels than males.

Table 39. Differences between ADHD and disruptive behavior disorder subpopulations on outcomes (continued)

Author, Year Comparison	Type of Analysis	Outcome	Authors' Conclusions
Snyder, 2002[62] *Risperidone vs. placebo*	Regression analysis by comorbidity, cotreatment, treatment history, condition	NCBRF conduct problem	The efficacy of risperidone was not affected by level of MR, presence of somnolence, ADHD, use of psychostimulants or type of disorder (CD, ODD, DBD–NOS). Conduct problems scores were lower in patients previously treated with risperidone than patients who were risperidone naïve.
		Weight	Cotreatment with psychostimulant had no impact on weight. Mean weight increase was similar between patients who were risperidone-naïve and those previously treated.
		Prolactin	Risperidone-naïve patients had significantly lower prolactin levels than those previously treated with risperidone at extension study entry.
		Sedation	Sedation increased among risperidone-naïve patients, but not among previously treated patients.

ABC = Aberrant Behavior Checklist; ADHD = attention deficit hyperactivity disorder; AE = Adverse Event; CD = conduct disorder; CGI–S = Clinical Global Impressions–Severity; CPRS = Children's Psychiatric Rating Scale; DBD = disruptive behavior disorder; IQ = intelligence quotient; MR = mental retardation; NCBRF = Nisonger Child Behavior Rating Form; NOS = not otherwise specified; ODD = oppositional defiant disorder; RAAPP = Rating of Aggression Against People and/or Property

Bipolar Disorder

Six studies examining bipolar disorder conducted an analysis of patient outcomes in different subpopulations (Table 40).[65,67,68,71-73] All studies were placebo-controlled and evaluated SGAs.

Sex, age, and race had no significant impact on YMRS scores in one placebo-controlled RCT comparing risperidone dosing regimens.[68] There was no impact of age on YMRS or Swanson, Nolan and Pelham Scale scores in patients treated with aripiprazole.[72] Another study[71] examined the impact of comorbidities and bipolar subtypes on CGI–BP and YMRS in patients treated with olanzapine. Diagnosis of comorbid ADHD and bipolar diagnostic subtypes did not alter treatment outcomes.[71] In addition, concomitant use of psychostimulants had no effect on YMRS scores.[71]

Two studies assessed the impact of sex on prolactin levels.[67,71] Prolactin levels were lower in males than females in one study.[67] Greater changes in prolactin levels were reported in males than females in a second study.[71] Age had no significant impact on total adverse events[68,73] and weight gain measures.[72] Adverse events were not affected by cotreatment in one placebo-controlled RCT of quetiapine.[73]

Table 40. Differences between bipolar disorder subpopulations on outcomes

Author, Year Comparison	Type of Analysis	Outcome	Authors' Conclusions
DelBello, 2009[65] *Quetiapine vs. placebo*	Subgroup analysis by inpatient status, site	Symptom rating scales	There was no difference in the change scores on rating scales between inpatient and outpatient participants, and study center.
Findling, 2009[67] *Low- vs. high-dose aripiprazole vs. placebo*	Subgroup analysis by sex	Prolactin	Decreases in prolactin levels were more pronounced for males than for females.
Haas, 2009[68] *Low- vs. high-dose risperidone vs. placebo*	Subgroup analysis by age	YMRS	Patients ≤12 and >12 years had significantly more improvement with risperidone than placebo.
		AE	The type and rate of AEs were generally similar between risperidone-treated patients ≤12 or >12 years. For the low dose risperidone, patients >12 years experienced slightly higher rates of somnolence and headache.
	Subgroup analysis by sex, race, diagnosis, or hospitalization	YMRS	Risperidone was consistently more effective than placebo regardless or sex, race, diagnosis, or hospitalization at screening.
NCT00090311, 2008[73] *Low- vs. high dose quetiapine vs. placebo*	Subgroup analysis by age, cotreatment	AEs	The most common AEs (increased appetite and tachycardia) occurred more frequently in quetiapine-treated patients in the 10–12 year age group. The incidence of individual common AEs was higher in concomitant psychostimulant users in the high-dose quetiapine group.
Tohen, 2007[71] *Olanzapine vs. placebo*	Regression analysis controlling for comorbidities, cotreatment, bipolar subtypes, age of onset, sex	CGI–BP	Current diagnosis of ADHD, number of previous depressive episodes and rapid cycling did not significantly alter the outcome.
		YMRS	There was no significant therapy-by-subgroup interaction on the YMRS for the following subgroups: mania type, rapid cycling, psychosis, ADHD, ODD, or age. Concomitant use of psychostimulants did not differentially affect YMRS scores.
		Prolactin	A greater proportion of males had changes in prolactin levels than females.
Tramontina, 2009[72] *Aripiprazole vs. placebo*	Regression analysis controlling for age	YMRS SNAP–IV Weight / BMI	There was no significant difference between patients ≤10 and >10 years of age for any primary outcome measure.

ADHD = attention deficit hyperactivity disorder; AE = Adverse Event; BMI = body mass index; CGI–BP = Clinical Global Impression–bipolar; ODD = oppositional defiant disorder; SNAP–IV = Swanson, Nolan and Pelham Scale–Version IV; YMRS = Young Mania Rating Scale

Schizophrenia and Related Psychosis

Ten studies examining the efficacy of antipsychotics in patients with schizophrenia and related psychoses conducted an analysis of patient outcomes in different subpopulations (Table 41).[69,78,80,84,89,90,93,96,109,117]

Three studies examined the impact of age on global clinical judgments rating,[90] treatment response,[89] and conversion to psychosis.[93] Younger patients experienced only mild or moderate improvement on the global clinical judgments rating scale on haloperidol than older patients.[90] Age had no impact on response rate or conversion to psychosis. One study[93] found that race (African American) predicted conversion to psychosis.

One study[89] investigated the effect of antipsychotic monotherapy compared with treatment with an antipsychotic plus concomitant antidepressant and/or mood stabilizers on response rate. The study found no significant difference in response rate between subgroups in patients given

haloperidol, olanzapine, or risperidone. Woods et al.[93] analyzed the effect of history of psychosis and duration of prodromal symptoms on neurocognitive performance in olanzapine-treated patients. Patients with first-episode psychosis were significantly more impaired on neurocognitive function test than patients at risk for psychosis. Two studies found no impact of illness duration on global clinical judgments rating[90] or neurocognitive performance.[93]

Five studies assessed the effect of sex on outcomes including weight gain,[96,117] BMI,[96] or prolactin levels.[69,78,109] Girls experienced greater weight and BMI increases than boys in one study.[96] In another study, weight gain greater than 7 percent from baseline occurred more frequently in males than in females.[117] Findings in both studies were not significant. Prolactin levels were significantly higher in females than males in patients given clozapine[109] or risperidone.[69,78] One study found no impact of illness duration or previous antipsychotic use on weight gain.[96]

Table 41. Differences between schizoprenia and related psychoses subpopulations on outcomes

Author, Year Comparison	Type of Analysis	Outcome	Authors' Conclusions
Crocq, 2007[117] *Olanzapine ODT vs. SOT vs. risperidone*	Subgroup analysis by sex	Weight	Weight and BMI increase was consistently but not statistically greater in girls than boys in all treatment groups.
Haas, 2009[78] *Low- vs. high-dose risperidone*	Subgroup analysis by sex	Prolactin	Mean increases in prolactin levels were greater in females than males.
Haas, 2009[69] *Low- vs. high-dose risperidone*	Subgroup analysis by sex	Prolactin	Mean change in prolactin levels were higher in females than males.
Kryzhanovskaya, 2009[80] *Olanzapine vs. placebo*	Subgroup analysis by country	Response	The response rate did not differ significantly by country.
NCT00090324, 2008[84] *Low- vs. high-dose quetiapine vs. placebo*	Subgroup analysis by geographical region	AE	Incidence of AEs was higher in treatment group over placebo, regardless of region.
Ratzoni, 2002[96] *Haloperidol vs. olanzapine vs. risperidone*	Regression analysis by sex, treatment history, illness duration, dose, baseline weight, parental BMI, concern about weight gain, history of diet	Weight	Patients with lower baseline weight showed a significantly greater increase in weight. Paternal, but not maternal, BMI was significantly correlated with patient weight gain. Weight gain ≥7% occurred more frequently among males than females (nonsignificant). History of dieting, previous antipsychotic use, medication dose and duration of illness were not associated with weight gain.
		BMI	Among patients who showed concerned about weight gain, males showing an increase in BMI, but females did not.

Table 41. Differences between schizoprenia and related psychoses subpopulations on outcomes (continued)

Author, Year Comparison	Type of Analysis	Outcome	Authors' Conclusions
Sikich, 2003[89] *Haloperidol vs. olanzapine vs. risperidone*	Subgroup analysis by age, cotreatment, treatment history, diagnosis, baseline symptom severity	Response	No significant relationship between response status and age, diagnosis, prior antipsychotic exposure or baseline severity of symptoms. Also, there was no significant difference in response rate between patients treated exclusively with antipsychotic, treated with either concomitant antidepressant or mood stabilizer, or both concomitant antidepressant and mood stabilizer.
Spencer, 1994[90] *Haloperidol vs. placebo*	Subgroup analysis by age, age of onset, IQ	Global clinical judgments rating	Patients with only mild or moderate improvement tended to be younger, have earlier onset of psychosis, be diagnosed with schizophrenia at a younger age and have a lower IQ.
Woods, 2003[93] *Olanzapine vs. placebo*	Subgroup analysis by age, race, IQ, baseline neuropsychological status	Conversion to psychosis	There was no difference between patients who converted to psychosis and those who did not in age, IQ or global neuropsychological status. Race, poor CPT performance and good WAIS–R digit symbol performance predicted conversion to psychosis.
		Time to progression to psychosis	Baseline neurocognitive status was not a significant predictor of time to progression to psychosis.
	Regression analysis by history of psychosis and duration of prodromal symptoms	Neurocogni-tive performance	Patients with first-episode psychosis were significantly more impaired than patients at-risk for psychosis on CPT, CVLT, WAIS–R digit symbol, working memory and verbal fluency measures. Cognitive performance was not significantly correlated with length of manifestation of prodromal symptoms.
Wudarsky, 1999[109] *Clozapine vs. haloperidol vs. olanzapine*	Subgroup analysis by sex	Prolactin	In patients receiving clozapine, females had significantly elevated prolactin levels than males. There was no significant sex difference in patients receiving haloperidol or olanzapine.

AE = Adverse Event; BMI = body mass index; CPT = Continuous performance task; CVLT = California Verbal Learning Test; IQ = intelligence quotient; ODT = orally disintegrating tablet; SOT = standard oral tablet; WAIS–R = Wechsler Adult Intelligence Scale revised

Tourette Syndrome

Three studies on Tourette syndrome conducted an analysis of patient outcomes in different subpopulations (Table 42).[99,100,111]

One study[111] investigated the effect of age on various disease-specific and nonspecific outcomes (i.e., CGI, Global Assessment of Functioning, Hamilton Anxiety Rating Scale, Patient Global Impressions, Tourette Symptom Severity Scale, and YBOCS) in pimozide- and risperidone-treated patients. Patients younger than 18 years of age had better efficacy scores at endpoint than patients older than 18 years, but the differences were not significant. In another study evaluating haloperidol and pimozide, Sallee et al.[100] assessed the effect of ADHD comorbidity on cognitive functioning. Patients with comorbid ADHD had a significantly higher error rate on continuous performance tasks than patients without ADHD.[100]

One placebo-controlled crossover RCT[99] comparing haloperidol with pimozide found no significant difference in prolactin levels by sex or Tanner stage. Bruggeman et al.[111] examined

the effect of age on weight gain in pimozide- and risperidone-treated patients. Patients younger than 18 years of age experienced more weight gain than patients older than 18 years (nonsignificant).

Table 42. Differences between Tourette syndrome subpopulations on outcomes

Author, Year Comparison	Type of Analysis	Outcome	Authors' Conclusions
Bruggeman, 2001[111] *Pimozide vs. risperidone*	Subgroup analysis by age	CGI, GAF, HAM–A, PGI,TSSS, YBOCS	Patients younger than 18 had consistently better scores at endpoint for efficacy measures than patients 18 and older; however, this trend was not significant. Change scores were comparable between groups.
		Weight	Patients <18 years had more weight gain than patients ≥18 years in the risperidone group, however this was not significant. Weight gain was comparable across age groups in the pimozide-treated patients.
Sallee, 1997[99] *Haloperidol vs. pimozide vs. placebo*	Subgroup analysis by sex, Tanner stage	Prolactin	No significant differences were found in prolactin levels by sex or Tanner scores.
Sallee, 1994[100] *Haloperidol vs. pimozide*	Regression analysis by comorbidity	CPT task commission and omission errors	Patients with ADHD had significantly higher commission and omission errors than patients without ADHD.

ADHD = attention deficit hyperactivity disorder; CGI = Clinical Global Impressions Scale; CPT = Continuous performance task; GAF = Global Assessment of Functioning; HAM–A = Hamilton Anxiety Rating Scale; PGI = Patient Global Impressions; TSSS = Tourette Symptom Severity Scale; (C)YBOCS = (Children's) Yale-Brown Obsessive Compulsive Scale

Behavioral Issues

Three studies that examined patients with behavioral issues conducted an analysis of outcomes in different subpopulations (Table 43).[103,105 106] Patients exhibited aggression,[103,105,106] agitation,[106] self-injury,[105] or property destruction.[105] Studies only evaluated SGAs.

Three studies investigated the effect of sex on outcomes including OAS,[103] response,[105] number of restraints, and time in restraints.[106] Aggression decreased more in males than females as measured using OAS, but the difference was not significant. Sex was not a significant predictor of response, number of restraints, or time in restraints.

Three studies investigated the effect of age on ABC–I,[105] OAS,[103] response,[105] dose required for symptom reduction,[106] and number of restraints and time in restraints.[106] Children experienced more irritability (measured on ABC–I) than adolescents and adults.[105] In addition, children ≤11 years of age showed decreased aggression than patients ≥12 years of age.[103] In another study, adolescents required a significantly higher dosage of olanzapine for reduction or agitation or aggression; however, age had no impact on number of restraints or time in restraints in this study.[106] One study[105] also investigated the impact of comorbid mental retardation, mood disorder, and cotreatment with antiseizure medications on response. Patients with severe mental retardation showed poorer response than patients with mild mental retardation, whereas mood disorders and concomitant antiseizure medications were not significant predictors of response.

One crossover RCT comparing two doses of risperidone found that children experienced greater weight gain and lower prolactin levels than adolescents and adults.[105]

Table 43. Differences between behavioral issues subpopulations on outcomes*

Author, Year Comparison	Type of Analysis	Outcome	Authors' Conclusions
Bastiaens, 2009[103] *Aripiprazole vs. ziprasidone*	Subgroup analysis by sex, age	OAS	Males improved more than females, and patients ≤11 years improved more than patients 12 years or older; however neither trend was significant.
Hellings, 2006[105] *Low- vs. high-dose risperidone*	Subgroup analysis by age	ABC irritability	Irritability scores were significantly higher in children than adolescents and adults. There was no significant difference between adolescents and adults.
	Subgroup analysis for sex, age, comorbidity, cotreatment, mood disorder	Response	Age and level of MR were significant predictors of response, with poor response in children and patients with severe MR. Sex, concomitant antiseizure medication, and mood disorder were not significant predictors of response.
	Subgroup analysis for age	Weight	Children and adolescents had greater weight gain than adults, but the differences between age groups were not significant.
		Prolactin	Adults had a greater acute increased in prolactin levels than children/ adolescents. Prolactin levels were significantly higher for adults than children/adolescents in the acute phase but not during maintenance.
Khan, 2006[106] *Olanzapine vs. ziprasidone*	Subgroup analysis for age	Dose required for symptom reduction	Adolescents (13–17 years) required a significantly higher dose of olanzapine than children (≤12 years). There was no difference between age groups for ziprasidone.
	Regression analysis controlling for sex and age	Number of restraints Time in restraint	Age and sex had no impact on differences between the groups for number of restraints or time in restraint after receiving the study medications.

ABC = Aberrant Behavior Checklist; MR = mental retardation; OAS = Overt Aggression Scale
* Behavioral issues included aggression,[103,105,106] agitation,[106] self-injury,[105] or property destruction.[105]

Multiple Conditions

Six cohort studies examining patients with a variety of psychiatric or behavioral diagnoses conducted an analysis of outcomes in different subpopulations (Table 44).[112,114-116,118,120] All six studies evaluated SGAs.

The effect of sex was assessed on weight gain,[114,115] BMI,[114,115] neuroleptic-induced movement disorders,[118] risk for adverse health outcomes,[115] and prolactin.[116,120] Males gained more weight than females in one study, but the difference was not significant.[115] Two studies found no effect of age on weight gain measures including BMI.[114,115]

Sex had no impact on substantial weight gain in two studies[114,115] or BMI in one study.[115] All patients who developed antipsychotic-induced movement disorders were female.[118] Males tended to be at risk of adverse health outcomes more frequently than females.[115] Females had significantly higher prolactin levels than males in one study.[120] In contrast, sex had no impact on prolactin level in a second study.[116]

Race had no impact on BMI in one study.[115] The study also examined the effect of comorbidities, including psychosis and substance abuse, on weight gain and risk for adverse health outcomes. These outcomes were not related to presence of psychosis, length of inpatient treatment, tobacco use, alcohol abuse, or cannabis abuse.[115] One study found psychosis to be associated with high drug dose.[118]

Cotreatment with antidepressants resulted in significantly less weight gain than monotherapy in one study,[115] whereas a second study found no effect of comedications on weight gain.[114] Risk for adverse health outcomes was not affected by cotreatments.[115] Two studies assessed the effect of previous antipsychotic treatment on weight gain[114,115] and risk of adverse health outcomes;[115] no significant effect was observed. Three studies found no impact of puberty or pubertal status on metabolic changes,[112] or prolactin.[116,120]

Table 44. Differences between multiple conditions subpopulations on outcomes

Author, Year Comparison	Type of Analysis	Outcome	Authors' Conclusions
Correll, 2009[112] *Aripiprazole vs. olanzapine vs. quetiapine vs. risperidone*	Subgroup analysis by pubertal status	Metabolic changes	Pubertal status was not related to metabolic changes in any of the treatment groups.
Fleischhaker, 2006[114] *Clozapine vs. olanzapine vs. risperidone*	Regression analysis by sex, age, cotreatment, treatment history, history of dieting, baseline weight	Weight change	Significant correlation between baseline weight and subsequent weight gain was noted. No strong association between sex and extreme weight gain was found. No significant correlation was found between age, drug history status (naïve vs. previous use), comedications or dieting history and weight measures.
Fraguas, 2008[115] *Olanzapine vs. quetiapine vs. risperidone*	Subgroup analysis by sex, age, race, comorbidities, cotreatment, duration of inpatient treatment, treatment history	Weight	Males gained more weight than females, but this trend was not significant. BMI increases were not related to race, age, presence of psychosis, alcohol abuse, cannabis abuse or length of inpatient treatment.
Fraguas, 2008[115] (continued)	See above	Substantial weight gain (≥0.5 increased in BMI z-score)	Patients receiving cotreatment with antidepressants had significantly less weight gain. Substantial weight gain was not associated with sex, psychosis, antipsychotic-naïve status, lifetime antipsychotic use, length of inpatient treatment, cotreatment with benzodiazepines, alcohol or cannabis abuse, or tobacco use.
		At risk for adverse health outcome	A nonsignificant trend showed a higher proportion of males to be at risk for adverse health outcomes than females. Risk for an adverse health outcome was significantly not related to antipsychotic naïve status, total lifetime antipsychotic use, treatment with benzodiazepines, anticholinergics or antidepressants, length of inpatient treatment, psychosis, tobacco use, or alcohol or cannabis abuse.
Friedlander, 2001[118] *Olanzapine vs. risperidone*	Subgroup analysis by psychosis	Drug dosage	Patients with psychosis were prescribed significantly higher dosages of risperidone, and nonsignificantly higher dosages of olanzapine, than patients without psychosis.
	Subgroup analysis by sex	Neuroleptic-induced movement disorders	All patients who developed neuroleptic-induced movement disorders were female.

Table 44. Differences between multiple conditions subpopulations on outcomes (continued)

Author, Year Comparison	Type of Analysis	Outcome	Authors' Conclusions
Migliardi, 2009[120] *Olanzapine vs. risperidone*	Regression analysis controlling for pubertal status, sex, treatment duration	Prolactin	Plasma olanzapine concentrations had a significant effect on prolactin levels in female, but not males. The effect of plasma risperidone concentrations at the end of 3 months was significant only in males but not in females. After adjusting for antipsychotic drug and gender, mean increases in prolactin levels at the end of 3 and 6 months were higher than those at the end of 1 and 12 months. Pubertal status did not have any significant effect on prolactin levels, adjusting for gender and treatment duration.
Saito, 2004[116] *Olanzapine vs. quetiapine vs. risperidone*	Subgroup analysis by sex, puberty	Prolactin	There was no significant difference in prolactin levels by gender. Postpubertal females were not significantly different in endpoint prolactin levels compared to all others.

BMI = body mass index

Summary and Discussion

This report provides a comprehensive synthesis of the evidence on the comparative effectiveness of first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) for the treatment of various psychiatric and behavioral conditions in children, adolescents, and young adults (ages≤24 years). The strength of the body of evidence for key efficacy and safety outcomes is summarized by condition in Table 45, Table 46, and Table 47.

For the majority of outcomes, data on the relative effectiveness of treatments were sparse and precluded drawing firm conclusions. Outcomes important to patients and parents were rarely assessed in the studies, including health-related quality of life, social and occupational functioning, and involvement with the legal system. Therefore, the potential applicability of these studies to children, youth, and their families who are affected by the psychiatric and behavioral conditions addressed in this report is limited. Disorder-specific symptoms and global measures of severity and improvement, as measured on the Clinical Global Impressions (CGI) scales, were reported more consistently across the studies, making study outcomes relevant for clinicians. The majority of studies reported adverse events; however, data on the persistence and reversibility of these events were very sparse. Few consistent trends were observed for the association of outcomes with various patient subpopulations.

The effects of antipsychotics for the treatment of schizophrenia and related psychoses were most frequently examined. Fewer studies provided evidence on the efficacy and safety of antipsychotics for treating off-label conditions, such as attention deficit hyperactivity disorder (ADHD) and disruptive behavior disorders, Tourette syndrome, and behavioral disturbances. We did not identify any evidence examining the use of antipsychotics for patients with obsessive compulsive disorder, post-traumatic stress disorder, and anorexia nervosa.

Data were provided primarily from randomized controlled trials (RCTs); however, in our quality assessment, nearly all of the trials were found to be at high risk of bias. Sample sizes varied considerably, with an overall median of 43 enrolled patients per study (interquartile range [IQR], 25 to 101). Young adults (ages 19 to 24 years) were included in approximately 25 percent of the schizophrenia studies and were rarely included in studies examining any other condition.

Overall, there were few significant differences between active drug comparisons. FGAs and SGAs were generally found to be superior to placebo on symptom improvement and other efficacy outcomes. The following is a summary of the evidence for the four key questions.

Key Question 1: Disorder-Specific and Nonspecific Symptoms

The findings for symptom improvement are presented for each condition in Table 45. With the exception of studies examining schizophrenia, the evidence comparing FGAs with SGAs and antipsychotics within each class was limited. For most conditions, the majority of the findings focused on the comparison of SGA versus placebo. Comparisons and outcomes for which the evidence was graded as insufficient are not discussed.

A total of 11 studies on 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 on the CGI. The strength of evidence for these findings was low.

Eight studies reported the effect 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 disorder 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 on the CGI and for 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 on the CGI or for 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 patients with behavioral issues, such as aggression. One study found greater improvement in autistic symptoms with risperidone than placebo (low strength of evidence).

Table 45. 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 (4 studies) (MD = -20.97; 95% CI: -31.1, -10.8), BPI (2 studies) (MD = -3.8; 95% CI: -6.2, -1.4), and NCBRF (4 studies) (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).

Table 45. Summary of the strength of evidence for symptoms (Key Question 1) (continued)

Outcome	Comparison (# Studies)	SOE	Summary
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).
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; 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 46. Although many studies reported on the incidence of adverse events, the evidence on the persistence and reversibility of harms was very limited.

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 for adverse events, there was insufficient evidence.

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).

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 was a significant effect in favor of aripiprazole for prolactin-related adverse events (moderate strength of evidence).

Table 46. 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 (cholesterol MD = 10.2, 95% CI, 3.1, 17.2; 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 46. Summary of the strength of evidence for adverse events (Key Question 2) (continued)

Outcome	Comparison (# studies)	SOE	Summary
SGA vs. SGA			
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)	Low	No significant difference.
	Olanzapine vs. placebo (3 RCTs)	Low	No significant difference.
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).

Table 46. Summary of the strength of evidence for adverse events (Key Question 2) (continued)

Outcome	Comparison (# Studies)	SOE	Summary
SGA vs. Placebo			
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

Key Question 3: Other Short- and Long-Term Outcomes

The findings for other short- and long-term outcomes are presented separately for each condition in Table 47. 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). There was no significant difference between SGAs and placebo for suicide-related behaviors (moderate 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 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 and two studies for Tourette syndrome and behavioral issues, respectively. The evidence was insufficient for all of the outcomes and comparisons examined in these studies.

Table 47. 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)	Low	No significant difference.
	Olanzapine vs. quetiapine (2 RCTs)	Low	No significant difference.
	Olanzapine vs. risperidone (4 RCTs, 1 PCS)	Low	No significant difference.
	SGA vs. placebo (2 RCTs)	Low	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

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. Two studies reported low intelligence to be associated with a lower treatment response rate. Six studies examined the association between sex and increases in prolactin levels during treatment; the results were discordant across the studies.

Applicability

The majority of the studies were small to moderate-sized RCTs that examined the efficacy of two or more intervention groups. Study populations generally excluded patients with additional diagnoses of psychiatric or behavioral conditions other than the condition of interest, as well as additional comorbidities such as mental retardation, psychosis, or substance abuse. Patients with a history of various adverse events, including tardive dyskinesia, suicide-related behaviors, neuroleptic malignant syndrome, or abnormal lab values, were often excluded.

Additional restrictions that were commonly applied were use of adjunctive medications (e.g., mood stabilizers or antidepressants) and previous unresponsiveness to the study medication. In addition, several studies excluded patients who did not meet minimum response criteria or were nonadherent during the run-in period prior to the double-blind treatment phase. 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. Exclusion of patients with

comorbidities or a history of various adverse events may have overestimated the estimates of the efficacy and underestimated the harm of antipsychotics.

The majority of the studies in this review excluded young adults; therefore, the results may have limited applicability to this population. Young adults were included in approximately 25 percent of studies of schizophrenia, despite the natural history of schizophrenia which typically has its peak onset during these years. Although this population would be included in studies of adults, there are numerous unique issues associated with patients between the ages of 19 and 24, particularly because patients frequently lose access to services once they become legal adults at age 18. For conditions other than schizophrenia, young adults were rarely included.

Applicability may also be limited due to monitoring practices to ensure treatment adherence throughout the trials. In typical practice settings, it is likely that will patients have lower rates of medication adherence and therefore less symptom improvement.

Another factor that restricts the applicability of the studies is the short duration of followup. In particular, the median study duration of 8 weeks is insufficient to assess some long-term efficacy outcomes, such as school performance, maturation, emotional development, legal system interactions, or detect some adverse events, such as development of diabetes and cardiovascular disease-related events. Adverse events were likely underestimated due to the short followup period.

Limitations of the Existing Evidence

The strength of the evidence was low or insufficient for the majority of outcomes across the various drug comparisons and conditions. These low grades were driven by a high risk of bias within individual studies and a lack of consistency and precision among studies.

Although the majority of studies providing data for this report were RCTs, nearly all of the trials had a high risk of bias as assessed using an empirically derived tool developed by the Cochrane Collaboration.[33] Approximately half of the RCTs were rated as having adequately generated the allocation sequence, concealed allocation, and blinded study investigators and participants. Measures employed by the study investigators to ensure that the allocation sequence was truly random and that allocation occurred without foreknowledge of treatment assignments was often unclear in the trials. These features can always be conducted in trials and should be routinely employed in order to avoid selection bias.

Inadequate blinding is another important limitation of this body of evidence, as lack of blinding can lead to exaggerated treatment effects. Many of the outcomes, such as improvement on symptom scales, were assessed by physicians; therefore, blinding should extend beyond patients to include all outcome assessors. Half of the trials had incomplete outcome data due to loss to followup and inadequate handling of missing data in the reporting and analyses, which may exaggerate treatment effects.

The most problematic trial feature was the source of funding: nearly 80 percent of the trials were funded by industry. Empirical evidence has shown that pharmaceutical company sponsorship greatly increases the chances of pro-industry findings. [34,124] Transparency in reporting the nature and extent of industry involvement in the design, conduct, and analysis of studies may help readers better evaluate the likelihood of industry bias in trials. We also encourage nonpharmaceutical organizations, such as government and advocacy groups, to become increasingly involved in funding future studies in this field in order to determine whether the results of industry trials can be replicated.

A total of 17 cohort studies were included in the review. Because these studies did not employ randomization, they are particularly vulnerable to selection bias and a lack of comparability between intervention groups. Moreover, the majority of the studies did not control for important potential confounders (e.g., age, disease severity) in their design or analyses.

Lack of consistency and precision of results across studies also contributed to the low strength of evidence grades for the majority of outcomes. Consistency was often unknown due to the few studies comparing the same interventions. In addition, lack of consistency is also attributable to the various scales and surrogate measures that were used to assess efficacy outcomes and adverse events. Precision was often poor due to the small sample sizes in many of the studies, which may have resulted in insufficient power to detect differences between groups. Both consistency and precision may have been affected by variations in the clinical populations assessed across the studies, such as the number, type, and severity of comorbidities, patient age, sex ratio, and dose of antipsychotics.

Currently, there is little consensus regarding which outcomes and measures are important to evaluate in studies in this field. Across the 81 studies included in this review, more than 60 outcome scales were reported. Although some outcomes and scales were assessed fairly consistently for some conditions, such as the Young Mania Rating Scale (YMRS) for bipolar disorder and the Positive and Negative Syndrome Scale (PANSS) for schizophrenia, there was great diversity in the scales used in studies for the other conditions. Further, response and remission were based on different outcome measures and criteria across studies. This heterogeneity makes comparisons across studies and interventions challenging. Professional associations in the field of child psychiatry should take a lead role in initiating discussion and consensus on which measures should be included in studies and what degree of change in these measures would be considered a clinically important finding. This information is necessary for designing future research (e.g., planning for adequate sample sizes) and interpreting the findings.

Further, few studies described the use of standardized scales to systematically assess the incidence of adverse events. As such, it is unclear whether studies simply evaluated side effects through passive elicitation by patients or open-ended questions. Studies also rarely reported definitions for what constituted various adverse events (e.g., criteria for metabolic syndrome) and whether adverse events were self-reported or assessed by clinicians. Varied time points at which outcomes were assessed also contributed to inconsistency.

The studies rarely evaluated key outcomes that are important to patients. These include health-related quality of life, social and occupational functioning, involvement with the legal system, and patient-, parent-, or care provider–reported outcomes. The duration of followup was brief in the majority of studies (median of 8 weeks; IQR, 6 to 12 weeks); therefore, long-term data are needed to assess the impact of antipsychotic use on these outcomes. Similarly, longer followup is needed to determine the association of acute adverse effects, such as antipsychotic-induced weight gain, on downstream effects such as diabetes, dyslipidemia, hypertension, and cardiovascular morbidity. Few studies reported on the persistence or reversibility of harms observed during the study period. Although many of the studies included open-label extension phases to assess efficacy or harm data, the majority failed to provide comparative data, precluding evaluation of effects between groups. Providing long-term comparative data for studies comparing an active treatment with a placebo may not be feasible. As such, observational studies are needed to provide data on patients using different antipsychotics over the course of several years to determine the comparative benefits and risks associated with these drugs.

Few discernable trends were noted for the effects of subpopulations on treatment outcomes due to heterogeneity in the patient factors and outcomes examined. The results of subgroup and

regression analyses were often poorly described in the studies (e.g., few studies reported whether an association was significant), limiting the conclusions that could be drawn. Information on patient subpopulations that are associated with positive and negative outcomes is crucial for informing clinical practice; therefore, future studies assessing the impact of important subgroups (e.g., sex, age) on key outcomes (e.g., prolactin levels, weight gain) are needed.

This comparative effectiveness review has several limitations. Only English-language studies were eligible for inclusion in the review; therefore, it is possible that relevant studies published in other languages may have affected the review findings. We based our assessments of methodological quality on study publications and did not contact authors to verify the methods used. Some studies may have been adequately conducted, but the methods were poorly reported. The scope of this report was limited to the direct comparison of various antipsychotics and the comparison of antipsychotics with placebo. As such, evidence on the use of other drug classes (e.g., anticonvulsants) that are frequently used in the treatment of these patient populations is not considered in this report.

This report presents a synthesis of the available evidence on the effectiveness and safety of antipsychotics in the pediatric and young adult populations. However, we do not make clinical recommendations on the use of these medications, as this is the purview of the user group. We trust that the evidence presented in this report will be helpful in the further development of clinical practice guidelines in this field.

Future Research

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

- Studies examining long-term 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. In particular, subgroup analyses examining young adults would be helpful in guiding clinical decisions due to the unique issues associated with this population.
- 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 study design and interpretation of 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 results.

This review identified several areas for which the evidence is sparse and which are priorities for future research. More than one third of the studies included in this review examined an FGA or SGA with only placebo and no active comparator. Based on the findings of this report, antipsychotics can be considered to have superior symptom improvement and inferior adverse event profiles than placebo. Evidence was insufficient to evaluate the comparative effectiveness of various antipsychotic agents. Future studies should be composed of two or more active treatment groups in order to address this evidence gap.

One of the greatest priorities for future research is the systematic evaluation of adverse events. The evidence for the safety of antipsychotics in the pediatric and young adult populations is sparse, resulting in much uncertainty and controversy regarding the use of these drugs in children. The dearth of safety data is of particular concern given that prescription rates of psychotropic medications among children and adolescents have nearly reached adult proportions, and adverse events may have greater long-term impact in children.[37] Although a high proportion of the studies included in this review reported some adverse events, few studies systematically evaluated harms using standardized measures. The use of standardized pediatric side-effect scales such as the Safety Monitoring Uniform Report Form[125] or a simplified version of this scale[126] have been recommended for all pediatric psychopharmacologic studies. Guidelines regarding which adverse events should be routinely monitored in studies evaluating the use of antipsychotics in children are available.[37] Cohort studies that examine the long-term comparative safety of drugs are also needed. Correll et al.[112] provides a good example of a well designed and conducted cohort study in this field.

Although numerous studies have investigated the use of antipsychotics for on-label conditions, such as schizophrenia, evidence for off-label use in treating behavior symptoms associated with conditions such as disruptive behavior disorders or Tourette syndrome is sparse. Future research efforts should examine whether these agents are effective in treating disorder-specific symptoms and how these agents compare with other available interventions.

Trials and cohort studies should be designed and conducted to minimize risk of bias where at all possible. Authors may find tools such as the CONSORT[127] and STROBE[128] statements helpful in designing and reporting on randomized controlled trials and cohort studies, respectively.

Conclusions

The efficacy and safety of FGAs and SGAs have been studied in children, adolescents, and young adults (ages≤24 years) for the following conditions: pervasive developmental disorders, ADHD and disruptive behavior disorders, bipolar disorder, schizophrenia, Tourette syndrome, and behavioral problems. Overall, data for head-to-head comparisons (FGAs vs. SGAs, FGAs vs. FGAs, and SGAs vs. SGAs) were generally of low strength of evidence; therefore, few conclusions regarding the relative efficacy and safety of antipsychotics could be drawn. However, evidence consistently showed that SGAs resulted in greater symptom improvement and a poorer safety profile than placebo. Evidence was sparse for several patient important outcomes, such as health-related quality of life, involvement with the legal system, and school performance. Few studies reported long-term data.

Treatment benefit and risks were examined most frequently for schizophrenia. Fewer studies examined other conditions. In addition, no eligible studies examining obsessive-compulsive disorder, post-traumatic stress disorder, or anorexia nervosa. Young adults were rarely examined, particularly for conditions other than schizophrenia. Additional research is needed to assess the

treatment efficacy, and particularly, the safety of antipsychotics in these populations. In addition, studies that examine outcomes separately for subpopulations are needed to better predict the effects of treatment for individual patients in clinical practice.

Future research should incorporate design elements to minimize bias in treatment effects including adequate allocation concealment, adequate blinding of patients and outcome assessors, comparability of study groups, and appropriate handling and reporting of missing data. Consensus is needed on outcomes and outcome measures, as well as minimum clinically important differences. Standardized assessment of adverse events, and analysis and comprehensive reporting of subpopulations in future studies will allow for more accurate interpretation of findings across studies as well as greater understanding with respect to the applicability of the findings.

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Acronyms and Abbreviations

ABC	Aberrant Behavior Checklist
ADHD	Attention deficit hyperactivity disorder
AHRQ	Agency for Healthcare Research and Quality
BMI	Body mass index
BPRS	Brief Psychiatric Rating Scale
CARS	Childhood Autism Rating Scale
CDRS	Children's Depression Rating Scale
CGAS	Children's Global Assessment Scale
CGI	Clinical Global Impressions Scale
CGI–BP	Clinical Global Impressions–Bipolar
CGI–I	Clinical Global Impressions–Improvement
CGI–S	Clinical Global Impressions–Severity
CI	Confidence interval
CPRS	Children's Psychiatric Rating Scale
CSQ	Caregiver Strain Questionnaire
(C)YBOCS	(Children's) Yale-Brown Obsessive Compulsive Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
EPC	Evidence-based Practice Center
FDA	U.S. Food and Drug Administration
FGA	First-generation antipsychotic
IQR	Interquartile range
MD	Mean difference
N	Number
NCBRF	Nisonger Child Behavior Rating Form
NRCT	Nonrandomized controlled trial
OAS	Overt Aggression Scale
PANSS	Positive and Negative Syndrome Scale
RCT	Randomized controlled trial
RR	Relative risk
SANS	Scale for the Assessment of Negative Symptoms
SGA	Second-generation antipsychotic
VAS	Visual analog scale
YGTSS	Yale Global Tic Severity Scale
YMRS	Young Mania Rating Scale

Appendix A. Literature Search Strings

Table A1. MEDLINE–Ovid Version

OvidSP_MEDLINE 1950 to February Week 1 2011	Searched: 22Apr10 and 01Feb11 Results: 3957

1. exp Child Development Disorders, Pervasive/
2. Child behavior disorders/
3. (child adj1 development adj1 disorder*).tw.
4. Asperger Syndrome/
5. (asperger* adj1 (syndrome or disorder)).tw.
6. Autistic Disorder/
7. (autism* or (autistic adj1 disorder*) or kanner* syndrome).tw.
8. Rett Syndrome/
9. (((rett or retts) adj1 (sydrome or disorder)) or cerebroatrophic hyperammonemia*).tw.
10. Schizophrenia, Childhood/
11. (child* adj2 schizophrenia*).tw.
12. aggression/
13. aggression.tw.
14. psychomotor agitation/
15. ((psychomotor adj1 (agitation or restlessness or hyperactivity or excitement)) or akathisia).tw.
16. "sleep initiation and maintenance disorders"/
17. ((sleep adj2 disorder*) or insomnia*).tw.
18. mood disorders/
19. ((mood or affective) adj1 disorder*).tw.
20. impulsive behavior/
21. (impulsive adj1 behavio?r).tw.
22. borderline personality disorder/
23. (borderline adj1 personality adj1 disorder*).tw.
24. personality disorders/
25. (affective adj2 dysregulation).tw.
26. (($behavioral adj2 dyscontrol) or (impulsive-behavioral adj2 deregulation)).tw.
27. (mood adj2 lability).tw.
28. (irritable or irritability).tw.
29. Self-Injurious Behavior/
30. (self-injurious behavio?r or self-mutilating behavio?r or self mutilation or self-desctructive behavio?r or deliberate self-harm or parasuicide).tw.
31. antisocial personality disorder/
32. "Attention Deficit and Disruptive Behavior Disorders"/
33. Attention Deficit Disorder with Hyperactivity/
34. ((attention adj deficit adj disorder) or hyperkinetic syndrome or adhd).tw.
35. Conduct Disorder/
36. (conduct adj disorder*).tw.
37. Childhood Disintegrative Disorder.tw.
38. "Pervasive Developmental Disorder Not Otherwise Specified".tw.
39. (atypical adj1 autism).tw.
40. Oppositional Defiant Disorder.tw.
41. "Disruptive Behavior Disorder Not Otherwise Specified".tw.
42. Schizophrenia/
43. Schizophrenia, Catatonic/
44. Schizophrenia, Disorganized/
45. Schizophrenia, Paranoid/
46. ((catatonic or disorganized or paranoid) adj schizophrenia).tw.
47. Psychotic Disorders/
48. ((Psychotic or schizoaffective or schizophreniform) adj disorder).tw.
49. (brief reactive psychos?s or psychoses).tw.
50. first episode schizophrenia.tw.
51. (prodrom$ and schizophren$).tw.
52. Schizotypal Personality Disorder/
53. (schizotypal personality disorder or ((borderline or pseudoneurotic or pseudopsychopathic or incipient or latent) adj2 schizophrenia)).tw.
54. Bipolar Disorder/
55. (((bipolar or manic) adj (disorder or psychos?s or depression)) or mania*).tw.
56. "Depressive Disorder, Major"/ and (refractory or chronic or resistant).ti,ab.
57. Depression/ and (refractory or chronic or resistant).ti,ab.

Table A1. MEDLINE–Ovid Version (continued)

58. Depressive Disorder/
59. ((depressive adj (disorder or neuroses or syndrome*)) or ((endogenous or neurotic or unipolar) adj depression*)).tw.
60. Obsessive-Compulsive Disorder/
61. (OCD or anankastic personalit* or (obsessive compulsive adj (disorder* or neuros*)) or (obsessive-compulsive adj (disorder* or neuros*))).tw.
62. exp anorexia nervosa/
63. ((anorexia adj nervosa*) or anorexia*).tw.
64. exp stress disorders, post-traumatic/
65. ((chronic or acute or delayed onset) and (post-traumatic adj stress adj disorder*)).tw.
66. ((posttraumatic or post-traumatic or post traumatic) adj (neuroses or disorder)).tw.
67. ptsd.tw.
68. exp tourette syndrome/
69. ($tourette* adj (syndrome or disorder or disease)).tw.
70. (tic adj disorder).tw.
71. (multiple adj motor adj vocal adj tic adj disorder).tw.
72. or/1-71
73. exp Antipsychotic Agents/
74. exp Tranquilizing Agents/
75. ((first or 1st) adj generation adj antipsychotic*).tw.
76. azaperone/
77. 1649-18-9.rn.
78. (Atsaperoni or Azaperon or Azaperona or Azaperone or Azaperonum or Eucalmyl or Fluoperidol or NSC 170976 or R 1929 or R-1929 or Sedaperone or Stresnil or Suicalm).mp.
79. Butyrophenones/ad, to, tu, ct, po, ae
80. Clopenthixol/
81. 982-24-1.rn.
82. (Chlorpenthixol or Clopenthixol or Clopenthixolum or Sordinol or Zuclopenthixol).mp.
83. chlorpromazine/
84. 50-53-3.rn.
85. (Aminazin or Aminazine or Ampliactil or BC 135 or Chlorpromazine or Chlorpromazinum or Clorpromazina or Chlor-Promanyl or Chlorpromados or Chlorderazin or Chlorpromazin or Contomin or Elmarin or Esmind or Fenactil or Fenaktyl or HL 5746 or Largactil or Largactilothiazine or Megaphen or Largactyl or Klooripromatsiini or Klorpromazin or 6 Copin or Trinicalm Forte or Diminex Balsamico Juven Tos or Largatrex or Phenactyl or Proma or Promactil or Promazil or Prozil or Psychozine or Sanpron or Thorazine or Torazina or Wintermin).mp.
86. Chlorprothixene/
87. 113-59-7.rn.
88. (Chlorprothixene or Chlorprothixen or Chlorprothixenum or Chlorprotixen or Chlorprotixene or Clorprotisene or Clorprotixeno or Laractan or Paxyl or Rentovet or Taractan or Tarasan or Traquilan or Trictal or Truxal or Truxaletten or Truxil or Vetacalm).mp.
89. Dibenzoxazepines/ad, to, tu, ct, po, ae
90. Droperidol/
91. 548-73-2.rn.
92. (Dehydrobenzoperidol or Dehydrobenzperidol or Deidrobenzperidolo or Dridol or Droleptan or Droperidol or Droperidoli or Droperidolis or Droperidolum or Disifelit or Halkan or Inapsin or Inapsine or Inopsin or Thalamonal or Nilperidol or Properidol or Sintodril or Vetkalm).mp.
93. Flupenthixol/
94. 2709-56-0.rn.
95. (Depixol or Emergil or Fluanxol or Flupenthixol or Flupentixol or Flupentixolum or Fluxanxol or Siplaril or Siplarol).mp.
96. fluphenazine/
97. 69-23-8.rn.
98. (Dapotum or Elinol or Flufenazina or Fluofenazine or Fluphenazine or Fluorphenazine or Fluphenazinum or Ftorphenazine or Moditen or Pacinol or Sevinol or Siqualon or Triflumethazine or Valamina or Vespazine).mp.
99. haloperidol/
100. 52-86-8.rn.
101. (Aldo or Aloperidin or Aloperidol or Aloperidolo or Brootopon or Dozic or Einalon S or Eukystol or Fortunan or Galoperidol or Haldol or Halojust or Halopal or Haloperidol or Haloperidoli or Haloperidolis or Haloperidolu or Halopoidol or Serenace or Halopidol or Haloper or Halperon or Keselan or Lealgin or Linton or Mixidol or Peluces or Pernox or Serenace or Serenefl or Sernas or Sernel or Serenase or Ulcolind or Uliolind or Vesalium).mp.

Table A1. MEDLINE–Ovid Version (continued)

102. Indoles/ad, to, tu, ct, po, ae
103. Lithium carbonate/
104. 554-13-2.rn.
105. (Camcolit or Candamide or Carbolith or Carbonic acid lithium salt or dilithium salt or Eskalith or Eutimin or Hypnorex or Limas or Lithium or Liskonum or Litard or Lithane or Lithea or Lithicarb or Lithinate or Lithionate or Lithotabs or Liticar or Manialith or Maniprex or Micalith or Neurolepsin or Pfi-lithium or Phasal or Plenur or Priadel or Quilonorm or Teralithe).mp.
106. loxapine/
107. 1977-10-2.rn.
108. (Cloxazepine or CL 62362 or Dibenzacepin or Dibenzoazepine or Hydrofluoride 3170 or LW 3170 or Lossapina or Loksapiini or Loxapin or Loxapina or Loxapine or Loxapinum or Oxilapine or Loxapac or SUM 3170 or Loxitane or Desconex).mp.
109. Methiothepin/
110. 20229-30-5.rn.
111. (Methiothepin or metitepine or Methiothepine or Methiothepin maleate or Metitepina or Metitepinum).mp.
112. Methotrimeprazine/
113. 60-99-1.rn.
114. (Dedoran or Hirnamin or Hirnamine or Levomepromazine or Levomepromazin or Levomepromazina or Levopromazioni or Levomepromazinum or Levoprome or Levotomin or Mepromazine or Methotrimeprazine or Neurocil or Neozine or Nirvan or Nocinan or Momizan or Nozinane or Sinogan or Levolam or Nozinan or Sinogan or Tisercin or Veractil).mp.
115. molindone/
116. 7416-34-4.rn.
117. (Molindona or Molindone or Molindonum).mp.
118. Penfluridol/
119. 26864-56-2.rn.
120. (Penfluridol or Penfluridolum or Semap).mp.
121. Perazine/
122. 84-97-9.rn.
123. (Pemazine Dimalonate or Peragal or Perazin or Perazine or Perazinum or Taxilan).mp.
124. perphenazine/
125. 58-39-9.rn.
126. (Chlorperphenazine or Chlorpiprazine or Decentan or Emesinal or Etaperazin or Etaperazine or Ethaperazine or Etrafon or F-mon or Fentazin or Mutabon or Perfenazin or Perfenazina or Perfenazinas or Perfenazine or Perphenazin or Perphenazine or Perfenazyna or Perphenazinum or Pertriptyl or Sch 3940 or Thilatazin or Tranquisan or Trifaron or Trilafon or Trilifan or Triptafen or Triphenot or Triavil).mp.
127. Phenothiazines/ad, to, tu, ct, po, ae [Administration & Dosage, Toxicity, Therapeutic Use, Contraindications, Poisoning, Adverse Effects]
128. Pimozide/
129. 2062-78-4.rn.
130. (Antalon or Opiran or Orap or Pimotsidi or Pimozid or Pimozida or Pimozidas or Pimozide or Pimozidum or Pimozyd).mp.
131. Prochlorperazine/
132. 58-38-8.rn.
133. (Apo-Prochlorazine or Capazine or Chlormeprazine or Compazine or Compro or Dhaperazine or Emelent or Kronocin or Nipodal or Novamin or Nu-Prochlor or Meterazin or Meterazine or Mitil or Prochlorpemazine or Prochlorperazinum or Proclorperazina or Prochlorperazine or Proklooriperatsiini or Proklorperazin or Prorazin or Phenothiazine or Seratil or Stemetil or Tementil or Temetid).mp.
134. Promazine/
135. 58-40-2.rn.
136. (Ampazine or Berophen or Esparin or Liranol or Neo-Hibernex or Prazin or Sparine or Sinophenin or Promazine hydrochloride or Protactyl or Promatsiini or Promazin or Promazine or Promazinum or Propazinum or Prazine or Promwill or Protactyl or Romtiazin or Sinophenin or Talofen or Talofen or Tomil or Verophen).mp.
137. Raclopride/
138. 84225-95-6.rn.
139. (raclopride or racloprida or raclopridum or rakloprid or raklopridl).mp.
140. Spiperone/
141. 749-02-0.rn.
142. (E 525 or Espiperona or Spiperone or Spiperonum or Spiroperidol or Spiropitan).mp.
143. thioridazine/
144. 50-52-2.rn.

Table A1. MEDLINE–Ovid Version (continued)

145. (Aldazine or Dazithin or Detril or Elperil or Mallorol or Malloryl or Melleril or Meleril or Mellaril or Mellerets or Mellerette or Melleretten or Melleril or Sonapax or Thioridazin or Thioridazine or Thioridazinum or Tioridatsiini or Tioridazin or Tioridazina or Tioridazinas).mp.
146. Thiothixene/
147. 5591-45-7.rn.
148. (Navane or Navaron or Orbinamon or Thiothixene or Tiotikseeni or Tiotixen or Tiotixeno or Tiotixenum or Thixit or Tiotixene).mp.
149. Thioxanthenes/ad, to, tu, ct, po, ae
150. Tiapride/
151. 51012-32-9.rn.
152. (Betaprid or Delpral or Doparid or Etiles or Equilium or Italiprid or Luxoben or Normagit or Porfanil or Sereprid or Tiacob or Tiapridal or Tiapride).mp.
153. Trifluperidol/
154. 749-13-3.rn.
155. (Flumoperone or Psicoperidol or Psychoperidol or Trifluperidol or Trifluperidoli or Trifluperidolum or Triperidol or Trisedil or Trisedyl).mp.
156. Trifluoperazine/
157. 117-89-5.rn.
158. (Cuait D or Cuait N or eskazine or flupazine or Jatrosom or Jalonac or Parstelin or Parmodalin or stelazine or Stelabid or Stelapar or Sycot or Terfluzine or Trifluoperazine or Trifluoperazini Hydrochloridum or triftazin or Trinicalm Forte or Trinicalm Plus).mp.
159. Triflupromazine/
160. 146-54-3.rn.
161. (Adazine or Fluopromazine or Phenothiazine or Psyquil or Siquil or Triflupromazina or Triflupromazine or Trifluopromazine or Vesprin or Vetame).mp.
162. Zuclopenthixol/
163. 53772-83-1.rn.
164. (Cisordinol or Clopixol or Ciatyl-Z or Clopenthixol or Clopentixol or Sedanxol or Zuclopenthixolum or Zuclopentixol or Zuclopenthixol or Zuklopentixol).mp.
165. or/73-164
166. (atypical adj antipsychotic*).tw.
167. ((second or 2nd) adj generation adj antipsychotic*).tw.
168. ((third or 3rd) adj generation adj antipsychotic*).tw.
169. Amisulpride.tw.
170. 71675-85-9.rn.
171. (Aminosultopride or Amisulprida or Amisulpridum or Solian or Sulpitac).mp.
172. aripiprazole.tw.
173. 129722-12-9.rn.
174. (Abilitat or Abilify or Aripiprazole or Discmelt or OPC 31 or OPC 14597).mp.
175. Asenapine.tw.
176. 65576-45-6.rn.
177. EINECS 265-829-4.mp.
178. Blonanserin.tw.
179. 132810-10-7.rn.
180. AD 5423.mp.
181. Clotiapine.tw.
182. 2058-52-8.rn.
183. (Clothiapine or Clotiapina or Clotiapinum or Dibenzothiazepine or Etumina or Etumine or Entumin or Etomine or Entumine or HF 2159 or LW 2159 or "BRN 0568276").mp.
184. clozapine/
185. 5786-21-0.rn.
186. (Clozapin or Clozapina or Clozapine or Clozapinum or Clorazil or Clozaril or FazaClo or Leponex or LX 100-129 or Zaponex).mp.
187. Diazepine.tw.
188. 12688-68-5.rn.
189. Dibenzazepines/ad, to, tu, ct, po, ae
190. Dibenzothiazepines/ct, ad, to, tu, ae, po
191. Fluvoxamine/
192. (54739-18-3 or 61718-82-9).rn.
193. (dumirox or DU23000 or Fluvoxamina or fluvoxamine or Fluvoaminum or Fluvoxamine Maleate or Fevarin or Luvox or SME 3110).mp.
194. Iloperidone.tw.195. 133454-47-4.rn.

Table A1. MEDLINE–Ovid Version (continued)

196. (Fanapt or HP 873 or Zomaril).mp.
197. Isoxazoles/ad, to, tu, ct, po, ae
198. Mesoridazine/
199. 5588-33-0.rn.
200. (Calodal or Lidanar or Lidanil or Mesoridazina or Mesoridazine or Mesoridazinum or Serentil or THD-2-SO).mp.
201. mosapramine.tw.
202. 89419-40-9.rn.
203. (Clospipramine or Cremin or Mosapramina).mp.
204. olanzapine.tw.
205. 132539-06-1.rn.
206. (Zyprexa or Olantsapiini or Olanzapin or Olanzapina or Olanzapinum or Olansek or Zalasta or Zypadhera).mp.
207. paliperidone.tw.
208. 144598-75-4.rn.
209. (9-Hydroxyrisperidone or Invega or R 76477 or RO76477).mp.
210. Perospirone.tw.
211. 150915-41-6.rn.
212. (lullan or perospirone hydrochloride).mp.
213. Piperidines/ad, to, tu, ct, po, ae
214. Piperazines/ad, tu, to, ct, po, ae
215. Pirenzepine/tu, ad, to, ct, po, ae
216. Pyrimidinones/ad, to, tu, ct, po, ae
217. quetiapine.tw.
218. 111974-69-7.rn.
219. (Co-Quetiapine or HSDB 7557 or Seroquel).mp.
220. Quinolones/to, po, ct, ad, tu, ae
221. Remoxipride/
222. 80125-14-0.rn.
223. (FLA 731 or Remoxiprida or Remoxipride or Remoxipridum).mp.
224. Risperidone/
225. 106266-06-2.rn.
226. (Apexidone or Psychodal or Risperdal or Risperidona or Risperidone or Risperidonum or Risperin or Risperilept or Rispolin or Spiron).mp.
227. Sertindole.tw.
228. 106516-24-9.rn.
229. (Lu 23-174 or Sertindol or Serdolect or Sertindolum).mp.
230. Sulpiride/
231. 15676-16-1.rn.
232. (Abilit or Aiglonyl or Alimoral or Calmoflorine or Championyl or Darleton or Desmenat or Dobren or Dogmatil or Dogmatyl or Dolmatil or Eclorion or Eglonil or Eglonyl or Enimon or Equilid or Eusulpid or Fardalan or Fidelan or Guastil or Isnamide or Kylistro or Lisopiride or Mariastel or Meresa or Miradol or Mirbanil or Neogama or Normum or Nufarol or Omiryl or Omperan or Ozoderpin or Psicocen or Pyrkappl or Sernevin or Splotin or Stamonevrol or Sulparex or Sulpirid or Sulpirida or Sulpiride or Sulpiridum or Sulpor or Suprium or Sulpyrid or Trilan or Valirem or Zemorcon).mp.
233. Thiazoles/ad, th, ct, po, to, ae
234. Zotepine.tw.
235. 26615-21-4.rn.
236. (Lodepin or Nipolept or Zotepina or Zotepinum or Zoleptil).mp.
237. ziprasidone.tw.
238. 146939-27-7.rn.
239. Zeldox.mp.
240. or/73-74,166-239
241. or/165,240
242. and/72,241
243. randomized controlled trial.pt.
244. controlled clinical trial.pt.
245. randomi?ed.ab.
246. placebo.ab.
247. drug therapy.fs.
248. randomly.ab.

Table A1. MEDLINE–Ovid Version (continued)

249. trial.ab.
250. groups.ab.
251. or/243-250
252. (humans not (animals and humans)).sh,hw.
253. 251 and 252
254. cohort studies/
255. followup studies/
256. longitudinal studies/
257. prospective studies/
258. Retrospective Studies/
259. Case-Control Studies/
260. (cohort$ or longitudinal or retrospective or prospective or followup or case-control).tw.
261. or/254-260
262. 261 and 252
263. exp infant/
264. exp child/
265. exp adolescent/
266. exp pediatrics/
267. ($child$ or adolescen$ or p*ediatric$).tw.
268. or/263-267
269. and/242,253,268
270. and/242,262,268
271. and/242,253
272. and/242,262
273. or/271-272
274. limit 273 to "all child (0 to 18 years)"
275. or/269-270
276. or/274-275
277. limit 276 to (english language and yr="1987 -Current")
278. limit 273 to "young adult (19 to 24 years)"
279. exp Young Adult/
280. (young adj adult*).tw.
281. ((college or university) adj2 (age or student*)).tw.
282. students/
283. or/279-282
284. and/242,253,283
285. and/242,262,283
286. or/284-285
287. or/278,286
288. limit 287 to (english language and yr="1987 -Current")
289. 277 or 288
290. (editorial or letter or comment).pt. or case reports/
291. 289 not 290

Table A2. Embase–Ovid Version

OvidSP_-EMBASE 1980 to February Week 1 2011	Searched: 12Feb10 and 01Feb11 Results: 3925

1. autism/
2. infantile autism/
3. (autism* or (autistic adj1 disorder*) or kanner* syndrome).tw.
4. asperger syndrome/
5. (asperger* adj1 (syndrome or disorder)).tw.
6. childhood disintegrative disorder/
7. (child adj1 development adj1 disorder*).tw.
8. "pervasive developmental disorder not otherwise specified"/
9. rett syndrome/
10. (((rett or retts) adj1 (sydrome or disorder)) or cerebroatrophic hyperammonemia*).tw.
11. atypical autism.mp.
12. behavior disorder/
13. disruptive behavior/
14. disruptive behavio$ disorder?.mp.
15. conduct disorder/
16. (conduct adj disorder*).tw.
17. oppositional defiant disorder/
18. "disruptive behavior disorder not otherwise specified".mp.
19. "pervasive developmental disorder?".mp.
20. schizophrenia/
21. catatonic schizophrenia/
22. hebephrenia/
23. latent schizophrenia/
24. negative syndrome/
25. paranoid schizophrenia/
26. positive syndrome/
27. residual schizophrenia/
28. schizoaffective psychosis/
29. schizophrenic reaction/
30. schizophreniform disorder/
31. simple schizophrenia/
32. first episode schizophrenia.mp.
33. prodromal schizophrenia/
34. ((catatonic or disorganized or paranoid) adj schizophrenia).tw.
35. psychosis/
36. schizotypal personality disorder/
37. ((Psychotic or schizoaffective or schizophreniform) adj disorder).tw.
38. (schizotypal personality disorder or ((borderline or pseudoneurotic or pseudopsychopathic or incipient or latent) adj2 schizophrenia)).tw.
39. bipolar disorder/
40. bipolar depression/
41. bipolar i disorder/
42. bipolar ii disorder/
43. bipolar mania/
44. cyclothymia/
45. manic depressive psychosis/
46. "mixed mania and depression"/
47. rapid cycling bipolar disorder/
48. (((bipolar or manic) adj (disorder or psychos?s or depression)) or mania*).tw.
49. depression/ and (refractory or chronic or resistant).ti,ab.
50. major depression/ and (refractory or chronic or resistant).ti,ab.
51. ((refractory or chronic or resistant) adj3 depression).mp.
52. ((depressive adj (disorder or neuroses or syndrome*)) or ((endogenous or neurotic or unipolar) adj depression*)).tw.
53. obsessive compulsive disorder/
54. (OCD or anankastic personalit* or (obsessive compulsive adj (disorder* or neuros*)) or (obsessive-compulsive adj (disorder* or neuros*))).tw.
55. exp anorexia nervosa/
56. (anorexia nervosa* or anorexia*).tw.
57. exp post traumatic stress disorder/
58. (post-traumatic adj stress adj disorder*).tw.
59. (posttraumatic adj stress adj disorder*).tw.

Table A2. Embase–Ovid Version (continued)

60. ((post-traumatic or posttraumatic) adj neuroses).tw.
61. (ptsd or (post adj traumatic adj neuroses)).tw.
62. exp gilles de la Tourette syndrome/
63. (de adj la adj tourette adj disease).tw.
64. (gilles adj de adj la adj tourette adj disease).tw.
65. (tourette adj disease).tw.
66. (tourette adj syndrome).tw.
67. exp tic/
68. (tic adj disorder*).tw.
69. (($behavioral adj2 dyscontrol) or (impulsive-behavioral adj2 deregulation)).tw.
70. borderline personality disorder/
71. (borderline adj1 personality adj1 disorder*).tw.
72. (affective adj2 dysregulation).tw.
73. (mood adj2 lability).tw.
74. (irritable or irritability).tw.
75. antisocial personality disorder/
76. aggression/
77. aggression.tw.
78. psychomotor agitation/
79. ((psychomotor adj1 (agitation or restlessness or hyperactivity or excitement)) or akathisia).tw.
80. "sleep initiation and maintenance disorders"/
81. ((sleep adj2 disorder*) or insomnia*).tw.
82. mood disorders/
83. ((mood or affective) adj1 disorder*).tw.
84. impulsive behavior/
85. (impulsive adj1 behavio?r).tw.
86. Self-Injurious Behavior/
87. (self-injurious behavio?r or self-mutilating behavio?r or self mutilation or self-destructive behavio?r or deliberate self-harm or parasuicide).tw.
88. or/1-87
89. neuroleptic agent/
90. ((first or 1st) adj generation adj antipsychotic*).tw.
91. Azaperone/
92. 1649-18-9.rn.
93. (Atsaperoni or Azaperon or Azaperona or Azaperone or Azaperonum or Eucalmyl or Fluoperidol or NSC 170976 or R 1929 or R-1929 or Sedaperone or Stresnil or Suicalm).mp.
94. Clopenthixol/
95. 982-24-1.rn.
96. (Chlorpenthixol or Clopenthixol or Clopenthixolum or Sordinol or Zuclopenthixol).mp.
97. chlorpromazine/
98. 50-53-3.rn.
99. (Aminazin or Aminazine or Ampliactil or BC 135 or Chlorpromazine or Chlorpromazinum or Clorpromazina or Chlor-Promanyl or Chlorpromados or Chlorderazin or Chlorpromazin or Contomin or Elmarin or Esmind or Fenactil or Fenaktyl or HL 5746 or Largactil or Largactilothiazine or Megaphen or Largactyl or Klooripromatsiini or Klorpromazin or 6 Copin or Trinicalm Forte or Diminex Balsamico Juven Tos or Largatrex or Phenactyl or Proma or Promactil or Promazil or Prozil or Psychozine or Sanpron or Thorazine or Torazina or Wintermin).mp.
100. Chlorprothixene/
101. 113-59-7.rn.
102. (Chlorprothixene or Chlorprothixen or Chlorprothixenum or Chlorprotixen or Chlorprotixene or Clorprotisene or Clorprotixeno or Laractan or Paxyl or Rentovet or Taractan or Tarasan or Traquilan or Trictal or Truxal or Truxaletten or Truxil or Vetacalm).mp.
103. dibenzoxazepine derivative/
104. Droperidol/
105. 548-73-2.rn.
106. (Dehydrobenzoperidol or Dehydrobenzperidol or Deidrobenzperidolo or Dridol or Droleptan or Droperidol or Droperidoli or Droperidolis or Droperidolum or Disifelit or Halkan or Inapsin or Inapsine or Inopsin or Thalamonal or Nilperidol or Properidol or Sintodril or Vetkalm).mp.
107. flupentixol/
108. 2709-56-0.rn.
109. (Depixol or Emergil or Fluanxol or Flupenthixol or Flupentixol or Flupentixolum or Fluxanxol or Siplaril or Siplarol).mp.
110. fluphenazine/
111. 69-23-8.rn.
112. (Dapotum or Elinol or Flufenazina or Fluofenazine or Fluphenazine or Fluorphenazine or Fluphenazinum or Ftorphenazine or Moditen or Pacinol or Sevinol or Siqualon or Triflumethazine or Valamina or Vespazine).mp.

Table A2. Embase–Ovid Version (continued)

113. haloperidol/
114. 52-86-8.rn.
115. (Aldo or Aloperidin or Aloperidol or Aloperidolo or Brootopon or Dozic or Einalon S or Eukystol or Fortunan or Galoperidol or Haldol or Halojust or Halopal or Haloperidol or Haloperidoli or Haloperidolis or Haloperidolu or Halopoidol or Serenace or Halopidol or Haloper or Halperon or Keselan or Lealgin or Linton or Mixidol or Peluces or Pernox or Serenace or Serenefl or Sernas or Sernel or Serenase or Ulcolind or Uliolind or Vesalium).mp.
116. indole derivative/
117. levomepromazine/
118. 60-99-1.rn.
119. (Dedoran or Hirnamin or Hirnamine or Levomepromazine or Levomepromazin or Levomepromazina or Levopromazioni or Levomepromazinum or Levoprome or Levotomin or Mepromazine or Methotrimeprazine or Neurocil or Neozine or Nirvan or Nocinan or Momizan or Nozinane or Sinogan or Levolam or Nozinan or Sinogan or Tisercin or Veractil).mp.
120. Lithium/
121. 554-13-2.rn.
122. (Camcolit or Candamide or Carbolith or Carbonic acid lithium salt or dilithium salt or Eskalith or Eutimin or Hypnorex or Limas or Lithium or Liskonum or Litard or Lithane or Lithea or Lithicarb or Lithinate or Lithionate or Lithotabs or Liticar or Manialith or Maniprex or Micalith or Neurolepsin or Pfi-lithium or Phasal or Plenur or Priadel or Quilonorm or Teralithe).mp.
123. loxapine/
124. 1977-10-2.rn.
125. (Cloxazepine or CL 62362 or Dibenzacepin or Dibenzoazepine or Hydrofluoride 3170 or LW 3170 or Lossapina or Loksapiini or Loxapin or Loxapina or Loxapine or Loxapinum or Oxilapine or Loxapac or SUM 3170 or Loxitane or Desconex).mp.
126. Metitepine/
127. 20229-30-5.rn.
128. (Methiothepin or metitepine or Methiothepine or Methiothepin maleate or Metitepina or Metitepinum).mp.
129. molindone/
130. 7416-34-4.rn.
131. (Molindona or Molindone or Molindonum).mp.
132. Penfluridol/
133. 26864-56-2.rn.
134. (Penfluridol or Penfluridolum or Semap).mp.
135. Perazine/
136. 84-97-9.rn.
137. (Pemazine Dimalonate or Peragal or Perazin or Perazine or Perazinum or Taxilan).mp.
138. perphenazine/
139. 58-39-9.rn.
140. (Chlorperphenazine or Chlorpiprazine or Decentan or Emesinal or Etaperazin or Etaperazine or Ethaperazine or Etrafon or F-mon or Fentazin or Mutabon or Perfenazin or Perfenazina or Perfenazinas or Perfenazine or Perphenazin or Perphenazine or Perfenazyna or Perphenazinum or Pertriptyl or Sch 3940 or Thilatazin or Tranquisan or Trifaron or Trilafon or Trilifan or Triptafen or Triphenot or Triavil).mp.
141. phenothiazine derivative/
142. Pimozide/
143. 2062-78-4.rn.
144. (Antalon or Opiran or Orap or Pimotsidi or Pimozid or Pimozida or Pimozidas or Pimozide or Pimozidum or Pimozyd).mp.
145. Prochlorperazine/
146. 58-38-8.rn.
147. (Apo-Prochlorazine or Capazine or Chlormeprazine or Compazine or Compro or Dhaperazine or Emelent or Kronocin or Nipodal or Novamin or Nu-Prochlor or Meterazin or Meterazine or Mitil or Prochlorpemazine or Prochlorperazinum or Proclorperazina or Prochlorperazine or Proklooriperatsiini or Proklorperazin or Prorazin or Phenothiazine or Seratil or Stemetil or Tementil or Temetid).mp.
148. Promazine/
149. 58-40-2.rn.
150. (Ampazine or Berophen or Esparin or Liranol or Neo-Hibernex or Prazin or Sparine or Sinophenin or Promazine hydrochloride or Protactyl or Promatsiini or Promazin or Promazine or Promazinum or Propazinum or Prazine or Promwill or Protactyl or Romtiazin or Sinophenin or Talofen or Talofen or Tomil or Verophen).mp.
151. Raclopride/
152. 84225-95-6.rn.
153. (raclopride or racloprida or raclopridum or rakloprid or raklopridl).mp.
154. Spiperone/
155. 749-02-0.rn.
156. (E 525 or Espiperona or Spiperonum or Spiroperidol or Spiropitan).mp.
157. thioridazine/

Table A2. Embase–Ovid Version (continued)

158. 50-52-2.rn.
159. (Aldazine or Dazithin or Detril or Elperil or Mallorol or Malloryl or Melleril or Meleril or Mellaril or Mellerets or Mellerette or Melleretten or Melleril or Sonapax or Thioridazin or Thioridazinum or Tioridatsiini or Tioridazin or Tioridazina or Tioridazinas).mp.
160. Tiapride/
161. 51012-32-9.rn.
162. tiotixene/
163. 5591-45-7.rn.
164. (Navane or Navaron or Orbinamon or Tiotixene or Tiotikseeni or Tiotixen or Tiotixeno or Tiotixenum or Thixit or Tiotixene).mp.
165. trifluoperazine/
166. 117-89-5.rn.
167. (Cuait D or Cuait N or eskazine or flupazine or Jatrosom or Jalonac or Parstelin or Parmodalin or stelazine or Stelabid or Stelapar or Sycot or Terfluzine or Trifluoperazine or Trifluoperazini Hydrochloridum or triftazin or Trinicalm Forte or Trinicalm Plus).mp.
168. Trifluperidol/
169. 749-13-3.rn.
170. (Flumoperone or Psicoperidol or Psychoperidol or Trifluperidol or Trifluperidoli or Trifluperidolum or Triperidol or Trisedil or Trisedyl).mp.
171. Triflupromazine/
172. 146-54-3.rn.
173. (Adazine or Fluopromazine or Phenothiazine or Psyquil or Siquil or Triflupromazina or Trifluopromazine or Vesprin or Vetame).mp.
174. Zuclopenthixol/
175. 53772-83-1.rn.
176. (Cisordinol or Clopixol or Ciatyl-Z or Clopenthixol or Clopentixol or Sedanxol or Zuclopenthixolum or Zuclopentixol or Zuclopenthixol or Zuklopentixol).mp.
177. or/89-176
178. atypical antipsychotic agent/
179. (atypical adj antipsychotic*).tw.
180. ((second or 2nd) adj generation adj antipsychotic*).tw.
181. ((third or 3rd) adj generation adj antipsychotic*).tw.
182. Amisulpride/
183. 71675-85-9.rn.
184. (Aminosultopride or Amisulprida or Amisulpride or Amisulpridum or Solian or Sulpitac).tw.
185. Aripiprazole/
186. 129722-12-9.rn.
187. (Abilitat or Abilify or Aripiprazole or Discmelt or OPC 31 or OPC 14597).mp.
188. Asenapine/
189. 65576-45-6.rn.
190. (Asenapine or EINECS 265-829-4).mp.
191. Blonanserin/
192. 132810-10-7.rn.
193. (Blonserin or AD 5423).mp.
194. Clospipramine/
195. 89419-40-9.rn.
196. (Clospipramine or Cremin or Mosapramina or Mosapramine).mp.
197. Clotiapine/
198. 2058-52-8.rn.
199. (Clothiapine or Clotiapina or Clotiapine or Clotiapinum or Dibenzothiazepine or Etumina or Etumine or Entumin or Etomine or Entumine or HF 2159 or LW 2159 or "BRN 0568276").mp.
200. clozapine/
201. 5786-21-0.rn.
202. (Clozapin or Clozapina or Clozapine or Clozapinum or Clorazil or Clozaril or FazaClo or Leponex or LX 100-129 or Zaponex).mp.
203. diazepine derivative/
204. 12688-68-5.rn.
205. dibenzazepine derivative/
206. Dibenzothiazepines.tw.
207. Fluvoxamine/
208. (54739-18-3 or 61718-82-9).rn.
209. (dumirox or DU23000 or Fluvoxamina or fluvoxamine or Fluvoaminum or Fluvoxamine Maleate or Fevarin or Luvox or SME 3110).mp.

Table A2. Embase–Ovid Version (continued)

210. Iloperidone/
211. 133454-47-4.rn.
212. (Fanapt or HP 873 or Illoperidone or Zomaril).mp.
213. Isoxazole derivative/
214. mesoridazine besylate/ or mesoridazine/
215. 5588-33-0.rn.
216. (Calodal or Lidanar or Lidanil or Mesoridazina or Mesoridazine or Mesoridazinum or Serentil or THD-2-SO).mp.
217. olanzapine/
218. 132539-06-1.rn.
219. (Zyprexa or Olantsapiini or Olanzapin or Olanzapina or Olanzapine or Olanzapinum or Olansek or Zalasta or Zypadhera).mp.
220. paliperidone/
221. 144598-75-4.rn.
222. (9-Hydroxyrisperidone or Invega or Paliperidone or R 76477 or RO76477).mp.
223. Perospirone/
224. 150915-41-6.rn.
225. (lullan or perospirone hydrochloride).mp.
226. piperidine derivative/
227. Piperazine derivative/
228. Pirenzepine/
229. pyrimidinone derivative/
230. Quetiapine/
231. 111974-69-7.rn.
232. (Co-Quetiapine or HSDB 7557 or Quetiapine or Seroquel).mp.
233. Quinolone derivative/
234. Remoxipride/
235. 80125-14-0.rn.
236. (FLA 731 or Remoxiprida or Remoxipride or Remoxipridum).mp.
237. risperidone/
238. 106266-06-2.rn.
239. (Apexidone or Psychodal or Risperdal or Risperidona or Risperidone or Risperidonum or Risperin or Risperilept or Rispolin or Spiron).mp.
240. Sertindole/
241. 106516-24-9.rn.
242. (Lu 23-174 or Sertindol or Sertindole or Serdolect or Sertindolum).mp.
243. Sulpiride/
244. 15676-16-1.rn.
245. (Abilit or Aiglonyl or Alimoral or Calmoflorine or Championyl or Darleton or Desmenat or Dobren or Dogmatil or Dogmatyl or Dolmatil or Eclorion or Eglonil or Eglonyl or Enimon or Equilid or Eusulpid or Fardalan or Fidelan or Guastil or Isnamide or Kylistro or Lisopiride or Mariastel or Meresa or Miradol or Mirbanil or Neogama or Normum or Nufarol or Omiryl or Omperan or Ozoderpin or Psicocen or Pyrkappl or Sernevin or Splotin or Stamonevrol or Sulparex or Sulpirid or Sulpirida or Sulpiride or Sulpiridum or Sulpor or Suprium or Sulpyrid or Trilan or Valirem or Zemorcon).mp.
246. Thiazole derivative/
247. Zotepine/
248. 26615-21-4.rn.
249. (Lodepin or Nipolept or Zotepina or Zotepine or Zotepinum or Zoleptil).mp.
250. ziprasidone/
251. 146939-27-7.rn.
252. (ziprasidone or zeldox).tw.
253. or/178-252
254. or/177,253
255. and/88,254
256. exp clinical trial/
257. randomi?ed.ti,ab.
258. placebo.ti,ab.
259. dt.fs.
260. randomly.ti,ab.
261. trial.ti,ab.
262. groups.ti,ab.
263. or/256-262
264. (animal not (animal and human)).sh.
265. 263 not 264
266. (book or book series or editorial or letter or note).pt. or case report/

Table A2. Embase–Ovid Version (continued)

267. 265 not 266
268. cohort analysis/
269. longitudinal study/
270. follow up/
271. retrospective study/
272. prospective study/
273. case control study/
274. comparative study/
275. observational study/
276. (cohort$ or longitudinal or retrospective or prospective or followup or case-control).tw.
277. or/268-276
278. 277 not 264
279. 278 not 266
280. exp infant/
281. exp child/
282. exp adolescent/
283. exp pediatrics/
284. (child$ or adolescen$ or p*ediatrics$).tw.
285. or/280-284
286. and/255,267,285
287. and/255,279,285
288. or/286-287
289. limit 288 to yr="1987 -Current"
290. limit 289 to english language
291. (and/255,267) or (and/255,279)
292. limit 291 to (infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
293. limit 292 to yr="1987 -Current"
294. limit 293 to english language
295. 290 or 294
296. (young adj adult*).mp.
297. ((college or university) adj2 (age or student*)).tw.
298. exp student/
299. or/296-298
300. and/255,267,299
301. and/255,279,299
302. or/300-301
303. limit 302 to yr="1987 -Current"
304. limit 303 to english language
305. 295 or 304

Table A3. PsycINFO–Ovid Version

OvidSP_-PsycINFO 1980 to February Week 1 2011	Searched: 16Apr10 and 01Feb11 Results: 4176
1. exp Pervasive Developmental Disorders/ 2. (child adj1 development adj1 disorder*).tw. 3. exp Aspergers Syndrome/ 4. (asperger* adj1 (syndrome or disorder)).tw. 5. exp Autism/ 6. (autism* or (autistic adj1 disorder*) or kanner* syndrome).tw. 7. exp Rett Syndrome/ 8. (((rett or retts) adj1 (sydrome or disorder)) or cerebroatrophic hyperammonemia*).tw. 9. exp Childhood Schizophrenia/ 10. (childhood* adj2 schizophrenia*).tw. 11. aggressive behavior/ 12. aggression.tw. 13. agitation/ 14. ((psychomotor adj1 (agitation or restlessness or hyperactivity or excitement)) or akathisia).tw. 15. Sleep Disorders/ 16. ((sleep adj2 disorder*) or insomnia*).tw. 17. affective disorders/ 18. ((mood or affective) adj1 disorder*).tw. 19. impulsiveness/ 20. (impulsive* or (impulsive adj1 behavio?r)).tw. 21. exp Movement Disorders/ 22. borderline personality disorder/ 23. (borderline adj1 personality adj1 disorder*).tw. 24. (affective adj2 dysregulation).tw. 25. (($behavioral adj2 dyscontrol) or (impulsive-behavioral adj2 deregulation)).tw. 26. (mood adj2 lability).tw. 27. (irritable or irritability).tw. 28. Self-Injurious Behavior/ 29. (self-injurious behavio?r or self-mutilating behavio?r or self mutilation or self-destructive behavio?r or deliberate self-harm or parasuicide).tw. 30. antisocial personality disorder/ 31. exp Attention Deficit Disorder/ 32. ((attention adj deficit adj disorder) or hyperkinetic syndrome or adhd).tw. 33. exp Behavior Disorders/ 34. exp Conduct Disorder/ 35. (conduct adj disorder*).tw. 36. (Childhood adj Disintegrative adj Disorder).tw. 37. "Pervasive Developmental Disorder Not Otherwise Specified".tw. 38. exp Oppositional Defiant Disorder/ 39. (Oppositional adj Defiant adj Disorder).tw. 40. (atypical adj1 autism).tw. 41. "Disruptive Behavior Disorder Not Otherwise Specified".mp. 42. exp Schizophrenia/ 43. exp Catatonic Schizophrenia/ 44. exp "Schizophrenia (Disorganized Type)"/ 45. exp Paranoid Schizophrenia/ 46. ((catatonic or disorganized or paranoid) adj schizophrenia).tw. 47. exp Psychosis/ 48. exp Schizoaffective Disorder/ 49. ((Psychotic or schizoaffective or schizophreniform) adj disorder).tw. 50. (brief reactive adj (psychos?s or psychoses)).tw. 51. first episode schizophrenia.tw. 52. (prodrom$ and schizophren$).tw. 53. exp Schizotypal Personality Disorder/ 54. exp Schizoid Personality Disorder/ 55. (schizotypal personality disorder or ((borderline or pseudoneurotic or pseudopsychopathic or incipient or latent) adj2 schizophrenia)).tw. 56. exp Bipolar Disorder/ 57. (((bipolar or manic) adj (disorder or psychos?s or depression)) or mania*).tw. 58. exp Major Depression/ 59. (depress* and (refractory or chronic or resistant)).mp.	

Table A3. PsycINFO–Ovid Version (continued)

60. exp Treatment Resistant Depression/
61. ((refractive or chronic or resistant) adj3 depression).tw.
62. (depressive adj2 disorder*).tw.
63. exp Obsessive Compulsive Disorder/
64. (OCD or anankastic personalit* or (obsessive compulsive adj (disorder* or neuros*)) or (obsessive-compulsive adj (disorder* or neuros*))).tw.
65. exp Anorexia Nervosa/
66. ((anorexia adj nervosa*) or anorexia*).tw.
67. exp Posttraumatic Stress Disorder/
68. ((chronic or acute or delayed onset) and (post-traumatic adj stress adj disorder*)).tw.
69. ((posttraumatic or post-traumatic or post traumatic) adj (neuroses or disorder)).tw.
70. ptsd.tw.
71. exp Tourette Syndrome/
72. exp Tics/
73. ($tourette* adj (syndrome or disorder or disease)).tw.
74. (tic adj disorder).tw.
75. (multiple adj motor adj vocal adj tic adj disorder).tw.
76. or/1-75
77. exp Neuroleptic Drugs/
78. exp Tranquilizing Drugs/
79. (antipsychotic adj (drug* or agent*)).tw.
80. ((first or 1st) adj generation adj antipsychotic*).tw.
81. azaperone.mp.
82. (Atsaperoni or Azaperon or Azaperona or Azaperone or Azaperonum or Eucalmyl or Fluoperidol or NSC 170976 or R 1929 or R-1929 or Sedaperone or Stresnil or Suicalm).mp.
83. Butyrophenones.tw.
84. Clopenthixol.mp.
85. (Chlorpenthixol or Clopenthixol or Clopenthixolum or Sordinol or Zuclopenthixol).mp.
86. exp Chlorpromazine/
87. (Aminazin or Aminazine or Ampliactil or BC 135 or Chlorpromazine or Chlorpromazinum or Clorpromazina or Chlor-Promanyl or Chlorpromados or Chlorderazin or Chlorpromazin or Contomin or Elmarin or Esmind or Fenactil or Fenaktyl or HL 5746 or Largactil or Largactilothiazine or Megaphen or Largactyl or Klooripromatsiini or Klorpromazin or 6 Copin or Trinicalm Forte or Diminex Balsamico Juven Tos or Largatrex or Phenactyl or Proma or Promactil or Promazil or Prozil or Psychozine or Sanpron or Thorazine or Torazina or Wintermin).mp.
88. Chlorprothixene/
89. (Chlorprothixene or Chlorprothixen or Chlorprothixenum or Chlorprotixen or Chlorprotixene or Clorprotisene or Clorprotixeno or Laractan or Paxyl or Rentovet or Taractan or Tarasan or Traquilan or Trictal or Truxal or Truxaletten or Truxil or Vetacalm).mp.
90. dibenzoxazepines.tw.
91. Droperidol.mp.
92. (Dehydrobenzoperidol or Dehydrobenzperidol or Deidrobenzperidolo or Dridol or Droleptan or Droperidol or Droperidoli or Droperidolis or Droperidolum or Disifelit or Halkan or Inapsin or Inapsine or Inopsin or Thalamonal or Nilperidol or Properidol or Sintodril or Vetkalm).mp.
93. flupentixol.mp.
94. (Depixol or Emergil or Fluanxol or Flupenthixol or Flupentixol or Flupentixolum or Fluxanxol or Siplaril or Siplarol).mp.
95. exp Fluphenazine/
96. (Dapotum or Elinol or Flufenazina or Fluofenazine or Fluphenazine or Fluorphenazine or Fluphenazinum or Ftorphenazine or Moditen or Pacinol or Sevinol or Siqualon or Triflumethazine or Valamina or Vespazine).mp.
97. exp Haloperidol/
98. (Aldo or Aloperidin or Aloperidol or Aloperidolo or Brootopon or Dozic or Einalon S or Eukystol or Fortunan or Galoperidol or Haldol or Halojust or Halopal or Haloperidol or Haloperidoli or Haloperidolis or Haloperidolu or Halopoidol or Serenace or Halopidol or Haloper or Halperon or Keselan or Lealgin or Linton or Mixidol or Peluces or Pernox or Serenace or Serenefl or Sernas or Sernel or Serenase or Ulcolind or Uliolind or Vesalium).mp.
99. indoles.tw.
100. Lithium/ or Lithium carbonate/
101. (Camcolit or Candamide or Carbolith or Carbonic acid lithium salt or dilithium salt or Eskalith or Eutimin or Hypnorex or Limas or Lithium or Liskonum or Litard or Lithane or Lithea or Lithicarb or Lithinate or Lithionate or Lithotabs or Liticar or Manialith or Maniprex or Micalith or Neurolepsin or Pfi-lithium or Phasal or Plenur or Priadel or Quilonorm or Teralithe).mp.
102. exp Loxapine/
103. (Cloxazepine or CL 62362 or Dibenzacepin or Dibenzoazepine or Hydrofluoride 3170 or LW 3170 or Lossapina or Loksapiini or Loxapin or Loxapina or Loxapine or Loxapinum or Oxilapine or Loxapac or SUM 3170 or Loxitane or Desconex).mp.
104. Methiothepin.mp.

Table A3. PsycINFO–Ovid Version (continued)

105. (Methiothepin or metitepine or Methiothepine or Methiothepin maleate or Metitepina or Metitepinum).mp.
106. Methotrimeprazine.mp.
107. (Dedoran or Hirnamin or Hirnamine or Levomepromazine or Levomepromazin or Levomepromazina or Levopromazioni or Levomepromazinum or Levoprome or Levotomin or Mepromazine or Methotrimeprazine or Neurocil or Neozine or Nirvan or Nocinan or Momizan or Nozinane or Sinogan or Levolam or Nozinan or Sinogan or Tisercin or Veractil).mp.
108. exp Molindone/
109. (Molindona or Molindone or Molindonum).mp.
110. Penfluridol.mp.
111. (Penfluridol or Penfluridolum or Semap).mp.
112. perazine.mp.
113. (Pemazine Dimalonate or Peragal or Perazin or Perazine or Perazinum or Taxilan).mp.
114. exp Perphenazine/
115. (Chlorperphenazine or Chlorpiprazine or Decentan or Emesinal or Etaperazin or Etaperazine or Ethaperazine or Etrafon or F-mon or Fentazin or Mutabon or Perfenazin or Perfenazina or Perfenazinas or Perfenazine or Perphenazin or Perphenazine or Perfenazyna or Perphenazinum or Pertriptyl or Sch 3940 or Thilatazin or Tranquisan or Trifaron or Trilafon or Trilifan or Triptafen or Triphenot or Triavil).mp.
116. exp Phenothiazine Derivatives/
117. Pimozide/
118. (Antalon or Opiran or Orap or Pimotsidi or Pimozid or Pimozida or Pimozidas or Pimozide or Pimozidum or Pimozyd).mp.
119. Prochlorperazine/
120. (Apo-Prochlorazine or Capazine or Chlormeprazine or Compazine or Compro or Dhaperazine or Emelent or Kronocin or Nipodal or Novamin or Nu-Prochlor or Meterazin or Meterazine or Mitil or Prochlorpemazine or Prochlorperazinum or Proclorperazina or Prochlorperazine or Proklooriperatsiini or Proklorperazin or Prorazin or Phenothiazine or Seratil or Stemetil or Tementil or Temetid).mp.
121. promazine/
122. (Ampazine or Berophen or Esparin or Liranol or Neo-Hibernex or Prazin or Sparine or Sinophenin or Promazine hydrochloride or Protactyl or Promatsiini or Promazin or Promazine or Promazinum or Propazinum or Prazine or Promwill or Protactyl or Romtiazin or Sinophenin or Talofen or Talofen or Tomil or Verophen).mp.
123. raclopride.mp.
124. (raclopride or racloprida or raclopridum or rakloprid or raklopridl).mp.
125. Spiroperidol/
126. (E 525 or Espiperona or Spiperone or Spiperonum or Spiroperidol or Spiropitan).mp.
127. exp Thiothixene/
128. (Navane or Navaron or Orbinamon or Tiotixene or Tiotikseeni or Tiotixen or Tiotixeno or Tiotixenum or Thixit or Tiotixene).mp.
129. exp Trifluoperazine/
130. (Cuait D or Cuait N or eskazine or flupazine or Jatrosom or Jalonac or Parstelin or Parmodalin or stelazine or Stelabid or Stelapar or Sycot or Terfluzine or Trifluoperazine or Trifluoperazini Hydrochloridum or triftazin or Trinicalm Forte or Trinicalm Plus).mp.
131. exp Thioridazine/
132. (Aldazine or Dazithin or Detril or Elperil or Mallorol or Malloryl or Melleril or Meleril or Mellaril or Mellerets or Mellerette or Melleretten or Melleril or Sonapax or Thioridazin or Thioridazinum or Tioridatsiini or Tioridazin or Tioridazina or Tioridazinas).mp.
133. exp Phenothiazine Derivatives/
134. (Adazine or Fluopromazine or Phenothiazine or Psyquil or Siquil or Triflupromazina or Trifluopromazine or Vesprin or Vetame).mp.
135. Zuclopenthixol.mp.
136. (Cisordinol or Clopixol or Ciatyl-Z or Clopenthixol or Clopentixol or Sedanxol or Zuclopenthixolum or Zuclopentixol or Zuclopenthixol or Zuklopentixol).mp.
137. or/77-136
138. atypical antipsychotic$.tw.
139. ((second or 2nd) adj generation adj antipsychotic*).tw.
140. ((third or 3rd) adj generation adj antipsychotic*).tw.
141. Amisulpride.mp.
142. (Aminosultopride or Amisulprida or Amisulpridum or Solian or Sulpitac).mp.
143. exp Aripiprazole/
144. (Abilitat or Abilify or Aripiprazole or Discmelt or OPC 31 or OPC 14597).mp.
145. Asenapine.mp.
146. EINECS 265-829-4.mp.
147. (Blonanserin or AD 5423).mp.
148. Clotiapine.mp.
149. (Clothiapine or Clotiapina or Clotiapinum or Dibenzothiazepine or Etumina or Etumine or Entumin or Etomine or Entumine or HF 2159 or LW 2159 or "BRN 0568276").mp.

Table A3. PsycINFO–Ovid Version (continued)

150. exp Clozapine/
151. (Clozapin or Clozapina or Clozapine or Clozapinum or Clorazil or Clozaril or FazaClo or Leponex or LX 100-129 or Zaponex).mp.
152. Diazepine.mp.
153. Dibenzazepines.mp.
154. Fluvoxamine/
155. (dumirox or DU23000 or Fluvoxamina or fluvoxamine or Fluvoaminum or Fluvoxamine Maleate or Fevarin or Luvox or SME 3110).mp.
156. Iloperidone.mp.
157. (Fanapt or HP 873 or Zomaril).mp.
158. Isoxazole*.mp.
159. Mesoridazine/
160. (Calodal or Lidanar or Lidanil or Mesoridazina or Mesoridazine or Mesoridazinum or Serentil or THD-2-SO).mp.
161. mosapramine.mp.
162. (Clospipramine or Cremin or Mosapramina).mp.
163. exp Olanzapine/
164. (Zyprexa or Olantsapiini or Olanzapin or Olanzapine or Olanzapina or Olanzapinum or Olansek or Zalasta or Zypadhera).mp.
165. paliperidone.tw.
166. (9-Hydroxyrisperidone or Invega or R 76477 or RO76477).mp.
167. Perospirone.tw.
168. (lullan or perospirone hydrochloride).mp.
169. Piperidines.mp.
170. Piperazines/ or piperazine*.mp.
171. Pirenzepine.mp.
172. Pyrimidinones.mp.
173. exp Quetiapine/
174. (Co-Quetiapine or HSDB 7557 or Quetiapine or Seroquel).mp.
175. Quinolones.mp.
176. Remoxipride.mp.
177. (FLA 731 or Remoxiprida or Remoxipride or Remoxipridum).mp.
178. exp Risperidone/
179. (Apexidone or Psychodal or Risperdal or Risperidona or Risperidone or Risperidonum or Risperin or Risperilept or Rispolin or Spiron).mp.
180. Sertindole.mp.
181. (Lu 23-174 or Sertindol or Sertindole or Serdolect or Sertindolum).mp.
182. Sulpiride/
183. (Abilit or Aiglonyl or Alimoral or Calmoflorine or Championyl or Darleton or Desmenat or Dobren or Dogmatil or Dogmatyl or Dolmatil or Eclorion or Eglonil or Eglonyl or Enimon or Equilid or Eusulpid or Fardalan or Fidelan or Guastil or Isnamide or Kylistro or Lisopiride or Mariastel or Meresa or Miradol or Mirbanil or Neogama or Normum or Nufarol or Omiryl or Omperan or Ozoderpin or Psicocen or Pyrkappl or Sernevin or Splotin or Stamonevrol or Sulparex or Sulpirid or Sulpirida or Sulpiride or Sulpiridum or Sulpor or Suprium or Sulpyrid or Trilan or Valirem or Zemorcon).mp.
184. thiazole.mp.
185. Zotepine.tw.
186. (Lodepin or Nipolept or Zotepina or Zotepinum or Zoleptil).mp.
187. ziprasidone.tw.
188. Zeldox.mp.
189. or/77-79,138-188
190. or/137,189
191. and/76,190
192. randomi?ed controlled trial.tw,pt.
193. exp Clinical Trials/
194. controlled clinical trial.tw,pt.
195. randomi?ed.ab.
196. placebo.ab.
197. exp drug therapy/
198. randomly.ab.
199. trial.ab.
200. groups.ab.
201. or/192-200
202. (cohort studies or cohort study).tw.
203. exp Followup Studies/
204. exp Longitudinal Studies/

Table A3. PsycINFO–Ovid Version (continued)

205. exp Prospective Studies/
206. exp Retrospective Studies/
207. (cohort$ or longitudinal or retrospective or prospective or followup or case-control).tw.
208. or/202-207
209. (animals not (humans and animals)).sh,hw.
210. 201 not 209
211. 208 not 209
212. (infant or $child$ or adolescen$ or p*ediatric$).tw.
213. and/191,210,212
214. and/191,211-212
215. or/213-214
216. and/191,210
217. and/191,211
218. or/216-217
219. limit 218 to ((childhood or adolescence <13 to 17 years>) and (100 childhood or 140 infancy or 160 preschool age or 180 school age or 200 adolescence))
220. limit 215 to ((childhood or adolescence <13 to 17 years>) and (100 childhood or 140 infancy or 160 preschool age or 180 school age or 200 adolescence))
221. or/219-220
222. limit 221 to human
223. limit 222 to english language
224. limit 223 to yr="1987 -Current"
225. ((college or university) adj2 (age or student*)).tw.
226. exp College Students/
227. (young adj adult*).tw.
228. or/225-227
229. and/191,210,228
230. and/191,211,228
231. limit 218 to 320 young adulthood
232. limit 215 to 320 young adulthood
233. 231 or 232
234. limit 233 to (human and english language and yr="1987 -Current")
235. 224 or 234

Table A4. CENTRAL–Ovid Version

OvidSP_-CENTRAL	Searched: 16Apr10 and 01Feb11
1980 to February Week 1 2011	Results: 1181

1. (child adj1 development adj1 disorder*).mp.
2. (asperger* adj1 (syndrome or disorder)).mp.
3. (autism* or (autistic adj1 disorder*) or kanner* syndrome).mp.
4. (atypical adj1 autism).mp.
5. (((rett or retts) adj1 (sydrome or disorder)) or cerebroatrophic hyperammonemia*).mp.
6. (child* adj2 schizophrenia*).mp.
7. aggression.mp.
8. ((psychomotor adj1 (agitation or restlessness or hyperactivity or excitement)) or akathisia).mp.
9. ((sleep adj2 disorder*) or insomnia*).mp.
10. ((mood or affective) adj1 disorder*).mp.
11. (impulsive adj1 behavio?r).mp.
12. (borderline adj1 personality adj1 disorder*).mp.
13. (affective adj2 dysregulation).mp.
14. (($behavioral adj2 dyscontrol) or (impulsive-behavioral adj2 deregulation)).mp.
15. (mood adj2 lability).mp.
16. (irritable or irritability).mp.
17. (self-injurious behavio?r or self-mutilating behavio?r or self mutilation or self-destructive behavio?r or deliberate self-harm or parasuicide).mp.
18. movement disorders.mp.
19. ((attention adj deficit adj disorder) or hyperkinetic syndrome or adhd).mp.
20. (conduct adj disorder*).mp.
21. oppositional defiant disorder.mp.
22. "Disruptive Behavior Disorder Not Otherwise Specified".mp.
23. (schizophrenia* or ((catatonic or disorganized or paranoid) adj schizophrenia)).mp.
24. ((Psychotic or schizoaffective or schizophreniform) adj disorder).mp.
25. (schizotypal personality disorder or ((borderline or pseudoneurotic or pseudopsychopathic or incipient or latent) adj2 schizophrenia)).mp.
26. (brief reactive psychos?s or psychoses).mp.
27. (prodrom$ and schizophren$).mp.
28. first episode schizophrenia.mp.
29. (major depression or depressive disorder).mp.
30. (depression and (refractory or chronic or resistant)).mp.
31. (schizotypal personality disorder or ((borderline or pseudoneurotic or pseudopsychopathic or incipient or latent) adj2 schizophrenia)).mp.
32. (((bipolar or manic) adj (disorder or psychos?s or depression)) or mania*).mp.
33. (OCD or anankastic personalit* or (obsessive compulsive adj (disorder* or neuros*)) or (obsessive-compulsive adj (disorder* or neuros*))).tw.
34. ((chronic or acute or delayed onset) and (post-traumatic adj stress adj disorder*)).mp.
35. ((posttraumatic or post-traumatic or post traumatic) adj (neuroses or disorder)).mp.
36. ptsd.mp.
37. ((anorexia adj nervosa*) or anorexia*).mp.
38. ($tourette* adj (syndrome or disorder or disease)).mp.
39. (tic adj disorder).mp.
40. (multiple adj motor adj vocal adj tic adj disorder).mp.
41. or/1-40
42. (antipsychotics or antipsychotic agent* or antipsychotic drug*).mp.
43. (tranquilizing agent* or tranquilizing drug*).mp.
44. ((first or 1st) adj generation adj antipsychotic*).mp.
45. 1649-18-9.rn.
46. (Atsaperoni or Azaperon or Azaperona or Azaperone or Azaperonum or Eucalmyl or Fluoperidol or NSC 170976 or R 1929 or R-1929 or Sedaperone or Stresnil or Suicalm).mp.
47. Butyrophenones.mp.
48. 982-24-1.rn.
49. (Chlorpenthixol or Clopenthixol or Clopenthixolum or Sordinol or Zuclopenthixol).mp.
50. 50-53-3.rn.
51. (Aminazin or Aminazine or Ampliactil or BC 135 or Chlorpromazine or Chlorpromazinum or Clorpromazina or Chlor-Promanyl or Chlorpromados or Chlorderazin or Chlorpromazin or Contomin or Elmarin or Esmind or Fenactil or Fenaktyl or HL 5746 or Largactil or Largactilothiazine or Megaphen or Largactyl or Klooripromatsiini or Klorpromazin or 6 Copin or Trinicalm Forte or Diminex Balsamico Juven Tos or Largatrex or Phenactyl or Proma or Promactil or Promazil or Prozil or Psychozine or Sanpron or Thorazine or Torazina or Wintermin).mp.
52. 113-59-7.rn.

Table A4. CENTRAL–Ovid Version (continued)

53. (Chlorprothixene or Chlorprothixen or Chlorprothixenum or Chlorprotixen or Chlorprotixene or Clorprotisene or Clorprotixeno or Laractan or Paxyl or Rentovet or Taractan or Tarasan or Traquilan or Trictal or Truxal or Truxaletten or Truxil or Vetacalm).mp.
54. Dibenzoxazepines.mp.
55. 548-73-2.rn.
56. (Dehydrobenzoperidol or Dehydrobenzperidol or Deidrobenzperidolo or Dridol or Droleptan or Droperidol or Droperidoli or Droperidolis or Droperidolum or Disifelit or Halkan or Inapsin or Inapsine or Inopsin or Thalamonal or Nilperidol or Properidol or Sintodril or Vetkalm).mp.
57. 2709-56-0.rn.
58. (Depixol or Emergil or Fluanxol or Flupenthixol or Flupentixol or Flupentixolum or Fluxanxol or Siplaril or Siplarol).mp.
59. 69-23-8.rn.
60. (Dapotum or Elinol or Flufenazina or Fluofenazine or Fluphenazine or Fluorphenazine or Fluphenazinum or Ftorphenazine or Moditen or Pacinol or Sevinol or Siqualon or Triflumethazine or Valamina or Vespazine).mp.
61. 52-86-8.rn.
62. (Aldo or Aloperidin or Aloperidol or Aloperidolo or Brootopon or Dozic or Einalon S or Eukystol or Fortunan or Galoperidol or Haldol or Halojust or Halopal or Haloperidol or Haloperidoli or Haloperidolis or Haloperidolu or Halopoidol or Serenace or Halopidol or Haloper or Halperon or Keselan or Lealgin or Linton or Mixidol or Peluces or Pernox or Serenace or Serenefl or Sernas or Sernel or Serenase or Ulcolind or Uliolind or Vesalium).mp.
63. indoles.mp.
64. 554-13-2.rn.
65. (Camcolit or Candamide or Carbolith or Carbonic acid lithium salt or dilithium salt or Eskalith or Eutimin or Hypnorex or Limas or Lithium or Liskonum or Litard or Lithane or Lithea or Lithicarb or Lithinate or Lithionate or Lithotabs or Liticar or Manialith or Maniprex or Micalith or Neurolepsin or Pfi-lithium or Phasal or Plenur or Priadel or Quilonorm or Teralithe).mp.
66. 1977-10-2.rn.
67. (Cloxazepine or CL 62362 or Dibenzacepin or Dibenzoazepine or Hydrofluoride 3170 or LW 3170 or Lossapina or Loksapiini or Loxapin or Loxapina or Loxapine or Loxapinum or Oxilapine or Loxapac or SUM 3170 or Loxitane or Desconex).mp.
68. 20229-30-5.rn.
69. (Methiothepin or metitepine or Methiothepine or Methiothepin maleate or Metitepina or Metitepinum).mp.
70. 60-99-1.rn.
71. (Dedoran or Hirnamin or Hirnamine or Levomepromazine or Levomepromazin or Levomepromazina or Levopromazioni or Levomepromazinum or Levoprome or Levotomin or Mepromazine or Methotrimeprazine or Neurocil or Neozine or Nirvan or Nocinan or Momizan or Nozinane or Sinogan or Levolam or Nozinan or Sinogan or Tisercin or Veractil).mp.
72. 7416-34-4.rn.
73. (Molindona or Molindone or Molindonum).mp.
74. 26864-56-2.rn.
75. (Penfluridol or Penfluridolum or Semap).mp.
76. 84-97-9.rn.
77. (Pemazine Dimalonate or Peragal or Perazin or Perazine or Perazinum or Taxilan).mp.
78. 58-39-9.rn.
79. (Chlorperphenazine or Chlorpiprazine or Decentan or Emesinal or Etaperazin or Etaperazine or Ethaperazine or Etrafon or F-mon or Fentazin or Mutabon or Perfenazin or Perfenazina or Perfenazinas or Perfenazine or Perphenazin or Perphenazine or Perfenazyna or Perphenazinum or Pertriptyl or Sch 3940 or Thilatazin or Tranquisan or Trifaron or Trilafon or Trilifan or Triptafen or Triphenot or Triavil).mp.
80. Phenothiazines.mp.
81. 2062-78-4.rn.
82. (Antalon or Opiran or Orap or Pimotsidi or Pimozid or Pimozida or Pimozidas or Pimozide or Pimozidum or Pimozyd).mp.
83. 58-38-8.rn.
84. (Apo-Prochlorazine or Capazine or Chlormeprazine or Compazine or Compro or Dhaperazine or Emelent or Kronocin or Nipodal or Novamin or Nu-Prochlor or Meterazin or Meterazine or Mitil or Prochlorpemazine or Prochlorperazinum or Proclorperazina or Prochlorperazine or Proklooriperatsiini or Proklorperazin or Prorazin or Phenothiazine or Seratil or Stemetil or Tementil or Temetid).mp.
85. 58-40-2.rn.
86. (Ampazine or Berophen or Esparin or Liranol or Neo-Hibernex or Prazin or Sparine or Sinophenin or Promazine hydrochloride or Protactyl or Promatsiini or Promazin or Promazine or Promazinum or Propazinum or Prazine or Promwill or Protactyl or Romtiazin or Sinophenin or Talofen or Talofen or Tomil or Verophen).mp.
87. 84225-95-6.rn.
88. (raclopride or racloprida or raclopridum or rakloprid or raklopridl).mp.
89. 749-02-0.rn.
90. (E 525 or Espiperona or Spiperone or Spiperonum or Spiroperidol or Spiropitan).mp.
91. 50-52-2.rn.

Table A4. CENTRAL–Ovid Version (continued)

92. (Aldazine or Dazithin or Detril or Elperil or Mallorol or Malloryl or Melleril or Meleril or Mellaril or Mellerets or Mellerette or Melleretten or Melleril or Sonapax or Thioridazin or Thioridazine or Thioridazinum or Tioridatsiini or Tioridazin or Tioridazina or Tioridazinas).mp.
93. 5591-45-7.rn.
94. (Navane or Navaron or Orbinamon or Thiothixene or Tiotikseeni or Tiotixen or Tiotixeno or Tiotixenum or Thixit or Tiotixene).mp.
95. Thioxanthenes.mp.
96. 51012-32-9.rn.
97. (Betaprid or Delpral or Doparid or Etiles or Equilium or Italiprid or Luxoben or Normagit or Porfanil or Sereprid or Tiacob or Tiapridal or Tiapride).mp.
98. 749-13-3.rn.
99. (Flumoperone or Psicoperidol or Psychoperidol or Trifluperidol or Trifluperidoli or Trifluperidolum or Triperidol or Trisedil or Trisedyl).mp.
100. 117-89-5.rn.
101. (Cuait D or Cuait N or eskazine or flupazine or Jatrosom or Jalonac or Parstelin or Parmodalin or stelazine or Stelabid or Stelapar or Sycot or Terfluzine or Trifluoperazine or Trifluoperazini Hydrochloridum or triftazin or Trinicalm Forte or Trinicalm Plus).mp.
102. 146-54-3.rn.
103. (Adazine or Fluopromazine or Phenothiazine or Psyquil or Siquil or Triflupromazina or Triflupromazine or Trifluopromazine or Vesprin or Vetame).mp.
104. 53772-83-1.rn.
105. (Cisordinol or Clopixol or Ciatyl-Z or Clopenthixol or Clopentixol or Sedanxol or Zuclopenthixolum or Zuclopentixol or Zuclopenthixol or Zuklopentixol).mp.
106. or/42-105
107. atypical antipsychotic*.mp.
108. ((second or 2nd) adj generation adj antipsychotic*).tw.
109. ((third or 3rd) adj generation adj antipsychotic*).tw.
110. 71675-85-9.rn.
111. (Aminosultopride or Amisulprida or Amisulpride or Amisulpridum or Solian or Sulpitac).mp.
112. 129722-12-9.rn.
113. (Abilitat or Abilify or Aripiprazole or Discmelt or OPC 31 or OPC 14597).mp.
114. 65576-45-6.rn.
115. (Asenapine or EINECS 265-829-4).mp.
116. 132810-10-7.rn.
117. (Blonserin or AD 5423).mp.
118. 2058-52-8.rn.
119. (Clothiapine or Clotiapina or Clotiapine or Clotiapinum or Dibenzothiazepine or Etumina or Etumine or Entumin or Etomine or Entumine or HF 2159 or LW 2159 or "BRN 0568276").mp.
120. 5786-21-0.rn.
121. (Clozapin or Clozapina or Clozapine or Clozapinum or Clorazil or Clozaril or FazaClo or Leponex or LX 100-129 or Zaponex).mp.
122. 12688-68-5.rn.
123. Diazepine.mp.
124. Dibenzazepines.mp.
125. Dibenzothiazepines.mp.
126. (54739-18-3 or 61718-82-9).rn.
127. (dumirox or DU23000 or Fluvoxamina or fluvoxamine or Fluvoaminum or Fluvoxamine Maleate or Fevarin or Luvox or SME 3110).mp.
128. 133454-47-4.rn.
129. (Fanapt or Iloperidone or HP 873 or Zomaril).mp.
130. Isoxazoles.mp.
131. 5588-33-0.rn.
132. (Calodal or Lidanar or Lidanil or Mesoridazina or Mesoridazine or Mesoridazinum or Serentil or THD-2-SO).mp.
133. 89419-40-9.rn.
134. (Clospipramine or Cremin or Mosapramina or Mosapramine).mp.
135. 132539-06-1.rn.
136. (Zyprexa or Olantsapiini or Olanzapin or Olanzapina or Olanzapine or Olanzapinum or Olansek or Zalasta or Zypadhera).mp.
137. 144598-75-4.rn.
138. (9-Hydroxyrisperidone or Invega or Paliperidone or R 76477 or RO76477).mp.
139. 150915-41-6.rn.
140. (lullan or perospirone*).mp.
141. Piperidines.mp.
142. Pirenzepine.mp.

Table A4. CENTRAL–Ovid Version (continued)

143. Pyrimidinones.mp.144. 111974-69-7.rn.
145. (Co-Quetiapine or HSDB 7557 or Quetiapine or Seroquel).mp.
146. Quinolones.mp.
147. 80125-14-0.rn.
148. (FLA 731 or Remoxiprida or Remoxipride or Remoxipridum).mp.
149. 106266-06-2.rn.
150. (Apexidone or Psychodal or Risperdal or Risperidona or Risperidone or Risperidonum or Risperin or Risperilept or Rispolin or Spiron).mp.
151. 106516-24-9.rn.
152. (Lu 23-174 or Sertindol or Sertindole or Serdolect or Sertindolum).mp.
153. 15676-16-1.rn.
154. (Abilit or Aiglonyl or Alimoral or Calmoflorine or Championyl or Darleton or Desmenat or Dobren or Dogmatil or Dogmatyl or Dolmatil or Eclorion or Eglonil or Eglonyl or Enimon or Equilid or Eusulpid or Fardalan or Fidelan or Guastil or Isnamide or Kylistro or Lisopiride or Mariastel or Meresa or Miradol or Mirbanil or Neogama or Normum or Nufarol or Omiryl or Omperan or Ozoderpin or Psicocen or Pyrkappl or Sernevin or Splotin or Stamonevrol or Sulparex or Sulpirid or Sulpirida or Sulpiride or Sulpiridum or Sulpor or Suprium or Sulpyrid or Trilan or Valirem or Zemorcon).mp.
155. thiazoles.mp.
156. 26615-21-4.rn.
157. (Lodepin or Nipolept or Zotepina or Zotepine or Zotepinum or Zoleptil).mp.
158. 146939-27-7.rn.
159. (ziprasidone or zeldox).tw.
160. or/107
161. or/106,160
162. infant.mp.
163. ($child$ or adolescen$ or p*ediatric$).mp.
164. or/162-163
165. and/41,161,164
166. limit 165 to yr="1987 -Current"
167. (young adj adult*).mp.
168. ((college or university) adj2 (age or student*)).tw.
169. or/167-168
170. and/41,161,169
171. limit 170 to yr="1987 -Current"
172. 166 or 171

Table A5. IPA–Ovid Version

OvidSP_-IPA 1980 to April Week 3 2010	Searched: 16Apr10 Results: 322

1. (child adj1 development adj1 disorder*).mp.
2. (asperger* adj1 (syndrome or disorder)).mp.
3. (autism* or (autistic adj1 disorder*) or kanner* syndrome).mp.
4. (atypical adj1 autism).mp.
5. (((rett or retts) adj1 (sydrome or disorder)) or cerebroatrophic hyperammonemia*).mp.
6. (child* adj2 schizophrenia*).mp.
7. aggression.mp.
8. ((psychomotor adj1 (agitation or restlessness or hyperactivity or excitement)) or akathisia).mp.
9. ((sleep adj2 disorder*) or insomnia*).mp.
10. ((mood or affective) adj1 disorder*).mp.
11. (impulsive adj1 behavio?r).mp.
12. (borderline adj1 personality adj1 disorder*).mp.
13. (affective adj2 dysregulation).mp.
14. (($behavioral adj2 dyscontrol) or (impulsive-behavioral adj2 deregulation)).mp.
15. (mood adj2 lability).mp.
16. (irritable or irritability).mp.
17. (self-injurious behavio?r or self-mutilating behavio?r or self mutilation or self-destructive behavio?r or deliberate self-harm or parasuicide).mp.
18. movement disorders.mp.
19. ((attention adj deficit adj disorder) or hyperkinetic syndrome or adhd).mp.
20. (conduct adj disorder*).mp.
21. oppositional defiant disorder.mp.
22. "Disruptive Behavior Disorder Not Otherwise Specified".mp.
23. (schizophrenia* or ((catatonic or disorganized or paranoid) adj schizophrenia)).mp.
24. ((Psychotic or schizoaffective or schizophreniform) adj disorder).mp.
25. (schizotypal personality disorder or ((borderline or pseudoneurotic or pseudopsychopathic or incipient or latent) adj2 schizophrenia)).mp.
26. (brief reactive psychos?s or psychoses).mp.
27. (prodrom$ and schizophren$).mp.
28. first episode schizophrenia.mp.
29. (major depression or depressive disorder).mp.
30. (depression and (refractory or chronic or resistant)).mp.
31. (schizotypal personality disorder or ((borderline or pseudoneurotic or pseudopsychopathic or incipient or latent) adj2 schizophrenia)).mp.
32. (((bipolar or manic) adj (disorder or psychos?s or depression)) or mania*).mp.
33. (OCD or anankastic personalit* or (obsessive compulsive adj (disorder* or neuros*)) or (obsessive-compulsive adj (disorder* or neuros*))).tw.
34. ((chronic or acute or delayed onset) and (post-traumatic adj stress adj disorder*)).mp.
35. ((posttraumatic or post-traumatic or post traumatic) adj (neuroses or disorder)).mp.
36. ptsd.mp.
37. ((anorexia adj nervosa*) or anorexia*).mp.
38. ($tourette* adj (syndrome or disorder or disease)).mp.
39. (tic adj disorder).mp.
40. (multiple adj motor adj vocal adj tic adj disorder).mp.
41. or/1-40
42. (antipsychotics or antipsychotic agent* or antipsychotic drug*).mp.
43. (tranquilizing agent* or tranquilizing drug*).mp.
44. ((first or 1st) adj generation adj antipsychotic*).mp.
45. 1649-18-9.rn.
46. (Atsaperoni or Azaperon or Azaperona or Azaperone or Azaperonum or Eucalmyl or Fluoperidol or NSC 170976 or R 1929 or R-1929 or Sedaperone or Stresnil or Suicalm).mp.
47. Butyrophenones.mp.
48. 982-24-1.rn.
49. (Chlorpenthixol or Clopenthixol or Clopenthixolum or Sordinol or Zuclopenthixol).mp.
50. 50-53-3.rn.
51. (Aminazin or Aminazine or Ampliactil or BC 135 or Chlorpromazine or Chlorpromazinum or Clorpromazina or Chlor-Promanyl or Chlorpromados or Chlorderazin or Chlorpromazin or Contomin or Elmarin or Esmind or Fenactil or Fenaktyl or HL 5746 or Largactil or Largactilothiazine or Megaphen or Largactyl or Klooripromatsiini or Klorpromazin or 6 Copin or Trinicalm Forte or Diminex Balsamico Juven Tos or Largatrex or Phenactyl or Proma or Promactil or Promazil or Prozil or Psychozine or Sanpron or Thorazine or Torazina or Wintermin).mp.
52. 113-59-7.rn.

Table A5. IPA–Ovid Version (continued)

53. (Chlorprothixene or Chlorprothixen or Chlorprothixenum or Chlorprotixen or Chlorprotixene or Clorprotisene or Clorprotixeno or Laractan or Paxyl or Rentovet or Taractan or Tarasan or Traquilan or Trictal or Truxal or Truxaletten or Truxil or Vetacalm).mp.
54. Dibenzoxazepines.mp.
55. 548-73-2.rn.
56. (Dehydrobenzoperidol or Dehydrobenzperidol or Deidrobenzperidolo or Dridol or Droleptan or Droperidol or Droperidoli or Droperidolis or Droperidolum or Disifelit or Halkan or Inapsin or Inapsine or Inopsin or Thalamonal or Nilperidol or Properidol or Sintodril or Vetkalm).mp.
57. 2709-56-0.rn.
58. (Depixol or Emergil or Fluanxol or Flupenthixol or Flupentixol or Flupentixolum or Fluxanxol or Siplaril or Siplarol).mp.
59. 69-23-8.rn.
60. (Dapotum or Elinol or Flufenazina or Fluofenazine or Fluphenazine or Fluorphenazine or Fluphenazinum or Ftorphenazine or Moditen or Pacinol or Sevinol or Siqualon or Triflumethazine or Valamina or Vespazine).mp.
61. 52-86-8.rn.
62. (Aldo or Aloperidin or Aloperidol or Aloperidolo or Brootopon or Dozic or Einalon S or Eukystol or Fortunan or Galoperidol or Haldol or Halojust or Halopal or Haloperidol or Haloperidoli or Haloperidolis or Haloperidolu or Halopoidol or Serenace or Halopidol or Haloper or Halperon or Keselan or Lealgin or Linton or Mixidol or Peluces or Pernox or Serenace or Serenefl or Sernas or Sernel or Serenase or Ulcolind or Uliolind or Vesalium).mp.
63. indoles.mp.
64. 554-13-2.rn.
65. (Camcolit or Candamide or Carbolith or Carbonic acid lithium salt or dilithium salt or Eskalith or Eutimin or Hypnorex or Limas or Lithium or Liskonum or Litard or Lithane or Lithea or Lithicarb or Lithinate or Lithionate or Lithotabs or Liticar or Manialith or Maniprex or Micalith or Neurolepsin or Pfi-lithium or Phasal or Plenur or Priadel or Quilonorm or Teralithe).mp.
66. 1977-10-2.rn.
67. (Cloxazepine or CL 62362 or Dibenzacepin or Dibenzoazepine or Hydrofluoride 3170 or LW 3170 or Lossapina or Loksapiini or Loxapin or Loxapina or Loxapine or Loxapinum or Oxilapine or Loxapac or SUM 3170 or Loxitane or Desconex).mp.
68. 20229-30-5.rn.
69. (Methiothepin or metitepine or Methiothepine or Methiothepin maleate or Metitepina or Metitepinum).mp.
70. 60-99-1.rn.
71. (Dedoran or Hirnamin or Hirnamine or Levomepromazine or Levomepromazin or Levomepromazina or Levopromazioni or Levomepromazinum or Levoprome or Levotomin or Mepromazine or Methotrimeprazine or Neurocil or Neozine or Nirvan or Nocinan or Momizan or Nozinane or Sinogan or Levolam or Nozinan or Sinogan or Tisercin or Veractil).mp.
72. 7416-34-4.rn.
73. (Molindona or Molindone or Molindonum).mp.
74. 26864-56-2.rn.
75. (Penfluridol or Penfluridolum or Semap).mp.
76. 84-97-9.rn.
77. (Pemazine Dimalonate or Peragal or Perazin or Perazine or Perazinum or Taxilan).mp.
78. 58-39-9.rn.
79. (Chlorperphenazine or Chlorpiprazine or Decentan or Emesinal or Etaperazin or Etaperazine or Ethaperazine or Etrafon or F-mon or Fentazin or Mutabon or Perfenazin or Perfenazina or Perfenazinas or Perfenazine or Perphenazin or Perphenazine or Perfenazyna or Perphenazinum or Pertriptyl or Sch 3940 or Thilatazin or Tranquisan or Trifaron or Trilafon or Trilifan or Triptafen or Triphenot or Triavil).mp.
80. Phenothiazines.mp.
81. 2062-78-4.rn.
82. (Antalon or Opiran or Orap or Pimotsidi or Pimozid or Pimozida or Pimozidas or Pimozide or Pimozidum or Pimozyd).mp.
83. 58-38-8.rn.
84. (Apo-Prochlorazine or Capazine or Chlormeprazine or Compazine or Compro or Dhaperazine or Emelent or Kronocin or Nipodal or Novamin or Nu-Prochlor or Meterazin or Meterazine or Mitil or Prochlorpemazine or Prochlorperazinum or Proclorperazina or Prochlorperazine or Proklooriperatsiini or Proklorperazin or Prorazin or Phenothiazine or Seratil or Stemetil or Tementil or Temetid).mp.
85. 58-40-2.rn.
86. (Ampazine or Berophen or Esparin or Liranol or Neo-Hibernex or Prazin or Sparine or Sinophenin or Promazine hydrochloride or Protactyl or Promatsiini or Promazin or Promazine or Promazinum or Propazinum or Prazine or Promwill or Protactyl or Romtiazin or Sinophenin or Talofen or Talofen or Tomil or Verophen).mp.
87. 84225-95-6.rn.
88. (raclopride or racloprida or raclopridum or rakloprid or raklopridl).mp.
89. 749-02-0.rn.
90. (E 525 or Espiperona or Spiperone or Spiperonum or Spiroperidol or Spiropitan).mp.
91. 50-52-2.rn.

Table A5. IPA–Ovid Version (continued)

92. (Aldazine or Dazithin or Detril or Elperil or Mallorol or Malloryl or Melleril or Meleril or Mellaril or Mellerets or Mellerette or Melleretten or Melleril or Sonapax or Thioridazin or Thioridazine or Thioridazinum or Tioridatsiini or Tioridazin or Tioridazina or Tioridazinas).mp.
93. 5591-45-7.rn.
94. (Navane or Navaron or Orbinamon or Thiothixene or Tiotikseeni or Tiotixen or Tiotixeno or Tiotixenum or Thixit or Tiotixene).mp.
95. Thioxanthenes.mp.
96. 51012-32-9.rn.
97. (Betaprid or Delpral or Doparid or Etiles or Equilium or Italiprid or Luxoben or Normagit or Porfanil or Sereprid or Tiacob or Tiapridal or Tiapride).mp.
98. 749-13-3.rn.
99. (Flumoperone or Psicoperidol or Psychoperidol or Trifluperidol or Trifluperidoli or Trifluperidolum or Triperidol or Trisedil or Trisedyl).mp.
100. 117-89-5.rn.
101. (Cuait D or Cuait N or eskazine or flupazine or Jatrosom or Jalonac or Parstelin or Parmodalin or stelazine or Stelabid or Stelapar or Sycot or Terfluzine or Trifluoperazine or Trifluoperazini Hydrochloridum or triftazin or Trinicalm Forte or Trinicalm Plus).mp.
102. 146-54-3.rn.
103. (Adazine or Fluopromazine or Phenothiazine or Psyquil or Siquil or Triflupromazina or Triflupromazine or Trifluopromazine or Vesprin or Vetame).mp.
104. 53772-83-1.rn.
105. (Cisordinol or Clopixol or Ciatyl-Z or Clopenthixol or Clopentixol or Sedanxol or Zuclopenthixolum or Zuclopentixol or Zuclopenthixol or Zuklopentixol).mp.
106. or/42-105
107. atypical antipsychotic*.mp.
108. ((second or 2nd) adj generation adj antipsychotic*).tw.
109. ((third or 3rd) adj generation adj antipsychotic*).tw.
110. 71675-85-9.rn.
111. (Aminosultopride or Amisulprida or Amisulpride or Amisulpridum or Solian or Sulpitac).mp.
112. 129722-12-9.rn.
113. (Abilitat or Abilify or Aripiprazole or Discmelt or OPC 31 or OPC 14597).mp.
114. 65576-45-6.rn.
115. (Asenapine or EINECS 265-829-4).mp.
116. 132810-10-7.rn.
117. (Blonserin or AD 5423).mp.
118. 2058-52-8.rn.
119. (Clothiapine or Clotiapina or Clotiapine or Clotiapinum or Dibenzothiazepine or Etumina or Etumine or Entumin or Etomine or Entumine or HF 2159 or LW 2159 or "BRN 0568276").mp.
120. 5786-21-0.rn.
121. (Clozapin or Clozapina or Clozapine or Clozapinum or Clorazil or Clozaril or FazaClo or Leponex or LX 100-129 or Zaponex).mp.
122. 12688-68-5.rn.
123. Diazepine.mp.
124. Dibenzazepines.mp.
125. Dibenzothiazepines.mp.
126. (54739-18-3 or 61718-82-9).rn.
127. (dumirox or DU23000 or Fluvoxamina or fluvoxamine or Fluvoaminum or Fluvoxamine Maleate or Fevarin or Luvox or SME 3110).mp.
128. 133454-47-4.rn.
129. (Fanapt or Iloperidone or HP 873 or Zomaril).mp.
130. Isoxazoles.mp.
131. 5588-33-0.rn.
132. (Calodal or Lidanar or Lidanil or Mesoridazina or Mesoridazine or Mesoridazinum or Serentil or THD-2-SO).mp.
133. 89419-40-9.rn.
134. (Clospipramine or Cremin or Mosapramina or Mosapramine).mp.
135. 132539-06-1.rn.
136. (Zyprexa or Olantsapiini or Olanzapin or Olanzapina or Olanzapine or Olanzapinum or Olansek or Zalasta or Zypadhera).mp.
137. 144598-75-4.rn.
138. (9-Hydroxyrisperidone or Invega or Paliperidone or R 76477 or RO76477).mp.
139. 150915-41-6.rn.
140. (lullan or perospirone*).mp.
141. Piperidines.mp.

Table A5. IPA–Ovid Version (continued)

142. Pirenzepine.mp.
143. Pyrimidinones.mp.
144. 111974-69-7.rn.
145. (Co-Quetiapine or HSDB 7557 or Quetiapine or Seroquel).mp.
146. Quinolones.mp.
147. 80125-14-0.rn.
148. (FLA 731 or Remoxiprida or Remoxipride or Remoxipridum).mp.
149. 106266-06-2.rn.
150. (Apexidone or Psychodal or Risperdal or Risperidona or Risperidone or Risperidonum or Risperin or Risperilept or Rispolin or Spiron).mp.
151. 106516-24-9.rn.
152. (Lu 23-174 or Sertindol or Sertindole or Serdolect or Sertindolum).mp.
153. 15676-16-1.rn.
154. (Abilit or Aiglonyl or Alimoral or Calmoflorine or Championyl or Darleton or Desmenat or Dobren or Dogmatil or Dogmatyl or Dolmatil or Eclorion or Eglonil or Eglonyl or Enimon or Equilid or Eusulpid or Fardalan or Fidelan or Guastil or Isnamide or Kylistro or Lisopiride or Mariastel or Meresa or Miradol or Mirbanil or Neogama or Normum or Nufarol or Omiryl or Omperan or Ozoderpin or Psicocen or Pyrkappl or Sernevin or Splotin or Stamonevrol or Sulparex or Sulpirid or Sulpirida or Sulpiride or Sulpiridum or Sulpor or Suprium or Sulpyrid or Trilan or Valirem or Zemorcon).mp.
155. thiazoles.mp.
156. 26615-21-4.rn.
157. (Lodepin or Nipolept or Zotepina or Zotepine or Zotepinum or Zoleptil).mp.
158. 146939-27-7.rn.
159. (ziprasidone or zeldox).tw.
160. or/107
161. or/106,160
162. infant.mp.
163. ($child$ or adolescen$ or p*ediatric$).mp.
164. or/162-163
165. and/41,161,164
166. limit 165 to yr="1987 -Current"
167. (young adj adult*).mp.
168. ((college or university) adj2 (age or student*)).tw.
169. or/167-168
170. and/41,161,169
171. limit 170 to yr="1987 -Current"
172. randomi$ed.ab. or randomly.tw. or random$.tw.
173. (placebo or groups or trials).ab.
174. $controlled clinical trial$.tw.
175. or/172-174
176. (cohort$ or longitudinal or retrospective or prospective or followup or case-control).tw.
177. 175 or 176
178. 165 and 177
179. limit 178 to (english language and yr="1987 -Current")
180. 169 and 177
181. limit 180 to (english language and yr="1987 -Current")
182. 179 or 181

Table A6. CINAHL–EBSCO Version

EBSCOHost_-CINAHL Plus with FullText	Searched: 23Feb10
1987 to April Week 3 2010	Results: 233

S83=S69 or S82
S82=S64 AND S78 AND S66 Limiters - Age Groups: Infant, Newborn 0-1 month, Infant, 1-23 months, Child, Preschool 2-5 years, Child, 6-12 years, Adolescence, 13-18 years
S81=S64 AND S78 AND S66 Limiters - English Language; Language: English
S80=S64 AND S78 AND S66 Limiters - Publication Year from: 1987-2010
S79=S64 AND S78 AND S66
S78=S77 AND (S35 OR S48)
S77=S70 or S71 or S72 or S73 or S74 or S75 or S76
S76=TX Tourette syndrome
S75=(MH "Tourette Syndrome")
S74=TX anorexia
S73=(MH "Anorexia Nervosa") or (MH "Anorexia")
S72=TX ptsd
S71=Post-traumatic stress and (disorder OR disease OR syndrome)
S70=(MH "Stress Disorders, Post-Traumatic+")
S69= S64 and S65 and S66 Limiters - Language: English; Age Groups: Infant, Newborn 0-1 month, Infant, 1-23 months, Child, Preschool 2-5 years, Child, 6-12 years, Adolescence, 13-18 years
S68=S64 and S65 and S66 Limiters - Publication Year from: 1987-2010; English Language
S67=S64 and S65 and S66
S66=S53 OR S58
S65=S19 ANd (S35 or S48)
S64=S59 or S60 or S61 or S62 or S63
S63=TX ($child$ OR adolescen$ OR p*ediatric$)
S62=(MH "Pediatrics+")
S61=(MH "Adolescence+")
S60=(MH "Child+")
S59=(MH "Infant+")
S58=S54 or S55 or S56 or S57
S57=TX (cohort$ OR longitudinal OR retrospective OR prospective OR followup OR case-control)
S56=(MH "Case Control Studies+")
S55=TX retrospective stud*
S54=(MH "Prospective Studies+")
S53=S49 or S50 or S51 or S52
S52=("Placebo") or (MH "Placebos")
S51=TX randomi$ed
S50=(MH "Cochrane Library")
S49=(MH "Clinical Trials+")
S48=S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47
S47=(MH "Antiinfective Agents, Quinolone")
S46=(MH "Thiazoles+")
S45=Pirenzepine
S44=(MH "Piperidines+")
S43=paliperidone
S42=(MH "Aripiprazole")
S41=ziprasidone
S40=(MH "Quetiapine")
S39=(MH "Olanzapine")
S38=(MH "Risperidone")
S37=(MH "Clozapine")
S36=atypical antipsychotics
S35=S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34
S34=(MH "Indoles")
S33=(MH "Antipsychotic Agents, Butyrophenone+")
S32=(MH "Antipsychotic Agents, Phenothiazine+")
S31=methotrimeprazine
S30=(MH "Thioridazine")
S29=(MH "Trifluoperazine Hydrochloride")
S28=Thiothixene
S27=perphenazine
S26=molindone
S25=loxapine

Table A6. CINAHL–EBSCO Version (continued)

S24=(MH "Haloperidol")
S23=(MH "Fluphenazine")
S22=(MH "Chlorpromazine")
S21=(MH "Tranquilizing Agents+")
S20=(MH "Antipsychotic Agents+")
S19=S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18
S18="depressive disorder"
S17=(MH "Obsessive-Compulsive Disorder+")
S16=TX (refractory OR chronic OR resistant) and depression
S15=(MH "Depression")
S14=(MH "Bipolar Disorder+")
S13=TX schizotypal personality disorder
S12="Oppositional defiant disorder"
S11=TX atypical autism
S10=(MH "Mental Disorders Diagnosed in Childhood+")
S9=(MH "Child Behavior Disorders+")
S8=(MH "Attention Deficit Hyperactivity Disorder")
S7=(MH "Movement Disorders+")
S6=(MH "Mental Retardation+")
S5=(MH "Schizophrenia, Childhood")
S4=(MH "Rett Syndrome")
S3=(MH "Autistic Disorder")
S2=(MH "Asperger Syndrome")
S1=(MH "Child Development Disorders, Pervasive+"

Table A7. SCOPUS–Elsevier

SCOPUS - Elsevier	Searched: 19Apr10
1987 to April Week 3 2010	Results: 858

(((TITLE-ABS-KEY((infant) OR (*child*) OR (adolescen*) OR (p?ediatric) OR (young W/1 adult*) OR (college) OR (university))) AND ((TITLE-ABS-KEY((asperger sydrome) OR (autism OR autistic) OR (rett syndrome) OR (schizophrenia) OR (aggression) OR (sleep W/3 disorder) OR (insomnia) OR (agitation) OR (borderline personality disorder) OR (mood disorder) OR (mood lability) OR (self-injurious OR self-mutilating OR self-harm) OR (conduct disorder) OR (adhd) OR (attention deficit) OR (bipolar) OR (ocd) OR (obsessive-compulsive) OR (depression) OR (depressive disorder) OR (ptsd) OR (post-traumatic) OR (anorexia nervosa) OR (anorexia) OR (tic disorder) OR (tourette syndrome))) AND ((TITLE-ABS-KEY((typical W/2 antipsychotic*) OR (tranquiliz*) OR (neuroleptic) OR (first W/2 antipsychotic*) OR (azaperone) OR (butyrophenones) OR (clopenthixol) OR (chlorpromazine) OR (chlorprothixene) OR (dibenzoxazepines) OR (droperidol) OR (flupenthixol) OR (fluphenazine) OR (haloperidol) OR (indoles) OR (lithium) OR (loxapine) OR (methiothepin) OR (methotrimeprazine) OR (molindone) OR (penfluridol) OR (perazine) OR (perphenazine) OR (pimozide) OR (prochlorperazine) OR (promazine) OR (raclopride) OR (spiperone) OR (thioridazine) OR (thiothixene) OR (thioxanthenes) OR (tiapride) OR (trifluperidol) OR (trifluoperazine) OR (triflupromazine) OR (zuclopenthixol))) OR (TITLE-ABS-KEY((atypical W/2 antipsychotic*) OR (second W/2 antipsychotic*) OR (third W/2 antipsychotic*) OR (amisulpride) OR (aripiprazole) OR (asenapine) OR (blonanserin) OR (clotiapine) OR (clozapine) OR (diazepine) OR (dibenzazepines) OR (dibenzothiazepines) OR (fluvoxamine) OR (iloperidone) OR (isoxazoles) OR (mesoridazine) OR (mosapramine) OR (olanzapine) OR (paliperidone) OR (perospirone) OR (piperidines) OR (piperazines) OR (pirenzepine) OR (pyrimidinones) OR (quetiapine) OR (quinolones) OR (remoxipride) OR (risperidone) OR (sertindole) OR (sulpiride) OR (thiazoles) OR (zotepine) OR (ziprasidone))))) AND ((((SRCTYPE((randomized controlled trial) OR (randomised controlled trial) OR (controlled clinical trial)) OR TITLE((randomi?ed) OR (placebo) OR (drug therapy) OR (randomly) OR (trial) OR (groups)))) OR ((SRCTYPE((cohort stud*) OR (followup stud*) OR (longitudinal stud*) OR (prospective stud*) OR (retrospective stud*) OR (case-control stud*)) OR TITLE((cohort*) OR (longitudinal) OR (retrospective) OR (prospective) OR (followup) OR (case-control)) OR ABS((cohort*) OR (longitudinal) OR (retrospective) OR (prospective) OR (followup) OR (case-control))))))) AND (PUBYEAR AFT 1986 AND LANGUAGE(english))) AND NOT (((((TITLE-ABS-KEY((asperger sydrome) OR (autism) OR (rett syndrome) OR (schizophrenia) OR (mental retardation) OR (conduct disorder) OR (adhd) OR (attention deficit disorder) OR (bipolar) OR (ocd) OR (obsessive-compulsive) OR (depression) OR (ptsd) OR (post-traumatic) OR (anorexia nervosa) OR (anorexia) OR (tourette syndrome))) AND ((TITLE-ABS-KEY((antipsychotic*) OR (tranquiliz*) OR (chloropromazine) OR (fluphenazine) OR (haloperidol) OR (loxapine) OR (molindone) OR (perphenazine) OR (thiothixene) OR (trifluoperazine) OR (thioridazine) OR (methotrimeprazine) OR (phenothiazine) OR (butyrophenones) OR (thioxanthenes) OR (dibenzoxazepines) OR (indoles))) OR (TITLE-ABS-KEY((atypical antipsychotic*) OR (clozapine) OR (risperidone) OR (olanzapine) OR (quetiapine) OR (ziprasidone) OR (aripiprazole) OR (paliperidone) OR (isoxazoles) OR (dibenzothiazepines) OR (piperazines) OR (thiazoles) OR (quinolones))))) AND (SRCTYPE((randomized controlled trial) OR (randomised controlled trial) OR (controlled clinical trial)) OR TITLE((randomi?ed) OR (placebo) OR (drug therapy) OR (randomly) OR (trial) OR (groups)))) OR (((TITLE-ABS-KEY((asperger sydrome) OR (autism) OR (rett syndrome) OR (schizophrenia) OR (mental retardation) OR (conduct disorder) OR (adhd) OR (attention deficit disorder) OR (bipolar) OR (ocd) OR (obsessive-compulsive) OR (depression) OR (ptsd) OR (post-traumatic) OR (anorexia nervosa) OR (anorexia) OR (tourette syndrome))) AND ((TITLE-ABS-KEY((antipsychotic*) OR (tranquiliz*) OR (chloropromazine) OR (fluphenazine) OR (haloperidol) OR (loxapine) OR (molindone) OR (perphenazine) OR (thiothixene) OR (trifluoperazine) OR (thioridazine) OR (methotrimeprazine) OR (phenothiazine) OR (butyrophenones) OR (thioxanthenes) OR (dibenzoxazepines) OR (indoles))) OR (TITLE-ABS-KEY((atypical antipsychotic*) OR (clozapine) OR (risperidone) OR (olanzapine) OR (quetiapine) OR (ziprasidone) OR (aripiprazole) OR (paliperidone) OR (isoxazoles) OR (dibenzothiazepines) OR (piperazines) OR (thiazoles) OR (quinolones))))) AND (SRCTYPE((cohort stud*) OR (followup stud*) OR (longitudinal stud*) OR (prospective stud*) OR (retrospective stud*) OR (case-control stud*)) OR TITLE((cohort*) OR (longitudinal) OR (retrospective) OR (prospective) OR (followup) OR (case-control)) OR ABS((cohort*) OR (longitudinal) OR (retrospective) OR (prospective) OR (followup) OR (case-control))))) AND (TITLE-ABS-KEY((infant) OR (*child*) OR (adolescen*) OR (p?ediatric)))) AND (LIMIT-TO(DOCTYPE, "ar") OR LIMIT-TO(DOCTYPE, "cp") OR LIMIT-TO(DOCTYPE, "ip") OR LIMIT-TO(DOCTYPE, "ar")) AND (LIMIT-TO(EXACTKEYWORD, "Human") AND LIMIT-TO(DOCTYPE, "ar") OR LIMIT-TO(DOCTYPE, "cp") OR LIMIT-TO(DOCTYPE, "ip")) AND (LIMIT-TO(LANGUAGE, "English") AND LIMIT-TO(DOCTYPE, "ar") OR LIMIT-TO(DOCTYPE, "cp") OR LIMIT-TO(DOCTYPE, "ip")) AND (LIMIT-TO(PUBYEAR, 2010) OR LIMIT-TO(PUBYEAR, 2009) OR LIMIT-TO(PUBYEAR, 2008) OR LIMIT-TO(PUBYEAR, 2007) OR LIMIT-TO(PUBYEAR, 2006) OR LIMIT-TO(PUBYEAR, 2005) OR LIMIT-TO(PUBYEAR, 2004) OR LIMIT-TO(PUBYEAR, 2003) OR LIMIT-TO(PUBYEAR, 2002) OR LIMIT-TO(PUBYEAR, 2001) OR LIMIT-TO(PUBYEAR, 2000) OR LIMIT-TO(PUBYEAR, 1999) OR LIMIT-TO(PUBYEAR, 1998) OR LIMIT-TO(PUBYEAR, 1997) OR LIMIT-TO(PUBYEAR, 1996) OR LIMIT-TO(PUBYEAR, 1995) OR LIMIT-TO(PUBYEAR, 1994) OR LIMIT-TO(PUBYEAR, 1993) OR LIMIT-TO(PUBYEAR, 1992) OR LIMIT-TO(PUBYEAR, 1991) OR LIMIT-TO(PUBYEAR, 1990) OR LIMIT-TO(PUBYEAR, 1989) OR LIMIT-TO(PUBYEAR, 1988) OR LIMIT-TO(PUBYEAR, 1987) AND LIMIT-TO(DOCTYPE, "ar") OR LIMIT-TO(DOCTYPE, "cp") OR LIMIT-TO(DOCTYPE, "ip")) AND (LIMIT-TO(EXACTKEYWORD, "Human") OR LIMIT-TO(EXACTKEYWORD, "Adolescent") OR LIMIT-TO(EXACTKEYWORD, "Child") OR LIMIT-TO(EXACTKEYWORD, "School child") OR LIMIT-TO(EXACTKEYWORD, "Child, Preschool") AND LIMIT-TO(DOCTYPE, "ar") OR LIMIT-TO(DOCTYPE, "cp") OR LIMIT-TO(DOCTYPE, "ip")) AND (LIMIT-TO(LANGUAGE, "English") AND LIMIT-TO(DOCTYPE, "ar") OR LIMIT-TO(DOCTYPE, "cp") OR LIMIT-TO(DOCTYPE, "ip")) AND (LIMIT-TO(SUBJAREA, "MEDI") OR LIMIT-TO(SUBJAREA, "NEUR") OR LIMIT-TO(SUBJAREA, "PSYC") OR

Table A7. SCOPUS–Elsevier (continued)

LIMIT-TO(SUBJAREA, "PHAR") OR LIMIT-TO(SUBJAREA, "MULT") AND LIMIT-TO(DOCTYPE, "ar") OR LIMIT-TO(DOCTYPE, "cp") OR LIMIT-TO(DOCTYPE, "ip")) AND (EXCLUDE(SUBJAREA, "AGRI") OR EXCLUDE(SUBJAREA, "ENVI") OR EXCLUDE(SUBJAREA, "CHEM") OR EXCLUDE(SUBJAREA, "DENT") OR EXCLUDE(SUBJAREA, "VETE") OR EXCLUDE(SUBJAREA, "MATH") OR EXCLUDE(SUBJAREA, "ENGI") OR EXCLUDE(SUBJAREA, "ECON") AND LIMIT-TO(DOCTYPE, "ar") OR LIMIT-TO(DOCTYPE, "cp") OR LIMIT-TO(DOCTYPE, "ip")) AND (LIMIT-TO(EXACTKEYWORD, "Human") AND LIMIT-TO(DOCTYPE, "ar")) AND (LIMIT-TO(EXACTKEYWORD, "Human") OR LIMIT-TO(EXACTKEYWORD, "Human")) AND (LIMIT-TO(LANGUAGE, "English") AND LIMIT-TO(EXACTKEYWORD, "Human")) AND (LIMIT-TO(EXACTKEYWORD, "Human") AND LIMIT-TO(PUBYEAR, 2010) OR LIMIT-TO(PUBYEAR, 2009) OR LIMIT-TO(PUBYEAR, 2008) OR LIMIT-TO(PUBYEAR, 2007) OR LIMIT-TO(PUBYEAR, 2006) OR LIMIT-TO(PUBYEAR, 2005) OR LIMIT-TO(PUBYEAR, 2004) OR LIMIT-TO(PUBYEAR, 2003) OR LIMIT-TO(PUBYEAR, 2002) OR LIMIT-TO(PUBYEAR, 2001) OR LIMIT-TO(PUBYEAR, 2000) OR LIMIT-TO(PUBYEAR, 1999) OR LIMIT-TO(PUBYEAR, 1998) OR LIMIT-TO(PUBYEAR, 1997) OR LIMIT-TO(PUBYEAR, 1996) OR LIMIT-TO(PUBYEAR, 1995) OR LIMIT-TO(PUBYEAR, 1994) OR LIMIT-TO(PUBYEAR, 1993) OR LIMIT-TO(PUBYEAR, 1992) OR LIMIT-TO(PUBYEAR, 1991) OR LIMIT-TO(PUBYEAR, 1990) OR LIMIT-TO(PUBYEAR, 1989) OR LIMIT-TO(PUBYEAR, 1988) OR LIMIT-TO(PUBYEAR, 1987)) AND (LIMIT-TO(EXACTKEYWORD, "Human") OR LIMIT-TO(EXACTKEYWORD, "Human") OR LIMIT-TO(EXACTKEYWORD, "Adolescent") OR LIMIT-TO(EXACTKEYWORD, "Child") OR LIMIT-TO(EXACTKEYWORD, "School child") OR LIMIT-TO(EXACTKEYWORD, "Child, Preschool")) AND (LIMIT-TO(LANGUAGE, "English") AND LIMIT-TO(EXACTKEYWORD, "Human")) AND (LIMIT-TO(SUBJAREA, "MEDI") OR LIMIT-TO(SUBJAREA, "NEUR") OR LIMIT-TO(SUBJAREA, "PSYC") OR LIMIT-TO(SUBJAREA, "PHAR") OR LIMIT-TO(SUBJAREA, "MULT") AND LIMIT-TO(EXACTKEYWORD, "Human")) AND (EXCLUDE(SUBJAREA, "AGRI") OR EXCLUDE(SUBJAREA, "ENVI") OR EXCLUDE(SUBJAREA, "CHEM") OR EXCLUDE(SUBJAREA, "DENT") OR EXCLUDE(SUBJAREA, "VETE") OR EXCLUDE(SUBJAREA, "MATH") OR EXCLUDE(SUBJAREA, "ENGI") OR EXCLUDE(SUBJAREA, "ECON") AND LIMIT-TO(EXACTKEYWORD, "Human")) AND (LIMIT-TO(LANGUAGE, "English") AND LIMIT-TO(DOCTYPE, "ar")) AND (LIMIT-TO(LANGUAGE, "English") AND LIMIT-TO(EXACTKEYWORD, "Human")) AND (LIMIT-TO(LANGUAGE, "English") OR LIMIT-TO(LANGUAGE, "English")) AND (LIMIT-TO(LANGUAGE, "English") AND LIMIT-TO(PUBYEAR, 2010) OR LIMIT-TO(PUBYEAR, 2009) OR LIMIT-TO(PUBYEAR, 2008) OR LIMIT-TO(PUBYEAR, 2007) OR LIMIT-TO(PUBYEAR, 2006) OR LIMIT-TO(PUBYEAR, 2005) OR LIMIT-TO(PUBYEAR, 2004) OR LIMIT-TO(PUBYEAR, 2003) OR LIMIT-TO(PUBYEAR, 2002) OR LIMIT-TO(PUBYEAR, 2001) OR LIMIT-TO(PUBYEAR, 2000) OR LIMIT-TO(PUBYEAR, 1999) OR LIMIT-TO(PUBYEAR, 1998) OR LIMIT-TO(PUBYEAR, 1997) OR LIMIT-TO(PUBYEAR, 1996) OR LIMIT-TO(PUBYEAR, 1995) OR LIMIT-TO(PUBYEAR, 1994) OR LIMIT-TO(PUBYEAR, 1993) OR LIMIT-TO(PUBYEAR, 1992) OR LIMIT-TO(PUBYEAR, 1991) OR LIMIT-TO(PUBYEAR, 1990) OR LIMIT-TO(PUBYEAR, 1989) OR LIMIT-TO(PUBYEAR, 1988) OR LIMIT-TO(PUBYEAR, 1987)) AND (LIMIT-TO(LANGUAGE, "English") AND LIMIT-TO(EXACTKEYWORD, "Human") OR LIMIT-TO(EXACTKEYWORD, "Adolescent") OR LIMIT-TO(EXACTKEYWORD, "Child") OR LIMIT-TO(EXACTKEYWORD, "School child") OR LIMIT-TO(EXACTKEYWORD, "Child, Preschool")) AND (LIMIT-TO(LANGUAGE, "English") OR LIMIT-TO(LANGUAGE, "English")) AND (LIMIT-TO(LANGUAGE, "English") AND LIMIT-TO(SUBJAREA, "MEDI") OR LIMIT-TO(SUBJAREA, "NEUR") OR LIMIT-TO(SUBJAREA, "PSYC") OR LIMIT-TO(SUBJAREA, "PHAR") OR LIMIT-TO(SUBJAREA, "MULT")) AND (LIMIT-TO(LANGUAGE, "English") AND EXCLUDE(SUBJAREA, "AGRI") OR EXCLUDE(SUBJAREA, "ENVI") OR EXCLUDE(SUBJAREA, "CHEM") OR EXCLUDE(SUBJAREA, "DENT") OR EXCLUDE(SUBJAREA, "VETE") OR EXCLUDE(SUBJAREA, "MATH") OR EXCLUDE(SUBJAREA, "ENGI") OR EXCLUDE(SUBJAREA, "ECON")) AND (EXCLUDE(SUBJAREA, "ENGI") OR EXCLUDE(SUBJAREA, "VETE") AND LIMIT-TO(DOCTYPE, "ar")) AND (EXCLUDE(SUBJAREA, "ENGI") OR EXCLUDE(SUBJAREA, "VETE") AND LIMIT-TO(EXACTKEYWORD, "Human")) AND (LIMIT-TO(LANGUAGE, "English") AND EXCLUDE(SUBJAREA, "ENGI") OR EXCLUDE(SUBJAREA, "VETE")) AND (EXCLUDE(SUBJAREA, "ENGI") OR EXCLUDE(SUBJAREA, "VETE") AND LIMIT-TO(PUBYEAR, 2010) OR LIMIT-TO(PUBYEAR, 2009) OR LIMIT-TO(PUBYEAR, 2008) OR LIMIT-TO(PUBYEAR, 2007) OR LIMIT-TO(PUBYEAR, 2006) OR LIMIT-TO(PUBYEAR, 2005) OR LIMIT-TO(PUBYEAR, 2004) OR LIMIT-TO(PUBYEAR, 2003) OR LIMIT-TO(PUBYEAR, 2002) OR LIMIT-TO(PUBYEAR, 2001) OR LIMIT-TO(PUBYEAR, 2000) OR LIMIT-TO(PUBYEAR, 1999) OR LIMIT-TO(PUBYEAR, 1998) OR LIMIT-TO(PUBYEAR, 1997) OR LIMIT-TO(PUBYEAR, 1996) OR LIMIT-TO(PUBYEAR, 1995) OR LIMIT-TO(PUBYEAR, 1994) OR LIMIT-TO(PUBYEAR, 1993) OR LIMIT-TO(PUBYEAR, 1992) OR LIMIT-TO(PUBYEAR, 1991) OR LIMIT-TO(PUBYEAR, 1990) OR LIMIT-TO(PUBYEAR, 1989) OR LIMIT-TO(PUBYEAR, 1988) OR LIMIT-TO(PUBYEAR, 1987)) AND (EXCLUDE(SUBJAREA, "ENGI") OR EXCLUDE(SUBJAREA, "VETE") AND LIMIT-TO(EXACTKEYWORD, "Human") OR LIMIT-TO(EXACTKEYWORD, "Adolescent") OR LIMIT-TO(EXACTKEYWORD, "Child") OR LIMIT-TO(EXACTKEYWORD, "School child") OR LIMIT-TO(EXACTKEYWORD, "Child, Preschool")) AND (LIMIT-TO(LANGUAGE, "English") AND EXCLUDE(SUBJAREA, "ENGI") OR EXCLUDE(SUBJAREA, "VETE")) AND (EXCLUDE(SUBJAREA, "ENGI") OR EXCLUDE(SUBJAREA, "VETE") OR LIMIT-TO(SUBJAREA, "MEDI") OR LIMIT-TO(SUBJAREA, "NEUR") OR LIMIT-TO(SUBJAREA, "PSYC") OR LIMIT-TO(SUBJAREA, "PHAR") OR LIMIT-TO(SUBJAREA, "MULT")) AND (EXCLUDE(SUBJAREA, "ENGI") OR EXCLUDE(SUBJAREA, "VETE") OR EXCLUDE(SUBJAREA, "AGRI") OR EXCLUDE(SUBJAREA, "ENVI") OR EXCLUDE(SUBJAREA, "CHEM") OR EXCLUDE(SUBJAREA, "DENT") OR EXCLUDE(SUBJAREA, "VETE") OR EXCLUDE(SUBJAREA, "MATH") OR EXCLUDE(SUBJAREA, "ENGI") OR EXCLUDE(SUBJAREA, "ECON"))

Table A8. ProQuest Dissertations International

ProQuest Dissertations International 1987 to February Week 3 2010	Searched: 26Feb10 Results: 13
((asperger) OR (autistic disorder) OR autism OR schizophrenia OR (bipolar disorder) OR (depression) OR (bipolar disorder) OR (obsessive-compulsive) OR (post-traumatic) OR (anorexia nervosa) OR anorexia) AND (antipsychotics) AND (child OR adolescent OR pediatric OR infant) AND PDN(>1/1/1987) AND PDN(<12/31/2010)	

Table A9. TOXLINE (TOXNET)

TOXLINE (TOXNET) 1987 to February Week 3 2010	Searched: 26Feb10 Results: 12
([na] (antipsychotics OR antipsychotic agents) AND ((asperger OR asperger syndrome) OR (autism OR autistic disorder) OR bipolar OR obsessive-compulsive OR (adhd OR attention deficit disorder with hyperactivity) OR (anorexia) OR post-traumatic OR (schizophrenia)) AND ((children OR child) OR (infant) OR (adolescent) OR (child))) AND 1987:2010 [yr] AND (eng [la])	

Table A10. ClinicalTrials.gov and WHO

ClinicalTrials.gov 1987 to February Week 3 2010	Searched: 23Feb10 Results: 200
((asperger) OR (autistic disorder) OR autism OR schizophrenia OR (bipolar disorder) OR (depression) OR (bipolar disorder) OR (obsessive-compulsive) OR (post-traumatic) OR (anorexia nervosa) OR anorexia) AND (antipsychotics) AND (child OR adolescent OR pediatric OR infant) AND PDN(>1/1/1987) AND PDN(<12/31/2010)	

Appendix B. Forms

B1. Eligibility Criteria

B2. Methodological Quality Assessment
Randomized Controlled and Controlled Clinical Trials
Cohort Studies

B3. Data Extraction

B1. Eligibility Criteria

CRITERIA	Yes	No	Unclear
1. PUBLICATION TYPE			
a) Report of primary research	☐	☐	☐
2. STUDY DESIGN			
a) Comparative study design; one of: i. Randomized controlled trial ii. Nonrandomized controlled trial iii. Cohort (prospective or retrospective)	☐	☐	☐
3. POPULATION			
a) Children, adolescents, or young adults (≤24 years); include if ≥80% enrolled patients ≤24 years or there is a subgroup analysis for ≤24	☐	☐	☐
b) Diagnosis of: • PDD (autistic, Rett, childhood disintegrative, Asperger's, PDD NOS) • DBD (ADHD, conduct, oppositional defiant, disruptive behavior NOS) • Bipolar disorder (manic/depressive phases, rapid cycling, mixed states) • Schizophrenia and schizophrenia-related psychoses (schizoaffective, drug-induced psychosis) • Tourette syndrome, OCD, PTSD, or anorexia nervosa OR behavior issues (aggression, agitation, behavioral dyscontrol, self-injurious, anxiety, or sleep disturbance behaviors)	☐	☐	☐
4. INTERVENTION			
a) Comparison of at least 2 of the following FDA-approved drugs, *OR* one drug vs. placebo, *OR* one drug with comparison of 2+ doses: • Second generation: aripiprazole, asenapine, clozapine, iloperidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone • First generation: chlorpromazine, droperidol, fluphenazine, haloperidol, loxapine, perphenazine, pimozide, prochlorperazine, thiothixene, thioridazine, trifluoperazine	☐	☐	☐
5. OUTCOME			
a) One of the following outcomes: • Symptom response (primary outcome) • Response rates, duration of response, remission, relapse, speed of response, 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/attendance • Work-related functional capacity • Patient insight into illness • Patient or parent/care provider reported outcomes, including levels of physical activity/inactivity, diet • Health-related quality of life • Legal/justice system interaction • Health-care system utilization • "outcomes that matter" to children, youth and families • AE (overall, specific, WAE, time to WAE, persistence, reversibility)	☐	☐	☐
Comments:			
REVIEWER'S DECISION : Include ☐ Exclude ☐ Unsure ☐			

ADHD = attention deficit and hyperactivitiy disorder; AE = adverse events; DBD = disruptive behavior disorder; FDA = Food and Drug Administration; NOS = not otherwise specified; OCD = obsessive-compulsive disorder; PDD = pervasive developmental disorder; PTSD = post-traumatic stress disorder; WAE = withdrawal due to adverse events

B2. Methodological Quality Assessment

Randomized Controlled Trials and Controlled Clinical Trials

The Cochrane Collaboration's Tool for Assessing Risk of Bias			
Domain	**Description**	**Review Authors' Judgment**	**Consensus (Circle)**
Sequence generation		Was the allocation sequence adequately generated? YES / NO / UNCLEAR	YES NO UNCLEAR
Allocation concealment		Was allocation adequately concealed? YES / NO / UNCLEAR	YES NO UNCLEAR
Blinding of participants, personnel and outcome assessors, *Outcome:*	Subjective measures	Was knowledge of the allocated intervention adequately prevented during the study? YES / NO / UNCLEAR	YES NO UNCLEAR
	Objective measures	YES / NO / UNCLEAR	
Incomplete outcome data, *Outcome:*	Subjective measures	Were incomplete outcome data adequately addressed? YES / NO / UNCLEAR	YES NO UNCLEAR
	Objective measures	YES / NO / UNCLEAR	
Selective outcome reporting		Are reports of the study free of suggestion of selective outcome reporting? YES / NO / UNCLEAR	YES NO UNCLEAR
Other sources of bias		Was the study apparently free of other problems that could put it at a high risk of bias? YES / NO / UNCLEAR	YES NO UNCLEAR
Overall risk of bias	Subjective measures	HIGH / LOW / UNCLEAR	HIGH LOW UNCLEAR
	Objective measures	HIGH / LOW / UNCLEAR	

Cohort Studies

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Selection

1) Representativeness of the cohort exposed to anti-psychotic drug
   a) truly representative of the diagnosis under study in a paediatric patient in the community ✵
   b) somewhat representative of the diagnosis under study in a paediatric patient in the community ✵
   c) selected group of users, for example all male patients, mental retardation comorbidity
   d) no description of the derivation of the cohort

2) Selection of the comparator cohorts
   a) drawn from the same community as the exposed cohort ✵
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (e.g., database, medical records) ✵
   b) structured interview ✵
   c) written self report
   d) no description

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for disease severity OR age ✵
   b) study controls for any additional factor ✵
   c) none

Outcome

1) Assessment of outcome
   a) independent blind assessment ✵
   b) record linkage ✵
   c) self report
   d) no description

2) Was followup long enough for outcomes to occur
   a) yes (time points to be specified for both short and long-term outcomes of interest) ✵
   b) no

3) Adequacy of followup of cohorts
   a) complete followup - all subjects accounted for ✵
   b) subjects lost to followup unlikely to introduce bias - small number lost - > 90% followup, or description provided of those lost) ✵
   c) followup rate < 75% and no description of those lost
   d) no statement

TOTAL: _____ ✵

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

B3. Data Extraction

I. Coder Information

Reference ID:	First Author:	Year:
DE initials:	DV initials:	Relevant to questions: ☐ KQ1; ☐ KQ2; ☐ KQ3; ☐ KQ4

II. Study Characteristics

Country:	Publication type:	Study design:
Trial type:	Number of centers:	Setting:
Study dates (e.g., Jan 1998 to Feb 2000):	Funding source: ☐ Industry ☐ No funding ☐ Government ☐ Other ☐ Academic ☐ ND ☐ Foundation	
Specify industry firms:	Specify "Other" funding:	

III. Study Phases

Did the study describe a run-in phase?	Run-in phase duration*:
Run-in phase protocol:	Blinding:
Washout period (crossover)*:	Treatment duration*:

IV. Clinical Population

Condition category:		Specify "multiple" categories:	
Primary diagnoses:			
PDD: ☐ Autism Spectrum ☐ Autistic ☐ Rett ☐ Childhood disintegrative ☐ Asperger's ☐ PDD NOS ☐ Specific diagnoses ND	*DBD:* ☐ ADHD ☐ Conduct disorder ☐ Oppositional defiant ☐ Disruptive behavior NOS ☐ Specific diagnoses ND	*Bipolar:* ☐ Manic or depressive phases ☐ Rapid cycling ☐ Mixed states ☐ Specific diagnoses ND	*Schizophrenia-related:* ☐ Schizophrenia spectrum ☐ Schizophrenia ☐ Schizoaffective disorder ☐ Substance-induce psychosis ☐ Specific diagnoses ND
Behavioral issues: ☐ Aggression ☐ Agitation ☐ Anxiety ☐ Behavioral dyscontrol ☐ Irritability ☐ Mood lability ☐ Self-injurious behavior ☐ Sleep disorder		*Other:* ☐ Anorexia nervosa ☐ Obsessive compulsive ☐ Post-traumatic stress disorder ☐ Tourette syndrome/tics	
Diagnostic criteria: ☐ DSM IV - TR ☐ DSM IV ☐ DSM III–TR ☐ ICD 10 ☐ ICD 9 ☐ Other ☐ ND		List other diagnostic criteria:	

Practitioner who made diagnosis:	Professionals providing care/monitoring:
Treatment history:	Psychotic episodes:
Inclusion criteria:	Exclusion criteria:

SECTION A: Notes/Comments

V. Intervention

	Group 1	Group 2	Group 3	Group 4
Generic drug name				
Co-intervention(s)				
Dosing variability				
Number of times per day				
Route of administration				
Initiation dose (mg/day)				
Target dose(s) (mg/day)				
Dose range (mg/day)				
Mean daily dose (mg/day)				
Rules for upward dose adjustment				
Rules for downward dose adjustment				
Permitted drugs (protocol)				
Prohibited drugs (protocol)				
Actual concurrent drugs (n)				
Actual concurrent non-pharmaceutical tx (n)				
Compliance measured	Specify "Other":			

VI. Baseline Characteristics

	Group 1	Group 2	Group 3	Group 4	TOTAL
Patients enrolled (n)					
Patients analyzed (n)					
Patients completed (n)					
Age–mean/SD					
Age–median					
Age–range					
Age–other					
Males (n)					
Males (%)					
Caucasian (%)					
Ethnicities (n)					

Parent SES (n)										
Treatment naïve (n)										
Inpatients (n)										
First episode psychosis (n)										
# past psychiatric admissions										
Tanner stage										
Age at onset										
Illness duration										
Weight (kg)										
Height (cm)										
BMI										
IQ										
Specify IQ measure										
PANSS										
CGI severity										
BPRS										
GAF										
YMRS										
Diagnosis breakdown (n)										
MR (n)										
Psychosis (n)										
Comorbid ADHD (n)										
Comorbid DBD (n)										
Comorbid substance abuse (n)										
Other comorbidities (n)										
Other:										
Other:										
Other:										
Other:										
Other:										
Other:										
Other:										

SECTION B: Notes/Comments

VII. Outcomes

a. SCALES (EFFICACY and SAFETY)

Scales	
☐ Aberrant behavior checklist	☐ Abnormal involuntary movements scale
☐ Behavior activity rating scale	☐ Brief psychiatric rating scale
☐ Calgary depression scale of schizophrenia	☐ Child mania rating scale
☐ Children's aggression scale	☐ Children's depression rating scale
☐ Children's global assessment scale	☐ Children's psychiatric rating scale
☐ Children's Yale-Brown obsessive compulsive scale	☐ Clinical global impression-Improvement
☐ Clinical global impressions–Severity	☐ Clinical global impressions–any other
☐ Global assessment of functioning	☐ Hamilton depression scale
☐ Montgomery-Asberg Depression rating scale	☐ Nisonger child behavior rating form
☐ Patient global impressions	☐ Positive and negative syndrome scale
☐ Ritvo-Freeman real life rating scale	☐ Scale assessment of negative symptoms
☐ Tourette symptom global scale	☐ Vineland adaptive behavior scales
☐ Yale global tic severity scale	☐ Young mania rating scale
Other Scales	

b. OTHER EFFICACY OUTCOMES

Other Short- and Long-term Outcomes		
☐ Response, remission, relapse , etc.	Specify:	
☐ Growth & maturation	Specify:	
☐ Cognitive & emotional development	Specify:	
☐ Suicide behaviors or death	Specify:	
☐ Medication adherence/persistence	Specify:	
☐ School performance/attendance	Specify:	
☐ Work-related functional capacity	Specify:	
☐ Patient insight into illness	Specify:	
☐ Patient/provider related outcomes, e.g. physical activity, diet, calories, etc.	Specify:	
☐ Health-related quality of life	Specify:	
☐ Legal/justice system interactions	Specify:	
☐ Health care system utilization	Specify:	
Other:		Other:
Other:		Other:
Other:		Other:

SAFETY

Major Adverse Events	
☐ Mortality (not suicide)	☐ Cerebrovascular disease-related events
☐ Development of diabetes mellitus	☐ Diabetic ketoacidosis
☐ Neuroleptic malignant syndrome	☐ Seizures
☐ Tardive dyskinesia	☐ Cardiomyopathies
☐ Cardiac arrhythmias	☐ Agranulocytosis
General Adverse Events	
☐ Extrapyramidal effects	☐ Weight gain
☐ Agitation	☐ Constipation
☐ Sedation	☐ Elevated cholesterol
☐ Elevated transaminases	☐ AE related to prolactin elevations
☐ Galactorrhea/bloody galactorrhea	☐ Exercise intolerance
☐ Precocious puberty	

Other Adverse Events (not listed above)		
☐ Abdominal pain/cramps	☐ Akathisia	☐ Allergic reaction
☐ Anxiety	☐ Appetite changes	☐ Blurred vision
☐ Breathing difficulty/asthma	☐ Chest pain	☐ Confusion
☐ Conjunctivitis	☐ Cough	☐ Depression
☐ Dizziness	☐ Dry skin	☐ Edema
☐ Enuresis	☐ Fatigue/tiredness	☐ Fever
☐ Headache	☐ Hostility	☐ Insomnia
☐ Itches	☐ Memory impairment	☐ Muscle rigidity
☐ Muscle pain	☐ Nasal congestion/pharyngitis	☐ Nausea
☐ Nervousness	☐ Otalgia (ear ache)	☐ Paresthesias
☐ Sialorrhea (excessive saliva)	☐ Somnolence	☐ Sweating
☐ Tremors	☐ Vomiting or dyspepsia	

VIII. Conclusions

Briefly summarize author conclusions:

REFERENCES TO BE CHECKED:

ASSOCIATED PUBLICATIONS:

ADHD = attention deficit hyperactivity disorder; AE = adverse event; BMI = body mass index; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; DBD = disruptive behavior disorder; DE = data extractor; DSM = Diagnositic and Statistical Manual of Mental Disorders; DV = data verifier; GAF = Global Assessment of Functioning; ICD = International Classification of Diseases; IQ = intelligence quotient; KQ = key question; MR = mental retardation; ND = not described; NOS = not otherwise specified; PANSS = Positive and Negative Syndrome Scale; PDD = pervasive developmental disorder; SD = standard deviation; SES = socioeconomic status; tx = treatment; YMRS = Young Mania Rating Scale

Appendix C. Methodological Quality of Studies Included in the Review

Table C1. Methodological quality of randomized controlled trials (RCTs) and nonrandomized controlled (NRCTs)

Author, Year Study Design	Sequence Generation	Allocation Concealment	Blinding (Subjective)	Blinding (Objective)	Incomplete Outcome (Subjective)	Incomplete Outcome (Objective)	Selective Outcome Reporting	Other Sources of Bias	Overall (Subjective)	Overall (Objective)
Aman et al., 2009 RCT	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	High	High
Aman et al., 2002 RCT	Yes	Unclear	Yes	Yes	No	No	Yes	No	High	High
Arango et al., 2009 RCT	Unclear	Unclear	Unclear	Yes	No	No	Yes	No	High	High
Armenteros et al., 2007 RCT	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	High	High
Berger et al., 2008 RCT	Yes	Yes	Yes	Yes	No	Unclear	Yes	No	High	High
Biederman et al., 2005 RCT	Unclear	Unclear	No	No	No	No	Unclear	No	High	High
Bierderman et al., 2004 RCT	Unclear	Unclear	No	No	Unclear	Unclear	Unclear	Unclear	High	High
Bruggeman et al., 2001 RCT	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	High	High
Buitelaar et al., 2001 RCT	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	High	High
Connor et al., 2008 RCT	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	No	High	High

Table C1. Methodological quality of randomized controlled trials (RCTs) and nonrandomized controlled (NRCTs) (continued)

Author, Year Study Design	Sequence Generation	Allocation Concealment	Blinding (Subjective)	Blinding (Objective)	Incomplete Outcome (Subjective)	Incomplete Outcome (Objective)	Selective Outcome Reporting	Other Sources of Bias	Overall (Subjective)	Overall (Objective)
Crocq et al., 2007 NRCT	No	No	NA	Yes	NA	Unclear	Yes	Unclear	NA	High
de Haan et al., 2003 RCT	Yes	Unclear	Unclear	NA	No	NA	Yes	Yes	High	NA
DelBello et al., 2009 RCT	Yes	Yes	Unclear	Yes	Unclear	Unclear	Yes	No	High	High
DelBello et al., 2008 RCT	Unclear	Unclear	No	Unclear	No	No	Yes	No	High	High
DelBello et al., 2002 RCT	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	No	High	High
Findling et al., 2009 RCT	Unclear	Unclear	Yes	Yes	No	No	Yes	No	High	High
Findling et al., 2008 RCT	Yes	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Yes	High	High
Findling et al., 2000 RCT	Yes	Yes	Yes	Yes	No	No	Yes	No	High	High
Gilbert et al., 2004 RCT	Yes	Yes	Yes	Yes	No	No	No	No	High	High
Haas et al., 2009 RCT	Unclear	Unclear	Unclear	Yes	No	No	Yes	No	High	High
Haas et al., 2009 RCT	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Yes	No	High	High
Haas et al., 2009 RCT	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	No	High	High

Table C1. Methodological quality of randomized controlled trials (RCTs) and nonrandomized controlled (NRCTs) (continued)

Author, Year Study Design	Sequence Generation	Allocation Concealment	Blinding (Subjective)	Blinding (Objective)	Incomplete Outcome (Subjective)	Incomplete Outcome (Objective)	Selective Outcome Reporting	Other Sources of Bias	Overall (Subjective)	Overall (Objective)
Hellings et al., 2006 RCT	Unclear	Yes	Unclear	Yes	No	No	Yes	No	High	High
Hollander et al., 2006 RCT	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	No	High	High
Jensen et al., 2008 RCT	Yes	Unclear	No	Unclear	Unclear	Unclear	Yes	No	High	High
Kryzhanovskaya et al., 2009 RCT	Unclear	Unclear	Unclear	Unclear	No	No	Yes	No	High	High
Kumra et al., 2008 RCT	Yes	Yes	Unclear	Yes	No	No	Yes	Yes	High	High
Kumra et al., 1996 RCT	Yes	Yes	Yes	Yes	No	No	Yes	Unclear	High	High
Luby et al., 2006 RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	High	High
Malone et al., 2001 RCT	Yes	Unclear	No	Yes	Yes	Yes	Yes	No	High	High
Marcus et al., 2009 RCT	Yes	Yes	Unclear	Unclear	No	No	Yes	No	High	High
McCracken et al., 2002 RCT	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear
Miral et al., 2008 RCT	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	No	High	High
Mozes et al., 2006 RCT	Unclear	Unclear	No	No	No	No	Yes	Unclear	High	High

Table C1. Methodological quality of randomized controlled trials (RCTs) and nonrandomized controlled (NRCTs) (continued)

Author, Year Study Design	Sequence Generation	Allocation Concealment	Blinding (Subjective)	Blinding (Objective)	Incomplete Outcome (Subjective)	Incomplete Outcome (Objective)	Selective Outcome Reporting	Other Sources of Bias	Overall (Subjective)	Overall (Objective)
Nagaraj et al., 2006 RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear
NCT00796081, 2007 RCT	Unclear	Unclear	No	No	Yes	Yes	No	No	High	High
NCT00090311, 2008 RCT	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	No	High	High
NCT00576732, 2010 RCT	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	High	High
NCT00090324, 2008 RCT	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	No	High	High
NCT00257166, 2008 RCT	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	High	High
NCT00257192, 2010 RCT	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	No	High	High
Perry et al., 1989 RCT	Unclear	Unclear	Yes	Yes	No	No	No	Unclear	High	High
Reyes et al., 2006 RCT	Unclear	Unclear	Yes	Yes	No	No	Yes	No	High	High
Robb et al., 2009 RCT	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	No	High	High
Sallee et al., 2000 RCT	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	No	High	High
Sallee et al., 1997 RCT	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	Unclear

Table C1. Methodological quality of randomized controlled trials (RCTs) and nonrandomized controlled (NRCTs) (continued)

Author, Year Study Design	Sequence Generation	Allocation Concealment	Blinding (Subjective)	Blinding (Objective)	Incomplete Outcome (Subjective)	Incomplete Outcome (Objective)	Selective Outcome Reporting	Other Sources of Bias	Overall (Subjective)	Overall (Objective)
Sallee et al., 1994 RCT	Unclear	Unclear	Unclear	Unclear	No	No	No	Yes	High	High
Scahill et al., 2003 RCT	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	High	High
Schulz et al., 1996 NRCT	No	No	NA	No	NA	Yes	Yes	Unclear	NA	High
Sehgal et al., 1999 RCT	Unclear	Yes	Yes	NA	Yes	NA	Yes	Yes	High	NA
Shaw et al., 2006 RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear
Shea et al., 2004 RCT	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	No	High	High
Sikich et al., 2008 RCT	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	Unclear
Sikich et al., 2004 RCT	Yes	Unclear	Unclear	Unclear	No	No	Yes	No	High	High
Spencer et al., 1994 RCT	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	Unclear
Swadi et al., 2010 RCT	Yes	Unclear	Unclear	Yes	No	No	Yes	No	High	High
Synder et al., 2002 RCT	Yes	Yes	Unclear	Yes	No	No	Yes	No	High	High
Tohen et al., 2007 RCT	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	No	High	High

Table C1. Methodological quality of randomized controlled trials (RCTs) and nonrandomized controlled (NRCTs) (continued)

Author, Year Study Design	Sequence Generation	Allocation Concealment	Blinding (Subjective)	Blinding (Objective)	Incomplete Outcome (Subjective)	Incomplete Outcome (Objective)	Selective Outcome Reporting	Other Sources of Bias	Overall (Subjective)	Overall (Objective)
Tramontina et al., 2009 RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	High	High
Troost et al., 2005 RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	High	High
Van Bellinghen et al., 2001 RCT	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	No	High	High
Van Bruggen et al., 2003 RCT	Unclear	Unclear	No	Yes	Yes	Yes	No	No	High	High
Woods et al., 2003 RCT	Yes	Yes	Unclear	Unclear	No	No	Unclear	No	High	High
Yen et al., 2004 RCT	Unclear	Unclear	Unclear	Unclear	No	No	Yes	Yes	High	High

NRCT = nonrandomized controlled trial; RCT = randomized controlled trial

Table C2. Methodological quality of cohort studies

Author, Year Study Design	Selection 1	Selection 2	Selection 3	Comparability	Outcome 1	Outcome 2	Outcome 3	Total Stars
Alacqua et al., 2008 RCS	B	A	A	C	B	A	A	6
Bastiaens et al., 2009 RCS	B	A	A	A and B	E	A	C	6
Correll et al., 2009 PCS	A	A	A	A and B	B	A	A	8
Findling et al., 2008 PCS	B	A	A	C	C	B	B	4
Fleischhaker et al., 2006 PCS	D	C	B	C	E	A	A	2
Fraguas et al., 2008 PCS	A	A	A	A and B	D	A	C	6
Friedlander et al., 2001 RCS	C	A	A	C	E	A	A	4
Gothelf et al., 2002 PCS	C	C	A	C	B	A	D	3
Hrdlicka et al., 2009 RCS	A	A	A	C	B	A	C	5
Jefferson et al., 1998 RCS	C	A	A	C	B	A	D	4
Khan et al., 2006 RCS	D	C	A	C	B	A	A	4
Kumra et al., 1998 PCS	B	A	B	C	E	A	A	5
Migliardi et al., 2009 RCS	B	A	A	B	B	A	A	7
Novaes et al., 2008 RCS	A	A	A	C	B	A	A	6
Ratzoni et al., 2002 PCS	D	C	B	C	E	A	A	3
Saito et al., 2004 PCS	B	A	A	B	D	A	A	6
Wudarsky et al., 1999 PCS	A	A	A	A	A	A	A	7

PCS = prospective cohort study; RCS = retrospective cohort study

Appendix D. Evidence Table

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Alacqua et al., 2008 Country: Italy Condition category: Multiple categories (DBD, PDD, schizophrenia-related, tics) Questions: KQ2 Funding: NR	Recruitment dates: Jan 2002 to Dec 2003 Study design: Retrospective cohort Diagnostic criteria: DSM-IV Setting: Outpatient/community	Enrolled: 73 Analyzed: 73 Completed: 50 GROUP 1 N: 2 Age, mean±SD (range): 15.5±0.7 Males %: 50 Caucasian %: NR Diagnostic breakdown (n): psychosis (1), schizophrenia (1)	Treatment duration: 3 mo Run-in phase: No Run-in phase duration: NR Permitted drugs: NR Prohibited drugs: NR GROUP 1 Drug name: Clozapine Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean±SD (range): 150±70.1	Symptomatology (KQ1): NR Other ST and LT outcomes (KQ3): NR AE (KQ2): Behavioral issues, dyskinesia, dystonia, dermatologic AE, liver function, hepatic volume, prolactin, prolactin-related AE, sedation,sleepness, total AE, weight change	Adverse events occurred frequently during first 3 months of treatment with atypical antipsychotics.

ABC = Aberrant Behavior Checklist; ABC-C = Aberrant Behavior Checklist-Community; ADI-R = Autism Diagnostic Interview-Revised; ADOS = Autism Diagnostic Observation Schedule; AE = Adverse Event; ASD = autism spectrum disorder; β-HCG = beta human chorionic gonadotropin; BMI = body mass index; BPRS = Brief Psychiatric Rating Scale; BPRS-A = Brief Psychiatric Rating Scale-Anchored; C-DISC 4 = Computerized Diagnostic Interview Schedule for Children, version four; CARS = Childhood Autism Rating Scale; CAS-P = Children's Aggression Scale-Parent; CAS-T = Children's Aggression Scale-Teacher; CBCL = Child Behavior Checklist; CD = conduct disorder; CDRS-R = Children's Depression Rating Scale, Revised; CGI-C = Clinical Global Impression-Change; CGI-I = Clinical Global Impressions-Improvement; CGI-S = Clinical Global Impressions-Severity; CNS = central nervous system; COPS = Criteria of Prodromal Syndromes; CPRS = Children's Psychiatric Rating Scale; day = day(s); CPT = Continuous performance task ; DBD = disruptive behavior disorder; DICA-R = Diagnostic Interview for Children and Adolescents-Revised; DSM = Diagnostic and Statistical Manual of Mental Disorders; ECG = electrocardiogram; FGA = first-generation antipsychotics; GAD = generalized anxiety disorder; HALFS = Health And Life Functioning Scale ; HIV = human immunodeficiency virus; hr = hour(s); IED = intermittent explosive disorder; IM = intramuscular; IQ = intelligence quotient; KID-SCID = childhood disorders form of the Structured Clinical Interview for DSM-IV Disorders; K-SADS = Kiddie-Schedule for Affective Disorders and Schizophrenia; K-SADS-E = Kiddie-Schedule for Affective Disorders and Schizophrenia (Epidemiological Version); K-SADS-P = Kiddie-Schedule for Affective Disorders and Schizophrenia (Present Episode Version); K-SADS-PL = Kiddie-Schedule for Affective Disorders and Schizophrenia (Present and Lifetime Version); KQ = key question; LT = long term; MAO-I = monoamine oxidase inhibitor; MDD = major depressive disorder; mo = month(s); MVLT = Modified Version of the California Verbal Learning Test; N = number; NCBRF = Nisonger Child Behavior Rating Form; NMS = neuroleptic malignant syndrome; NOS = not otherwise specified; NR = not reported; NRCT = non-randomized controlled trial; NSAID = non-steroidal anti-inflammatory drug; OAS = Overt Aggression Scale; ODD = oppositional defiant disorder; P-LES-Q = Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire; PANSS = Positive and Negative Syndrome Scale; PDD = pervasive developmental disorder; PTSD = post-traumatic stress disorder; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; RCT = randomized controlled trial; SA = substance abuse; SCID-I/P = Clinical Interview for DSM-IV-TR Axis I Disorders-Patient Edition; SGA = second-generation antipsychotic; SSRI = selective serotonin reuptake inhibitor; ST = short term; TBI = traumatic brain injury; TSGS = Tourette Syndrome Global Scale; TSSS = Tourette Symptom Severity Scale; VABS = Vineland Adaptive Behavior Scale; WASH-U-KSADS = Washington University in St. Louis Kiddie Schedule for Affective Disorders

and Schizophrenia; WISC = Wechsler Intelligence Scale for Children; YBOCS = Yale-Brown Obsessive Compulsive Scale; YGTSS = Yale Global Tic Severity Scale; YMRS = Young Mania Rating Scale; yr = year(s)

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Newcastle-Ottawa Scale: 6 stars	**Inclusion criteria:** (1) ≤18 yr, (2) received an incident treatment with atypical antipsychotics or SSRIs during the study period **Exclusion criteria:** NR	**Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 24 **Age, mean±SD (range):** 14.7±2.3 **Males %:** 42 **Caucasian %:** NR **Diagnostic breakdown (n):** affective disorder (2), anxiety disease (4), autism (1), CD (1), MR (3), personality disorder (2), psychosis (9), schizophrenia (2) **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 3** **N:** 2 **Age, mean±SD (range):** 16.5±1.5 **Males %:** 100 **Caucasian %:** NR **Diagnostic breakdown (n):** psychosis (2) **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR	**Concurrent treatments:** NR **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 7.1±4.4 **Concurrent treatments:** NR **GROUP 3** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 375±318.2 **Concurrent treatments:** NR **GROUP 4** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2±1.3 **Concurrent treatments:** NR	**Subpopulations (KQ4):** NR	

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Alacqua et al., 2008 (continued)		**GROUP 4** **N:** 45 **Age, mean±SD (range):** 13±3.9 **Males %:** 80 **Caucasian %:** NR **Diagnostic breakdown (n):** ADHD (1), anxiety disease (2), autism (14), CD (7), conversion disorder (2), MR (8), psychosis (7), schizophrenia (2), tic disorder (2) **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR			

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Aman et al., 2009 **Country:** USA **Condition category:** DBD **Questions:** KQ1, KQ2, KQ3 **Funding:** NR **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (crossover) **Diagnostic criteria:** DSM-IV, IQ test (Stanford-Binet, Weschsler Intelligence, Kaufman Brief) **Setting:** Inpatient and outpatient **Inclusion criteria:** (1) 4–14 yr, (2) IQ ≤84, (3) ODD or CD, (4) dx of austistic or PDD NOS, (5) availability of a reliable informant, (6) good physical health **Exclusion criteria:** (1) presence of psychosis, (2) history of NMS, (3) history of severe drug allergy/hypersensitivity, (4) medical disease, (5) pregnancy	**Enrolled:** 16 **Analyzed:** 15 **Completed:** NR **GROUP 1** **N:** 16 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 16 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 4 wk **Run-in phase:** Yes **Run-in phase duration:** 1 wk **Permitted drugs: c**lonidine, lithium **Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.7±1.3 (0.4–5) **Concurrent treatments:** psychostimulants (5) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Symptomatology (KQ1):** ABC, NCBRF **Other ST and LT outcomes (KQ3):** Cognitive (MTS, STRM, CPT, GHT) **AE (KQ2):** Dyskinesia, SBP, DBP, pulse **Subpopulations (KQ4):** NR	Risperidone may have a beneficial effect on efficiency or responding, activity level, static tremor, and aspects of behavior.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Aman et al., 2002 **Country:** USA **Condition category:** DBD **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-IV, NCBRF **Inclusion criteria:** (1) total rating of ≥24 on the conduct problem subscale of the NCBRF, (2) dx of CD, ODD, or DBD NOS, (3) dx of subaverage IQ (≥36 and ≤84) and a VABS score ≤84, (4) patients with ADHD eligible if meeting all other criteria, (5) healthy, (6) 5–12 yr, (7) symptoms sufficiently severe for antipsychotic treatment, (8) a responsible person to accompany patient to study visits, provide reliable assessments, dispense study medication **Exclusion criteria:** (1) dx of PDD, schizophrenia, other psychotic disorders, (2) head injury as a cause of intellectual disability,	**Enrolled:** 119 **Analyzed:** 118 **Completed:** 118 **GROUP 1** **N:** NR **Age, mean±SD (range):** 8.7±2.1 **Males %:** 85 **Caucasian %:** 51 **Diagnostic breakdown (n):** CD (9), CD + ADHD (12), DBD (1) DBD + ADHD (4), ODD (12), ODD+ ADHD (17) **Treatment naïve (n):** 55 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (33), MR (borderline (32), mild (16), moderate (7)) **GROUP 2** **N:** NR **Age, mean±SD (range):** 8.1±2.3 **Males %:** 79 **Caucasian %:** 62 **Diagnostic breakdown (n):** CD (12), CD + ADHD (14), DBD (1) DBD + ADHD (2), ODD (13), ODD + ADHD (21) **Treatment naïve (n):** 63 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (37), MR (borderline (28), mild	**Treatment duration:** 6 wk (11 mo extension) **Run-in phase:** Yes **Run-in phase duration:** 1 wk **Permitted drugs:** antihistamines, chloral hydrate, medication for EPS, melatonin, psychostimulants (dose stable for ≥30 day before study) **Prohibited drugs:** anticonvulsants, antidepressants, antipsychotics, carbamazepine, cholinesterase inhibitors, lithium, medications for sleep/anxiety, valproic acid **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.2±0.6 **Concurrent treatments:** all groups: methylphenidate hydrochloride (35) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** see group 1	**Symptomatology (KQ1):** ABC, BPI, CGI-I, NCBRF, VAS-MS **Other ST and LT outcomes (KQ3):** Medication adherence, response (CGI) **AE (KQ2):** ECG changes, EPS, prolactin, prolactin-related AE, SAE, sedation, total AE, WAE, weight change **Subpopulations (KQ4):** Sex (prolactin)	Risperidone was well tolerated and effective in children with disturbed behaviors and subaverage intelligence.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Aman et al., 2002 (continued)	(3) seizure disorder/ neuroleptics, (4) known hypersensitivity to risperidone or neuroleptics, (5) history of tardive dyskinesia or NMS, (6) serious or progressive illnesses, (7) presence of HIV, (8) use of an investigational drug within the previous 30 day, (9) previously received risperidone, (10) lab values outside of normal range unless not clinically relevant, (11) females of childbearing age, sexually active and not using birth control, (12) patients whose NCBRF conduct problem subscale score was reduced to <24 in response to a 1 wk placebo treatment before the study	(22), moderate (13))			

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Arango et al., 2009 **Country:** Spain **Condition category:** Schizophrenia and related **Questions:** KQ1, KQ2, KQ3 **Funding:** Industry, Academic **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient **Diagnostic criteria:** DSM-IV, K-SADS-PL **Inclusion criteria:** (1) adolescents admitted to the hospital with psychosis (schizophrenia or any other psychotic disorder (DSM-IV)) **Exclusion criteria:** (1) psychotic symptoms appearing to result from acute intoxication or withdrawal (if psychotic symptoms did not persist after 14 day of a negative urine drug screening), (2) DSM-IV criteria for any substance abuse, MR, or PDD, (3) organic CNS disorder, (4) history of TBI with loss of consciousness, (5) IQ <70 and a clinical criterion of impaired functioning prior to the onset of the disorder, (6) pregnant or breast	**Enrolled:** 50 **Analyzed:** 49 **Completed:** 32 **GROUP 1** **N:** 26 **Age, mean±SD (range):** 15.7±1.4 **Males %:** 76 **Caucasian %:** 76 **Diagnostic breakdown (n):** bipolar disorder (5), other psychoses (12: major depressive episode with psychotic features (3), psychosis NOS (4), schizoaffective disorder (3), schizophreniform disorder (2)), schizophrenia (9) **Treatment naïve (n):** 10 **Inpatients (n):** all **First episode psychosis (n):** all **Comorbidities:** psychosis (all) **GROUP 2** **N:** 24 **Age, mean±SD (range):** 16.3±1.1 **Males %:** 79.2 **Caucasian %:** 87.5 **Diagnostic breakdown (n):** bipolar disorder (8), other psychoses (8; major depressive episode with psychotic features (2), psychosis NOS (2),	**Treatment duration:** 6 mo **Run-in phase:** Yes **Run-in phase duration:** 3–5 day **Permitted drugs:** adjunctive medications **Prohibited drugs:** antipsychotics **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 9.7±6.6 **Concurrent treatments:** anticholinergics (8), antidepressants (10), antiepileptics (7), benzodiazepines (17), β-blockers (1), lithium (2) **GROUP 2** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 532.8±459.6 **Concurrent treatments:** analgesics (2), anticholinergics (3), antidepressants (8), antiepileptics (7), benzodiazepines (14), β-blockers (2), cough medications (1), iron compouNRs (1), lithium (6), NSAIDs (1)	**Symptomatology (KQ1):** CGAS, CGI-S, PANSS, SDQ, YMRS **Other ST and LT outcomes (KQ3):** Cognitive (cognitive domains), medication adherence **AE (KQ2):** Akathisia, behavioral issues, BMI, constipation, hypokinesia, Orthostatic dizziness prolactin-related AE, SAE, sedation, tachycardia, total AE, weight change **Subpopulations (KQ4):** NR	Psychotic symptoms in adolescents were reduced with both olanzapine and quetiapine, but cognitive measures were not improved. Significantly more weight gain was observed in patients treated with olanzapine.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Arango et al., 2009 (continued)	feeding, (7) taking olanzapine or quetiapine before enrolment	schizoaffective disorder (2), schizophreniform disorder (2)), schizophrenia (8) **Treatment naïve (n):** 15 **Inpatients (n):** all **First episode psychosis (n):** all **Comorbidities:** psychosis (all)			

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Armenteros et al., 2007 **Country:** USA **Condition category:** ADHD with aggression **Questions:** KQ1, KQ2, KQ3 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV, C-DISC 4 **Inclusion criteria:** (1) 7–12 yr, (2) constant dose of stimulant medication in the past 3 wk, (3) 3 acts of aggression in the past wk, 2 of which had to be acts of physical aggression against other people, objects, or self, (4) Aggression Questionnaire Predatory-Affective index score ≤0, (5) CGI-S ≥4, (6) Full Scale IQ ≥75, (7) normal results at screening from physical examination and laboratory tests **Exclusion criteria:** (1) substance use disorder, (2) unstable medical or neurological illness, (3) history of intolerance or failure to respond to an adequate trial of risperidone, (4) suicidal or homicidal	**Enrolled:** 25 **Analyzed:** 25 **Completed:** 23 **GROUP 1** **N:** 12 **Age, mean±SD (range):** 7.3±3.7 **Males %:** 83.3 **Caucasian %:** 50 **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (0), ODD (13), conduct disorder (6), GAD (1), separation anxiety disorder (3) **GROUP 2** **N:** 13 **Age, mean±SD (range):** 8.8±3.1 **Males %:** 92.3 **Caucasian %:** 46 **Diagnostic breakdown (n):** **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see group1	**Treatment duration:** 4 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** current psychostimulants **Prohibited drugs:** all medications other than current psychostimulants **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.1±0.6 **Concurrent treatments:** all groups: methylphenidate (15), mixed salts amphetamine (10) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1±0.5 **Concurrent treatments:** see group 1	**Symptomatology (KQ1):** CGI-I, CGI-S **Other ST and LT outcomes (KQ3):** Medication adherence, response (CAS-P, CAS-T, CGI-I) **AE (KQ2):** Behavioral issues, BMI, somnolence, total AE, WAE, weight change **Subpopulations (KQ4):** NR	Compared to placebo, risperidone was modestly effective in combination with psychostimulants for treatment-resistant agression in ADHD.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Bastiaens et al., 2009 **Country:** USA **Condition category:** Behavioral issues (aggression) **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Internal funding **Newcastle-Ottawa Scale:** 6 stars	**Recruitment dates:** Dec 2004 to Sep 2005 **Study design:** Retrospective cohort **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV, Mini International Neuropsychiatric Interview for Children and Adolescents, Child/Adolescent Symptom Inventory **Inclusion criteria:** (1) 6–18 yr, (2) clinically significant aggressive behavior **Exclusion criteria:** NR	**Enrolled:** 46 **Analyzed:** 34 **Completed:** 34 **GROUP 1** **N:** 24 **Age, mean±SD (range):** 11.7±2.4 **Males %:** 83 **Caucasian %:** NR **Diagnostic breakdown (n):** bipolar disorder (6), CD (8), depressive disorder (0), mood disorder NOS (6), PDD (0), psychotic disorder (4) **Treatment naïve (n):** 18 **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 22 **Age, mean±SD (range):** 12.1±2.9 **Males %:** 91 **Caucasian %:** NR **Diagnostic breakdown (n):** bipolar disorder (6), CD (6), depressive disorder (6), mood disorder NOS (2), PDD (2), psychotic disorder (0) **Treatment naïve (n):** 16 **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 8.7 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** stable doses of concomitant medications **Prohibited drugs:** NR **GROUP 1** **Drug name:** Aripiprazole **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 4.5±2.3 **Concurrent treatments:** atomoxetine (8), stimulants (2) **GROUP 2** **Drug name:** Ziprasidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 42.9±18 **Concurrent treatments:** atomoxetine (6), stimulants (8)	**Symptomatology (KQ1):** CGI-I, GAF, OAS, YMRS **Other ST and LT outcomes (KQ3):** Health related quality of life (HALFS) **AE (KQ2):** Behavioral issues, EPS, sedation, WAE, weight change **Subpopulations (KQ4):** Age, Sex (OAS)	Aripiprazole and ziprasidone were effective in treating aggressive behavior in children and adolescents with a variety of pyschiatric diagnoses.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Berger et al., 2008 **Country:** Australia **Condition category:** Schizophrenia and related **Questions:** KQ1, KQ2, KQ3 **Funding:** Industry, Academic **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** July 2003 to Jan 2006 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, SCID-I/P **Inclusion criteria:** (1) 15–25 yr, (2) first episode psychosis, (3) ≥1 of the following symptoms, present daily for ≥1 wk according to BPRS: somatic concerns, guilt, suspiciousness, hallucinations, unusual thought content, bizarre behavior, and/or conceptual disorganization **Exclusion criteria:** (1) previous treatment with antipsychotic medication (>1 wk), (2) presence of concurrent manic syndrome, MR (IQ<70), organic disorders presenting with a psychotic syndrome, epilepsy, (3) clinically significant physical	**Enrolled:** 141 **Analyzed:** 126 **Completed:** 126 **GROUP 1** **N:** 69 **Age, mean±SD (range):** 19.7±2.6 (15–24) **Males %:** 71 **Caucasian %:** NR **Treatment naïve (n):** 22 **Inpatients (n):** NR **First episode psychosis (n):** all **Comorbidities:** MR (0), psychosis (all), SA (28) **GROUP 2** **N:** 72 **Age, mean±SD (range):** 19±2.9 (15–24) **Males %:** 64.1 **Caucasian %:** NR **Treatment naïve (n):** 25 **Inpatients (n):** NR **First episode psychosis (n):** all **Comorbidities:** MR (0), psychosis (all), SA (30)	**Treatment duration:** 4 wk (8 wk extension) **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** anticholinergics, benzodiazepines, sertraline (50–200 mg/day), zopiclone, zolpidem **Prohibited drugs:** antipsychotics **GROUP 1** **Drug name:** Quetiapine (low) **Dosing variability:** fixed **Target dose (mg/day):** 200 **Daily dose (mg/day), mean±SD (range):** 200 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Quetiapine (high) **Dosing variability:** fixed **Target dose (mg/day):** 400 **Daily dose (mg/day), mean±SD (range):** 400 **Concurrent treatments:** NR	**Symptomatology (KQ1):** BPRS, CGI-S, GAF, SANS, SOFAS, YMRS **Other ST and LT outcomes (KQ3):** Health care system utilization, legal interaction, medication adherence, response, suicide **AE (KQ2):** Blood pressure, EPS, sedation, sexual dysfunction, somnolence, WAE, weight change **Subpopulations (KQ4):** NR	Quetiapine was safe and well-tolerated in acutely ill drug naïve first-episode psychosis patients.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Berger et al., 2008 (continued)	illness, (4) history of brain surgery or brain infarct, (5) concomitant medications that prolong the QT interval, (6) 20% deviation from normal-range laboratory values at baseline, (7) participation in any other studies involving investigational or marketed products concomitantly or within 30 days (8) having donated blood or blood products within the past 4 wk, (9) pregnant or lactating women, or women of childbearing potential not using an acceptable method of contraception				

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Biederman et al., 2005 **Country:** USA **Condition category:** Bipolar **Questions:** KQ1, KQ2, KQ3 **Funding:** Government, Academic **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV, K-SADS **Inclusion criteria:** (1) 4–6 yr, (2) DSM-IV bipolar I or II disorder or bipolar disorder NOS with current manic, hypomanic , or mixed symptoms (with or without psychotic features), (3) YMRS score >15 **Exclusion criteria:** (1) any serious, unstable medical illness, (2) history of treatment with both study medications	**Enrolled:** 31 **Analyzed:** 31 **Completed:** 24 **GROUP 1** **N:** 15 **Age, mean±SD (range):** 5.0±0.8 **Males %:** 67 **Caucasian %:** 100 **Diagnostic breakdown (n):** major depression (11), mania (all) **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** ADHD (15), DBD (8) **GROUP 2** **N:** 16 **Age, mean±SD (range):** 5.3±0.8 **Males %:** 75 **Caucasian %:** 94 **Diagnostic breakdown (n):** major Depression (11), mania (all) **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** ADHD (14), DBD (5)	**Treatment duration:** 8 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** benztropine mesylate (max 2 mg/day), lorazepam (≤2 mg/day) **Prohibited drugs:** antidepressants, antimanic or mood-stabilizing medications **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 6.3±2.3 (1.3–10) **Concurrent treatments:** all groups: benztropine (1), lorazepam (1) **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.4±0.5 (0.3–2.0) **Concurrent treatments:** see group 1	**Symptomatology (KQ1):** BPRS, CDRS, YMRS **Other ST and LT outcomes (KQ2):** Response **AE (KQ3):** Behavioral issues, blood pressure, cardiovascular AE, dermatologic AE, glucose, lipid profile, neurologic AE, prolactin, pulse, sedation, weight change **Subpopulations (KQ4):** NR	Rispiradone and olanzapine showed reduction of symptoms of mania in preschool children with bipolar disorder.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Biederman et al., 2004 **Country:** USA **Condition category:** Bipolar **Questions:** KQ1, KQ2 **Funding:** NR **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** NR **Inclusion criteria:** (1) score of 15 or greater at baseline on the YMRS **Exclusion criteria:** NR	**Enrolled:** 101 **Analyzed:** NR **Completed:** 72 **GROUP 1** **N:** 19 **Age, mean±SD (range):** all groups: 10.2±2.7 **Males %:** all groups: 67 **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 2** **N:** 19 **Age, mean±SD (range):** see group 1 **Males %:** see group 1 **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 3** **N:** 42 **Age, mean±SD (range):** see group 1 **Males %:** see group 1 **Caucasian %:** NR	**Treatment duration:** 8 wk **Run–in phase:** NR **Run–in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 8.5±3.2 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 213.1±150.5 **Concurrent treatments:** NR **GROUP 3** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.36±0.7 **Concurrent treatments:** NR **GROUP 4** **Drug name:** Ziprasidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 56.2±34.3	**Symptomatology (KQ1):** YMRS **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** Weight, prolactin **Subpopulations (KQ4):** NR	Second-generation antipsychotics reduce manic symptomatology in children and adolescents with bipolar disorder.

Biederman et al., 2004 (continued)	**Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 4** **N:** 21 **Age, mean±SD (range):** see group 1 **Males %:** see group 1 **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR	**Concurrent treatments:** NR

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Bruggeman et al., 2001 **Country:** Belgium, Netherlands, South Africa **Condition category:** Tourette syndrome **Questions:** KQ2, KQ4 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-III-TR **Inclusion criteria:** (1) 10–65 yr, (2) primary dx of Tourette syndrome (DSM-III-R), (3) ≥3 on TSSS and CGI-S **Exclusion criteria:** NR	**Enrolled:** 50 **Analyzed:** 50 **Completed:** 41 **GROUP 1** **N:** 24 **Age, mean±SD (range):** NR (11–45) **Males %:** 87.5 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** ADHD (1), GAD (2), OCD (14) **GROUP 2** **N:** 26 **Age, mean±SD (range):** NR (11–50) **Males %:** 88.5 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** ADHD (1), GAD (1), OCD (9)	**Treatment duration:** 2.8 mo **Run-in phase:** Yes **Run-in phase duration:** 2–5 wk **Permitted drugs:** antiparkinsonian medication and benzodiazepines (discontinued during washout period, limited during treatment) **Prohibited drugs:** antiparkinsonian medication and benzodiazepines (discontinued during washout period, limited during treatment), psychotropics (within 2 wk prior to and during study) **GROUP 1** **Drug name:** Pimozide **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2. 9 (1–6) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 3.8 (0.5–6) **Concurrent treatments:** NR	**Symptomatology (KQ1):** NR **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** Weight **Subpopulations (KQ4):** Age (CGI, GAF, HAM-A, PGI,TSSS, Y-BOCS, weight)	Risperidone and pimozide were efficacious and well tolerated in patients with Tourette syndrome, but risperidone had a more favorable efficacy and tolerability profile.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Buitelaar et al., 2001 **Country:** Netherlands **Condition category:** ADHD with aggression **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) overt aggressive behavior persisted during hospitalization (modified OAS score ≥1), (2) failure to respond to behavioral treatment approaches, (3) clinical indication for drug treatment, (4) 12–18 yr, (5) principal dx of CD, ODD, or ADHD according to DSM-IV, (6) full-scale IQ 60–90 (WISC-R) **Exclusion criteria:** (1) neurologic, cardiac, pulmonary, or hepatic diseases, (2) primary mood disorders, schizophrenia or other active psychosis, or suicidality, (3) comorbid substance abuse disorder (DSM-IV), (4) pregnant or use of inadequate	**Enrolled:** 38 **Analyzed:** 38 **Completed:** 35 **GROUP 1** **N:** 19 **Age, mean±SD (range):** 14.0±1.5 (11–18) **Males %:** 89.5 **Caucasian %:** NR **Diagnostic breakdown (n):** CD (14), DBD NOS (1), ODD (4) **Treatment naïve (n):** 13 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (14), MR (6) **GROUP 2** **N:** 19 **Age, mean±SD (range):** 13.7±2 (11–18) **Males %:** 84.2 **Caucasian %:** NR **Diagnostic breakdown (n):** CD (16), DBD NOS (1), ODD (2) **Treatment naïve (n):** 13 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (12), anxiety disorder (3), MR (8)	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** 2 wk **Permitted drugs:** biperidine, medication for somatic illness, oxazepam **Prohibited drugs:** psychotropics **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2.9 (1.5–4) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Symptomatology (KQ1):** ABC, CGI-S, OAS-M **Other ST and LT outcomes (KQ3):** Medication adherence **AE (KQ2):** Akathisia, dyskinesia, dystonia, ECG changes, fatigue, oculogyric crisis, parkinsonism, prolactin, prolactin-related AE, SAE, somnolence, total AE, weight change **Subpopulations (KQ4):** IQ and use of prior medication (CGI-S, ABC)	Risperidone may be effective for severe aggression in adolescents with disruptive behavior disorders and subaverage intelligence.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Buitelaar et al., 2001 (continued)	contraception, (5) major change in treatment strategy expected, (6) not feasible to discontinue current psychotropic medication				

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Connor et al., 2008 **Country:** USA **Condition category:** DBD **Questions:** KQ1, KQ2, KQ3 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Nov 2003 to May 2005 **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** K-SADS-E **Inclusion criteria:** (1) 12–17 yr, (2) primary psychiatric dx of CD, (3) moderate to severe aggression (OAS score ≥25), (4) at least moderate severity of symptoms (CGI-S score ≥4) **Exclusion criteria:** (1) comorbid schizophrenia, schizoaffective disorder, psychotic disorder NOS, bipolar disorder, psychotic depression, or bipolar disorder NOS, (2) alcohol or substance abuse or dependence within 3 mo, (3) significantly subaverage IQ, (4) current or past history of leticular abnormality or juvenile cataracts, (5) seizure disorder, (6) concurrent	**Enrolled:** 19 **Analyzed:** 19 **Completed:** 11 **GROUP 1** **N:** 9 **Age, mean±SD (range):** 13.1±1.2 **Males %:** 78 **Caucasian %:** 78 **Treatment naïve (n):** 2 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (8), DBD (8), depression (1), dysthymia (2), GAD (3), MR (0), OCD (2), panic disorder (1), psychosis (0), PTSD (2), SA (1), separation anxiety (2), social phobia (2) **GROUP 2** **N:** 10 **Age, mean±SD (range):** 15±1.4 **Males %:** 70 **Caucasian %:** 70 **Treatment naïve (n):** 1 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (7), DBD (10), depression (3), dysthymia (3), GAD (0), MR (0), OCD (1), panic disorder (0), psychosis (0), PTSD (1) SA (5), separation anxiety	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** 1–4 wk **Permitted drugs:** benztropine **Prohibited drugs:** psychotropics, rescue medications for aggression **GROUP 1** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** 200 **Daily dose (mg/day), mean±SD (range):** 294±78 (200–600) **Concurrent treatments:** benztropine (0) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** 200 **Daily dose (mg/day), mean±SD (range):** 530±245 **Concurrent treatments:** benztropine (0)	**Symptomatology (KQ1):** CGI-I, CGI-S, Conner PRS, OAS **Other ST and LT outcomes (KQ3):** Quality of life (Q-LES-Q), school attendance **AE (KQ2):** Akathisia, Behavioral issues, ECG changes, EPS, prolactin, pulse, SAE, sedation, severity of AE, WAE, weight change **Subpopulations (KQ4):** NR	Quetiapine may be efficacious in the treatment of CD, but further research is required.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Connor et al., 2008 (continued)	administration of any psychoactive medication, (7) pregnant or lactating females, (8) women of childbearing potential not using a medically accepted means of birth control, (9) unstable medical disease	(1), social phobia (1)			

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Correll et al., 2009 **Country:** USA **Condition category:** Multiple categories (bipolar, DBD, PDD, schizophrenia-related) **Questions:** KQ2, KQ4 **Funding:** Government, Academic **Newcastle-Ottawa Scale:** 8 stars	**Recruitment dates:** Dec 2001 to Sep 2007 **Study design:** Prospective cohort **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, chart review, discussion with treating clinician, clinical interview **Inclusion criteria:** (1) 4–19 yr, (2) <1 wk lifetime antipsychotic treatment, (3) psychiatric illness prompting antipsychotic medication initiation, (4) consent, (5) baseline anthropometric and biochemical assessments obtained within 7 day of antipsychotic medication initiation **Exclusion criteria:** (1) treatment with >1 antipsychotic agent, (2) active or past eating disorder, (3) biochemical evidence of thyroid dysfunction, (4) acute medical disorders, (5) pregnancy or	**Enrolled:** 312 **Analyzed:** 257 **Completed:** 192 **GROUP 1** **N:** 47 **Age, mean±SD (range):** 13.4±3.1 (7–19.7) **Males %:** 56.1 **Caucasian %:** NR **Diagnostic breakdown (n):** disruptive or aggressive behavior spectrum disorder (9: ASD (4), ODD, CD, IED, ICD (5)), mood disorder spectrum (11: bipolar (3), MDD (10), NOS (5)), schizophrenia spectrum (14: psychosis NOS (11), schizophrenia/ schizoaffective disorder (3)) **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 52 **Age, mean±SD (range):** 14.7±3.2 (6.6–18.6) **Males %:** 64.4 **Caucasian %:** NR **Diagnostic breakdown (n):** disruptive or aggressive behavior spectrum disorder (9: ASD (2), ODD, CD, IED, ICD (7)), mood disorder spectrum (16: bipolar (9),	**Treatment duration:** 2.8 mo **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** co-medications as necessary **Prohibited drugs:** co-medications as necessary **GROUP 1** **Drug name:** Aripriprazole **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** anticholinergics (2), antidepressants (13), anxiolytics or hypnotics (1), mood stabilizers (6), none (16), psychostimulants (5), psychotropics (4) **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** anticholinergics (0), antidepressants (10), anxiolytics or hypnotics (3), mood stabilizers (18), none (14), psychostimulants (4), psychotropics (1) **GROUP 3** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** NR	**Symptomatology (KQ1):** NR **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** Fat mass, glucose, insulin resistance, lipid profile, metabolic syndrome, waist circumference, WAE, weight change **Subpopulations (KQ4):** Pubertal status (metabolic changes)	First-time SGA medication use was associated with significant weight gain and variable metabolic changes for each medication.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Correll et al., 2009 (continued)	breastfeeding, (6) wards of the state, (7) leaving the catchment area within 4 wk	MDD (8), NOS (4)), schizophrenia spectrum (14: psychosis NOS (5), schizophrenia/ schizoaffective disorder (9)) **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 3** **N:** 45 **Age, mean±SD (range):** 14±3.1 (6.1–19.4) **Males %:** 36.1 **Caucasian %:** NR **Diagnostic breakdown (n):** disruptive or aggressive behavior spectrum disorder (6: ASD (2), ODD, CD, IED, ICD (4)), mood disorder spectrum (9: bipolar (10), MDD (8), NOS (6)), schizophrenia spectrum (6: psychosis NOS (4), schizophrenia/ schizoaffective disorder (2)) **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 4** **N:** 168 **Age, mean±SD (range):** 13.6±4 (4.3–19.9) **Males %:** 62.2 **Caucasian %:** NR	**Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** anticholinergics (2), antidepressants (10), anxiolytics or hypnotics (1), mood stabilizers (15), none (8), psychostimulants (4), psychotropics (1) **GROUP 4** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** anticholinergics (18), antidepressants (43), anxiolytics or hypnotics (13), mood stabilizers (32), none (32), psychostimulants (26), psychotropics (9)		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Correll et al., 2009 (continued)		**Diagnostic breakdown (n):** disruptive or aggressive behavior spectrum disorder (34: ASD (13), ODD, CD, IED, ICD (21)), mood disorder spectrum (55: bipolar (17), MDD (19), NOS (19)), schizophrenia spectrum (46: psychosis NOS (33), schizophrenia/ schizoaffective disorder (13)) **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR			

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Crocq et al., 2007 **Country:** France **Condition category:** Schizophrenia and related **Questions:** KQ2, KQ4 **Funding:** NR **Risk of bias:** NA (subjective), High (objective)	**Recruitment dates:** NR **Study design:** NRCT (parallel) **Setting:** Inpatient **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) hospitalized adolescents with schizophreniform disorder **Exclusion criteria:** NR	**Enrolled:** NR **Analyzed:** 52 **Completed:** NR **GROUP 1** **N:** NR **Age, mean±SD (range):** 16.5±1.7 **Males %:** 31.3 **Caucasian %:** all **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR **GROUP 2** **N:** NR **Age, mean±SD (range):** 17±1.3 **Males %:** 60 **Caucasian %:** all **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR **GROUP 3** **N:** NR **Age, mean±SD (range):** 15.2±1.4 **Males %:** 57.7 **Caucasian %:** all **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR	**Treatment duration:** 2.8 mo **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine (oral disintegrating tablet) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 16.6±4.4 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Olanzapine (standard oral tablet) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 18±4.2 **Concurrent treatments:** NR **GROUP 3** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2. 8±1.2 **Concurrent treatments:** NR	**Symptomatology (KQ1):** NR **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** BMI, weight **Subpopulations (KQ4):** Sex (weight)	Significantly greater increases in weight and BMI were found for olanzapine SOT compared to olanzapine ODT, as well as for olanzapine ODT compared to risperidone.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
de Haan et al., 2003 **Country:** Netherlands **Condition category:** Schizophrenia and related **Questions:** KQ1, KQ2, KQ3 **Funding:** Government **Risk of bias:** High (subjective), NA (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) 17–28 yr, (2) DSM-IV criteria for schizophrenia, (3) admitted to the Adolescent Clinic **Exclusion criteria:** (1) neurological or endocrine disease, (2) MR, (3) use of adjunctive medications such as mood stabilizers or antidepressants, (4) history of treatment with clozapine, (5) history of unresponsiveness to haloperidol or olanzapine, (6) intramuscular antipsychotic treatment within the last yr	**Enrolled:** 24 **Analyzed:** 19 **Completed:** 20 **GROUP 1** **N:** 12 **Age, mean±SD (range):** 21.0±2.8 (17–26) **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** 9 **Comorbidities:** MR (0) **GROUP 2** **N:** 12 **Age, mean±SD (range):** 21±2.3 (17–25) **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** 11 **Comorbidities:** MR (0)	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** 1 wk **Permitted drugs:** oxazepam **Prohibited drugs:** antidepressants, antipsychotics, mood stabilizers **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2.5 **Concurrent treatments:** oxazepam (6) **GROUP 2** **Drug name:** Olanzapine **Dosing variability: f**ixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 7.5 **Concurrent treatments:** oxazepam (5)	**Symptomatology (KQ1):** CGI-I, PANSS **Other ST and LT outcomes (KQ3):** Health related quality of life (Subjective Well-being under Neuroleptics scale), medication adherence **AE (KQ2):** Akathisia, parkinsonism **Subpopulations (KQ4):** NR	Olanzapine showed no superior subjective response over haloperidol in patients with recent-onset schizophrenia.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
DelBello et al., 2009 **Country:** USA **Condition category:** Bipolar **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Mar 2006 to June 2007 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV-TR, WASH-U-KSADS **Inclusion criteria:** (1) 12–18 yr, (2) dx of bipolar I disorder, depressive episode, (3) screening and baseline CDRS-R score ≥40 **Exclusion criteria:** (1) substance use disorder (other than nicotine) within the previous 3 mo, (2) unstable medical or neurological illness, (3) history of intolerance or nonresponse to quetiapine monotherapy, (4) treatment with an antidepressant (other than fluoxetine), an anticonvulsant (other than valproate or carbamazepine), antipsychotic or atomoxetine within 3 day, fluoxetine within 4 wk, or a psychostimulant within 48 hr of baseline, (5) risk of suicide	**Enrolled:** 32 **Analyzed:** 32 **Completed:** 20 **GROUP 1** **N:** 17 **Age, mean±SD (range):** 16.0±2 **Males %:** 29 **Caucasian %:** 82 **Treatment naïve (n):** 12 **Inpatients (n):** 7 **First episode psychosis (n):** NR **Comorbidities:** ADHD (2), anxiety disorder (5), DBD (6), psychosis (2) **GROUP 2** **N:** 15 **Age, mean±SD (range):** 15±2 **Males %:** 33 **Caucasian %:** 80 **Treatment naïve (n):** 11 **Inpatients (n):** 8 **First episode psychosis (n):** NR **Comorbidities:** ADHD (2), anxiety disorder (3), DBD (2), psychosis (1)	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** NR **Permitted drugs:** lorazepam (max 4 mg/day days 1–7, 2 mg/day days 8–14) **Prohibited drugs:** antidepressants (<3 day), anticonvulsants (<3 day), antipsychotics or atomoxetine (<3 day), fluoxetine (<4 wk), psychostimulant (<48 hr) **GROUP 1** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** 600 **Daily dose (mg/day), mean±SD (range):** 403±133 (300–600) **Concurrent treatments:** lorazepam (0) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** 600 **Daily dose (mg/day), mean±SD (range):** 413±151 (300–600) **Concurrent treatments:** lorazepam (0)	**Symptomatology (KQ1):** CDRS, CGI-BP, HAM-A, YMRS **Other ST and LT outcomes (KQ3):** Response (response, remission, suicide attempt) **AE (KQ2):** Blood pressure, BMI, diabetes, EPS, glucose, LFT, lipid profile, mania, prolactin, pulse, SAE, sedation, tachycardia, WAE, weight change **Subpopulations (KQ4):** inpatient status, site (symptomalogy)	Quetiapine monotherapy was no more effective in treating depression in adolescents with bipolar disorder than treatment with placebo.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
DelBello et al., 2008 **Country:** USA **Condition category:** Multiple categories (bipolar, schizophrenia-related) **Questions:** KQ1, KQ2, KQ3 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV-TR **Inclusion criteria:** (1) 10–17 yr, (2) bipolar I disorder (YMRS score ≥17), (3) schizophrenia-related disorder (BPRS-A score ≥35, with a score of ≥4 on at least one of: unusual thought content, hallucinations, suspiciousness, or conceptual disorganization), (4) BMI between 5th and 95th percentile **Exclusion criteria:** (1) currently on stable well-tolerated treatment, (2) substance-induced psychotic disorder, (3) treatment with clozapine within 12 wk, (4) depot antipsychotic within 4 wk, (5) MAO-I within 2 wk, (6) imminent risk of suicide or homicide, (7) MR, (8) autism or other	**Enrolled:** 63 **Analyzed:** 63 **Completed:** 38 **GROUP 1** **N:** 23 **Age, mean±SD (range):** 13.2 (bipolar), 14.4 (schiz) **Males %:** 52 **Caucasian %:** NR **Diagnostic breakdown (n):** bipolar I (15), schizophrenia or schizoaffective disorder (8) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (0), SA (0) **GROUP 2** **N:** 40 **Age, mean±SD (range):** 13.8 (bipolar), 14.7 (schiz) **Males %:** 75 **Caucasian %:** NR **Diagnostic breakdown (n):** biploar I (31), schizophrenia or schizoaffective disorder (9) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (0), SA (0)	**Treatment duration:** 3 wk (5.5 mo extension) **Run-in phase:** Yes **Run-in phase duration:** 24 hr **Permitted drugs:** benztropine and/or propranolol, lorazepam or similar benzodiazepine **Prohibited drugs:** antidepressants, mood stabilizers, stimulants **GROUP 1** **Drug name:** Ziprasidone (low) **Dosing variability:** fixed **Target dose (mg/day):** 80 **Daily dose (mg/day), mean±SD (range):** (20–80) **Concurrent treatments:** benztropine (3) **GROUP 2** **Drug name:** Ziprasidone (high) **Dosing variability:** fixed **Target dose (mg/day):** 160 **Daily dose (mg/day), mean±SD (range):** (40–160) **Concurrent treatments:** benztropine (4)	**Symptomatology (KQ1):** BPRS, CGI-S, YMRS **Other ST and LT outcomes (KQ3):** Suicide **AE (KQ2):** Akathisia, behavioral issues, dystonia, ECG changes, EPS, fatigue, glucose, lipid profile, prolactin, SAE, sedation, somnolence, WAE, weight change **Subpopulations (KQ4):** NR	Neither low- nor high-dose ziprasidone was associated with unexpected tolerability findings, and a starting dose of 20 mg/d, titrated to 80–160 mg/d over 1–2 wk was optimal.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
DelBello et al., 2008 (continued)	PDD, (8) pregnancy, breastfeeding, or unwillingness to use birth control, (9) serious unstable medical or neurologic illness, (10) any screening laboratory value that deviated significantly from reference range, (11) clinically significant hypokalemia or hypomagnesemia, (12) history of cardiac arryhthmias, conduction abnormalities, QTc prolongation, or genetic risk for prolonged QT syndrome, (13) psychoactive substance or alcohol abuse or dependence (other than nicotine or caffeine) within 1 mo (DSM-IV-TR)				

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
DelBello et al., 2002 **Country:** USA **Condition category:** Bipolar **Questions:** KQ1, KQ2, KQ3 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** May 2000 to May 2001 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, WASH-U-KSADS **Inclusion criteria:** (1) 12–18 yr, (2) DSM-IV criteria for bipolar I disorder, currently mixed or manic, (3) YMRS score ≥20 **Exclusion criteria:** (1) pregnant, (2) manic symptoms secondary to substance intoxication or withdrawal, (3) substance use disorder within the past 3 mo, (4) MR, (5) unstable medical or neurological disorder, cataracts, or clinically significant baseline laboratory abnormalities, (6) history of hypersensitivity, intolerance, or nonresponse to quetiapine or valproate, (7) treated with a depot	**Enrolled:** 30 **Analyzed:** 30 **Completed:** 22 **GROUP 1** **N:** 15 **Age, mean±SD (range):** 14.1±2 **Males %:** 53 **Caucasian %:** 80 **Diagnostic breakdown (n):** mixed episode (10) **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR **Comorbidities:** ADHD (10), psychosis (7) **GROUP 2** **N:** 15 **Age, mean±SD (range):** 14.5±2 **Males %:** 53 **Caucasian %:** 87 **Diagnostic breakdown (n):** mixed episode (13) **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR **Comorbidities:** ADHD (8), psychosis (7)	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** NR **Permitted drugs:** lorazepam (≤2 mg/day for first 14 day) **Prohibited drugs:** NR **GROUP 1** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** 450 **Daily dose (mg/day), mean±SD (range):** 432 **Concurrent treatments:** lorazepam (2) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** lorazepam (3)	**Symptomatology (KQ1):** YMRS **Other ST and LT outcomes (KQ3):** Medication adherence, response **AE (KQ2):** Blood cells, blood pressure, ECG changes, prolactin, SAE, sedation, thyroid function, WAE, weight change **Subpopulations (KQ4):** NR	Quetiapine in combination with divalproate is more effective for the treatment of adolescent bipolar mania than divalproate with placebo.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
DelBello et al., 2002 (continued)	neuroleptic within 3 mo, an antidepressant or antipsychotic within 1 wk (fluoxetine within 1 mo), a benzodiazepine or psychostimulant within 72 hr, or other antiepileptic agents within 72 hr				

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Findling et al., 2009 **Country:** USA **Condition category:** Bipolar **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Mar 2005 to Feb 2007 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, K-SADS-PL **Inclusion criteria:** (1) 10–17 yr, (2) bipolar I disorder with current manic or mixed episodes, with or without psychotic features (DSM-IV), (3) YMRS score ≥20 **Exclusion criteria:** (1) bipolar II disorder, bipolar disorder NOS, PDD, schizophrenia, schizoaffective disorder, psychosis due to other medical condition or concomitant medication, (2) MR, (3) DSM-IV substance or alcohol use disorder, (4) positive drug screen for cocaine or other substances of abuse during screening, (5) sexual activity without contraceptive use, pregnancy,	**Enrolled:** 296 **Analyzed:** 294 **Completed:** 237 **GROUP 1** **N:** 98 **Age, mean±SD (range):** 13.7±2.2 **Males %:** 53.1 **Caucasian %:** 66.3 **Diagnostic breakdown (n):** manic (41), mixed (43), unknown (14) **Treatment naïve (n):** 41 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (48), DBD (28) **GROUP 2** **N:** 99 **Age, mean±SD (range):** 13.3±2.3 **Males %:** 51.5 **Caucasian %:** 68.7 **Diagnostic breakdown (n):** manic (40), mixed (39), unknown (20) **Treatment naïve (n):** 49 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (50), DBD (34) **GROUP 3** **N:** 99	**Treatment duration:** 4 wk **Run-in phase:** Yes **Run-in phase duration:** 3 day **Permitted drugs:** anticholinergics, benzodiazepines **Prohibited drugs:** Mood stabilizers, other psychotropics **GROUP 1** **Drug name:** Aripiprazole (low) **Dosing variability:** variable **Target dose (mg/day):** 10 **Daily dose (mg/day), mean±SD (range):** (2–10) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Aripiprazole (high) **Dosing variability:** variable **Target dose (mg/day):** 30 **Daily dose (mg/day), mean±SD (range):** (2–30) **Concurrent treatments:** NR **GROUP 3** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Symptomatology (KQ1):** CDRS, CGAS, CGI-BP, GBI, YMRS **Other ST and LT outcomes (KQ3):** Health related quality of life (P-QLES-Q), response, suicide **AE (KQ2):** Akathisia, BMI, dyskinesia, dystonia, ECG changes, EPS, fatigue, glucose, lipid profile, mortality, parkinsonism, prolactin, SAE, somnolence, total AE, WAE, weight change **Subpopulations (KQ4):** Sex (prolactin)	Aripiprazole in daily doses of 10 mg or 30 mg was effective and generally well-tolerated for acute treatment of pediatric subjects with bipolar I mania or mixed episodes.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Findling et al., 2009 (continued)	lactation, (6) other medical reason determined by investigator, (7) noncompliance with medication washout, (8) inability to swallow tablets whole, (9) history of antipsychotic treatment resistance or NMS, (10) suicide attempt in the past 6 mo, score >3 on the Suicidal Ideation item of the CDRS-R, or determined by the investigator to be at risk of suicide, (11) clinically important laboratory test results, vital signs, or ECG, and unstable medical conditions, diabetes melitus, epilepsy, (12) prior participation in an aripiprazole study, allergy or hypersensitivity to aripiprazole, or participation in an investigational drug trial in the past mo	**Age, mean±SD (range):** 13.3±2.1 **Males %:** 56.6 **Caucasian %:** 60.6 **Diagnostic breakdown (n):** manic (38), mixed (43), unknown (18) **Treatment naïve (n):** 36 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (55), DBD (31)			

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Findling et al., 2008 **Country:** Asia, Caribbean, Europe, South Africa, South America, USA **Condition category:** Schizophrenia and related **Questions:** KQ1, KQ2, KQ3 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, K-SADS-PL **Inclusion criteria:** (1) 13–17 yr, (2) primary dx of schizophrenia (DSM-IV Axis I, confirmation with K-SADS-PL), (3) baseline PANSS ≥ 70 **Exclusion criteria:** (1) current psychiatric comorbidity requiring pharmacology, (2) evidence of suicide risk, (3) history, or current dx of schizoaffective disorder, MR, major depressive episodes, NMS, any neurologic disorder other than Tourette syndrome, severe head trauma, unstable medical condition, (4) resistant to antipsychotics according to trials of two different antipsychotics of adequate dose and duration, (5) pregnancy,	**Enrolled:** 302 **Analyzed:** 294 **Completed:** 258 **GROUP 1** **N:** 100 **Age, mean±SD (range):** 15.6±1.3 **Males %:** 45 **Caucasian %:** 54 **Treatment naïve (n):** 25 **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 102 **Age, mean±SD (range):** 15.4±1.4 **Males %:** 63.7 **Caucasian %:** 60.8 **Treatment naïve (n):** 27 **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 3** **N:** 100 **Age, mean±SD (range):** 15.4±1.4 **Males %:** 61 **Caucasian %:** 64 **Treatment naïve (n):** 27 **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** ≥3 day **Permitted drugs:** anticholinergics, benzodiazepines **Prohibited drugs:** antidepressants, atomoxetine, mood stabilizers, other psychotropics, stimulants **GROUP 1** **Drug name:** Aripiprazole (low) **Dosing variability:** variable **Target dose (mg/day):** 10 **Daily dose (mg/day), mean±SD (range):** 9.8 (2–10) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Aripiprazole (high) **Dosing variability:** variable **Target dose (mg/day):** 30 **Daily dose (mg/day), mean±SD (range):** 28.9 (2–30) **Concurrent treatments:** NR **GROUP 3** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Symptomatology (KQ1):** CGAS, CGI-I, CGI-S, PANSS **Other ST and LT outcomes (KQ3):** Health related quality of life (P-QLES-Q), response, suicide **AE (KQ2):** Akathisia, behavioral issues, BMI, dyskinesia, dystonia, ECG changes, EPS, EPS (SAS), glucose, lipid profile, mortality, prolactin, parkinsonism, SAE, somnolence, WAE, weight change **Subpopulations (KQ4):** NR	Aripiprazole (10 or 30 mg/d) was well tolerated and was more effective than placebo in improving symptoms of schizophrenia.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Findling et al., 2008 (continued)	breast-feeding, sexually active patients who refused abstinence or birth control, (6) positive screens for illegal drugs within 3 mo of baseline or during study, (7) hospitalized for acute schizophrenia within 4 wk of baseline				

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Findling et al., 2008 **Country:** USA **Condition category:** Multiple categories (bipolar, DBD, OCD, PDD, schizophrenia, Tourette syndrome) **Questions:** KQ2 **Funding:** Industry **Newcastle-Ottawa Scale:** 4 stars	**Recruitment dates:** NR **Study design:** Prospective cohort **Setting:** NR **Diagnostic criteria:** NR **Inclusion criteria:** (1) 10–17 yr, (2) primary psychiatric dx of bipolar, schizophrenia spectrum disorder, or other at investigator discretion **Exclusion criteria:** (1) sexual activity without practicing double-barrier birth control, (2) pregnancy or lactation, (3) current or former drug or alcohol abuse, (4) MR, (5) neurologic disorders (except PDD, ADHD or Tourette syndrome), (6) use of antipsychotic or psychotropic medication, CYP2D6 and CYP3A4 inhibitors, or CYP3A4 inducers within previous 14 day, (7) participation in another clinical study in previous mo (or 6 mo if study involved psychotropic medication), (8) major	**Enrolled:** 21 **Analyzed:** 20 **Completed:** 17 **GROUP 1** **N:** 8 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (0) **GROUP 2** **N:** 7 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (0) **GROUP 3** **N:** 6 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (0)	**Treatment duration:** low dose 3.1 wk, medium dose 3.4 wk, high dose 3.7 wk **Run-in phase:** Yes **Run-in phase duration:** ≤12 day **Permitted drugs:** NR **Prohibited drugs:** antipsychotics or psychotropics, CYP2D6 and CYP3A4 inhibitors, CYP3A4 inducers (within 14 day) **GROUP 1** **Drug name:** Aripiprazole (low) **Dosing variability:** fixed **Target dose (mg/day):** 20 **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** all groups (14): analgesics (5), anesthetics (4), antacids (1), antibacterials (1), antiasthmatics (2), antidiabetics (1), antiinflammatories or antirheumatics (2), antiparkinsonianism drugs (2), antipyretics including antihistamines (1), nasal preparations (1) **GROUP 2** **Drug name:** Aripiprazole (medium) **Dosing variability:** fixed **Target dose (mg/day):** 25 **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** see group 1 **GROUP 3** **Drug name:** Aripiprazole (high) **Dosing variability:** fixed	**Symptomatology (KQ1):** NR **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** Dystonia, fatigue, mortality, SAE, sedation, somnolence, total AE, weight change **Subpopulations (KQ4):** NR	Aripiprazole at doses of 20, 25, and 30 mg/d were generally safe and well tolerated in children and adolescents with psychiatric disorders.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Findling et al., 2008 (continued)	surgery or blood transfusion/donation within previous 30 day, (9) abnormal physical, ECG or clinical laboratory examination, (10) significant risk of suicide or homicide		**Target dose (mg/day):** 30 **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** see group 1		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Findling et al., 2000 **Country:** USA **Condition category:** DBD **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Industry, Foundation **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV, K-SADS, clinical interview **Inclusion criteria:** (1) outpatients with primary dx of CD, (2) 5–15 yr, (3) at least moderate degree of overall symptom severity (CGI), (4) Aggression subscale T-score ≥2 SD above the mean for age- and gender-matched peers (CBCL) **Exclusion criteria:** (1) moderate/severe ADHD, (2) significant psychiatric comorbidity (including mood disorder), (3) treatment with a psychotropic medication within 1 wk of initiating double-blind therapy, (4) positive toxicology screen, (5) suicide attempt within the past mo, (6) organic mental syndromes, (7) pregnant	**Enrolled:** 20 **Analyzed:** 20 **Completed:** 9 **GROUP 1** **N:** 10 **Age, mean±SD (range):** 10.7±3.4 **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR **GROUP 2** **N:** 10 **Age, mean±SD (range):** 8.2±1.9 **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR	**Treatment duration:** 10 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** benztropine **Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 0±0.004 (0.8–1.5) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** (0.3–3) **Concurrent treatments:** NR	**Symptomatology (KQ1):** CBCL, CGI-I, CGI-S, Conner PRS, RAAPP **Other ST and LT outcomes (KQ3):** Medication adherence **AE (KQ2):** Dermatologic AE, EPS, liver function, sedation, total AE, WAE **Subpopulations (KQ4):** age, race, baseline RAAPP & CGI-S scores (completion of study, RAAPP, CPRS)	Low doses of risperidone may be effective in the treatment of youths with CD and are not associated with extrapyramidal symptoms.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Findling et al., 2000 (continued)	or nursing females and females of childbearing potential who were not using an acceptable method of birth control, (8) a standard score equivalent to <70 on the Peabody Picture Vocabulary Test-Revised				

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Fleischhaker et al., 2006 **Country:** Germany **Condition category:** Multiple categories (anorexia nervosa, DBD, OCD, PDD, schizophrenia, Tourette syndrome) **Questions:** KQ2, KQ4 **Funding:** NR **Newcastle-Ottawa Scale:** 2 stars	**Recruitment dates:** NR **Study design:** Prospective cohort **Setting:** Inpatient **Diagnostic criteria:** ICD-10 **Inclusion criteria:** NR **Exclusion criteria:** NR	**Enrolled:** 51 **Analyzed:** 51 **Completed:** 51 **GROUP 1** **N:** 16 **Age, mean±SD (range):** 17.2±1.8 (14.4–21.3) **Males %:** 68.9 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 16 **Age, mean±SD (range):** 15.8±1.4 (12.8–17.8) **Males %:** 56.3 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 3** **N:** 19 **Age, mean±SD (range):** 15.6±2.6 (9.7–19) **Males %:** 68.4 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 7.4 wk (mean) **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Clozapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 321.9±156.5 (125–600) **Concurrent treatments:** all groups: amisulpride, biperiden, chlorprotixene, fluboxamine, fluoxetine, haloperidol, imipramine, lactulose, levomepromazine, lorazepam, metixene, metoclopramid, metoprolol, paroxetine, perazine, pimozide, pipamperone, pirenzepine, promethazine **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 16.6±7.1 (7.5–30) **Concurrent treatments:** see group 1 **GROUP 3** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 3.9±1.7 (1–6) **Concurrent treatments:** see group 1	**Symptomatology (KQ1):** NR **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** Akathisia, behavioral issues, bradycardia, blood cells, blood pressure, BMI, constipation, dystonia, dermatologic AE, ECG changes, liver functiontachycardia, tardive dyskinesia, weight change **Subpopulations (KQ4):** Sex, age, co-treatment, treatment history, history of dieting, baseline weight (weight change)	Olanzapine caused significant weight gain in children and adolescents, potentially influencing medication compliance and health risk. Clozapine and risperidone were associated with less marked changes in weight, but gains were still more pronounced than those seen in adults.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Fraguas et al., 2008 **Country:** Spain **Condition category:** Multiple categories (bipolar, DBD, PDD, schizophrenia) **Questions:** KQ2, KQ4 **Funding:** Government, Foundation, Other NR **Newcastle-Ottawa Scale:** 6 stars	**Recruitment dates:** Mar 2005 to Oct 2006 **Study design:** Prospective cohort **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) new prescription of olanzapine, risperidone of quetiapine within 30 days, (2) no history of prior lifetime antipsychotic treatment **Exclusion criteria:** (1) receiving >1 antipsychotic or needed another antipychotic during followup	**Enrolled:** 92 **Analyzed:** 66 **Completed:** 66 **GROUP 1** **N:** 25 **Age, mean±SD (range):** 15.9±1.5 (12–17) **Males %:** 65 **Caucasian %:** 90 **Diagnostic breakdown (n):** bipolar (2), depression (1), eating disorders (3), PDD (1), psychosis NOS (5), schizophrenia (3), schizophreniform (5) **Treatment naïve (n):** 9 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** psychosis (14), SA (12) **GROUP 2** **N:** 29 **Age, mean±SD (range):** 16.3±1.3 (13–18) **Males %:** 58.3 **Caucasian %:** 95.8 **Diagnostic breakdown (n):** ADHD (0), bipolar (5), CD (1), depression (2), eating disorders (2), OCD (2), PDD (0), psychosis NOS (4), schizophrenia (4), schizophreniform (4) **Treatment naïve (n):** 8 **Inpatients (n):** NR	**Treatment duration:** 6 mo **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** anticholinergics, antidepressants, benzodiazepines **Prohibited drugs:** antipsychotics **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 9.8±5.6 **Concurrent treatments:** antidepressants (3), benzodiazepines (14), biperiden (4) **GROUP 2** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 390.8±321.2 **Concurrent treatments:** antidepressants (9), benzodiazepines (12), biperiden (4) **GROUP 3** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 3.5±3.1 **Concurrent treatments:** antidepressants (9), benzodiazepines (11), biperiden (6)	**Symptomatology (KQ1):** NR **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** Blood pressure, BMI, glucose, lipid profile, thyroid function, weight change **Subpopulations (KQ4):** Sex, age, race, comorbidities, co-treatment, duration of inpatient treatment, treatment history (weight, at risk for AE)	Metabolic and hormonal adverse events should be carefully monitored when prescribing SGAs.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Fraguas et al., 2008 (continued)		**First episode psychosis (n):** NR **Comorbidities:** psychosis (14), SA (18) **GROUP 3** **N:** 38 **Age, mean±SD (range):** 13.4±4 (4–17) **Males %:** 77.3 **Caucasian %:** 81.8 **Diagnostic breakdown (n):** ADHD (4), bipolar (1), CD (7), depression (1), eating disorders (1), OCD (2), PDD (1), psychosis NOS (3), schizophrenia (2), schizophreniform (0) **Treatment naïve (n):** 8 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** psychosis (6), SA (13)			

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Friedlander et al., 2001 **Country:** Canada **Condition category:** Multiple categories (bipolar, DBD, OCD, PDD, schizophrenia-related, Tourette syndrome) **Questions:** KQ2, KQ4 **Funding:** NR **Newcastle-Ottawa Scale:** 4 stars	**Recruitment dates:** NR **Study design:** Retrospective cohort **Setting:** NR **Diagnostic criteria:** DSM-IV, author consensus on chart review **Inclusion criteria:** (1) 13–24 yr, (2) developmental disabilities and complex psychiatric problems, (3) active files with the mental health sites in the Greater Vancouver area **Exclusion criteria:** NR	**Enrolled:** 44 **Analyzed:** 44 **Completed:** NR **GROUP 1** **N:** 14 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** Addison's disease (1), hypothyroidism (4), MR (borderline (1), mild (17), moderate (15), severe (9)), Neurodevelopmental syndrome (15), Seizure disorder (9) **GROUP 2** **N:** 40 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see group 1	**Treatment duration:** 6 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** all groups: anticholinergics (5), anticonvulsants (12), anxiolytics (9), clonidine (1), mood stabilizers (21), non-SSRI antidepressants (8), SSRIs (9), stimulants (2), tetrabenazine (2) **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** see group 1	**Symptomatology (KQ1):** NR **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** Akathisia, dyskinesia, dystonia, EPS, prolactin-related AE, sedation, total AE, WAE, weight change **Subpopulations (KQ4):** Sex (Neuroleptic-induced movement disorders); psychosis (drug dosage)	Adolescents and young adults with developmental disabilities treated with SGAs for multiple conditions were particularly sensitive to neuroleptic induced movement disorders.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Gilbert et al., 2004 **Country:** USA **Condition category:** Tourette syndrome **Questions:** KQ1, KQ2 **Funding:** Industry, Government **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (crossover) **Setting:** NR **Diagnostic criteria:** DSM-IV-TR, clinical assessment **Inclusion criteria:** (1) 7–17 yr, (2) Tourette syndrome or chronic motor tic disorder, (3) CGI tic severity score >4 after 2 wk with no medication **Exclusion criteria:** (1) transient tic disorder, anorexia nervosa, PDD, substance/alcohol abuse or dependence within the past yr, or any psychotic disorder, (2) serious or unstable medical illness or abnormal ECG or laboratory findings, (3) sexually active females of childbearing potential not using contraceptives	**Enrolled:** 19 **Analyzed:** NR **Completed:** 13 **GROUP 1** **N:** 19 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (7), conduct disorder (1), learning disorder (3), OCD (2), oppositional defiant disorder (2) **GROUP 2** **N:** 19 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see group 1	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** 2 wk **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Pimozide **Dosing variability:** variable **Target dose (mg/day):** 4 **Daily dose (mg/day), mean±SD (range):** 2.4 (1–4) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** 4 **Daily dose (mg/day), mean±SD (range):** 2.5 (1–4) **Concurrent treatments:** NR	**Symptomatology (KQ1):** CGI-I, TSSR, YGTSS **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** EPS (ESRS), ECG changes, side effect check list, weight changes **Subpopulations (KQ4):** NR	Risperidone was superior to pimozide for tic suppression but it induced weight gain.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Gothelf et al., 2002 **Country:** Israel **Condition category:** Schizophrenia and related **Questions:** KQ2 **Funding:** Government **Newcastle-Ottawa Scale:** 3 stars	**Recruitment dates:** NR **Study design:** Prospective cohort (NR) **Setting:** Inpatient **Diagnostic criteria:** DSM-IV, K-SADS **Inclusion criteria:** NR **Exclusion criteria:** (1) taking medications that affect weight	**Enrolled:** 20 **Analyzed:** NR **Completed:** NR **GROUP 1** **N:** 10 **Age, mean±SD (range):** 17.0±1.6 **Males %:** 100 **Caucasian %:** NR **Treatment naïve (n):** ND **Inpatients (n):** all **First episode psychosis (n):** NR **GROUP 2** **N:** 10 **Age, mean±SD (range):** 17±1.6 **Males %:** 100 **Caucasian %:** NR **Treatment naïve (n):** 1 **Inpatients (n):** all **First episode psychosis (n):** NR	**Treatment duration:** 4 wk **Run-in phase:** Yes **Run-in phase duration:** 17.6 day (mean) **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 6.5±3.4 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 14±4.1 **Concurrent treatments:** NR	**Symptomatology (KQ1):** NR **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** Abdominal circumference, BMI, weight **Subpopulations (KQ4):** NR	Body mass index significantly increased in adolescent male inpatients treated with olanzapine but not in those given haloperidol.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Haas et al., 2009 **Country:** USA **Condition category:** Bipolar **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Dec 2003 to Dec 2005 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, K-SADS-PL **Inclusion criteria:** (1) 10–17 yr, (2) medically stable, (3) acute manic/mixed episode (K-SADS-PL), (4) total score ≥20 at screening and baseline on YMRS, (5) responsible caregiver **Exclusion criteria:** (1) known intellectual impairment	**Enrolled:** 170 **Analyzed:** 169 **Completed:** 137 **GROUP 1** **N:** 50 **Age, mean±SD (range):** NR (10–17) **Males %:** 56 **Caucasian %:** 70 **Diagnostic breakdown (n):** manic episode (20), mixed episode (30) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (25), DBD (27) **GROUP 2** **N:** 61 **Age, mean±SD (range):** NR (10–17) **Males %:** 43 **Caucasian %:** 82 **Diagnostic breakdown (n):** manic episode (21), mixed episode (40) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (33), DBD (40) **GROUP 3** **N:** 58	**Treatment duration:** 3 wk **Run-in phase:** Yes **Run-in phase duration:** ≤5 day **Permitted drugs:** medication for EPS; sedatives/hypnotics (run-in and wk 1 only) **Prohibited drugs:** anticonvulsants, antidepressants, antimanic medications, other antipsychotics (including herbal substances); methylphenidate/other medication for ADHD **GROUP 1** **Drug name:** Risperidone (low) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** (0.5–2.5) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Risperidone (high) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 3 (26%), 4 (19%), 5 (15%), 6 (41%) (3–6) **Concurrent treatments:** NR **GROUP 3** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Symptomatology (KQ1):** BPRS, CGI-BP, YMRS **Other ST and LT outcomes (KQ3):** Medication adherence, response, suicide **AE (KQ2):** Behavioral issues, BMI, dermatologic AE, EPS, fatigue, glucose, lipid profile, mortality, prolactin, prolactin-related AE, SAE, sedation, somnolence, tardive dyskinesia, total AE, WAE, weight change **Subpopulations (KQ4):** Age (YMRS, AE); Sex, race, diagnostic subgroup, or hospitalization at screening (YMRS)	A significant reduction in manic symptoms was seen in youth when treated with risperidone (0.5–2.5 mg/d or 3–6 mg/d) compared to placebo.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Haas et al., 2009 (continued)		**Age, mean±SD (range):** NR (10–17) **Males %:** 48 **Caucasian %:** 78 **Diagnostic breakdown (n):** manic episode (19), mixed episode (39) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (27), DBD (34)			

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Haas et al., 2009 **Country:** Belgium, Bulgaria, Czech Republic, Estonia, Germany, Poland, Romania, USA **Condition category:** Schizophrenia and related **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Apr 2001 to Mar 2006 **Study design:** RCT (parallel) **Setting:** Inpatient **Diagnostic criteria:** DSM-IV, K-SADS-PL **Inclusion criteria:** (1) 13–17 yr, (2) schizophrenia, (3) currently hospitalized for an acute episode (PANSS total score 60–120) **Exclusion criteria:** (1) significant risk for suicidal or violent behavior, (2) history of NMS, tardative dyskinesia, or a known or suspected seizure disorder, (3) BMI <5th percentile or >95th percentile, (4) schizophreniform disorder	**Enrolled:** 257 **Analyzed:** 255 **Completed:** 172 **GROUP 1** **N:** 132 **Age, mean±SD (range):** 15.6±1.32 (13–17) **Males %:** 61 **Caucasian %:** 85 **Diagnostic breakdown (n):** catatonic (3), disorganized (6), paranoid (92), residual (7), undifferentiated (24) **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR **GROUP 2** **N:** 125 **Age, mean±SD (range):** 15.6±1.25 (13–17) **Males %:** 52 **Caucasian %:** 85 **Diagnostic breakdown (n):** catatonic (4), disorganized (13), paranoid (83), residual (0), undifferentiated (25) **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** ≥7 day **Permitted drugs:** antiparkinsonian medications (first 3 wk), propranolol, rescue medications (diazepam, hydroxyzine, lorazepam, zolpidem, zopiclone) **Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone (low) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 0.4 (0.2–0.6) **Concurrent treatments:** all groups: rescue medication (133) **GROUP 2** **Drug name:** Risperidone (high) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 4 (1.5–6) **Concurrent treatments:** see group 1	**Symptomatology (KQ1):** CGI-I, CGI-S, PANSS **Other ST and LT outcomes (KQ3):** Medication adherence, response, suicide **AE (KQ2):** Akathisia, behavioral issues, dyskinesia, dystonia, ECG changes, EPS, glucose, mortality, prolactin, prolactin-related AE, SAE, somnolence, tachycardia, total AE, WAE, weight change **Subpopulations (KQ4):** Sex (prolactin)	A greater improvement in total PANSS score was found with high dose risperidone than with low dose risperidone.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Haas et al., 2009 **Country:** India, Russia, Ukraine, USA **Condition category:** Schizophrenia and related **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Aug 2004 to Dec 2005 **Study design:** RCT (parallel) **Setting:** Inpatient/outpatient **Diagnostic criteria:** DSM-IV, K-SADS-PL **Inclusion criteria:** (1) male and females, (2) aged 13 to 17 years, (3) DSM-IV diagnosis of schizophrenia, (4) inpatients or outpatients, experiencing an acute episode with a total PANSS score of 60 to 120 (inclusive), (5) no serious illnesses or neurological conditions, (6) females were required to a have negative pregnancy test and to be using an acceptable form of contraception. **Exclusion criteria:** (1) DSM-IV criteria for dissociative disorder, bipolar disorder, MDD, schizoaffective disorder, schizophreniform disorder, autistic	**Enrolled:** 160 **Analyzed:** 158 **Completed:** 125 **GROUP 1** **N:** 55 **Age, mean±SD (range):** 15.7±1.3 **Males %:** 55 **Caucasian %:** 60 **Diagnostic breakdown (n):** Paranoid (38), Undifferentiated (8), Disorganized (8), Catatonic (1), Residual (0) **Treatment naïve (n):** NR **Inpatients (n):** 30 **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 2** **N:** 51 **Age, mean±SD (range):** 15.7±1.3 **Males %:** 73 **Caucasian %:** 47 **Diagnostic breakdown (n):** Paranoid (34), Undifferentiated (13), Disorganized (4), Catatonic (0), Residual (0) **Treatment naïve (n):** NR **Inpatients (n):** 25 **First episode psychosis (n):** NR **Comorbidities:** NR	**Treatment duration:** 6 wk **Run–in phase:** Yes **Run–in phase duration:** ≤5 day **Permitted drugs:** Propanolol was allowed for treatment-emergent akathisia. Antiparkinsonian medications could be initiated for treatment-emergent EPS. Use of all rescue medications was kept to a minimum, and the permitted doses of certain medications progressively decreased over the course of the study. Subjects could receive limited supportive psychotherapy or psychoeducation. **Prohibited drugs:** antidepressants, mood stabilizers, anticonvulsants, psychostimulants, direct dopamine agonists, cholinesterase inhibitors, herbal or over-the-counter medications with psychotripic properties, or antipsychotic other than the study medication. Drugs with sedative, hypnotic, or anxiolytic properties were not allowed, with some exceptions. Subjects were not permitted to receive insight-oriented or cognitive-behavioral psychotherapy. **GROUP 1** **Drug name:** Risperidone (low) **Dosing variability:** fixed **Target dose (mg/day):** 1–3 **Daily dose (mg/day), mean±SD (range):** NR (1–3) **Concurrent treatments:** NR	**Symptomatology (KQ1):** CGAS, CGI-I, CGI-S, PANSS **Other ST and LT outcomes (KQ3):** Response, suicide **AE (KQ2):** Behavioral issues, BMI, EPS, glucose-related AE, mortality, prolactin, prolactin-related AE, SAE, somnolence, tachycardia, tardive dyskinesia, total AE, WAE, weight change **Subpopulations (KQ4):** Sex (prolactin)	Risperidone treatment for 6-weeks was safe and effective at daily doses of 1–3 and 4–6 mg in adolescents experiencing acute exacerbations of schizophrenia

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Haas et al., 2009 (continued)	disorder, or primary substance-induced psychotic disorder at screening, (2) MR (IQ<70), (3) substance dependence diagnosed by DSM-IV criteria in 3 months preceding screening, (4) significant risk of suicide or violent behavior, (5) failed to respond to adequate treatment with >2 antipsychotic drugs during the current psychotic episode, (6) hypersensitivity or intolerance to risperidone, (7) history of neuroleptic malignant syndrome or any severe drug allergy,	**GROUP 3** **N:** 54 **Age, mean±SD (range):** 15.5±1.4 **Males %:** 65 **Caucasian %: 50** **Diagnostic breakdown (n):** Paranoid (38), Undifferentiated (12), Disorganized (3), Catatonic (0), Residual (1) **Treatment naïve (n):** NR **Inpatients (n):** 23 **First episode psychosis (n):** NR **Comorbidities:** NR	**GROUP 2** **Drug name:** Risperidone (high) **Dosing variability:** fixed **Target dose (mg/day):** 4–6 **Daily dose (mg/day), mean±SD (range):** NR (4–6) **Concurrent treatments:** NR **GROUP 3** **Drug name:** Placebo **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Hellings et al., 2006 **Country:** USA **Condition category:** Behavioral issues (aggression, property destruction, self-injury) **Questions:** KQ1, KQ3, KQ4 **Funding:** Industry, Government **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (crossover) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) 6–65 yr, (2) MR (IQ <70), (3) at least 6 mo history of aggression, property destruction, or self-injury, (4) above normal baseline Irritability score for age, gender and setting (ABC-C) **Exclusion criteria:** (1) previous risperidone hypersensitivity, (2) history of NMS, (3) seizures within the past yr, (4) degenerative brain disease, (5) problematic living situation	**Enrolled:** 26 **Analyzed:** 26 **Completed:** NR **GROUP 1** **N:** 26 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** Autistic Disorder (ND), MR (Mild (8), moderate (6), severe (8), profound (4)), PDD-NOS (ND) **GROUP 2** **N:** 26 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see group 1 **GROUP 3** **N:** 26 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see group 1	**Treatment duration:** 5.1 mo (5.5 mo extension) **Run-in phase:** Yes **Run-in phase duration:** 5–7 wk **Permitted drugs:** divalproex, gabapentin (if epilepsy was in remission ≥1 yr) **Prohibited drugs:** psychotropics, including stimulants **GROUP 1** **Drug name:** Risperidone (low) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** all groups: divalproex (5), gabapentin (1) **GROUP 2** **Drug name:** Risperidone (high) **Dosing variability:** variable **Target dose (mg/day):** 0.05 mg/kg/day **Daily dose (mg/day), mean±SD (range):** 2 (1.2–2.9) **Concurrent treatments:** see group 1 **GROUP 3** **Drug name:** Placebo II **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** see group 1	**Symptomatology (KQ1):** ABC, CGI-I, PAC, VAS **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** NMS, tardive dyskinesia, weight change **Subpopulations (KQ4):** Age (ABC irritability, prolactin, weight), Sex, age, comorbidity, co-treatment, mood disorder (response)	Compared to placebo, risperidone was more effective in treating problematic behaviors in children and adolescents with MR. Low doses were better tolerated and were equally effective compared to high doses.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Hollander et al., 2006 **Country:** USA **Condition category:** PDD **Questions:** KQ1, KQ2, KQ3 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-IV, ADI-R, ADOS **Inclusion criteria:** (1) 6–17 yr, (2) meets DSM-IV and ADI-R criteria with a rating of at least moderate (≥4) on the CGI **Exclusion criteria:** (1) response to prior pharmacological treatment, (2) psychotic disorders and a history of any clinically significant medical illness (with the exception of a stable seizure disorder)	**Enrolled:** 11 **Analyzed:** 11 **Completed:** 8 **GROUP 1** **N:** 6 **Age, mean±SD (range):** 9.3±2.9 (6–14.8) **Males %:** 100 **Caucasian %:** 50 **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (normal (2), mild (2), severe (2)) **GROUP 2** **N:** 5 **Age, mean±SD (range):** 8.9±2.1 (6.1–11) **Males %:** 60 **Caucasian %:** 80 **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (normal (2), mild (3))	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** 4 wk **Permitted drugs:** anticonvulsants (stable dose ≥3 mo), clonidine, chloral hydrate **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 10±2 (7.5–12.5) **Concurrent treatments:** none **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 10±2 (7.5–12.5) **Concurrent treatments:** none	**Symptomatology (KQ1):** CGI-I **Other ST and LT outcomes (KQ3):** Response (CGI-I, CPRS) **AE (KQ2):** Constipation, EPS, sedation, weight change **Subpopulations (KQ4):** NR	Olazapine improved global functioning in children and adolescents with PDD, but was associated with a significant risk of weight gain.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Hrdlicka et al., 2009 **Country:** Czech Republic **Condition category:** Schizophrenia and related **Questions:** KQ2 **Funding:** Government, Academic **Newcastle-Ottawa Scale:** 5 stars	**Recruitment dates:** 1997 to 2007 **Study design:** Retrospective cohort **Setting:** Inpatient **Diagnostic criteria:** ICD-10 **Inclusion criteria:** (1) schizophrenia dx (F20-29), (2) medical record quality sufficient to evaluate the patient, (3) the first treatment used following admission was considered (with the exception of clozapine), (4) only antipsychotic treatments initiated after admission to the Department of Child Psychiatry were analyzed **Exclusion criteria:** NR	**Enrolled:** 109 **Analyzed:** NR **Completed:** 52 **GROUP 1** **N:** 24 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 85 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 6 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Typical (Haloperidol, Perphenazine, Sulpiride) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** Haloperidol 6.8±1.1, Perphenazine 12±6.9, Sulpiride 450±409.3 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Atypical (Clozapine, Olanzapine, Risperidone, Ziprasidone) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** Clozapine 247.5±118, Olanzapine 15±6.1, Risperidone 2.7±1.3, Ziprasidone 80±0 **Concurrent treatments:** NR	**Symptomatology (KQ1):** NR **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** Weight changes **Subpopulations (KQ4):** NR	Weight gain did not differ between the groups on typical and atypical antipsychotics.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Jefferson et al., 1998 **Country:** USA **Condition category:** Multiple categories (bipolar, DBD, PDD, schizophrenia-related) **Questions:** KQ2 **Funding:** NR **Newcastle-Ottawa Scale:** 4 stars	**Recruitment dates:** 1997 **Study design:** Retrospective cohort **Setting:** Inpatient **Diagnostic criteria:** NR **Inclusion criteria:** NR **Exclusion criteria:** NR	**Enrolled:** 20 **Analyzed:** NR **Completed:** NR **GROUP 1** **N:** 2 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 17 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 3** **N:** 1 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 3 mo **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** psychotropics **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 7.5 (5–10) **Concurrent treatments:** all groups: antidepressants (1), clonidine (1), mood stabilizers (6), psychostimulants (1) **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2.8 (1–7) **Concurrent treatments:** see group 1 **GROUP 3** **Drug name:** Olanzapine + Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** see group 1	**Symptomatology (KQ1):** NR **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** Blood pressure, EPS, hepatic enzyme, sedation, tardive dyskinesia **Subpopulations (KQ4):** NR	Risperidone and olanzapine were well tolerated at relatively low doses and in combination with other psychotropic agents.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Jensen et al., 2008 **Country:** USA **Condition category:** Schizophrenia and related **Questions:** KQ1, KQ2, KQ3 **Funding:** NR **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** May 2003 to June 2006 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, K-SADS **Inclusion criteria:** (1) 10–18 yr, (2) schizophrenia/ schizoaffective disorder, schizophreniform, or psychotic disorder NOS, (3) ≥1 positive or negative symptom associated with schizophrenia present throughout the past 2 wk (PANSS) **Exclusion criteria:** (1) MR or affective disorder with psychotic features, (2) current alcohol or drug dependence or abuse, (3) history of serious adverse reactions or nonresponse to an adequate trial of any of the proposed treatments, (4) pregnant or refusal to practice	**Enrolled:** 30 **Analyzed:** 29 **Completed:** 21 **GROUP 1** **N:** 10 **Age, mean±SD (range):** 15.3±1.5 **Males %:** 50 **Caucasian %:** 50 **Diagnostic breakdown (n):** psychotic disorder NOS (6), schizophrenia, schizoaffective, schizophreniform disorder (4) **Treatment naïve (n):** NR **Inpatients (n):** 9 **First episode psychosis (n):** NR **Comorbidities:** MR (0), psychosis (all) **GROUP 2** **N:** 10 **Age, mean±SD (range):** 14.8±2.3 **Males %:** 70 **Caucasian %:** 60 **Diagnostic breakdown (n):** psychotic disorder NOS (3), schizophrenia, schizoaffective, schizophreniform disorder (7) **Treatment naïve (n):** NR **Inpatients (n):** 9 **First episode psychosis (n):** NR	**Treatment duration:** 2.8 mo **Run-in phase:** Yes **Run-in phase duration:** 2 wk **Permitted drugs:** diphenhydramine (≤100 mg/day), lorazepam (0.5–2 mg/day) **Prohibited drugs:** antidepressants, mood stabilizers, and stimulants (discontinued prior to or within first 2 wk of trial) **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** 20 **Daily dose (mg/day), mean±SD (range):** 14±4.6 (5–20) **Concurrent treatments:** anticholinergics (0), dietary counselling, psychoeducation **GROUP 2** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** 800 **Daily dose (mg/day), mean±SD (range):** 611±253.4 (100–800) **Concurrent treatments:** anticholinergics (0), dietary counselling, psychoeducation **GROUP 3** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** 6 **Daily dose (mg/day), mean±SD**	**Symptomatology (KQ1):** CGAS, CGI-S **Other ST and LT outcomes (KQ3):** Medication adherence, response **AE (KQ2):** Akathisia, behavioral issues, dyskinesia, EPS, mastitis, sedation, WAE, weight change **Subpopulations (KQ4):** NR	There was no statistically significant difference between groups in the reduction of PANSS scores; however a larger RCT may be warranted to test the clinical significance of differences between treatment with quetiapine and risperidone.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Jensen et al., 2008 (continued)	contraception, (5) serious and unstable medical condition	**Comorbidities:** MR (0), psychosis (all) **GROUP 3** **N:** 10 **Age, mean±SD (range):** 15.6±2.5 **Males %:** 80 **Caucasian %:** 70 **Diagnostic breakdown (n):** psychotic disorder NOS (0), schizophrenia, schizoaffective, schizophreniform disorder (10) **Treatment naïve (n):** NR **Inpatients (n):** 9 **First episode psychosis (n):** NR **Comorbidities:** MR (0), psychosis (all)	**(range):** 3.4±1.5 (1–6) **Concurrent treatments:** anticholinergics (0), dietary counselling, psychoeducation,		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Khan et al., 2006 **Country:** USA **Condition category:** Behavioral issues (agitation, aggression) **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** NR **Newcastle-Ottawa Scale:** 4 stars	**Recruitment dates:** Jan 2003 to Jan 2005 **Study design:** Retrospective cohort **Setting:** Inpatient **Diagnostic criteria:** NR **Inclusion criteria:** (1) <18 yr, (2) hospitalized with any mental illness, (3) treatment with IM ziprasidone or olanzapine for acute agitation/agression, (4) hospitalized during study period **Exclusion criteria:** (1) >18 yr, (2) moderate, severe or profound MR, (3) patients who did not receive IM ziprasidone/ olanzapine for agitation or agression during their inpatient stay, (4) patients receiving both IM ziprasidone and olanzapine	**Enrolled:** 100 **Analyzed:** 100 **Completed:** 100 **GROUP 1** **N:** 50 **Age, mean±SD (range):** 13.7±2.4 **Males %:** 68 **Caucasian %:** 60 **Diagnostic breakdown (n):** any Axis I dx with psychosis (18) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** PTSD (18), SA (27) **GROUP 2** **N:** 50 **Age, mean±SD (range):** 14.6±2.1 **Males %:** 32 **Caucasian %:** 68 **Diagnostic breakdown (n):** any Axis I dx with psychosis (16) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see group 1	**Treatment duration:** Olanzapine 3.7 (2.4) wk, Ziprasidone 4.9 (3.4) wk (mean(SD)) **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** total 8.2±2.4, children 6±2.2, adolescents 9.20±1.8 **Concurrent treatments:** antipsychotic other than ziprasidone (41); aripiprazole, quetiapine most commonly prescribed **GROUP 2** **Drug name:** Ziprasidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** total 19.1±2.7, children 15.7±4.4, adolescents 19.5±2.1 **Concurrent treatments:** antipsychotics (48) (olanzapine (13), clozapine (4)); aripiprazole, quetiapine the most commonly prescribed	**Symptomatology (KQ1):** Number of aggressive episodes **Other ST and LT outcomes (KQ3):** Health care system utilization **AE (KQ2):** Dermatologic AE, pseudoparkinsonism, sedation **Subpopulations (KQ4):** Age (dosage), Sex and age (restraints)	IM ziprasidone and IM olanzapine may be equally effective for the treatment of children and adolescents with agitation and aggression.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Kryzhanovskaya et al., 2009 **Country:** Russia, USA **Condition category:** Schizophrenia and related **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Nov 2002 to Apr 2005 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV-TR, K-SADS **Inclusion criteria:** (1) 13–17 yr, (2) schizophrenia (paranoid, disorganized, catatonic, undifferentiated, and residual types), (3) able to perform all protocol–required examinations, (4) total score ≥35 on the anchored version of the BPRS-C16 and a score ≥3 on at least one of the following BPRS-C items at enrolment and randomization: hallucinations, delusions, or peculiar fantasies, (5) previously treated with clozapine and other atypical antipsychotics **Exclusion criteria:** (1) previous participation in a clinical trial of oral olanzapine, (2)	**Enrolled:** 107 **Analyzed:** 107 **Completed:** 64 **GROUP 1** **N:** 72 **Age, mean±SD (range):** 16.1±1.3 (13–18) **Males %:** 70.8 **Caucasian %:** 72.2 **Treatment naïve (n):** 21 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (0), SA (0) **GROUP 2** **N:** 35 **Age, mean±SD (range):** 16.3±1.6 (13.1–18) **Males %:** 68.6 **Caucasian %:** 71.4 **Treatment naïve (n):** 5 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (0), SA (0)	**Treatment duration:** 6 wk (6 mo extension) **Run-in phase:** Yes **Run-in phase duration:** 2–14 day **Permitted drugs:** anticholinergics (2–6mg/day), benzodiazepines (2 mg/day lorazepam equivalents for ≤3 consecutive days) **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 11.1 (2.5–20) **Concurrent treatments:** anticholinergics (3), benzodiazepines (21) **GROUP 2** **Drug name:** Placebo **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** anticholinergics (2), benzodiazepines (18)	**Symptomatology (KQ1):** BPRS-C, PANSS, CGI-I, CGI-S, OAS **Other ST and LT outcomes (KQ3):** Medication adherence, response, suicide **AE (KQ2):** BMI, ECG changes, glucose, hepatic enzyme, lipid profile, mortality, prolactin, sedation, schizophrenia, somnolence, WAE, weight change **Subpopulations (KQ4):** Country (response)	Adolescents with schizophrenia experienced significant symptom improvement when treated with olanzapine compared to placebo.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Kryzhanovskaya et al., 2009 (continued)	treatment within 30 day of the trial with a drug without regulatory approval for any indication, (3) documented olanzapine allergic reaction, (4) previous nonresponse to an adequate dose/duration of olanzapine treatment, (5) potential safety concerns, (6) pregnancy, nursing, or refusal to practice acceptable contraception, (7) acute/unstable medical conditions, (8) current/expected use of any concomitant psychotropic medications (except for permitted drugs), (9) baseline prolactin ≥200 ng/mL, (10) clinically significant laboratory abnormalities, (11) DSM-IV-TR substance dependence within 30 day (except nicotine and caffeine) (12) current DSM-IV-TR dx of a comorbid psychiatric or developmental disorder				

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Kumra et al., 2008 **Country:** USA **Condition category:** Schizophrenia and related **Questions:** KQ1, KQ2, KQ3 **Funding:** NR **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Sep 2001 to Mar 2006 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, K-SADS-PL, structured interview **Inclusion criteria:** (1) 10–18 yr, (2) schizophrenia or schizoaffective disorder, (3) treatment refractoriness (documented treatment failure of ≥2 prior adequate antipsychotic trials and a baseline BRPS total score ≥35 and at least moderate on one or more psychotic items on the BRPS) **Exclusion criteria:** (1) premorbid dx of MR, (2) history of serious adverse reactions to the proposed treatments, (3) pregnant, (4) serious and unstable medical condition, (5) failed an adequate trial of clozapine (≥12 wk) at adequate doses (≥300mg/day) and/or failed an adequate trial of olanzapine (≥8wk) at high doses (≥20mg/day)	**Enrolled:** 40 **Analyzed:** 39 **Completed:** 28 **GROUP 1** **N:** 19 **Age, mean±SD (range):** 15.8±2.2 **Males %:** 44.4 **Caucasian %:** 11.1 **Diagnostic breakdown (n):** schizoaffective disorder (7), schizophrenia (11) **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** 0 **Comorbidities:** MR (0) **GROUP 2** **N:** 21 **Age, mean±SD (range):** 15.5±2.1 **Males %:** 61.9 **Caucasian %:** 28.6 **Diagnostic breakdown (n):** schizoaffective disorder (7), schizophrenia (14) **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** 0 **Comorbidities:** MR (0)	**Treatment duration:** 2.8 mo (2.8 mo extension) **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** current medications tapered as tolerated (first 4 wk of trial) **Prohibited drugs:** NR **GROUP 1** **Drug name:** Clozapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 403.1±201.8 (50–700) **Concurrent treatments:** all groups: antidepressants (4), depakoate (3), lithium (7), mood stabilizer (6), naltrexone (1), stimulant (1); group 1: n=6 **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 26.2±6.5 (10–30) **Concurrent treatments:** see group 1; group 2: n=11	**Symptomatology (KQ1):** BPRS, CGAS, CGI-I, CGI-S, SANS **Other ST and LT outcomes (KQ3):** Response **AE (KQ2):** Blood cells, BMI, constipation, diabetes, EPS, glucose, lipid profile, prolactin, SAE, WAE, weight change **Subpopulations (KQ4):** NR	A greater number of children diagnosed with schizophrenia/ schizoaffective disorder and treated with clozapine met drug response criteria than children treated with olanzapine. Clinicians should be aware of potential metabolic adverse events of long-term clozapine treatment.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Kumra et al., 1998 **Country:** USA **Condition category:** Schizophrenia and related **Questions:** KQ1, KQ2, KQ3 **Funding:** Industry **Newcastle-Ottawa Scale:** 5 stars	**Recruitment dates:** NR **Study design:** Prospective cohort **Setting:** Inpatient **Diagnostic criteria:** DSM-III-TR, K-SADS-E **Inclusion criteria:** (1) schizophrenia with psychotic symptoms documented by 12 yr (DSM-III-R), (2) failure of two prior neuroleptic treatments, (3) communication capability, (4) premorbid Full Scale IQ >70 **Exclusion criteria:** (1) any significant unstable neurological or medical disorder, (2) current serious suicidal risk, (3) active alcohol or drug abuse	**Enrolled:** 23 **Analyzed:** 23 **Completed:** 21 **GROUP 1** **N:** 15 **Age, mean±SD (range):** 13.6±1.5 **Males %:** 53.3 **Caucasian %:** NR **Diagnostic breakdown (n):** disorganized (8), paranoid (2), undifferentiated (5) **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR **GROUP 2** **N:** 8 **Age, mean±SD (range):** 15.3±2.3 **Males %:** 50 **Caucasian %:** NR **Diagnostic breakdown (n):** disorganized (3), paranoid (1), undifferentiated (4) **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR	**Treatment duration:** Clozapine 6 wk, Olanzapine 8 wk **Run-in phase:** Yes **Run-in phase duration:** 17.5 day (mean) **Permitted drugs:** benzodiazepines (<8 mg/day) **Prohibited drugs:** NR **GROUP 1** **Drug name:** Clozapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 317±147 (100–600) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 17.5±2.3 (12.5–20) **Concurrent treatments:** benzodiazepines (7), lithium (1)	**Symptomatology (KQ1):** BPRS, SANS, SAPS **Other ST and LT outcomes (KQ3):** Response **AE (KQ2):** Behavioral issues, blood cells, constipation, EPS, liver function, seizure, somnolence, tachycardia, weight change **Subpopulations (KQ4):** NR	Preliminary data suggested clozapine and olanzapine were efficacious in children and adolescents with treatment-refractory schizophrenia.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Kumra et al., 1996 **Country:** USA **Condition category:** Schizophrenia and related **Questions:** KQ1, KQ2, KQ3 **Funding:** NR **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient **Diagnostic criteria:** DSM-III-TR, K-SADS, DICA-R **Inclusion criteria:** (1) schizophrenia with documented psychotic symptoms by 12 yr (DSM-III-TR), (2) intolerance, nonresponse, or both to ≥2 different neuroleptic drugs, (3) full-scale IQ ≥70 **Exclusion criteria:** (1) neurologic or medical disease	**Enrolled:** 21 **Analyzed:** 21 **Completed:** 17 **GROUP 1** **N:** 11 **Age, mean±SD (range):** 13.7±1.6 **Males %:** 54.6 **Caucasian %:** NR **Diagnostic breakdown (n):** disorganized (5), paranoid (1), undifferentiated (5) **Treatment naïve (n):** NR **Inpatients (n):** 11 **First episode psychosis (n):** 0 **GROUP 2** **N:** 10 **Age, mean±SD (range):** 14.4±2.9 **Males %:** 50 **Caucasian %:** NR **Diagnostic breakdown (n):** disorganized (5), undifferentiated (5) **Treatment naïve (n):** NR **Inpatients (n):** 10 **First episode psychosis (n):** 0	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** 6 wk **Permitted drugs:** group 1: benztropine mesylate (≤6 mg/day); group 2: identical placebo; all: atenolol, antibiotics, anticonvulsants **Prohibited drugs:** NR **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 16±8 (7–27) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Clozapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 176±149 (25–525) **Concurrent treatments:** amoxicillin (1), penicillin (1)	**Symptomatology (KQ1):** BPRS-C, CGAS, CGI-I, SANS, SAPS **Other ST and LT outcomes (KQ3):** NR **AE (KQ2): B**lood cells, blood pressure, EPS (SAS, AIMS), drowsiness, hepatic enzyme, NMS, seizure, tachycardia, weight **Subpopulations (KQ4):** NR	Clozapine was more effective in controlling positive and negative symptoms in treatment-refractory childhood onset schizophrenia than haloperidol.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Luby et al., 2006 **Country:** USA **Condition category:** PDD **Questions:** KQ1, KQ2 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Nov 1999 to Nov 2002 **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) 2.5–6 yr, (2) autism or PDD-NOS (DSM-IV), (3) absence of other known significant CNS disorders, (4) absence of significant medical problems or other psychiatric disorders requiring pharmacotherapy **Exclusion criteria:** NR	**Enrolled:** 24 **Analyzed:** 23 **Completed:** NR **GROUP 1** **N:** 12 **Age, mean±SD (range):** 4.1±0.9 **Males %:** 75 **Caucasian %:** 91 **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 12 **Age, mean±SD (range):** 4±1.1 **Males %:** 66.7 **Caucasian %:** 92 **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 6 mo **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.1±0.3 (0.5–1.5) **Concurrent treatments:** applied behavior analysis (mean 21.2 hr/wk) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.4±0.6 (0.5–1.5) **Concurrent treatments:** applied behavior analysis (mean 11.3 hr/wk)	**Symptomatology (KQ1):** CARS **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** Constipation, EPS, mortality, prolactin, SAE, sedation, WAE, weight change **Subpopulations (KQ4):** NR	Risperidone was well tolerated in preschoolers, but only minimal improvement in target symptoms was evident.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Malone et al., 2001 **Country:** USA **Condition category:** PDD **Questions:** KQ1, KQ2, KQ3 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) primary dx of PDD, (2) 5–17 yr, (3) at least moderate impairment on ≥2 of the first 28 items on the CPRS **Exclusion criteria:** (1) major medical problems, (2) seizure disorder or gross neurological deficit, (3) treatment with concomitant psychotropic medication, (4) history of previous treatment with haloperidol or olanzapine	**Enrolled:** 12 **Analyzed:** 12 **Completed:** 12 **GROUP 1** **N:** 6 **Age, mean±SD (range):** 7.3±1.9 (5–10.1) **Males %:** 66.7 **Caucasian %:** 66.7 **Diagnostic breakdown (n):** autistic disorder (5), PDD NOS (1) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (mild (1), moderate (2), severe (3)) **GROUP 2** **N:** 6 **Age, mean±SD (range):** 8.5±2.4 (4.9–11.8) **Males %:** 66.7 **Caucasian %:** 50 **Diagnostic breakdown (n):** autistic disorder (all) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (mild (0), moderate (3), severe (2))	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** 1 wk **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.4±0.7 (0.5–2.5) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 7.9±2.5 (5–10) **Concurrent treatments:** NR	**Symptomatology (KQ1):** CGI-S, CPRS **Other ST and LT outcomes (KQ3):** Response (CGI-I) **AE (KQ2):** Dermatologic AE, EPS (AIMS), EPS, fatigue, tachycardia, weight changes **Subpopulations (KQ4):** NR	The use of olanzapine is promising in children with autistic disorder, although placebo-controlled and long-term studies are needed.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Marcus et al., 2009 **Country:** USA **Condition category:** PDD **Questions:** KQ1, KQ2, KQ3 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** June 2006 to Jun 2008 **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV-TR, ADI-R **Inclusion criteria:** (1) 6–17 yr, (2) DSM-IV-TR criteria for autistic disorder and behaviors such as tantrums, aggression, self–injury, or a combination, with a dx corroborated by ADI-R certified trainer, (3) CGI-S score ≥4 and ABC Irritability subscale score ≥18 at screening and baseline, (4) ≥15 kg, (5) stable nonpharmacologic therapy **Exclusion criteria:** (1) bipolar disorder, psychosis, schizophrenia, major depression, fragile X syndrome, or another ASD, (2) history of NMS, (3) significant risk of committing suicide, (4)	**Enrolled:** 218 **Analyzed:** 213 **Completed:** 178 **GROUP 1** **N:** 53 **Age, mean±SD (range):** 9.0±2.8 **Males %:** 88.7 **Caucasian %:** 69.8 **Treatment naïve (n):** 43 **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 59 **Age, mean±SD (range):** 10±3.2 **Males %:** 84.7 **Caucasian %:** 69.5 **Treatment naïve (n):** 45 **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 3** **N:** 54 **Age, mean±SD (range):** 9.5±3.1 **Males %:** 92.6 **Caucasian %:** 77.8 **Treatment naïve (n):** 44 **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 4**	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** ≤6 wk **Permitted drugs:** anxiolytics, benztropine or propranolol, diphenhydramine (≤50 mg/day), psychotropic medication, sleep aids **Prohibited drugs:** antidepressants, antipsychotics, anxiolytics, mood stabilizers, neuroleptics, psychostimulants (washout ≥4 day) **GROUP 1** **Drug name:** Aripiprazole (low) **Dosing variability:** fixed **Target dose (mg/day):** 5 **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** analgesics and antipyretics (12), anxiolytics (2), benztropine (2), hypnotics and sedatives (2), propranolol (2) **GROUP 2** **Drug name:** Aripiprazole (medium) **Dosing variability:** fixed **Target dose (mg/day):** 10 **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** analgesics and antipyretics (12), anxiolytics (1), benztropine (1), hypnotics and sedatives (1) **GROUP 3** **Drug name:** Aripiprazole (high)	**Symptomatology (KQ1):** ABC, CYBOCS, CGI-I, CGI-S **Other ST and LT outcomes (KQ3):** medication adherence, response (ABC-I, CGI-I), suicide **AE (KQ2):** Akathisia, BMI, dermatologic AE, ECG changes, EPS, EPS (AIMS, Barnes, SAS), fatigue, glucose, lipid profile, mortality, prolactin, SAE, sedation, seizure/convulsion, somnolence, total AE, WAE, weight change **Subpopulations (KQ4):** NR	Aripiprazole was efficacious, safe, and well tolerated in children and adolescents with irritability assocated with autistic disorder.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Marcus et al., 2009 (continued)	seizure in the past yr, (5) history of severe head trauma or stroke, (6) history or current evidence of any unstable medical condition or or an abnormal laboratory test result considered clinically significant, (7) antipsychotic treatment resistant, (8) known allergy or hypersensitivity to aripiprazole	**N:** 52 **Age, mean±SD (range):** 10.2±3.1 **Males %:** 92.3 **Caucasian %:** 67.3 **Treatment naïve (n):** 40 **Inpatients (n):** NR **First episode psychosis (n):** NR	**Dosing variability:** fixed **Target dose (mg/day):** 15 **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** analgesics and antipyretics (12), anxiolytics (1), benzotropine (5), hypnotics and sedatives (1) **GROUP 4** **Drug name:** Placebo **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** analgesics and antipyretics (9), anxiolytics (3), hypnotics and sedatives (2), propranolol (1)		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
McCracken et al., 2002 **Country:** USA **Condition category:** PDD **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Industry, Government, Foundation **Risk of bias:** Unclear (subjective), Unclear (objective)	**Recruitment dates:** Jun 1999 to Apr 2001 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, ADI-R **Inclusion criteria:** (1) ASD (DSM-IV), (2) 5–17 yr, (3) weight ≥15 kg, (4) score ≥18 on the Irritability subscale of the ABC at baseline, (5) free of serious medical disorders and of other psychiatric disorders requiring medication, (6) medication free for at least 2 wk for all psychotropic medications (4 wk for fluoxetine or depot neuroleptics), (7) anticonvulsants used for the treatment of a seizure disorder were permitted if the dosage had been stable for 4 wk and the patient had been seizure free for ≥6 mo, (8) CGI-S score ≥ 4 at baseline, (9) mental age ≥18 mo as	**Enrolled:** 101 **Analyzed:** 101 **Completed:** 80 **GROUP 1** **N:** 49 **Age, mean±SD (range):** NR **Males %:** 80 **Caucasian %:** NR **Treatment naïve (n):** 45 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (average/above average IQ (3), borderline IQ (8), mild/ moderate retardation (20), severe retardation (15)) **GROUP 2** **N:** 52 **Age, mean±SD (range):** NR **Males %:** 83 **Caucasian %:** NR **Treatment naïve (n):** 51 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (average/above average IQ (2), borderline IQ (4), mild/ moderate retardation (23), severe retardation (16))	**Treatment duration:** 8 wk (4 mo extension for risperidone responders; 8 wk extension for placebo nonresponders) **Run-in phase:** Yes **Run-in phase duration:** 1–4 wk **Permitted drugs:** anticonvulsants (constant dose ≥4 wk and seizure-free for ≥6 mo), benztropine **Prohibited drugs:** antihistamines, ceterazine, erythromycin, metoclopromide, pseudoephedrine, and any drug that may impact risperidone concentrations or lead to drug interactions; psychotropics **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.8±0.7 (0.5–3.5) **Concurrent treatments:** anticonvulsants (2) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2.4±0.6 (0.5–3.5) **Concurrent treatments:** anticonvulsants (2)	**Symptomatology (KQ1):** ABC, CYBOCS, CGI-I, RFRLRS, VAS **Other ST and LT outcomes (KQ3):** Cognitive, medication adherence, patient, parent/care provider reported outcomes (diet/intake, sleep), response **AE (KQ2):** Behavioral issues, blood cells, BMI, constipation, dyskinesia, dermatologic AE, ECG changes, EPS, fatigue, liver function, prolactin, prolactin-related AE, SAE, seizure, tachycardia, WAE, weight change **Subpopulations (KQ4):** Age, IQ, baseline ABC irritability (relapse, weight); Dose, Sex, site, Tanner stage, Child Symptom Inventory, CY-BOCS, heart rate,	Risperidone was effective and well tolerated for the treatment of tantrums, aggression, or self-injurious behavior in children with autistic disorder. Discontinuation, after 6 month of treatment, was associated with rapid return of disruptive and aggressive behavior in most subjects.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
McCracken et al., 2002 (continued)	measured by the age-appropriate form of the IQ test, (10) inpatients or outpatients **Exclusion criteria:** (1) receiving a psychotropic drug that was deemed effective for the treatment of aggression, tantrums, or self-injurious behavior, (2) positive β-HCG pregnancy test, (3) evidence of a prior adequate trial with risperidone, (4) evidence of hypersensitivity to risperidone, (5) past history of NMS, (6) DSM-IV dx of schizophrenia, another psychotic disorder, or substance abuse, (7) significant medical condition, (8) weight <15 kg			BP, weight, initial leptin change (weight); age, baseline BMI, caloric intake (BMI)	

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Miral et al., 2008 **Country:** Turkey **Condition category:** PDD **Questions:** KQ1, KQ2 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) 8–18 yr, (2) parental informed consent, (3) agree to followup **Exclusion criteria:** (1) epilepsy, (2) concomitant neuropsychiatric illness, (3) psychotic disorder or symptoms, (4) other PDDs	**Enrolled:** 30 **Analyzed:** 28 **Completed:** 28 **GROUP 1** **N:** 15 **Age, mean±SD (range):** 10.9±2.9 (7–17) **Males %:** 86.7 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (0), psychosis (0) **GROUP 2** **N:** 15 **Age, mean±SD (range):** 10±2.7 (7–17) **Males %:** 73.3 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (0), psychosis (0)	**Treatment duration:** 2.8 mo (2.8 mo extension) **Run-in phase:** Yes **Run-in phase duration:** 1–2 wk **Permitted drugs:** antianalgesics, antibiotics, anticholinergics, antipyretics, decongestants **Prohibited drugs:** benzodiazepines/other sedatives **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** variable **Target dose (mg/day):** 0.08 mg/kg/day **Daily dose (mg/day), mean±SD (range):** 2.6±1.3 (1–5.7) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** 0.08 mg/kg/day **Daily dose (mg/day), mean±SD (range):** 2.6±0.8 (1.2–4.0) **Concurrent treatments:** NR	**Symptomatology (KQ1):** ABC, CGI, RFRLRS **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** Blood pressure, constipation, EPS (ESRS), height, parkinsonism/ dystonia/ dyskinesia (ESRS), prolactin-related AE, SAE, weight **Subpopulations (KQ4):** NR	Risperidone was more effective than haloperidol, showing improvements in behavioral symptoms and social skills.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Migliardi et al., 2009 **Country:** Italy **Condition category:** Multiple categories (PDD, DBD, Schizophrenia, bipolar, OCD, tic disorder) **Questions:** KQ2, KQ4 **Funding:** NR **Risk of bias:** 7 stars	**Recruitment dates:** NR **Study design:** Retrospective cohort **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) children and adolescents seen at the Division of Child and Neurology at the University of Messina, Italy, (2) not previously treated with antipsychotics for various psychiatric disorders, (3) completed at least 12 months of treatment on only one antipsychotic and no co-medication **Exclusion criteria:** NR	**Enrolled:** 42 **Analyzed:** 41 **Completed:** 42 **GROUP 1** **N:** 13 **Age, mean±SD (range):** 14.1 **Males %:** 53.8 **Caucasian %:** NR **Treatment naïve (n):** all **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 2** **N:** 29 **Age, mean±SD (range):** 10.7 **Males %:** 78.6 **Caucasian %:** NR **Treatment naïve (n):** all **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** NR	**Treatment duration:** 12 mo. **Run–in phase:** No **Run–in phase duration:** NA **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 8.1 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.8 **Concurrent treatments:** NR	**Symptomatology (KQ1):** NR **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** prolactin-related AE, prolactin **Subpopulations (KQ4):** Sex (prolactin)	After adjusting for dose and greater potency of risperidone, the increase in prolactin levels during risperidone treatment was 10.3 times higher than during olanzapine treatment.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Mozes et al., 2006 **Country:** Israel **Condition category:** Schizophrenia and related **Questions:** KQ1, KQ2, KQ3 **Funding:** No funding **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient **Diagnostic criteria:** DSM-IV, K-SADS **Inclusion criteria:** (1) hospitalized childhood-onset schizophrenic children **Exclusion criteria:** (1) MR	**Enrolled:** 25 **Analyzed:** 25 **Completed:** 20 **GROUP 1** **N:** 12 **Age, mean±SD (range):** 11.5±1.6 (8.5–14) **Males %:** 41.7 **Caucasian %:** NR **Diagnostic breakdown (n):** disorganized schizophrenia (3), paranoid schizophrenia (2), schizophreniform disorder (6), unspecified schizoprehenia (1) **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR **Comorbidities:** ADHD (2), familial mediterranean fever (1), MR (0), tic disorder (1) **GROUP 2** **N:** 13 **Age, mean±SD (range):** 10.7±1.4 (8.8–13.3) **Males %:** 38.5 **Caucasian %:** NR **Diagnostic breakdown (n):** disorganized schizophrenia (4), paranoid schizophrenia (4), schizophreniform disorder (4), unspecified schizoprehenia (1) **Treatment naïve (n):** NR **Inpatients (n):** all	**Treatment duration:** 2.8 mo **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** biperiden, prior nonantipsychotics (continued for 2–12 wk) **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 8.2±4.4 (2.5–20) **Concurrent treatments:** biperiden (2), carbamazepine (2), citalopram (1), colchicine (1), methylphenidate (2), promethizine (2), valproic acid (1) **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.6±1 (0.3–4.5) **Concurrent treatments:** biperiden (4), citalopram (2), fluoxetine (1), phenytoin (1), promethizine (1), valproic acid (1)	**Symptomatology (KQ1):** BPRS, CGAS, PANSS **Other ST and LT outcomes (KQ3):** Response **AE (KQ2):** Akathisia, prolactin, WAE, weight change **Subpopulations (KQ4):** NR	Risperidone and olanzapine were efficacious and well tolerated in pediatric inpatients with child-onset schizophrenia.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Mozes et al., 2006 (continued)		**First episode psychosis (n):** NR **Comorbidities:** ADHD (1), epilepsy (2), MR (0), neurofibromatosis (1), OCD (3)			

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Nagaraj et al., 2006 **Country:** India **Condition category:** PDD **Questions:** KQ1, KQ2, KQ3 **Funding:** Industry, Academic **Risk of bias:** Unclear (subjective), Unclear (objective)	**Recruitment dates:** Jan 2002 to Dec 2003 **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) ≤12 yr, (2) autism (DSM-IV) **Exclusion criteria:** (1) severe MR, (2) any significant coexisting disease or illness, (3) severe malnutrition	**Enrolled:** 40 **Analyzed:** 39 **Completed:** 39 **GROUP 1** **N:** 19 **Age, mean±SD (range):** 4.8±1.7 **Males %:** 84.2 **Caucasian %:** NR **Treatment naïve (n):** 15 **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** aggression (9), irritability (17), seizures (5), self-injurious behavior (7) **GROUP 2** **N:** 21 **Age, mean±SD (range):** 5.3±1.7 **Males %:** 90 **Caucasian %:** NR **Treatment naïve (n):** 16 **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** aggression (11), irritability (19), seizures (3), self-injurious behavior (5)	**Treatment duration:** 6 mo **Run-in phase:** Yes **Run-in phase duration:** ≥1 mo **Permitted drugs:** antiepileptics **Prohibited drugs:** no other drugs permitted **GROUP 1** **Drug name:** Risperidone **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1 (0.5–1) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1 (0.5–1) **Concurrent treatments:** NR	**Symptomatology (KQ1):** CARS, CGAS **Other ST and LT outcomes (KQ3):** Response (CARS, CGAS, Global Impression of Parents) **AE (KQ2):** Dyskinesia, sedation, weight change **Subpopulations (KQ4):** NR	Risperidone improved global functioning and social responsiveness, reduced hyperactivity and aggression, and was well tolerated in children with autism.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
NCT00090324, 2008 **Country:** ND **Condition category:** Schizophrenia and related **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Oct 2004 to June 2007 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, K-SADS-PL **Inclusion criteria:** (1) inpatients and outpatients, (2) 13–17 yr, (3) schizophrenia (DSM-IV, confirmed by K-SADS-PL), (4) PANSS total score ≥60 and a score ≥4 on delusions, conceptual disorganization, or hallucinations **Exclusion criteria:** NR	**Enrolled:** 222 **Analyzed:** 222 **Completed:** 222 **GROUP 1** **N:** 73 **Age, mean±SD (range):** 15.5±1.3 (13–17) **Males %:** 58.9 **Caucasian %:** 61.6 **Diagnostic breakdown (n):** disorganized (6), paranoid (53), residual (0), undifferentiated (14) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 74 **Age, mean±SD (range):** 15.5±1.3 (13–17) **Males %:** 59.5 **Caucasian %:** 59.5 **Diagnostic breakdown (n):** disorganized (5), paranoid (50), residual (1), undifferentiated (18) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 3** **N:** 75 **Age, mean±SD (range):** 15.3±1.4 (13–17)	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** 1 day–4 wk **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Quetiapine (low) **Dosing variability:** variable **Target dose (mg/day):** 400 **Daily dose (mg/day), mean±SD (range):** 400 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Quetiapine (high) **Dosing variability:** variable **Target dose (mg/day):** 800 **Daily dose (mg/day), mean±SD (range):** 800 **Concurrent treatments:** NR **GROUP 3** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Symptomatology (KQ1):** CGAS, CGI-I, CGI-S, PANSS **Other ST and LT outcomes (KQ3):** Care provider reported outcome (Caregiver Strain Questionnaire), response **AE (KQ2):** Behavioral issues, ECG changes, EPS, fatigue, lipid profile, mortality, prolactin, pulse, SAE, sedation, somnolence, tachycardia, thyroid function, total AE, WAE, weight change **Subpopulations (KQ4):** Geographical region (AE)	ND

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
NCT00090324, 2008 (continued)		**Males %:** 57.5 **Caucasian %:** 63 **Diagnostic breakdown (n):** disorganized (5), paranoid (52), residual (0), undifferentiated (16) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR			

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
NCT00257166, 2008 **Country:** Canada, USA **Condition category:** Bipolar **Questions:** KQ1, KQ2, KQ3 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Jan 2006 to Jul 2007 **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-IV, K-SADS **Inclusion criteria:** (1) 10–17 yr, (2) primary dx of bipolar I disorder (DSM-IV, confirmed by K-SADS), (3) current symptoms present for ≥7 day prior to screening, (4) YMRS score >17 at screening and baseline visits, (5) BMI Z-score 1.65–2.00, inclusive **Exclusion criteria:** NR	**Enrolled:** 238 **Analyzed:** 237 **Completed:** NR **GROUP 1** **N:** 149 **Age, mean±SD (range):** 13.6 **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 88 **Age, mean±SD (range):** 13.7 **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 4 wk **Run-in phase:** Yes **Run-in phase duration:** 1–10 day **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Ziprasidone **Dosing variability:** variable **Target dose (mg/day):** 60–80 (<45 kg), 120–160 (>45 kg) **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** 60–80 (<45 kg), 120–160 (>45 kg) **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Symptomatology (KQ1):** YMRS **Other ST and LT outcomes (KQ3):** Cognetive (Speed of processing score), suicide **AE (KQ2):** Behavioral issues, dystonia, ECG changes, fatigue, liver function, mortality, SAE, sedation, somnolence, total AE, WAE, weight change **Subpopulations (KQ4):** NR	Oral ziprasidone was shown to be effective in the treatment of children and adolescents with bipolar I disorder (manic or mixed) compared to placebo.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
NCT00257192, 2010 **Country:** Canada, Columbia, Costa Rica, Germany, India, Malaysia, Mexico, Peru, Russia, Singapore, Sweden, Ukraine, USA **Condition category:** Schizophrenia and related **Questions:** KQ1, KQ2, KQ3 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Apr 2006 to Mar 2009 (terminated prematurely) **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-IV, KID-SCID **Inclusion criteria:** (1) 13–17 yr, (2) schizophrenia (DSM-IV, confirmed by KID-SCID), (3) current symptoms present for ≥7 days prior to screening, (4) first episode psychosis allowed, (5) BPRS Anchored score ≥35 and a score ≥4 on ≥1 of the following items: unusual thought content, hallucinations, suspiciousness, or conceptual disorganization at screening and baseline visits, (6) BMI Z-score 1.65–2.00, inclusive **Exclusion criteria:** NR	**Enrolled:** 284 **Analyzed:** 283 **Completed:** NR **GROUP 1** **N:** NR **Age, mean±SD (range):** 15.3 **Males %:** NR **Caucasian %:** NR **Diagnostic breakdown (n):** paranoid type (127) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** NR **Age, mean±SD (range):** 15.4 **Males %:** NR **Caucasian %:** NR **Diagnostic breakdown (n):** paranoid type (57) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** 1–10 day **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Ziprasidone **Dosing variability:** variable **Target dose (mg/day):** 60–80 (<45 kg), 120–160 (≥45 kg) **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** 60–80 (<45 kg), 120–160 (≥45 kg) **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Symptomatology (KQ1):** BPRS-A **Other ST and LT outcomes (KQ3):** Health related quality of life (Child Health Questionnaire), suicide **AE (KQ2):** Akathisia, behavioral issues, dermatologic AE, ECG changes, fatigue, EPS, liver function, mortality, SAE, somnolence, total AE, WAE, weight change **Subpopulations (KQ4):** NR	Oral ziprasidone failed to demonstrate superiority over placebo in adolescents with schizophrenia.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
NCT00090311, 2008 **Country:** USA **Condition category:** Bipolar **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Aug 2004 to Jul 2006 **Study design:** RCT (parallel) **Setting:** Inpatient/outpatient **Diagnostic criteria:** DSM-IV, KID-SCAD-PL **Inclusion criteria:** (1) Male and female inpatients and outpatients, (2) aged 10 to 17 years, (3) DSM-IV diagnosis of Bipolar I mania as confirmed by K-SADS-PL, (4) YMRS total score of ≥20 at both screening and randomization **Exclusion criteria:** NR	**Enrolled:** 284 **Analyzed:** 277 **Completed:** NR **GROUP 1** **N:** 93 **Age, mean±SD (range):** 13.1±2.2 **Males %:** 50.5 **Caucasian %:** 78.5 **Diagnostic breakdown (n):** manic (92), mixed (1) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 95 **Age, mean±SD (range):** 13.2±2.2 **Males %:** 57.9 **Caucasian %:** 76.8 **Diagnostic breakdown (n):** manic (91), mixed (4) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 3** **N:** 89 **Age, mean±SD (range):** 13.3±2.1 **Males %:** 60.7 **Caucasian %:** 74.2 **Diagnostic breakdown (n):** manic (all)	**Treatment duration:** 3 wk **Run–in phase:** Yes **Run–in phase duration:** 1–28 day **Permitted drugs:** Psychostimulants **Prohibited drugs:** NR **GROUP 1** **Drug name:** Quetiapine **Dosing variability:** fixed **Target dose (mg/day):** 400 **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 2** **Drug name:** Quetiapine **Dosing variability:** fixed **Target dose (mg/day):** 600 **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 3** **Drug name:** Placebo **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Symptomatology (KQ1):** CGAS, CGI-BP, YMRS **Other ST and LT outcomes (KQ3):** Response, remission, suicidal ideation, CGSQ **AE (KQ2):** total AE, SAE, WAE, mortality, weight gain, weight, diabetes-related AEs, glucose metabolism measures, lipid values, liver function, thyroid function, somnolence, sedation, tachycardia, pulse, heart rate, neutropenia, prolactin, elevated prolactin, behavior SE **Subpopulations (KQ4):** Age, cotreatment (AEs)	Quetiapine 400 mg and 600 mg were superior to placebo in improving a broad range of mania symptoms in children and adolescents.

NCT00090311, 2008 (continued)	**Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
NCT00796081, 2007 **Country:** NR **Condition category:** Schizophrenia and related **Questions:** KQ2 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Mar to Aug 2006 **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-IV-TR **Inclusion criteria:** (1) male or female, (2) aged 10 to 17 years, (3) height and weight within the 5th to 95th percentile for age and sex, (4) DSM-IV-TR diagnosis of schizophrenia of any subtype, schizoaffective or schizophreniform (3) otherwise healthy, (4) CGI-S score of =< 3 **Exclusion criteria:** NR	**Enrolled:** 25 **Analyzed:** 25 **Completed:** 24 **GROUP 1** **N:** 8 **Age, mean±SD (range):** all groups: 14.6±2.2 (10–17) **Males %:** all groups: 72 **Caucasian %:** all groups: 56 **Diagnostic breakdown (n):** all groups: schizophreniform disorder (8), schizoaffective disorder (7), paranoid (6), undifferentiated (3), disorganized (1) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 9 **Age, mean±SD (range):** see group 1 **Males %:** see group 1 **Caucasian %:** see group 1 **Diagnostic breakdown (n):** see group 1 **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 3** **N:** 8 **Age, mean±SD (range):** see group 1	**Treatment duration:** 7 days **Run–in phase:** Yes **Run–in phase duration:** 21 days maximum **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Paliperidone **Dosing variability:** fixed **Target dose (mg/day):** 0.086 mg/kg/day **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 2** **Drug name:** Paliperidone **Dosing variability:** fixed **Target dose (mg/day):** 0.129 mg/kg/day **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 3** **Drug name:** Paliperidone **Dosing variability:** fixed **Target dose (mg/day):** 0.171 mg/kg/day **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Symptomatology (KQ1):** NR **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** total AE, WAE, mortality, prolactin, prolactin-related AE, orthostatic hypotension, ECG changes **Subpopulations (KQ4):** NR	Pediatric subjects tolerated doses from 4 to 12 mg paliperidone ER (corresponding to weight-adjusted doses ranging from 0.086 and 0.171 mg/kg).

NCT00796081, 2007 (continued)	**Males %:** see group 1 **Caucasian %:** see group 1 **Diagnostic breakdown (n):** see group 1 **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
NCT00576732, 2010 **Country:** USA **Condition category:** PDD **Questions:** KQ1, KQ2 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Mar to Aug 2006 **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-IV-TR, ADI-R **Inclusion criteria:** (1) Male or female 5–17 years old, (2) Body weight of >20 kg (3) DSM-IV diagnosis of Autistic Disorder (299.00), corroborated by standard cut-off scores on the ADI-R, ABC-I Subscale score of 18 or more, CGI-S of >4, (4) mental age >18 months, (5) good physical health, (6) no history of prior or current DSM-IV psychotic disorders, (7) no history of PDD-NOS, (8) no history of Asperger's or Retts, (9) no neurologic disorders, (10) no history of existing moderate or severe EPS or tardive dyskinesia **Exclusion criteria:** NR	**Enrolled:** 96 **Analyzed:** 96 **Completed:** 77 **GROUP 1** **N:** 30 **Age, mean±SD (range):** NR **Males %:** all groups: 88 **Caucasian %:** 70 **Diagnostic breakdown (n):** autistic disorder (all) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 31 **Age, mean±SD (range):** NR **Males %:** see group 1 **Caucasian %:** 81 **Diagnostic breakdown (n):** autistic disorder (all) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 3** **N:** 35 **Age, mean±SD (range):** NR **Males %:** see group 1 **Caucasian %:** 57 **Diagnostic breakdown (n):** autistic disorder (all) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis:**NR	**Treatment duration:** 6 wk **Run–in phase:** No **Run–in phase duration:** NR **Permitted drugs:** Antihistamines, anti-inflammatory drugs, antibacterials, analgesics, and psycholeptics **Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone **Dosing variability:** fixed **Target dose (mg/day):** 0.125 (<45 kg), 0.175 (≥45kg) **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** methylphenidate (1) **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** 1.25 (<45 kg), 1.75 (≥45kg) **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** methylphenidate (1) **GROUP 3** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** methylphen-idate (1), alprazolam (1), melatonin (2)	**Symptomatology (KQ1):** ABC-I **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** Total AE, WAE, mortality, prolactin, prolactin-related AE, orthostatic hypotension, ECG changes **Subpopulations (KQ4):** NR	The risperidone high dose group was effective in the treatment of irritability and related behaviors associated with Autistic Disorder in children and adolescents. Efficacy was not demonstrated in the risperidone low dose group relative to placebo. Safety data were consistent with the known profile of risperidone.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Novaes et al., 2008 **Country:** Brazil **Condition category:** PDD **Questions:** KQ3, KQ4 **Funding:** Foundation **Newcastle-Ottawa Scale:** 6 stars	**Recruitment dates:** Jan 2001 to June 2006 **Study design:** Retrospective cohort **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) ASD, (2) behavioral disturbances (psychomotor agression or agitation) **Exclusion criteria:** NR	**Enrolled:** 26 **Analyzed:** 26 **Completed:** 26 **GROUP 1** **N:** 1 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** Aggression/Agitation (26), MR (20) **GROUP 2** **N:** 13 and 5 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** see group 1 **GROUP 3** **N:** 4 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see group 1 **GROUP 4** **N:** 3 **Age, mean±SD (range):** NR	**Treatment duration:** 17 mo (mean) **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Typical antipsychotic **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 2** **Drug name:** Risperidone/Risperidone + Typical antipsychotic **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 3** **Drug name:** Atypical antipsychotic (not risperidone) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 4** **Drug name:** Typical + atypical	**Symptomatology (KQ1):** NR **Other ST and LT outcomes (KQ3):** Response (CGI-I) **AE (KQ2):** NR **Subpopulations (KQ4):** Age, comorbidity (MR), co-treatment (non-pharmacological), duration of treatment, health-care setting (response)	SGAs appeared to reduce agitation and aggression in patients with ASD.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Novaes et al., 2008 (continued)		**Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see group 1	antipsychotic **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** one treatment (12), ≥2 treatments (7)		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Perry et al., 1989 **Country:** USA **Condition category:** PDD **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Industry, Government, Foundation **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-III-TR **Inclusion criteria:** (1) dx of infantile autism, full syndrome present, (2) only children with good response to haloperidol and requiring further drug treatment were accepted into the study **Exclusion criteria:** (1) identifiable cause for autism, (2) seizure disorder, (3) preexisting movement disorder	**Enrolled:** 70 **Analyzed:** 60 **Completed:** 52 **GROUP 1** **N:** 34 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 36 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 6 mo **Run-in phase:** Yes **Run-in phase duration:** 2 wk **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Haloperidol (continuous) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.2 (0.5–4) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Haloperidol (discontinuous) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1 (0.5–4.0) **Concurrent treatments:** NR	**Symptomatology (KQ1):** CGI-I **Other ST and LT outcomes (KQ3):** Response (CGI-I, CGI-S) **AE (KQ2):** Dyskinesia, parkinsonism, sedation **Subpopulations (KQ4):** Age, developmental quotient, baseline rating scores (CGI-I)	Haloperidol, administered on a long-term basis, effectively reduced maladaptive symptoms in austic children. Drug efficacy was not deminished by discontinuous drug administration.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Ratzoni et al., 2002 **Country:** Israel **Condition category:** Schizophrenia and related (DBD, Schizophrenia) **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Government, Foundation **Newcastle-Ottawa Scale:** 3 stars	**Recruitment dates:** Jan 2000 to Aug 2000 **Study design:** Prospective cohort **Setting:** Inpatient **Diagnostic criteria:** DSM-IV, K-SADS-PL (Hebrew version), consensus of 2 child psychiatrists **Inclusion criteria:** (1) adolescent patients who started treatment with olanzapine, risperidone, or haloperidol from Jan to Aug 2000 **Exclusion criteria:** (1) receiving other medications that cause weight gain/loss, (2) alcohol/substance abuse, (3) medical illnesses affecting body weight	**Enrolled:** 50 **Analyzed:** 50 **Completed:** 36 **GROUP 1** **N:** 8 **Age, mean±SD (range):** 17.3±1.3 (15–19) **Males %:** 62.5 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR **GROUP 2** **N:** 21 **Age, mean±SD (range):** 17±1.6 (14–19) **Males %:** 66.7 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR **GROUP 3** **N:** 21 **Age, mean±SD (range):** 17.1±2.1 (13–20.5) **Males %:** 57.1 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR	**Treatment duration:** 2.8 mo **Run-in phase:** Yes **Run-in phase duration:** 5.2 day (mean) **Permitted drugs:** anticholinergics, lorazepam **Prohibited drugs:** antipsychotics, heterocyclic antidepressants, lithium, medications that can cause weight gain/loss, SSRIs, valproic acid **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 7.6±4 (3–15) **Concurrent treatments:** biperiden (6), lorazepam (5), trihexyphenidyl (2) **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 12.7±3.1 (7.5–20) **Concurrent treatments:** biperiden (6), lorazepam (5), trihexyphenidyl (2) **GROUP 3** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 3.2±1.1 (1–5) **Concurrent treatments:** biperiden (6), lorazepam (5), trihexyphenidyl (2)	**Symptomatology (KQ1):** PANSS **Other ST and LT outcomes (KQ3):** Medication adherence **AE (KQ2):** Akathisia, behavioral issues, BMI, constipation, dermatologic AE, dystonia, EPS, fatigue, hypokinesia-akinesia, sedation, seizure, sexual desire, tachycardia, WAE, weight **Subpopulations (KQ4):** Sex, treatment history, illness duration, dose, baseline weight, parental BMI, concern about weight gain, history of diet (BMI, weight)	Adolsecents experienced greater weight gain when taking olanzapine or risperidone compared to effects reported in adults.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Reyes et al., 2006 **Country:** Belgium, Germany, Great Britain, Israel, Netherlands, Poland, South Africa, Spain **Condition category:** DBD **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Aug 2001 to Sep 2003 **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-IV, K-SADS-PL **Inclusion criteria:** (1) 5–17 yr, (2) no moderate or severe intellectual impairment (IQ ≥55), (3) CD serious enough to warrant clinical treatment, (4) score ≥24 on the conduct problem subscale of the NCBRF, (5) responsible caregiver **Exclusion criteria:** (1) schizophrenia and bipolar disorder	**Enrolled:** 335 **Analyzed:** 335 **Completed:** 162 **GROUP 1** **N:** 172 **Age, mean±SD (range):** 10.9±2.9 **Males %:** 82 **Caucasian %:** NR **Diagnostic breakdown (n):** CD (62), DBD NOS (3), ODD (107) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (117) **GROUP 2** **N:** 163 **Age, mean±SD (range):** 10.8±2.9 **Males %:** 91 **Caucasian %:** NR **Diagnostic breakdown (n):** CD (61), DBD NOS (5), ODD (97) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (110)	**Treatment duration:** 7.4 mo **Run-in phase:** Yes **Run-in phase duration:** 6 wk **Permitted drugs:** medication for EPS (only after dose reduction attempted), psychostimulants **Prohibited drugs:** anticonvulsants, antidepressants, antipsychotics, lithium **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 0.8±0.3 (<50 kg), 1.2±0.4 (≥50 kg) **Concurrent treatments:** analgesics (26), psychostimulants (36) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** analgesics (20), psychostimulants (36)	**Symptomatology (KQ1):** CGAS, CGI-I, CGI-S, NCBRF, VAS-MS **Other ST and LT outcomes (KQ3):** Cognitive (MVLT, CPT), growth (tannar stages), response (relapse, symptom recurrence) **AE (KQ2):** Akathisia, BMI, dystonia, EPS, fatigue, parkinsonism, prolactin, prolactin-related AE, SAE, somnolence, tardive dyskinesia, total AE, WAE, weight change **Subpopulations (KQ4):** Sex, age, diagnosis, disease severity (relapse); Age (AE, weight); Sex (prolactin)	Patients who responded to initial treatment with risperidone benefited from continued, long-term treatment. Risperidone was safe and well tolerated during a 1-year extension.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Robb et al., 2009 **Country:** ND **Condition category:** Schizophrenia and related **Questions:** KQ1, KQ2, KQ3 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Jul 2007 to Mar 2009 **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-IV, K-SADS-PL **Inclusion criteria:** (1) 12–17 yr, (2) body weight ≥29 kg, (3) DSM-IV criteria for schizophrenia ≥1 yr before screening, (4) PANSS total score 60–120, (5) physically healthy based on medical history, physical examination, ECG, and laboratory test results **Exclusion criteria:** (1) dissociative disorder, bipolar disorder, MDD, schizoaffective disorder, schizophreniform disorder, autistic disorder, or primary substance induced psychotic disorder (DSM-IV), (2) mild, moderate, or severe MR, (3) pregnant, (4) known or suspected history of seizure	**Enrolled:** 201 **Analyzed:** NR **Completed:** 139 **GROUP 1** **N:** 54 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 48 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 3** **N:** 48 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 4** **N:** 51 **Age, mean±SD (range):** NR **Males %:** NR	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** ≤3 wk **Permitted drugs:** NR **Prohibited drugs:** alcohol, antidepressants, drugs of abuse, lithium **GROUP 1** **Drug name:** Paliperidone ER (low) **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 2** **Drug name:** Paliperidone ER (medium) **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 3** **Drug name:** Paliperidone ER (high) **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 4** **Drug name:** Placebo **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD	**Symptomatology (KQ1):** CGAS, CGI-S, PANSS, VAS-sleep **Other ST and LT outcomes (KQ3):** Suicide **AE (KQ2):** Blood pressure, ECG changes, glucose, insulin resistance, mortality, NMS, SAE, seizure, total AE, WAE, weight change **Subpopulations (KQ4):** NR	The medium dose paliperidone ER group was statistically superior to the placebo group according to the primary efficacy analysis by weight-based, fixed-dose treatment group. When analyzed by actual dose group, all three doses of paliperidone showed improvement relative to placebo.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Robb et al., 2009 (continued)	disorder, NMS, encephalopathic syndrome, tardive dyskinesia, or insulin dependent diabetes mellitus, (5) presence of any significant or unstable systemic disease	**Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR	**(range):** NR **Concurrent treatments:** NR		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Saito et al., 2004 **Country:** USA **Condition category:** Multiple categories (schizophrenia, DBD, PDD) **Questions:** KQ2, KQ4 **Funding:** Government **Risk of bias:** 6 stars	**Recruitment dates:** Sept 2001 to Mar 2003 **Study design:** Prospective cohort **Setting:** Inpatient/outpatient **Diagnostic criteria:** NR **Inclusion criteria:** (1) male and females, (2) aged 5 to 18 years, (3) treatment naïve or at least a 1-month interval since their last treatment with antipsychotic agents, (4) inpatients or outpatients at a suburban children's hospital **Exclusion criteria:** (1) females receiving hormonal contraception	**Enrolled:** 40 **Analyzed:** 40 **Completed:** 40 **GROUP 1** **N:** 13 **Age, mean±SD (range):** all groups: 13.4±3.4 (5–18) **Males %:** all groups: 55 **Caucasian %:** NR **Diagnostic breakdown (n):** all groups: schizophrenia or other psychosis (14), mood disorders (14), DBD (9), intermittent explosive disorder (1), PDD NOS (1), eating disorder NOS (1) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 6 **Age, mean±SD (range):** see group 1 **Males %:** see group 1 **Caucasian %:** NR **Diagnostic breakdown (n):** see group 1 **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 3** **N:** 21 **Age, mean±SD (range):** see	**Treatment duration:** 11.2 wk **Run–in phase:** Yes **Run–in phase duration:** 1 mo. **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 7.8±4.2 **Concurrent treatments:** all groups: divalproex sodium (7), lithium (5), SSRI (11), stimulants (9), benzodiazepines (3), alpha-adrenergic agonists (3) **GROUP 2** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 283.3±222.9 **Concurrent treatments:** see group 1 **GROUP 3** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2.2±2 **Concurrent treatments:** see group 1	**Symptomatology (KQ1):** NR **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** prolactin, prolactin-related AEs **Subpopulations (KQ4):** Sex (prolactin)	Prolactin levels were significantly increased in children and adolescents treated with risperidone, compared to those treated with olanzapine or quetiapine.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Saito et al., 2004 (continued)		group 1 **Males %:** NR **Caucasian %:** NR **Diagnostic breakdown (n):** see group 1 **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR			

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Sallee et al., 2000 **Country:** USA **Condition category:** Tourette syndrome **Questions:** KQ1, KQ2, KQ4 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) 7–17 yr, (2) DSM-IV dx of Tourette syndrome or chronic tic disorder, with symptoms severe enough to warrant medication, (3) not pregnant or breast feeding **Exclusion criteria:** (1) secondary tic disorder, (2) DSM-IV criteria for major depression, PDD, autism, MR, anorexia nervosa/bulimia, substance abuse, or any psychotic disorder	**Enrolled:** 28 **Analyzed:** 27 **Completed:** 24 **GROUP 1** **N:** 16 **Age, mean±SD (range):** 11.3 (7–14) **Males %:** 87.5 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (9), DBD (4), OCD (10; all groups), learning disability (2; all groups) **GROUP 2** **N:** 12 **Age, mean±SD (range):** 11.8 (8–16) **Males %:** 66.7 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (6), DBD (1), OCD (10; all groups), learning disability (2; all groups)	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** 4–8 wk **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Ziprasidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 28.2±9.6 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Symptomatology (KQ1):** CGI-TS, CYBOCS, YGTSS **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** Akathisia, prolactin, prolactin-related AESAE, sedation, somnolence, total AE, WAE, weight change **Subpopulations (KQ4):** Comorbidity (CYBOCS)	Ziprasidone was well tolerated in children and adolscents with Tourette syndrome, and may also be an effective anti-tic medication.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Sallee et al., 1997 **Country:** USA **Condition category:** Tourette syndrome **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Industry, Government **Risk of bias:** Unclear (subjective), Unclear (objective)	**Recruitment dates:** NR **Study design:** RCT (crossover) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-III-TR, K-SADS-P **Inclusion criteria:** (1) principal DSM-III-R dx of Tourette syndrome; may have multiple Axis I and II dx, (2) 7–16 yr, 11 mo, (3) TSGS score >20, (4) previous exposure to neuroleptics permitted, but treatment must have been withdrawn ≥2 wk before baseline **Exclusion criteria:** (1) chronic motor tic disorder or transient tic disorder, (2) serious medical illness, (3) abnormal ECG, (4) inability to perform required measurements, (5) use of concurrent medication that may alter or interact with haloperidol or pimozide, (6) history of drug or alcohol abuse, (7) autism or childhood schizophrenia	**Enrolled:** 22 **Analyzed:** 22 **Completed:** 22 **GROUP 1** **N:** 22 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (13), OCD (5) **GROUP 2** **N:** 22 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see G1 **GROUP 3** **N:** 22 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see G1	**Treatment duration:** 5.5 mo **Run-in phase:** Yes **Run-in phase duration:** >2 wk **Permitted drugs:** diphenhydramine hydrochloride **Prohibited drugs:** adjunctive treatment, anticholinergics, concomitant medications **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 3.5±2.2 (1–8) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Pimozide **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 3.4±1.6 (1–6) **Concurrent treatments:** NR **GROUP 3** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Symptomatology (KQ1):** CGAS, CGI-S **Other ST and LT outcomes (KQ3):** Medication adherence, response **AE (KQ2):** Akathisia, akinesia, behavioral issues, electrocardiovascular, EPS (AIMS, ESRS), prolactin, treatment limiting AE, WAE, weight change **Subpopulations (KQ4):** Sex, Tanner score (prolactin)	Pimozide is superior to haloperidol for controlling symptoms of Tourette syndrome in children and adolescents.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Sallee et al., 1994 **Country:** USA **Condition category:** Tourette syndrome **Questions:** KQ1, KQ3, KQ4 **Funding:** Foundation **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-III-TR, TSGS **Inclusion criteria:** (1) consecutive outpatient children who met DSM-III-R criteria for Tourette syndrome and severity criteria using the TSGS **Exclusion criteria:** NR	**Enrolled:** 41 **Analyzed:** 41 **Completed:** NR **GROUP 1** **N:** 17 **Age, mean±SD (range):** 10.4 **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (6) **GROUP 2** **N:** 24 **Age, mean±SD (range):** 10.8 **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (7)	**Treatment duration:** 6 wk (3 wk extension) **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.5±0.6 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Pimozide **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 3.7±1.4 **Concurrent treatments:** NR	**Symptomatology (KQ1):** CBCL-TRF **Other ST and LT outcomes (KQ3):** Cognitive (CPT, MST) **AE (KQ2):** NR **Subpopulations (KQ4):** Comorbidity (CPT)	The effect of pimozide treatment on cognotion was superior to haloperidol in children with Tourette syndrome with comorbid ADHD.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Scahill et al., 2003 **Country:** USA **Condition category:** Tourette syndrome **Questions:** KQ1, KQ2, KQ3 **Funding:** Industry, Government **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV, joint parent and child interview **Inclusion criteria:** (1) 7–65 yr, (2) Tourette syndrome (DSM-IV), (3) Total Tic score ≥22 on the YGTSS **Exclusion criteria:** (1) evidence of current major depression, GAD, separation anxiety disorder, or psychotic symptoms (clinical evaluation or DSM-IV), (2) WISC age-appropriate IQ <70, (3) prior adequate trial of risperidone (dose ≥1.0 mg/day for ≥2 wk), (4) psychotropic medication within 2 wk, (5) significant medical problem, (6) moderate or greater obsessive-compulsive symptoms (YBOCS>15)	**Enrolled:** 26 **Analyzed:** 26 **Completed:** NR **GROUP 1** **N:** 12 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (11), MR (0), OCD (4) **GROUP 2** **N:** 14 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see group 1	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** 1–2 wk **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** 3 **Daily dose (mg/day), mean±SD (range):** 2.5±0.9 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** 3 **Daily dose (mg/day), mean±SD (range):** 3.3±0.9 **Concurrent treatments:** NR	**Symptomatology (KQ1):** CGI-I, YGTSS **Other ST and LT outcomes (KQ3):** Response **AE (KQ2):** Constipation, EPS, fatigue, prolactin-related AE, sedation, weight change **Subpopulations (KQ4):** NR	For short-term treatment of tics in children, risperidone appeared to be safe and effective.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Schulz et al., 1996 **Country:** Germany **Condition category:** Schizophrenia and related **Questions:** KQ2 **Funding:** Industry **Risk of bias:** NA (subjective), High (objective)	**Recruitment dates:** May 1991 to Oct 1992 **Study design:** NRCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-III-TR **Inclusion criteria:** (1) adolescents, (2) DSM-III-TR diagnostic criteria for schizophrenia or schizoaffective psychosis **Exclusion criteria:** NR	**Enrolled:** 40 **Analyzed:** 40 **Completed:** 40 **GROUP 1** **N:** 20 **Age, mean±SD (range):** 18.8±2.3 **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** 0 **Inpatients (n):** all **First episode psychosis (n):** NR **Comorbidities:** psychosis (all), SA (0), **GROUP 2** **N:** 20 **Age, mean±SD (range):** 19.5±2.1 **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** 0 **Inpatients (n):** all **First episode psychosis (n):** NR **Comorbidities:** psychosis (all), SA (0),	**Treatment duration:** 18 mo **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Typical antipsychotic **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 465±317 chlorpromazine-equivalents **Concurrent treatments:** β-blockers, biperiden, laxatives, sympathomimetics (15) **GROUP 2** **Drug name:** Clozapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 324±178 chlorpromazine-equivalents (75–600) **Concurrent treatments:** β-blockers or sympathomimetics (4)	**Symptomatology (KQ1):** NR **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** Prolactin **Subpopulations (KQ4):** NR	Prolactin levels were elevated with typical neuroleptics but not with clozapine in adolescent and young adults with schizophrenia.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Sehgal et al., 1999 **Country:** USA **Condition category:** Tourette syndrome **Questions:** KQ2, KQ3 **Funding:** Industry, Government, Foundation **Risk of bias:** High (subjective), NA (objective)	**Recruitment dates:** Oct 1993 to Nov 1995 **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-III-TR **Inclusion criteria:** (1) DSM-III-R diagnostic criteria for Tourette syndrome at participating medical centers **Exclusion criteria:** NR	**Enrolled:** 10 **Analyzed:** 10 **Completed:** 8 **GROUP 1** **N:** 4 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 6 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 8 mo **Run-in phase:** Yes **Run-in phase duration:** 4 mo **Permitted drugs:** NR **Prohibited drugs:** antidepressants, benzodiazepines, clonidine, stimulants (washout ≥2 wk prior to enrolment) **GROUP 1** **Drug name:** Pimozide (short-term) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 3. 8 (2–6) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Pimozide (long-term) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 3.5 (1–7) **Concurrent treatments:** NR	**Symptomatology (KQ1):** NR **Other ST and LT outcomes (KQ3):** Response **AE (KQ2):** Tardive dyskinesia **Subpopulations (KQ4):** NR	In children with Tourette syndrome, longer term treatment with pimozide appears to be more effective on the course of tics than a short-term course of the drug used to suppress an acute exacerbation of tics.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Shaw et al., 2006 **Country:** USA **Condition category:** Schizophrenia and related **Questions:** KQ1, KQ2, KQ3 **Funding:** NR **Risk of bias:** Unclear (subjective), Unclear (objective)	**Recruitment dates:** Jan 1998 to June 2005 **Study design:** RCT (parallel) **Setting:** Inpatient **Diagnostic criteria:** DSM-IV, K-SADS, medical and school record review, interview with child and parents **Inclusion criteria:** (1) schizophrenia with definite onset of symptoms ≤13 yr , (2) IQ >70, (3) no history of progressive neurological or medical disorders, (4) failure to respond to 2 antipsychotic medications (typical or atypical) used at adequate doses (>100 mg chlorpromazine equivalents) and for adequate duration (>4 wk unless terminated owing to intolerable adverse effects) **Exclusion criteria:** (1) nonresponse to an adequate trial of olanzapine or clozapine (8 wk of olanzapine at 20 mg/d or of clozapine at 200 mg/d)	**Enrolled:** 25 **Analyzed:** 25 **Completed:** 24 **GROUP 1** **N:** 12 **Age, mean±SD (range):** 11.7±2.3 **Males %:** 66.7 **Caucasian %:** 58.3 **Treatment naïve (n):** 0 **Inpatients (n):** all **First episode psychosis (n):** 0 **Comorbidities:** ADHD (4), anxiety disorders (6), MR (0) **GROUP 2** **N:** 13 **Age, mean±SD (range):** 12.8±2.4 **Males %:** 53.8 **Caucasian %:** 53.8 **Treatment naïve (n):** 0 **Inpatients (n):** all **First episode psychosis (n):** 0 **Comorbidities:** ADHD (3), anxiety disorders (1), MR (0)	**Treatment duration:** 8 wk (2 yr extension) **Run-in phase:** Yes **Run-in phase duration:** 3 wk **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Clozapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 327±113 (150–500) **Concurrent treatments:** diphenhydramine hydrochloride (4), guanfacine hydrochloride (1), lorazepam (2), sedatives (4), ≤4 hr specialized education, recreational and occupational therapy **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 18.1±4.3 **Concurrent treatments:** clomipramine hydrochloride (1), diphenhydramine hydrochloride (6), lorazepam (3), sedatives (3), valproate sodium (2), ≤4 hr specialized education, recreational and occupational therapy	**Symptomatology (KQ1):** BPRS-24, CGI-S, SANS, SAPS **Other ST and LT outcomes (KQ3):** Response **AE (KQ2):** Behavioral issues, blood cells, blood pressure, constipation, dermatologic AE, ECG changes, EPS, lipid profile, seizure, sleepness, somnolence, tachycardia, weight change **Subpopulations (KQ4):** NR	Clozapine had a more favorable profile of clinical response and adverse events than olanzapine.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Shea et al., 2004 **Country:** Canada **Condition category:** PDD **Questions:** KQ1, KQ2, KQ3 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) physically healthy outpatients, (2) 5–12 yr, (3) DSM-IV Axis I dx of PDD, (4) a total score >30 on the CARS with or without MR **Exclusion criteria:** (1) patients with schizophrenia, other psychotic disorders, clinically relevant nonneurologic disease, clinically significant laboratory abnormalities, or a seizure disorder for which they were receiving >1 anticonvulsant or if they had had a seizure in the last 3 mo, (2) history of hypersensitivity to neuroleptics, tardive dyskinesia, NMS, drug or alcohol abuse, or HIV infection, (3) used	**Enrolled:** 80 **Analyzed:** 79 **Completed:** 72 **GROUP 1** **N:** 41 **Age, mean±SD (range):** 7.6±0 (5–12) **Males %:** 72.5 **Caucasian %:** NR **Diagnostic breakdown (n):** Asperger's disorder (5), autistic disorder (27), childhood disintegrative disorder (1), PDD NOS (7), Rett disorder (0) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (15) **GROUP 2** **N:** 39 **Age, mean±SD (range):** 7.3±0 (5–12) **Males %:** 82.1 **Caucasian %:** NR **Diagnostic breakdown (n):** Asperger's disorder (7), autistic disorder (28), childhood disintegrative disorder (0), PDD NOS (4), Rett disorder (0) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 8 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** anticholinergics, anticonvulsants and/or medications for sleep or anxiety (constant dose ≥30 days before enrolment), medications for preexisting organic disorders **Prohibited drugs:** α-2 antagonists, antidepressants, antipsychotics, cholinesterase inhibitors, clonidine, guanfacine, lithium, naltrexone, psychostimulants **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.2 **Concurrent treatments:** analgesics (15), anti-asthmatics (6), antibiotics (5), anticholinergics (3), cough and cold preparations (10), sedatives/hypnotics (11) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** analgesics (7), anti-asthmatics (4), antibiotics (5), anticholinergics (1), cough and cold preparations (4), sedatives/hypnotics (9)	**Symptomatology (KQ1):** ABC, NCBRF, VAS-MS **Other ST and LT outcomes (KQ3):** Response (ABC-I, CGI-C) **AE (KQ2):** Anorexia, behavioral issues, blood pressure, constipation, EPS, fatigue, hyperkinesias, pulse, SAE, somnolence, tachycardia, tardive dyskinesia, total AE, WAE, weight change **Subpopulations (KQ4):** NR	In children with PDD, risperidone was well tolerated and efficacious in the treatment of autism associated behavioral symptoms.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Shea et al., 2004 (continued)	risperidone in the last 3 mo or previously unresponsive or intolerant to risperidone, (4) using a prohibited medication	**Comorbidities:** MR (12)			

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Sikich et al., 2008 **Country:** USA **Condition category:** Schizophrenia and related **Questions:** KQ1, KQ2, KQ3 **Funding:** Government **Risk of bias:** Unclear (subjective), Unclear (objective)	**Recruitment dates:** Feb 2002 to May 2006 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, KID-SCID **Inclusion criteria:** (1) 8–19 yr, (2) DSM-IV dx of schizophrenia, schizoaffective disorder, or schizophreniform disorder with current positive psychotic symptoms of at least moderate intensity, (PANSS or BRRS-C), (3) good physical health, (4) able to provide informed consent and guardian's written informed consent **Exclusion criteria:** (1) premorbid dx of MR, (2) current major depressive episode, active substance abuse, (3) history of intolerance or nonresponse to any of the study treatments during a prior episode, (4) history of successful	**Enrolled:** 78 **Analyzed:** 76 **Completed:** 45 **GROUP 1** **N:** 41 **Age, mean±SD (range):** NR **Males %:** 57.5 **Caucasian %:** 70 **Diagnostic breakdown (n):** schizoaffective disorder (14), schizophrenia (26) **Treatment naïve (n):** 16 **Inpatients (n):** 4 **First episode psychosis (n):** 35 **Comorbidities:** ADHD (12), affective disorder (9), anxiety disorder (6), ASD (2), DBD (4), learning disability (7), MR (0), none (14), psychosis (7), SA (4) **GROUP 2** **N:** 36 **Age, mean±SD (range):** NR **Males %:** 71.4 **Caucasian %:** 60 **Diagnostic breakdown (n):** schizoaffective disorder (13), schizophrenia (22) **Treatment naïve (n):** 13 **Inpatients (n):** 2 **First episode psychosis (n):** 33 **Comorbidities:** ADHD (13), affective disorder (7), anxiety disorder (9), ASD (2), DBD	**Treatment duration:** 8 wk (10.1 mo extension) **Run-in phase:** Yes **Run-in phase duration:** 2 wk **Permitted drugs:** antidepressants or non-antipsychotic mood stabilizers (≥4 wk prior to study entry); anticholinergics, benzodiazepines, propranolol (concomitant); thymoleptics (maintenance phase) **Prohibited drugs:** NR **GROUP 1** **Drug name:** Molindone **Dosing variability:** variable **Target dose (mg/day):** 140 **Daily dose (mg/day), mean±SD (range):** 59. 9±33.5 (10–140) **Concurrent treatments:** antidepressants (4), benzodiazepines (3), mood stabilizers (3), propranolol (13%) **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** 20 **Daily dose (mg/day), mean±SD (range):** 11.4±5 (2.5–20) **Concurrent treatments:** antidepressants (4), benzodiazepines (3), benztropine (14%), mood stabilizers (2), propranolol (11%) **GROUP 3** **Drug name:** Risperidone	**Symptomatology (KQ1):** BPRS-C, CGI-I, CGI-S, PANSS **Other ST and LT outcomes (KQ3):** Medication adherence, response, suicide **AE (KQ2):** Akathisia, behavioral issues, blood pressure, BMI, constipation, dystonia, ECG changes, EPS, glucose, homeostasis, insulin, lipid profile, liver function, prolactin, prolactin-related AE, pulse, SAE, sedation, tardive dyskinesia, total AE, WAE, weight change **Subpopulations (KQ4):** NR	Rispiridone and olanzapine failed to show superior efficacy over molindone in the treatment of early-onset schizophrenia and schizoaffective disorder.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Sikich et al., 2008 (continued)	use of the study treatments during the current episode (≥8 wk of treatment, including ≥2 wk at the maximal dose allowed in the current study), (5) imminent risk of harming themselves or others, (6) bipolar disorder, primary PTSD, primary personality disorder, or psychosis NOS (dx by clinician, confirmed by KID-SCID), (7) endocrinological or neurological conditions that confound the dx or are a contraindication to treatment, (8) pregnancy or refusal to practice contraception during the study, (9) use of a depot antipsychotic within the past 6 mo	(6), learning disability (1), MR (0), none (17), psychosis (4), SA (2) **GROUP 3** **N:** 42 **Age, mean±SD (range):** NR **Males %:** 65.9 **Caucasian %:** 61 **Diagnostic breakdown (n):** schizoaffective disorder (13), schizophrenia (28) **Treatment naïve (n):** 9 **Inpatients (n):** 6 **First episode psychosis (n):** 40 **Comorbidities:** ADHD (9), affective disorder (12), anxiety disorder (12), ASD (3), DBD (10), learning disability (2), MR (0), none (15), psychosis (6), SA (2)	**Dosing variability:** variable **Target dose (mg/day):** 6 **Daily dose (mg/day), mean±SD (range):** 2.8±1.4 (0.5–6) **Concurrent treatments:** antidepressants (5), benzodiazepines (6), benztropine (34%), mood stabilizers (4), propranolol (7%)		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Sikich et al., 2004 **Country:** USA **Condition category:** Schizophrenia and related **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Industry, Government, Foundation **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Nov 1997 to May 2001 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, K-SADS-P **Inclusion criteria:** (1) ≥1 positive psychotic symptom of moderate or greater severity on the BPRS-C, present throughout the past 2 wk, (2) full scale IQ >69, (3) patients with current or recent dx of ADHD, Tourette syndrome, OCD, or a history of substance abuse or dependence were allowed to participate only if their psychotic symptoms were not better accounted for by the comorbid disorder **Exclusion criteria:** (1) psychotic symptoms resulting from acute substance intoxication or withdrawal, (2) history of serious adverse reactions or nonresponse to an	**Enrolled:** 50 **Analyzed:** 50 **Completed:** 32 **GROUP 1** **N:** 15 **Age, mean±SD (range):** 15.4±2.2 **Males %:** 53 **Caucasian %:** 73 **Diagnostic breakdown (n):** affective disorders (7), schizophrenia spectrum (8) **Treatment naïve (n):** NR **Inpatients (n):** 10 **First episode psychosis (n):** 12 **GROUP 2** **N:** 16 **Age, mean±SD (range):** 14.6±3.1 **Males %:** 56 **Caucasian %:** 63 **Diagnostic breakdown (n):** affective disorders (11), schizophrenia spectrum (5) **Treatment naïve (n):** NR **Inpatients (n):** 12 **First episode psychosis (n):** 12 **GROUP 3** **N:** 19 **Age, mean±SD (range):** 14.6±2.9 **Males %:** 68 **Caucasian %:** 47	**Treatment duration:** 8 wk (2.8 mo extension) **Run-in phase:** Yes **Run-in phase duration:** 1–2 wk **Permitted drugs:** amantadine (200 mg/day), antidepressants and mood stabilizers (if taken ≥4 wk preceding study entry or if clinically significant affective symptoms persisted after 4 wk of study treatment), benztropine (1–3 mg/day), lorazepam (0.5–3 mg/day), propranolol (20–60 mg/day), trihexyphenidyl (4–6 mg/day) **Prohibited drugs:** NR **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** variable **Target dose (mg/day):** 1–5 **Daily dose (mg/day), mean±SD (range):** 5±2 (1–5) **Concurrent treatments:** amantadine (1), benztropine/trihexyphenidyl (7), buproprion (4), citalopram (1), gabapentin (1), lithium (1), lorazepam (3), paroxetine (1), sertraline (3), valproate (2), venlaflaxine (1), inpatient or residential treatment (9) **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** 2.5–12.5 **Daily dose (mg/day), mean±SD (range):** 12.3±3.5 (2.5–12.5) **Concurrent treatments:**	**Symptomatology (KQ1):** BPRS-C, CPRS, CGI-I, CGI-S **Other ST and LT outcomes (KQ3):** Medication adherence, response **AE (KQ2):** Akathisia, BMI, constipation, dermatolodic AE, dystonia, ECG changes, EPS, glucose, lipid profile, prolactin, prolactin-related AE, sedation, WAE, weight changes, white blood cells **Subpopulations (KQ4):** age, co-treatment, treatment history, diagnosis, baseline symptom severity (response)	Risperidone and olanzapine were effective in acutely reducing symptoms in psychotic youth.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Sikich et al., 2004 (continued)	adequate trial of any of the study medications during this psychotic episode, (3) prior dx of PDD or a serious medical or neurological disorder, (4) pregnancy or refusal to practice contraception, (5) imminent risk in current setting to harm self or others	**Diagnostic breakdown (n):** affective disorders (6), schizophrenia spectrum (13) **Treatment naïve (n):** NR **Inpatients (n):** 15 **First episode psychosis (n):** 15	benztropine/trihexyphenidyl (5), buproprion (2), carbamazepine (1), fluoxetine (2), fluvoxamine (1), lithium (1), lorazepam (1), paroxetine (1), propranolol (2), sertraline (1), valproate (1), inpatient or residential treatment (10) **GROUP 3** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** 0.5–3 **Daily dose (mg/day), mean±SD (range):** 4±1.2 (0.5–3) **Concurrent treatments:** amantadine(2), benztropine/ trihexyphenidyl (4), citalopram (1), clomipramine (1), gabapentin with lamotrigine (1), lorazepam(2), propranolol (1), sertraline (2), trazadone (1), valproate (3), inpatient or residential treatment (11)		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Snyder et al., 2002 **Country:** Canada, South Africa, USA **Condition category:** DBD **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Foundation **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, VABS **Inclusion criteria:** (1) CD, ODD, or DBD-NOS (DSM-IV), (2) parent/ caregiver rating ≥24 on the Conduct Problem subscale of the NCBRF, (3) IQ 36–84 inclusive, (4) VABS score ≤84, (5) healthy on the basis of a pretrial physical examination, medical history, and ECG, (6) consent by parent/ caregiver, (7) 5–12 yr **Exclusion criteria:** (1) PDD, schizophrenia, or other psychotic disorders, (2) head injury as a cause of impaired IQ, (3) seizure condition requiring medication, (4) females who were sexually active without a reliable form of birth control, (5) serious or progressive	**Enrolled:** 110 **Analyzed:** 110 **Completed:** 85 **GROUP 1** **N:** 53 **Age, mean±SD (range):** 8.6±0.3 (5–12) **Males %:** 77.4 **Caucasian %:** 78.8 **Diagnostic breakdown (n):** CD (3), CD/ADHD (16), Combined/No ADHD (9), ODD/ DBD (6), ODD/DBD/ADHD (28) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (44) **GROUP 2** **N:** 57 **Age, mean±SD (range):** 8.8±0.3 (5–12) **Males %:** 73.7 **Caucasian %:** 73.7 **Diagnostic breakdown (n):** CD (7), CD/ADHD (15), Combined/No ADHD (17), ODD/ DBD (10), ODD/DBD/ADHD (25) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (40)	**Treatment duration:** 6 wk (11 mo extension) **Run-in phase:** Yes **Run-in phase duration:** 1 wk **Permitted drugs:** stable doses (≥30 days prior to study) of anticholinergics, antihistamines, chloral hydrate, medication for preexisting medical conditions, melatonin, psychostimulants (comorbid ADHD) **Prohibited drugs:** no other medication permitted **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1±0.1 SE (0.4–3.8) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Symptomatology (KQ1):** ABC, BPI, CGI-I, CGI-S, NCBRF, VAS **Other ST and LT outcomes (KQ3):** Medication adherence **AE (KQ2):** Anorexia, behavioral issues, Bucco-linguo-masticatory score, BMI, ECG changes, EPS, fatigue, parkinsonism, prolactin, prolactin-related AE, pulse, SAE, somnolence, tardive dyskinesia, total AE, WAE, weight change **Subpopulations (KQ4):** Comorbidity, co-treatment, treatment history, condition (NCBRF, prolactin, sedation, weight)	Risperidone was adequately tolerated and was effective in treating children with subaverage IQs and severe disruptive behaviors.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Snyder et al., 2002 (continued)	illness or clinically abnormal laboratory values, (6) history of tardive dyskinesia, NMS, or hypersensitivity to any antipsychotic drug, (7) known presence of HIV, (8) previous treatment with risperidone				

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Spencer et al., 1994 **Country:** USA **Condition category:** Schizophrenia and related **Questions:** KQ1, KQ2, KQ4 **Funding:** Industry, Government **Risk of bias:** Unclear (subjective), Unclear (objective)	**Recruitment dates:** Sep 1989 to May 1991 **Study design:** RCT (crossover) **Setting:** Inpatient **Diagnostic criteria:** DSM-III-TR, DICA-R **Inclusion criteria:** (1) actively psychotic prepubertal patients, (2) 5–11 yr, (3) admitted to the Bellevue Hospital Children's Inpatient Psychiatric Unit, (4) schizophrenia **Exclusion criteria:** (1) intercurrent systemic illness, (2) seizure disorder, (3) MR below borderline, (4) tardive dyskinesia, (5) infantile autism, (6) receipt of psychoactive medication within 4 wk of double-blind treatment	**Enrolled:** 16 **Analyzed:** 16 **Completed:** 16 **GROUP 1** **N:** 16 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 16 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** 2 wk **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2 (0.5–3.5) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2.5±0.5 (0.5–3.5) **Concurrent treatments:** NR	**Symptomatology (KQ1):** BPRS-C, CGI-I, CGI-S, CPRS **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** Drowsiness, dystonia **Subpopulations (KQ4):** Age, illness duration, IQ (Global clinical judgments rating)	Haloperidol improved the target psychotic symptoms in children with schizophrenia.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Swadi et al., 2010 **Country:** New Zealand **Condition category:** Schizophrenia and related **Questions:** KQ1, KQ2, KQ3 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) <19 yr, (2) first onset psychotic disorder or a mood disorder with psychotic features **Exclusion criteria:** (1) alcohol or substance dependence not in full remission, (2) prior treatment with atypical antipsychotic drugs	**Enrolled:** 22 **Analyzed:** 22 **Completed:** 22 **GROUP 1** **N:** 11 **Age, mean±SD (range):** NR **Males %:** 54.5 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR **GROUP 2** **N:** 11 **Age, mean±SD (range):** NR **Males %:** 63.6 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR	**Treatment duration:** 6 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 607 (100–800) **Concurrent treatments:** anticholinergics (1), cognitive behavioral therapy, family work, activity-based interventions allowed **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2.9 (1.5–5) **Concurrent treatments:** anticholinergics (5), cognitive behavioral therapy, family work, activity-based interventions allowed	**Symptomatology (KQ1):** BPRS, PANSS **Other ST and LT outcomes (KQ3):** Response (BPRS, CGI-S, HAM-D, PANSS, YMRS) **AE (KQ2):** Blood pressure, EPS, glucose, lipid profile, liver function, prolactin, sedation, weight change **Subpopulations (KQ4):** NR	Risperidone may be more beneficial than quetiapine for adolescent patients with bipolar disorder.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Tohen et al., 2007 **Country:** Puerto Rico, USA **Condition category:** Bipolar **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Nov 2002 to May 2005 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV-TR, K-SADS-PL **Inclusion criteria:** (1) 12–17 yr, (2) manic or mixed bipolar episodes (with or without psychotic features), (3) inpatient or outpatient, (4) total score ≥20 on the Adolescent Structured YMRS **Exclusion criteria:** (1) prior nonreponse to olanzapine, (2) treatment within the previous 30 day with an experimental medication not available for clinical use, (3) suicide risk, (4) clinically significant abnormal laboratory values at baseline, (5) DSM-IV-TR substance dependence (excluding nicotine and caffeine) within the last 30 days, (6) treatment with long-lasting neuroleptic within 14 day prior to randomization	**Enrolled:** 161 **Analyzed:** 161 **Completed:** 120 **GROUP 1** **N:** 107 **Age, mean±SD (range):** 15.1±1.3 **Males %:** 57 **Caucasian %:** 66.4 **Diagnostic breakdown (n):** mixed (61), psychotic features (22), rapid cycling (25) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (45), DBD (37) **GROUP 2** **N:** 54 **Age, mean±SD (range):** 15.4±1.2 **Males %:** 44.4 **Caucasian %:** 75.9 **Diagnostic breakdown (n):** mixed (25), psychotic features (7), rapid cycling (5) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (13), DBD (12)	**Treatment duration:** 3 wk (6 mo extension) **Run-in phase:** Yes **Run-in phase duration:** 2–14 day **Permitted drugs:** anticholinergics (2–6mg/day), benzodiazepines/hypnotics (≤2 mg/day lorazepam equivalents for ≤3 consecutive days), psychostimulants (constant dose ≥30 day prior to randomization and through study) **Prohibited drugs:** anticholinergics **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 8.9 (2.5–20) **Concurrent treatments:** anticholinergics (4.7%), benzodiazepines (12.1%) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** anticholinergic medication (0), benzodiazepines (7.4%)	**Symptomatology (KQ1):** CDRS, CGI-BP, OAS, YMRS **Other ST and LT outcomes (KQ3):** Response, suicide **AE (KQ2):** Bipolar exacerbation, blood cells, blood pressure, BMI, ECG changes, EPS (AIMS, Barnes, SAS), glucose, hepatic enzyme, lipid profile, mortality, prolactin, prolactin-related AE, pulse, SAE, weight change **Subpopulations (KQ4):** Comorbidities, co-treatment, bipolar subtypes, age of onset, Sex (CGI-BP, YMRS, prolactin)	Olanzapine was more effective in treating adolescents with bipolar mania and placebo; however, it resulted in significantly greater weight gain.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Tramontina et al., 2009 **Country:** Brazil **Condition category:** Bipolar with ADHD **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Industry, Government, Hospital **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Jan 2005 to Nov 2007 **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV, K-SADS-E **Inclusion criteria:** (1) 8–17 yr, (2) DSM IV bipolar I or II disorder comorbid with ADHD, (3) clear reports of ADHD symptom onset preceding any mood symptomology, (4) acutely manic or mixed states (YMRS score ≥20 at baseline visit) **Exclusion criteria:** (1) estimated IQ < 70 (WISC-III), (2) use of any medication 4 wk prior to entering the study, (3) dx of PDD, schizophrenia, or substance abuse or dependence, (4) severe suicide/homicide risk, (5) previous use of aripiprazole, (6) other acute or chronic diseases, (7) pregnancy	**Enrolled:** 43 **Analyzed:** 43 **Completed:** 41 **GROUP 1** **N:** 18 **Age, mean±SD (range):** 11.7±2.7 **Males %:** 33 **Caucasian %:** 83 **Treatment naïve (n):** ND **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** ADHD (all), anxiety disorders (8), DBD (15), psychosis (8), SA (0) **GROUP 2** **N:** 25 **Age, mean±SD (range):** 12.2±2.8 **Males %:** 56 **Caucasian %:** 96 **Treatment naïve (n):** ND **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** ADHD (all), anxiety disorders (13), DBD (20), psychosis (8), SA (0)	**Treatment duration:** 6 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Aripiprazole **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 13.6±5.4 (5–20) **Concurrent treatments:** none **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 15±3.2 (10–20) **Concurrent treatments:** none	**Symptomatology (KQ1):** CDRS, CGI-S, CMRS-P, YMRS **Other ST and LT outcomes (KQ3):** Medication adherence, response, suicide **AE (KQ2):** Akathisia, behavioral issues, dermatologic AE, dyskinesia, EPS, fatigue, seizure, somnolence, weight change **Subpopulations (KQ4):** Age (YMRS, SNAP-IV, weight/BMI)	Aripiprazole was effective in decreasing mania symptoms and improving global functioning without resulting in severe advserse events or weight gain.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Troost et al., 2005 **Country:** Netherlands **Condition category:** PDD **Questions:** KQ1, KQ2, KQ3 **Funding:** Industry, Foundation **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV-TR, ADI-R **Inclusion criteria:** (1) DSM-IV-TR criteria for PDD, (2) demonstrated clinically significant tantrums, aggression, self-injurious behavior, or a combination of these, (3) 5–17 yr, (4) weight ≥15 kg, (5) mental age ≥18 mo **Exclusion criteria:** (1) children on effective psychotropic drug treatment for disruptive behavior	**Enrolled:** 24 **Analyzed:** 24 **Completed:** NR **GROUP 1** **N:** 12 **Age, mean±SD (range):** 9.4±3.4 **Males %:** 91.6 **Caucasian %:** 100 **Diagnostic breakdown (n):** Asperger's disorder (1), autistic disorder (3), PDD NOS (8) **Treatment naïve (n):** 11 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (2) **GROUP 2** **N:** 12 **Age, mean±SD (range):** 8.7±1.2 **Males %:** 91.6 **Caucasian %:** 83 **Diagnostic breakdown (n):** Asperger's disorder (1), autistic disorder (3), PDD NOS (8) **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (0)	**Treatment duration:** 6 mo **Run-in phase:** Yes **Run-in phase duration:** 1–4 wk **Permitted drugs:** anticonvulsants (stable dose for ≥4 wk and patient seizure-free for ≥6 mo), stimulants (comorbid ADHD) **Prohibited drugs:** psychotropics **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.9±0.7 **Concurrent treatments:** stimulants (1), stimulant and anticonvulsant (1) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.7±0.5 **Concurrent treatments:** stimulants (2)	**Symptomatology (KQ1):** ABC **Other ST and LT outcomes (KQ3):** Cognitive (focused attention task), response (relapse) **AE (KQ2):** Dyskinesia **Subpopulations (KQ4):** NR	Risperidone was effective in reducing disruptive behavior in about half of children with autism spectrum disorders.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Van Bellinghen et al., 2001 **Country:** Belgium **Condition category:** Behavioral issues (agitation, aggression, hostility, hyperactivity, or irritability) **Questions:** KQ1, KQ2 **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient **Diagnostic criteria:** clinical assessment and parent interview **Inclusion criteria:** (1) 6–18 yr, (2) IQ 45–85, (3) demonstrating persistent behavioral disturbances **Exclusion criteria:** (1) presence of a clinically relevant non-neurologic disease, (2) abnormal laboratory tests, (3) epileptic crisis in the previous 3 mo, (4) participation in a drug trial in the previous 4 wk, (5) remoxipride treatment in the previous 4 wk, (6) oral neuroleptics and other psychotropics in the previous wk, (6) previous treatment with remoxipride combined with abnormal hematologic values, (7) a depot neuroleptic injection within one	**Enrolled:** 13 **Analyzed:** 13 **Completed:** 13 **GROUP 1** **N:** 6 **Age, mean±SD (range):** NR (6–14) **Males %:** 33.3 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** anxiety (0), depression (0), mania (0), MR (all) **GROUP 2** **N:** 7 **Age, mean±SD (range):** NR (7–14) **Males %:** 42.9 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** anxiety (0), depression (0), mania (0), MR (all)	**Treatment duration:** 4 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** antiepileptics **Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.2 **Concurrent treatments:** valproate (1) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Symptomatology (KQ1):** ABC, CGI-I, PAC, VAS **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** Parkinsonism, pulse, somnolence, total AE, weight change **Subpopulations (KQ4):** NR	Risperidone was well tolerated, and there was no difference between risperidone- and placebo-treated groups with respect to the occurrence of extrapyramidal side effects.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Van Bellinghen et al., 2001 (continued)	treatment cycle of the time of selection, (8) female patients of reproductive age if their contraceptive use was considered inadequate, (9) pregnant or lactating				

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Van Bruggen et al., 2003 **Country:** Netherlands **Condition category:** Schizophrenia and related psychoses **Questions:** KQ1, KQ2, KQ3 **Funding:** Industry, Government **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) 16–28 yr, (2) first or second psychotic episode according to DSM-IV criteria of schizophrenia, schizofreniform or schizoaffective disorder, (3) actively symptomatic at study entry (PANSS score of moderate or higher on items for delusions, conceptual disorganization, or hallucinations) **Exclusion criteria:** (1) epilepsy, (2) toxic psychosis or infectious disorder, (3) a primary dx of substance abuse (drugs or alcohol), (4) MR, (5) pregnant or lactating female patients, (6) concomitant use of other antipsychotic agents, (7) treatment with an	**Enrolled:** 44 **Analyzed:** 42 **Completed:** NR **GROUP 1** **N:** 18 **Age, mean±SD (range):** 21.0±2.8 **Males %:** 72 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** 16 **GROUP 2** **N:** 26 **Age, mean±SD (range):** 20.6±3.0 **Males %:** 85 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** 22	**Treatment duration:** Olanzapine 9.8 wk, Risperidone 6.7 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 15.6±4 (5–30) **Concurrent treatments:** anticholinergics (2), antidepressants (0), benzodiazepines (7), mood stabilizers (0) **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 4.4±1.5 (1–8) **Concurrent treatments:** anticholinergics (7), antidepressants (4), benzodiazepines (8), mood stabilizers (0)	**Symptomatology (KQ1):** PANSS **Other ST and LT outcomes (KQ3):** Medication adherence, response **AE (KQ2):** Akathisia, parkinsonism, prolactin, prolactin-related AE, sedation, seizure, sexual dysfunction, somnolence, tachycardia, tardive dyskinesia, weight change **Subpopulations (KQ4):** NR	Symptom response was similar in the olanzapine and risperidone groups.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Van Bruggen et al., 2003 (continued)	injectable depot neuroleptic less than one dosing interval before study entry, (8) narrow-angle glaucoma and known hypersensitivity to olanzapine or risperidone, (9) insufficient knowledge of the Dutch language				

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Woods et al., 2003 **Country:** Canada, USA **Condition category:** Schizophrenia and related **Questions:** KQ1, KQ2, KQ3, KQ4 **Funding:** Industry, Government **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Jan 1998 to July 2001 **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV, COPS, Presence of Psychosis Scale **Inclusion criteria:** (1) help-seeking persons responding to advertisements or refered by clinicians, (2) 12–45 yr, (3) prodromal syndromes criteria using the Structured Interview for Prodromal Syndromes, (4) ability to understand and communicate with investigator, (5) informed consent/assent **Exclusion criteria:** (1) past or current DSM-IV psychotic disorder, (2) treatable psychiatric disorder that could account for prodromal symptoms, (3) suicidal or homicidal,	**Enrolled:** 60 **Analyzed:** 59 **Completed:** NR **GROUP 1** **N:** 31 **Age, mean±SD (range):** 18.2±5.5 **Males %:** 67.7 **Caucasian %:** 74.2 **Treatment naïve (n):** 28 **Inpatients (n):** NR **First episode psychosis (n):** all **Comorbidities:** SA (18) **GROUP 2** **N:** 29 **Age, mean±SD (range):** 17.2±4 **Males %:** 62.1 **Caucasian %:** 58.6 **Treatment naïve (n):** 26 **Inpatients (n):** NR **First episode psychosis (n):** all **Comorbidities:** SA (9)	**Treatment duration:** 1 yr (1 yr extension) **Run-in phase:** Yes **Run-in phase duration:** 3–14 day **Permitted drugs:** antidepressants, benztropine mesylate or biperiden (≤6 mg/day), chloral hydrate (max 1000 mg/day), diazepam (max 40 mg/day), lorazepam (max 8 mg/day), nizatidine (300–600 mg/day), propranalol hydrochloride **Prohibited drugs:** psychoactive medications **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 8±3.1 (5–15) **Concurrent treatments:** anticholinergics (1), benzodiazepines (7), nizatidine (1) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 9.3±2.8 (5–15) **Concurrent treatments:** anticholinergics (2), benzodiazepines (2)	**Symptomatology (KQ1):** CGI-S, GAF, PANSS, YMRS **Other ST and LT outcomes (KQ3):** Cognitive (neurocognitive measures), medication adherence, response **AE (KQ2):** Behavioral issues, blood pressure, EPS (AIMS, Barnes, ASA), glucose, fatigue, lipid profile, pulse, somnolence, WAE, weight change **Subpopulations (KQ4):** Age, race, IQ, baseline neuropsychological status (psychosis); History of psychosis and duration of prodromal symptoms (Neurocognitive performance)	The conversion-to-psychosis rate was not significantly different between treatment groups; however, olanzapine might reduce the conversion rate and delay onset of psychosis. Compared to placebo, olanzapine was efficacious for positive prodromal symptoms but induced weight gain.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Woods et al., 2003 (continued)	(4) prodromal symptoms primarily sequelae of alcohol or drug use, (5) IQ <80, (6) seizure disorder without a clear or resolved etiology, (7) pregant or lactating, (8) took nonprotocol psychotropic medications				

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Wudarsky et al., 1999 **Country:** USA **Condition category:** Schizophrenia and related **Questions:** KQ2, KQ4 **Funding:** NR **Newcastle-Ottawa Scale:** 7 stars	**Recruitment dates:** NR **Study design:** Prospective cohort **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV, DSM-III-TR, structured interviews **Inclusion criteria:** (1) DSM dx of schizophrenia, (2) resistant to treatment with two different FGAs **Exclusion criteria:** (1) onset of symptoms at ≥13 yr, (2) neurological or medical disease, (3) premorbid IQ <70	**Enrolled:** 47 **Analyzed:** 35 **Completed:** NR **GROUP 1** **N:** 15 **Age, mean±SD (range):** 13.7±1.5 **Males %:** 60 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 22 **Age, mean±SD (range):** 14.7±2.3 **Males %:** 72.7 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 3** **N:** 10 **Age, mean±SD (range):** 14.2±2.9 **Males %:** 70 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** 3 wk **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 15.3±8.2 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Clozapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 325.4±211 **Concurrent treatments:** NR **GROUP 3** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 17±3.5 **Concurrent treatments:** NR	**Symptomatology (KQ1):** NR **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** Prolactin **Subpopulations (KQ4):** Sex (prolactin)	Mean prolactin levels were significantly elevated after 6 weeks of treatment with haloperidol, clozapine, and olanzapine in patients with childhood-onset schizophrenia

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Yen et al., 2004 **Country:** Taiwan **Condition category:** Schizophrenia and related **Questions:** KQ1 **Funding:** Hospital **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-III-TR **Inclusion criteria:** (1) 18–65 yr, (2) total score >60 on PANSS **Exclusion criteria:** (1) psychoses other than schizophrenia, (2) early childhood brain damage, (3) unable to comply with the medication, (4) severe illness, (5) pregnant or lactating women	**Enrolled:** 8 **Analyzed:** 8 **Completed:** 8 **GROUP 1** **N:** 2 **Age, mean±SD (range):** 24.0 (24) **Males %:** 0 **Caucasian %:** NR **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 6 **Age, mean±SD (range):** 20.7 (20–22) **Males %:** 66.7 **Caucasian %:** NR **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 2.8 mo **Run-in phase:** Yes **Run-in phase duration:** 1–4 wk **Permitted drugs:** biperiden or trihexylphenidyl; lorazepam, oxazepam or temazepam **Prohibited drugs:** NR **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 11.2±6.9 (2–25) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 4.4±2.6 (1–8) **Concurrent treatments:** NR	**Symptomatology (KQ1):** PANSS **Other ST and LT outcomes (KQ3):** NR **AE (KQ2):** NR **Subpopulations (KQ4):** NR	Risperidone was superior to haloperidol in improving negative symptoms and better tolerated during the treatment of schizophrenia.

Appendix E. List of Excluded Studies and Unobtained Studies

One thousand four studies were excluded. The reasons for exclusion are as follows: (1) the study population was >24 years of age (N = 748), (2) the study was not primary research (N = 89), (3) inappropriate study design (N = 70), (4) the study intervention did not meet our criteria (N = 41), (5) there were no outcome of interest reported (N = 19), (6) the study population did not have the condition/diagnosis of interest (N = 18), (7) the article was a duplicate publication (N = 9), (8) the study was not published in English (N = 7), and (9) the study was published before 1987 (N = 3). In addition, 38 studies could not be retrieved through the univeristy interlibrary loan service.

Excluded – Age>24 (N = 748)

The following studies were excluded because the participants were older than 24 years of age.

1. How do different atypical antipsychotics impact cognitive function in schizophrenia? Brown Univ Psychopharmacol Update 2005;16(2):1.

2. Abraham G, Paing WW, Kaminski J, et al. Effects of elevated serum prolactin on bone mineral density and bone metabolism in female patients with schizophrenia: a prospective study. Am J Psychiatry 2003;160(9):1618-20.

3. Addington DE, Labelle A, Kulkarni J, et al. A comparison of ziprasidone and risperidone in the long-term treatment of schizophrenia: a 44-week, double-blind, continuation study. Can J Psychiatr Rev Canad Psychiatr 2009;54(1):46-54.

4. Addington DEN, Pantelis C, Dineen M, et al. Efficacy and Tolerability of Ziprasidone Versus Risperidone in Patients With Acute Exacerbation of Schizophrenia or Schizoaffective Disorder: an 8-Week, Double-Blind, Multicenter Trial. J Clin Psychiatry 2004;65(12):1624-33.

5. Adler LE, Olincy A, Cawthra EM, et al. Varied effects of atypical neuroleptics on P50 auditory gating in schizophrenia patients. Am J Psychiatry 2004;161(10):1822-8.

6. Agelink MW, Majewski T, Wurthmann C, et al. Effects of newer atypical antipsychotics on autonomic neurocardiac function: a comparison between amisulpride, olanzapine, sertindole, and clozapine. J Clin Psychopharmacol 2001;21(1):8-13.

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Excluded – Not primary research (N = 89)

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Excluded – Ineligible study design (N = 70)

The following studies were excluded because the study design did not meet the eligibility criteria.

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Excluded – Not intervention of interest (N = 41)

The following studies were excluded because they did not examine an intervention of interest for this review.

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34. Sloman L. Haloperidol versus clomipramine in autistic disorder. 151st Annual Meeting of the American Psychiatric Association;1998 Jun.

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39. Weng S, Tang J, Wang G, et al. Comparison of the addition of Siberian Ginseng (Acanthopanax senticosus) versus fluoxetine to lithium for the treatment of bipolar disorder in adolescents: a randomized, double-blind trial. Curr Ther Res Clin Exp 2007 Jul;68(4):280-90.

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41. Zhang LD, Xu SH, Tang YH, et al. A comparative study of the treatment of schizophrenia with electric acupuncture, herbal decoction and Chlorpromazine. Am J Acupunct 1990;18(1):11-4.

Excluded – No outcome of interest (N = 19)

The following studies were excluded because they did not report any outcome of interest for this review.

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2. Alfaro CL, Wudarsky M, Nicolson R, et al. Correlation of antipsychotic and prolactin concentrations in children and adolescents acutely treated with haloperidol, clozapine, or olanzapine. J Child Adolesc Psychopharmacol 2002;12(2):83-91.

3. Delbello M. CHQ and CGAS in an open-label study of ziprasidone in pediatric patients with bipolar disorder, schizophrenia, or schizoaffective disorder. 46th Annual NCDEU (New Clinical Drug Evaluation Unit) Meeting; 2006;2006-15.

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18. Staller J. The effect of long-term antipsychotic treatment on prolactin. J Child Adolesc Psychopharmacol 2006 Jun;16(3):317-26.

19. Stevens JR, Kymissis PI, Baker AJL. Elevated prolactin levels in male youths treated with risperidone and quetiapine. J Child Adolesc Psychopharmacol 2005 Dec;15(6):893-900.

Excluded – Not diagnosis of interest (N = 18)

The following studies were excluded because the participants did not have the condition (diagnosis) of interest for this review.

1. Backman ML, Aberg LE, Aronen ET, et al. New antidepressive and antipsychotic drugs in juvenile neuronal ceroid lipofuscinoses: a pilot study. Eur J Paediatr Neurol 2001;5(Suppl. A):163-6.

2. Bloch M, Stager S, Braun A, et al. Pimozide-induced depression in men who stutter. J Clin Psychiatry 1997;58(10):433-6.

3. Flanders SC, Findling RL, Youngstrom EA, et al. Observed clinical and health services outcomes in pediatric inpatients treated with atypical antipsychotics: 1999-2003. J Child Adolesc Psychopharmacol 2007 Jun;17(3):312-27.

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10. Kapetanovic S, Aaron L, Montepiedra G, et al. The use of second-generation antipsychotics and the changes in physical growth in children and adolescents with perinatally acquired HIV. AIDS Patient Care STDS 2009;23(11):939-47.

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17. Soloff PH, Cornelius J, George A, et al. Efficacy of phenelzine and haloperidol in borderline personality disorder. Arch Gen Psychiatry 1993;50(5):377-85.

18. Zesiewicz MF, Natta MB, Kupst MJ. Effects of psychiatric hospitalization and psychotropic medications on weight in children. J Am Acad Child Adolesc Psychiatry 1987;Vol.26(6):854-7.

Excluded – Duplicates (N = 9)

The following articles were excluded because they were duplicates.

1. Chiu CC, Chen KP, Liu HC, et al. The early effect of olanzapine and risperidone on insulin secretion in atypical-naive schizophrenic patients. J Clin Psychopharmacol 2006;26(5):504-7.

2. Quetiapine equal to placebo for teen bipolar depression. Brown Univ Child Adolesc Psychopharmacol Update 2009;11(9):4-5.

3. DelBello MP, Schwiers ML, Rosenberg HL, et al. A double, randomized, placebo-controlled study of quetiapine adjunctive treatment for adolescent mania. J Am Acad Child Adolesc Psychiatry2002;41(10):1216-23.

4. Dougle CJ SL. Risperidone for the core symptom domains of autism: results from the study by the autism network of the research units on pediatric psychopharmacology. Am J Psychiatry 2005;(6):1142-8.

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Excluded – Non-English (N = 7)

The following studies were excluded because they were published in a language other than English.

1. A study of risperidone in the treatment of child schizophrenia. J Clin Psychol Med 2003;(2):80-1.

2. Comparison study of childhood schizophrenia treated with risperidone and chlorpromazine. Guizhou Med J 2004;(8):697-8.

3. Gao C. A comparative study of risperidone and perphenazine in the treatment of child schizophrenia. Chin J Health Psychol 2007;(10):950-1.

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Excluded – Published before 1987 (N = 3)

The following studies were excluded because they were published before 1987.

1. Anderson LT, Campbell M, Adams P, et al. The effects of haloperidol on discrimination learning and behavioral symptoms in autistic children. J Autism Dev Disord 1989;19(2):227-39.

2. Greenhill LL, Halperin JM, Barmack J. Cognitive effects of neuroleptic treatment in children with conduct disorder. 1996. p. 85-119.

3. Klein RG. Thioridazine effects on the cognitive performance of children with attention-deficit hyperactivity disorder. J Child Adolesc Psychopharmacol 1990;1(4):263-70.

[1] The primary study was published in 1984.
[2] Data of this study was collected in 1976.
[3] The primary study was published in 1985.

Unobtained Studies (N = 38)

The following articles could not be obtained through the university interlibrary loan system.

1. Assessment of therapeutic efficacy versus sedation with antipsychotic agents. J Clin Psychiatry 1996;57(6):1-12.

2. Allan ER, Sison CE, Alpert M, et al. The relationship between negative symptoms of schizophrenia and extrapyramidal side effects with haloperidol and olanzapine. Psychopharmacol Bull 1998;34(1):71-4.

3. Barzega G, Bogetto F, Maina G, et al. Quetiapine in schizophrenic patients: a high- and low-dose double-blind comparison. Eur J Psychiatr 2000;14(4):221-32.

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6. Biederman J. The treatment of psychotic symptoms in children and adolescents with bipolar disorder. 158th Annual Meeting of the American Psychiatric Association; 2005;2005-26.

7. Ceskova E, Svestka J, Buresova A, et al. Zuclopenthixol acetate in the treatment of acute psychoses. Homeost Health Dis 1994;35(6):297-8.

8. Chappell PB SF. Ziprasidone in Tourette's syndrome [abstract]. 151st Annual Meeting of the American Psychiatric Association; 1998 Jun.

9. Delbello M. Ziprasidone in the treatment of children and adolescents with bipolar mania or schizophrenia: an open label, dose ranging safety and tolerability study. 45th Annual NCDEU (New Clinical Drug Evaluation Unit) Meeting; 2005;2005-9.

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12. Eli L. Olanzapine versus placebo in the treatment of mania in adolescents with Bipolar I Disorder. Control Trials 2006.

13. Hamer AM. Update on children and adolescents with bipolar disorder. Psychiatr Times 2004;21(5):1-5.

14. Jakovljevic M, Dossenbach MR, Friedel P, et al. Olanzapine versus fluphenazine in the acute (6-week) treatment of schizophrenia. Psychiatr Danub 1999;11(1-2):3-11.

15. Jing Y. Health outcomes assessment for children and adolescents with bipolar disorder treated with and without atypical antipsychotics [dissertation]. United States, Ohio: University of Cincinnati; 2009.

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17. Klebovich A. Utilization of olanzapine and risperidone in Hungary with special concern to the treatment of schizophrenia in the psychiatric rehabilitation; 2009.

18. Kumra S, Frazier JA, Jacobsen LK, et al. Childhood-onset schizophrenia: a double-blind clozapine-haloperidol comparison; 1998: p.365-378.

19. Aman MG, Findling R. Risperidone versus placebo for conduct disorder in mentally retarded children. Pharmacotherapy: Annual Meeting of the American College of Clinical Pharmacy, Kansas, Missouri, USA 24-27, 1999;(10):1214.

20. Marder SR. Risperidone: clinical development: North American results. Clin Neuropharmacol 1992;15(Suppl 93A).

21. Martinez R. A double-blind study of risperidone versus placebo in conduct disorder in mentally retarded children conference abstract. Schizophrenia Research: abstracts of The VIIth International Congress on Schizophrenia Research, Santa Fe New Mexico USA 1999;17-21(288):1999.

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23. Peuskens J, Trivedi J, Malyarov S, et al. Prevention of schizophrenia relapse with extended release quetiapine fumarate dosed once daily: a randomized, placebo-controlled trial in clinically stable patients. Psychiatry 2007;4(11):34-50.

24. Qureshi NA, Al-Beyari TH, Al-Amri AH, et al. Neuroleptic malignant syndrome: a report of nine suspected cases. Saudi Pharmaceutical Journal 1996;4(3-4):179-89.

25. Rapoport J. The spectrum of extrapyramidal symptoms in children and young adults conference abstract. 150th Annual Meeting of the American Psychiatric Association 1111;San:Diego-22.

26. Reich DB WSH. Risperidone treatment of PTSD related to childhood abuse. 157th Annual Meeting of the American Psychiatric Association; 2004;2004-6.

27. Sallee FR NL. Double-blind, controlled comparison of haloperidol and pimozide in children with gilles de la Tourette's Syndrome. 149th Annual Meeting of the American Psychiatric Association; 1996;1996-9.

28. Sherritze S. Society for Neuroscience, 35th Annual Meeting. P and T 2006 Jan;31(1):52-6.

29. Sikich L. A double blind comparison of typical versus atypical antipsychotic agents on selected neurocognitive functions in children and adolescents with psychotic disorders [abstract]. Schizophr Res 2001;(1-2 Suppl):245.

30. Song D-H. Aripiprazole valuable in pediatric tic disorder or Tourette syndrome. P and T 2006 Dec;31(12):727-8.

31. Tohen M. Olanzapine in the treatment of acute mania in adolescents with bipolar I disorder: a 3-week randomized double-blind placebo-controlled study. Bipolar Disord.

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33. Trabert W. 100 years of delusional parasitosis: meta-analysis of 1,223 case reports. Psychopathology 1995;28(5):238-46.

34. Turgay A. A new generation antipsychotic risperidone versus placebo for severe conduct disorder in children with mental retardation [abstract]. Schizophr Res 2001;(1-2 Suppl):248-9.

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