Draft Comparative Effectiveness Review

Number XXX

Comparative Effectiveness of First and Second Generation Antipsychotics in the Pediatric and Young Adult Populations

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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 State Children's Health Insurance Program (SCHIP).

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 http://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 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.

Acknowledgments

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Structured Abstract

Objectives: To review and synthesize the evidence on first and second generation antipsychotics for the treatment of various psychiatric and behavioral conditions in children and young adults (aged ≤24 years).

Data Sources: Comprehensive literature searches were conducted in 10 electronic databases from 1987 to May 2010. Searches of the grey literature, trial registries, and reference lists were conducted to identify additional studies.

Methods: Study selection and quality assessment were conducted independently by several investigators in duplicate. Discrepancies were resolved by consensus or third-party adjudication. Data were extracted by one reviewer and verified by a second reviewer. Descriptive analysis was conducted for all studies and meta-analysis was performed when appropriate.

Results: In total, 74 unique studies were included in the review (57 trials and 15 cohort studies). The majority of the trials were considered to have a high risk of bias (n = 51, 89 percent). The methodological quality of the cohort studies was moderate. The following conditions were examined in the included studies: pervasive developmental disorders (11 studies), ADHD and disruptive behavior disorders (eight studies), bipolar disorder (eight studies), schizophrenia and schizophrenia-related psychosis (28 studies), Tourette syndrome (seven studies), behavior symptoms (four studies), and multiple conditions (eight studies). Results that were supported by a moderate level of evidence are described below; the level of evidence for all other outcomes was low or insufficient.

Fifty-nine studies evaluated the efficacy of antipsychotics for treating symptoms. Second generation antipsychotics to be superior to placebo for the following outcomes: behavior symptoms (ADHD and disruptive behavior disorders), clinical impressions (ADHD and disruptive behavior disorders, bipolar disorder, and schizophrenia), positive and negative symptoms (schizophrenia), and tic severity (Tourette syndrome).

Seventy-one studies provided data for at least one adverse event. There was a moderate level of evidence for several comparisons of second generation antipsychotics: the incidence of dyslipidmia was less for risperidone than olanzapine, prolactin-related adverse events were less common for olanzapine than risperidone, and there was less increase in weight/body composition for quetiapine and risperidone than for olanzapine. The incidence of the following adverse events was less for placebo than for one or more second generation antipsychotics: dyslipidemia, extrapyramidal symptoms, prolactin-related adverse events, sedation, and less increase in weight/body composition. There were fewer prolactin-related adverse events for aripiprazole compared with placebo.

Fifty-two studies examined the efficacy of antipsychotics for other short- and long-term outcomes. There was no significant difference in suicide-related behavior between second generation antipsychotics and placebo for bipolar disorder. The evidence for medication adherence, health-related quality of life, legal interactions, and other patient- and parent-reported outcomes was low or insufficient.

A total of 32 studies compared outcomes for various patient subpopulations. Most subpopulations were found to have no impact on outcomes or results were discordant across studies.

Conclusion: There was moderate evidence that second generation antipsychotics have superior symptom improvement and inferior adverse event profiles than placebo. Generally, data was too limited to make definite conclusions on the relative differences between various antipsychotics.

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Executive Summary

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

The full report and this summary are available at (URL to be inserted)

Introduction

Antipsychotic medications are widely used to treat a number of psychiatric disorders and are commonly categorized into two classes. First generation antipsychotics were initially developed in the 1950s. While they are used to treat psychotic symptoms, they are commonly associated with various side effects including extrapyramidal symptoms, dry mouth, sedation, and, in severe cases, tardive dyskinesia and neuroleptic malignant syndrome. Second generation antipsychotics emerged in the 1980s. They are generally thought to have a lower risk of motor side effects, but are associated with a higher risk of weight gain, elevated lipids and prolactin levels, and have been associated with the development of type 2 diabetes.

Use of antipsychotics for children and youth has increased over the past 20 years.[1-5] Prescribing antipsychotics to the pediatric population is controversial because there is limited high quality and longitudinal data on which to base clinical practice recommendations. In children and youth, antipsychotic medications have both approved and unapproved indications. Approved indications include treatment of childhood schizophrenia and bipolar disorders in the United States, while unapproved indications include behavioral symptoms (e.g., irritability and aggression) in younger children that are related to diagnosable conditions (e.g., pervasive developmental disorder). In general, the choice of medication in children and youth is often driven by side effect profiles that may affect normative 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 United States Food and Drug Administration (FDA)-approved first and second generation antipsychotics in children and young adults 24 years of age and younger.

Key Questions

The following key questions were investigated in the report:

KQ1. What is the comparative efficacy or effectiveness of first and second generation antipsychotics for treating disorder/illness specific and nonspecific symptoms in children, youth, and young adults (≤24 years) for the following disorders or illnesses:

1. Pervasive developmental disorders, including autistic disorder, Rett disorder, childhood disintegrative disorder, Asperger syndrome, and pervasive developmental disorder not otherwise specified (NOS)?
2. Attention deficit hyperactivity disorder (ADHD) and disruptive behavior disorders, including conduct disorder, oppositional defiant disorder, and disruptive behavior disorder?
3. Bipolar disorder, including manic or depressive phases, rapid cycling, mixed states?
4. Schizophrenia and schizophrenia-related psychoses, including schizoaffective disorder, drug-induced psychosis?
5. Tourette syndrome?
6. Obsessive-compulsive disorder (OCD)?
7. Posttraumatic stress disorder (PTSD)?
8. Anorexia nervosa?
9. Behavioral symptoms, including aggression, agitation, anxiety, behavioral dyscontrol, irritability, mood lability, self-injurious behaviors, and sleep disorders?

KQ2. Do first and second generation antipsychotics differ in the following medication-associated adverse events when used in children, youth, and young adults (≤24 years):

1. Overall adverse events?
2. Specific adverse events?
3. Withdrawals/time to withdrawal due to adverse events?
4. Persistence and reversibility of adverse events?

KQ3. Do first and second generation antipsychotics differ in the following other short- and long-term outcomes when used in children, youth, and young adults (≤24 years) (short-term outcomes are defined as outcomes occurring within 6 months; long-term outcomes are defined as outcomes occurring post-6 months):

1. Response rate with corresponding dose, duration of response, remission, relapse, speed of response, time to discontinuation of medication?
2. Growth and maturation?
3. Cognitive and emotional development?
4. Suicide-related behaviors (including ideation) or death by suicide?
5. Medication adherence and persistence?
6. School performance/attendance?
7. Work-related functional capacity?
8. Patient insight into illness?
9. Patient or parent/care provider reported outcomes, including levels of physical activity/inactivity, and diet (i.e., caloric intake, food preferences)?
10. Health-related quality of life?
11. Legal/justice system interaction (i.e., arrests, detention)?
12. Health care system utilization (e.g., protective services, social services)?
13. "Outcomes that matter" to children, youth and young adults, and their families?

KQ4. Do the efficacy and risks of first and second generation antipsychotics vary in differing subpopulations including:

1. Gender?

2. Age group (<6 years, 6–12 years, 13–18 years, 19–24 years)?
3. Race?
4. Comorbidities, including substance abuse, ADHD?
5. Cotreatment versus monotherapy?
6. First episode psychosis versus treatment in context of history of prior episodes (related to schizophrenia)?
7. Duration of illness?
8. Treatment naïve versus history of previous antipsychotics use?

Methods

Literature Search

The following bibliographic databases were searched systematically for studies published from 1987 to April 2010: MEDLINE®, Embase, CENTRAL, PsycINFO, IPA, CINAHL®, Scopus®, ProQuest Dissertations International, MedEffect Canada, and TOXLINE. Language restrictions were applied to restrict results to English language only. Age limits were applied to restrict results to children and young adults under 24 years of age. Filters for randomized controlled trials and cohort studies were applied to search results. Hand searches were conducted to identify literature from symposia proceedings from the following scientific meetings: American Academy of Child and Adolescent Psychiatry (2007-2008), International College of Neuropsychopharmacology (2007-2009), and International Society for Bipolar Disorders (2007-2009). Ongoing studies were identified by searching clinical trials registers, and reference lists of relevant studies were searched to identify additional studies. In addition, drug manufacturers were contacted to request published and unpublished study data. FDA documents related to the eligible drugs were retrieved and reviewed to identify additional data.

Study Selection

Two reviewers independently screened titles and abstracts using broad inclusion criteria. The full text of all articles identified as "include" or "unclear" were retrieved for formal review. Each article was independently assessed by two reviewers using detailed a priori inclusion criteria and a standardized form. Disagreements were resolved by consensus or by third-party adjudication.

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

Quality Assessment and Rating the Body of Evidence

Two reviewers independently assessed the methodological quality of included studies. The Cochrane Collaboration's risk of bias tool was used to assess randomized and nonrandomized controlled trials. Cohort studies were assessed using a modified Newcastle-Ottawa Quality Assessment scale. In addition, the source of funding was recorded for all studies. Decision rules regarding application of the tools was developed a priori through discussions with the lead

investigators. Discrepancies in quality assessment were resolved through consensus or third-party adjudication.

The body of evidence was rated by two independent reviewers using the EPC GRADE approach and discrepancies were resolved by consensus. The strength of evidence was assessed for the following key symptoms identified to be most important by the clinical investigators: aggression, anxiety, autistic symptoms, clinical impression of functioning, depression, manic symptoms, obsessive-compulsive symptoms, positive and negative symptoms of schizophrenia, social/occupational functioning and tics. Strength of evidence was also assessed for dyslipidemia, extrapyramidal symptoms, insulin-resistance, prolactin-related and sexual side effects, sedation and weight, as well as for health-related quality of life, legal/justice system interactions, medication adherence, patient or parent-reported outcomes and suicide. The following four major domains were assessed: risk of bias (low, medium, high), consistency (no inconsistency, inconsistency present, unknown or not applicable), directness (direct, indirect), and precision (precise, imprecise). The overall strength of evidence was graded as high, moderate, low, or insufficient.

Data Extraction

Data were extracted by one reviewer using a standardized form and verified for accuracy and completeness by a second reviewer. Extracted data included study characteristics, inclusion/exclusion criteria, participant characteristics, interventions, and outcomes. Reviewers resolved discrepancies by consensus or in consultation with a third party.

Data Analysis

Evidence tables and qualitative description of results were presented for all included studies. Studies were considered appropriate to combine in a meta-analysis if the study design, population, interventions being compared, and outcomes were deemed sufficiently similar. Results were combined using random effects models. Statistical heterogeneity was quantified using the I-squared (I^2) statistic.

Results

Description of Included Studies

The search strategy identified 9,693 citations; 74 unique studies met the eligibility criteria and were included in the review. The studies included 55 RCTs, two NRCTs, and 15 cohort studies (eight prospective and seven retrospective). The number of participants in the studies ranged from 8 to 335 (median = 42 [IQR, 24 to 99]). The mean age of study participants ranged from 4.0 to 21.5 years (median = 13.7 [IQR, 10.0 to 15.2]). The following conditions of interest were examined in the included studies: pervasive developmental disorders (11 studies), ADHD with aggression (one study), disruptive behavior disorders (seven studies), bipolar disorder (eight studies), schizophrenia and schizophrenia-related psychosis (28 studies), and Tourette syndrome (seven studies). Four studies examined patients with specific behavioral symptoms and eight studies included patients diagnosed with various psychiatric and behavioral conditions. There were no studies that met the eligibility criteria that examined OCD, PTSD, or anorexia nervosa.

Forty-eight studies provided head-to-head comparisons of antipsychotics. Of these, 14 studies compared first generation drugs with second generation drugs, four studies compared two or more first generation drugs, and 33 studies compared two or more second generation drugs (three studies provided head-to-head comparisons of both first versus second generation drugs

and multiple second generation drugs). There were 34 placebo-controlled studies, including two studies comparing a first generation antipsychotic with placebo and 32 comparing a second generation antipsychotic with placebo.

Methodological Quality of Included Studies

The majority of the RCTs were considered to have a high risk of bias for both subjective (n = 51, 89 percent) and objective outcomes (n = 49, 86 percent). Of the remaining RCTs, six were considered to have an unclear risk of bias. The two NRCTs had a high risk of bias. The most common sources of potential bias were inadequate allocation concealing, inadequate blinding, and incomplete outcome data. Most of the trials (78 percent) received industry funding, which introduces a risk of overestimation of the treatment effect. The methodological quality of the cohort studies was moderate, with a median score of 5 stars on a possible score of 8 stars (IQR: 4 to 6). Common weaknesses in the design of the studies included lack of independent blind outcome assessment and failure to adequately control for potential confounding factors.

Results of Included Studies

The results of the included studies are presented by the key question(s) they address. Table with the summary of findings for efficacy and safety are presented below.

KQ1: Disorder specific and nonspecific symptoms. Fifty-nine studies evaluated the efficacy of antipsychotics for treating symptoms: 10 for pervasive developmental disorders, eight for ADHD and disruptive behavior disorders, nine for bipolar disorder, 24 for schizophrenia and schizophrenia-related psychosis, five for Tourette syndrome, and four for behavioral symptoms (one study examined bipolar disorder and schizophrenia).

For pervasive developmental disorder, the level of evidence was low or insufficient for all symptom outcomes. For ADHD and disruptive behavior disorders, a moderate level of evidence based on seven studies found second generation antipsychotics to be superior to placebo for behavior symptoms and clinical impressions. For bipolar disorder and schizophrenia, a moderate level of evidence favored second generation antipsychotics over placebo for clinical impressions (based on five studies each); moderate evidence based on five studies also favored second generation antipsychotics over placebo for positive and negative symptoms in schizophrenia. For Tourette syndrome, a significant effect of second generation antipsychotics over placebo for reducing tic severity was supported by a moderate level of evidence from two studies. Data was too insufficient to make conclusions for first episode psychosis and behavioral symptoms due to the few studies that examined these populations. All other outcomes were rated as low or insufficient.

KQ2: Adverse events. Seventy-one studies provided data for at least one adverse event. The evidence was rated as low or insufficient to make conclusions for head-to-head comparisons of first versus second generation and first versus first generation antipsychotics. There was a moderate level of evidence for several comparisons of second generation antipsychotics: a significant effect favoring risperidone over olanzapine for dyslipidemia (five studies), favoring olanzapine over risperidone for prolactin-related adverse events (10 studies), and favoring quetiapine and risperidone over olanzapine for less increase in weight/body composition (4 studies and 13 studies, respectively). The evidence for all other outcomes comparing second generation antipsychotic was graded as low or insufficient.

There was insufficient evidence for making conclusions regarding first generation antipsychotics versus placebo. There was a moderate level of evidence favoring placebo over

various second generation antipsychotics for the following adverse events: dyslipidemia (quetiapine [two studies]), extrapyramidal symptoms (aripiprazole [four studies] and risperidone [14 studies]), prolactin-related adverse events (olanzapine [two studies] and risperidone [eight studies]), sedation (risperidone [12 studies] and ziprasidone [three studies]), and less increase in weight/body composition (aripiprazole, olanzapine, and quetiapine [four studies each]; risperidone [12 studies]). A moderate level of evidence from three studies found fewer prolactin-related adverse events for aripiprazole compared with placebo.

KQ3: Short- and long-term outcomes. Fifty-two studies examined the efficacy of antipsychotics for other short- and long-term outcomes. Data were provided for pervasive developmental disorders (nine studies), ADHD and disruptive behavior disorders (eight studies), bipolar disorder (nine studies), schizophrenia (17 studies), psychosis (four studies), Tourette syndrome (four studies), and behavioral symptoms (two studies), with one study providing data for two conditions.

There was a low level of evidence showing no significant difference in medication adherence between second generation antipsychotics and placebo for pervasive developmental disorder, ADHD and disruptive behavior disorder, and schizophrenia. A low level of evidence showed less medication adherence for second generation antipsychotics than placebo for bipolar disorder. For schizophrenia, a low level of evidence also showed no difference in medication adherence between first versus second generation antipsychotics and olanzapine versus risperidone. No significant difference in suicide-related behavior between second generation antipsychotics and placebo was supported by moderate evidence for bipolar disorder and by low evidence for schizophrenia. The evidence was rated as insufficient to make conclusions for health-related quality of life, legal interactions, and other patient- and parent-reported outcomes.

KQ4: Subpopulations. A total of 32 studies compared outcomes for various patient subpopulations. Gender and age were examined most frequently. Few associations between the patient or clinical variables and outcomes were supported by more than one study. The majority of subpopulations were found to have no impact on outcomes or the associations varied across studies. Two studies reported low intelligence to be associated with less response to second generation antipsychotics. Four studies found greater increases in prolactin level in females than males during treatment with second generation antipsychotics; however, this result was not consistent across studies.

Summary of the strength of evidence for efficacy outcomes

Outcome	Comparison (# studies)	Strength of evidence	Summary
Pervasive developmental disorder			
Aggression	None	Insufficient	No data
Anxiety	SGA vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Autistic symptoms	FGA vs. SGA (2 RCTs)	Low	No significant difference.
	Low-dose vs. medium-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (6 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 impressions	FGA vs. SGA (2 RCTs)	Insufficient	The evidence was too limited to make a conclusion.
	Continuous vs. discontinuous haloperidol (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. medium-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (3 RCTs)	Low	No significant difference.
OC symptoms	Low-dose vs. medium-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (3 RCTs)	Low	Significant effect in favor of SGA (MD = -1.7; 95% CI: -3.2, -0.3)
Social/occupational functioning	None	Insufficient	No data
HRQL	None	Insufficient	No data
Legal interactions	None	Insufficient	No data
Medication adherence	Low-dose vs. medium-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (2 RCTs)	Low	No significant difference.
Patient/parent-reported outcomes	SGA vs. placebo (1 RCT) for sleep and food frequency questionnaire	Insufficient	The evidence was too limited to make a conclusion.
Suicide-related behaviors	Low-dose vs. medium-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
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 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)
OC symptoms	None	Insufficient	No data
Social/occupational functioning	None	Insufficient	No data
HRQL	SGA vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Legal interactions	None	Insufficient	No data

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; HRQL = health-related quality of life; MD = mean difference; NCBRF = Nisonger Child Behavior Rating Scale; NR = not reported; OC = obsessive-compulsive; PCS = prospective cohort study; RCS = retrospective cohort study; RCT = randomized controlled trial; RR = relative risk; SGA = second generation antipsychotic

Summary of the strength of evidence for efficacy outcomes (continued)

Outcome	Comparison (# studies)	Strength of evidence	Summary
ADHD and disruptive behaviour disorder (continued)			
Medication adherence	SGA vs. placebo (5 RCTs)	Low	No significant difference.
Patient/parent-reported outcomes	None	Insufficient	No data
Suicide-related behaviors	None	Insufficient	No data
Bipolar Disorder			
Aggression	SGA vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Clinical impressions	Low-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose ziprasidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (5 RCTs)	Moderate	Significant effect in favor of SGA (MD = -0.7; 95% CI: -0.9, -0.5)
Depression	Olanzapine vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (4 RCTs)	Low	No significant difference.
Manic symptoms	Olanzapine vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose ziprasidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (7 RCTs)	Low	All except one study significantly favored SGA (studies not pooled due to high heterogeneity)
OC symptoms	None	Insufficient	No data
Positive & negative symptoms	None	Insufficient	No data
Social/occupational functioning	None	Insufficient	No data
HRQL	None	Insufficient	No data
Legal interactions	None	Insufficient	No data
Medication adherence	Low-dose vs. high-dose risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (2 RCTs)	Low	Significant effect in favor of placebo (RR = 2.0; 95% CI: 1.0, 4.0)
Patient/parent-reported outcomes	SGA vs. placebo (1 RCT) for switch to depression	Insufficient	The evidence was too limited to make a conclusion.
Suicide-related behaviors	Low-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose ziprasidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (6 RCTs)	Moderate	No significant difference for suicide-related deaths, attempts, or ideation.

Summary of the strength of evidence for efficacy outcomes (continued)

Outcome	Comparison (# studies)	Strength of evidence	Summary
Schizophrenia			
Aggression	SGA vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Clinical impressions	FGA vs. SGA (2 RCTs)	Low	Significant effect in favor of SGA (MD = -0.86; 95% CI: -1.6, -0.08)
	Clozapine vs. olanzapine (2 RCTs)	Low	No significant difference.
	Olanzapine vs. quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. risperidone (2 RCTs)	Low	No significant difference.
	Low-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose paliperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose risperidone (1 RCT)	Low	Significant effect in favor of high-dose risperidone (MD = 0.6; 95% CI: 0.3, 0.9)
	Low-dose ziprasidone vs. high-dose ziprasidone	Insufficient	The evidence was too limited to make a conclusion.
	Haloperidol vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (5 RCTs)	Moderate	Significant effect in favor of SGA (MD = -0.4; 95% CI: -0.6, -0.3)
Depression	None	Insufficient	No data
Manic symptoms	SGA vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
OC symptoms	None	Insufficient	No data
Positive and negative symptoms	FGA vs. SGA (3 RCTs, 1 PCS)	Low	No significant difference.
	Clozapine vs. risperidone (2 RCTs, 1 PCS)	Low	No significant difference.
	Olanzapine vs. risperidone (3 RCTs, 1 PCS)	Low	No significant difference.
	Low-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose paliperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose risperidone (1 RCT)	Low	Significant effect in favor of high-dose risperidone (MD = 0.6; 95% CI: 0.3, 0.9)
	Low-dose vs. high-dose ziprasidone	Insufficient	The evidence was too limited to make a conclusion.
	Haloperidol vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (5 RCTs)	Moderate	Significant effect in favor of SGA (MD = -0.4; 95% CI: -0.6, -0.3)
Social/occupational functioning	None	Insufficient	No data
HRQL	FGA vs. SGA (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Legal interactions	None	Insufficient	No data
Medication adherence	FGA vs. SGA (1 RCT, 1 PCS)	Low	No significant difference
	Olanzapine vs. quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. risperidone (3 RCTs, 1 PCS)	Low	No significant difference

Summary of the strength of evidence for efficacy outcomes (continued)

Outcome	Comparison (# studies)	Strength of evidence	Summary
Schizophrenia (continued)			
Medication adherence (continued)	Low-dose vs. high-dose risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (2 RCTs)	Low	No significant difference.
Patient/parent-reported outcomes	Low-dose vs. high-dose quetiapine (1 RCT) for caregiver strain	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (1 RCT) for caregiver strain	Insufficient	The evidence was too limited to make a conclusion.
Suicide-related behaviors	Olanzapine vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose paliperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose ziprasidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (4 RCTs)	Low	No significant difference.
Psychosis			
Aggression	None	Insufficient	No data
Anxiety	None	Insufficient	No data
Clinical impressions	FGA vs. SGA (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Depression	None	Insufficient	No data
Manic symptoms	Olanzapine vs. quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
OC symptoms	None	Insufficient	No data
Positive and negative symptoms	Olanzapine vs. quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Quetiapine vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose quetiapine vs. high-dose quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Social/occupational functioning	Low-dose vs. high-dose quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
HRQL	None	Insufficient	No data
Legal interactions	Low-dose vs. high-dose quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Medication adherence	FGA vs. SGA (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Patient/parent-reported outcomes	None	Insufficient	No data
Suicide-related behaviors	Low-dose vs. high-dose quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.

Summary of the strength of evidence for efficacy outcomes (continued)

Outcome	Comparison (# studies)	Strength of evidence	Summary
Tourette Syndrome			
Aggression	None	Insufficient	No data
Anxiety	None	Insufficient	No data
Clinical impressions	Pimozide vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Haloperidol vs. pimozide (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	FGA vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (2 RCTs)	Insufficient	The evidence was too limited to make a conclusion.
OC symptoms	SGA vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Social/occupational functioning	Haloperidol vs. pimozide (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Tics	Pimozide vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (2 RCTs)	Moderate	Significant effect in favor of SGA (MD = -6.98 (95% CI: -10.3, -3.6)
HRQL	None	Insufficient	No data
Legal interactions	None	Insufficient	No data
Medication adherence	Haloperidol vs. pimozide (1 RCT)	Insufficient	No data
	FGA vs. placebo (1 RCT)	Insufficient	No data
Patient/parent-reported outcomes	Short-term vs. long-term pimozide (1 RCT) for time to dose increase due to tic exacerbation	Insufficient	The evidence was too limited to make a conclusion.
Suicide-related behaviors	None	Insufficient	No data
Behavioral symptoms			
Aggression	Aripiprazole vs. ziprasidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. ziprasidone	Insufficient	The evidence was too limited to make a conclusion.
Anxiety	None	Insufficient	No data
Autistic symptoms	Low-dose vs. high-dose risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	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
Clinical impressions	Aripiprazole vs. ziprasidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Risperidone vs. placebo	Insufficient	The evidence was too limited to make a conclusion.
Depression	None	Insufficient	No data
Manic symptoms	Aripiprazole vs. ziprasidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
OC symptoms	None	Insufficient	No data
Positive and negative symptoms	None	Insufficient	No data
Social/occupational functioning	None	Insufficient	No data
Tics	None	Insufficient	No data
HRQL	Aripiprazole vs. ziprasidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
Legal interactions	None	Insufficient	No data
Medication adherence	None	Insufficient	No data
Patient/parent-reported outcomes	None	Insufficient	No data
Suicide-related behaviors	None	Insufficient	No data

Summary of the strength of evidence for adverse events

Outcome	Comparison (# studies)	Strength of evidence	Summary
First vs. second generation antipsychotic			
Dyslipidemia	Haloperidol vs. olanzapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Haloperidol vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
EPS	Haloperidol vs. clozapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Haloperidol vs. olanzapine (2 RCTs, 1 PCS)	Low	Significant effect in favor of olanzapine (MD = 3.53, 95% CI:1.14, 10.93)
	Haloperidol vs. risperidone (2 RCTs, 1 PCS)	Insufficient	The evidence was too limited to make a conclusion.
Insulin resistance	Haloperidol vs. olanzapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Haloperidol vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Prolactin-related and sexual AE	FGAs vs. clozapine (1 NRCT)	Insufficient	The evidence was too limited to make a conclusion.
	Haloperidol vs. clozapine	Insufficient	The evidence was too limited to make a conclusion.
	Haloperidol vs. olanzapine (1 RCT, 1 PCS)	Low	No significant difference.
	Haloperidol vs. risperidone (2 RCTs)	Low	No significant difference.
Sedation	Haloperidol vs. clozapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	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. clozapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Haloperidol vs. olanzapine (2 RCTs, 2 PCS)	Low	Significant effect in favor of haloperidol (MD = -5.79, 95% CI: -8.6, -2.98)
	Haloperidol vs. risperidone (2 RCTs, 1 PCS)	Low	No significant difference.
	Pimozide vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
First vs. first generation antipsychotic			
Dyslipidemia	None	Insufficient	No data
EPS	Haloperidol vs. pimozide (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Insulin resistance	None	Insufficient	No data
Prolactin-related and sexual AE	Haloperidol vs. pimozide (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Sedation	None	Insufficient	No data
Weight/ body composition	Haloperidol vs. pimozide (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Second vs. second generation antipsychotic			
Dyslipidemia	Aripiprazole vs. olanzapine (1 PCS)	Low	Significant effect in favor of aripiprazole (MD = -11.9, 95% CI, -23.4, -0.3).
	Aripiprazole vs. quetiapine (1 PCS)	Low	Significant effect in favor of aripiprazole (MD = -39.4, 95% CI, -71.3, -7.4).
	Aripiprazole vs. risperidone (1 PCS)	Insufficient	The evidence was too limited to make a conclusion.
	Clozapine vs. olanzapine (2 RCTs)	Low	No significant difference.
	Olanzapine vs. quetiapine (2 PCSs)	Low	No significant difference.

Summary of the strength of evidence for adverse events (continued)

Outcome	Comparison (# studies)	Strength of evidence	Summary
Second vs. second generation antipsychotic (continued)			
Dyslipidemia (continued)	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 PCS)	Low	No significant difference.
EPS	Aripiprazole vs. ziprasidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Clozapine vs. olanzapine (1 RCT, 1 PCS, 1 RCS)	Low	No significant difference.
	Clozapine vs. quetiapine (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	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 PCS, 3 RCS)	Low	No significant difference
	Olanzapine vs. ziprasidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Quetiapine vs. risperidone (3 RCTs)	Low	No significant difference.
Insulin resistance	Aripiprazole vs. olanzapine (1 PCS)	Insufficient	The evidence was too limited to make a conclusion.
	Aripiprazole vs. quetiapine (1 PCS)	Insufficient	The evidence was too limited to make a conclusion.
	Aripiprazole vs. risperidone (1 PCS)	Insufficient	The evidence was too limited to make a conclusion.
	Clozapine vs. olanzapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. quetiapine (2 PCS)	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)
	Clozapine vs. quetiapine (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Clozapine vs. risperidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. quetiapine (1 RCT, 1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. risperidone (7 RCTs, 3 PCSs)	Moderate	Significant effect in favor of olanzapine (MD = -18.7, 95% CI, -30.2, -7.2)
	Quetiapine vs. risperidone (3 RCTs)	Low	No significant difference.

Summary of the strength of evidence for adverse events (continued)

Outcome	Comparison (# studies)	Strength of evidence	Summary
Second vs. second generation antipsychotic (continued)			
Sedation	Aripiprazole vs. ziprasidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Clozapine vs. olanzapine (1 RCT, 1 PCS, 1 RCS)	Low	No significant difference.
	Clozapine vs. quetiapine (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Clozapine vs. risperidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. quetiapine (2 RCTs, 1 RCS)	Low	No significant difference.
	Olanzapine vs. risperidone (5 RCTs, 2 PCS, 2 RCS)	Low	No significant difference.
	Olanzapine vs. ziprasidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	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)	Insufficient	The evidence was too limited to make a conclusion.
	Aripiprazole vs. risperidone (1 PCS)	Insufficient	The evidence was too limited to make a conclusion.
	Aripiprazole vs. ziprasidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Clozapine vs. olanzapine (2 RCTs, 2 PCS, 1 RCS)	Low	No significant difference.
	Clozapine vs. quetiapine (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Clozapine vs. risperidone (1 RCS, 1 PCS)	Low	No significant difference.
	Olanzapine vs. quetiapine (2 RCTs, 2 PCSs)	Moderate	Significant effect in favor of quetiapine (MD = 6.8, 95% CI: 1.4, 12.2).
	Olanzapine vs. risperidone (7 RCTs, 1 NRCT, 4 PCSs, 1 RCS)	Moderate	Significant effect in favor of risperidone (MD = 2.4, 95% CI: 1.3, 3.4)
	Quetiapine vs. risperidone (3 RCTs, 2 PCSs)	Low	No significant difference.
First generation antipsychotic vs. placebo			
Dyslipidemia	None	Insufficient	No data
EPS	Haloperidol and pimozide vs. placebo	Insufficient	The evidence was too limited to make a conclusion.
Insulin resistance	None	Insufficient	No data
Prolactin-related and sexual AE	Haloperidol and pimozide vs. placebo	Insufficient	The evidence was too limited to make a conclusion.
Sedation	Haloperidol vs. placebo	Insufficient	The evidence was too limited to make a conclusion.
Weight/ body composition	Haloperidol and pimozide vs. placebo	Insufficient	The evidence was too limited to make a conclusion.

Summary of the strength of evidence for adverse events (continued)

Outcome	Comparison (# studies)	Strength of evidence	Summary
Second generation antipsychotic vs. placebo			
Dyslipidemia	Aripiprazole vs. placebo (2 RCTs)	Low	Significant effect in favor of placebo (MD = 2.5, 95% CI: 1.4, 4.4).
	Olanzapine vs. placebo (2 RCTs)	Low	Significant effect in favor of placebo (MD = 2.4, 95% CI: 1.2, 4.9).
	Quetiapine vs. placebo (2 RCTs)	Moderate	Significant effect in favor of placebo (MD = 29.1, 95% CI: 7.3, 50.9).
	Risperidone vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
EPS	Aripiprazole vs. placebo (4 RCTs)	Moderate	Significant effect in favor of placebo (MD = 4.6, 95% CI: 2.4, 9.1)
	Olanzapine vs. placebo (3 RCTs)	Low	No significant difference.
	Quetiapine vs. placebo (3 RCTs)	Low	No significant difference.
	Risperidone vs. placebo (14 RCTs)	Moderate	Significant effect in favor of placebo (MD = 2.7, 95% CI: 1.4, 4.9).
	Ziprasidone vs. placebo (3 RCTs)	Low	Significant effect in favor of placebo (MD = 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.
	Paliperidone vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Quetiapine vs. placebo (2 RCTs)	Insufficient	The evidence was too limited to make a conclusion.
	Risperidone vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
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 (4 RCTs)	Low	No significant difference.
	Risperidone vs. placebo (8 RCTs)	Moderate	Significant effect in favor of placebo (MD = 21.9, 95% CI: 8.9, 35.0).
	Ziprasidone vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Sedation	Aripiprazole vs. placebo (4 RCTs)	Low	Significant effect in favor of placebo (MD = 2.7, 95% CI: 1.1, 6.5)
	Olanzapine vs. placebo (3 RCTs)	Low	No significant difference.
	Quetiapine vs. placebo (4 RCTs)	Low	No significant difference.
	Risperidone vs. placebo (12 RCTs)	Moderate	Significant effect in favor of placebo (MD = 2.9, 95% CI: 1.5, 5.5)
	Ziprasidone vs. placebo (3 RCTs)	Moderate	Significant effect in favor of placebo (MD = 2.98, 95% CI: 1.7, 5.2)
Weight/ body composition	Aripiprazole vs. placebo (4 RCTs)	Moderate	Significant effect in favor of placebo (MD = 0.77, 95% CI: 0.40, 1.15)
	Olanzapine vs. placebo (4 RCTs)	Moderate	Significant effect in favor of placebo (MD = 4.6, 95% CI: 3.1, 6.1).
	Paliperidone vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Quetiapine vs. placebo (4 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.

Future Research

Recommendations for future research are as follows:

- 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. In addition, independent/investigator driven research efforts are needed to reduce the potential for overestimated treatment effects associated with industry-funded research and to supplement existing evidence.
- Studies examining the long-term efficacy and, particularly, the safety of antipsychotics over the course of several years are needed.
- Consensus on clinicallyand patient-important 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.
- Future studies should evaluate patient-important outcomes which have rarely been assessed in the evidence to date including health-related quality of life, school performance, and legal interactions.
- Studies examining associations between important outcomes and key patient subpopulations are needed to inform clinical practice.
- Large-scale effectiveness studies that apply few patient selection restrictions and closely match typical clinical practice are needed to achieve greater generalizability of results.

Conclusions

The quality of most of the evidence upon which to base conclusions regarding the efficacy of head-to-head comparisons of first versus second generation, first versus first generation, and second versus second generation antipsychotics for symptom improvement and other short- and long-term outcomes was low or insufficient. Few conclusions could be made regarding the comparison of adverse event profiles across different antipsychotics. Second generation antipsychotics were consistently found to result in greater symptom improvement and were found to be associated with greater risk for adverse events compared with placebo. Treatment benefits and risks were examined most frequently for schizophrenia, while the evidence for conditions such as pervasive developmental disorders, disruptive behaviour disorders, and Tourette syndrome was sparse. Future research is needed in order to determine the relative effectiveness among various antipsychotics for on-label and off-label uses in children and young adults.

Comparative Effectiveness Review

Chapter 1. Introduction

Antipsychotic medications, or antipsychotics, are widely used to treat a number of psychiatric disorders in pediatric and adult populations, including schizophrenia, bipolar mania, and psychotic depression. Antipsychotics are commonly categorized into two classes, first generation and second generation, marking two waves of historical development. First generation antipsychotics were initially developed in the 1950s. While they provide treatment for psychotic symptoms, they are commonly associated with various side effects including extrapyramidal symptoms (e.g., akathesia, parkinsonism, and dystonias), dry mouth, sedation, and in severe cases, tardive dyskinesia or neuroleptic malignant syndrome. Second generation antipsychotics emerged in the 1980s. They generally have lower risk of motor side effects, but are associated with significant weight gain, elevated lipid and prolactin levels, and have been associated with the development of type 2 diabetes.

Studies have shown that prescriptions for psychotropics in general in children and youth have increased over the last 20 years; this includes the use of antipsychotic medications.[1-5] The use of antipsychotics in the pediatric population is controversial mainly because of a lack of high-quality and longitudinal data, especially with regard to safety, on which to base conclusive clinical practice recommendations. In children and youth, antipsychotic medications vary in their on-label and off-label usage depending on the country and psychiatric condition. For example, approved indications are available for treatment of childhood schizophrenia and bipolar disorders in the United States. Off-label prescriptions are given to younger children for behavioral symptoms (e.g., irritability and aggression) that are related to diagnosable conditions (e.g., pervasive developmental disorder). In some instances, however, off-label use may be for behaviors that are also part of a child's normal developmental trajectory and/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 normative growth and development, medication adherence and persistence, as well as 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 examining the benefits and harms associated with the use of U.S. Food and Drug Administration (FDA)-approved first and second generation antipsychotics in pediatric and young adult populations (24 years of age and younger). The report is intended for a broad audience including professional societies developing clinical practice guidelines, patients and their care providers, and researchers conducting studies in this field.

Antipsychotic Drugs

A list of the first and second generation antipsychotics evaluated in this report, along with the FDA-approved indications and ages for the drugs, is presented in Table 1 and

Table 2, respectively. There is no consensus on the terminology to be used to describe antipsychotic medications (e.g., first and second generation, typical and atypical). For the purposes of this review, the terms "first generation" and "second generation" antipsychotics will be used.

Table 1. FDA-approved first generation antipsychotics

Generic name	Brand name(s)	Indications	Age group for which approved or studied in
Chlorpromazine	NA	Schizophrenia	Adults Children (1-12 years)
		Bipolar disorder (mania)	
		Hyperactivity	
		Uncontrolled hiccups, nausea and vomiting	
Fluphenazine	NA	Schizophrenia	Adults & children >12 years
		Bipolar disorder (mania)	
Haloperidol	Haldol®	Schizophrenia	Adults
		Tourette syndrome	
Loxapine	NA	Schizophrenia	Adults
Perphenazine	NA	Schizophrenia	Adults
Pimozide	Orap®	Tourette syndrome	Adults and children ≥8 years; limited evidence in children <12 years.
Prochlorperazine	Compro®	Schizophrenia	Adults and children
		Severe nausea and vomiting	Children >2 years and >20 pounds
Thiothixene	Navane®	Schizophrenia	Adults
Thioridazine	NA	Schizophrenia	Adults and children
Trifluoperazine	NA	Schizophrenia	Adults and children (6-12 years)

NA = not applicable

Table 2. FDA-approved second generation antipsychotics

Generic name	Brand name(s)	Indications	Age group for which approved or studied in
Aripiprazole	Abilify®	Schizophrenia	Adults & adolescents (13-17 years)
		Bipolar disorder (manic/mixed) monotherapy or adjunctive to lithium or valproate	Adults & children (10 -17 years)
		Adjunctive treatment of major depressive disorder	Adults
		Autistic disorder, Injection	Children (6-17 years)
Asenapine	Saphris®	Acute schizophrenia	Adults
		Bipolar disorder type 1 (manic/mixed)	
Clozapine	Clozaril® Fazaclo®	Treatment resistant schizophrenia	Adults
		Reduce the risk of suicidal behavior in younger patients with schizophrenia.	
Iloperidone	Fanapt®	Acute schizophrenia	Adults
Olanzapine	Zyprexa® Zyprexa® Zydis®	Schizophrenia Bipolar disorder (manic/mixed)	Adults & adolescents (13-17 years)
		Bipolar disorder Treatment resistant depression	Adults
Paliperidone	Invega®	Schizophrenia Schizoaffective disorder	Adult
Quetiapine	Seroquel® Seroquel XRTM	Schizophrenia	Adults & adolescents (13-17 years)
		Bipolar disorder (acute manic)	Adults, children & adolescents (10-17 years)
		Bipolar disorder (depression)	Adults
		Bipolar disorder (maintenance)	Adults

NA = not applicable

Table 2. FDA-approved second generation antipsychotics (continued)

Generic name	Brand name(s)	Indications	Age group for which approved
Risperidone	Risperdal® Risperdal® Consta® Risperidal®M-TAB®	Schizophrenia	Adults & adolescents (13-17 years)
		Bipolar disorder (manic/mixed)	Adults & adolescents (10-17 years)
		Irritability associated with autism	Children (5-16 yr) Safety and effectiveness in pediatric schizophrenic patients <13 years, BD mania <10 years & autism <5 years have not been established.
Ziprasidone	Geodon®	Schizophrenia	Adults
		Bipolar disorder (manic/mixed)	
		Bipolar disorder (maintenance)	

Conditions and Prevalence

The Evidence-based Practice Center was asked to examine the use of first and second generation antipsychotics for the following conditions: pervasive developmental disorders, attention deficit hyperactivity disorder (ADHD), disruptive behavior disorders, bipolar disorder, schizophrenia and schizophrenia-related psychosis, Tourette syndrome, obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), and behavioral symptoms (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 prior to the age 3 years and persist to varying degrees across the lifespan. The most commonly diagnosed disorders are autism (0.05 percent), and Asperger syndrome and pervasive developmental disorders not otherwise specified (NOS) combined (0.04 percent).[8]

The presentation of pervasive developmental disorders is affected strongly by the age and developmental level of the child, and the child's intellectual level. Key features of pervasive developmental disorders 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, as well as interpreting, language and non-verbal cues for communication.

Psychotropic medications are used as part of the management of pervasive developmental disorder-related symptoms, including managing aggressive outbursts in the context of emotional reactivity, reducing hyperactivity or repetitive behaviors (which can sometimes harm the child or others and interfere with development), and to promote sleep onset and continuity.

ADHD and Disruptive Behavior Disorders

ADHD and disruptive behavior disorders (including oppositional defiant disorders 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, and the prevalence of conduct disorder may be slightly less.[9] The rates of disorder vary by age and sex, but the most marked difference is the 6:1 ratio of boys to girls with ADHD prior to puberty. In general, sex differences are less for oppositional defiant disorder and conduct disorder in children 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, therefore, parent and teacher education and training about how to help shape a child's behavior at home and school. When children are six 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, anxiety) which, untreated, may also worsen impulsivity. Antipsychotic medications are also used 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 1 (manic episodes and depressive episodes occur independently of each other), bipolar 2 (hypomanic episodes and depressive episodes occur independently of each other), and bipolar disorder NOS (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 its validity as a condition is a focus of much research.[10] Bipolar 1 and bipolar 2 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 disorders includes the use of traditional mood stabilizing medications and antipsychotic medications. However, even when psychosis is not present, antipsychotics may be used as the first-line medication in children and adolescents because it is difficult to clinically diagnose an episode of mania in a child and 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 onset and at reducing impulsivity, psychotic symptoms, self harm, and hostility and aggression.

Schizophrenia and Schizophrenia-Related Psychosis

Schizophrenia and schizophrenia-like psychoses 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 schizophrenia-like psychoses are not common in pre-adolescents, and prevalence estimates are not known. In adolescents, the prevalence is estimated to be 0.1 percent, with about twice as many boys affected than girls.[11] The onset of the conditions is usually insidious with classification criteria being met over a long followup period. 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 affected typically by both types of symptoms and, depending on circumstances, a person may have little or no insight into their symptoms. However, patient insight is difficult to assess, particularly for young children or those with developmental delays. 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. While some individuals have only motor or verbal tics, a diagnosis of Tourette disorder requires that both types of tics must 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 than girls are affected.[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 (50 percent) and/or obsessive-compulsive disorder (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 (tardive Tourette disorder). Antipsychotics may also have a beneficial impact on comorbid conditions.

Obsessive-Compulsive Disorder

OCD is an anxiety disorder characterized by developmentally inappropriate and persistent anxiety with associated behaviorial disturbances that include obsessions and/or compulsions severe enough to be time consuming (more than 1 hour per day) and significantly interfere with daily activities. Obsessions are recurrent, persistent, unwanted, and may involve disturbing thoughts, images, or impulses that are intrusive and inappropriate, and that cause a great deal of anxiety, distress, fear, or worry. Obsessions 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, ordering, checking, hoarding) or mental acts (e.g., preoccupation with praying, counting, word repetition) or 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. However, performing these behaviors reduces the anxiety temporarily, and 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.

Posttraumatic Stress Disorder

PTSD is the development of an anxiety disorder following a reaction of intense fear, helplessness, or horror as a result of exposure to or after learning about an event that involves actual or threatened death or serious injury to oneself or another person's physical integrity. Characteristic symptoms of PTSD, which may appear soon after the event or several years later, include a persistent reexperience of the traumatic event (e.g., images, thoughts, dreams, flashbacks), persistent avoidance of stimuli associated with the trauma, numbing of general responsiveness, and persistent symptoms of increased arousal (e.g., difficulty sleeping, irritability, outbursts of anger) that 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 PTSD 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 between risk groups with the highest rates ranging between one-third to more than half among victims of rape and survivors of military combat, captivity, and 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 accepted 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 three consecutive months) due to abnormally low levels of estrogen, which is included as a diagnostic criterion.

This eating disorder includes two subtypes, restricting and binge-eating/purging, which are defined by behavioural indicators. 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, while the individual with the binge/purge subtype may engage

in recurrent bingeing, the 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 aged 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 outcome measures have been used to assess symptomatology and extrapyramidal side effects in pediatric patients with psychiatric and behavioral disorders. The studies reviewed in this report assessed outcomes using checklists and scales that varied in being 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 efficacy outcomes and extrapyramidal effects is provided in Table 3 and Table 4, respectively.

Table 3. Common efficacy outcome measures

Outcome Measure	Outcome/ Description	Domains/Items	Assessor	Scaling	Psychometric Properties
Aberrant Behavior Checklist (ABC)[17]	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)	Health care staff	58 items are rated on a 4-point scale (0—not a problem to 3—to 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]	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	Clinician	21 items are rated on a 7-point scale (0—not present, very mild, mild, moderate, moderately severe, severe, 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 (non-anchored); 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]	To assess the severity of depression in children aged 6–12 years of age	1) Mood (i.e. depressed feelings) 2) Somatic (i.e. appetite) 3) Subjective (i.e. self-esteem) 4) Behavior (i.e. social withdrawal)	Clinician	17 items are rated on a 7 point scale (0—unable to rate, 1—normal, 2—doubtful, 3-4—mild, 5-6—moderate, to 7—severe); score totalled 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]	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	Clinician	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 with 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]	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)	Clinician	*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 efficacy outcome measures (continued)

Outcome Measure	Outcome/ Description	Domains/Items	Assessor	Scaling	Psychometric Properties
Nisonger Child Behavior Rating Form (NCBRF)[24]	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	Parent/ Teacher	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]	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	Family/ Health care staff	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]	To measure the prevalence of positive and negative syndromes in schizophrenia	1) Positive scale (PS) 2) Negative scale (NS) 3) General psychopathology scale (GPS)	Clinician	30 items are rated on a 7-point scale (1—absent, minimal, mild, moderate, moderate-sever, severe, 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]	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-though disorder 8) Content 9) Disruptive-aggressive behavior 10) Appearance 11) Insight	Clinician	11 domains are rated on a 4-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

Table 4. Extrapyramidal symptom outcome measures

Outcome Measure	Outcome/ Description	Domains/Items	Assessor	Scaling	Psychometric Properties
Abnormal Involuntary Movements Scale (AIMS)[28]	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)	Clinician	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 Akathesia Scale (BAS)[29]	To rate drug-induced akathesia	1) Objective measures *Subjective measures:* 2a) Awareness of restlessness 2b) Distress related to restlessness 3) Global clinical assessment of akathesia	Clinician	*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, questionable, mild, moderate, marked, to 5—severe)	Cohen's κ: 0.738 (Domain 1), 0.827 (Domain 2a), 0.901 (Domain 2b), 0.955 (Domain 3)
Extrapyrimidal Symptom Rating Scale (ESRS)[30,31]	To measure extrapyramidal symptoms in patients on neuroleptic drug treatments	1) Parkinsonism symptoms questionnaire 2) Physician examination: [i]Parkinsonism and Akathesia, [ii] Dystonia, [iii] Dyskinetic Movements 3) Global impression for severity of dyskinesia, parkinsonism, dystonia, akathesia	Clinician	*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]	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	Clinician	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)

Scope and Key Questions

The key questions investigated for the pediatric and young adult (≤ 24 years) populations in this report are presented below. An analytic framework is presented in Figure 1.

KQ1. What is the comparative efficacy or effectiveness of first and second generation antipsychotics for treating disorder/illness specific and nonspecific symptoms in children, youth, and young adults (≤24 years) for the following disorders or illnesses:

1. Pervasive developmental disorders, including autistic disorder, Rett disorder, childhood disintegrative disorder, Asperger syndrome, and pervasive developmental disorder NOS?
2. ADHD and disruptive behavior disorders, including conduct disorder, oppositional defiant disorder, and disruptive behavior disorder NOS?
3. Bipolar disorder, including manic or depressive phases, rapid cycling, mixed states?
4. Schizophrenia and schizophrenia-related psychoses, including schizoaffective disorder, drug-induced psychosis?
5. Tourette syndrome?
6. Obsessive-compulsive disorder (OCD)?
7. Posttraumatic stress disorder (PTSD)?
8. Anorexia Nervosa?
9. Behavioral symptoms, including aggression, agitation, anxiety, behavioral dyscontrol, irritability, mood lability, self-injurious behaviors, and sleep disorders?

KQ2. Do first and second generation antipsychotics differ in the following medication-associated adverse events when used in children, youth, and young adults (≤ 24 years):

1. Overall adverse events?
2. Specific adverse events?
3. Withdrawals/time to withdrawal due to adverse events?
4. Persistence and reversibility of adverse events?

KQ3. Do first and second generation antipsychotics differ in the following other short- and long-term outcomes when used in children, youth, and young adults (≤ 24 years) (short-term outcomes are defined as outcomes occurring within 6 months; long-term outcomes are defined as outcomes occurring post-6 months):

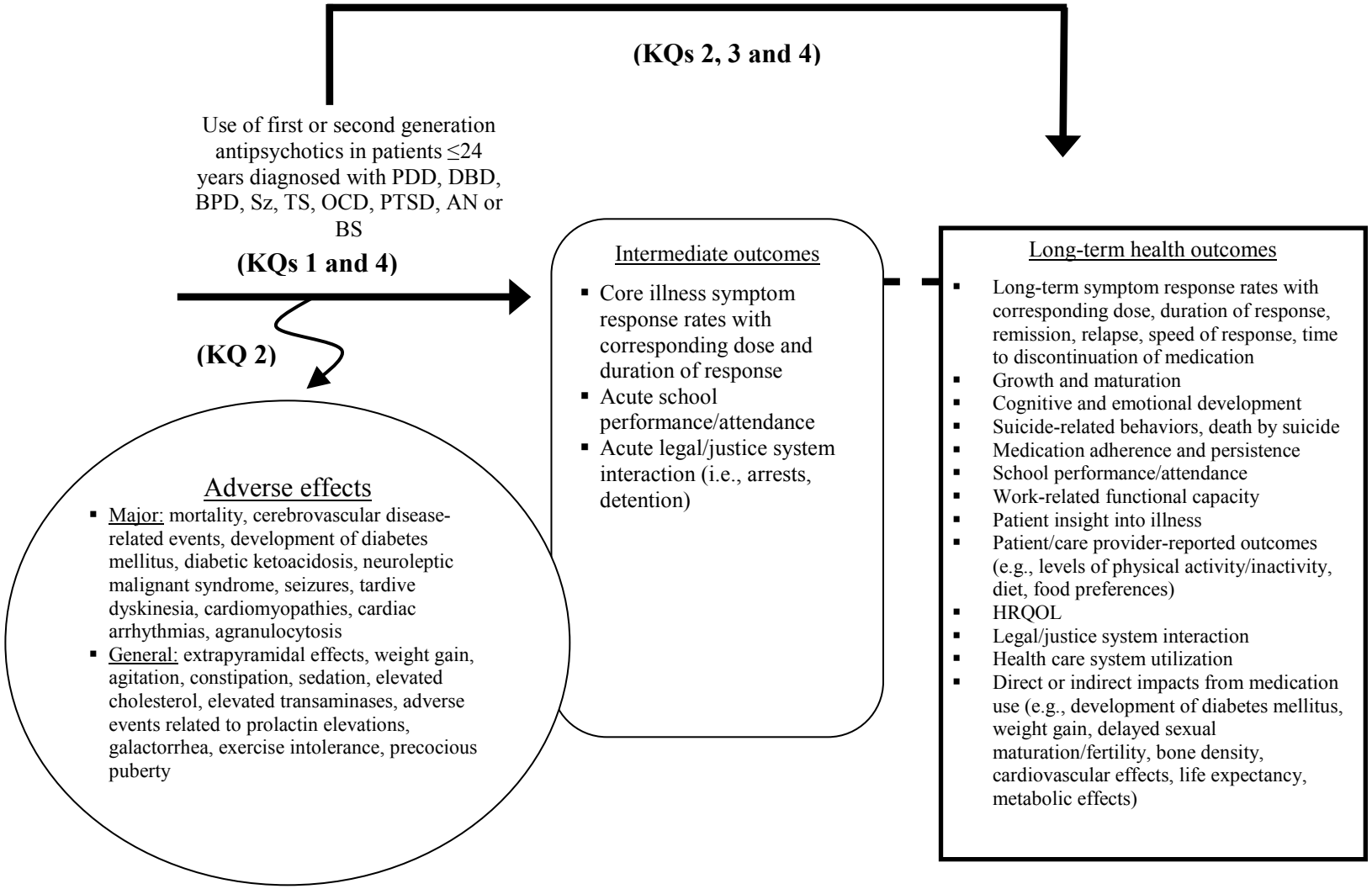
1. Response rate with corresponding dose, duration of response, remission, relapse, speed of response, time to discontinuation of medication?
2. Growth and maturation?
3. Cognitive and emotional development?
4. Suicide-related behaviors (including ideation) or death by suicide?
5. Medication adherence and persistence?
6. School performance/attendance?
7. Work-related functional capacity?
8. Patient insight into illness?
9. Patient or parent/care provider reported outcomes, including levels of physical activity/inactivity, and diet (i.e., caloric intake, food preferences)?
10. Health-related quality of life?

11. Legal/justice system interaction (i.e., arrests, detention)?
12. Health care system utilization (e.g., protective services, social services)?
13. "Outcomes that matter" to children, youth and young adults, and their families?

KQ4. Do the efficacy and risks of first and second generation antipsychotics vary in differing subpopulations including:

1. Gender?
2. Age group (<6 years, 6–12 years, 13–18 years, 19–24 years)?
3. Race?
4. Comorbidities including substance abuse, ADHD?
5. Cotreatment versus monotherapy?
6. First episode psychosis versus treatment in context of history of prior episodes (related to schizophrenia)?
7. Duration of illness?
8. Treatment naïve versus history of previous antipsychotics use?

Figure 1. Analytic framework
This framework evaluates the comparative effectiveness of FDA-approved first generation and second generation antipsychotics in the pediatric and young adult population diagnosed with pervasive developmental disorder (PDD), disruptive behavior disorder (DBD), bipolar disorder (BPD), schizophrenia or other psychotic illnesses (Sz), obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), Tourette syndrome (TS), anorexia nervosa (AN) and behavioral symptoms (BS)



Chapter 2. Methods

This chapter describes the topic refinement process and the prospectively designed protocol that the EPC used to synthesize the evidence on the effectiveness and safety of first and second generation antipsychotics for the treatment of pediatric and young adult patients with psychiatric and behavioral disorders.

Topic Refinement and Technical Expert Panel

The EPC was commissioned to conduct a preliminary literature review to gauge the available evidence that addresses the review topic and to draft the key research questions for a comprehensive comparative effectiveness review. In consultation with AHRQ and the Scientific Resource Center, a panel of key informants was created to provide input in the development of the key questions and scope of the evidence report. The public was invited to comment on these key questions over a period of 1 month. After reviewing the public comments, the key questions were finalized and submitted to AHRQ for approval.

A technical expert panel was subsequently created to provide content and methodological expertise throughout the development of the comparative effectiveness review. The technical experts are identified in Appendix A.

Literature Search Strategy

Search strategies were designed and implemented to identify evidence relevant to the report. The following bibliographic databases were searched systematically for studies published from 1987 to April 2010: MEDLINE®, Embase, CENTRAL, PsycINFO, IPA, CINAHL®, Scopus®, and ProQuest Dissertations International. In addition, MedEffect Canada and TOXLINE were searched for information on adverse events. The search results were restricted to studies including children and young adults 24 years of age or less and published in the English language. Filters for randomized controlled trials (RCTs) and cohort studies were also applied to the search results. (See Appendix B for the detailed search strategies.)

Search terms were selected by scanning search strategies of systematic reviews on similar topics and examining index terms of potentially relevant studies. A combination of patient headings and textwords was adapted for each electronic resource and included terms for: 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, ADHD, conduct disorder, oppositional defiant disorder, psychotic disorders, bipolar disorder, depressive disorder, OCD, anorexia nervosa, Tourette syndrome, and PTSD and terms for FDA-approved first and second generation antipsychotic drugs (chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, pimozide, prochlorperazine, thiothixene, thioridazine, trifluoperazine, aripiprazole, asenapine, clozapine, clopenthixol, iloperidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone). The search strategy was peer reviewed independently by a second research librarian (TD).

Reference lists of relevant studies were screened to identify additional potentially relevant studies. Conference proceedings of the following scientific meetings were hand searched: American Academy of Child and Adolescent Psychiatry (2007, 2008), International College of

Neuropsychopharmacology (2007-2009), and International Society for Bipolar Disorders (2007-2009). Online trial registries (WHO and ClinicalTrials.gov) were searched to identify unpublished and ongoing trials. In addition, drug manufacturers were contacted to request published and unpublished study data. As well, the FDA documents related to the eligible drugs were retrieved and reviewed for additional data.

The results from the literature searches were entered into and managed in a Reference Manager© for Windows version 11.0 (2004-2005 Thomson ResearchSoft) bibliographic database.

Criteria for Study Selection

The study inclusion and exclusion criteria were developed in consultation with the technical expert panel and are presented in

Table **5**. Our population of interest was children, adolescents and young adults 24 years of age and younger with psychiatric or behavioral disorders. Studies that enrolled adults were included only when over 80 percent of the included patients were 24 years of age or younger or when subgroup analyses or individual patient data for patients within the eligible age range were provided. Studies that enrolled patients from various condition categories (e.g., pervasive developmental disorder and schizophrenia) were included only if they reported efficacy data separately by condition; adverse event data aggregated for all patients across conditions was not an exclusion criterion. Studies with mixed populations were classified as addressing "multiple conditions". Patients were not excluded for polypharmacy; however, cotreatments that were given systematically to only one group (e.g., olanzapine + citalopram vs. ziprasidone) and that precluded the effect of the antipsychotic from being determined 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 (randomized and nonrandomized) and cohort studies (prospective or retrospective)
Population	Children, youth, and young adults (≤24 years) with one or more of the following conditions: PDD, ADHD, DBD, bipolar disorder, schizophrenia or schizophrenia-related psychosis, Tourette syndrome, OCD, PTSD, Anorexia Nervosa or other behavioral symptoms.
Intervention	Any FDA-approved FGA (chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, pimozide, prochlorperazine, thiothixene, thioridazine, trifluoperazine) or 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 and maturation, cognitive and emotional development, suicide-related behaviors, medication adherence, school performance, work-related functional capacity, patient insight into illness, patient or 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 and hyperactivity disorder; DBD = disruptive behavior disorder; FGA = first generation antipsychotic; OCD = obsessive-compulsive disorder; PDD = pervasive developmental disorder; PTSD = posttraumatic stress disorder; SGA = second generation antipsychotic

Article screening was conducted 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 for study design, population and antipsychotic intervention. Each article was rated as "include," "exclude," or "unclear". The full text of all articles classified as "include" or "unclear" by at least one of the reviewers was retrieved for detailed review. Two reviewers independently assessed each study using a detailed standard inclusion/exclusion form (Appendix C1). Disagreements were resolved by consensus or third-party adjudication.

FDA reports were screened for relevance by a single reviewer. An a priori decision was made to consider only studies which included patients 18 years of age or younger to be potentially relevant, due to the complexities of determining the age of study participants referenced in the FDA reports.

Assessment of Methodological Quality

The internal validity of RCTs and nonrandomized controlled trials (NRCTs) was assessed using the Cochrane Collaboration risk of bias tool (Appendix C2).[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 is rated "yes," "unclear," or "no." Blinding and incomplete outcome data were assessed separately for subjective outcomes (e.g., health-related quality of life or symptom scales) and objective clinical outcomes (e.g., laboratory measures). For "other" sources of bias, baseline imbalances between groups, early stopping for benefit, and funding source were assessed. The overall assessment was based on the responses to individual domains. If one or more individual domains were assessed as having a high risk of bias, the overall score was rated as high risk of bias. The overall risk of bias was rated as low only if all components were assessed as having a low risk of bias. The overall risk of bias for all other studies was rated as unclear.

Cohort studies were assessed using a modified version of the Newcastle-Ottawa Quality Assessment Scale (Appendix C2).[34] The scale comprises seven items assessing sample selection, comparability of cohorts, and the assessment of outcomes. Each item that was adequately addressed in the study was awarded one star, with the exception of the comparability of cohorts for which a maximum of two stars could be given. The overall score was calculated by tallying the stars. In addition, information on the source of funding was collected for each study.[35]

Two reviewers independently assessed the methodological quality of the included studies. Each assessment form was pilot tested on a sample of studies, and decision rules regarding application of the tools was developed a priori through discussions with the lead investigators. Discrepancies in quality assessment were resolved through consensus or third-party adjudication.

Data Extraction

Data were extracted using an electronic form and imported into a Microsoft Excel™ 2007 spreadsheet (Microsoft Corp., Redmond, WA) (Appendix C3). Data were extracted by one reviewer and checked for accuracy and completeness by a second reviewer. Reviewers resolved discrepancies by consensus or in consultation with a third party. Extracted data included study

and participant characteristics (including inclusion/exclusion criteria, age, sex, ethnicity, and diagnosis), intervention and co-intervention characteristics (including dose, frequency, and duration), and outcome data. We reported outcomes only if quantitative data was reported or could be derived from graphs. Outcomes that were only described qualitatively (e.g., "there was no difference between the groups") or reported only as a p-value were not included in the data analysis. Studies that directly compared one antipsychotic with another antipsychotic were classified "head-to-head"; studies that compared an antipsychotic with placebo were classified as "placebo" studies. As several studies included both active comparator and placebo arms, a single study could provide data both for "head-to-head" and "placebo" comparisons.

When more than one publication reported the results of a single study, the earliest published report of the main outcome data was considered to be the primary publication. Data were extracted first from the primary publication and then supplemented with any additional outcome data reported in the secondary publications. The primary publication is referenced throughout the evidence report and a list of companion articles is provided in Appendix F.

For efficacy outcomes addressing disorder specific and nonspecific symptoms (Key Question 1), decisions regarding which efficacy outcome measures would be extracted were made in consultation with clinical experts. A list of outcome measures extracted for each condition is provided in Table 6 below. Outcome measures used in studies that enrolled patients with behavioral symptoms or multiple conditions are listed in the "other" category. The total score was extracted for each outcome measure; when the total score was not provided, all reported subscores were extracted. For each study arm, the mean baseline and endpoint or change scores, standard deviations, and sample size were extracted. Outcome data was not extracted for those studies that did not provide a followup change or endpoint mean, or from which followup scores could not be calculated.

Table 6. Efficacy outcome measures extracted in the comparative effectiveness review

Outcome measure	PDD	ADHD / DBD	Bipolar	Schizophrenia	Tourette	Other
Aberrant behavior checklist (ABC)	X	X		X		X
Behavior problems inventory (BPI)		X				
Brief psychiatric rating scale (BPRS)			X	X		X
Childhood autism rating scale (CARS)	X					
Child behavior checklist (CBCL)	X	X		X		
Child mania rating scale (CMRS)			X			
Children's aggression scale (CAS)		X				
Children's depression rating scale (CDRS)			X			
Children's global assessment scale (CGAS)	X	X	X	X	X	
Clinical global impressions (CGI)	X	X	X	X	X	X
Children's psychiatric rating scale (CPRS)	X			X		
Children's Yale-Brown obsessive-compulsive scale (CYBOCS)	X				X	
Connor's parent/ teacher rating scale (CPTRS)		X		X		
Gilliam autism rating scale (GARS)	X					
General behavior inventory (GBI)			X			
Global assessment of functioning (GAF)				X	X	X
Hamilton anxiety rating scale (HARS)			X			
Hamilton depression scale (HDS)			X			
Nisonger child behavior rating scale (NCBRS)	X	X				
Overt aggression scale (OAS)	X	X	X	X		X
Rating of aggression against people and/or property scale (RAAPP)		X				
Personal assessment checklist (PAC)						X
Positive and negative symptom scale (PANSS)			X	X		
Ritvo-Freeman real life rating scale (RFRLRS)	X					
Scale for the assessment of negative symptoms (SANS)				X		
Scale for the assessment of positive symptoms (SAPS)				X		
Social and occupational functioning assessment scale (SOFAS)				X		
Strength and difficulties questionnaire				X		
Tic symptom self-report (TSSR)					X	
Total child symptom inventory (TCSI)		X				
Vineland adaptive behavior scales (VABS)	X	X		X		
Yale global tics severity score (YGTSS)					X	
Young mania rating scale (YMRS)			X	X		X

ADHD = attention deficit and hyperactivity disorder; DBD = disruptive behavior disorder; PDD = pervasive developmental disorder

Similarly, using adverse event monitoring guidelines provided by Correll et al.,[36] the lead investigators specified which adverse event data should be collected for each of the outcome categories specified in Key Question 2. Adverse events included in this review are listed in Table

7. For each adverse event, the number of patients in each treatment or placebo group and the number of patients with an adverse event were recorded. Each event was counted as if it corresponded to a unique individual. Since 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. Only quantitative adverse event data describing the number of patients who experienced an event were extracted (i.e., 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, prolactin levels), the mean change or endpoint score, standard deviation, and sample size were extracted.

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

Broad AE categories	Specific outcome data extracted
Mortality	—
Cerebrovascular events	—
Weight / 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, akathesia, tardive and withdrawal dyskinesia, dystonia
Cardiac	MI, cardiomyopathies, myocarditis, cardio 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
Thyroid dysfunction	Serum total T4, serum free thyroxine, TSH
Seizures	—
Neuroleptic malignant syndrome	—
Constipation	—
Exercise intolerance	—
Precocious puberty	—
Dermatological	—

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; TSH = thyroid stimulating hormone; WBC = white blood cell

For other short-term and long-term efficacy outcomes (Key Question 3), treatment response and remissions were reported as defined by the study authors. For outcomes measured using scales (e.g., health-related quality of life or cognitive outcomes), the total score was extracted. When the total score was not provided, all reported subscores were extracted.

To assess whether the efficacy of antipsychotics varied in different subpopulations (Key Question 4), for each study 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.

Applicability

The applicability of the body of evidence was assessed following the PICOTS (population, intervention, comparator, outcomes, timing of outcome measurement, setting) format. Factors that may potentially weaken the applicability of individual studies are described in the evidence tables (Appendix E).

Grading the Body of Evidence

We used the EPC GRADE approach[37] to assess the strength of the evidence for the following outcomes: aggression, anxiety, autistic symptoms, clinical impressions of functioning, depression, manic symptoms, obsessive-compulsive symptoms, positive and negative symptoms of schizophrenia, social/occupational functioning, tics, dyslipidemia, extrapyramidal symptoms, insulin-resistance, prolactin-related and sexual side effects, sedation, and weight, as well as for health-related quality of life, legal/justice system interactions, medication adherence, patient or parent-reported outcomes, and suicide-related behaviors. The following four major domains were examined for each outcome: risk of bias (rated as low, medium, or high), consistency (rated as no inconsistency, inconsistency present, unknown, or not applicable), directness (rated as direct or indirect), and precision (rated as precise or imprecise). When no studies were available for an outcome, the evidence was graded as insufficient. Each key outcome for each comparison of interest was given one of the following overall evidence grades based on the ratings for the individual domains: high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research may change our confidence in the estimate of effect and may change the estimate), low (further research is likely to change the confidence in the estimate of effect and is likely to change the estimate), or insufficient (evidence either is unavailable or does not permit estimation of an effect). The body of evidence was graded by two independent reviewers and discrepancies were resolved by consensus.

Data Analysis

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

Evidence tables and qualitative description of results are presented for all included studies. When appropriate, meta-analyses were performed to synthesize the available data on the efficacy of antipsychotic medications.

Evidence for efficacy was summarized separately for each condition. Data within each condition category are presented both by individual drug comparison and across drug class (e.g., all second generation antipsychotics). Evidence on adverse events was summarized separately for each drug across all conditions.

The following a priori criteria were used to decide whether results from individual studies should be pooled. Studies were considered appropriate to combine if the study design, study population, interventions being compared, and outcomes were sufficiently similar. Cohort studies were analyzed separately from trials. Study populations were considered similar if the

condition category and ages of participants were comparable among eligible studies. Meta-analyses were conducted when two or more studies compared the same intervention.

Quantitative results were meta-analyzed in Review Manager version 5.0 (The Cochrane Collaboration, Copenhagen, Denmark). For continuous variables, mean differences (MD) were calculated for individual studies. Relative risks (RR) were computed to estimate between-group differences in studies that reported dichotomous outcomes. If no events were 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 risk ratio. When no events were reported in both of the treatment arms, the RR was undefined and was denoted as "not calculated (NC)" in the results tables. All results are reported with 95% CI when possible.

All meta-analyses used a random effects model. Statistical heterogeneity was quantified using the I-squared (I^2) statistic. An I^2 value greater than 50 percent was considered substantial heterogeneity.[38,39] A meta-analysis was not conducted when heterogeneity exceeded 80 percent.

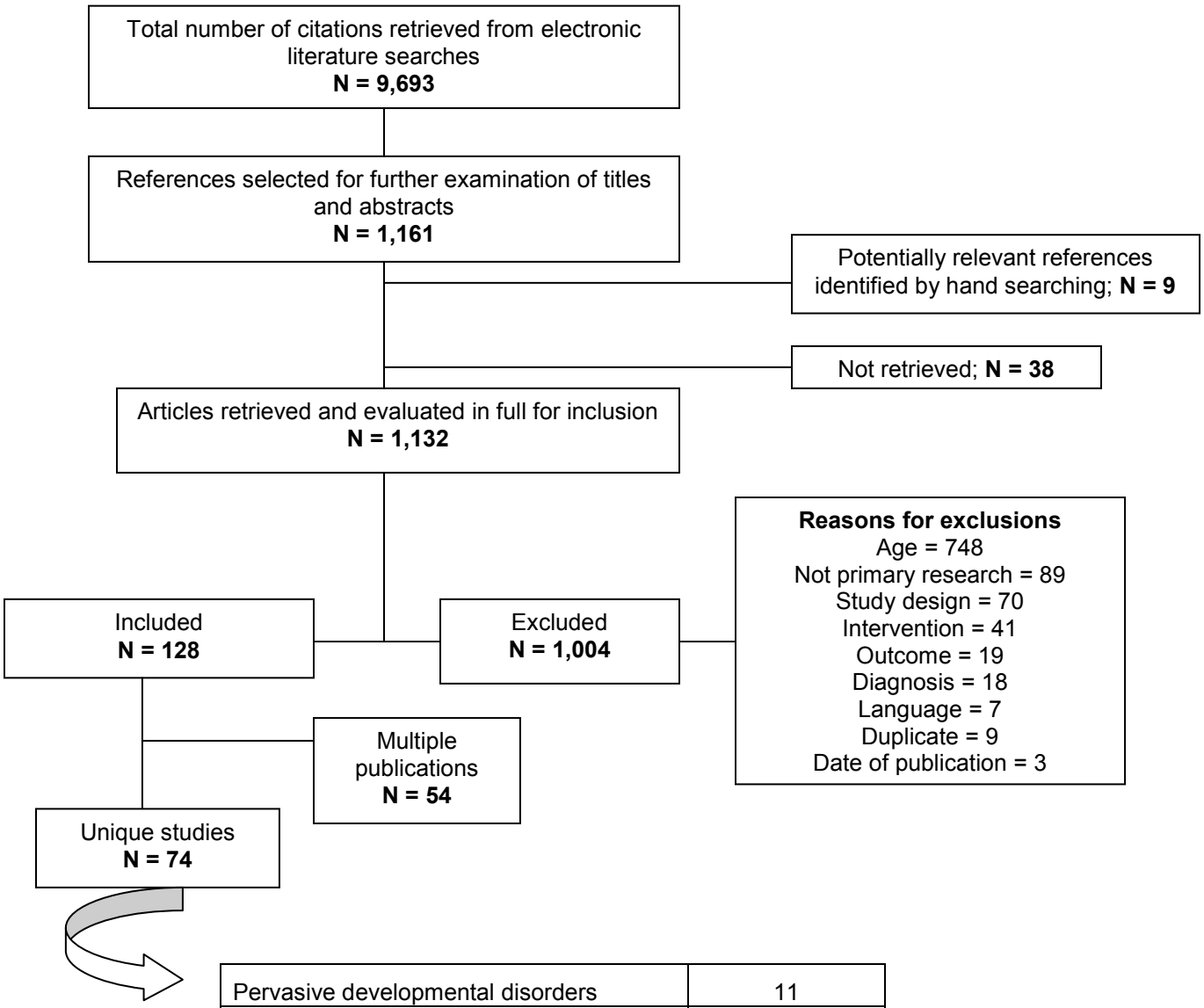
Chapter 3. Results

Literature Search

The search strategy identified 9,693 citations from electronic databases. Screening based on titles and abstracts identified 1,161 potentially relevant studies. Nine additional studies were identified by hand searching the reference lists from included studies, conference proceedings, or clinical trial registries. The full text of 38 studies could not be retrieved through the university interlibrary loan service (Appendix G). Therefore, the full texts of 1,132 potentially relevant reports were retrieved and evaluated for inclusion in the review. Using the detailed selection criteria, 128 studies were included and 1,004 were excluded. Of the 128 included studies, 54 were identified as companion publications; therefore, 74 unique studies were included (Figure 2). A list of companion articles to the included unique studies is provided in Appendix F.

The most frequent reasons for exclusion were: 1) ineligible age of study participants (n = 748); 2) the article did not report on primary research (n = 89); 3) ineligible study design (n = 70); 4) the study did not compare two antipsychotic drugs or an antipsychotic drug with placebo (n = 41); 5) no outcome data of interest were reported (n = 19); and 6) study participants were not diagnosed with any of the conditions (n = 18). Twenty-eight studies were excluded for other reasons (Figure 2). A complete list of excluded studies and reasons for exclusion is provided in Appendix G.

Figure 2. Flow diagram of study retrieval and selection



Pervasive developmental disorders	11
ADHD and disruptive behavior disorders	8
Pediatric bipolar disorder	9
Schizophrenia and related psychosis	27
Tourette syndrome	7
Behavioral symptoms	4
Multiple conditions	8
OCD, PTSD, and Anorexia Nervosa	0
TOTAL	**74**

Description of Included Studies

Seventy-four unique studies provided evidence on the four key questions addressed in this report. The evidence tables provide information on the key characteristics of the included studies (Appendix E). Studies were published between 1989 and 2010 (median = 2006 [interquartile range (IQR), 2002 to 2008]). Most of the studies (93 percent) were published in peer-reviewed publications; the remainder were industry reports (5 percent) or abstracts (1 percent). Studies were conducted in the U.S. (51 percent), Europe (18 percent), Israel (4 percent), Canada (3 percent), other regions (11 percent), as well as in multiple countries (14 percent).

Fifty-nine studies (80 percent)[40-98] examined the comparative effectiveness of antipsychotics on disorder-specific and nonspecific symptoms (Key Question 1). Adverse events (Key Question 2) were reported in 71 studies (96 percent).[40-82,84-97,99-112] Fifty-two studies[40-55,57,58,60-64,66,68-70,72-81,83-89,91-94,96,97,111,113] (70 percent) presented data on other short-term and long-term outcomes (Key Question 3). Thirty-two (43 percent) studies[41,44,47,50,54,55,57-59,62,63,70,74,77-79,81,83,88-90,92,93,97,100-102,104-106,112,113] reported whether outcomes differed in various subpopulations (Key Question 4).

Of the 74 studies, 57 (77 percent) were RCTs and two were NRCTs (3 percent). Five used a crossover design,[40,56,59,81,90] and the remaining used a parallel group design. Eight trials had three arms[53,54,57,59,61,74,81,88] and two trials had four arms.[69,80] There were 15 cohort studies (eight prospective[66,78,101,103-105,107,112] and seven retrospective[44,62,99,106,108,109,113]).

The following conditions of interest were examined in the included studies: pervasive developmental disorders (11 studies),[60,67-71,73,77,86,94,113] disruptive behavior disorders (seven studies),[40,41,47 48,55,79,89] ADHD with aggression (one study),[43] bipolar disorder (eight studies),[46,50,52,54,57,75,92,93] schizophrenia (24 studies),[49,53,58,61,63-66,72,74,76,78,80,85,87,90,96-98,102,107,108,110,112] psychosis (four studies),[42,45,88,91] and Tourette syndrome (seven studies).[56,81-84,100,111] Four studies[44,59,62,95] enrolled patients with specific behavioral symptoms and eight studies[51,99,101,103-106,109] included patients diagnosed with various psychiatric and behavioral conditions. There were no studies that met the eligibility criteria that examined OCD, PTSD, or anorexia nervosa.

The number of enrolled participants ranged from 8 to 335 (median = 42 [IQR, 24 to 99]). The mean age of study participants ranged from 4.0 to 21.5 years (median = 13.7 years [IQR, 10.0 to 15.2 years]). The mean age was less than 12 years in 29 studies (39 percent).[40,41,43,44,46,53,55,56,60,67-71,72,73,77-79,81-84,86,89,90,93,94,111]

Forty-eight studies provided head-to-head comparisons of antipsychotics. Of these, 14 studies compared first generation drugs with second generation drugs,[49,56,65,68,71,78,88,98,100,107,108,110,112,113] four studies compared two or more first generation drugs,[77,81,83,111] and 33 studies compared two or more second generation drugs.[42,44-46,51,53,54,57-59,61,62,64,66,69,72,74,78,80,85,87,88,91,96,99,101-106,109,112] Three studies[78,88,112] provided head-to-head comparisons of both first versus second generation drugs and multiple second generation drugs. There were 34 placebo-controlled studies, including two studies[81,90] comparing a first generation antipsychotic with placebo and 32 comparing a second generation antipsychotic with placebo.[40,41,43,47,48,50,52-55,57,59,60,63,67,69,70,73-76,79,80,82,84,86,89,92-95,97]

Methodological Quality of Included Studies

The methodological quality of each included study was assessed by two independent reviewers, and the consensus ratings are presented in Appendix D, Tables D1 to D2.

Randomized and Nonrandomized Controlled Trials

The risk of bias assessments for the 57 RCTs and two NRCTs are presented in Appendix D, Table D1. The majority of the RCTs were considered to have a high risk of bias for both subjective (n = 51, 89 percent) and objective outcomes (n = 49, 86 percent). Of the remaining studies, six RCTs were considered to have an unclear risk of bias for both subjective and objective outcomes,[70,73,81,85,87,90] and two studies did not report objective outcomes.[49,111] The allocation sequence was adequately generated in 30 trials (53 percent),[40,41,43,45,47,49,50,52,53,55,56,58,61,64,65,67-70,73,81,85,87-89,91,93,94,97,100] while allocation concealment was adequate in 23 studies (40 percent).[45,48,50,52,55,56,59,64,65,67,69,73,75,76,81,84,85,87,89,93,94,97,111] Blinding was considered adequate for subjective outcomes in 28 studies (49 percent)[40,41,43,45,47,48,54-56,60,65,67,70,73,75-77,79-81,84,85,87,90,93,94,100,111] and for objective outcomes in 39 studies (68 percent).[40-43,45,47,48,50,54-60,64,65,67,68,70,71,73,75-77,79-81,84,85,87,89-91,93-96,100] Half of the studies adequately addressed incomplete outcome data (29 studies reporting subjective outcomes,[40,43,47,52,53,60,67,68,70,71,73-76,80-82,84-87,90,92-96,100,111] and 28 reporting objective outcomes.[40,43,47,52,53,60,67,68,70,71,73-76,80-82,84-87,90,92-96,100]) Forty-five studies[40-43,45,47-52,54,55,57-61,63-65,67-74,76,79,80,82,84,85,88,89,91-95,98,100,111] (79 percent) were free of selective outcome reporting, while seven studies[49,53,64,83,87,98,111] (12 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.[102,110] Sequence generation and allocation concealment were inadequate in both studies, blinding was adequate in one study,[102] and incomplete outcome data was adequate in another.[110] Both studies were free of selective outcome reporting and were rated unclear for other sources of bias.

The most common sources of funding for trials were industry (46 trials, 78 percent) and government (15 trials, 45 percent). Other sources of funding included academic institutions (3 trials, 5 percent),[42,46,73] foundation (7 trials, 12 percent),[55,70,77,83,88,89,94] and private (4 trials, 7 percent).[45,93,98,111] One trial reported receiving no funding[72] and funding was not described in six trials.[40,61,64,65,85,102] Several trials received funding from multiple sources.[42,45,46,55,56,59,70,73,77,81,84,88,90,93,94,96,97,111]

Cohort Studies

The detailed results of the quality assessment of the 15 cohort studies using the Newcastle-Ottawa scale is presented in Appendix D, Table D2. Data were prospectively collected in eight studies and retrospectively collected in seven. 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 (9 studies, 60 percent).[44,66,99,101,103,105,108,112,113] The nonexposed cohort was drawn from the same community as the exposed cohort in 11 studies; in four studies the nonexposed cohort was drawn from a different source.[62,78,104,107] In all studies exposure status was based on data from a secure source, most commonly from medical records. Only four studies[44,101,105,112] controlled for potential confounding variables in their design or analysis. Half of the studies[62,99,101,107-109,112,113] (8 studies, 53 percent) used independent blind assessment or record linkage to determine outcomes. All studies but one[103] had a sufficient followup duration for outcomes to occur. The rate of followup was considered unlikely to introduce bias in the majority of studies (10 studies, 67 percent); however, three studies were considered to have inadequate followup[44,105,108] and two studies did not report the followup rate.[107,109]

The cohort studies received funding from government (5 studies, 33 percent).[78,101,105,107,108] Two studies (13 percent) reported receiving funding from each of the following sources: industry,[66,103] academic institutions,[101,108] foundations,[78,113] and private sponsors.[44,105] Six studies (40 percent)[62,99,104,106,109,112] did not report their source of funding.

Results of Included Studies

This section is organized by the four key research questions addressed in this report. An overview of the key findings for each key question is presented at the beginning of each subsection. For efficacy of disorder specific and nonspecific symptoms (Key Question 1) and other short-term and long-term outcomes (Key Question 3), the results are presented by condition and then by class and drug comparisons. For adverse events (Key Question 2), results are presented by drug comparison across all conditions. Head-to-head comparisons (i.e., first generation versus second generation, first generation versus first generation, and second generation versus second generation antipsychotics) are presented followed by placebo comparisons (first generation drugs versus placebo, second generation drugs versus placebo). Grading of the body of evidence is presented for key efficacy outcomes and adverse events in Appendix H. Descriptions of outcomes and harms by subpopulations are presented in tables for Key Question 4.

Question 1: Disorder Specific and Nonspecific Symptoms

Fifty-nine studies examined the efficacy of antipsychotics for treating disorder specific and nonspecific symptoms. Data on symptom severity and improvement were provided for the following conditions: pervasive developmental disorders (10 studies), ADHD with aggression (one study), disruptive behavior disorders (seven studies), bipolar disorder (eight studies), schizophrenia (19 studies), psychosis (four studies), Tourette syndrome (five studies) and behavioral symptoms (four studies). In addition, one study[51] provided separate data for both bipolar disorder and schizophrenia.

Pervasive Developmental Disorders

Summary. Ten RCTs compared the efficacy of first and second generation antipsychotics for treating of symptoms in patients with pervasive developmental disorders. The following is a summary of the results by comparison:

- Two RCTs compared first generation versus second generation antipsychotics. Malone et al.[68] found a significantly greater reduction in anger and hyperactivity in patients treated with olanzapine compared with haloperidol ($p \leq 0.05$). Miral et al.[71] found significantly greater reduction in aberrant behavior (ABC) at 12 weeks ($p = 0.006$) and greater improvement in clinical global impressions ($p = 0.02$) and language ($p = 0.04$) at 24 weeks for risperidone compared with haloperidol. Overall, the evidence comparing first generation versus second generation antipsychotics was graded low for autistic symptoms, and insufficient for making conclusions for other outcomes.
- One RCT[77] found no significant difference in clinical global impressions of improvement between continuous and discontinuous administration of haloperidol. Evidence was too limited to make conclusions.

- One RCT[69] compared two dosing regimens of aripiprazole and found high-dose aripiprazole to result in significantly greater improvement in the ABC lethargy/social withdrawal subscale (p = 0.05) compared with low-dose aripiprazole (insufficient evidence).
- Seven RCTs[60,67,69 70,73,86,94] compared a second generation antipsychotic with placebo. Meta-analysis found second generation antipsychotics to be superior to placebo for aberrant behavior on the Aberrant Behaviour Checklist (ABC) (MD = -18.29; 95% 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 Clinical Global Impressions of Improvement (CGI-I). Single studies found significant improvement favoring risperidone over placebo for the following outcomes: the Ritvo-Freeman real life rating score (RFRLRS) and maladaptive behavior,[70] clinical global assessment (CGAS),[73] behavior subscales (parent-rated Nisonger Child Behavior Rating Form [NCBRF]) and improvement of most troublesome symptom.[86] Evidence for this comparison was rated as low.

Results by individual study. Ten RCTs[60,67-71,73,77,86,94] examined the efficacy of antipsychotics for treating symptoms in patients with pervasive developmental disorders. The number of participants ranged from 11 to 218 (median = 35 participants [IQR, 24 to 78]). All of the studies included patients with autistic disorder; three studies[60,86,94] included patients with Asperger syndrome, one study[86] included childhood disintegrative disorder, and four studies included patients with pervasive developmental disorders NOS.[60,67,86,94] Two studies compared first generation versus second generation antipsychotics,[68,71] while one study compared two dosing regimens of the same first generation antipsychotic.[77] One study[69] compared two doses of the same second generation antipsychotic, and seven studies[60,67,69 70,73,86,94] compared a second generation antipsychotic with placebo. Meta-analyses were conducted comparing second generation antipsychotics with placebo for scores on the ABC, CARS, CYBOCS, and CGI-I. Patient and study characteristics and outcome data are presented in Table 10 and Table 11, respectively.

First generation versus second generation antipsychotics. Two RCTs compared the efficacy of first generation versus second generation antipsychotics in treating symptoms. The studies compared haloperidol with olanzapine[68] and haloperidol with risperidone.[71]

Malone et al.[68] assessed the efficacy of haloperidol compared with olanzapine in children with pervasive developmental disorders. Twelve children (aged 5 to 17 years) were randomized to haloperidol (n = 6) or olanzapine (n = 6) for 6 weeks. Primary diagnoses using the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for autism (n = 11) or pervasive developmental disorder NOS (n = 1) were made in children experiencing varying levels of cognitive functioning. All but one child had mild to severe mental retardation. Mean doses were 1.4±0.7 mg/day for haloperidol and 7.9±2.5 mg/day for olanzapine. Patients were assessed using the Clinical Global Impressions of Severity (CGI-S) and Children's Psychotic Rating Scale (CPRS). There was a significant difference between the groups for the CPRS anger and hyperactivity subscales, favoring olanzapine (p = 0.05 and p = 0.01, respectively). The CGI-S and other CPRS subscales were similar between treatment groups.

Miral et al.[71] conducted an RCT to compare the efficacy of haloperidol and risperidone in children (aged 8 to 18 years) with autistic disorder. Primary diagnosis was made according to

DSM-IV criteria. Thirty patients were randomized to haloperidol (n = 15) or risperidone (n = 15) and received treatment for 12 weeks. Long-term evaluation of efficacy was conducted during an open-label maintenance phase for an additional 12 weeks. Mean daily doses were 2.6±0.8 mg in the haloperidol group and 2.6±1.3 mg in the risperidone group at the 12-week followup. Patients were assessed with ABC, CGI and RF-RLRS scales. Compared with haloperidol, risperidone had significantly greater reduction in ABC scores at 12 weeks (p = 0.006) and CGI scores at 24 weeks (p = 0.02). Significant improvements on the language subscale of the RFRLRS was noted in the risperidone group at week 24 (p = 0.04) compared with the haloperidol group.

First generation versus first generation antipsychotics. One study[77] compared continuous haloperidol with discontinuous haloperidol in an RCT. Autistic children were randomly assigned to continuous (n = 34) or discontinuous (n = 36) drug regimens for 6 months. Patients, aged 2.3 to 7.9 years, were diagnosed with infantile autism using DSM-III criteria. Intellectual functioning ranged from normal to severely mentally retarded. The discontinuous drug administration schedule consisted of 5 days on haloperidol with 2 days on placebo compared with continuous administration of haloperidol. However, the prescribed dose of haloperidol was not significantly different between the groups (1.2 mg/day in the continuous group and 1.0 mg/day in the discontinuous group). Patients were assessed using CGI-I and groups were not significantly different at endpoint.

Second generation versus second generation antipsychotics. One placebo-controlled trial[69] evaluated low, medium, and high doses of aripiprazole for the treatment of irritability in children and adolescents (aged 6 to 17 years) with autistic disorder. Two-hundred and eighteen patients were randomized to a daily fixed-dose regimen of aripiprazole at 5 mg (n = 53), 10 mg (n = 59), 15 mg (n = 54), or placebo (n = 52) for 8 weeks. Autistic disorder diagnosis met DSM-IV-TR criteria confirmed with autism diagnostic interview-revised (ADI-R). Participants also demonstrated behaviors of irritability, agitation, and/or self-injury. Patients were assessed using the ABC (primary outcome: irritability subscale), CYBOCS (compulsions only), and CGI. The high-dose aripiprazole group had significantly greater improvement in the ABC lethargy/social withdrawal subscale (p = 0.05); however, no other differences were found between the dosing regimens.

Second generation antipsychotics versus placebo. Second generation antipsychotics were compared with placebo in seven studies: aripiprazole,[69] olanzapine,[60] and risperidone[67,70,73,86,94] with placebo.

Marcus et al.[69] evaluated the efficacy of aripiprazole for the treatment of irritability in children (aged 6 to 17 years) with autistic disorder. Two-hundred and eighteen patients were randomized to a daily fixed-dose regimen of aripiprazole at 5 mg (n = 53), 10 mg (n = 59), 15 mg (n = 54) or placebo (n = 52) for 8 weeks (described previously). Patients were assessed using the ABC, CYBOCS, and CGI. Aripiprazole showed significantly greater improvement in irritability symptom reduction ($p<0.05$ for all groups on ABC irritability subscale), the CGI-I ($p<0.005$), and CYBOCS score (p = 0.03, for high-dose aripiprazole only) compared with placebo. Aripiprazole groups also showed significant improvement compared with placebo for the ABC stereotype and hyperactivity subscales ($p\leq0.01$), but not for the ABC lethargy/social withdrawal or inappropriate speech subscale.

Hollander et al.[60] conducted an RCT to compare the efficacy of olanzapine versus placebo in children (aged 6 to 14 years). Patients were diagnosed with autism (n = 6), Asperger syndrome (n = 1) or pervasive developmental disorder NOS (n = 4) using DSM-IV, ADI-R, and Autism Diagnostic Observation Schedule criteria. Seven patients had concomitant mental retardation.

Eleven patients were randomly assigned to olanzapine, (n = 6, mean dose: 10±2.04 mg/day) or placebo (n = 5) for 8 weeks. Patients were assessed using the CGI-I scale. Symptoms improved significantly from baseline to endpoint in the olanzapine group.

Luby et al.[67] compared the efficacy of risperidone versus placebo for the treatment of autistic spectrum disorders in preschoolers. Twenty-four children (aged 2.5 to 6.0 years) with DSM-IV criteria for autism or pervasive developmental disorders NOS were randomized to risperidone (n = 12) or placebo (n = 12) for 6 months. Mean daily final dose was 1.1±0.3 mg for risperidone. Patients were assessed using CARS. Autism severity scores improved significantly in both groups; however, no significant differences in treatment effects between the risperidone and placebo groups were observed.

McCracken et al.[70] conducted an RCT comparing the efficacy of risperidone versus placebo for the treatment of behavioral disturbances in children (aged 5 to 17 years) with autistic disorder. Participants were randomly assigned to receive risperidone (n = 49) or placebo (n = 52) for 8 weeks. The mean dose was 1.8±0.7 mg/day of risperidone. All children met DSM-IV and ADI-R criteria for autistic disorder with tantrums, aggression, self-injurious behavior, or a combination of these problems. Patients with mild or moderate (n = 43) and severe (n = 31) mental retardation were included. Patients were assessed using the ABC, CYBOCS, CGI, RFRLRS, and Vineland Adaptive Behavior Scale. At 8 weeks, risperidone was superior to placebo for symptom reduction on all efficacy outcome measures.

Nagaraj et al.[73] assessed the efficacy of risperidone compared with placebo in children (aged 2 to 9 years) diagnosed with autism according to DSM-IV criteria. Forty participants were randomly assigned to risperidone (n = 19) given orally in liquid formulation at a dose of 1 mg/day or placebo (n = 21) for 6 months. At baseline, all children had severe language impairment and behavioral complaints (irritability [n = 36], aggression [n = 20], self-injurious behavior [n = 12]), or seizures (n = 8). CARS and CGAS scales were used to evaluate symptomology. Risperidone showed significant symptom reduction on both scales ($p<0.001$).

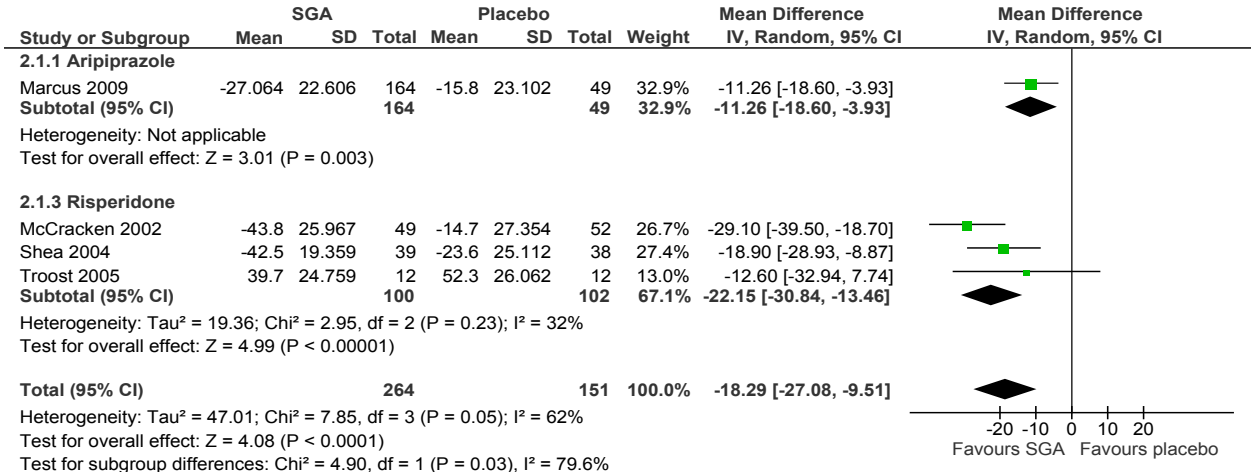
Shea et al.[86] conducted an RCT to determine the efficacy of risperidone to treat behavioral symptoms in children (aged 5 to 12 years) with pervasive developmental disorders. Participants were randomized to risperidone (n = 41, mean dose 1.2 mg/day) or placebo (n = 39) for 8 weeks. Autistic disorder (n = 55), Asperger syndrome (n = 12), childhood disintegrative disorder (n = 1), and pervasive developmental disorder NOS (n = 11) were diagnosed with DSM-IV criteria in patients with (n = 27) or without mental retardation. Efficacy assessments were made using the ABC, NCBRF (parent version), and VAS of the most troublesome symptom. The risperidone group showed statistically significant greater mean decreases in symptoms on all measures and subscales ($p\leq0.05$) compared with the placebo group, with the exception of the NCBRF self-isolated/ritualistic and self-injurious/stereotypic subscales.

Troost et al.[94] evaluated the efficacy of risperidone in a placebo-discontinuation study in children (aged 5 to 17 years) with autism spectrum disorder after 6 months of open label treatment. Twenty-four risperidone "short-term responders" (assessed at 8 weeks) were randomly assigned to continued active treatment (n = 12) or gradual placebo withdrawal (n = 12) consisting of 3 weeks of tapering drug dose and 5 weeks of placebo alone. Patients were diagnosed with DSM-IV-TR criteria for autistic disorder (n = 6), Asperger syndrome (n = 2) and pervasive developmental disorder NOS (n = 16) using ADI-R. Two patients were described as mentally retarded. The mean daily dose of risperidone before randomization was 1.9±0.7 mg for continued active treatment and 1.7±0.5 mg for placebo. Patients were assessed using ABC scale. The ABC irritability subscale was significantly reduced in patients treated with continued

risperidone compared with the patients given placebo (p<0.05), but no statistically significant differences in other subscales were observed.

Four RCTs[69,70,86,94] contributed data to a meta-analysis comparing second generation antipsychotics with placebo on ABC scores (Figure 3). For the three studies[70,86,94] comparing risperidone with placebo, the pooled estimate showed risperidone to be superior to placebo on change in ABC scores (MD = -22.15; 95% CI, -30.84 to -13.46). Heterogeneity was moderate (p = 0.23, I^2 = 32 percent) and may be attributable to differences in the proportion of patients with intellectual disabilities who were enrolled in the studies. The total combined estimate for all studies similarly favored second generation antipsychotics over placebo (MD = -18.29; 95% CI, -27.08 to -9.51). Heterogeneity was substantial (p = 0.05, I^2 = 62 percent) and may be a result of differences in the second generation drug used as the comparator.

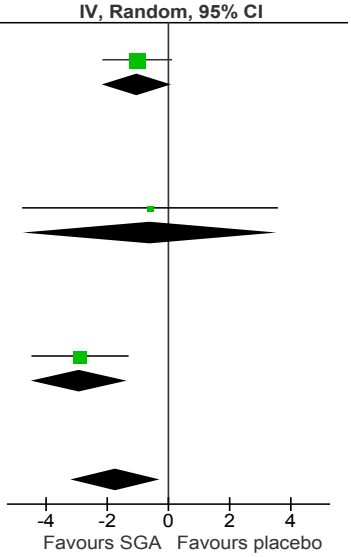
Figure 3. Second generation antipsychotics versus placebo on ABC in pervasive developmental disorders



Three RCTs[60,69,70] were combined in a meta-analysis comparing second generation antipsychotics and placebo for obsessive-compulsive behaviors on the CYBOCS (Figure 4). The effect estimate showed a significantly greater decrease in obsessive-compulsive symptoms with use of second generation antipsychotics compared with placebo (MD = -1.71; 95% CI, -3.17 to -0.25). Heterogeneity was high (p = 0.14, I^2 = 49 percent) and may be attributable to differences in the second generation antipsychotics.

Figure 4. Second generation antipsychotics versus placebo on CYBOCS in pervasive developmental disorders

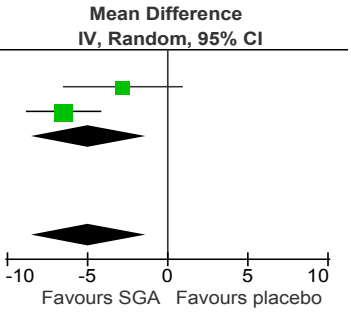
Study or Subgroup	SGA Mean	SGA SD	SGA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
2.2.1 Aripiprazole								
Marcus 2009	-2.722	3.431	164	-1.7	3.5	49	50.3%	-1.02 [-2.13, 0.09]
Subtotal (95% CI)			**164**			**49**	**50.3%**	**-1.02 [-2.13, 0.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.80 (P = 0.07)								
2.2.2 Olanzapine								
Hollander 2006	0	3.5	6	0.602	3.5	5	10.5%	-0.60 [-4.76, 3.55]
Subtotal (95% CI)			**6**			**5**	**10.5%**	**-0.60 [-4.76, 3.55]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.28 (P = 0.78)								
2.2.3 Risperidone								
McCracken 2002	-3.86	3.555	49	-0.97	4.419	52	39.2%	-2.89 [-4.45, -1.33]
Subtotal (95% CI)			**49**			**52**	**39.2%**	**-2.89 [-4.45, -1.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.63 (P = 0.0003)								
Total (95% CI)			**219**			**106**	**100.0%**	**-1.71 [-3.17, -0.25]**
Heterogeneity: Tau² = 0.78; Chi² = 3.89, df = 2 (P = 0.14); I² = 49%								
Test for overall effect: Z = 2.30 (P = 0.02)								
Test for subgroup differences: Chi² = 3.89, df = 2 (P = 0.14), I² = 48.5%								



A meta-analysis of two RCTs[67,73] examining autistic behaviors on the CARS compared risperidone with placebo (Figure 5). The pooled estimate indicated significantly greater improvement of autism symptoms in the risperidone groups compared with placebo (MD = -4.94; 95% CI, -8.52 to -1.36). There was substantial heterogeneity between the studies (p = 0.10, I^2 = 64 percent). The study by Nagaraj et al.[73] included patients who were slightly older and had a higher proportion of male participants compared with Luby et al.[67]

Figure 5. Risperidone versus placebo on CARS in pervasive developmental disorders

Study or Subgroup	SGA Mean	SGA SD	SGA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
2.5.3 Risperidone								
Luby 2006	-4.6	4	11	-1.8	5.003	12	42.1%	-2.80 [-6.49, 0.89]
Nagaraj 2006	-7.5	4.041	19	-1	3.221	20	57.9%	-6.50 [-8.80, -4.20]
Subtotal (95% CI)			**30**			**32**	**100.0%**	**-4.94 [-8.52, -1.36]**
Heterogeneity: Tau² = 4.39; Chi² = 2.78, df = 1 (P = 0.10); I² = 64%								
Test for overall effect: Z = 2.71 (P = 0.007)								
Total (95% CI)			**30**			**32**	**100.0%**	**-4.94 [-8.52, -1.36]**
Heterogeneity: Tau² = 4.39; Chi² = 2.78, df = 1 (P = 0.10); I² = 64%								
Test for overall effect: Z = 2.71 (P = 0.007)								
Test for subgroup differences: Not applicable								



Two RCTs[60,69] provided data for a meta-analysis comparing second generation antipsychotics with placebo on CGI-I rating (Figure 6). While the combined estimate favored second generation antipsychotics, the result was not statistically significant (MD = -1.22; 95% CI, -2.50 to 0.06). There was substantial heterogeneity between the studies (p = 0.11, I^2 = 61 percent). Nearly all of the patients in the study by Hollander[60] had mild to severe mental retardation, which may account for some of the observed heterogeneity.

Figure 6. Second generation antipsychotics versus placebo on CGI-I in pervasive developmental disorders

Study or Subgroup	SGA Mean	SGA SD	SGA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
2.4.1 Aripiprazole								
Marcus 2009	2.532	1.185	164	3.3	1.185	49	67.8%	-0.77 [-1.15, -0.39]
Subtotal (95% CI)			**164**			**49**	**67.8%**	**-0.77 [-1.15, -0.39]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.98 (P < 0.0001)								
2.4.2 Olanzapine								
Hollander 2006	1.83	1.419	6	4	1.419	5	32.2%	-2.17 [-3.85, -0.49]
Subtotal (95% CI)			**6**			**5**	**32.2%**	**-2.17 [-3.85, -0.49]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.53 (P = 0.01)								
Total (95% CI)			**170**			**54**	**100.0%**	**-1.22 [-2.50, 0.06]**
Heterogeneity: Tau² = 0.60; Chi² = 2.53, df = 1 (P = 0.11); I² = 61%								
Test for overall effect: Z = 1.86 (P = 0.06)								
Test for subgroup differences: Chi² = 2.53, df = 1 (P = 0.11), I² = 60.5%								

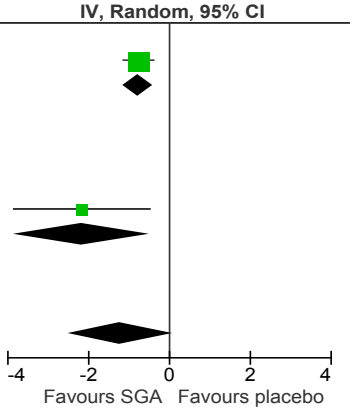


Table 8. Study and patient characteristics for studies examining pervasive developmental disorders

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Hollander, 2006[60] RCT, 8 wk	**G1:** Olanzapine (6), 10±2 mg/day **G2:** Placebo (5)	**G1:** 9.3±2.9 (6-14.8) yr / Male: all / Caucasian: 50% **G2:** 8.9±2.1 (6.1-11) yr / Male: 60% / Caucasian: 80% Comorbidities: MR (mild (5), severe (2))	Asperger syndrome (1), autism (6), PDD NOS (4) NR, NR
Luby, 2006[67] RCT, 6 mo	**G1:** Risperidone (12), 1.1±0.3 mg/day **G2:** Placebo (12)	**G1:** 4.1±0.9 yr / Male: 75% / Caucasian: 91% **G2:** 4.0±1.1 yr / Male: 67% / Caucasian: 92% Comorbidities: NR	autistic disorder (NR), PDD NOS (NR) NR, NR
Malone, 2001[68] RCT, 6 wk	**G1:** Haloperidol (6), 1.4±0.7 mg/day **G2:** Olanzapine (6), 7.9±2.5 mg/day	**G1:** 7.3±1.9 (5-10.1) yr / Male: 67% / Caucasian: 67% **G2:** 8.5±2.4 (4.9-11.8) yr / Male: 67% / Caucasian: 50% Comorbidities: MR (mild (1), moderate (5), severe (5))	autistic disorder (11), PDD NOS (1) NR, 3
Marcus, 2009[69] RCT, 8 wk	**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% / Caucasian: 70% **G2:** 10.0±3.2 yr / Male: 85% / Caucasian: 70% **G3:** 9.5±3.1 yr / Male: 93% / Caucasian: 78% **G4:** 10.2±3.1 / Male: 92% / 67% Comorbidities: NR	autistic disorder NR, 172
McCracken, 2002[70] RCT, 8 wk (4 mo extension for risperidone responders)	**G1:** Risperidone (49), 1.8±0.7 mg/day **G2:** Placebo (52)	**G1:** NR / Male: 80% / Caucasian: NR **G2:** NR / Male: 83% / Caucasian: NR Comorbidities: MR (borderline (12), mild or moderate (43), severe (31))	autistic disorder NR, 96
Miral, 2008[71] RCT, 12 wk (12 wk extension)	**G1:** Haloperidol (15), 2.6±1.3 mg/day **G2:** Risperidone (15), 2.6±0.8 mg/day	**G1:** 10.9±2.9 (7-17) yr / Male: 87% / Caucasian: NR **G2:** 10.0±2.7 (7-17) yr / Male: 73% / Caucasian: NR Comorbidities: ADHD (0), psychosis (0)	autistic disorder NR, NR
Nagaraj, 2006[73] RCT, 6 mo	**G1:** Risperidone (19), 1 mg/day **G2:** Placebo (21)	**G1:** 4.8±1.7 yr / Male: 84% / Caucasian: NR **G2:** 5.3±1.7 yr / Male: 90% / Caucasian: NR Comorbidities: Aggression (20), irritability (36), self-injurious behavior (12), seizures (8)	autistic disorder NR, 31

ADHD = attention deficit and hyperactivity disorder; G = group; Mg = milligram; Mo = month; MR = mental retardation; N = number; NOS = not otherwise specified; NR = not reported; PDD = pervasive developmental disorder; RCT = randomized controlled trial; SD = standard deviation; wk = week; yr = year

Table 8. Study and patient characteristics for studies examining pervasive developmental disorders (continued)

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Perry, 1989[77] RCT, 6 mo	**G1:** Haloperidol (continuous) (34), 1.2 mg/day **G2:** Haloperidol (discontinuous) (36), 1 mg/day	**G1:** NR / Male: NR / Caucasian: NR **G2:** NR / Male: NR / Caucasian: NR Comorbidities: NR	autistic disorder NR, NR
Shea, 2004[86] RCT, 8 wk	**G1:** Risperidone (41), 1.2 mg/day **G2:** Placebo (39)	**G1:** 7.6 (5-12) yr / Male: 73% / Caucasian: NR **G2:** 7.3 (5-12) yr / Male: 82% / Caucasian: NR Comorbidities: MR (27)	Asperger syndrome (12), autistic disorder (55), childhood disintegrative disorder (1), PDD NOS (11) NR, NR
Troost, 2005[94] RCT, 6 mo	**G1:** Risperidone (12), 1.9±0.7 mg/day **G2:** Placebo (12)	**G1:** 9.4±3.4 yr / Male: 92% / Caucasian: 100% **G2:** 8.7±1.2 yr / Male: 92% / Caucasian: 83% Comorbidities: MR (2)	Asperger syndrome (2), autistic disorder (6), PDD NOS (16) NR, 23

Table 9. Outcome data for studies assessing pervasive developmental disorders

Author, Year	Intervention (N analyzed)	Outcome	G1: BL mean (SD) / Followup mean (SD)	G2: BL mean (SD) / Followup mean (SD)	G3: BL mean (SD) / Followup mean (SD)	P-value
Hollander, 2006[60]	G1: Olanzapine (6) G2: Placebo (5)	CGI–I	4.5 (0.84) / 8 wk: 2.25 (1.26)	4.4 (0.55) / 8 wk: 3.5 (1.0)	NA	0.01
Luby, 2006[67]	G1: Risperidone (11) G2: Placebo (12)	CARS	37.6 (4.0) / 8 wk: 32.6 (4.8) / 16 wk: 32.6 (4.3) / 24 wk: 33.0 (4.0)	33.3 (4.9) / 8 wk: 29.6 (3.4) / 16 wk: 29.6 (3.9) / 24 wk: 31.5 (5.1)	NA	24 wk: 0.11
Malone, 2001[68]	G1: Haloperidol (6) G2: Olanzapine (6)	CGI–S	5.5 (1.1) / 7 wk: 5.08 (1.24)	5.92 (0.58) / 7 wk: 4.83 (0.88)	NA	0.24
		CPRS autism factor	4.87 (1.48) / 7 wk: 4.33 (1.4)	5.4 (0.65) / 7 wk: 4.52 (0.69)	NA	0.56
		CPRS anger/ uncooperative	3.31 (1.4) / 7 wk: 3.46 (1.43)	4.42 (0.67) / 7 wk: 2.93 (1.58)	NA	0.05
		CPRS hyperactivity	2.97 (1.0) / 7 wk: 3.33 (0.69)	3.47 (0.99) / 7 wk: 2.17 (0.83)	NA	0.01
		CPRS speech deviance	2.17 (1.03) / 7 wk: 1.91 (0.97)	2.42 (1.11) / 7 wk: 2.7 (1.15)	NA	>0.05
Marcus, 2009[69]	G1: Aripiprazole, 5 mg/day (52) G2: Aripiprazole, 10 mg/day (59) G3: Aripiprazole, 15 mg/day (53) G4: Placebo (49)	ABC irritability, change	28.6 (7.6) / 8 wk: -12.4	28.2 (7.4) / 8 wk: -13.2	G3: 28.9 (6.4) / 8 wk: -14.4 G4: 28.0 (6.9) / 8 wk: -8.4	G1 vs. G4: 0.032 G2 vs. G4: 0.008 G3 vs. G4: 0.001
		ABC, lethargy/social withdrawal, change	17.7 (10.1) / 8 wk: -5.8 (8.7)	16.8 (10.0) / 8 wk: -4.9 (8.4)	G3: 18.9 (10.2) / 8 wk: -7.9 (8.0) G4: 18.0 (10.5) / 8 wk: -5.2 (8.4)	G1 vs. G2: 0.58 G1 vs. G3: 0.20 G1 vs. G4: 0.72 G2 vs. G3: 0.05 G2 vs. G4: 0.85 G3 vs. G4: 0.10
		ABC, stereotypy, change	11.4 (5.8) / 8 wk: -4.5 (4.9)	11.6 (6.1) / 8 wk: -4.2 (4.8)	G3: 11.6 (5.8) / 8 wk: -4.5 (4.8) G4: 10.7 (5.6) / 8 wk: -1.8 (4.8)	G1 vs. G2: 0.75 G1 vs. G3: 1.00 G1 vs. G4: 0.005 G2 vs. G3: 0.74 G2 vs. G4: 0.01 G3 vs. G4: 0.005

ABC = Aberrant Behavior Checklist; BL = baseline; CARS = Childhood Autism Rating Scale; CGAS = Children's Global Assessment Scale; CGI–I = Clinical Global Impressions–Improvement; CGI–S = Clinical Global Impressions–Severity; CPRS = Children's Psychiatric Rating Scale; CYBOCS = Children's Yale-Brown Obsessive-compulsive Scale; G = group; mg = milligram; N = number; NA = not applicable; NCBRF = Nisonger Child Behavior Rating Scale; NR = not reported; RFRLRS = Ritvo-Freeman Real Life Rating Scale; SD = standard deviation; VABS = Vineland Adaptive Behavior Scale; VAS–MS: visual analog scale for most troublesome symptoms; wk = week

Table 9. Outcome data for studies assessing pervasive developmental disorders (continued)

Author, Year	Intervention (N analyzed)	Outcome	G1: BL mean (SD) / Followup mean (SD)	G2: BL mean (SD) / Followup mean (SD)	G3: BL mean (SD) / Followup mean (SD)	P-value
Marcus, 2009 (continued)		ABC, hyperactivity, change	33.1 (10.1) / 8 wk: -14.0 (11.5)	33.7 (9.99) / 8 wk: -13.3 (11.5)	G3: 32.2 (10.2) / 8 wk: -16.3 (11.6) G4: 31.0 (9.8) / 8 wk: -7.7 (11.9)	G1 vs. G2: 0.75 G1 vs. G3: 0.31 G1 vs. G4: 0.007 G2 vs. G3: 0.17 G2 vs. G4: 0.01 G3 vs. G4: <0.001
		ABC, inappropriate speech, change	5.8 (4.3) / 8 wk: -2.0 (3.6)	6.8 (3.8) / 8 wk: -1.8 (3.1)	G3: 6.3 (3.6) / 8 wk: -2.3 (2.9) G4: 5.9 (4.2) / 8 wk: -1.1 (3.5)	G1 vs. G2: 0.76 G1 vs. G3: 0.64 G1 vs. G4: 0.20 G2 vs. G3: 0.38 G2 vs. G4: 0.28 G3 vs. G4: 0.06
		CYBOCS (compulsions only), change	13.9 (4.3) / 8 wk: -2.6 (3.6)	13.5 (3.8) / 8 wk: -2.4 (3.1)	G3: 14.1 (3.6) / 8 wk: -3.2 (3.6) G4: 13.7 (4.2) / 8 wk: -1.7 (3.5)	G1 vs. G2: 0.76 G1 vs. G3: 0.39 G1 vs. G4: 0.20 G2 vs. G3: 0.21 G2 vs. G4: 0.28 G3 vs. G4: 0.03
		CGI–I, change	NR / 8 wk: 2.6	NR / 8 wk: 2.5	NR / G3: 8 wk: 2.5 NR / G4: 8 wk: 3.3	G1 vs. G4: 0.003 G2 vs. G4: <0.001 G3 vs. G4: <0.001
		CGI–S, change	5.0 (0.72) / 8 wk: -0.9 (1.4)	4.9 (0.77) / 8 wk: -1.0 (0.73)	G3: 5.1 (0.73) / 8 wk: -1.1 (1.46) G4: 4.7 (0.7) / 8 wk: -0.6 (1.4)	G1 vs. G2: 0.64 G1 vs. G3: 0.47 G1 vs. G4: 0.28 G2 vs. G3: 0.65 G2 vs. G4: 0.07 G3 vs. G4: 0.08
McCracken, 2002[70]	G1: Risperidone (49) G2: Placebo (52)	ABC irritability	26.2 (7.9) / 8 wk: 11.3 (7.4)	25.5 (6.6) / 8 wk: 21.9 (9.5)	NA	<0.001
		ABC social withdrawal	16.4 (8.2) / 8 wk: 8.9 (6.4)	16.1 (8.7) / 8 wk: 12.0 (8.3)	NA	0.03
		ABC stereotypy	10.6 (4.9) / 8 wk: 5.8 (4.6)	9.0 (4.4) / 8 wk: 7.3 (4.8)	NA	<0.001
		ABC hyperactivity	31.8 (9.6) / 8 wk: 17.0 (9.7)	32.3 (8.5) / 8 wk: 27.6 (10.6)	NA	<0.001
		ABC inappropriate speech	4.8 (4.1) / 8 wk: 3.0 (3.1)	6.5 (3.6) / 8 wk: 5.9 (3.8)	NA	0.03
		CYBOCS, modified compulsion scale	15.51 (2.73) / 8 wk: 11.65 (4.02)	15.18 (3.88) / 8 wk: 14.21 (4.81)	NA	0.005

Table 9. Outcome data for studies assessing pervasive developmental disorders (continued)

Author, Year	Intervention (N analyzed)	Outcome	G1: BL mean (SD) / Followup mean (SD)	G2: BL mean (SD) / Followup mean (SD)	G3: BL mean (SD) / Followup mean (SD)	P-value
McCracken, 2002 (continued)		CGI–I, % difference between groups pts rated for improvement	4 wk: 44% / 8 wk: 64%		NA	4 and 8 wk: <0.001 (favors G1)
		RFRLRS overall	0.94 (0.36) / 4 wk: 0.54 (0.36) / 8 wk: 0.45 (0.31)	1.03 (0.37) / 4 wk: 0.84 (0.39) / 8 wk: 0.88 (0.40)	NA	8 wk: <0.001
		VABS, maladaptive behavior	33.26 (8.38) / 8 wk: 20.34 (7.93)	33.51 (8.29) / 8 wk: 30.27 (8.87)	NA	8 wk: <0.001
Miral, 2008[71]	G1: Haloperidol (15) G2: Risperidone (13)	ABC	67.1 (25.1) / 12 wk: 45.8 (20.2) / 24 wk: 58.1 (32.2)	85.6 (27.3) / 12 wk: 36.8 (13.8) / 24 wk: 52.0 (14.9)	NA	12 wk: 0.006 24 wk: 0.07
		CGI	CGI-S: 5.1 (0.99) / 12 wk CGI-I: 2.5 (0.6)	CGI-S: 5.3 (0.95) / 12 wk CGI-I: 3 (0.6)	NA	12 wk: 0.65, 24 wk: 0.02
		RFRLRS, sensory motor	0.69 (0.47) / 12 wk: 0.50 (0.44) / 24 wk: 0.57 (0.48)	0.90 (0.52) / 12 wk: 0.36 (0.34) / 24 wk: 0.44 (0.42)	NA	12 wk: 0.10 24 wk: 0.18
		RFRLRS, social	0.50 (0.41) / 12 wk: 0.02 (0.57) / 24 wk: 0.68 (0.59)	0.62 (0.50) / 12 wk: -0.11 (0.38) / 24 wk: 0.69 (0.42)	NA	12 wk: 0.25 24 wk: 0.61
		RFRLRS, affect	1.05 (0.61) / 12 wk: 0.64 (0.48) / 24 wk: 1.36 (0.68)	1.09 (0.41) / 12 wk: 0.54 (0.34) / 24 wk: 1.27 (0.37)	NA	12 wk: 0.56 24 wk: 0.61
		RFRLRS, sensory	0.86 (0.44) / 12 wk: 0.58 (0.49) / 24 wk: 0.81 (0.59)	0.98 (0.46) / 12 wk: 0.51 (0.25) / 24 wk: 0.82 (0.35)	NA	12 wk: 0.25 24 wk: 0.76
		RFRLRS, language	0.15 (0.44) / 12 wk: -0.05 (0.5) / 24 wk: 0.32 (0.51)	0.52 (0.37) / 12 wk: 0.04 (0.25) / 24 wk: 0.44 (0.33)	NA	12 wk: 0.08 24 wk: 0.04
Nagaraj, 2006[73]	G1: Risperidone (19) G2: Placebo (20)	CARS, median score (range)	39.5 (32.5–46) / 6 mo: 32.0 (24.5 –40.5)	38.5 (31.5–43) / 6 mo: 37.5 (30–42.5)	NA	<0.001
		CGAS	29.79 (7.27) / 6 mo: 40.94 (7.83)	32.65 (7.95) / 6 mo: 35.2 (9.38)	NA	<0.001
Perry, 1989[77]	G1: Haloperidol (continuous) (30) G2: Haloperidol (discontinuous) (22)	CGI-I	6 mo: 2.63 (0.96)	6 mo: 2.86 (0.99)	NA	NR
Shea, 2004[86]	G1: Risperidone (40) G2: Placebo (39)	ABC irritability, change	18.9 (8.8) / 8 wk: -12.1 (5.8)	21.2 (9.7) / 8 wk: -6.5 (8.4)	NA	8 wk: ≤0.001

Table 9. Outcome data for studies assessing pervasive developmental disorders (continued)

Author, Year	Intervention (N analyzed)	Outcome	G1: BL mean (SD) / Followup mean (SD)	G2: BL mean (SD) / Followup mean (SD)	G3: BL mean (SD) / Followup mean (SD)	P-value
Shea, 2004 (continued)		ABC hyperactivity-noncompliance, change	27.3 (9.7) / 8 wk: -14.9 (6.7)	30.9 (8.8) / 8 wk: -7.4 (9.7)	NA	8 wk: ≤0.001
		ABC inappropriate speech, change	4.6 (3.4) / 8 wk: -2.6 (2.6)	4.8 (3.7) / 8 wk: -1.6 (3.0)	NA	8 wk: ≤0.05
		ABC lethargy-social withdrawal, change	13.7 (7.0) / 8 wk: -8.6 (5.9)	14.3 (8.2) / 8 wk: -5.7 (6.9)	NA	8 wk: ≤0.01
		ABC stereotypic behavior, change	7.9 (5.0) / 8 wk: -4.3 (3.8)	8.1 (5.6) / -2.4 (4.0)	NA	8 wk: ≤0.05
		NCBRF-P (parent), conduct problem, change	16.8 (9.4) / 8 wk: -10.4 (7.4)	23.3 (12.0) / 8 wk: -6.6 (9.5)	NA	8 wk: ≤0.001
		NCBRF-P hyperactive, change	17.2 (5.8) / 8 wk: -8.1 (4.6)	18.9 (5.3) / 8 wk: -5.6 (6.6)	NA	8 wk: 0.035
		NCBRF-P self-isolated/ritualistic, change	7.5 (4.1) / 8 wk : -4.8 (3.9)	8.2 (4.5) / 8 wk : -3.6 (4.6)	NA	8 wk: >0.05
		NCBRF-P insecure/ anxious, change	8.7 (8.1) / 8 wk: -4.6 (6.5)	10.6 (7.6) / 8 wk: -3.5 (5.5)	NA	8 wk: 0.039
		NCBRF-P overly sensitive, change	6.9 (3.4) / 8 wk: -3.8 (2.8)	7.4 (3.5) / 8 wk: -2.7 (3.2)	NA	8 wk: 0.038
		NCBRF-P self-injurious/ stereotypic, change	4.2 (4.2) / 8 wk: -2.6 (3.3)	3.5 (4.2) / 8 wk: -1.3 (2.8)	NA	8 wk: >0.05
		VAS-MS, change	81.0 (13.3) / 8 wk: -38.4 (28.9)	84.8 (14.1) / 8 wk: -26.2 (29.2)	NA	8 wk: ≤0.05
Troost, 2005[94]	G1: Risperidone (12) G2: Placebo (12)	ABC irritability	11.1 (8.1) / 8 wk: 12.6 (9.8)	12.7 (7.7) / 8 wk: 20.3 (10.2)	NA	8 wk: 0.043
		ABC social withdrawal	5.0 (6.0) / 8 wk: 2.8 (3.1)	6.7 (6.9) / 8 wk: 4.8 (3.5)	NA	8 wk: 1.0
		ABC stereotypy	2.3 (3.2) / 8 wk: 3.3 (3.5)	4.7 (4.3) / 8 wk: 3.4 (4.6)	NA	8 wk: 0.31
		ABC hyperactivity	16.8 (11.5) / 8 wk: 18.0 (11.8)	15.8 (9.4) / 8 wk: 20.8 (12.1)	NA	8 wk: 0.12
		ABC inappropriate speech	3.2 (3.2) / 8 wk: 3.0 (2.8)	2.3 (1.9) / 8 wk: 3.0 (2.3)	NA	8 wk: 0.30

ADHD and Disruptive Behavior Disorders

Summary. Eight placebo-controlled RCTs evaluated the efficacy of second generation antipsychotics in treating symptoms of patients with ADHD and disruptive behavior disorders. The following is a summary of the results by comparison:

- Moderate level of evidence favored risperidone over placebo for reduction in behavior problems. Three meta-analyses supported this finding using various measures: ABC from four RCTs[40,41,47,89] (MD = -20.97; 95% CI, -31.11 to -10.83), BPI from two RCTs[41,89] (MD = -3.77; -6.16 to -1.39), and NCBRF from four RCTs[40,41,79,89] (MD = -6.93; -10.38 to -3.49).
- Two RCTs[48,55] compared patients who received risperidone or quetiapine using the Connor's Parent/Teacher Rating Scale (CPTRS). The results of both studies significantly favored risperidone (studies not pooled due to heterogeneity).
- Five RCTs[43,47,48,55,79] provided moderate evidence of a significant difference between groups favoring second generation antipsychotics over placebo for CGI-S (MD = -1.33; 95% CI, -2.15 to -0.50). The results of three RCTs[43,55,79] favored risperidone over placebo for CGI-I (MD = -0.95; 95% CI, -1.66 to -0.25).
- A meta-analysis of two RCTs[41,89] found significantly greater improvement in clinical symptoms on a VAS for risperidone compared with placebo (MD = -21.61; 95% CI, -26.32 to -16.90).
- A meta-analysis of two RCTs[47,48] found no difference between second generation antipsychotics and placebo for aggression (MD= -15.81, 95% CI, -51.56 to 19.94) (low evidence).
- A single RCT[55] found a significant reduction in delinquent behavior and aggression for patients treated with risperidone versus placebo (low evidence).

Results by individual study. Eight RCTs examined the efficacy of antipsychotics for treating symptoms in patients with ADHD with aggression[43]and disruptive behavior disorders.[40,41,47,48,55,79,89] The number of patients ranged from 16 to 335 (median = 32 [IQR, 20 to 112]. All of the RCTs were placebo-controlled trials examining second generation antipsychotics, quetiapine[48] and risperidone.[40,41,43,47,55,79,89] Meta-analyses were conducted for the following outcome scales: ABC, BPI, CGI-I, CGI-S, NCBRF, Overt Aggression Scale (OAS) and VAS of symptom improvement. Patient and study characteristics and outcome data are presented in Table 10 and Table 11, respectively.

Second generation antipsychotics versus placebo. Connor et al.[48] assessed the efficacy of quetiapine for treating conduct disorder in adolescents with moderate to severe aggression. Nineteen patients (aged 12 to 17 years) were randomly assigned to quetiapine (n = 9) or placebo (n = 10) for 6 weeks. Conduct disorder was diagnosed by psychiatrists using Kiddie Schedule for Affective Disorders and Schizophrenia-Epidemiological Version (K-SADS-E). The most common comorbid psychiatric diagnoses included oppositional defiant disorder (n = 18) and ADHD (n = 15). The mean dose of quetiapine was 294±78 mg/day. Patients were assessed using the CGI-I, CGI-S, CPTRS, and OAS. Quetiapine significantly improved clinical global

impressions compared with placebo (CGI-I scores, $p<0.001$; CGI-S, $p<0.01$). No statistically significant differences were observed in the OAS and CPTRS.

Aman et al.[40] conducted a crossover RCT to assess the effects of risperidone in children receiving maintenance therapy. Sixteen children (aged 4 to 14 years) were randomly assigned to alternate 2 weeks' treatment of risperidone and placebo. The study participants had the following diagnoses based on DSM-IV criteria: ADHD (n = 1), ADHD and conduct disorder (n = 2), ADHD and oppositional defiant disorder (n = 6), autism spectrum disorder (n = 3), conduct disorder (n = 1), and oppositional defiant disorder (n = 3). The participants also varied in cognitive function: average intellectual functioning (n = 1), borderline mental retardation (n = 10), mild mental retardation (n = 4), and moderate mental retardation (n = 1). The mean daily dose of risperidone was 1.7±1.3 mg. Patients were assessed using the ABC and NCBRF. Risperidone was superior to placebo for the NCBRF conduct problem ($p = 0.02$), hyperactivity ($p = 0.03$), and overly sensitive ($p = 0.007$) subscales, and the ABC hyperactivity/non-compliance subscale ($p = 0.01$).

Aman et al.[41] assessed the short- and long-term efficacy of risperidone for severe disruptive behaviors in children (aged 5 to 12 years) with subaverage intelligence. One hundred and nineteen children (1 dropout prior to treatment) were randomly assigned to risperidone (n = 55) or placebo (n = 63) for 6 weeks. All patients were enrolled in a 48-week open-label extension study to evaluate long-term efficacy of risperidone. The diagnoses based on DSM-IV criteria were conduct disorder (n = 21), conduct disorder and ADHD (n = 26), disruptive behavior disorder and ADHD (n = 6), disruptive behavior disorder NOS (n = 2), oppositional defiant disorder (n = 25), and oppositional defiant disorder and ADHD (n = 38). Participants varied in level of cognitive function: borderline (n = 60), mild (n = 38), or moderate (n = 20) intellectual disability. The mean daily dosage of risperidone was 1.2±0.6 mg at 6 weeks. Efficacy was assessed using ABC, BPI, CGI-I, NCBRF, and VAS for the most troublesome symptom. Risperidone was associated with significantly greater improvement than placebo on several ABC subscales (irritability, $p<0.001$; lethargy, $p = 0.007$; hyperactivity, $p<0.001$), the BPI aggression subscale ($p = 0.004$), the CGI-I ($p<0.001$), VAS for the most troublesome symptoms ($p<0.001$), and all NCBRF subscales ($p<0.02$) at 6 weeks. Risperidone was associated with rapid, significant improvement in NCBRF conduct score in patients previously treated with placebo. Improvement was maintained during the 48 weeks of long-term treatment in patients previously treated with risperidone.

Armenteros et al.[43] evaluated the efficacy of risperidone augmentations for treating aggression in children currently being treated with a psychostimulant (aged 7 to 12 years) with ADHD. Twenty-five patients were randomly assigned to risperidone augmentation (n = 12) or placebo (n = 13) for 4 weeks. ADHD diagnosis was established using DSM-IV and Computerized Diagnostic Interview Schedule for Children-Version Four. The mean daily dose at endpoint was 1.1±0.6 mg for risperidone and 1.0±0.5 mg for placebo. Patients were assessed using CGI-I and CGI-S scales and no significant effect was observed from baseline to endpoint in either group for either measure.

Buitelaar et al.[47] conducted an RCT to assess the efficacy of risperidone for the treatment of aggression in adolescents with disruptive behavior disorders and below average intelligence. Hospitalized adolescents were randomized to risperidone (n = 19) or placebo (n = 19) for 6 weeks. The principal diagnoses, based on DSM-IV criteria, were conduct disorder (n = 30), oppositional defiant disorder (n = 6), and disruptive behavior disorder NOS (n = 2). Comorbidities included ADHD (n = 26), mental retardation (n = 14), and anxiety disorder (n =

3). The mean daily dose of risperidone was 2.9 mg at the end of the study. Patients were assessed using ABC, CGI-S, and a modified OAS. Risperidone showed significant improvement on the CGI-S ($p<0.001$) and the ABC overall score at school ($p<0.05$) compared with placebo. No statistically significant differences were observed in OAS.

Findling et al.[55] conducted an RCT to compare the efficacy of risperidone for treating conduct disorder in children and adolescents (aged 5 to 15 years). Patients were randomly assigned to risperidone (n = 10) or placebo (n = 10) for 10 weeks. The mean dose of risperidone at the end of the study was 0.028±0.004 mg/kg/day. Primary diagnosis of conduct disorder was made using DSM-IV and SADS-E. Patients were assessed using the Child Behavior Checklist, CGI-I, CGI-S, CPTRS, and Rating of Aggression Against People and/or Property scale. Significant differences between groups on Rating of Aggression Against People and/or Property scale ($p = 0.03$), CGI-S ($p = 0.003$), and CGI-I ($p = 0.002$) scores indicate that patients treated with risperidone were less aggressive and showed greater improvement in global symptom severity than patients treated with placebo. Risperidone patients also had greater reductions in the conduct problem and psychosomatic subscales of CPTRS ($p<0.001$ and $p = 0.04$, respectively) and in delinquency subscale of Child Behavior Checklist ($p = 0.04$).

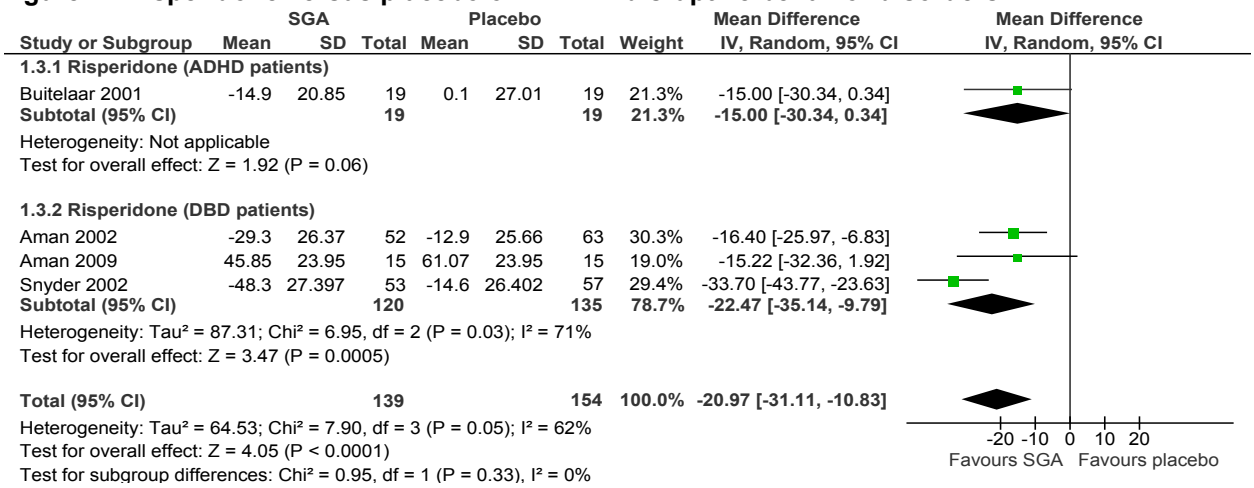
Reyes et al.[79] evaluated the efficacy of risperidone maintenance therapy for treating children (aged 5 to 17 years) with disruptive behavior disorders. Three hundred thirty-five patients who responded to risperidone treatment were randomly assigned to risperidone (n = 172) or placebo (n = 163) for 6 months. The following primary diagnoses were established using DSM-IV and K-SADS-PL: conduct disorder (n = 123), oppositional defiant disorder (n = 204), and disruptive behavior disorder NOS (n = 8). Comorbidities included ADHD (n = 227). The mean daily dose of risperidone was 0.81±0.34 mg for patients <50 kg and 1.22±0.36 mg for patients ≥50 kg. Patients were assessed using CGAS, CGI, NCBRF, and VAS of the most troublesome symptom. The risperidone group had a statistically significant improvements in symptoms compared with the placebo group on CGAS ($p<0.001$), CGI-I ($p<0.001$), CGI-S ($p<0.001$), VAS of the most troublesome symptom ($p<0.001$), and all NCBRF subscales except insecure/anxious, self-injury/stereotypic, and self-isolated/ritualistic behavior.

Snyder et al.[89] conducted an RCT to evaluate the short- and long-term efficacy of risperidone for symptoms associated with disruptive behavior disorders in children (aged 5 to 12 years) with below average intelligence (intelligence quotient: 36 to 84). Participants were randomized to risperidone (n = 53) or placebo (n = 57) for 6 weeks. A 48-week open-label extension study was conducted to evaluate long-term efficacy. Participants were diagnosed with conduct disorder (n = 41) and oppositional defiant disorder (n = 69) based on DSM-IV criteria. Eighty-four patients had comorbid ADHD. The mean daily dose of risperidone at 6 weeks was 1.0±0.73 mg. Patients were rated using ABC, BPI, CGI, NCBRF, and VAS of the most troublesome symptom. A statistically significant difference between the risperidone and placebo groups for symptom reduction was observed on all outcomes and subscales, with the exception of the BPI self-injurious and stereotypic behavior subscales, and the NCBRF overly sensitive subscale.

Four RCTs[40,41,47,89] provided data comparing risperidone with placebo for ABC scores were pooled (Figure 7). The study by Buitelaar[47] that included only patients with ADHD and aggression is 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 between the studies was substantial ($p = 0.05$, $I^2 = 62$ percent). Studies were similar in terms of design,

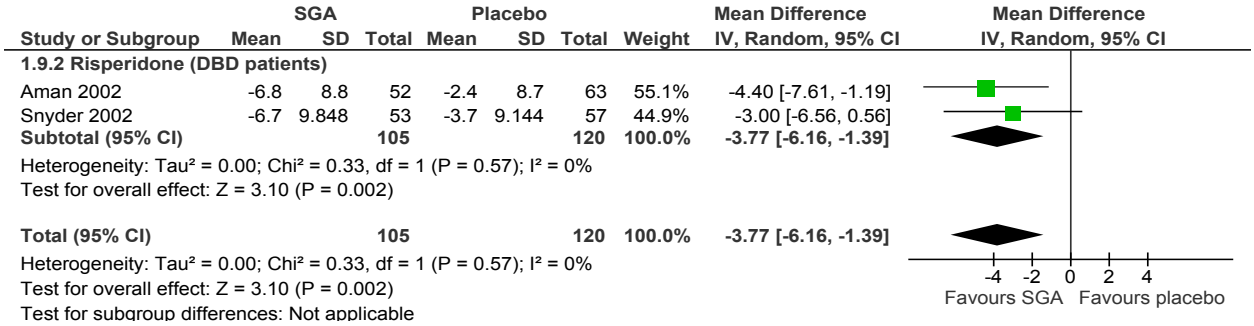
followup duration, and comorbidities. Patients in the study by Buitelaar[47] were older than those enrolled in the other studies.

Figure 7. Risperidone versus placebo on ABC in disruptive behavior disorders



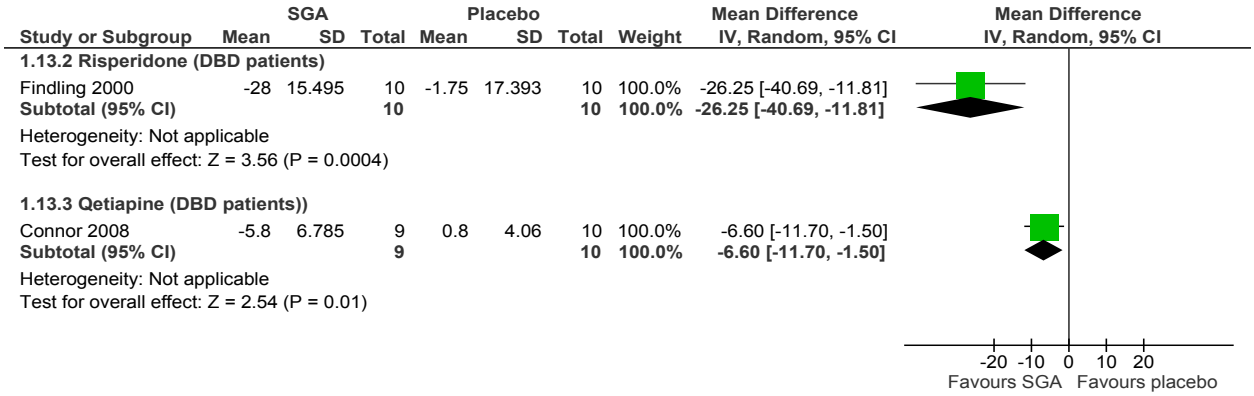
Two RCTs[41,89] were compared in a meta-analysis examining risperidone versus placebo on the BPI (Figure 8). The combined estimate showed a significant difference favoring risperidone for behavior problems (MD = -3.77; -6.16 to -1.39) with no evidence of heterogeneity (p = 0.57, I^2 = 0 percent).

Figure 8. Risperidone versus placebo on BPI in disruptive behavior disorders



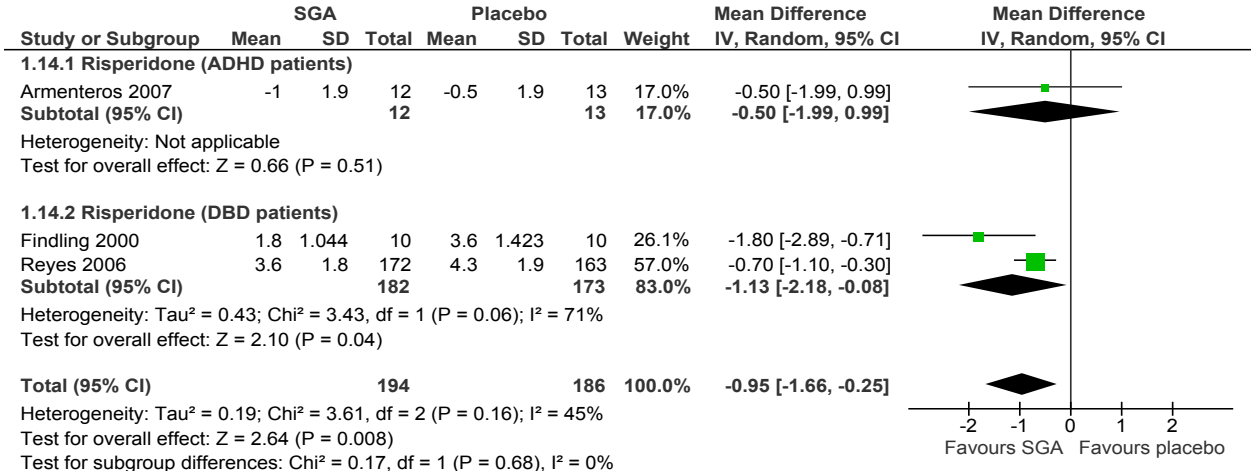
Two RCTs[48,55] evaluated patients receiving risperidone and quetiapine on CPTRS (Figure 9). The studies were not pooled due to substantial heterogeneity (p = 0.01, I^2 = 84 percent). Patients in the study by Findling et al.[55] were predominantly treatment naïve and were younger in general than those in the study by Connor et al.[48] Both studies significantly favored the second generation antipsychotic; however, the effect was greater in patients treated with risperidone.[55]

Figure 9. Second generation antipsychotics versus placebo on CPTRS in disruptive behavior disorders



Three RCTs[43,55,79] provided data for a meta-analysis comparing CGI-I scores in patients receiving treatment with risperidone versus placebo (Figure 10). The pooled estimate showed a significant difference between groups favoring risperidone (MD = -0.95; 95% CI, -1.66 to -0.25); however, there was considerable heterogeneity (p = 0.16, I^2 = 45 percent). The studies differed in patients' diagnosis (one study[43] enrolled patients with ADHD and aggression, the others examined disruptive behavior disorders), and followup duration, which ranged from 4 weeks to 6 months.

Figure 10. Risperidone versus placebo on CGI-I in disruptive behavior disorders

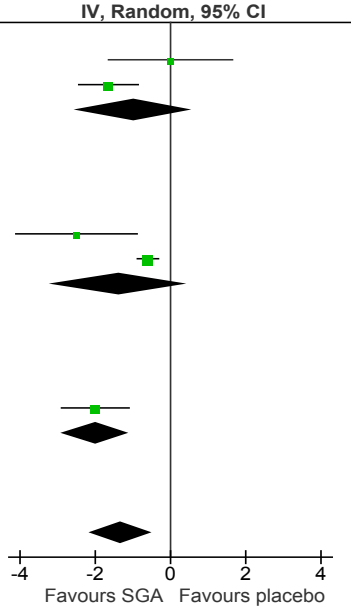


Five RCTs[43,47,48,55,79] provided data for a comparison of CGI-S scores (Figure 11). All but one study[43] favored second generation antipsychotics. Overall, the combined estimate showed a significant difference in symptom severity between groups that favored second generation antipsychotics (MD = -1.33; 95% CI, -2.15 to -0.50). However, there was substantial heterogeneity (p = 0.001, I^2 = 78 percent). Reyes et al.[79] indicated a smaller difference between risperidone and placebo than the other studies, a difference that may be due to the longer followup time (6 months versus 10 weeks); it is possible that the medication effects are reduced over time. In addition, heterogeneity may be a result of different patient populations. In addition, differences in the conditions being treated may have contributed to the difference in effect: Armenteros et al.[43] examined patients with ADHD and aggression, while the remaining four

studies examined patients with disruptive behavior disorders with or without ADHD comorbidity.

Figure 11. Second generation antipsychotics versus placebo on CGI-S in disruptive behavior disorders

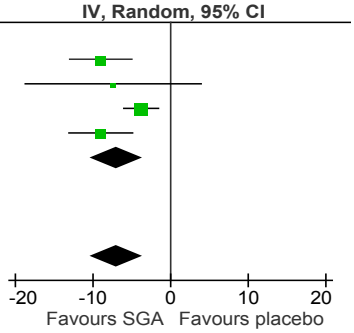
Study or Subgroup	SGA Mean	SGA SD	SGA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
1.4.1 Risperidone (ADHD patients)								
Armenteros 2007	-1.3	2.1	12	-1.3	2.1	13	13.5%	0.00 [-1.65, 1.65]
Buitelaar 2001	1.66	1.4	19	3.31	1	17	23.0%	-1.65 [-2.44, -0.86]
Subtotal (95% CI)			**31**			**30**	**36.4%**	**-0.99 [-2.57, 0.59]**
Heterogeneity: Tau² = 0.93; Chi² = 3.13, df = 1 (P = 0.08); I² = 68%								
Test for overall effect: Z = 1.22 (P = 0.22)								
1.4.2 Risperidone (DBD patients)								
Findling 2000	-2.58	1.55	10	-0.08	2.087	10	13.8%	-2.50 [-4.11, -0.89]
Reyes 2006	0.6	1.2	172	1.2	1.4	163	28.1%	-0.60 [-0.88, -0.32]
Subtotal (95% CI)			**182**			**173**	**41.9%**	**-1.38 [-3.21, 0.45]**
Heterogeneity: Tau² = 1.46; Chi² = 5.19, df = 1 (P = 0.02); I² = 81%								
Test for overall effect: Z = 1.47 (P = 0.14)								
1.4.3 Qetiapine (DBD patients))								
Connor 2008	-2.5	0.954	9	-0.5	1.039	10	21.6%	-2.00 [-2.90, -1.10]
Subtotal (95% CI)			**9**			**10**	**21.6%**	**-2.00 [-2.90, -1.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.37 (P < 0.0001)								
Total (95% CI)			**222**			**213**	**100.0%**	**-1.33 [-2.15, -0.50]**
Heterogeneity: Tau² = 0.61; Chi² = 18.39, df = 4 (P = 0.001); I² = 78%								
Test for overall effect: Z = 3.15 (P = 0.002)								
Test for subgroup differences: Chi² = 10.07, df = 2 (P = 0.007), I² = 80.1%								



Four RCTs[40,41,79,89] provided data comparing risperidone with placebo for behavior scores on the NCBRF (Figure 12). The pooled MD showed a significantly greater reduction in problem behaviors for the risperidone group (MD = -6.93; -10.38 to -3.49). There was substantial heterogeneity (p = 0.05, I^2 = 62 percent). The study with the largest sample size[79] showed the most precision, and the confidence intervals of the smaller studies overlap with the effect estimate of this study.

Figure 12. Second generation antipsychotics versus placebo on NCBRF in disruptive behavior disorders

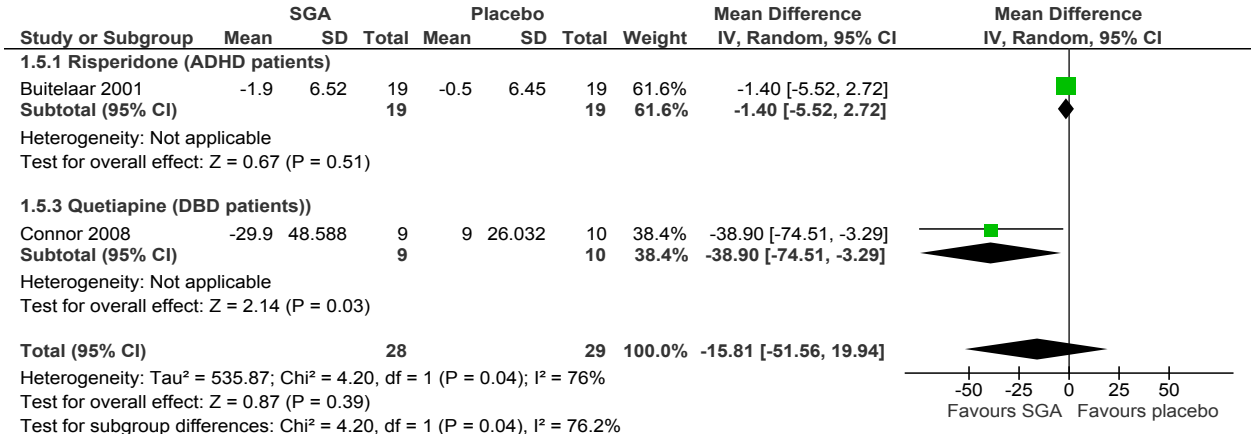
Study or Subgroup	SGA Mean	SGA SD	SGA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
1.6.2 Risperidone (DBD patients)								
Aman 2002	-15.2	10.6	52	-6.2	11.2	63	27.8%	-9.00 [-12.99, -5.01]
Aman 2009	18.73	15.82	15	26.13	15.82	15	7.6%	-7.40 [-18.72, 3.92]
Reyes 2006	5	9.5	172	8.8	11.2	163	37.4%	-3.80 [-6.03, -1.57]
Snyder 2002	-15.8	10.344	53	-6.8	11.58	57	27.2%	-9.00 [-13.10, -4.90]
Subtotal (95% CI)			**292**			**298**	**100.0%**	**-6.93 [-10.38, -3.49]**
Heterogeneity: Tau² = 6.95; Chi² = 7.98, df = 3 (P = 0.05); I² = 62%								
Test for overall effect: Z = 3.95 (P < 0.0001)								
Total (95% CI)			**292**			**298**	**100.0%**	**-6.93 [-10.38, -3.49]**
Heterogeneity: Tau² = 6.95; Chi² = 7.98, df = 3 (P = 0.05); I² = 62%								
Test for overall effect: Z = 3.95 (P < 0.0001)								
Test for subgroup differences: Not applicable								



Two RCTs[47,48] compared second generation antipsychotics with placebo for aggression on the OAS (Figure 13). 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 percent). The studies were

similar in length of followup, patient age and comorbidities; the heterogeneity may be explained partially by differences between the second generation antipsychotics used in the studies.

Figure 13. Second generation antipsychotics versus placebo on OAS in disruptive behavior disorders



Two RCTs[41,89] compared risperidone with placebo on a VAS for symptom improvement (Figure 14). The pooled estimate significantly favored risperidone (MD = -21.61; 95% CI, -26.32 to -16.90). There was moderate heterogeneity (p = 0.23, I^2 = 31 percent). Study duration, patient characteristics, comorbidities, and drug dosing were comparable between the studies.

Figure 14. Second generation antipsychotics versus placebo on VAS in disruptive behavior disorders

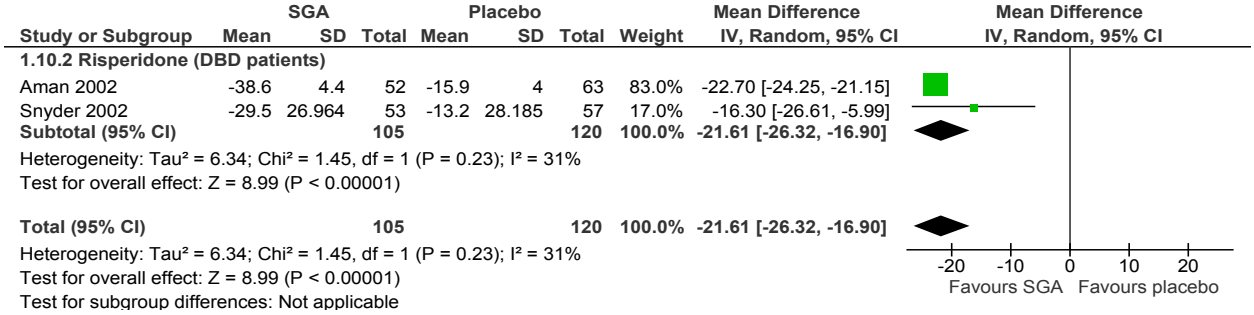


Table 10. Study and patient characteristics for studies examining ADHD and disruptive behavior disorders

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Aman, 2009[40] RCT (crossover), 4 wk	**G1:** Risperidone (16),* 1.7±1.3 mg/day **G2:** Placebo (16)*	**G1:** NR / Male : NR / Caucasian: NR **G2:** NR / Male : NR / Caucasian: NR Comorbidities: MR (borderline (10), mild (4), moderate (1))	ADHD (1), ADHD + CD (2), ADHD + ODD (6), ASD (3), CD (1), ODD (3) NR, NR
Aman, 2002[41] RCT, 6 wk (48 wk extension)	**G1:** Risperidone (55), 1.2±0.6 mg/day **G2:** Placebo (63)	**G1:** 8.7±2.1 yr / Male: 85% / Caucasian: 51% **G2:** 8.1±2.3 yr / Male: 79% / Caucasian: 62% Comorbidities: ADHD (70), MR (borderline (60), mild (38), moderate (20))	CD (21), CD + ADHD (26), DBD (2), DBD + ADHD (6), ODD (25), ODD + ADHD (38) NR, 118
Armenteros, 2007[43] ADHD with aggression RCT, 4 wk	**G1:** Risperidone (12), 1.1±0.6 mg/day **G2:** Placebo (13)	**G1:** 7.3±3.7 yr / Male: 83% / Caucasian: 50% **G2:** 8.8±3.1yr / Male: 92% / Caucasian: 46% Comorbidities: MR (0), generalized anxiety disorder (1), ODD (13), separation anxiety disorder (3)	ADHD (all) NR, 0
Buitelaar, 2001[47] RCT, 6 wk	**G1:** Risperidone (19), 2.9 mg/day **G2:** Placebo (19)	**G1:** 14.0±1.5 (11-18) yr / Male: 90% / Caucasian: NR **G2:** 13.7±2 (11-18) yr / Male: 84% / Caucasian: NR Comorbidities: ADHD (26), aggression (all), anxiety disorder (3), MR (14)	ADHD (all), CD (30), DBD NOS (2), ODD (6) NR, 26
Connor, 2008[48] RCT, 6 wk	**G1:** Quetiapine (9), 294±78 mg/day **G2:** Placebo (10)	**G1:** 13.1±1.2 yr / Male: 78% / Caucasian: 78% **G2:** 15±1.4 yr / Male: 70% / Caucasian: 70% Comorbidities: ADHD (15), depression (4), dysthymia (5), generalized anxiety disorder (3), MR (0), OCD (3), ODD (18), panic disorder (1), psychosis (0), PTSD (3), SA (6), separation anxiety (3), social phobia (3)	CD (all) NR, 3
Findling, 2000[55] RCT, 10 wk	**G1:** Risperidone (10), 0.028±0.004 mg/kg/day **G2:** Placebo (10)	**G1:** 10.7±3.4 yr / Male: NR / Caucasian: NR **G2:** 8.2±1.9 yr / Male: NR / Caucasian: NR Comorbidities: NR	CD (all) NR, 19

ADHD = attention deficit hyperactivity disorder; CD = conduct disorder; DBD = disruptive behavior disorder; G = group; 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 = posttraumatic stress disorder; RCT = randomized controlled trial; SA = substance abuse; wk = week
*All patients experienced each of the treatment arms in this crossover study

Table 10. Study and patient characteristics for studies examining ADHD and disruptive behavior disorders (continued)

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Reyes, 2006[79] RCT, 6 mo	**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% / Caucasian: NR **G2:** 10.8±2.9 yr / Male: 91% / Caucasian: NR Comorbidities: ADHD (227)	CD (123), DBD NOS (8), ODD (204) NR, NR
Snyder, 2002[89] RCT, 6 wk (48 wk extension)	**G1:** Risperidone (53), 1±0.73 mg/day **G2:** Placebo (57)	**G1:** 8.6±0.3 (5-12) yr / Male: 77% / Caucasian: 79% **G2:** 8.8±0.3 (5-12) yr / Male: 74% / Caucasian: 74% Comorbidities: ADHD (84), MR (borderline (53), mild (42), moderate (15))	CD (10), CD + ADHD (31), ODD (16), ODD + ADHD (53) NR, NR

Table 11. Outcome data for studies assessing ADHD and development behavior disorders

Author, Year	Intervention (N analyzed)	Outcome	G1: BL mean (SD) / Followup mean (SD)	G2: BL mean (SD) / Followup mean (SD)	P-value
Aman, 2009[40]	G1: Risperidone (15) G2: Placebo (15)	ABC irritability	NR / 2 wk: 16.00	NR / 2 wk: 20.73	0.07
		ABC lethargy	NR / 2 wk: 5.06	NR / 2 wk: 5.06	0.88
		ABC stereotypic behavior	NR / 2 wk: 0.93	NR / 2 wk: 2.20	0.25
		ABC inappropriate speech	NR / 2 wk: 3.87	NR / 2 wk: 4.14	0.39
		ABC hyperactivity/ noncompliance	NR / 2 wk: 20.00	NR / 2 wk: 28.94	0.01
		NCBRF conduct problems	NR / 2 wk: 18.73	NR / 2 wk: 26.13	0.02
		NCBRF insecurity	NR / 2 wk: 11.07	NR / 2 wk: 14.2	0.07
		NCBRF hyperactivity	NR / 2 wk: 11.47	NR / 2 wk: 14.94	0.03
		NCBRF self-injury	NR / 2 wk: 0.67	NR / 2 wk: 1.07	0.13
		NCBRF ritualistic	NR / 2 wk: 2.53	NR / 2 wk: 3.00	0.49
		NCBRF overly sensitive	NR / 2 wk: 5.13	NR / 2 wk: 7.80	0.007
Aman, 2002[41]	G1: Risperidone (52) G2: Placebo (63)	ABC irritability, change	23.5 (7.2) / 6 wk: -10.0 (9.3)	23.6 (10.4) / 6 wk: -4.4 (8.9)	<0.001
		ABC lethargy, change	10.1 (8.8) / 6 wk: -4.6 (6.6)	9.8 (8.9) / 6 wk:-1.7 (7.1)	0.007
		ABC stereotypic behavior, change	3.4 (4.9) / 6 wk: -1.7 (3.9)	3.1 (5.4) / 6 wk: -0.9 (3.2)	0.13
		ABC inappropriate speech, change	4.9 (3.2) / 6 wk: 1.7 (2.5)	4.8 (3.1) / 6 wk: -0.9 (2.6)	0.17
		ABC hyperactivity/ noncompliance, change	36.2 (8.7) / 6 wk: -14.7 (11.1)	36.7 (9.9) / 6 wk: -5.0 (10.7)	<0.001
		BPI aggression	19.4 (8.9) / 6 wk: -6.8 (8.8)	18.1 (8.4) / 6 wk: -2.4 (8.7)	0.004
		BPI self-injurious	8.9 (10.8) / 6 wk: -3.9 (7.5)	8.1 (11.3) / 6 wk: -3.3 (7.6)	0.99
		BPI stereotyped	4.5 (6.8) / 6 wk: -1.6 (4.7)	3.2 (5.6) / 6 wk: -0.8 (3.6)	0.71
		CGI–I, pts very much improved	28 (53.8)	5 (7.9)	<0.001
		NCBRF compliant/ calm, change	4.9 (2.6) / 6 wk: 2.7 (3.4)	4.6 (2.7) / 6 wk: 0.7 (3.0)	<0.001
		NCBRF adaptive / social, change	3.7 (1.9) / 6 wk: 1.6 (2.4)	3.6 (2.0) / 6 wk: 0.1 (2.2)	<0.001
		NCBRF conduct problem, change	32.9 (7.7) / 6 wk: -15.2 (10.6) / 48 wk extension: -14.6 (11.9)	34.5 (7.0) / 6 wk: -6.2 (11.2) / 48 wk extension: -14.3 (12.3)	6 wk: <0.001
		NCBRF insecure/ anxious, change	18.4 (8.5) / 6 wk: -8.4 (6.6)	16.9 (8.6) / 6 wk: -3.0 (7.8)	<0.001

ABC = Aberrant Behavior Checklist; ADHD = attention deficit and hyperactivity disorder; BPI = Behavior Problems Inventory; BL = baseline; CGAS = Children's Global Assessment Scale; CGI–I = Clinical Global Impressions–Improvement; CGI–S = Clinical Global Impressions–Severity; CPTRS = Connor's Parent Teacher Rating Scale; CBCL = Child Behavior Checklist; G = group; NA = not applicable; mm = millimeter; N = number; NR = not reported; NCBRF = Nisonger Child Behavior Rating Form; OAS (M) = Overt Aggression Scale (modified); RAAPP = Rating of aggression Against People and/or Property scale; SD = standard deviation; VAS–MS: visual analog scale for the most troublesome symptom; wk = week

Table 11. Outcome data for studies assessing ADHD and development behavior disorders (continued)

Author, Year	Intervention (N analyzed)	Outcome	G1: BL mean (SD) / Followup mean (SD)	G2: BL mean (SD) / Followup mean (SD)	P-value
Aman, 2002 (continued)		NCBRF hyperactive, change	19.3 (5.2) / 6 wk: -6.3 (5.5)	18.7 (5.5) 6 wk: -2.7 (5.3)	<0.001
		NCBRF self-injury/ stereotypic, change	3.0 (3.8) / 6 wk: -2.1 (3.6)	3.1 (4.3) 6 wk: -1.0 (3.4)	6 wk: <0.02
		NCBRF self-isolated / ritualistic, change	6.2 (4.6) / 6 wk: -3.2 (3.7)	5.7 (4.8) / 6 wk: -1.6 (3.5)	<0.02
		NCBRF overly sensitive, change	8.9 (3.1) / 6 wk: -3.5 (4.1)	7.7 (3.4) / 6 wk: -1.2 (3.1)	0.002
		VAS–MS (mm)	83.7 (18.7) / 6 wk: -38.6 (4.4) / 48 wk extension: -8.7 (29.9)	82.8 (17.4) / 6 wk: -15.9 (4.0) / 48 wk extension: -28.5 (31.8)	6 wk: <0.001
Armenteros, 2007[43] ADHD	G1: Risperidone (12) G2: Placebo (13)	CGI–I	NR / -1.0	NR / -0.5	>0.05
		CGI–S	4.5 / 4 wk: 3.2	4.5 / 4 wk: 3.2	>0.05
Buitelaar, 2001[47] ADHD	G1: Risperidone (19) G2: Placebo (19)	ABC (ward)	55.4 (21.2) / 6 wk: 37.8 (19.9)	51.7 (15.7) / 6 wk: 46.5 (21.8)	0.06
		ABC (school)	43.8 (20.7) / 6 wk: 28.9 (21.0)	36.3 (22.4) / 6 wk: 32.6 (29.6)	<0.05
		CGI–S	4.3 (1.4) / 6 wk: 2.7 (1.2)	4.2 (0.9) / 6 wk: 4.4 (1.0)	<0.001
		CGI–S ≥5, pts (%)	15 (79) / 6 wk: 4 (21)	15 (79) / 6 wk: 16 (84)	NR
		OAS–M (ward)	11.5 (8.2) / 6 wk: 6.7 (6.3)	9.0 (7.4) / 6 wk: 8.1 (6.9)	>0.05
		OAS–M (school)	7.5 (6.2) / 6 wk: 5.6 (6.8)	7.2 (5.5) / 6 wk: 6.7 (7.1)	>0.05
Connor, 2008[48]	G1: Quetiapine (9) G2: Placebo (10)	CGI–I, pts with score ≤2	8 (0.89)	1 (0.10)	<0.001
		CGI–S	5.9 (0.6) / 6 wk: 3.4 (1.1)	5.5 (1.2) / 6 wk: 5.0 (0.6)	<0.01
		Conner PRS–conduct problem	17.1 (15.1) / 6 wk: 11.3 (7.7)	11.4 (3.6) / 6 wk: 12.2 (4.4)	>0.05
		OAS	73.2 (34.3) / 6 wk: 43.3 (55.6)	40.4 (23.8) / 6 wk: 49.4 (27.8)	>0.05
Findling, 2000[55]	G1: Risperidone (10) G2: Placebo (10)	CBCL aggressive behavior, change	87.4 (7.8) / 10 wk: -24.2 (17.1)	85.8 (6.0) / 10 wk: -11.5 (14.2)	0.11
		CBCL anxious/ depressed, change	60.8 (13.2) / 10 wk: -13.1 (30.9)	53.7 (25.0) / 10 wk: -0.6 (28.5)	0.34
		CBCL attention problems, change	74.1 (10.8) / 10 wk: -19.3 (26.1)	71.7 (10.4) / 10 wk: -10.3 (24.0)	0.44
		CBCL delinquent behavior, change	81.1 (7.8) / 10 wk: -27.1 (32.7)	66.7 (27.2) / 10 wk: 4.5 (30.9)	0.04
		CBCL somatic complaints, change	55.2 (9.6) / 10 wk: -9.4 (27.6)	51.6 (22.1) / 10 wk: 2.1 (25.2)	0.35

Table 11. Outcome data for studies assessing ADHD and development behavior disorders (continued)

Author, Year	Intervention (N analyzed)	Outcome	G1: BL mean (SD) / Followup mean (SD)	G2: BL mean (SD) / Followup mean (SD)	P-value
Findling, 2000 (continued)		CBCL social problems, change	70.2 (10.2) / 10 wk: -17.1 (33.0)	57.6 (26.2) / 10 wk: 4.0 (30.4)	0.16
		CBCL thought problems, change	68.2 (13.5) / 10 wk: -16.4 (32.7)	55.1 (24.7) / 10 wk: 6.0 (30.0)	0.13
		CBCL withdrawn, change	62.1 (12.9) / 10 wk: -12.3 (30.6)	53.8 (23.4) / 10 wk: 1.8 (28.1)	0.31
		CGI–I, change	NR / 10 wk: 1.80 (1.04)	NR / 10 wk: 3.60 (1.42)	0.002
		CGI–S, change	4.9 / 10 wk: -2.58 (1.55)	5 / 10 wk: -0.08 (2.1)	0.003
		Conner PRS conduct problem, change	92.9 (10.2) / 10 wk: -28.0 (13.9)	88.0 (9.0) / 10 wk: -1.75 (16.5)	0.0005
		Conner anxiety, change	47.9 (10.2) / 10 wk: 1.0 (17.0)	48.4 (12.3) / 10 wk: -4.6 (19.2)	0.52
		Conner hyperactivity index, change	85.6 (5.9) / 10 wk: -20.0 (15.6)	78.8 (14.1) / 10 wk: -9.7 (18.6)	0.22
		Conner impulsive-hyperactive, change	79.1 (5.9) / 10 wk: -19.3 (36)	73.6 (10.8) / 10 wk: -12.0 (15.0)	0.28
		Conner learning problem, change	79.9 (7.4) / 10 wk: -14.6 (16.1)	66.7 (20.1) / 10 wk: -8.1 (19.2)	0.45
		Conner psychosomatic, change	59.9 (17.0) / 10 wk: -13.7 (11.3)	48.7 (9.9) / 10 wk: -2.1 (11.7)	0.04
		RAAPP, change	3.89 / 10 wk: -1.65 (1.71)	3.7 / 10 wk: -0.16 (0.54)	0.03
Reyes, 2006[79]	G1: Risperidone (172) G2: Placebo (163)	CGAS, change	NR / 6 mo: -3.5 (12.4); Extension BL: 67.3 (14.1) / 12 mo: 70.4 (13.4)	NR / 6 mo: -10.2 (14.5); Extension BL: 61.2 (14.3) / 12 mo: 68.4 (14.2)	6 mo: <0.001
		CGI–I, change	NR / 6 mo: 3.6 (1.8)	NR / 6 mo: 4.3 (1.9)	<0.001
		CGI–S, change	NR / 0.6 (1.2); Extension BL: 3.3 (1.4) / 12 mo: 3.0 (1.9)	NR / 6 mo: 1.2 (1.4); Extension BL: 4.0 (1.6) / 12 mo: 3.1 (1.3)	6 mo: <0.001
		NCBRF conduct problems, change	NR / 6 mo: 5.0 (9.5); Extension BL: 11.0 (7.9) / 12 mo: 7.3 (4.6)	NR / 6 mo: 8.8 (11.2); Extension BL: 13.5 (8.9) / 12 mo: 7.6 (5.1)	6 mo: <0.001
		NCBRF insecure/ anxious, change	NR / 6 mo: 1.9 (6.2)	NR / 6 mo: 2.7 (6.5)	0.20
		NCBRF hyperactive, change	NR / 6 mo: 0.8 (4.4)	NR / 6 mo: 2.4 (5.4)	0.007
		NCBRF self-injury/ stereotypic, change	NR / 6 mo: 0.3 (1.5)	NR / 6 mo: 0.5 (1.8)	0.34
		NCBRF self-isolated/ ritualistic, change	NR / 6 mo: 0.8 (2.6)	NR / 6 mo: 0.9 (2.8)	0.67

Table 11. Outcome data for studies assessing ADHD and development behavior disorders (continued)

Author, Year	Intervention (N analyzed)	Outcome	G1: BL mean (SD) / Followup mean (SD)	G2: BL mean (SD) / Followup mean (SD)	P-value
Reyes, 2006 (continued)		NCBRF overly sensitive, change	NR / 6 mo: 0.4 (2.8)	NR / 6 mo: 1.0 (3.19)	0.0054
		NCBRF compliant/ calm, change	NR / 6 mo: -1.5 (3.8)	NR / 6 mo: -2.8 (4.4)	<0.001
		NCBRF adaptive social, change	NR / 6 mo: -0.9 (2.5)	NR / 6 mo: -1.7 (2.9)	0.006
		VAS–MS, change	NR / 6 mo: 7.2 (26.9); Extension BL: 37.5 (27.6) / 12 mo: 29.8 (24.8)	NR / 6 mo: 14.1 (27.8); Extension BL: 49.5 (31.0) / 12 mo: 32.0 (26.8)	6 mo: 0.01
Snyder, 2002[89]	G1: Risperidone (53) G2: Placebo (57)	ABC irritability	22.7 (8.7) / 6 wk: 1.9 (9.0)	20.2 (7.6) / 6 wk: 16.0 (9.4)	<0.001
		ABC lethargy / social withdrawal	9.8 (7.8) / 6 wk: 3.3 (4.7)	7.7 (6.8) / 6 wk: 6.0 (6.7)	<0.001
		ABC stereotypic behavior	4.0 (5.4) / 6 wk: 1.6 (3.1)	2.2 (4.1) / 6 wk: 2.3 (4.1)	<0.001
		ABC hyperactivity/ noncompliance	35.6 (10.8) / 6 wk: 19.7 (12.0)	32.6 (9.6) / 6 wk: 24.5 (12.3)	<0.001
		ABC inappropriate speech	5.3 (3.4) / 6 wk: 2.6 (2.7)	3.5 (2.9) / 6 wk: 2.8 (2.6)	<0.01
		BPI aggression	14.6 (9.6) / 6 wk: 7.9 (7.7)	17.2 (9.8) / 6 wk: 13.5 (10.6)	<0.01
		BPI self-injurious behavior	6.8 (9.8) / 6 wk: 4.0 (5.4)	5.4 (7.2) / 6 wk: 4.3 (6.2)	>0.05
		BPI stereotypic behavior	4.2 (5.1) / 6 wk: 2.0 (3.8)	2.3 (3.5) / 6 wk: 2.0 (4.2)	>0.05
		CGI–I, n (%)	6 wk: Score of 1 or 2: 16 (38.1), score of 3: 20 (47.6), score ≥4: 6 (14.3)	6 wk: Score of 1 or 2: 6 (16.2), score of 3: 8 (21.6), score ≥4: 23 (62.1)	<0.001
		CGI–S, n (%)	48 wk: Score ≥5: 7 (0.18)	48 wk: Score ≥5: 6 (0.15)	NR
		NCBRF compliant/ calm	5.3 (3.3) / 6 wk: 7.5 (4.7)	4.9 (2.9) / 6 wk: 5.8 (3.7)	<0.05
		NCBRF adaptive social	4.3 (2.2) / 6 wk: 5.8 (3.0)	3.9 (2.0) / 6 wk: 4.2 (2.6)	<0.01
		NCBRF conduct problem	33.4 (6.3) / 6 wk: 17.6 (11.9) / 48 wk: 16.8	32.6 (6.3) / 6 wk: 25.8 (13.4) / 48 wk: 15.3	<0.001
		NCBRF insecure/ anxious	19.4 (7.9) / 6 wk: 9.8 (7.6)	15.9 (8.1) / 6 wk: 12.8 (6.9)	<0.001
		NCBRF hyperactive	19.6 (5.4) / 6 wk: 11.8 (6.8)	17.2 (5.1) / 6 wk: 13.5 (6.3)	<0.01
		NCBRF self-injury/ stereotypic	2.7 (3.6) / 6 wk: 0.8 (3.4)	2.0 (3.0) / 6 wk: 1.4 (2.9)	<0.05
		NCBRF self-isolated/ ritualistic	6.7 (3.9) / 6 wk: 2.5 (4.0)	5.5 (4.1) / 6 wk: 3.8 (3.9)	<0.01
		NCBRF overly sensitive	8.8 (3.6) / 6 wk: 5.5 (3.6)	7.6 (2.9) / 6 wk: 5.3 (3.1)	>0.05
		VAS symptom	79.6 (21.6) / 6 wk: 50.1 (30.2) / 48 wk change: -43.5 (28.2)	77.7 (19.0) / 6 wk: 64.5 (32.4) / 48 wk change: -47.1 (30.4)	6 wk: <0.001 48 wk: <0.001

Bipolar Disorder

Summary. Nine RCTs compared the efficacy of second generation antipsychotics with other drugs of the same class or placebo for treating symptoms in children and adolescents with bipolar disorder. The following is a summary of the results by comparison:

- One RCT[46] compared olanzapine versus risperidone in young children (aged 4 to 6 years). No significant differences were found between the antipsychotics for depression or mania. The evidence was too limited to make conclusions.
- Three RCTs compared low- versus high-dose aripiprazole,[54] risperidone,[57] and ziprasidone.[51] No significant differences were found between the dosing regimens for any of the antipsychotics. The evidence was too limited to make conclusions.
- Two studies examining aripiprazole[54,93] found significantly greater improvement on manic symptoms and clinical global impressions for aripiprazole compared with placebo.
- Two studies[50,52] comparing quetiapine with placebo showed a statistically significant difference for manic symptoms in favor of quetiapine; however, the absolute difference of one point was not clinically important.
- Seven placebo-controlled trials examined aripiprazole,[54,93] olanzapine,[92] quetiapine,[50,52] risperidone,[57] and ziprasidone.[75] All but one study[50] found a statistically significant difference in favor of the second generation antipsychotics for manic symptoms (low evidence). Moderate evidence showed a significant difference favoring second generation antipsychotics over placebo for clinical global impressions. Low evidence showed no difference between groups for depression.

Results by individual study. Nine RCTs[46,50-52,54,57,75,92,93]examined the efficacy of antipsychotics for treating symptoms in patients with bipolar disorder. The number of participants ranged from 30 to 296 (median = 63 [IQR, 32 to 170]). All of the studies included patients with bipolar I disorder; one study[93] also included patients with bipolar II disorder. Second generation antipsychotics were compared with another second generation antipsychotic in one study,[46] with another dose of the same antipsychotic in three studies,[51,54,57] and with placebo in seven studies.[50,52,54,57,75,92,93] Meta-analyses were conducted for depressive symptoms on the Children's Depression Rating Scale (CDRS), CGI, and manic symptoms on the Young Mania Rating Scale (YMRS). Patient and study characteristics and outcome data are presented in Table 12 and Table 13, respectively.

Second generation versus second generation antipsychotics. Four RCTs compared the efficacy of two second generation antipsychotics for treating symptoms. One study compared olanzapine and risperidone,[46] while the remaining three studies compared different doses of the same second generation antipsychotic, including aripiprazole,[54] risperidone,[57] and ziprasidone.[51]

Biederman et al.[46] conducted an RCT to compare the efficacy of olanzapine and risperidone in children (aged 4 to 6 years) with bipolar disorder based on DSM-IV and K-SADS criteria. Thirty-one patients were randomly assigned to the interventions (15 to olanzapine, 16 to risperidone) and all patients were followed to the study endpoint at 8 weeks. The majority of patients had comorbidities including ADHD (19 patients), conduct disorder (13 patients), and major depressive disorder (22 patients). The mean dosage of the drugs was 6.3±2.3 mg/day and

1.4±0.5 mg/day for olanzapine and risperidone, respectively. Patients were assessed using the BPRS, CDRS, and YMRS. Symptoms improved from baseline to endpoint in both groups; however, there were no statistically significant differences between the groups on any of the outcome measures.

Findling et al.[54] conducted an RCT to evaluate the efficacy of different aripiprazole dosing regimens for treating bipolar I disorder in adolescents (aged 10 to 17 years) with mixed or manic episodes with or without psychosis. Patients were randomized to aripiprazole 10 mg/day (n = 98) or 30 mg/day (n = 99) or placebo (n = 99) for 4 weeks. Primary diagnosis was established with DSM-IV criteria and confirmed using K-SADS-PL. Patients with current or past comorbid ADHD (n = 153), conduct disorder (n = NR), oppositional defiant disorder (n = 93), or anxiety disorders (n = NR) were included in the study. Participants had a current mixed (n = 119) or manic (n = 125) episode and psychotic features (n = 14). Patients were assessed using the CDRS, CGAS, CGI-BP, General Behavior Inventory, and YMRS (primary outcome) scales. There were no significant differences in the baseline to endpoint change scores for the two aripiprazole doses.

Haas et al.[57] assessed risperidone monotherapy in children and adolescents (aged 10 to 17 years) with manic and mixed episodes associated with bipolar I disorder. Patients were randomly assigned to receive placebo (n = 58) or risperidone at a daily dose of 0.5 to 2.5 mg (n = 50) or 3–6 mg (n = 61) for 3 weeks. Diagnosis of bipolar manic (n = 60) and mixed episodes (n = 109) and comorbid disruptive behavior disorder (n = 101) and ADHD (n = 85) were based on DSM-IV and K-SADS-PL criteria. Assessments included the YMRS change (primary efficacy measure), the CGI-BP, and the BPRS for Children (BPRS-C) scales. There were no significant differences between the low- and high-dose risperidone groups.

An RCT conducted by DelBello et al.[51] compared the efficacy of low- and high-dose ziprasidone in treating children (aged 10 to 17 years) with bipolar mania, schizophrenia, and schizoaffective disorder based on DSM-IV-TR criteria. Separate analyses were provided for patients with bipolar disorder. Participants were randomly assigned to low-dose (80 mg/day; 15 participants) or high-dose (160 mg/day; 31 participants) ziprasidone for 3 weeks. Patients were assessed using the CGI-S and the YMRS. No significant differences were found between the two groups.

Second generation antipsychotics versus placebo. Seven RCTs compared a second generation antipsychotic with placebo for alleviating symptoms. The second generation antipsychotics examined were aripiprazole,[54,93] olanzapine,[92] quetiapine,[50,52] risperidone,[57] and ziprasidone.[75]

An RCT by Findling et al.[54] (described previously) compared the efficacy of two doses of aripiprazole with placebo in children (aged 10 to 17 years). Patients were assessed using the CDRS, CGAS, CGI-BP, General Behavior Inventory, and YMRS scales. Both the low- and high-dose aripiprazole groups showed significantly greater improvement compared with placebo on all outcome measures except for the CDRS and General Behavior Inventory depression scores, which were significant only for the low dose-placebo comparison in the parent-rated version in favor of low-dose aripiprazole.

Tramontina et al.[93] evaluated the efficacy of aripiprazole in children and adolescents (aged 8 to 17 years) with bipolar disorder comorbid with ADHD. Patients were randomly assigned to aripiprazole (n = 18) or placebo (n = 25) for 6 weeks. DSM-IV criteria were confirmed with K-SADS-E. Baseline characteristics of patients with bipolar I (n = 35) and II (n = 8) included ADHD combined type (n = 34), psychosis (n = 16), disruptive behavior disorders (n = 35), and

anxiety disorders (n = 21). The mean daily dosage was 13.6±5.4 mg for aripiprazole and 15±3.2 mg for placebo. The aripiprazole group showed a significantly greater reduction in YMRS (p = 0.02), Child Mania Rating Scale parent version (p = 0.02), and CGI-S (p = 0.04) scores compared with placebo. No significant difference between groups was observed for CDRS. Manic symptoms and global functioning improved in patients given aripiprazole, but no treatment effect was observed for ADHD symptoms.

Tohen et al.[92] evaluated the efficacy of olanzapine for the treatment of acute manic or mixed episodes in adolescents (aged 13 to 17 years). Patients were randomized to receive either 2.5 to 20 mg/day of olanzapine (n = 107; mean daily dose 8.9 mg) or placebo (n = 54) for 3 weeks. All patients met diagnostic criteria for bipolar disorder according to DSM-IV and confirmed with K-SADS. Patients had mixed episodes (n = 30), psychotic features (n = 29), and current or past comorbid diagnosis of ADHD (n = 58) and oppositional defiant disorder (n = 49). Assessment scales included the CDRS, CGI-S, OAS, and YMRS. The olanzapine group showed a significantly greater improvement in symptoms from baseline to endpoint compared with placebo on all outcome measures (p<0.001) except for depressive symptoms as measured by the CDRS, which was no statistically significant.

DelBello et al.[50] compared quetiapine versus placebo for the treatment of depressive episodes in adolescents (12 to 18 years) with bipolar I disorder. Patients had a baseline CDRS Revised score of 40 or greater and a diagnosis based on DSM-IV-R criteria and Washington University (St. Louis) KSADS interview. Thirty-two patients were randomly assigned to quetiapine 300 to 600 mg/day (n = 17) or placebo (n = 15) for 8 weeks. There were comparable rates of concurrent ADHD (n = 4), anxiety disorders (n = 8), disruptive behavior disorders (n = 8), and psychosis (n = 3) in the groups. At endpoint, the mean daily drug dose was 403±133 mg for quetiapine and 413±151 mg for placebo. Efficacy measures included CDRS Revised, Hamilton Anxiety Rating Scale, YMRS, and CGI-BP-S. No statistically significant differences were found between groups for any outcomes.

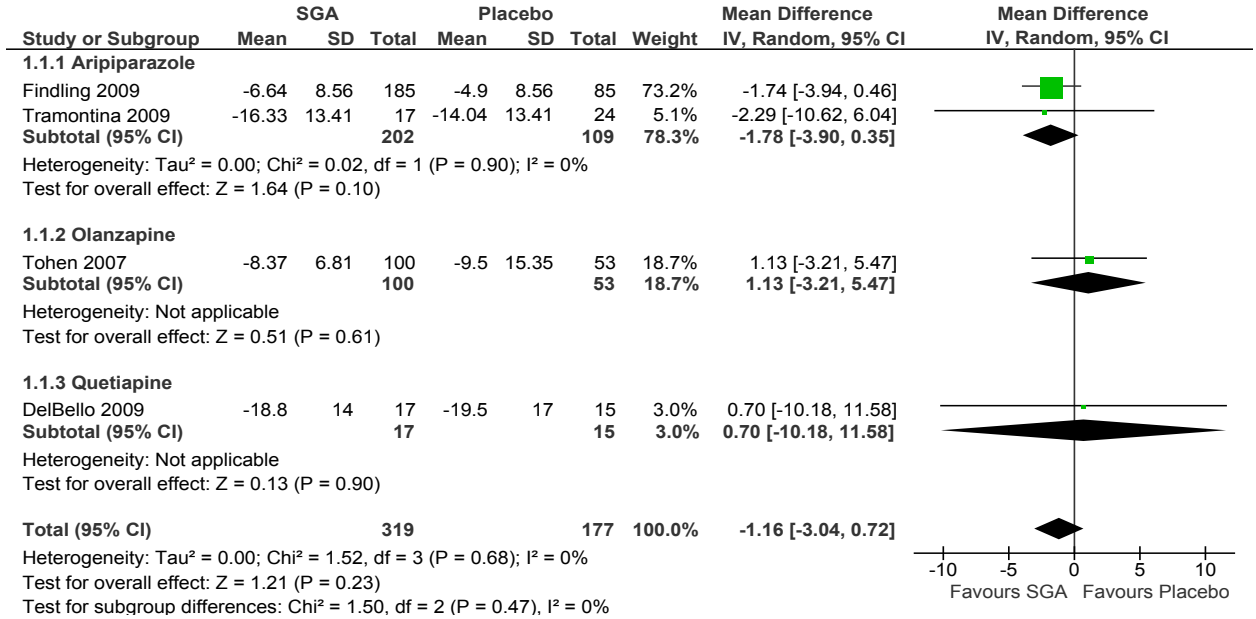
DelBello et al.[52] examined the efficacy of quetiapine as an adjunct to divalproex (DVP) for the treatment of acute mania in hospitalized adolescents (aged 12 to 18 years). Thirty manic or mixed bipolar I adolescents were randomly assigned to combination therapy with quetiapine (n = 15) titrated to 450 mg/day or placebo (n = 15) for 6 weeks. Patients were diagnosed using DSM-IV criteria, rated with KSADS, and had a baseline YMRS score of 20 or greater. Some patients experienced mixed episodes (n = 23), ADHD (n = 18), or psychosis (n = 14); no significant group differences were noted. Mean dosage of quetiapine was 432 mg/day. YMRS change scores showed a significantly greater reduction in manic symptoms associated with bipolar disorder in patients treated with quetiapine and DVP compared with placebo and DVP (p = 0.03).

Haas et al.[57] compared low- and high-dose risperidone with placebo in children and adolescents (aged 10 to 17 years) with bipolar I disorder (described previously). Outcome measures included the YMRS, CGI-BP, and BPRS-C scales. Improvements in all three outcome measures were significantly greater for patients treated with risperidone than for those in the placebo group (p<0.001 for all outcomes).

In a 4 week RCT,[75] oral ziprasidone was compared with placebo for treating children and adolescents (aged 10 to 18 years) with manic or mixed bipolar I disorder as defined by DSM-IV criteria and confirmed by K-SADS. Patients were randomized to flexibly dosed ziprasidone (n = 149) or placebo (n = 88). Patients were assessed using YMRS change score; oral ziprasidone was significantly more effective than placebo (p<0.001).

Four RCTs[50,54,92,93] provided data for a meta-analysis of the efficacy of second generation antipsychotics versus placebo on depression symptoms as measured by the CDRS (Figure 15). For the two aripiprazole studies, the combined estimate of change in the depression score favored aripiprazole over placebo; however, the pooled results were not statistically significant (MD = -1.78; 95% CI, -3.90 to 0.35). The pooled estimate for change across all second generation antipsychotics was not statistically significant. There was no evidence of heterogeneity (p = 0.68, I^2 = 0 percent).

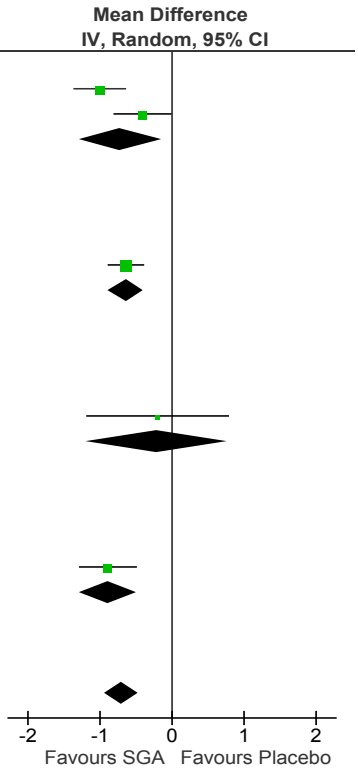
Figure 15. Second generation antipsychotics versus placebo on CDRS in bipolar disorder



Five RCTs[50,54,57,92,93] provided data for a meta-analysis of the efficacy of second generation antipsychotics versus placebo for CGI (Figure 16). One study used the CGI–S[93] and four studies used the CGI–BP. Two studies[54,93] 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 between the studies (p = 0.03, I^2 = 79 percent). The heterogeneity between these studies may be related to variability in the followup duration (4 weeks[54] versus 6 weeks)[93] and in the proportion of patients with comorbid ADHD. The combined estimate of all studies favored second generation antipsychotics (MD = -0.70; 95% CI, -0.94 to -0.47). There was moderate heterogeneity (p = 0.13, I^2 = 43 percent).

Figure 16. Second generation antipsychotics versus placebo on CGI in bipolar disorder

Study or Subgroup	SGA Mean	SGA SD	SGA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 Aripiparazole								
Findling 2009	-1.803	1.43	195	-0.8	1.43	92	22.7%	-1.00 [-1.36, -0.65]
Tramontina 2009	-2.05	0.63	17	-1.64	0.63	24	20.3%	-0.41 [-0.80, -0.02]
Subtotal (95% CI)			**212**			**116**	**42.9%**	**-0.71 [-1.29, -0.13]**
Heterogeneity: Tau² = 0.14; Chi² = 4.84, df = 1 (P = 0.03); I² = 79%								
Test for overall effect: Z = 2.40 (P = 0.02)								
1.3.2 Olanzapine								
Tohen 2007	-1.63	0.71	105	-0.99	0.75	54	31.7%	-0.64 [-0.88, -0.40]
Subtotal (95% CI)			**105**			**54**	**31.7%**	**-0.64 [-0.88, -0.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.19 (P < 0.00001)								
1.3.3 Quetiapine								
DelBello 2009	-1.8	1.41	17	-1.6	1.41	15	5.0%	-0.20 [-1.18, 0.78]
Subtotal (95% CI)			**17**			**15**	**5.0%**	**-0.20 [-1.18, 0.78]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.40 (P = 0.69)								
1.3.4 Risperidone								
Haas 2009	-1.89	1.25	109	-1	1.2	57	20.4%	-0.89 [-1.28, -0.50]
Subtotal (95% CI)			**109**			**57**	**20.4%**	**-0.89 [-1.28, -0.50]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.47 (P < 0.00001)								
Total (95% CI)			**443**			**242**	**100.0%**	**-0.70 [-0.94, -0.47]**
Heterogeneity: Tau² = 0.03; Chi² = 7.06, df = 4 (P = 0.13); I² = 43%								
Test for overall effect: Z = 5.98 (P < 0.00001)								
Test for subgroup differences: Chi² = 2.22, df = 3 (P = 0.53), I² = 0%								



Seven RCTs[50,52,54,57,75,92,93] evaluated the efficacy of second generation antipsychotics versus placebo for manic symptoms, as measured by the YMRS (Figure 17). A meta-analysis of two studies[54,93] comparing aripiprazole with placebo showed a statistically 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 percent). Two studies[50,52] comparing quetiapine with placebo showed a statistically significant difference favoring quetiapine; however, the absolute difference was small and not clinically important (MD = -1.08; 95% CI, -2.01, -0.14). There was no evidence of heterogeneity (p = 0.98, I^2 = 0 percent). We did not pool the seven studies due to the substantial heterogeneity (I^2>80 percent), which is mainly attributed to the two quetiapine studies.[50,52]

Figure 17. Second generation antipsychotics versus placebo on YMRS in bipolar disorder

Study or Subgroup	SGA Mean	SGA SD	SGA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
1.4.1 Aripiparazole								
Findling 2009	-15.37	8.73	195	-8.2	8.73	92	62.2%	-7.17 [-9.33, -5.01]
Tramontina 2009	-27.22	10.44	17	-19.52	10.44	24	37.8%	-7.70 [-14.19, -1.21]
Subtotal (95% CI)			**212**			**116**	**100.0%**	**-7.22 [-9.28, -5.17]**
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%								
Test for overall effect: Z = 6.90 (P < 0.00001)								
1.4.2 Olanzapine								
Tohen 2007	-17.65	6.55	105	-9.99	6.23	54	100.0%	-7.66 [-9.74, -5.58]
Subtotal (95% CI)			**105**			**54**	**100.0%**	**-7.66 [-9.74, -5.58]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 7.21 (P < 0.00001)								
1.4.3 Quetiapine								
DelBello 2002	-2.45	1.32	15	-1.37	1.32	15	63.9%	-1.08 [-2.02, -0.14]
DelBello 2009	-5	9.41	17	-4	9.41	15	36.1%	-1.00 [-7.53, 5.53]
Subtotal (95% CI)			**32**			**30**	**100.0%**	**-1.08 [-2.01, -0.14]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%								
Test for overall effect: Z = 2.26 (P = 0.02)								
1.4.4 Risperidone								
Haas 2009	-17.41	10.04	108	-9.1	11	57	100.0%	-8.31 [-11.74, -4.88]
Subtotal (95% CI)			**108**			**57**	**100.0%**	**-8.31 [-11.74, -4.88]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.75 (P < 0.00001)								
1.4.5 Ziprasidone								
NCT00257166	-13.83	11.07	133	-8.61	10.14	85	100.0%	-5.22 [-8.08, -2.36]
Subtotal (95% CI)			**133**			**85**	**100.0%**	**-5.22 [-8.08, -2.36]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.58 (P = 0.0003)								

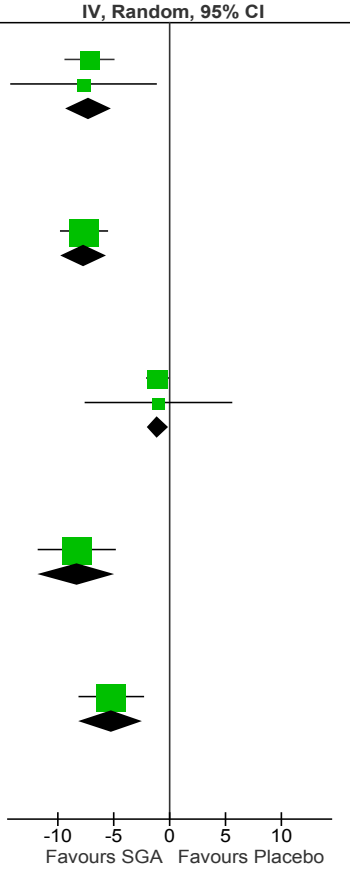


Table 12. Study and patient characteristics for studies examining bipolar disorder

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Biederman, 2005[46] RCT, 8 wk	**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% / Caucasian: 100% **G2:** 5.3±0.8 yr / Male: 75% / Caucasian: 94% Comorbidities: ADHD (19), CD (13), MDD (22)	Bipolar I (27), type not specified (4), mania (all) NR, NR
DelBello, 2009[50] RCT, 8 wk	**G1:** Quetiapine (17), 403±133 mg/day **G2:** Placebo (15)	**G1:** 16.0±2 yr / Male: 29% / Caucasian: 82% **G2:** 15±2 yr / Male: 33% / Caucasian: 80% Comorbidities: ADHD (4), anxiety disorder (8), DBD (8), psychosis (3)	Bipolar I with depressive episode (all) NR, 23
DelBello, 2008[51] RCT, 3 wk (24 wk extension)	**G1:** Ziprasidone (low) (15), target: 80 mg/day **G2:** Ziprasidone (high) (31), target: 160 mg/day	**G1:** 13.2±2.1 yr / Male: 47% / Caucasian: NR **G2:** 13.8±2.4 yr / Male: 77% / Caucasian: NR Comorbidities: MR (0), SA (0)	Bipolar I (all) NR, NR
DelBello, 2002[52] RCT, 6 wk	**G1:** Quetiapine (15), 432 mg/day **G2:** Placebo (15)	**G1:** 14.1±2 yr / Male: 53% / Caucasian: 80% **G2:** 14.5±2 yr / Male: 53% / Caucasian: 87% Comorbidities: ADHD (18), psychosis (14)	Bipolar I (all), mixed episode (23) NR, NR
Findling, 2009[54] RCT, 4 wk	**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% / Caucasian: 66% **G2:** 13.3±2.3 yr / Male: 52% / Caucasian: 69% **G3:** 13.3±2.1 yr / Male: 57% / Caucasian: 61% Comorbidities: ADHD (153), DBD (93), psychosis (14)	Bipolar I (all), mania (119), mixed (125), unknown (52) NR, 126
Haas, 2009[57] RCT, 3 wk	**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 (10-17) yr / Male: 56% / Caucasian: 70% **G2:** NR (10-17) yr / Male: 43% / Caucasian: 82% **G3:** NR (10-17) yr / Male: 48% / Caucasian: 78% Comorbidities: ADHD (85), DBD (101)	Bipolar I (all), manic episode (60), mixed episode (109) NR, NR
NCT00257166, 2008[75] RCT, 4 wk	**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 / Caucasian: NR **G2:** 13.7 yr / Male: NR / Caucasian: NR Comorbidities: NR	Bipolar I (all) NR, NR

ADHD = attention deficit hyperactivity disorder; CD = conduct disorder; DBD = disruptive behavior disorder; G = group; kg = kilogram; MDD = major depressive disorder; mg = milligrams; mo = month; MR = mental retardation; N = number; NR = not reported; RCT = randomized controlled trial; SA = substance abuse; SD = standard deviation; wk = week; yr = year

Table 12. Study and patient characteristics for studies examining bipolar disorder (continued)

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Tohen, 2007[92] RCT, 3 wk (6 mo extension)	**G1:** Olanzapine (107), 8.9 mg/day **G2:** Placebo (54)	**G1:** 15.1±1.3 yr / Male: 57% / Caucasian: 66% **G2:** 15.4±1.2 yr / Male: 44% / Caucasian: 76% Comorbidities: ADHD (58), DBD (49)	Bipolar I (all), mixed (86), psychotic features (29), rapid cycling (30) NR, NR
Tramontina, 2009[93] Bipolar with ADHD RCT, 6 wk	**G1:** Aripiprazole (18), 13.6±5.4 mg/day **G2:** Placebo (25)	**G1:** 11.7±2.7 yr / Male: 33% / Caucasian: 83% **G2:** 12.2±2.8 yr / Male: 56% / Caucasian: 96% Comorbidities: ADHD (all), anxiety disorders (21), DBD (35), psychosis (16)	Bipolar type I (35), type II (8) NR, NR

Table 13. Outcome data for studies assessing bipolar disorder

Author, Year	Intervention (N analyzed)	Outcome	G1: BL mean (SD) / Followup mean (SD)	G2: BL mean (SD) / Followup mean (SD)	G3: BL mean (SD) / Followup mean (SD)	P-value
Biederman, 2005[46]	G1: Olanzapine (15) G2: Risperidone (16)	BPRS	46.7 (13.5) / 8 wk: 37.8 (11.9)	46.4 (12.4) / 8 wk: 33.3 (10.6)	NA	0.40
		CDRS	42.4 (14.8) / 8 wk: 34.1 (11.5)	39.7 (10.5) / 8 wk: 27.0 (6.3)	NA	0.40
		YMRS	34.2 (6.4) / 8 wk: 22.1 (8.3)	35.2 (8.2) / 8 wk: 16.4 (12.0)	NA	0.20
DelBello, 2009[50]	G1: Quetiapine (17) G2: Placebo (15)	CDRS	53.5 (7.8) / 8 wk: 34.7 (15.1)	53.9 (7.9) / 8 wk: 34.4 (14.8)	NA	0.89
		CGI–BP	5.4 (0.7) / 8 wk: 3.6 (1.7)	5.5 (0.6) / 8 wk: 3.9 (1.8)	NA	0.9
		HAM–A	15 (7) / 8 wk: 11 (9)	13 (7) / 8 wk: 8 (6)	NA	0.74
		YMRS	15 (6) / 8 wk: 10 (7)	20 (7) / 8 wk: 16 (10)	NA	0.76
DelBello, 2008[51]	G1: Ziprasidone, 80 mg (15) G2: Ziprasidone, 160 mg (31)	CGI–S	5.3 (0.6) / 3 wk: -1.6 (1.4)	4.7 (0.6) / 3 wk: -1.7 (1.2)	NA	0.81
		YMRS, change	29.2 (5.4) / 3 wk: -17.2 (8.2)	26.2 (6.9) / 3 wk: -13.1 (8.9)	NA	0.12
DelBello, 2002[52]	G1: Quetiapine + DVP (15) G2: Placebo + DVP (15)	YMRS	34.5 / 6 wk: 10.00	31.4 / 6 wk: 17.73	NA	0.03
Findling, 2009[54]	G1: Aripiprazole, 10 mg (98) G2: Aripiprazole, 30 mg (99) G3: Placebo (97)	CDRS, change	35.2 / 4 wk: -7.2	34.1 / 4 wk: -6.1	33.8 / 4 wk: -4.9	G1 vs. G3: 0.08 G2 vs. G3: 0.35
		CGAS, change	46.9 / 4 wk: 15.1	47.5 / 4 wk: 17.3	45.5 / 4 wk: 5.8	G1 vs. G3: <0.0001 G2 vs. G3: <0.0001
		CGI–BP, change	4.7 / 4 wk: -1.6	4.6 / 4 wk: -2.0	4.8 / 4 wk: -0.8	G1 vs. G3: <0.0001 G2 vs. G3: <0.0001
		GBI total, parent/ guardian (mania), change	17.7 / 4 wk: -9.9	17.4 / 4 wk: -9.5	19.1 / 4 wk: -4.0	G1 vs. G3: <0.0001 G2 vs. G3: <0.0001
		GBI total, parent/ guardian (depression), change	13.4 / 4 wk: -5.9	12.4 / 4 wk: -4.1	13.4 / 4 wk: -3.8	G1 vs. G3: 0.04 G2 vs. G3: 0.77

BL = baseline; BPRS = Brief Psychiatric Rating Scale; CDRS = Children's Depression Rating Scale; CGAS = Children's Global Assessment Scale; CGI–BP = Clinical Global Impressions–Bipolar; CGI–S = Clinical Global Impressions–Severity; CMRS = Child Mania Rating Scale; DVP = divalproex; G = group; GBI = General Behavior Inventory; HAM–A = Hamilton Anxiety Rating Scale; mg = milligram; N = number; NA = not applicable; NR = not reported; OAS = Overt Aggression Scale; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; wk = week; YMRS = Young Mania Rating Scale

Table 13. Outcome data for studies assessing bipolar disorder (continued)

Findling, 2009 (continued)		GBI total, patient (mania), change	15.1 / 4 wk: -6.4	14.8 / 4 wk: -6.6	14.8 / 4 wk: -4.6	G1 vs. G3: 0.05 G2 vs. G3: 0.03
		GBI total, patient (depression), change	12.1 / 4 wk: -3.4	11.3 / 4 wk: -3.3	10.5 / 4 wk: -3.4	G1 vs. G3: 0.94 G2 vs. G3: 0.84
		YMRS, change	29.8 (6.5) / 4 wk: -14.2	29.5 (6.3) / 4 wk: -16.5	30.7 (6.8) / 4 wk: -8.2	G1 vs. G3 and G2 vs. G3: <0.0001
Haas, 2009[57]	G1: Risperidone, (50) G2: Risperidone, (61) G3: Placebo (58)	BPRS, change	31.1 (11.1) / 3 wk: -17.9 (10.1)	33.7 (10.7) / 3 wk: -16.6 (12.4)	33.4 (13.0) / 3 wk: -11.6 (12.2)	G1 vs. G2: 0.54 G1 vs. G3: <0.001 G2 vs. G3: <0.05
		CGI–BP, change	4.6 (0.7) / 3 wk: -2.0 (1.2)	4.5 (0.7) / / 3 wk: -1.8 (1.3)	4.5 (0.7) / 3 wk: -1.0 (1.2)	G1 vs. G2: 0.27 G1 vs. G3: <0.001 G2 vs. G3: <0.001
		YMRS, change	31.1 (6.0) / 3 wk: -18.5 (9.70)	30.5 (5.9) / 3 wk: -16.5 (10.29)	31.0 (7.5) / 3 wk: -9.1 (10.95)	G1 vs. G2: 0.29 G2 vs. G3: <0.001 G1 vs. G3: <0.001
NCT00257166, 2008[75]	G1: Ziprasidone (149) G2: Placebo (88)	YMRS, change	NR / 4 wk: -13.83 (11.7)	NR / 4 wk: -8.61 (10.3)	NA	< 0.001
Tohen, 2007[92]	G1: Olanzapine (107) G2: Placebo (54)	CDRS, change	40.43 (15.60) / 3 wk: -8.37	35.77 (15.35) / 3 wk: -9.50	NA	0.508
		CGI–BP, change	4.81 (0.71) / 3 wk: -1.63	4.83 (0.75) / 3 wk: -0.99	NA	<0.001
		OAS, change	6.34 (3.67) / 3 wk: -3.60	5.73 (2.94) / 3 wk: -1.90	NA	<0.001
		YMRS, change	33.08 (6.55) / 3 wk: -17.65	32.04 (6.23) / 3 wk: -9.99	NA	<0.001
Tramontina, 2009[93]	G1: Aripiprazole (18) G2: Placebo (25)	CDRS	49.27 (13.82) / 6 wk: 16.33	49.32 (13.91) / 6 wk: 14.04	NA	6 wk: 0.59
		CGI–S, change	4.05 (1.21) / 6 wk: -2.05	4.40 (1.19) / 6 wk: -1.64	NA	6 wk: 0.04
		CMRS–P, change	33.33 (11.30) / 6 wk: 21.16	33.16 (10.79) / 6 wk: 15.52	NA	6 wk: 0.02
		YMRS, change	35.94 (8.55) / 6 wk: 27.22	40.56 (9.01) / 6 wk: 19.52	NA	6 wk: 0.02

Schizophrenia and Psychosis

Summary. A total of 24 studies examined the efficacy of first and second generation antipsychotics for treating symptoms in patients with schizophrenia and schizophrenia-related psychosis. Twenty studies included patients with schizophrenia in 20 studies and four studies included patients experiencing a first episode of psychosis. The following is a summary of the results by comparison.

Schizophrenia:

- Four studies (three RCTs[49,65,98] and one prospective cohort study[78]) compared the following first and second generation antipsychotics: haloperidol versus clozapine,[65] haloperidol versus olanzapine,[49,78] and haloperidol versus risperidone.[78,98] Low evidence showed a significant difference between drug classes on CGI, favoring second generation antipsychotics (two studies[49,65,78]), but no difference for positive and negative symptoms (two studies[49,98]). Significant differences favoring second generation antipsychotics on the BPRS, CGAS, and SANS/ Scale for the Assessment of Positive Symptoms were found in a single study.[65]
- Eight studies (six RCTs and two prospective cohort studies[66,78]) compared two or more of the following second generation antipsychotics: clozapine versus olanzapine,[64,66,85] olanzapine versus quetiapine,[61] and olanzapine versus risperidone.[61,72,78,87,96] In meta-analyses, clozapine was found to be superior to olanzapine on the BPRS, but there was no significant difference for the CGI-S or the SANS. One study[61] found no significant difference between olanzapine and quetiapine on the CGI-S. Meta-analyses showed no significant differences between olanzapine and risperidone on the BPRS or for positive and negative symptoms on the PANSS. Evidence for all comparisons was graded low or insufficient.
- Five RCTs compared two doses of the same second generation antipsychotic: aripiprazole,[53] paliperidone,[80] quetiapine,[74] risperidone,[58] and ziprasidone.[51] The high-dose risperidone group showed greater symptom improvement than the low-dose group on CGI-I, CGI-S, and PANSS in one study (low evidence).[58] No other significant differences were found between doses.
- One crossover RCT[90] compared haloperidol with placebo. Both the positive and negative syndrome scores on the CPRS improved significantly in the haloperidol group compared with placebo ($p<0.01$). The evidence was too limited to make conclusions.
- Six RCTs compared the following second generation drugs with placebo: aripiprazole,[53] olanzapine,[63,97] paliperidone,[80], quetiapine,[74] and ziprasidone.[76] A statistically significant difference was found favoring second generation antipsychotics on the CGAS, clinical global impressions (moderate evidence), and PANSS (moderate evidence). No difference was found for BPRS.

First episode psychosis:

- One study[88] compared haloperidol with olanzapine and risperidone. Significant differences were found favoring olanzapine over haloperidol on the BPRS ($p = 0.02$) and favoring risperidone over haloperidol for the CGI-S and CPRS ($p = 0.03$ for both outcomes).

- Three RCTs provided data on the efficacy of two different second generation antipsychotics. Comparisons included olanzapine versus quetiapine,[42] olanzapine versus risperidone,[88] and quetiapine versus risperidone.[91] Olanzapine was significantly favored over quetiapine for strengths and difficulties (SDQ) as rated by patients ($p = 0.03$). None of the other outcomes and comparisons showed statistical significance.
- One RCT[45] compared two doses of quetiapine. Reduction in global impressions of symptom severity was significantly greater in the high-dose quetiapine group ($p = 0.03$). There were no differences between doses for any other outcomes.
- Evidence across all comparisons and outcomes was too limited to make conclusions.

Results by individual study: Schizophrenia. Twenty studies (18 RCTs,[49,51,53,58,61,63-65,72,74,76,80,85,87,90,96-98] and two prospective cohort studies[66,78]) examined the efficacy of antipsychotics for treating symptoms in patients with schizophrenia. The number of participants ranged from 8 to 302 (median = 47 [IQR, 25 to 131]). First generation antipsychotics were compared with second generation antipsychotics in four studies.[49,65,78,98] One study compared a first generation drug with placebo.[90] Thirteen studies[51,53,58,61,64,66,72,74,78,80,85,87,96] compared two or more second generation antipsychotics and six studies[53,63,74,76,80,97] compared a second generation drug with placebo. Meta-analyses were conducted to compare first versus second generation antipsychotics on the CGI-I and PANSS, clozapine and olanzapine on the BPRS, CGI-S and SANS, and olanzapine and risperidone on the BPRS and PANSS. Meta-analyses were also conducted for the second generation antipsychotics versus placebo on the BPRS, CGAS, CGI-I, CGI-S and PANSS. Patient and study characteristics and outcome data are presented in Table 14 and Table 15, respectively.

First generation versus second generation antipsychotics. Four studies provided data on the following first generation versus second generation drug comparisons: haloperidol versus clozapine,[65] haloperidol versus olanzapine,[49,78] and haloperidol versus risperidone.[78,98]

Kumra et al.[65] conducted an RCT to compare the efficacy of haloperidol and clozapine. Patients were diagnosed using the DSM-III-TR, K-SADS, and Diagnostic Interview for Children and Adolescents-Revised criteria. Ten patients had disorganized schizophrenia, one patient had paranoid schizophrenia, and 10 had undifferentiated schizophrenia. Twenty-one patients were randomly assigned to the interventions (11 to haloperidol, 10 to clozapine) and 17 patients were followed to the study endpoint at 6 weeks. The mean dosage of the drugs was 16±8 mg/day and 176±149 mg/day for the haloperidol and clozapine groups, respectively. 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 ($p<0.05$).

De Haan et al.[49] conducted an RCT to compare the efficacy of haloperidol and olanzapine in adolescents and young adults (aged 17 to 26 years). Patients were diagnosed using the DSM-IV criteria. Twenty-four patients were randomly assigned to the interventions (12 to haloperidol, 12 to olanzapine) and patients were followed to the study endpoint at 6 weeks. 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 was no significant difference in endpoint between the groups.

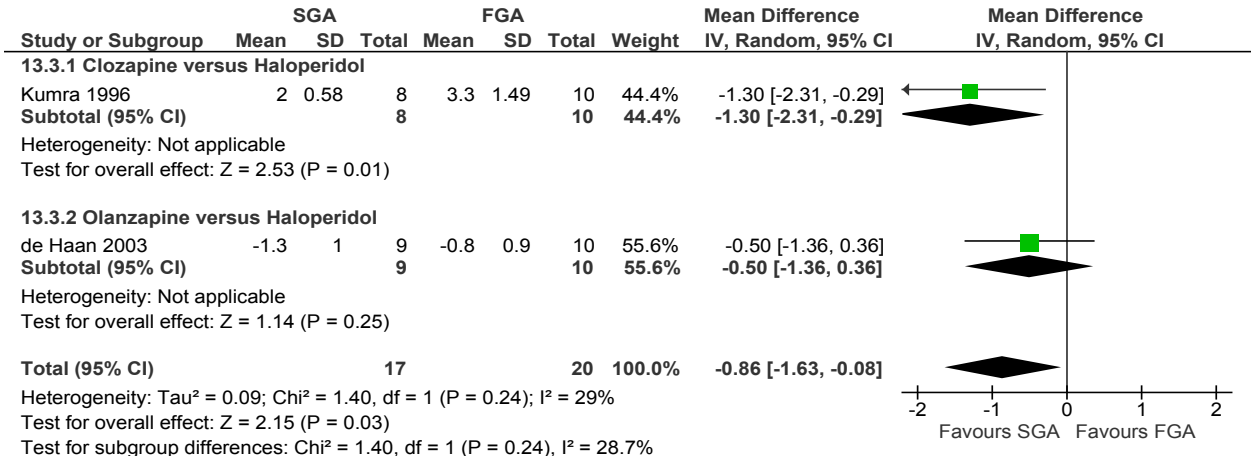
Ratzoni et al.[78] conducted a prospective cohort study to compare the efficacy of haloperidol, olanzapine, and risperidone in adolescents with schizophrenia (n = 46), schizoaffective disorder (n = 2), and conduct disorder (n = 2). Patients were diagnosed using the DSM-IV and K-SADS-

PL (Hebrew version) criteria and the consensus of two child psychiatrists. Fifty patients were given the interventions (8 to haloperidol, 21 to olanzapine, 21 to risperidone) and 36 patients were followed to the study endpoint at 12 weeks. The mean dosage was 7.6±4 mg/day, 12.7±3.1 mg/day and 3.2±1.1 mg/day for haloperidol, olanzapine and risperidone, respectively. Patients were assessed using the PANSS. Changes in positive and negative symptoms did not differ significantly between haloperidol and the second generation antipsychotics.

Yen et al.[98] conducted an RCT to compare the efficacy of haloperidol and risperidone in patients with schizophrenia (aged 18 to 65 years). Data for eight patients aged 24 years or younger were presented separately. Patients were diagnosed using the DSM-III-TR criteria and were randomly assigned to the interventions (2 to haloperidol, 6 to risperidone). All patients were followed to the study endpoint at 12 weeks. The mean dosage was 11.2±6.9 mg/day and 4.4±2.6 mg/day for haloperidol and risperidone, respectively. Patients were assessed using the PANSS. The risperidone group demonstrated significantly greater improvement in positive and negative symptoms than the haloperidol group (p = 0.03).

Two RCTs[49,65] provided data for a meta-analysis on the efficacy of first generation versus second generation antipychotics on CGI-I (Figure 18). A pooled estimate of the change scores was statistically significant and favored second generation antipsychotics over haloperidol (MD = -0.86; 95% CI, -1.63 to -0.08). There was evidence of moderate heterogeneity (p = 0.24, I^2 = 29 percent), which may be attributed to different dosing of haloperidol (mean 16.8 mg/day[65] versus 2.5 mg/day[49]), differences in participant mean ages, and the use of different comparator drugs.

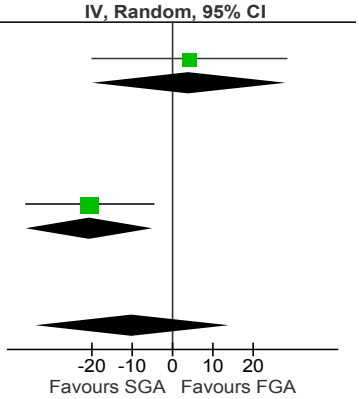
Figure 18. First generation versus second generation antipsychotics on CGI-I in schizophrenia



Two RCTs[49,98] provided data for a meta-analysis on the efficacy of first versus second generation antipsychotics on positive and negative symptoms as measured by the PANSS (Figure 19). 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 percent), which may be attributable to the use of different second generation antipsychotics. A higher dose of the first generation antipsychotic in one study[98] may also have contributed to the heterogeneity.

Figure 19. First generation versus second generation antipsychotics on PANSS in schizophrenia

Study or Subgroup	SGA Mean	SGA SD	SGA Total	FGA Mean	FGA SD	FGA Total	Weight	Mean Difference IV, Random, 95% CI
13.5.1 Olanzapine versus Haloperidol								
de Haan 2003	-7.2	31.9	9	-11.4	19.5	10	43.0%	4.20 [-19.89, 28.29]
Subtotal (95% CI)			**9**			**10**	**43.0%**	**4.20 [-19.89, 28.29]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.34 (P = 0.73)								
13.5.3 Risperidone versus Haloperidol								
Yen 2004	-31.5	15.527	6	-11	7.071	2	57.0%	-20.50 [-36.32, -4.68]
Subtotal (95% CI)			**6**			**2**	**57.0%**	**-20.50 [-36.32, -4.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.54 (P = 0.01)								
Total (95% CI)			**15**			**12**	**100.0%**	**-9.89 [-33.85, 14.08]**
Heterogeneity: Tau² = 196.91; Chi² = 2.82, df = 1 (P = 0.09); I² = 65%								
Test for overall effect: Z = 0.81 (P = 0.42)								
Test for subgroup differences: Chi² = 2.82, df = 1 (P = 0.09), I² = 64.6%								



Second generation versus second generation antipsychotics. Thirteen studies examined the efficacy of second generation antipsychotics. Of these, five compared two doses of aripiprazole,[53] paliperidone,[80] quetiapine,[74] risperidone,[58] and ziprasidone.[51] Clozapine was compared with olanzapine in three studies,[64,66,85] olanzapine versus quetiapine in one study,[61] and olanzapine versus risperidone in five studies.[61,72,78,87,96]

Findling et al.[53] conducted an RCT to compare the efficacy of low-dose aripiprazole, high-dose aripiprazole, and placebo in adolescents with schizophrenia (aged 13 to 17 years). Patients were diagnosed using the DSM-IV and K-SADS-PL criteria. A total of 302 patients were randomly assigned to the interventions (100 to low-dose aripiprazole, 102 to high-dose aripiprazole, and 100 to placebo) and 258 patients were followed to the study endpoint at 6 weeks. The mean dosage of the drugs was 9.8 mg/day and 28.9 mg/day for the low- and high-dose aripiprazole groups, respectively. Patients were assessed using the CGAS, CGI-I, CGI-S, and PANSS. There were no significant differences between the low- and high-dose aripiprazole groups on any of the outcomes.

Kumra et al.[64] conducted an RCT comparing the efficacy of clozapine and olanzapine in adolescents (aged 10 to 18 years) with schizophrenia (n = 25) or schizoaffective disorder (n = 14). Patients were diagnosed using the DSM-IV and K-SADS-PL criteria combined with a structured interview. Forty patients were randomly assigned to the interventions (19 to clozapine, 21 to olanzapine), and 28 patients were followed to the study endpoint at 12 weeks with a 12-week extension. The mean dosage was 403.1±201.8 mg/day and 26.2±6.5 mg/day for the clozapine and olanzapine groups, respectively. Patients were assessed using the BPRS, CGAS, CGI-I, CGI-S, and SANS. 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). There was significantly greater improvement in CGI-I in the olanzapine group compared with clozapine at 24 weeks. There were no statistically significant differences between the groups for any outcomes.

Kumra et al.[66] conducted a prospective cohort study comparing the efficacy of clozapine and olanzapine in children (aged 6 to 18) with schizophrenia. Patients were diagnosed using the DSM-III-TR and K-SADS-E criteria. Eleven patients had disorganized schizophrenia, 3 had paranoid schizophrenia, and 9 had undifferentiated schizophrenia. Twenty-three patients received open-label treatment with clozapine (n = 15) or olanzapine (n = 8) and the patients were followed to the study endpoint at 6 weeks (clozapine group) and 8 weeks (olanzapine group). The mean drug dosage was 317±147 mg/day and 17.5±2.3 mg/day for clozapine and olanzapine,

respectively. 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.

Shaw et al.[85] conducted an RCT comparing the efficacy of clozapine and olanzapine in children (aged 7 to 16) with schizophrenia. Patients were diagnosed using the DSM-IV and K-SADS criteria, a medical and school record review, and an interview with the child and parents. Comorbid ADHD was present in seven patients and anxiety disorders in seven patients. Twenty-five patients were randomly assigned to the interventions (12 to clozapine, 13 to olanzapine), and all patients were followed to the study endpoint at 8 weeks with a 2-year extension. The mean drug dosage was 327±113 mg/day and 18.1±4.3 mg/day for clozapine and olanzapine, respectively. Patients were assessed using the BPRS-24, CGI-S, SANS, and Scale for the Assessment of Positive Symptoms. The clozapine group showed significantly greater improvement on the CGI-S ($p = 0.04$) and SANS ($p = 0.003$) compared with the olanzapine group.

Jensen et al.[61] conducted an RCT comparing the efficacy of olanzapine, quetiapine, and risperidone in children (aged 10 to 18 years) with schizophrenia-related conditions. Patients were diagnosed using the DSM-IV and K-SADS criteria. Sixteen patients had schizophrenia or schizoaffective disorder, five patients had schizophreniform disorder, and nine had a psychotic disorder NOS. Thirty patients were randomly assigned to the interventions (10 to olanzapine, 10 to quetiapine, 10 to risperidone), and 21 patients were followed to the study endpoint at 12 weeks. The mean dosage of the drugs was 14±4.6 mg/day, 611±253.4 mg/day, and 3.4±1.5 mg/day for olanzapine, quetiapine, and risperidone, respectively. Patients were assessed using the CGI-S and no difference was found among groups.

Mozes et al.[72] conducted an RCT comparing the efficacy of olanzapine and risperidone in children with schizophrenia. Patients were diagnosed using the DSM-IV and K-SADS criteria. Seven patients had disorganized schizophrenia, six had paranoid schizophrenia, 10 had schizophreniform disorder, and two had unspecified schizophrenia. Eleven patients had additional comorbidities: ADHD ($n = 3$), OCD ($n = 3$), epilepsy ($n = 2$), familial mediterranean fever ($n = 1$), tic disorder ($n = 1$), and neurofibromatosis ($n = 1$). Twenty-five patients were randomly assigned to the interventions (12 to olanzapine, 13 to risperidone), and 20 patients were followed to the study endpoint at 12 weeks. The mean drug dosage was 8.2±4.4 mg/day and 1.6±1 mg/day for the olanzapine and risperidone groups, respectively. Patients were assessed using the BPRS, CGAS, and PANSS. No statistically significant differences were found for any outcome.

Ratzoni et al.[78] compared the effectiveness of olanzapine and risperidone in a prospective cohort study (described previously). Fifty patients were given the interventions (eight haloperidol, 21 olanzapine, 21 risperidone), and 36 patients were followed to the study endpoint at 12 weeks. The mean dosage of the drugs was 7.6±4 mg/day, 12.7±3.1 mg/day and 3.2±1.1 mg/day for haloperidol, olanzapine, and risperidone, respectively. Patients were assessed using the PANSS. Changes in positive and negative symptoms did not differ significantly between olanzapine and risperidone.

Sikich et al.[87] conducted an RCT comparing the efficacy of olanzapine and risperidone in children and adolescents (aged 8 to 19 years) with schizophrenia-related disorders (50 with schizophrenia, 26 with schizoaffective disorder). Patients were diagnosed using the DSM-IV and Childhood disorders form of the Structured Clinical Interview for DSM-IV Disorders criteria. Comorbidities included ADHD ($n = 22$), anxiety disorder ($n = 21$), affective disorder ($n = 19$),

disruptive behavior disorders (n = 16), psychosis (n = 10), autism spectrum disorder (n = 5), learning disability (n = 3), and substance abuse (n = 4). Seventy-eight patients were randomly assigned to the interventions (36 to olanzapine, 42 to risperidone) and were followed to the study endpoint at 8 weeks with a 44-week extension. The mean dosage of the drugs was 11.4±5 mg/day and 2.8±1.4 mg/day for olanzapine and risperidone, respectively. Patients were assessed using the BPRS-C, CGI-I, CGI-S, and PANSS. There were no statistically significant differences between the groups for any outcomes.

Van Bruggen et al.[96] conducted an RCT comparing the efficacy of olanzapine and risperidone in patients (aged 16 to 28 years) with a first or second psychotic episode with schizophrenia, schizophreniform disorder, or schizoaffective disorder. Patients were diagnosed using the DSM-IV criteria. Forty-four patients were randomly assigned to the interventions (18 to olanzapine, 26 to risperidone) and the data from 42 patients were analyzed after a mean followup period of 9.8 weeks for olanzapine and 6.7 weeks for risperidone. The mean dosage of the drugs was 15.6±4 mg/day and 4.4±1.5 mg/day for the olanzapine and risperidone groups, respectively. Patients were assessed using the PANSS. Change in positive and negative symptoms was not significantly different between the olanzapine and risperidone groups.

Robb et al.[80] conducted an RCT comparing the efficacy of low, medium, and high doses of extended release paliperidone versus placebo in adolescents (aged 12 to 17 years) with schizophrenia. Patients were diagnosed using the DSM-IV and K-SADS-PL criteria. One hundred forty-three patients had a diagnosis of paranoid schizophrenia and 58 had other diagnoses. Two hundred and one patients were randomly assigned to the interventions (54 to low-dose paliperidone, 48 to medium-dose paliperidone, 48 to high-dose paliperidone, 51 to placebo) and 139 patients were followed to the study endpoint at 6 weeks. Patients were assessed using the CGAS, CGI-S, PANSS, and VAS for sleep. No significant differences were reported for the different drug doses.

One RCT[74] compared the efficacy of low-dose quetiapine, high-dose quetiapine, and placebo in adolescents (aged 13 to 17 years) with schizophrenia. Patients were diagnosed using the DSM-IV and K-SADS-PL criteria. Schizophrenia subtypes included paranoid (n = 155), undifferentiated (n = 48), disorganized (n = 16), and residual (n = 1). Two hundred twenty-two patients were randomly assigned to the interventions (73 to low-dose quetiapine, 74 to high-dose quetiapine, 75 to placebo) and all patients were followed to the study endpoint at 6 weeks. The mean dosage of the drugs was 400 mg/day and 800 mg/day for low- and high-dose quetiapine, respectively. Patients were assessed using the CGAS, CGI-I, CGI-S, and PANSS. There were no significant differences between the low- and high-dose quetiapine groups for all outcomes.

Haas et al.[58] conducted an RCT comparing the efficacy of low- and high- dose risperidone in adolescents (aged 13 to 17 years). Patients were diagnosed using the DSM-IV and K-SADS-PL criteria: 175 patients with paranoid schizophrenia, 49 with undifferentiated schizophrenia, 19 with disorganized schizophrenia, and 7 patients each with catatonic and residual schizophrenia. Two hundred fifty-seven patients were randomly assigned to the interventions (132 to low-dose risperidone, 125 to high-dose risperidone) and 172 patients were followed to the study endpoint at 8 weeks. The mean dosage of the drugs was 0.4 mg/day and 4 mg/day for the low- and high-dose risperidone groups, respectively. 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 ($p<0.001$).

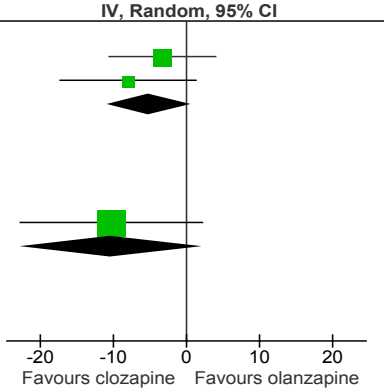
DelBello et al.[51] conducted an RCT comparing the efficacy of low- and high-dose ziprasidone in treating children and adolescents (aged 10 to 17 years) with bipolar mania,

schizophrenia, and schizoaffective disorder. Patients were diagnosed using the DSM-IV-TR. Separate analyses were provided for patients with schizophrenia. Participants were randomly assigned to low-dose (80 mg/day; eight participants) or high-dose (160 mg/day; nine participants) ziprasidone and were followed for 3 weeks. Patients were assessed using the BPRS and CGI-S. No significant differences were found between the two groups.

Three studies (two RCTs[64,85] and one prospective cohort study[66]) provided data for a meta-analysis comparing clozapine with olanzapine on the BPRS (Figure 20). The pooled mean difference of the trials and the cohort study showed no statistically significant difference between the two second generation antipsychotics.

Figure 20. Clozapine versus olanzapine on BPRS in schizophrenia

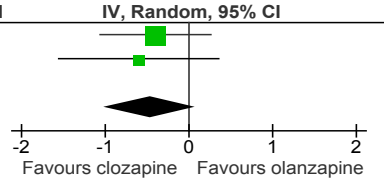
Study or Subgroup	Clozapine Mean	Clozapine SD	Clozapine Total	Olanzapine Mean	Olanzapine SD	Olanzapine Total	Weight	Mean Difference IV, Random, 95% CI
3.1.1 RCT								
Kumra 2008	-21.9	10.9	18	-18.6	12.32	21	61.9%	-3.30 [-10.59, 3.99]
Shaw 2006	-9	10.6	13	-1	12.88	12	38.1%	-8.00 [-17.29, 1.29]
Subtotal (95% CI)			**31**			**33**	**100.0%**	**-5.09 [-10.82, 0.64]**
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 1 (P = 0.44); I² = 0%								
Test for overall effect: Z = 1.74 (P = 0.08)								
3.1.2 Non-RCT								
Kumra 1998	-20.69	12.93	15	-10.4	15.3	8	100.0%	-10.29 [-22.75, 2.17]
Subtotal (95% CI)			**15**			**8**	**100.0%**	**-10.29 [-22.75, 2.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.62 (P = 0.11)								



The two trials[64,85] comparing clozapine with olanzapine were pooled for CGI-S (Figure 21). The pooled estimate favored clozapine for reduction in symptom severity; however, this was not statistically significant (MD = -0.46; 95% CI, -1.01, 0.08). There was no evidence of heterogeneity (p = 0.74, I^2 = 0 percent).

Figure 21. Clozapine versus olanzapine on CGI-S in schizophrenia

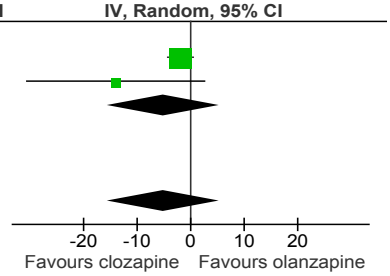
Study or Subgroup	Clozapine Mean	Clozapine SD	Clozapine Total	Olanzapine Mean	Olanzapine SD	Olanzapine Total	Weight	Mean Difference IV, Random, 95% CI
Kumra 2008	-1.5	0.954	18	-1.1	1.153	21	67.6%	-0.40 [-1.06, 0.26]
Shaw 2006	-1.1	1.41	13	-0.5	1.01	12	32.4%	-0.60 [-1.56, 0.36]
Total (95% CI)			**31**			**33**	**100.0%**	**-0.46 [-1.01, 0.08]**
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%								
Test for overall effect: Z = 1.67 (P = 0.09)								



The same trials[64,85] also provided data for a meta-analysis of negative symptoms, as measured by the SANS (Figure 22). The pooled analysis showed no significant difference between the two second generation antipsychotics on improvement in negative symptoms (MD = -5.05, 95% CI, -15.45 to 5.35). There was substantial heterogeneity between the two trials (p = 0.16, I^2 = 50 percent), which may be attributable to the higher mean dose of olanzapine in the study by Kumra et al.[64]

Figure 22. Clozapine versus olanzapine on SANS in schizophrenia

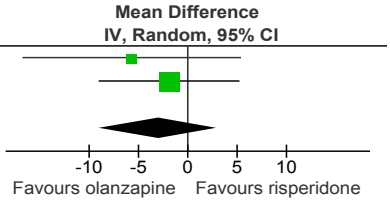
Study or Subgroup	Clozapine Mean	Clozapine SD	Clozapine Total	Olanzapine Mean	Olanzapine SD	Olanzapine Total	Weight	Mean Difference IV, Random, 95% CI
3.5.1 RCT								
Kumra 2008	-3.7	4.06	18	-1.8	3.387	21	74.0%	-1.90 [-4.27, 0.47]
Shaw 2006	-22	22.09	13	-8	20.24	12	26.0%	-14.00 [-30.59, 2.59]
Subtotal (95% CI)			**31**			**33**	**100.0%**	**-5.05 [-15.45, 5.36]**
Heterogeneity: Tau² = 36.64; Chi² = 2.00, df = 1 (P = 0.16); I² = 50%								
Test for overall effect: Z = 0.95 (P = 0.34)								
Total (95% CI)			**31**			**33**	**100.0%**	**-5.05 [-15.45, 5.36]**
Heterogeneity: Tau² = 36.64; Chi² = 2.00, df = 1 (P = 0.16); I² = 50%								
Test for overall effect: Z = 0.95 (P = 0.34)								



Two studies[72,87] comparing olanzapine with risperidone reported data for the BPRS (Figure 23). The meta-analysis showed no significant difference between the two second generation antipsychotics (MD = -3.0; 95% CI, -8.94 to 2.93). There was no evidence of heterogeneity (p = 0.57, I^2 = 0 percent).

Figure 23. Olanzapine versus risperidone on BPRS in schizophrenia

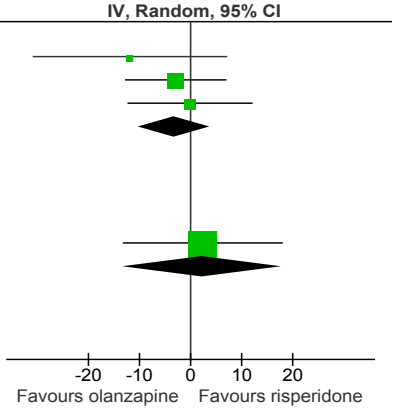
Study or Subgroup	Olanzapine Mean	Olanzapine SD	Olanzapine Total	Risperidone Mean	Risperidone SD	Risperidone Total	Weight	Mean Difference IV, Random, 95% CI
Mozes 2006	-23.92	13.21	12	-18.23	14.84	13	29.2%	-5.69 [-16.69, 5.31]
Sikich 2008	-17.3	11.2	35	-15.4	19.6	41	70.8%	-1.90 [-8.95, 5.15]
Total (95% CI)			**47**			**54**	**100.0%**	**-3.00 [-8.94, 2.93]**
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%								
Test for overall effect: Z = 0.99 (P = 0.32)								



Four studies, (three RCTs[72,87,96] and one prospective cohort study[78]) were combined in a meta-analysis comparing olanzapine and risperidone for treating positive and negative symptoms. The pooled results of the three trials showed no significant difference between the antipsychotics (MD = -3.20; 95% CI, -10.26, 3.86) and no evidence of heterogeneity between the trials (p = 0.59, I^2 = 0 percent). A similar, nonsignificant finding was observed in the cohort study.

Figure 24. Olanzapine versus risperidone on PANSS in schizophrenia

Study or Subgroup	Olanzapine Mean	Olanzapine SD	Olanzapine Total	Risperidone Mean	Risperidone SD	Risperidone Total	Weight	Mean Difference IV, Random, 95% CI
5.3.1 RCT								
Mozes 2006	-42.25	23.32	12	-30.38	24.87	13	14.0%	-11.87 [-30.76, 7.02]
Sikich 2008	-26.6	17.8	35	-23.7	25.5	41	52.0%	-2.90 [-12.68, 6.88]
van Bruggen 2003	-15.1	23.76	18	-15	12.74	24	34.0%	-0.10 [-12.20, 12.00]
Subtotal (95% CI)			**65**			**78**	**100.0%**	**-3.20 [-10.26, 3.86]**
Heterogeneity: Tau² = 0.00; Chi² = 1.06, df = 2 (P = 0.59); I² = 0%								
Test for overall effect: Z = 0.89 (P = 0.37)								
5.3.2 non-RCT								
Ratzoni 2002	-13.9	20.81	17	-16.3	23.61	15	100.0%	2.40 [-13.11, 17.91]
Subtotal (95% CI)			**17**			**15**	**100.0%**	**2.40 [-13.11, 17.91]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.30 (P = 0.76)								



First generation antipsychotics versus placebo. Spencer et al.[90] conducted a crossover RCT comparing haloperidol with placebo in children (aged 5 to 11 years) with schizophrenia based on the DSM-III-TR and Diagnostic Interview for Children and Adolescents-Revised criteria. Prior

psychiatric diagnoses were atypical pervasive developmental disorder (n = 5), atypical psychosis (n = 3), borderline personality disorder (n = 1), conduct disorder (n = 1), pica (n = 1), and schizophrenia (n = 1). Sixteen patients were given haloperidol and placebo in random order and were followed to the study endpoint at 8 weeks. The mean dosage of the drugs was 2 mg/day and 2.5±0.5 mg/day for haloperidol and placebo, respectively. 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 placebo ($p<0.01$). Comparisons between the two groups were not reported for the remaining outcome measures.

Second generation antipsychotics versus placebo. Six studies compared a second generation drug with placebo: aripiprazole,[53] olanzapine,[63,97] paliperidone,[80], quetiapine,[74] and ziprasidone.[76]

Findling et al.[53] conducted an RCT to compare the efficacy of low-dose and high-dose aripiprazole with and 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 compared with placebo for all outcomes ($p\leq0.05$).

Kryzhanovskaya et al.[63] conducted an RCT to evaluate the efficacy of olanzapine compared with placebo in adolescents (aged 13 to 18 years) with schizophrenia. Patients were diagnosed using the DSM-IV-TR and K-SADS criteria. One hundred seven patients were randomly assigned to the interventions (72 to olanzapine, 35 to placebo) and patients were followed to the study endpoint at 6 weeks with a 6-month extension. The mean dosage of olanzapine was 11.1 mg/day. Patients were assessed using the BPRS-C, CGI-I, CGI-S, OAS, and PANSS. The olanzapine group showed statistically significant improvements over placebo for all outcomes ($p\leq0.05$).

Robb et al.[80] conducted an RCT to compare the efficacy of low-, medium-, and high-dose extended release paliperidone and placebo in adolescents (aged 12 to 17 years). Patients were diagnosed using the DSM-IV and K-SADS-PL criteria. One hundred forty-three patients had a diagnosis of paranoid schizophrenia and 58 had other diagnoses. Two hundred one patients were randomly assigned to the interventions (54 to low-dose paliperidone, 48 to medium-dose paliperidone, 48 to high-dose paliperidone, 51 to placebo) and 139 patients were followed to the study endpoint at 6 weeks. Patients were assessed using the CGAS, CGI-S, PANSS, and VAS sleep. The medium-dose paliperidone group showed statistical superiority versus the placebo group on the CGAS ($p<0.001$). There were no other differences on any of the outcomes regardless of dose level.

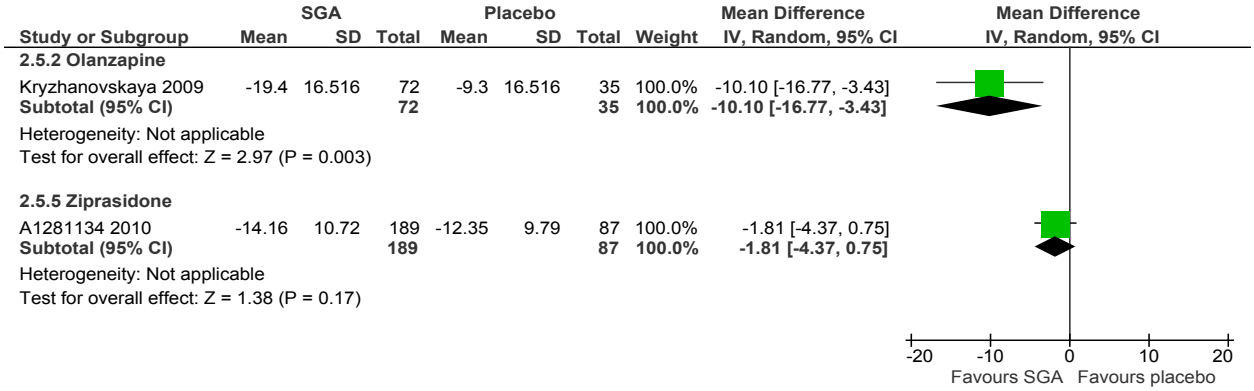
One RCT[74] compared the efficacy of low-dose quetiapine, high-dose quetiapine, and placebo (described previously). Patients were assessed using the CGAS, CGI-I, CGI-S, and PANSS. Compared with the placebo group, both low- and high-dose quetiapine showed significantly greater improvement for the CGI-I and PANSS ($p<0.05$), and high-dose group for the CGAS ($p = 0.02$) and CGI-S ($p = 0.02$).

Another RCT[76] evaluated the efficacy of ziprasidone compared with placebo in adolescents with schizophrenia (aged 13 to 17 years). Patients were diagnosed using the DSM-IV and Childhood disorders form of the Structured Clinical Interview for DSM-IV Disorders criteria. One hundred eighty-four patients were diagnosed with paranoid type schizophrenia; no subtypes were reported for the remaining patients. Two hundred eighty-four patients were randomly assigned to the interventions and were followed to the study endpoint at 6 weeks. The target dosage for each of the drugs was 60 to 80 mg/day for patients <45 kg and 120 to 160 mg/day for patients ≥45 kg. Patients were assessed using the BPRS-Anchored version. There was no difference in symptom change between the ziprasidone and placebo groups.

Woods et al.[97] conducted an RCT to evaluate the efficacy of olanzapine compared with placebo in patients (aged 12 to 45 years, mean age: 17.7 years) with prodromal syndromes. Patients were diagnosed using the DSM-IV, Criteria of Prodromal Syndromes, and Presence of Psychosis Scale criteria. Comorbid marijuana abuse was present in 16 patients and other substance abuse (except nicotine) was present in 11 patients. Sixty patients were randomly assigned to the interventions (31 to olanzapine, 29 to placebo) and 59 patients were followed to the study endpoint at 1 year with a 1 year extension. The mean dosage of the drugs was 8±3.1 mg/day and 9.3±2.8 mg/day for olanzapine and placebo, respectively. Patients were assessed using the CGI-S, GAF, PANSS, and YMRS. No statistically significant differences were found between the groups for any outcomes.

Two RCTs compared two second generation antipsychotics (olanzapine[63] and ziprasidone[76]) with placebo using BPRS scores (Figure 25). Results were not pooled because of the substantial heterogeneity ($p = 0.02$, $I^2 = 81$ percent). The heterogeneity is possibly due to the use of different second generation drugs, since the study design, duration of followup, and characteristics of the enrolled patients were comparable.

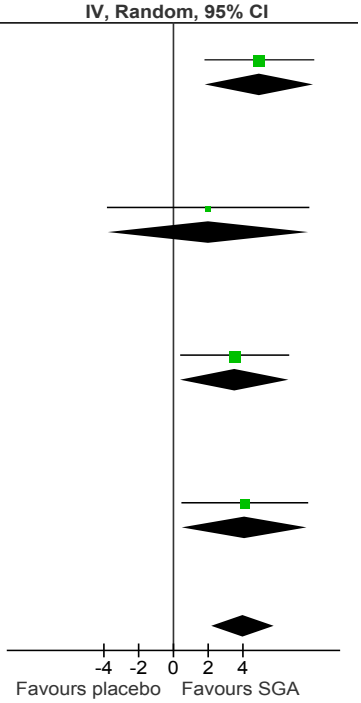
Figure 25. Second generation antipsychotics versus placebo on BPRS in schizophrenia



Four RCTs[53,74,80,97] contributed data to a meta-analysis comparing second generation antipsychotics with placebo on the CGA (Figure 26). With the exception of one study examining olanzapine,[97] all trials significantly favored the second generation antipsychotics. The pooled estimate showed a statistically significant improvement in CGAS scores for second generation antipsychotics compared with placebo (MD = 3.99; 95% CI, 2.21 to 5.77). There was no evidence of heterogeneity ($p = 0.82$, $I^2 = 0$ percent).

Figure 26. Second generation antipsychotics versus placebo on CGAS in schizophrenia

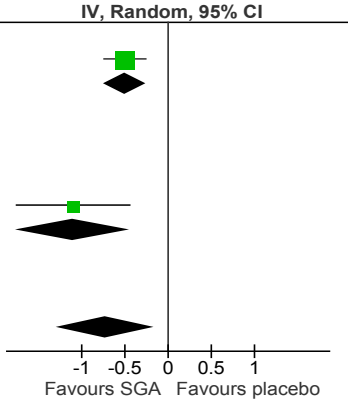
Study or Subgroup	SGA Mean	SGA SD	SGA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
2.1.1 Aripiparazole								
Findling 2008	14.75	12.8	196	9.8	12.87	98	32.7%	4.95 [1.83, 8.07]
Subtotal (95% CI)			**196**			**98**	**32.7%**	**4.95 [1.83, 8.07]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.11 (P = 0.002)								
2.1.2 Olanzapine								
Woods 2003	5.1	12.85	30	3.1	9.62	29	9.5%	2.00 [-3.78, 7.78]
Subtotal (95% CI)			**30**			**29**	**9.5%**	**2.00 [-3.78, 7.78]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.68 (P = 0.50)								
2.1.3 Paliperidone								
Robb 2009	8.53	9.73	150	5	9.73	51	33.3%	3.53 [0.44, 6.62]
Subtotal (95% CI)			**150**			**51**	**33.3%**	**3.53 [0.44, 6.62]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.24 (P = 0.03)								
2.1.4 Quetiapine								
NCT00090324 2008	14	12.95	147	9.89	12.95	75	24.5%	4.11 [0.51, 7.71]
Subtotal (95% CI)			**147**			**75**	**24.5%**	**4.11 [0.51, 7.71]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.24 (P = 0.03)								
Total (95% CI)			**523**			**253**	**100.0%**	**3.99 [2.21, 5.77]**
Heterogeneity: Tau² = 0.00; Chi² = 0.91, df = 3 (P = 0.82); I² = 0%								
Test for overall effect: Z = 4.39 (P < 0.0001)								



Two RCTs comparing aripiprazole[53] and olanzapine[63] with placebo reported global impression of improvement scores (Figure 27). The pooled estimate significantly favored second generation antipsychotics over placebo (MD = -0.72; 95% CI, -1.29 to -0.15). There was substantial heterogeneity (p = 0.09, I^2 = 65 percent), which was driven by differences between the second generation antipsychotic comparators. All other patient and study characteristics appeared to be similar between the two studies.

Figure 27. Second generation antipsychotics versus placebo on CGI-I in schizophrenia

Study or Subgroup	SGA Mean	SGA SD	SGA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
2.2.1 Aripiparazole								
Findling 2008	2.6	0.993	196	3.1	0.994	98	63.4%	-0.50 [-0.74, -0.26]
Subtotal (95% CI)			**196**			**98**	**63.4%**	**-0.50 [-0.74, -0.26]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.07 (P < 0.0001)								
2.2.2 Olanzapine								
Kryzhanovskaya 2009	2.7	1.622	72	3.8	1.622	35	36.6%	-1.10 [-1.76, -0.44]
Subtotal (95% CI)			**72**			**35**	**36.6%**	**-1.10 [-1.76, -0.44]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.29 (P = 0.0010)								
Total (95% CI)			**268**			**133**	**100.0%**	**-0.72 [-1.29, -0.15]**
Heterogeneity: Tau² = 0.12; Chi² = 2.84, df = 1 (P = 0.09); I² = 65%								
Test for overall effect: Z = 2.49 (P = 0.01)								
Test for subgroup differences: Chi² = 2.84, df = 1 (P = 0.09), I² = 64.8%								

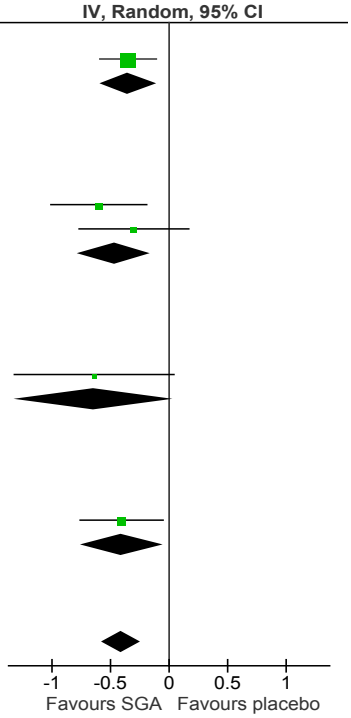


Five RCTs[53,63 74,76,80,97] provided data for a meta-analysis comparing second generation antipsychotics with placebo for global impression of severity (Figure 28). Patients treated with second generation antipsychotics had a statistically significant reduction in symptom severity

compared with those receiving placebo (MD = -0.41; 95% CI, -0.57 to -0.25). There was no evidence of heterogeneity (p = 0.79, I^2 = 0 percent).

Figure 28. Second generation antipsychotics versus placebo on CGI-S in schizophrenia

Study or Subgroup	SGA Mean	SGA SD	SGA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
2.3.1 Aripiparazole								
Findling 2008	-1.25	0.993	196	-0.9	0.994	98	45.4%	-0.35 [-0.59, -0.11]
Subtotal (95% CI)			**196**			**98**	**45.4%**	**-0.35 [-0.59, -0.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.85 (P = 0.004)								
2.3.2 Olanzapine								
Kryzhanovskaya 2009	-1.1	1.012	72	-0.5	1.012	35	15.8%	-0.60 [-1.01, -0.19]
Woods 2003	-0.2	0.81	30	0.1	1.01	29	12.0%	-0.30 [-0.77, 0.17]
Subtotal (95% CI)			**102**			**64**	**27.8%**	**-0.47 [-0.78, -0.16]**
Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 1 (P = 0.34); I² = 0%								
Test for overall effect: Z = 2.99 (P = 0.003)								
2.3.3 Paliperidone								
Robb 2009	-0.64	2.144	150	0	2.144	51	5.7%	-0.64 [-1.32, 0.04]
Subtotal (95% CI)			**150**			**51**	**5.7%**	**-0.64 [-1.32, 0.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.84 (P = 0.07)								
2.3.4 Quetiapine								
NCT00090324 2008	-1.215	1.272	147	-0.81	1.272	75	21.1%	-0.41 [-0.76, -0.05]
Subtotal (95% CI)			**147**			**75**	**21.1%**	**-0.41 [-0.76, -0.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.24 (P = 0.02)								
Total (95% CI)			**595**			**288**	**100.0%**	**-0.41 [-0.57, -0.25]**
Heterogeneity: Tau² = 0.00; Chi² = 1.72, df = 4 (P = 0.79); I² = 0%								
Test for overall effect: Z = 4.97 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.82, df = 3 (P = 0.84), I² = 0%								



The results of five RCTs[53,63,74,80,97] reporting positive and negative symptoms of schizophrenia using the PANSS were combined in a meta-analysis (Figure 29). The pooled estimate found second generation antipsychotics to be superior to placebo in reducing positive and negative symptoms (MD= -7.03; 95% CI, -9.73 to -4.33). There was no evidence of heterogeneity (p=0.68, I^2=0 percent).

Figure 29. Second generation antipsychotics versus placebo on PANSS in schizophrenia

Study or Subgroup	SGA Mean	SGA SD	SGA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
2.4.1 Aripiparazole								
Findling 2008	-27.64	14.805	196	-21.2	18.809	98	40.1%	-6.44 [-10.70, -2.18]
Subtotal (95% CI)			**196**			**98**	**40.1%**	**-6.44 [-10.70, -2.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.96 (P = 0.003)								
2.4.2 Olanzapine								
Kryzhanovskaya 2009	-21.3	21.61	72	-8.8	21.61	35	9.6%	-12.50 [-21.23, -3.77]
Woods 2003	-6.73	19.22	30	-1.66	15.08	29	9.4%	-5.07 [-13.87, 3.73]
Subtotal (95% CI)			**102**			**64**	**19.0%**	**-8.81 [-16.09, -1.53]**
Heterogeneity: Tau² = 7.61; Chi² = 1.38, df = 1 (P = 0.24); I² = 28%								
Test for overall effect: Z = 2.37 (P = 0.02)								
2.4.3 Paliperidone								
Robb 2009	-13.48	16.93	150	-7.9	16.93	51	25.2%	-5.58 [-10.96, -0.20]
Subtotal (95% CI)			**150**			**51**	**25.2%**	**-5.58 [-10.96, -0.20]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.03 (P = 0.04)								
2.4.4 Quetiapine								
NCT00090324 2008	-27.88	24.52	147	-19.15	24.52	75	15.7%	-8.73 [-15.55, -1.91]
Subtotal (95% CI)			**147**			**75**	**15.7%**	**-8.73 [-15.55, -1.91]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.51 (P = 0.01)								
Total (95% CI)			**595**			**288**	**100.0%**	**-7.03 [-9.73, -4.33]**
Heterogeneity: Tau² = 0.00; Chi² = 2.29, df = 4 (P = 0.68); I² = 0%								
Test for overall effect: Z = 5.11 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.91, df = 3 (P = 0.82), I² = 0%								

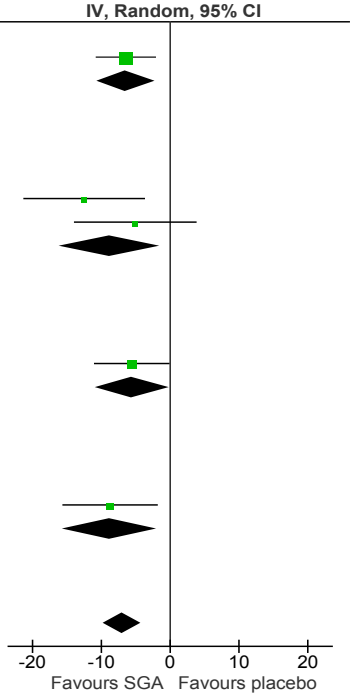


Table 14. Study and patient characteristics for studies examining schizophrenia

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
de Haan, 2003[49] RCT, 6 wk	**G1:** Haloperidol (12), 2.5 mg/day **G2:** Olanzapine (12), 7.5 mg/day	**G1:** 21.0±2.8 (17-26) yr / Male: NR / Caucasian: NR **G2:** 21±2.3 (17–25) yr / Male: NR / Caucasian: NR Comorbidities: MR (0)	disorganized (6), paranoid (13), undifferentiated (5) 20, 0
DelBello, 2008[51] RCT, 3 wk (24 wk extension)	**G1:** Ziprasidone (low) (8), target: 80 mg/day **G2:** Ziprasidone (high) (9), target: 160 mg/day	**G1:** 14.4±2.3 yr / Male: 52% / Caucasian: NR **G2:** 14.7±2.0 yr / Male: 75% / Caucasian: NR Comorbidities: MR (0), SA (0)	NR NR, NR
Findling, 2008[53] RCT, 6 wk	**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% / Caucasian: 54% **G2:** 15.4±1.4 yr / Male: 64% / Caucasian: 61% **G3:** 15.4 ±1.4 yr / Male: 61% / Caucasian: 64% Comorbidities: NR	NR NR, 79
Haas, 2009[58] RCT, 8 wk	**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% / Caucasian: 85% **G2:** 15.6±1.3 (13-17) yr / Male: 52% / Caucasian: 85% Comorbidities: NR	catatonic (7), disorganized (19), paranoid (175), residual (7), undifferentiated (49) NR, NR
Jensen, 2008[61] RCT, 12 wk	**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% / Caucasian: 50% **G2:** 14.8±2.3 yr / Male: 70% / Caucasian: 60% **G3:** 15.6±2.5 yr / Male: 80% / Caucasian: 70% Comorbidities: MR (0), psychosis (all)	psychotic disorder NOS (9), schizophrenia/schizoaffective disorder (16), schizophreniform disorder (5) NR, 23
Kryzhanovskaya, 2009[63] RCT, 6 wk (6 mo extension)	**G1:** Olanzapine (72), 11.1 mg/day **G2:** Placebo (35)	**G1:** 16.1±1.3 (13-18) yr / Male: 71% / Caucasian: 72% **G2:** 16.3±1.6 (13.1-18) yr / Male: 69% / Caucasian: 71% Comorbidities: MR (0), SA (0)	NR NR, 26
Kumra, 2008[64] RCT, 12 wk (12 wk extension)	**G1:** Clozapine (19), 403.1±201.8 mg/day **G2:** Olanzapine (21), 26.2±6.5 mg/day	**G1:** 15.8±2.2 yr / Male: 44% / Caucasian: 11% **G2:** 15.5±2.1 yr / Male: 62% / Caucasian: 29% Comorbidities: MR (0)	schizoaffective disorder (14), schizophrenia (25) 0, 0

ADHD = attention deficit hyperactivity disorder; ASD = autism spectrum disorder; CD = conduct disorder; ER = extended release; G = group; mg =milligram; mo = month; MR = mental retardation; N = number; NR = not reported; NRCT = nonrandomized controlled trial; OCD = obsessive-compulsive disorder; PDD = pervasive developmental disorder; RCT = randomized controlled trial; SA = substance abuse; SD = standard deviation; wk = week; yr = year

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

Table 14. Study and patient characteristics for studies examining schizophrenia (continued)

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Kumra, 1998[66] Prospective cohort, G1: 6 wk, G2: 8 wk	**G1:** Clozapine (15), 317±147 mg/day **G2:** Olanzapine (8), 17.5±2.3 mg/day	**G1:** 13.6±1.5 yr / Male: 53% / Caucasian: NR **G2:** 15.3±2.3 yr / Male: 50% / Caucasian: NR Comorbidities: NR	disorganized (11), paranoid (3), undifferentiated (9) NR, NR
Kumra, 1996[65] RCT, 6 wk	**G1:** Haloperidol (11), 16±8 mg/day **G2:** Clozapine (10), 176±149 mg/day	**G1:** 13.7±1.6 yr / Male: 55% / Caucasian: NR **G2:** 14.4±2.9yr / Male: 50% / Caucasian: NR Comorbidities: NR	disorganized (10), paranoid (1), undifferentiated (10) 0, NR
Mozes, 2006[72] RCT, 12 wk	**G1:** Olanzapine (12), 8.2±4.4 mg/day **G2:** Risperidone (13), 1.6±1 mg/day	**G1:** 11.5±1.6 (8.5-14) yr / Male: 42% / Caucasian: NR **G2:** 10.7±1.4 (8.8-13.3) yr / Male: 39% / Caucasian: NR Comorbidities: ADHD (3), epilepsy (2), familial mediterranean fever (1), MR (0), neurofibromatosis (1), OCD (3), tic disorder (1)	disorganized schizophrenia (7), paranoid schizophrenia (6), schizophreniform disorder (10), unspecified schizoprehenia (2) NR, 24
NCT00090324, 2008[74] RCT, 6 wk	**G1:** Quetiapine (low) (73), 400 mg/day **G2:** Quetiapine (high) (74), 800 mg/day **G3:** Placebo (75)	**G1:** 15.5±1.3 (13-17) yr / Male: 59% / Caucasian: 62% **G2:** 15.5±1.3 (13-17) yr / Male: 60% / Caucasian: 60% **G3:** 15.3±1.4 (13-17) yr / Male: 58% / Caucasian: 63% Comorbidities: NR	disorganized (16), paranoid (155), residual (1), undifferentiated (48) NR, NR
NCT00257192, 2010[76] RCT, 6 wk	**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 / Caucasian: NR **G2:** 15.4 yr / Male: NR / Caucasian: NR Comorbidities: NR	paranoid type (184) NR, NR
Ratzoni, 2002[78] Prospective cohort, 12 wk	**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 (15-19) yr / Male: 63% / Caucasian: NR **G2:** 17±1.6 (14-19) yr / Male: 67% / Caucasian: NR **G3:** 17.1±2.1 (13-20.5) yr / Male: 57% / Caucasian: NR Comorbidities: NR	CD (2), schizoaffective disorder (2), schizophrenia (46) NR, 9
Robb, 2009[80] RCT, 6 wk	**G1:** Paliperidone ER (low) (54), NR **G2:** Paliperidone ER (medium) (48), NR **G3:** Paliperidone ER (high) (48), NR **G4:** Placebo (51)	**G1:** NR / Male: NR / Caucasian: NR **G2:** NR / Male: NR / Caucasian: NR **G3:** NR / Male: NR / Caucasian: NR **G4:** NR / Male: NR / Caucasian: NR Comorbidities: NR	paranoid schizophrenia (143), other (58) NR, NR
Shaw, 2006[85] RCT, 8 wk (2 yr extension)	**G1:** Clozapine (12), 327±113 mg/day **G2:** Olanzapine (13), 18.1±4.3 mg/day	**G1:** 11.7±2.3 yr / Male: 67% / Caucasian: 58% **G2:** 12.8±2.4 yr / Male: 54% / Caucasian: 54% Comorbidities: ADHD (7), anxiety disorders (7), MR (0)	NR 0, 0

Table 14. Study and patient characteristics for studies examining schizophrenia (continued)

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Sikich, 2008[87] RCT, 8 wk (44 wk extension)	**G1:** Olanzapine (36), 11.4±5 mg/day **G2:** Rispiradone (42), 2.8±1.4 mg/day	**G1:** NR / Male: 71% / Caucasian: 60% **G2:** NR / Male: 66% / Caucasian: 61% Comorbidities: ADHD (22), affective disorder (19), anxiety disorder (21), ASD (5), DBD (16), learning disability (3), MR (0), psychosis (10), SA (4)	schizoaffective disorder (26), schizophrenia (50) 73, 22
Spencer, 1994[90] RCT (crossover), 8 wk	**G1:** Haloperidol (16),* 2 mg/day **G2:** Placebo (16)*	**G1:** NR / Male: NR / Caucasian: NR **G2:** NR / Male: NR / Caucasian: NR Comorbidities: Prior diagnoses: atypical PDD (5), atypical psychosis (3), borderline personality disorder (1), CD (1), pica (1), schizophrenia (1)	NR NR, NR
van Bruggen, 2003[96] RCT, olanzapine 9.8 wk, risperidone 6.7 wk	**G1:** Olanzapine (18), 15.6±4 mg/day **G2:** Risperidone (26), 4.4±1.5 mg/day	**G1:** 21±2.8 yr / Male: 72% / Caucasian: NR **G2:** 20.6±3 yr / Male: 85% / Caucasian: NR Comorbidities: NR	NR 38, NR
Woods, 2003[97] RCT, 8 wk (12 mo extension)	**G1:** Olanzapine (31), 8±3.1 mg/day **G2:** Placebo (29)	**G1:** 18.2±5.5 yr / Male: 68% / Caucasian: 74% **G2:** 17.2±4 yr / Male: 62% / Caucasian: 59% Comorbidities: SA (marijuana (16), other (11))	NR all, 53
Yen, 2004[98] RCT, 12 wk	**G1:** Haloperidol (2), 11.2±6.9 mg/day **G2:** Risperidone (6), 4.4±2.6 mg/day	**G1:** 24 yr / Male: 0 / Caucasian: NR **G2:** 20.7 (20-22) yr / Male: 67% / Caucasian: NR Comorbidities: NR	NR NR, 0

Table 15. Outcome data for studies assessing schizophrenia

Author, Year	Intervention (N analyzed)	Outcome	G1: BL mean (SD) / Followup mean (SD)	G2: BL mean (SD) / Followup mean (SD)	G3: BL mean (SD) / Followup mean (SD)	P-value
de Haan, 2003[49]	G1: Haloperidol (10) G2: Olanzapine (9)	CGI–I, change	-0.8 (0.9)	-1.3 (1.0)	NA	>0.05
		PANSS	-11.4 (19.5)	-7.2 (31.9)	NA	>0.05
DelBello, 2008[51]	G1: Ziprasidone, 80 mg/day (8) G2: Ziprasidone, 160 mg/day (9)	BPRS, change	51.5 (13.6) / -9.5 (11.0)	52.8 (12.6) / -15.2 (3.2)	NA	0.16
		CGI–S	4.6 (0.9) / 3 wk: -0.7 (0.8)	4.9 (0.8) / 3 wk: -0.8 (0.5)	NA	0.76
Findling, 2008[53]	G1: Aripiprazole, 10 mg/day (99) G2: Aripiprazole, 30 mg/day (97) G3: Placebo (98)	CGAS, change	46.7 (125.4) / 6 wk: 14.7 (14.9)	45.6 (118.2) / 6 wk: 14.8 (12.8)	45.4 (110.9) / 6 wk: 9.8 (12.9)	G1 vs. G2: 0.94 G1 vs. G3: 0.006; G2 vs. G3: 0.005
		CGI–I, change	NA / 6 wk: 2.7 (0.99)	NA / 6 wk: 2.5 (0.99)	NA / 6 wk: 3.1 (0.99)	G1 vs. G2: 0.16 G1 vs. G3: 0.02; G2 vs. G3: 0.0004
		CGI–S, change	4.5 (7.96) / 6 wk: -1.2 (0.99)	4.6 (5.9) / 6 wk: -1.3 (0.99)	4.6 (7.9) / 6 wk: -0.9 (0.99)	G1 vs. G2: 0.48 G1 vs. G3: 0.008; G2 vs. G3: 0.002
		PANSS, change	93.7 (156.2) / 6 wk: -26.7 (18.9)	94.9 (152.7) / 6 wk: -28.6 (8.86)	95.0 (153.4) / 6 wk: -21.2 (18.8)	G1 vs. G2: 0.37 G1 vs. G3: 0.05; G2 vs. G3: 0.007
Haas, 2009[58]	G1: Risperidone, 0.15–0.6 mg/day (131) G2: Risperidone, 1.5 to 6.0 mg/day (124)	CGI–I, change	NA / 8 wk: 3.2 (1.41)	NA / 8 wk: 2.6 (1.28)	NA	<0.001
		CGI–S, change	4.9 (0.84) / 8 wk: -0.9 (1.22)	5.1 (0.83) / 8 wk: -1.4 (1.23)	NA	<0.001
		PANSS, change	93.3 (14.14) / 8 wk: -12.5 (20.32)	96.4 (15.39) / 8 wk: -23.6 (22.83)	NA	<0.001
Jensen, 2008[61]	G1: Olanzapine (10) G2: Quetiapine (10) G3: Risperidone (9)	CGI–S, pts who decreased in severity by 1 level	n = 2	n = 0	n = 1	0.33
Kryzhanovskaya, 2009[63]	G1: Olanzapine (72) G2: Placebo (35)	BPRS–C, change	50.3 (10.0) / 6 wk: -19.4	50.1 (8.6) / 6 wk: -9.3	NA	0.003
		CGI–S, change	4.8 (0.7) / 6 wk: -1.1	4.9 (0.8) / 6 wk: -0.5	NA	0.004
		CGI–I, change	NA / 6 wk: 2.7	NA / 6 wk: 3.8	NA	<0.001
		OAS, change	2.0 / 6 wk: -0.9	2.4 / 6 wk: -0.2	NA	0.051

BL = baseline; BPRS–C = Brief Psychiatric Rating Scale for Children; CGAS = Children's Global Assessment Scale; CGI–I = Clinical Global Impressions–Improvement; CGI–S = Clinical Global Impressions–Severity; CPRS = Children's Psychiatric Rating Scale; ES = effect size; G = group; mg = milligram; GAF = Global Assessment of Functioning; N = number; NA = not applicable; NR = not reported; OAS = Overt Aggression Scale; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SD = standard deviation; SDQ = Strength and Difficulties Questionnaire; SOFAS = Social and Occupational Functioning Assessment Scale; VAS–MS: visual analog scale; wk = week; YMRS = Young Mania Rating Scale

Table 15. Outcome data for studies assessing schizophrenia (continued)

Author, Year	Intervention (N analyzed)	Outcome	G1: BL mean (SD) / Followup mean (SD)	G2: BL mean (SD) / Followup mean (SD)	G3: BL mean (SD) / Followup mean (SD)	P-value
Kryzhanovskaya, 2009 continued		PANSS, change	95.2 (14.1) / 6 wk: -21.3	95.5 (14.1) / 6 wk: -8.8	NA	0.005
Kumra, 2008[64]	G1: Clozapine (18) G2: Olanzapine (21)	BPRS	53.3 (12.0) / 12 wk: 31.4 (9.3) / 24 wk: 31.7 (12.1)	52.9 (10.4) / 12 wk: 34.3 (13.6) / 24 wk: 30.3 (9.8)	NA	12 wk: 0.78; 24 wk: 0.25
		CGAS	28.4 (16.6) / 12 wk: 50.5 (15.0) / 24 wk: 46.9 (16.8)	26.5 (8.9) / 12 wk: 46.4 (19.4) / 24 wk: 55.6 (17.5)	NA	12 wk: 0.91; 24 wk: 0.17
		CGI–I	NA / 12 wk: 2.03 (1.4) / 24 wk: 2.4 (1.3)	NA / 12 wk: 3.1 (1.3) / 24 wk: 1.9 (0.78)	NA	12 wk: 0.38; 24 wk: 0.007
		CGI–S	4.8 (0.9) / 12 wk: 3.3 (1.0)	5.0 (0.9) / 12 wk: 3.9 (1.3)	NA	0.80
		SANS	10.3 (3.6) / 12 wk: 6.6 (4.4) / 24 wk: 6.6 (4.9)	9.4 (2.7) / 12 wk: 7.6 (3.8) / 24 wk: 5.4 (3.8)	NA	12 wk: 0.02; 24 wk: 0.06
Kumra, 1998[66]	G1: Clozapine (15) G2: Olanzapine (8)	BPRS, ES relative to baseline	NR / 6 wk: 1.60	NR / 8 wk: 0.68	NA	NR
		SANS, ES relative to baseline	NR / 6 wk: 2.26	NR: 8 wk: 0.75	NA	NR
		SAPS, ES relative to baseline	NR / 6 wk: 2.47	NR / 8 wk: 0.42	NA	NR
Kumra, 1996[65]	G1: Haloperidol (11) G2: Clozapine (10)	BPRS–C	84.7 (17.6) / 6 wk: 64.7 (18.1)	83.7 (14.0) / 6 wk: 52.5 (12.6)	NA	0.04
		CGAS	23.2 (12.5) / 6 wk: 27.9 (12.1)	26.3 (11.9) / 6 wk: 44.9 (9.5)	NA	0.01
		CGI–I	NR / 6 wk: 3.30 (1.49)	NR / 6 wk: 2.00 (0.58)	NA	0.03
		SANS	83.0 (26.1) / 6 wk: 72.2 (24.7)	77.9 (36.0) / 6 wk: 46.0 (30.3)	NA	0.002
		SAPS	59.0 (24.9) / 6 wk: 35.9 (15.6)	53.9 (25.8) / 6 wk: 19.1 (11.7)	NA	0.01
Mozes, 2006[72]	G1: Olanzapine (12) G2: Risperidone (13)	BPRS	53.00 (15.20) / 12 wk: 29.08 (6.45)	54.15 (17.02) / 12 wk: 35.92 (10.27)	NA	0.254
		CGAS	3.83 (0.93) / 12 wk: 6.25 (1.86)	3.84 (1.51) / 12 wk: 5.69 (2.39)	NA	0.791
		PANSS	92.75 (26.93) / 12 wk: 50.5 (13.33)	93.84 (27.13) / 12 wk: 63.46 (21.72)	NA	0.236

Table 15. Outcome data for studies assessing schizophrenia (continued)

Author, Year	Intervention (N analyzed)	Outcome	G1: BL mean (SD) / Followup mean (SD)	G2: BL mean (SD) / Followup mean (SD)	G3: BL mean (SD) / Followup mean (SD)	P-value
NCT00090324, 2008[74]	G1: Quetiapine, 400 mg/day (73) G2: Quetiapine, 800 mg/day (74) G3: Placebo (75)	CGAS, change	43.4 (9.16) / 6 wk: 13.04	42.6 (11.12) / 6 wk: 14.94	41.8 (11.39) / 6 wk: 9.89	G1 vs. G3: 0.14; G2 vs. G3: 0.02
		CGI–I, % pts with improvement	60	56	42	G1 vs. G2: 0.33 G1 vs. G3: 0.009; G2 vs. G3: 0.01
		CGI–S, change	4.7 (0.77) / 6 wk: -1.15	4.6 (0.76) / 6 wk: -1.28	4.7 (0.67) / 6 wk: -0.81	G1 vs. G3: 0.10; G2 vs. G3: 0.02
		PANSS, change	98.1 (15.41) / 6 wk: -27.31	97.7 (15.32) / 6 wk: -28.44	97.2 (16.83) / 6 wk: -19.15	G1 vs. G3: 0.04; G2 vs. G3: 0.009
NCT00257192, 2008[76]	G1: Ziprasidone (189) G2: Placebo (87)	BPRS-A, change	6 wk: -14.16 (10.7)	6 wk: -12.35 (9.8)	NA	0.15
Ratzoni, 2002[78]	G1: Haloperidol (8) G2: Olanzapine (21) G3: Risperidone (21)	PANSS	86.1 (24.2) / 8 wk: 66.3 (21.8)	71.6 (23.8) / 8 wk: 61.6 (28.4)	90.2 (26.4) / 8 wk: 73.9 (19.1)	G1 vs. G2: 0.33 G1 vs. G3: 0.72 G2 vs. G3: 0.42
Robb, 2009[80]	G1: Paliperidone, low (NR) G2: Paliperidone, medium (NR) G3: Paliperidone, high (NR) G4: Placebo (NR)	CGAS, change	NR / 6 wk: 4.4	NR / 6 wk: 13.1	NR / 6 wk: 8.6 G4: NR / 6 wk: 5.0	G2 vs. G4: <0.001; G3 vs. G4: 0.067
		CGI–S, change	NR / 6 wk: 0.0	NR / 6 wk: -1.0	NR / 6 wk: -1.0 G4: NR / 6 wk: 0.0	<0.05
		PANSS, change	NR / 6 wk: -9.8	NR / 6 wk: -17.3	NR / 6 wk: -13.8 G4: NR / 6 wk: -7.9	G3 vs. G4: 0.086
		VAS sleep, change	NR / 6 wk: 6.6	NR / 6 wk: 16.0	NR / 6 wk: 14.4 G4: NR / 6 wk: -0.3	NR
Shaw, 2006[85]	G1: Clozapine (12) G2: Olanzapine (13)	BPRS–24, change	61 (12) / 8 wk: -9 / 24 mo: -8	57 (8) / 8 wk: -1	NA	Change over time: >0.1
		CGI–S, change	5.5 (0.7) / 8 wk: -1.1 / 24 mo: 0	5.2 (0.7) / 8 wk: -0.5	NA	Change over time: 0.04
		SANS, change	48 (23) / 8 wk: -22 / 24 mo: 8	46 (20) / 8 wk: -8	NA	Change over time: 0.003
		SAPS, change	35 (16) / 8 wk: -12 / 24 mo: 7	29 (15) / 3	NA	Change over time: >0.1

Table 15. Outcome data for studies assessing schizophrenia (continued)

Author, Year	Intervention (N analyzed)	Outcome	G1: BL mean (SD) / Followup mean (SD)	G2: BL mean (SD) / Followup mean (SD)	G3: BL mean (SD) / Followup mean (SD)	P-value
Sikich, 2008[87]	G1: Olanzapine (35) G2: Risperidone (41)	BPRS–C, change	38.6 (10.2) / 8 wk: -17.3 (11.2) / 52 wk: -16.2 (15.7)	48.1 (12.5) / 8 wk: -15.4 (19.6) / 52 wk: -24.0 (15.2)	NA	>0.05
		CGI–I, improvement of score ≥1 level (%)	17 (49)	19 (46)	NA	NR
		CGI–S	5.4 (0.7) / 8 wk: 3.4 (1.4) / 52 wk change: -1.9 (1.9)	6.0 (0.9) / 8 wk: 3.6 (1.3) / 52 wk change: -2.2 (1.1)	NA	>0.05
		PANSS, change	94.8 (17.2) / 8 wk: -26.6 (17.8) / 52 wk: -25.6 (21.0)	109.4 (22.3) / 8 wk: -23.7 (25.5) / 52 wk: -35.0 (22.4)	NA	>0.05
Spencer, 1994[90]	G1: Haloperidol (16) G2: Placebo (16)	BPRS-C	51.75 / 8 wk: 36.10	51.75 / 8 wk: 47.26	NA	NR
		CGI–I	3.37 / 8 wk: 1.51	3.37 / 8 wk: 2.58	NA	NR
		CGI–S	5.32 / 8 wk: 3.10	5.32 / 8 wk: 4.34	NA	NR
		CPRS, positive syndrome	3.30 / 8 wk: 1.98	3.38 / 8 wk: 3.20	NA	<0.01
		CPRS, negative syndrome	2.02 / 8 wk: 1.50	1.84 / 8 wk: 1.89	NA	<0.01
van Bruggen, 2003[96]	G1: Olanzapine (18) G2: Risperidone (24)	PANSS, change	90.7 (15.3) / 10 wk: 15.1 (23.8)	90.4 (18.8) / 10 wk: -15.0 (12.7)	NA	>0.05
Woods, 2003[97]	G1: Olanzapine (30) G2: Placebo (29)	CGI–S	3.73 (0.74) / 8 wk: -0.20 (0.81)	3.76 (1.12) / 8 wk: 0.10 (1.01)	NA	0.21
		GAF	42.03 (9.29) / 8 wk: 5.10 (12.85)	41.90 (11.33) / 8 wk: 3.10 (9.62)	NA	0.47
		PANSS, change	66.43 (17.49) / 8 wk: -6.73 (19.22)	63.26 (16.72) / 8 wk: -1.66 (15.08)	NA	0.30
		YMRS	4.17 (3.51) / 8 wk: -0.83 (4.62)	4.24 (3.54) / 8 wk: 1.00 (4.32)	NA	0.15
Yen, 2004[98]	G1: Haloperidol (2) G2: Risperidone (6)	PANSS	77 (4.2) / 3 mo: 66 (11.3)	89.5 (13.7) / 3 mo: 58 (17.7)	NA	0.03

Results by individual study: First episode psychosis. Four RCTs[42,45,88,91] examined the efficacy of antipsychotics for treating first episode psychosis. The number of participants ranged from 22 to 141 (median = 50). One study[88] compared a first generation (haloperidol) with second generation antipsychotics (olanzapine and risperidone). The four trials also compared the efficacy of two second generation antipsychotics (olanzapine versus quetiapine,[42] olanzapine versus risperidone,[88] low- versus high-dose quetiapine,[45] and quetiapine versus risperidone[91]). The studies were not pooled since each study examined a difference comparison. Patient and study characteristics and outcome data are presented in Table 16 and Table 17, respectively.

First generation versus second generation antipsychotics. One RCT[88] compared the efficacy of haloperidol with olanzapine and risperidone in children with psychosis (24 with affective disorders, 26 with schizophrenia spectrum). Patients were diagnosed using the DSM-IV and K-SADS present episode version criteria. Fifty patients were randomly assigned to the interventions (15 to haloperidol, 16 to olanzapine, 19 to risperidone) and 32 patients were followed to the endpoint at 8 weeks. The mean dosage of the drugs was 5±2 mg/day, 12.3±3.5 mg/day and 4±1.2 mg/day for haloperidol, olanzapine, and risperidone, respectively. Patients were assessed using the BPRS-C, CPRS, CGI-I, and CGI-S. There was no significant difference between haloperidol and the second generation antipsychotics for the CGI-I. However, there were significant differences on the BPRS favoring olanzapine over haloperidol ($p = 0.02$) and for the CGI-S and CPRS favoring risperidone over haloperidol ($p = 0.03$ for both outcomes).

Second generation versus second generation antipsychotics. Three RCTs[42,88,91] compared two different second generation antipsychotics and one RCT[45] compared two doses of quetiapine.

Arango et al.[42] conducted an RCT to compare the efficacy of olanzapine and quetiapine in adolescents with psychosis. Patients were diagnosed using the DSM-IV and K-SADS-PL criteria. Fifty patients were randomly assigned to the interventions (26 to olanzapine, 24 to quetiapine) and patients were followed to the endpoint at 6 months. Thirteen patients had bipolar disorder, 17 had schizophrenia, and 20 had other psychoses: major depressive episode with psychotic features (5 patients), schizoaffective disorder (5 patients), schizophreniform disorder (4 patients) and psychosis NOS (6 patients). 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. Patients were assessed using the CGAS, CGI-S, PANSS, SDQ (patient, parent and teacher), and YMRS. There was a statistically significant difference between the groups for strengths and difficulties (SDQ) as rated by patients favoring olanzapine ($p = 0.03$). No differences were found for any other outcomes.

Berger et al.[45] conducted an RCT to compare the efficacy of low- and high-dose quetiapine in patients with first episode psychosis (aged 15 to 25 years). No patients had comorbid mental retardation but 58 had problems with substance abuse. Patients were diagnosed using the DSM-IV and Clinical Interview for DSM-IV-TR Axis I Disorders-Patient Edition criteria. One hundred forty-one patients were randomly assigned to the interventions (69 to low-dose quetiapine, 72 to high-dose quetiapine) and were followed to the endpoint at 4 weeks with an 8-week extension. The mean drug dosage was 200 mg/day and 400 mg/day for low- and high-dose quetiapine, respectively. Patients were assessed using the BPRS, CGI-S, GAF, SANS, SOFAS, and YMRS. 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, $p = 0.03$). There were no other statistically significant differences between the outcomes.

Sikich et al.[88] conducted an RCT to compare the efficacy of olanzapine, risperidone, and haloperidol (described previously). Patients were assessed using the BPRS-C, CPRS, CGI-I, and CGI-S. There were no significant differences in symptom improvement between olanzapine and risperidone for any of the outcomes.

Swadi et al.[91] conducted an RCT to compare quetiapine and risperidone in adolescents (aged under 19 years) with first onset psychosis. Twenty-two patients were randomized to receive quetiapine (n = 11) or risperidone (n = 11) for 6 weeks. The mean daily dosage was 607 mg/day of quetiapine and 2.9 mg/day of risperidone. Diagnoses of first onset psychotic disorder or mood disorder with psychotic features were made using DSM-IV criteria. There were no statistically significant differences between the risperidone and quetiapine groups for improvement in total positive and negative symptoms.

Table 16. Study and patient characteristics for studies examining psychosis

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Arango, 2009[42] RCT, 6 mo	**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% / Caucasian: 77% **G2:** 16.3±1.1 yr / Male: 79% / Caucasian: 88% Comorbidities: NR	Bipolar disorder (13), schizophrenia (17), other psychoses (20) [MDD with psychotic features (5), psychosis NOS (6), schizoaffective disorder (5), schizophreniform disorder (4)] all, 25
Berger, 2008[45] RCT, 4 wk (8 wk extension)	**G1:** Quetiapine (low) (69), 200 mg/day **G2:** Quetiapine (high) (72), 400 mg/day	**G1:** 19.7±2.6 (15-24) yr / Male: 71% / Caucasian: NR **G2:** 19±2.9 (15-24) yr / Male: 64% / Caucasian: NR Comorbidities: MR (0), psychosis (all), SA (58)	NR all, 47
Sikich, 2004[88] RCT, 8 wk (12 wk extension)	**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% / Caucasian: 73% **G2:** 14.6±3.1 yr / Male: 56% / Caucasian: 63% **G3:** 14.6±2.9 yr / Male: 68% / Caucasian: 47% Comorbidities: NR	Affective disorders (24), schizophrenia spectrum (26) 39, 18
Swadi, 2010[91] RCT, 6 wk	**G1:** Quetiapine (11), 607 mg/day **G2:** Risperidone (11), 2.9 mg/day	**G1:** NR / Male: 55% / Caucasian: NR **G2:** NR / Male: 64% / Caucasian: NR Comorbidities: NR	NR NR, NR

G = group; MDD = major depressive disorder; mg = milligram; mo = month; MR = mental retardation; N = number; NR = not reported; NOS = not otherwise specified; RCT = randomized controlled trial; SD = standard deviation; wk = week; yr = year

Table 17. Outcome data for studies assessing psychosis

Author, Year	Intervention (N analyzed)	Outcome	G1: BL mean (SD) / Followup mean (SD)	G2: BL mean (SD) / Followup mean (SD)	G3: BL mean (SD) / Followup mean (SD)	P-value
Arango, 2009[42]	G1: Olanzapine (25) G2: Quetiapine (24)	CGAS	37.58 (17.33) / 6 mo: 61.88 (16.01)	41.17 (15.56) / 6 mo: 67.79 (16.79)	NA	0.12
		CGI–S	5.46 (0.86) / 6 mo: 3.54 (1.30)	5.04 (1.30) / 6 mo: 2.96 (1.40)	NA	0.61
		PANSS	105.65 (19.97) / 6 mo: 71.62 (17.33)	91.05 (21.42) / 6 mo: 67.29 (17.86)	NA	0.41
		SDQ Patient	23.52 (5.1) / 6 mo: 20.82 (5.96)	24.16 (5.08) / 6 mo: 24.36 (6.15)	NA	0.03
		SDQ Parent	23.70 (5.29) / 6 mo: 22.81 (6.35)	22.13 (7.67) / 6 mo: 21.63 (7.51)	NA	0.91
		SDQ Teacher	21.50 (5.25) / 6 mo: 21.71 (4.77)	22.14 (4.60) / 6 mo: 21.3 (5.46)	NA	0.19
		YMRS	18.73 (12.69) / 6 mo: 6.34 (9.62)	15.70 (12.85) / 6 mo: 5.50 (6.39)	NA	0.46
Berger, 2008[45]	G1: Quetiapine, 200 mg/day (46) G2: Quetiapine, 400 mg/day (45)	BPRS	66.7 (9.4) / 4 wk: 51.2 (11.0)	59.4 (8.2) / 4 wk: 47.1 (12.1)	NA	>0.05
		CGI–S	5.2 (0.9) / 4 wk: 4.1 (1.0) / 12 wk change: -1.5 (1.0)	4.8 (0.6) / 4 wk: 3.7 (0.8) / 12 wk change: -1.8 (1.1)	NA	4 wk: >0.05, 12 wk: 0.03
		GAF	45.1 (10.8) / 4 wk: 52.9 (13.9)	51.0 (11.3) / 4 wk: 55.3 (10.7)	NA	>0.05
		SANS	39.2 (16.9) / 4 wk: 31.1 (17.2)	32.6 (13.9) / 4 wk: 26.1 (14.0)	NA	>0.05
		SOFAS	46.6 (11.9) / 4 wk: 53.8 (13.2)	51.9 (9.9) / 4 wk: 53.7 (10.3)	NA	>0.05
		YMRS	10.9 (6.8) / 4 wk: 8.9 (7.1)	8.8 (6.3) / 4 wk: 6.4 (7.4)	NA	>0.05
Sikich, 2004[88]	G1: Haloperidol (15) G2: Olanzapine (16) G3: Risperidone (19)	BPRS–C	49 (14) / 8 wk: 33 (19)	50 (10) / 8 wk: 22 (12)	54 (13) / 8 wk: 27 (20)	G1 vs. G2: 0.02 G1 vs. G3: 0.07 G2 vs. G3: 0.84
		CGI–I	4 (0) / 8 wk: 2.7 (1.3)	4 (0) / 8 wk: 2.0 (1.1)	4 (0) / 8 wk: 2.1 (1.2)	G1 vs. G2: 0.11 G1 vs. G3: 0.17 G2 vs. G3: 0.80
		CGI–S	5.6 (1.0) / 8 wk: 4.5 (1.2)	5.3 (1.2) / 8 wk: 3.6 (1.3)	5.8 (1.2) / 8 wk: 3.8 (1.3)	G1 vs. G2: 0.16 G1 vs. G3: 0.03 G2 vs. G3: 0.48

BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGAS = Children's Global Assessment Scale; CGI–I = Clinical Global Impressions–Improvement; CGI–S = Clinical Global Impressions–Severity; CPRS = Children's Psychiatric Rating Scale; G = group; GAF = global assessment of functioning; mg = milligram; mo = month; N = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for the Assessment of Negative Symptoms; SD = standard deviation; SDQ = strength and difficulties questionnaire; SOFAS = Social and Occupational Functioning Assessment Scale; wk = week; YMRS = Young Mania Rating Scale

Table 17. Outcome data for studies assessing psychosis (continued)

Author, Year	Intervention (N analyzed)	Outcome	G1: BL mean (SD) / Followup mean (SD)	G2: BL mean (SD) / Followup mean (SD)	G3: BL mean (SD) / Followup mean (SD)	P-value
Sikich, 2004 (continued)		CPRS	110 (35) / 8 wk: 70 (39)	105 (25) / 8 wk: 53 (27)	114 (32) / 8 wk: 60 (48)	G1 vs. G2: 0.16 G1 vs. G3: 0.03 G2 vs. G3: 0.48
Swadi, 2010[91]	G1: Quetiapine (11) G2: Risperidone (11)	BPRS, change	58.91 (9.98) / 6 wk: -17.1	59.36 (18.04) / 6 wk: -20.8	NA	NR
		PANSS, change	89.00 (16.92) / 6 wk: -20.5	87.09 (16.60) / 6 wk: -25.3	NA	NR

Tourette Syndrome

Summary. Five RCTs assessed the efficacy of antipsychotics for treating symptoms in children and adolescents with Tourette syndrome. The following is a summary of the results by comparison:

- One RCT[56] compared pimozide with risperidone. Risperidone was shown to be significantly more effective in reducing tic severity.
- Two RCTs[81,83] compared haloperidol with pimozide. One study[83] found greater improvement favoring pimozide for the Child Behavior Checklist working hard subscale.
- One RCT[81] compared two first generation antipsychotics (haloperidol and pimozide) with placebo. There was statistically significant improvement in symptom severity and in global assessment for both haloperidol and pimozide compared with placebo.
- Two RCTs[82,84] compared two different second generation antipsychotics (risperidone and ziprasidone) compared with placebo. Moderate evidence favored the antipsychotic group for tic symptom severity.[82,84] Significant differences were also found for global impression of improvement,[84] and obsessive-compulsive symptoms.[82] No difference between groups was found for global impressions of severity.

Results by individual study. Five RCTs[56,81-84] examined the efficacy of antipsychotics for treating symptoms in patients with Tourette syndrome. The number of participants ranged from 19 to 41 (median = 26). One study compared pimozide with risperidone,[56] two studies compared haloperidol with pimozide[81,83] (one of which had an additional placebo group[81]), one study compared risperidone with placebo,[84] and one study compared ziprasidone with risperidone.[82] A meta-analysis was conducted for the comparison of second generation antipsychotics versus placebo. Patient and study characteristics and outcome data are presented in Table 18 and Table 19, respectively.

First generation versus second generation antipsychotics. One crossover RCT[56] examined the efficacy of pimozide and risperidone in children (aged 7 to 17 years) with Tourette syndrome (n = 16) or chronic motor tic disorder (n = 3). Patients were diagnosed using the DSM-IV-TR criteria and a clinical assessment. Comorbidities included ADHD (seven patients), OCD (two patients), oppositional defiant disorder (two patients), and conduct disorder (one patient). Nineteen patients were randomly assigned to the sequence in which they would receive the interventions (4 weeks per drug) and 13 patients were followed to the study endpoint at 8 weeks. The mean dosage of the drugs was 2.4 mg/day and 2.5 mg/day for the pimozide and risperidone groups, respectively. Patients were assessed using the CGI, TSSR, and YGTSS. Risperidone was significantly more effective than pimozide in reducing tic severity on the YGTSS ($p = 0.05$). There was no significant difference between the groups for the CGI or TSSR.

First generation versus first generation antipsychotics. Sallee et al.[81] conducted a placebo-controlled crossover RCT to compare the efficacy of haloperidol and pimozide in children (aged 7 to 16 years) with Tourette syndrome. Patients were diagnosed using the DSM-III-TR and K-SADS present episode version criteria. Thirteen patients had comorbid ADHD and five had OCD. Twenty-two patients were randomly assigned an intervention sequence. 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. All patients were followed to the study endpoint at 24 weeks. The mean dosage of the drugs was 3.5±2.2 mg/day and 3.4±1.6 mg/day

for the haloperidol and pimozide groups, respectively. Patients were assessed using the CGAS and CGI-S. No statistically significant differences were found between groups for any of the outcomes.

In a second RCT, Sallee et al.,[83] assessed the efficacy of haloperidol and pimozide in children (aged 7 to 16 years). Thirteen patients had comorbid ADHD. Patients were diagnosed using the DSM-III-TR and Tourette Syndrome Global Scale criteria. Forty-one patients were randomly assigned to the interventions (17 to haloperidol, 24 to pimozide) and all patients were followed to the study endpoint at 8 weeks. The mean dosage of the drugs was 1.5±0.6 mg/day and 3.7±1.4 mg/day for the haloperidol and pimozide groups, respectively. Patients were assessed using the school performance, working hard, learning, and function subscales of the Child Behavior Checklist. Scores on the working hard subscale were significantly improved in the pimozide group compared with the haloperidol group ($p<0.05$). There were no statistically significant differences between the groups for any of the other subscales.

First generation antipsychotics versus placebo. One RCT[81] (described previously) compared the efficacy of both haloperidol and pimozide with placebo. Patients were assessed using the CGAS and CGI-S. Symptoms significantly improved from baseline to endpoint in both the haloperidol and pimozide groups compared with the placebo (CGAS $p<0.05$; CGI-S $p = 0.01$).

Second generation antipsychotics versus placebo. Scahill et al.[84] conducted an RCT to evaluate the efficacy of risperidone versus placebo in children and adults (aged 7 to 65 years) with Tourette syndrome. Data were provided separately for a subgroup of 26 pediatric patients (mean age: 11.1±2.2 years). Patients were diagnosed using the DSM-IV criteria combined with a joint parent and child interview. Eleven patients also had a diagnosis of ADHD and four patients had comorbid OCD. Patients were randomly assigned to the interventions (12 to risperidone, 14 to placebo) and all patients were analyzed at the study endpoint at 8 weeks. The mean dosage of the drugs was 2.5±0.9 mg/day and 3.3±0.9 mg/day for the risperidone and placebo groups, respectively. Patients were assessed using the CGI-I and YGTSS. There was a statistically significant improvement in symptoms in the risperidone group compared with placebo for the CGI-I ($p = 0.003$) and YGTSS ($p = 0.002$).

An RCT conducted by Sallee et al.[82] evaluated the efficacy of ziprasidone compared with placebo in children (aged 7 to 17 years) with Tourette syndrome or chronic tic disorder. Patients were diagnosed using the DSM-IV criteria. Comorbidities included ADHD (15 patients), OCD (10 patients), disruptive behavior disorder (5 patients), and learning disabilities (2 patients). Twenty-eight patients were randomly assigned to the interventions (16 to ziprasidone, 12 to placebo) and 24 patients were followed to the study endpoint at 8 weeks. The mean dosage of ziprasidone was 28.2±9.6 mg/day. Patients were assessed using the CGI-TS, CYBOCS, and YGTSS. 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 statistically significant difference between groups on the CGI-TS.

The results of the two RCTs[82,84] were pooled (Figure 30). The combined estimate of change from baseline in tic score shows a significant difference between the groups favoring second generation antipsychotics (MD = -6.98; 95% CI, -10.34 to -3.62). There was no evidence of heterogeneity ($p = 0.95$, $I^2 = 0$ percent)

Figure 30. Second generation antipsychotics versus placebo on YGTSS in Tourette syndrome

Study or Subgroup	SGA Mean	SGA SD	SGA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
3.2.1 Risperidone versus Placebo								
Scahill 2003	-9.7	4.891	12	-2.6	8.35	14	42.1%	-7.10 [-12.28, -1.92]
Subtotal (95% CI)			**12**			**14**	**42.1%**	**-7.10 [-12.28, -1.92]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.69 (P = 0.007)								
3.2.2 Ziprasidone versus Placebo								
Sallee 2000	-8.6	6.7	16	-1.7	5	11	57.9%	-6.90 [-11.32, -2.48]
Subtotal (95% CI)			**16**			**11**	**57.9%**	**-6.90 [-11.32, -2.48]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.06 (P = 0.002)								
Total (95% CI)			**28**			**25**	**100.0%**	**-6.98 [-10.34, -3.62]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%								
Test for overall effect: Z = 4.07 (P < 0.0001)								

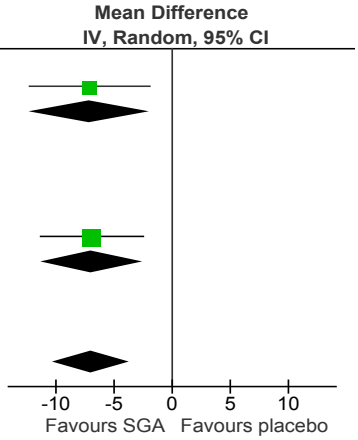


Table 18. Study and patient characteristics for studies examining Tourette syndrome

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Gilbert, 2004[56] RCT (crossover), 8 wk	**G1:** Pimozide (7), 2.4 mg/day **G2:** Risperidone (12), 2.5 mg/day	**G1:** NR / Male: NR / Caucasian: NR **G2:** NR / Male: NR / Caucasian: NR Comorbidities: ADHD (7), CD (1), learning disorder (3), OCD (2), ODD (2)	Chronic tic disorder (3), Tourette syndrome (16) NR, 18
Sallee, 2000[82] RCT, 8 wk	**G1:** Ziprasidone (16), 28.2±9.6 mg/day **G2:** Placebo (12)	**G1:** 11.3 (7-14) yr / Male: 87.5% / Caucasian: NR **G2:** 11.8 (8-16) yr / Male: 66.7% / Caucasian: NR Comorbidities: ADHD (15), DBD (5), learning disability (2), OCD (10)	NR NR, NR
Sallee, 1997[81] RCT (crossover), 24 wk	**G1:** Haloperidol (22)*, 3.5±2.2 mg/day **G2:** Pimozide (22)*, 3.4±1.6 mg/day **G3:** Placebo (22)*	**G1:** NR / Male: NR / Caucasian: NR **G2:** NR / Male: NR / Caucasian: NR Comorbidities: ADHD (13), OCD (5)	NR NR, NR
Sallee, 1994[83] RCT, 6 wk (3 wk extension)	**G1:** Haloperidol (17), 1.5±0.6 mg/day **G2:** Pimozide (24), 3.7±1.4 mg/day	**G1:** 10.4 yr / Male: NR / Caucasian: NR **G2:** 10.8 yr / Male: NR / Caucasian: NR Comorbidities: ADHD (13)	NR NR, NR
Scahill, 2003[84] RCT, 8 wk	**G1:** Risperidone (12), 2.5±0.9 mg/day **G2:** Placebo (14)	**G1:** NR / Male: NR / Caucasian: NR **G2:** NR / Male: NR / Caucasian: NR Comorbidities: ADHD (11), OCD (4)	NR NR, 24

ADHD = attention deficit hyperactivity disorder; CD = conduct disorder; DBD = disruptive behavior disorder; G = group; mg = milligrams; N = number; NR = not reported; OCD = obsessive-compulsive disorder; ODD = oppositional defiant disorder; RCT = randomized controlled trial; SD = standard deviation; wk = week

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

Table 19. Outcome data for studies assessing Tourette syndrome

Author, Year	Intervention (N analyzed)	Outcome	G1: BL mean (SD) / Followup mean (SD)	G2: BL mean (SD) / Followup mean (SD)	G3: BL mean (SD) / Followup mean (SD)	P-value
Gilbert, 2004[56]	G1: Pimozide (NR) G2: Risperidone (NR)	CGI–S at baseline, CGI–I at followup	4.2 (0.9) / 4 wk: 3.1 (1.4)	4.2 (0.9) / 4 wk: 2.1 (1.1)	NA	0.12
		TSSR	21.7 (16.2) / 4 wk: 16.9 (11.6)	21.7 (16.2) / 4 wk: 10.8 (9.4)	NA	0.06
		YGTSS	43.3 (17.5) / 4 wk: 34.2 (14.2)	43.3 (17.5) / 4 wk: 25.2 (13.6)	NA	0.05
Sallee, 2000[82]	G1: Ziprasidone (16) G2: Placebo (11)	CGI–TS, change	4.6 (0.9) / 8 wk: -1.4 (1.0)	4.5 (1.0) / 8 wk: -0.7 (0.9)	NA	0.11
		CYBOCS, change	19.6 (2.6) / 8 wk: -5.2 (5.4)	13.2 (9.0) / 8 wk: 0.6 (2.9)	NA	0.0003
		YGTSS total tic score, change	24.7 (6.8) / 8 wk: -8.6 (6.7)	24.6 (9.6) / 8 wk: -1.7 (5.0)	NA	0.008
		YGTSS global severity score	46.9 (13.8) / 8 wk: -18.3 (9.9)	46.9 (17.7) / 8 wk: -7.6 (10.6)	NA	0.016
Sallee, 1997[81]	G1: Haloperidol (NR) G2: Pimozide (NR) G3: Placebo (NR)	CGAS	61.4 (9.8) / 24 wk: 73.6 (16.5)	61.4 (9.8) / 24 wk: 75.9 (16.6)	61.4 (9.8) / 24 wk: 66.4 (12.8)	G1 vs. G2: 0.60 G1 & G2 vs. G3: <0.05
		CGI–S	NR / 24 wk: 3.1 (1.4)	NR / 24 wk: 3.1 (1.4)	NR / 24 wk: 4.6 (1.0)	G1 vs. G2: 1.0 G1 & G2 vs. G3: <0.01
Sallee, 1994[83]	G1: Haloperidol (12) G2: Pimozide (13)	CBCL-TRF, school performance	44	46	NA	>0.05
		CBCL-TRF, working hard	41	49	NA	<0.05 (favors G2)
		CBCL-TRF, learning	42	48	NA	>0.05
		CBCL-TRF, total function	39	45	NA	>0.05
Scahill, 2003[84]	G1: Risperidone (12) G2: Placebo (14)	CGI–I, level 1 or 2	9 (0.78)	1 (0.07)	NR	0.003
		YGTSS	27.0 (5.02) / 4 wk: 21.6 (5.98) / 8 wk: 17.3 (4.75)	28.6 (8.00) / 4 wk: 24.7 (9.24) / 8 wk: 26.0 (8.66)	NA	8 wk: 0.002

BL = baseline; CBCL = Child Behavior Checklist; CGAS = Children's Global Assessment Scale; CGI–I = Clinical Global Impressions–Improvement; CGI–S = Clinical Global Impressions–Severity; CGI–TS = Clinical Global Impressions–Tic Severity; CYBOCS = Children's Yale-Brown Obsessive-compulsive Scale; G = group; GAF = Global Assessment of Functioning; N = number; NA = not applicable; NR = not reported; SD = standard deviation; TSSR = Tic Symptom Self-Report; YGTSS = Yale Global Tic Severity Score

Behavioral symptoms

Summary. Four studies making four comparisons evaluated the efficacy of antipsychotics in treating behavioral disturbances in children and adolescents. The following is a summary of the results by comparison:

- One RCT[44] comparing aripiprazole with ziprasidone found no differences between the treatment groups for global impressions of functioning and improvement, aggression, or manic symptoms. The evidence was too limited to make conclusions.
- One retrospective cohort study[62] compared olanzapine with ziprasidone. No difference was found in the number of aggressive episodes between the groups. The evidence was too limited to make conclusions.
- One crossover RCT[59] compared low- and high-dose risperidone. There was no difference in aberrant behavior scores between the two groups.
- Two RCTs[59,95] compared risperidone with placebo. Low level of evidence showed a statistically significant difference favoring risperidone for improving symptoms on the ABC, CGI, VAS, and the social relationship and occupational attitude subscales of the PAC ($p<0.05$) in one study.[95]

Results by individual study. Four studies (two RCTs[44,95] and two retrospective cohort studies[59,62]) examined the efficacy of antipsychotics for treating symptoms in patients with behavioral disturbances. The number of participants ranged from 13 to 100 (median = 36). Two studies compared two second generation antipsychotics (aripiprazole versus ziprasidone,[44] olanzapine versus ziprasidone,[62]) and one study compared two doses of risperidone.[59] Risperidone was compared with placebo in two studies.[59,95] No meta-analyses could be conducted due to differences in comparisons and outcomes. Patient and study characteristics and outcome data are presented in Table 20 and Table 21, respectively.

Second generation versus second generation antipsychotics. Bastiaens et al.[44] conducted a retrospective cohort study to evaluate the efficacy of aripiprazole and ziprasidone in children and adolescents (aged 6 to 17 years) with aggressive behavior. Forty-six patients were randomized to the treatment groups (24 to aripiprazole, 22 to ziprasidone). Participants were diagnosed with conduct disorder (n = 14), bipolar disorder (n = 12), mood disorder NOS (n = 8), depressive disorder (n = 6), pervasive developmental disorder (n = 2), and psychotic disorder (n = 4). Diagnoses were made using DSM-IV criteria with Mini International Neuropsychiatric Interview for Children and Child/Adolescent Symptom Inventory. A total of 34 patients were followed to the 2-month endpoint. The mean daily dosage of drugs was 4.5±2.3 mg and 42.9±18 mg for aripiprazole and ziprasidone, respectively. Patients were assessed using CGI-I, GAF, OAS, and YMRS-P. Both aripiprazole and ziprasidone were effective for treating aggressive behavior; however, the differences were not statistically significant for any outcomes.

Hellings et al.[59] conducted a crossover RCT to investigate the efficacy of risperidone to treat aggression, self-injury, and destructive behaviors in children and adults (aged 8 to 56 years) with mental retardation. Data were available for 26 pediatric patients. Each patient was randomized to low- (1 mg) or high-dose (2 mg) risperidone for 4 weeks; doses were then switched and continued for an additional 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. Upon completion of the crossover study, patients were enrolled in a 24-week open-

label maintenance phase. Patients were assessed using the ABC. There were no differences in the endpoint scores on the ABC subscales between the low- and high-dose groups.

Khan et al.[62] conducted a retrospective cohort study comparing olanzapine and ziprasidone for treating agitation and aggression in children and youth under 18 years of age. Of the 100 enrolled patients, 34 had concurrent psychosis, 27 had substance abuse, and 18 had posttraumatic stress disorder. In this retrospective cohort study, hospitalized psychiatric patients were given olanzapine (n = 50) or ziprasidone (n = 50) intramuscularly. The mean daily dose was 8.2±2.4 mg for olanzapine and 19.1±2.6 mg for ziprasidone. The mean duration of treatment was 3.7±2.4 weeks for olanzapine and 4.9±3.4 weeks for ziprasidone. The number of aggressive episodes was reported and no significant difference was found between the two groups.

Second generation antipsychotics versus placebo. A crossover RCT conducted by Hellings et al.[59] compared two doses of risperidone with placebo for treating children with behavior disturbances (aggression, self-injurious behaviors, or property destruction) and mental retardation (described previously). All patients received low- and high-dose risperidone each for 4 weeks (the sequence was randomized) and the placebo for 3 to 5 weeks. The ABC was used to assess symptom severity. All ABC subscales were lower in the risperidone groups compared with placebo; however, p-values were not reported and could not be calculated.

Van Bellinghen et al.[95] assessed the efficacy of risperidone for treating persistent behavioral disturbances in mentally retarded children and adolescents (aged 6 to 18 years). Thirteen patients were randomized to risperidone (n = 6) or placebo (n = 7) for 4 weeks. Psychiatric diagnoses were made based on individual assessment and interview with parents. The mean daily dose of risperidone at endpoint was 1.2 mg. Outcomes were assessed using ABC, CGI, PAC, and VAS. There was a significant difference favoring the risperidone group in improving symptoms on ABC ($p<0.001$), CGI ($p<0.05$), VAS ($p<0.001$), and the social relationship and occupational attitude subscales of the PAC ($p<0.05$).

Table 20. Study and patient characteristics for studies examining behavioral symptoms

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Bastiaens, 2009[44] Aggression Retrospective cohort, 2 mo	**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% / Caucasian: NR **G2:** 12.1±2.9 yr / Male: 91% / Caucasian: NR Comorbidities: NR	Bipolar (12), CD (14), depressive disorder (6), mood disorder NOS (8), PDD (2), psychotic disorder (4) NR, 34
Hellings, 2006[59] Aggression, self-injury, or property destruction RCT (crossover), 22 wk (24 wk extension)	**G1:** Risperidone (low) (26),* 1 mg/day **G2:** Risperidone (high) (26),* 2 mg/day **G3:** Placebo (26)*	**G1:** NR / Male: NR / Caucasian: NR **G2:** NR / Male: NR / Caucasian: NR **G3:** NR / Male: NR / Caucasian: NR Comorbidities: ASD (NR), MR (all) [mild (8), moderate (6), severe (8), profound (4)]	NR NR, NR
Khan, 2006[62] Agitation & aggression Retrospective cohort, 1 mo	**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% / Caucasian: 60% **G2:** 14.6±2.1 yr / Male: 32% / Caucasian: 68% Comorbidities: MR (0), PTSD (18), SA (27)	Psychosis (34) NR, NR
van Bellinghen, 2001[95] Behavior disturbances RCT, 4 wk	**G1:** Risperidone (6), 1.2 mg/day **G2:** Placebo (7)	**G1:** NR (6–14) yr / Male: 33% / Caucasian: NR **G2:** NR (7–14) yr / Male: 43% / Caucasian: NR Comorbidities: anxiety (0), depression (0), mania (0), MR (all)	NR NR, NR

ASD = autism spectrum disorder; CD = conduct disorder; G = group; mg = milligrams; mo = month; MR = mental retardation; N = number; NOS = not otherwise specified; NR = not reported; PDD = pervasive developmental disorder; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; SA = substance abuse; SD = standard deviation; wk = week; yr = year

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

Table 21. Outcome data for studies assessing behavioral symptoms

Author, Year	Intervention (N analyzed)	Outcome	G1: BL mean (SD) / Followup mean (SD)	G2: BL mean (SD) / Followup mean (SD)	G3: BL mean (SD) / Followup mean (SD)	P-value
Bastiaens, 2009[44]	G1: Aripiprazole (20) G2: Ziprasidone (14)	CGI–I	NA / 2 mo: 2.0 (1.2)	NA / 2 mo: 2.3 (1.4)	NA	0.68
		GAF	50.0 (4.3) / 2 mo: 61.0 (7.7)	47.3 (2.6) / 2 mo: 57.9 (7.6)	NA	0.42
		OAS	7 (1.7) / 2 mo: 2.3 (2.9)	7 (2.0) / 2 mo: 3.1 (2.0)	NA	0.52
		YMRS–Parent	23.4 (9.2) / 2 mo: 9.8 (8.2)	21.6 (6.7) / 2 mo: 8.7 (7.0)	NA	0.78
Hellings, 2006[59]	G1: Risperidone, low (26) G2: Risperidone, high (26) G3: Placebo (26)	ABC, irritability	NR / 13.4	NR / 14.2	NR / 21.2	NR
		ABC, lethargy	NR / 6.1	NR / 7.3	NR / 8.0	NR
		ABC, stereotypy	NR / 4.7	NR / 5.5	NR / 5.3	NR
		ABC, hyperactivity	NR / 15.1	NR / 14.7	NR / 20.4	NR
		ABC, excessive speech	NR / 3.4	NR / 3.1	NR / 4.3	NR
Khan, 2006[62]	G1: Olanzapine (50) G2: Ziprasidone (50)	Number of aggressive episodes	9 (8)	14 (15)	NA	0.50
van Bellinghen, 2001[95]	G1: Risperidone (6) G2: Placebo (7)	ABC, change	46.7 / 4 wk: -30.3	46.9 / 4 wk: -3.3	NA	<0.001
		CGI–I, change	4.7 / 4 wk: -2.2	4.6 / 4 wk: -0.2	NA	<0.05
		PAC, change	34.7 / 4 wk: 9.2	33 / 4 wk: -0.8	NA	NR
		VAS symptom	86.7 / 4 wk: -49.5	81.7 / 4 wk: 1.7	NA	<0.05

ABC = Aberrant Behavior Checklist; BL = baseline; CGI–I = Clinical Global Impressions–Improvement; G = group; GAF = Global Assessment of Functioning; N = number; NA = not applicable; NR = not reported; OAS = Overt Aggression Scale; PAC = Personal Assessment Checklist; SD = standard deviation; VAS: visual analog scale; wk = week; YMRS = Young Mania Rating Scale

Question 2: Adverse Events

Seventy-one studies[40-82,84-97,99-112] reported data on adverse events in pediatric or young adult patients receiving first generation or second generation antipsychotics. Data are presented separately for each antipsychotic comparison across all conditions.

Head-to-Head Comparison

Forty-five studies provided adverse event data for head-to-head comparisons of antipsychotics. Adverse events were compared between first generation and second generation antipsychotics in 12 studies.[49,56,65,68,71,78,88,100,107,108,110,112] Three studies[77,81,111] reported adverse event data for the comparison of two first generation drugs; 33 studies compared two second generation drugs.[42,44-46,51,53,54,57-59,61,62,64,66,69,72,74,78,80,85,87,88,91,96,99,101-106,109,112] All adverse event data are provided in Appendix I. Statistically significant findings are highlighted in the descriptions and summary tables below.

Summary. The following is a summary of the adverse event findings for studies making head-to-head comparisons of first generation and second generation antipsychotics:

First generation versus second generation:

- Mean weight gain was significantly higher for patients receiving olanzapine compared with haloperidol in a meta-analysis of three studies.[68,78,88] No differences were found for haloperidol versus risperidone and pimozide versus risperidone.
- Prolactin levels were higher in patients receiving first generation antipsychotics compared with clozapine in two studies.[110,112]
- Extrapyramidal symptoms were found to affect significantly more patients and be more severe with haloperidol treatment compared with olanzapine[68,78,88] and risperidone.[71,78,88]
- Fatigue occurred significantly more frequently for clozapine than for haloperidol,[65] and for haloperidol than for risperidone.[78]
- One study[88] found AST levels to be significantly higher for olanzapine and risperidone than for haloperidol.
- A higher rate of depression occurred in patients receiving haloperidol than those receiving olanzapine and risperidone.[78]
- No significant differences were found for dyslipidemia, cardiac adverse events, neutropenia and agranulocytosis, seizures, neuroleptic malignant syndrome, constipation, and dermatological side effects.

First generation versus first generation:

- Prolactin levels were significantly higher in patients receiving pimozide compared with patients receiving haloperidol in one study.[81]
- Rate of withdrawal dyskinesia were higher among patients receiving discontinuous haloperidol compared with patients receiving continuous haloperidol in one study.[77]
- No differences between first generation antipsychotics were found for total adverse events, cerebrovascular events, weight gain, sedation, neuromotor, cardiac, or behavioral side effects.

Second generation versus second generation:

- Withdrawal due to adverse events was greater among patients taking aripiprazole compared with ziprasidone in one study.[44] Total adverse events were experienced in more patients treated with risperidone than olanzapine.[87,99,106]
- Aripiprazole showed less increase than olanzapine in mean weight gain, fat mass, BMI, and waist circumference; less increase than quetiapine for mean weight gain, and less increase than risperidone for mean percent change from baseline.[101] Quetiapine and risperidone were significantly superior to olanzapine on various measures of weight gain and body composition based on results from four studies,[42,61,101,105] and 12 studies,[46,72,78,87,88,96,99,101,102,104-106] respectively. None of the other comparisons were significantly different for weight gain.
- 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[46,87,101,105] and five studies,[46,87,88,101,105] respectively. Single studies found lipid profiles were lower for aripiprazole compared with olanzapine and quetiapine,[101] for quetiapine compared with olanzapine,[101] and for quetiapine compared with risperidone.[91]
- One study[101] reported high insulin levels in a significantly greater proportion of patients receiving olanzapine than for those receiving risperidone.
- Prolactin levels were significantly higher in patients receiving olanzapine than those receiving clozapine,[64,112] and in those receiving risperidone than for those receiving olanzapine.[46,87,88]
- One study found a significant difference favoring olanzapine and risperidone over quetiapine in the incidence of dyskinesia.[99]
- Patients treated with clozapine experienced hypertension more frequently than those treated with olanzapine in two studies.[85,104]
- Somnolence occurred significantly more frequently for risperidone than for olanzapine.[96]
- Mean ALT and AST levels were significantly higher for patients treated with olanzapine than for those treated with risperidone.[87,88]
- Thyroid stimulating hormone levels were significantly higher in patient receiving quetiapine than for those receiving risperidone.[105]
- No significant differences were observed for cerebrovascular events, neutropenia and agranulocytosis, or behavioral side effects.

First generation versus second generation antipsychotics. Twelve studies reported on the relative rates of adverse events between first and second generation antipsychotics. Comparisons included various first generation versus various second generation drugs in one study,[108] various first generation antipsychotics versus clozapine in one study,[110] haloperidol versus clozapine in two studies,[65,112] haloperidol versus olanzapine in six studies,[49,68,78,88,107,112] haloperidol versus risperidone in three studies,[71,78,88] and pimozide versus risperidone in two studies.[56,100] No data were provided for the following adverse events: mortality, cerebrovascular events, thyroid dysfunction, exercise intolerance, and precocious puberty. Effect estimates and 95 percent confidence intervals for the significant findings are presented in

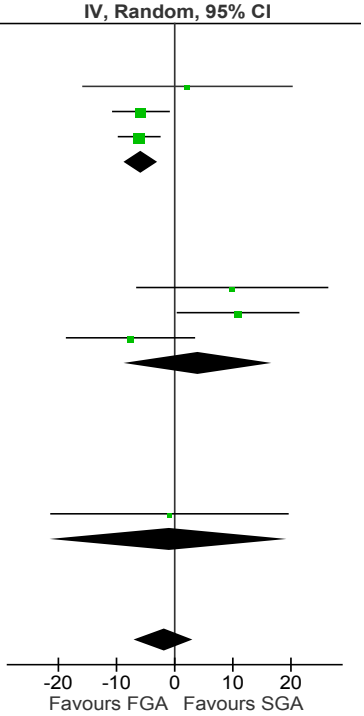
Table 22.

Total adverse events. Severe adverse events were reported in a study comparing haloperidol with risperidone; no events were reported for either treatment group.[71]

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.[68] A meta-analysis of three studies[68,78,88] comparing haloperidol with olanzapine found significantly less weight gain in patients receiving haloperidol (MD = -5.8 kg; 95% CI: -8.6 to -2.98 kg) (Figure 31). There was no significant difference between the other first generation versus second generation drug comparisons.

Figure 31. First generation versus second generation antipsychotics for mean weight gain (kg)

Study or Subgroup	FGA Mean	FGA SD	FGA Total	SGA Mean	SGA SD	SGA Total	Weight	Mean Difference IV, Random, 95% CI
1.11.1 Haloperidol versus Olanzapine								
1020	0	0	10	77.6	22.3	10		Not estimable
1377	76.1	24.8	15	73.9	26.2	16	6.5%	2.20 [-15.75, 20.15]
1853	3.2	4.9	6	9	3.5	6	25.4%	-5.80 [-10.62, -0.98]
3985	1.1	3.3	8	7.2	6.3	21	28.4%	-6.10 [-9.63, -2.57]
Subtotal (95% CI)			**39**			**53**	**60.3%**	**-5.79 [-8.61, -2.98]**
Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 2 (P = 0.67); I² = 0%								
Test for overall effect: Z = 4.03 (P < 0.0001)								
1.11.2 Haloperidol versus Risperidone								
1377	76.1	24.8	15	66.2	23.4	19	7.5%	9.90 [-6.48, 26.28]
157	48.4	18.2	15	37.5	8.9	13	13.9%	10.90 [0.50, 21.30]
3985	61.9	11.4	8	69.5	17.8	21	13.0%	-7.60 [-18.57, 3.37]
Subtotal (95% CI)			**38**			**53**	**34.4%**	**3.98 [-8.80, 16.76]**
Heterogeneity: Tau² = 86.91; Chi² = 6.46, df = 2 (P = 0.04); I² = 69%								
Test for overall effect: Z = 0.61 (P = 0.54)								
1.11.3 Pimozide versus Risperidone								
1348	2.7	0	0	4.5	0	0		Not estimable
1778	1	21.5	7	1.9	22.4	12	5.3%	-0.90 [-21.25, 19.45]
Subtotal (95% CI)			**7**			**12**	**5.3%**	**-0.90 [-21.25, 19.45]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.09 (P = 0.93)								
Total (95% CI)			**84**			**118**	**100.0%**	**-1.85 [-6.95, 3.25]**
Heterogeneity: Tau² = 20.61; Chi² = 13.41, df = 6 (P = 0.04); I² = 55%								
Test for overall effect: Z = 0.71 (P = 0.48)								



Dyslipidemia. No significant differences between first generation and second generation antipsychotics were reported.

Insulin resistance and diabetes. One study[88] found significantly higher glucose levels for olanzapine than for haloperidol.

Prolactin-related and sexual adverse events. Prolactin levels were significantly higher in patients receiving various first generation antipsychotics compared with those receiving clozapine in one study.[110] A second study[112] found prolactin levels to be higher for haloperidol compared with clozapine.

Neuromotor adverse events. Significantly more patients experienced dystonia[78,88] and any extrapyramidal side effects[68,78] in the haloperidol group compared with olanzapine. Similarly, one study[88] found extrapyramidal symptoms as measured by the SAS to be significantly more severe for patients treated with haloperidol than for those treated with olanzapine. Akathesia occurred significantly more frequently among patients treated with haloperidol than those treated with risperidone in a meta-analysis of two studies.[78,88] Similarly, extrapyramidal symptoms as measured by the ESRS and the SAS were significantly more severe in patients treated with haloperidol than for those treated with risperidone in two studies.[71,88]

Cardiac adverse events. No significant differences between first generation and second generation antipsychotics were reported.

Sedation. A significantly greater proportion of patients receiving clozapine reported drowsiness compared with those receiving haloperidol in one study.[65] A single study found the rate of fatigue to be significantly greater in patients receiving haloperidol than those receiving risperidone.[78]

Liver toxicity. Aspartate amino transferase (AST) levels were significantly higher for patients treated with olanzapine and risperidone than those receiving haloperidol in one study.[88]

Neutropenia and agranulocytosis. No significant differences between first generation and second generation antipsychotics were reported.

Seizures. No significant differences between first generation and second generation antipsychotics were reported.

Neuroleptic malignant syndrome. No significant differences between first generation and second generation antipsychotics were reported.

Constipation. No significant differences between first generation and second generation antipsychotics were reported.

Behavioral side effects. The rate of depression was found to be significantly higher in patients receiving haloperidol than in those receiving olanzapine or risperidone in one study.[78]

Dermatological adverse events. No significant differences between first generation and second generation antipsychotics were reported.

Table 22. Significant findings for first generation versus second generation antipsychotics

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)	3	39	53	MD = -5.79	(-8.6, -2.98)	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	(1.02, 65.5)	Olanzapine
EPS	2	13	25	RR = 3.53	(1.1, 10.9)	Olanzapine
EPS (SAS)	1	15	16	MD = 3.3	(0.29, 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)						
Akathesia	2	22	36	RR = 6.93	(1.26, 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; EPS = extrapyramidal symptom; ERES = extrapyramidal symptom rating scale; FGA = first generation antipsychotic; MD = mean difference; N = number; SAS = Simpson Angus Scale; RR = relative risk

* denotes the drug with the better adverse event profile

First generation versus first generation antipsychotics. Three studies reported on the relative rates of adverse events between different first generation antipsychotics. Comparisons included haloperidol versus haloperidol,[77] haloperidol versus pimozide,[81] and pimozide versus pimozide.[111] The following adverse event categories were not reported: mortality, 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 23.

Total adverse events. No significant differences between first generation antipsychotics were reported.

Cerebrovascular events. No significant differences between first generation antipsychotics were reported.

Weight gain/body composition: No significant differences between first generation antipsychotics were reported.

Prolactin-related and sexual adverse events. Prolactin levels were significantly higher in patients receiving pimozide compared with patients receiving haloperidol.[81]

Neuromotor adverse events. A significantly higher rate of withdrawal dyskinesia was reported in patients receiving discontinuous haloperidol compared with patients receiving continuous haloperidol.[77]

Cardiac adverse events. No significant differences between first generation antipsychotics were reported.

Sedation. No significant differences between first generation antipsychotics were reported.

Behavioral side effects. No significant differences between first generation antipsychotics were reported.

Table 23. Significant findings for first generation versus first generation antipsychotics

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; MD = mean difference; N = number; RR = relative risk
* denotes the drug with the better adverse event profile

Second generation versus second generation antipsychotics. Thirty-three studies reported on the relative rates of adverse events between different second generation antipsychotics. The following comparisons were made (presented alphabetically by generic drug name): aripiprazole versus olanzapine,[101] aripiprazole versus quetiapine,[101] aripiprazole versus risperidone,[101] aripiprazole versus ziprasidone,[44] clozapine versus olanzapine,[64,66,85,99,104,112] clozapine versus quetiapine,[99] clozapine versus risperidone,[99,104] olanzapine versus quetiapine,[42,61,99,101,105] olanzapine versus risperidone,[46,61,72,78,87,88,96,99,101,102,104-106,109] olanzapine versus ziprasidone,[62] and quetiapine versus risperidone.[61,91,99,101,105] The following adverse event categories were not reported in any of the studies: mortality, seizures, neuroleptic malignant syndrome, constipation, and exercise intolerance. Effect estimates and 95 percent confidence intervals for the significant findings are presented in Table 24.

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.[44] A meta-analysis of three studies[87,99,106] found that a significantly greater proportion of patients receiving risperidone experienced any adverse events, compared with olanzapine.

Cerebrovascular events. No significant differences between second generation antipsychotics were reported.

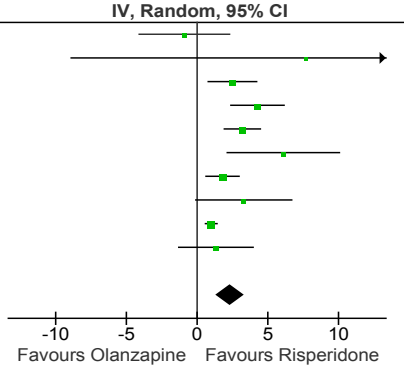
Weight gain/body composition. Weight gain greater than seven percent and BMI increase greater than 10 percent occurred significantly more frequently in patients receiving olanzapine

than those receiving aripiprazole in one study.[101] Similarly, olanzapine resulted in significantly greater mean increase in weight, percent change from baseline weight, fat mass, BMI, and waist circumference compared with aripiprazole.[101] 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.[101] In addition, increase in mean weight was significantly greater for quetiapine than for aripiprazole, while percent weight change from baseline was significantly greater for risperidone than with aripiprazole.[101] Weight gain greater than seven percent,[61,101] BMI increase greater than 10 percent,[101] and BMI over the 85th percentile[105] occurred in a greater proportion of patients in the olanzapine group compared with the quetiapine group. Similarly, the olanzapine group experienced significantly greater increase in mean weight gain,[42,101,105] BMI,[42,101,105] fat mass,[101] and waist circumference than quetiapine.[101] Significantly more patients receiving olanzapine experienced any weight gain,[87,99,104,106] and BMI increase greater than 10 percent[101] compared with those receiving risperidone. Similarly, a meta-analysis of 10 studies[46,72,78,87,88,96,101,102,104,105] (Figure 32) found a greater increase in mean weight for olanzapine than risperidone (MD = 2.35; 95% CI: 1.31 to 3.39); studies also found less increase for risperidone than olanzapine in weight,[46,101,102] fat mass,[101] BMI,[78,87,88,101,102,104,105] BMI percentile,[87,101] and waist circumference.[101] Fewer patients treated with risperidone transitioned from normal weight to overweight to obese than those treated with quetiapine.[101]

Figure 32. Olanzapine versus risperidone for mean weight gain (kg)

Study or Subgroup	Olanzapine Mean	Olanzapine SD	Olanzapine Total	Risperidone Mean	Risperidone SD	Risperidone Total	Weight	Mean Difference IV, Random, 95% CI
1181	3.6	3.8	15	4.5	5.2	16	6.8%	-0.90 [-4.09, 2.29]
1377	73.9	26.2	16	66.2	23.4	19	0.4%	7.70 [-8.90, 24.30]
16	6.1	3.6	35	3.6	4	41	12.5%	2.50 [0.79, 4.21]
166	5.27	4.536	26	1	1.8	26	11.7%	4.27 [2.39, 6.15]
2413	8.54	4.25	52	5.34	3.5	168	14.8%	3.20 [1.93, 4.47]
268	11.1	7.8	20	5	4.8	22	5.1%	6.10 [2.14, 10.06]
3420	4.6	1.9	15	2.8	1.3	15	15.3%	1.80 [0.63, 2.97]
3985	7.2	6.3	21	3.9	4.8	21	6.3%	3.30 [-0.09, 6.69]
555	3.2	0.7	15	2.2	0.4	16	18.4%	1.00 [0.60, 1.40]
734	5.78	3.11	11	4.45	2.87	9	8.6%	1.33 [-1.30, 3.96]
Total (95% CI)			**226**			**353**	**100.0%**	**2.35 [1.31, 3.39]**

Heterogeneity: Tau² = 1.49; Chi² = 31.58, df = 9 (P = 0.0002); I² = 72%
Test for overall effect: Z = 4.42 (P < 0.00001)



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 HDL cholesterol, were significantly greater in patients receiving olanzapine than those receiving aripiprazole in one study.[101] There was a significantly greater increase in mean triglycerides and in the ratio of triglycerides to HDL cholesterol for quetiapine than aripiprazole.[101] Olanzapine-treated patients experienced significantly more dyslipidemia than quetiapine-treated patients in one study.[101] Abnormal lipid profile favored quetiapine over risperidone 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[46,87,101,105] and five studies,[46,87,88,101,105] respectively. Ratio of triglycerides to HDL cholesterol was also significantly higher for quetiapine than risperidone in one study.[105]

Insulin resistance and diabetes. One study[101] 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 levels was significantly higher for patients treated with olanzapine than those treated with clozapine in a

meta-analysis of two studies.[64,112] Prolactin levels were high in a greater proportion of patients[72,96,99] and had a significantly higher mean[46,87,88] in patients treated with risperidone than patients treated with olanzapine in meta-analyses of three studies.

Neuromotor adverse events. Dyskinesia was experienced in a significantly greater proportion of patients treated with quetiapine than olanzapine or risperidone in one small study.[99]

Cardiac adverse events. Hypertension was significantly more common in the clozapine group than in the olanzapine group in two studies.[85,104]

Sedation. One study[96] found somnolence to occur significantly more frequently for patients receiving risperidone than for those receiving olanzapine.

Liver toxicity. Mean ALT and AST levels were significantly higher for patients treated with olanzapine than for those treated with risperidone in meta-analyses of two studies.[87,88]

Neutropenia and agranulocytosis. No significant differences between second generation antipsychotics were reported.

Thyroid dysfunction. Thyroid stimulating hormone levels were significantly higher in patients receiving quetiapine than in patients receiving risperidone based on one study.[105]

Behavioral side effects. No significant differences between second generation antipsychotics were reported.

Table 24. Significant findings for second generation versus second generation antipsychotics

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, -0.67)	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 triglyderides 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 triglyderides 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

ALT = alanine transaminase; AST = aspartate aminotransferase; BMI = body mass index; CI = confidence interval; HDL = high density lipoproteins; LDL = low density lipoproteins; MD = mean difference; N = number; ODT = orally disintegrating tablet; RR = relative risk; SOT = standard oral tablet; TSH = thyroid stimulating hormone; WAE = withdrawal due to adverse event
* denotes the drug with the better adverse event profile

Table 24. Significant findings for second generation versus second generation antipsychotics (continued)

Adverse Event	# studies	N (Drug 1)	N (Drug 2)	Effect estimate	95% CI	Favors*
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 (kg)	3	98	93	MD = 6.79	(1.4, 12.2)	Quetiapine
Weight–gain ≥7%	2	55	46	RR = 1.47	(1.1, 2.0)	Quetiapine
BMI	3	98	93	MD = 2.32	(0.5, 4.2)	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
Olanzapine (Drug 1) versus Risperidone (Drug 2)						
Total AE	3	73	126	RR = 0.87	(0.7, 1.0)	Olanzapine
Weight (kg)	10	226	353	MD = 2.35	(1.3, 3.4)	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
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 (ng/dL)	3	66	76	MD = -18.7	(-30.2, -7.2)	Olanzapine
Prolactin, high	3	54	104	RR = 0.26	(0.1, 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
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
Abnormal lipid profile	1	11	11	RR = 5.50	(1.6, 19.3)	Risperidone
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

Second generation drug dosing and formulation comparisons. Adverse event data were provided for dosing comparisons of the following drugs: aripiprazole,[53,54,69,103] paliperidone,[80] quetiapine,[45,74] risperidone,[57,58] and ziprasidone.[51] In addition, one study[102] compared orally disintegrating versus standard oral olanzapine tablets.

Four studies provided data on adverse events for comparisons of aripiprazole dosing.[53,54,69,103] One study[69] found a greater proportion of patients experiencing weight gain in moderate-dose (10 mg/day) aripiprazole compared with low-dose (5 mg/day). Extrapyramidal side effects were found to be significantly more frequent in patients receiving higher doses (30 mg) compared with those receiving lower doses (10 mg) in two studies.[53,54] In addition, QTc intervals decreased significantly in the high-dose aripiprazole (30 mg/day) groups compared with low-dose (10 mg/day).[53] One study[69] found higher incidence of fatigue in patients receiving

moderate- or high-dose aripiprazole (15 mg/day) compared with low-dose (5 mg/day) aripiprazole. No other significant differences were found.

One study[80] compared three doses of paliperidone. Total adverse events were significantly more common for the high-dose group versus the low/medium-dose group.

Two drug formulations for olanzapine were compared in one study.[102] Weight and BMI increased significantly more in patients receiving the standard oral tablet than in patients receiving the orally disintegrating tablet.

Two studies[45,74] reported adverse events comparing low-dose and high-dose quetiapine, and no significant differences were found.

Two studies[57,58] compared low-dose and high-dose risperidone. Weight gain, prolactin elevation, extrapyramidal symptoms (including dystonia and hyperkinesia), and somnolence were experienced by significantly more patients receiving lower doses (0.001-0.05 mg/kg/day and 0.5-2.5 mg/day) compared with higher doses (0.01-0.5 mg/kg/day and 3-6 mg/day). In addition, one study[57] found significantly higher mean triglyceride levels and significantly lower prolactin levels in the low-dose group.

One study[51] 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 (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.[48,78,82] In two studies, mean time to adverse event resolution was reported for akathesia[48,82] and somnolence.[82] Akathesia resolved in 48 hours for quetiapine-treated patients[48] in one study and ziprasidone-treated patients in another study. In ziprasidone-treated patients, somnolence resolved in 20 days.[82] 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.[78]

Placebo comparisons

Adverse event data were reported in 34 placebo-controlled studies. First generation antipsychotics were compared with placebo in two studies,[81,90] while second generation antipsychotics were compared with placebo in 32 studies.[40,41,43,47,48,50,52-55,57,59,60,63,67,69,70,73-76,79,80,82,84,86,89,92-95,97] All adverse event data are provided in Appendix I. Summary tables highlighting the significant findings are provided below.

Summary. The following is a summary of adverse event findings for placebo-controlled studies examining first generation and second generation antipsychotics:

First generation antipsychotics:

- One study[81] reported significantly more treatment-limiting adverse events and sedation in haloperidol than placebo. The same study found prolactin levels to be significantly higher for haloperidol and pimozide than for placebo.
- No significant differences were reported for weight, neuromotor, cardiac, or behavioral adverse events.

Second generation antipsychotics:

- Significantly fewer patients in the placebo group experienced adverse events compared with those in the aripiprazole group,[54,69] quetiapine,[74] risperidone,[41,43,47,55,57,79,86,89,95] and ziprasidone.[75,76,82]
- Meta-analyses found that mean weight gain was significantly higher for patients treated with aripiprazole, olanzapine, quetiapine, and risperidone compared with placebo. No significant difference was found between ziprasidone and placebo.
- Placebo was favored over aripiprazole[54,69] and olanzapine[92] for cholesterol elevation, and over olanzapine[63,92] and quetiapine for triglyceride elevation.[50,74]
- Prolactin levels were significantly decreased with aripiprazole compared with placebo,[53,54,69] yet levels increased with olanzapine[63,92] and risperidone compared with placebo.[41,47,57,67,70,79,89] No difference was found for quetiapine and placebo.
- Extrapyramidal symptoms were more frequent or severe in patients treated with aripiprazole, quetiapine, risperidone, and ziprasidone compared with placebo.
- Rate of tachycardia was higher among patients treated with quetiapine[50,74] and risperidone[70,89] versus placebo in two meta-analyses. Blood pressure and pulse were lower for placebo versus olanzapine, quetiapine, and risperidone.
- Sedation, somnolence, or fatigue were more common among patients treated with various second generation antipsychotics (i.e., aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone) compared with placebo.
- One study found higher mean levels of ALT, AST, and gamma-glutamyl transpeptidase with olanzapine treatment versus placebo.[92]
- White blood cell count was significantly lower in patients treated with quetiapine than placebo in one study.[52]
- Constipation occurred significantly more frequently among patients treated with risperidone versus placebo in a meta-analysis of three studies.[67,70,86]
- One study reported higher rates of schizophrenia as an adverse event for placebo versus olanzapine.[63]
- No differences were found between second generation antipsychotics and placebo for cerebrovascular event, insulin resistance or diabetes, and thyroid dysfunction.

First generation antipsychotics versus placebo. Two studies reported on the relative rates of adverse events between first generation antipsychotics and placebo. First generation drug comparisons with placebo included haloperidol in two studies,[81,90] and pimozide in one study.[81] 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 25.

Total adverse events. Treatment-limiting adverse events occurred in a significantly greater proportion of patients treated with haloperidol compared with placebo.[81]

Weight gain/body composition. No significant differences between first generation antipsychotics and placebo were reported.

Prolactin-related and sexual adverse events. Prolactin levels were significantly higher in patients treated with haloperidol and pimozide compared with placebo.[81]

Neuromotor adverse events. No significant differences between first generation antipsychotics and placebo were reported.

Cardiac adverse events. No significant differences between first generation antipsychotics and placebo were reported.

Sedation. One study[81] found a significantly greater rate of drowsiness in the haloperidol group compared with placebo.

Behavioral side effects. No significant differences between first generation antipsychotics and placebo were reported.

Table 25. Significant findings for first generation antipsychotics 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	(7.09, 22.5)	Placebo

CI = confidence interval; MD = mean difference; N = number; RR = relative risk; SE = side effect
* denotes the drug with the better adverse event profile

Second generation antipsychotics versus placebo. Thirty-three studies reported the relative rates of adverse events between second generation antipsychotics and placebo. Second generation drug comparisons included aripiprazole,[53,54,69,93] olanzapine,[60,63,92,97,114] paliperidone,[80] quetiapine,[48,50,52,74] risperidone,[40,41,43,47,55,57,59,67,70,73,79,84,86,89,94,95] and ziprasidone.[75,76,82] The following adverse events were not reported: mortality, cerebrovascular events, seizures, neuroleptic malignant syndrome, exercise intolerance, precocious puberty, and dermatological adverse events. Effect estimates and 95 percent confidence intervals for the significant findings are presented in Table 26.

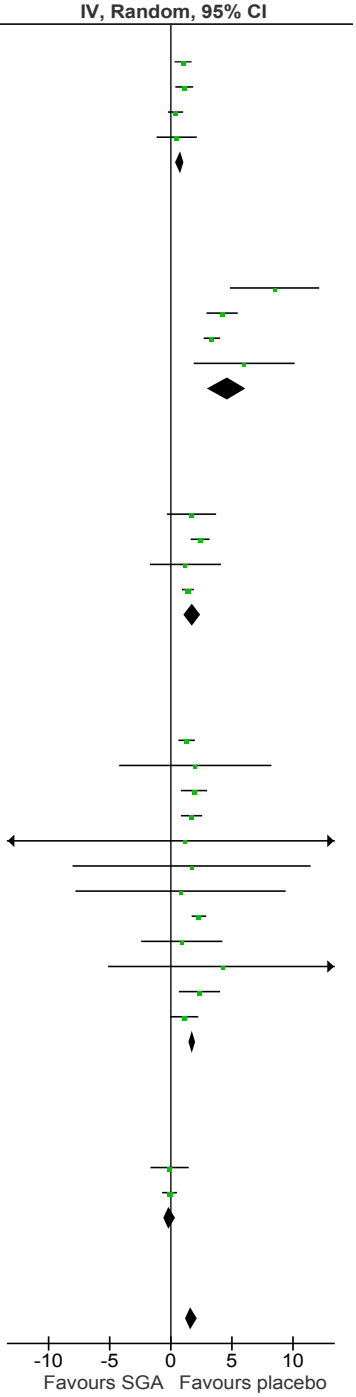
Total adverse events. Total adverse events were significantly higher for patients treated with aripiprazole compared with placebo in a meta-analysis of two studies.[54,69] A significantly greater number of patients receiving quetiapine experienced any adverse event compared with placebo.[74] A meta-analysis of nine studies[41,43,47,55,57,79,86,89,95] showed a significantly greater number of patients in the risperidone group experienced an adverse event compared with the placebo group. Treatment with ziprasidone resulted in significantly more patients with adverse events than placebo in a meta-analysis of three studies.[75,76,82]

Weight gain/body composition. A meta-analysis of two studies[53,69] 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[53,54,69,93] (Figure 33) and change in BMI.[53,54,69] Overall weight gain and weight gain of greater than seven percent occurred significantly more frequently in olanzapine-treated patients compared with placebo in a meta-analysis of four studies.[60,63,92,97] Similarly, mean weight gain and change in BMI favored placebo over olanzapine (Figure 33). Quetiapine-treated patients experienced weight gain greater than seven percent more frequently than placebo-treated patients[74] and had greater increase in mean weight and BMI compared with placebo. Risperidone-treated patients showed a

significantly greater increase in mean weight in a meta-analysis of 12 studies[41,43,47,57,59,67,70,73,79,86,89,95] (MD = 1.79; 95% CI: 1.48 to 2.10) (Figure 33) and BMI in a meta-analysis of five studies.[43,57,70,79,89]

Figure 33. Second generation antipsychotics versus placebo for mean weight gain (kg)

Study or Subgroup	SGA Mean	SGA SD	SGA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
2.21.1 Aripiprazole								
17	0.2	2.6	196	-0.8	2.6	98	6.0%	1.00 [0.37, 1.63]
2417	1.4	2.1	165	0.3	2.1	51	6.0%	1.10 [0.44, 1.76]
286	0.95	2.14	148	0.56	2.14	97	6.1%	0.39 [-0.16, 0.94]
296	1.2	2.6	18	0.72	2.6	25	4.1%	0.48 [-1.10, 2.06]
Subtotal (95% CI)			**527**			**271**	**22.2%**	**0.77 [0.40, 1.15]**
Heterogeneity: Tau² = 0.02; Chi² = 3.45, df = 3 (P = 0.33); I² = 13%								
Test for overall effect: Z = 4.03 (P < 0.0001)								
2.21.2 Olanzapine								
1076	8.79	9.05	30	0.3	4.24	29	1.6%	8.49 [4.90, 12.08]
351	4.3	3.3	72	0.1	2.8	34	4.8%	4.20 [2.99, 5.41]
526	3.66	2.18	107	0.3	1.67	54	6.0%	3.36 [2.75, 3.97]
732	7.5	4.8	6	1.5	1.5	5	1.3%	6.00 [1.94, 10.06]
Subtotal (95% CI)			**215**			**122**	**13.8%**	**4.60 [3.07, 6.13]**
Heterogeneity: Tau² = 1.37; Chi² = 9.94, df = 3 (P = 0.02); I² = 70%								
Test for overall effect: Z = 5.89 (P < 0.00001)								
2.21.3 Quetiapine								
1334	4.2	3.2	15	2.5	2.1	15	3.4%	1.70 [-0.24, 3.64]
20035	2	3.2	147	-0.4	2.1	75	5.9%	2.40 [1.70, 3.10]
237	2.3	3.2	9	1.1	3.1	10	2.2%	1.20 [-1.64, 4.04]
67	2.3	0.6	17	0.9	0.6	15	6.3%	1.40 [0.98, 1.82]
Subtotal (95% CI)			**188**			**115**	**17.8%**	**1.78 [1.10, 2.47]**
Heterogeneity: Tau² = 0.21; Chi² = 5.86, df = 3 (P = 0.12); I² = 49%								
Test for overall effect: Z = 5.12 (P < 0.00001)								
2.21.4 Risperidione								
1017	2.2	1.8	55	0.9	1.5	63	6.0%	1.30 [0.70, 1.90]
1335	39.9	15.41	38	37.9	11.9	39	0.6%	2.00 [-4.16, 8.16]
1380	2.7	2.9	49	0.8	2.2	52	5.3%	1.90 [0.89, 2.91]
1390	2.7	2	40	1	1.6	38	5.7%	1.70 [0.90, 2.50]
1726	1.8	17.3	6	0.6	12.1	7	0.1%	1.20 [-15.29, 17.69]
1776	2.3	17.3	19	0.6	12.1	17	0.3%	1.70 [-7.97, 11.37]
5152	35.4	9.6	12	34.6	12.1	13	0.3%	0.80 [-7.73, 9.33]
524	2.1	2.7	172	-0.2	2.2	163	6.2%	2.30 [1.77, 2.83]
66	1.6	17.3	111	0.7	1.9	58	1.8%	0.90 [-2.36, 4.16]
716	48.4	17.3	24	44.1	14	19	0.3%	4.30 [-5.06, 13.66]
729	2.96	2.53	11	0.61	1.1	12	4.0%	2.35 [0.73, 3.97]
749	2.81	2.04	19	1.71	1.3	20	5.1%	1.10 [0.02, 2.18]
Subtotal (95% CI)			**556**			**501**	**35.8%**	**1.79 [1.48, 2.10]**
Heterogeneity: Tau² = 0.00; Chi² = 8.89, df = 11 (P = 0.63); I² = 0%								
Test for overall effect: Z = 11.27 (P < 0.00001)								
2.21.5 Ziprasidone								
1850	0.7	1.5	16	0.8	2.3	12	4.3%	-0.10 [-1.59, 1.39]
20031	0.7	1.5	149	0.8	2.3	88	6.2%	-0.10 [-0.64, 0.44]
Subtotal (95% CI)			**165**			**100**	**10.4%**	**-0.10 [-0.61, 0.41]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%								
Test for overall effect: Z = 0.39 (P = 0.70)								
Total (95% CI)			**1651**			**1109**	**100.0%**	**1.71 [1.19, 2.23]**
Heterogeneity: Tau² = 1.06; Chi² = 152.89, df = 25 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 6.47 (P < 0.00001)								



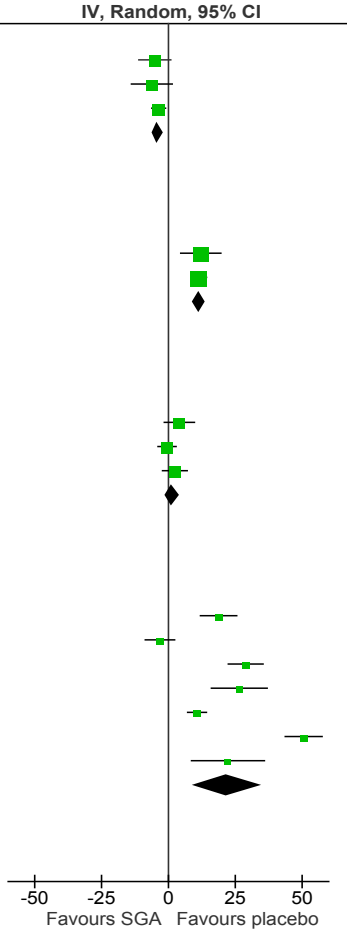
Dyslipidemia. Total cholesterol levels were elevated in a significantly greater proportion of patients treated with aripiprazole than those receiving placebo.[54] Two meta-analyses found elevated triglycerides[63,92] and abnormal cholesterol[92] to be significantly more frequent with olanzapine than placebo. Mean triglycerides levels were higher for olanzapine in one study[63] and for quetiapine in two studies.[50,74]

Insulin resistance and diabetes. No significant differences between second generation antipsychotics and placebo were reported.

Prolactin-related and sexual adverse events. Mean prolactin levels showed greater decrease with aripiprazole than with placebo in a meta-analysis of three studies (Figure 34).[53,54,69] The proportion of patients with high prolactin as well as mean prolactin levels (Figure 34) were significantly greater for olanzapine versus placebo in a meta-analysis of two studies.[63,92] No significant difference was seen for prolactin levels between quetiapine and placebo. Placebo was significantly favored over risperidone for change in prolactin levels in a meta-analysis of seven studies (Figure 34).[41,47,57,67,70,79,89]

Figure 34. Second generation antipsychotics versus placebo for change in prolactin levels (ng/mL)

Study or Subgroup	SGA Mean	SGA SD	SGA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
2.29.1 Aripiprazole								
17	-13.55	24.23	190	-8.45	24.23	96	33.2%	-5.10 [-11.05, 0.85]
2417	-5.3	24.23	165	0.9	24.23	51	32.0%	-6.20 [-13.81, 1.41]
286	-3.75	6.35	68	-0.11	6.35	37	34.8%	-3.64 [-6.18, -1.10]
Subtotal (95% CI)			**423**			**184**	**100.0%**	**-4.07 [-6.30, -1.83]**
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 2 (P = 0.77); I² = 0%								
Test for overall effect: Z = 3.57 (P = 0.0004)								
2.29.2 Olanzapine								
351	8.8	17.9	55	-3.3	14.8	25	48.0%	12.10 [4.61, 19.59]
526	13.168	11.612	107	1.777	6.749	54	52.0%	11.39 [8.55, 14.23]
Subtotal (95% CI)			**162**			**79**	**100.0%**	**11.48 [8.82, 14.14]**
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%								
Test for overall effect: Z = 8.47 (P < 0.00001)								
2.29.3 Quetiapine								
1334	-1.6	6.9	15	-5.7	8.7	15	32.8%	4.10 [-1.52, 9.72]
237	7.1	2.7	10	7.6	4.7	10	33.9%	-0.50 [-3.86, 2.86]
67	2.47	8.53	17	0.05	4.27	15	33.3%	2.42 [-2.17, 7.01]
Subtotal (95% CI)			**42**			**40**	**100.0%**	**1.30 [-1.35, 3.95]**
Heterogeneity: Tau² = 0.71; Chi² = 2.28, df = 2 (P = 0.32); I² = 12%								
Test for overall effect: Z = 0.96 (P = 0.34)								
2.29.4 Risperidione								
1017	27.139	21.244	41	8.372	6.777	53	14.7%	18.77 [12.01, 25.52]
1335	11.65	22.4	76	14.805	9.5	78	15.1%	-3.15 [-8.61, 2.30]
1380	39	19.2	42	10.1	8.8	36	14.8%	28.90 [22.42, 35.38]
1776	33.4	22.4	19	6.9	5.4	17	13.3%	26.50 [16.11, 36.89]
524	20.3	21.3	172	9.6	9.5	163	15.5%	10.70 [7.20, 14.20]
66	51.682	22.4	44	1.109	6.807	53	14.6%	50.57 [43.71, 57.44]
729	33.38	14.48	11	11.11	18.74	12	12.0%	22.27 [8.64, 35.90]
Subtotal (95% CI)			**405**			**412**	**100.0%**	**21.94 [8.91, 34.98]**
Heterogeneity: Tau² = 292.83; Chi² = 173.57, df = 6 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 3.30 (P = 0.0010)								



Neuromotor adverse events. Extrapyramidal side effects, including Parkinsonism and residual events, occurred significantly more frequently with aripiprazole than with versus

placebo in a meta-analysis of four studies.[53,54,69,93] Extrapyramidal symptoms were significantly more common among risperidone-treated patients compared with patients receiving placebo in a meta-analysis of eight studies.[41,55,57,70,79,84,86,89] Similarly, extrapyramidal symptom scores were significantly lower for placebo than for risperidone treated patients in two studies.[57,70] One study[76] 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[50,74] and risperidone treatment[70,89] than placebo. Supine systolic blood pressure[92] and pulse[92,97] were significantly lower for placebo than for olanzapine. Blood pressure and pulse were significantly higher with quetiapine than with placebo in one study.[50] A meta-analysis of four studies[40,86,89,95] showed a greater increase in pulse with risperidone than placebo.

Sedation. Sedation[69] and somnolence[53,54,69,93] occurred significantly more frequently in the aripiprazole group than in the placebo group. Rate of fatigue[97] was significantly higher with olanzapine than with placebo. Somnolence was significantly more common among patients treated with quetiapine than placebo.[74] Two meta-analyses showed rates of sedation[41,55,57,67,73] and fatigue[47,57,70,79,86,89] occurred significantly more frequently for risperidone than for placebo. Ziprasidone resulted in significantly greater rates of somnolence[75,76,82] and fatigue[75,76] than placebo.

Liver toxicity. Patients treated with olanzapine experienced elevated ALT and AST significantly more frequently than patients who received placebo in one study.[92] Mean ALT, AST, and gamma-glutamyl transpeptidase levels were significantly higher with olanzapine than with placebo.[63,92]

Neutropenia and agranulocytosis. White blood cell count was significantly lower in patients treated with quetiapine than in those receiving placebo.[52]

Thyroid dysfunction. No significant differences between second generation antipsychotics and placebo were reported.

Constipation. A meta-analysis of three studies[67,70,86] showed that constipation occurred significantly more frequently among patients treated with risperidone than those receiving placebo.

Behavioral adverse events. One study reported higher incidence of schizophrenia as an adverse event in the placebo group compared with the olanzapine group.[63]

Table 26. Significant findings for second generation antipsychotics 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	(0.40, 1.15)	Placebo
Weight gain	1	361	149	RR = 3.81	(1.2, 12.4)	Placebo
BMI	3	508	214	MD = 0.23	(0.07, 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
EPS residual event	2	399	197	RR = 3.98	(2.2, 7.1)	Placebo

AE = adverse event; AIMS = abnormal involuntary movement scale; ALT = alanine transaminase; AST = aspartate aminotransferase; BMI = body mass index; CI = confidence interval; DBP = diastolic blood pressure; EPS = extrapyramidal symptom; GGT = gamma-glutamyl transpeptidase; HDL = high density lipoproteins; LDL = low density lipoproteins; MD = mean difference; N = number; RR = relative risk; SAS = Simpson Angus Rating Scale; WBC = white blood cell; WAE = withdrawal due to adverse event

* denotes the drug with the better adverse event profile

Table 26. Significant findings for second generation antipsychotics versus placebo (continued)

Adverse Event	# studies	N (Drug 1)	N (Drug 2)	Effect estimate	95% CI	Favors*
Aripiprazole (Drug 1) versus Placebo (Drug 2) (continued)						
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	(3.07, 6.13)	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, 1.59)	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
Schizophrenia	1	72	35	RR = 0.28	(0.09, 0.9)	Olanzapine
Quetiapine (Drug 1) versus Placebo (Drug 2)						
Total AE	1	113	147	RR = 1.28	(1.0, 1.6)	Placebo
Weight (kg)	4	188	115	MD = 1.78	(1.10, 2.47)	Placebo
Weight–gain ≥7%	1	30	147	RR = 3.06	(1.2, 7.6)	Placebo
BMI	1	17	15	MD = 0.6	(0.4, 0.8)	Placebo
Triglyceride (mg/dL)	2	164	90	MD = 29.1	(7.27, 50.9)	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	(5.68, 22.3)	Placebo
Tachycardia	2	164	90	RR = 8.24	(1.1, 62.0)	Placebo
WBC (10^3/µL)	1	15	15	MD = -1.5	(-2.0, -1.0)	Placebo
Somnolence	1	147	75	RR = 4.29	(1.8, 10.4)	Placebo
Risperidone (Drug 1) versus Placebo (Drug 2)						
Total AE	9	463	411	RR = 1.25	(1.0, 1.5)	Placebo
Weight (kg)	12	556	501	MD = 1.79	(1.48, 2.10)	Placebo
BMI	5	397	343	MD = 0.57	(0.38, 0.75)	Placebo
Prolactin (ng/mL)	7	405	412	MD = 21.94	(8.91, 35.0)	Placebo
EPS (Barnes)	1	109	57	MD = 0.22	(0.08, 0.4)	Placebo
EPS (SAS)	2	157	109	MD = 0.22	(0.11, 0.33)	Placebo
EPS	8	431	380	RR = 2.65	(1.4, 4.9)	Placebo
Pulse	4	114	117	MD = 6.42	(3.5, 9.35)	Placebo
Tachycardia	2	89	90	RR = 7.53	(1.4, 40.5)	Placebo
Sedation	5	206	163	RR = 2.90	(1.5, 5.5)	Placebo

Table 26. Significant findings for second generation antipsychotics versus placebo (continued)

Adverse Event	# studies	N (Drug 1)	N (Drug 2)	Effect estimate	95% CI	Favors*
Risperidone (Drug 1) versus Placebo (Drug 2) (continued)						
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

Question 3: Other Short-term and Long-term Outcomes

Fifty-two studies examined the efficacy or effectiveness of antipsychotics for other short- and long-term outcomes. Data were provided for the following conditions: pervasive developmental disorders (nine studies), ADHD and disruptive behavior disorders (eight studies), bipolar disorder (nine studies), schizophrenia (17 studies), psychosis (four studies), Tourette syndrome (four studies), and behavioral symptoms (two studies). In addition, one study[51] provided separate data for both bipolar disorder and schizophrenia.

Pervasive Developmental Disorders

Summary. Nine studies provided data on a variety of short- and long-term outcomes for patients with pervasive developmental disorders. The following is a summary of the results by outcome:

- *Response and remission*. Response rate did not differ between haloperidol and olanzapine in one RCT[68] or between continuous and discontinuous administration of haloperidol in another.[77] A meta-analysis of five RCTs[60,69,70,73,86] comparing second generation antipsychotics with placebo found a significantly higher response rate in patients receiving second generation antipsychotics (RR = 2.69; 95% CI, 1.52 to 4.74). The relapse rate was significantly lower for risperidone compared with placebo in two RCTs (RR = 0.31; 95% CI, 0.13 to 0.73), as was the time to relapse (p = 0.01).[70,94]
- *Cognitive and emotional development*. Two RCTs[70,94] 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.[70] Similarly, reaction time did not differ between groups.[94]
- *Suicide-related behaviors.* One RCT[69] comparing three doses of aripiprazole with placebo found no suicide-related behaviors (including ideation) in the aripiprazole groups, while three patients in the placebo group experienced suicide-related behaviors. This finding was statistically significant (p = 0.04). There was insufficient evidence upon which to draw a conclusion.
- *Medication adherence and persistence.* Medication adherence was reported in two RCTs[69,70] comparing second generation antipsychotics with placebo. The strength of evidence supporting no difference in the adherence rate of the groups was considered low.
- *Patient or parent/care provider reported outcomes.* One RCT[70] 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). There was insufficient evidence upon which to draw a conclusion.
- *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.

Results by individual study. Nine studies (eight RCTs[60,68-70,73,77,86,94] and one retrospective cohort study[113]) examined the effect of first generation and second generation antipsychotics on short- and long-term outcomes in patients with pervasive developmental disorders. The number of participants ranged from 11 to 218 (median = 40 [IQR, 24 to 80]). Two studies provided data comparing first generation with second generation antipsychotics,[68,113] one study compared two doses of a first generation drug,[77] two studies compared various second generation antipsychotics,[69,113] and six studies compared second generation antipsychotics with placebo.[60,69,70,73,86,94] Patient and study characteristics and outcome data are presented in Table 27 and Table 28, respectively.

First generation versus second generation antipsychotics. One RCT[68] compared haloperidol with olanzapine and a retrospective cohort study[113] compared various first generation with second generation drugs. Since all except one patient received first generation antipsychotics in combination with second generation antipsychotics, no outcome data for this comparison were provided.

Malone et al.[68] conducted an RCT investigating the efficacy of haloperidol versus olanzapine. Twelve children (aged 5 to 17 years) were randomized to haloperidol (6 patients) or olanzapine (6 patients) for 6 weeks. The primary diagnoses using the DSM-IV criteria were autism (11 patients) and pervasive developmental disorders NOS (1 patient). Eleven patients had various degrees of mental retardation: mild (n = 1), moderate (n = 5), or severe (n = 5). Mean doses were 1.4±0.7 mg/day for haloperidol and 7.9±2.5 mg/day for olanzapine. Response rate (defined as CGI-I score ≤2) was similar in both groups.

First generation versus first generation antipsychotics. One study[77] compared two dosing regimens of haloperidol in children (aged 2 to 8 years) diagnosed with infantile autism using DSM-III criteria. Autistic children with delays in intellectual functioning were randomized to continuous (n = 34) or discontinuous (n = 36) haloperidol for 6 months. The discontinuous drug administration schedule consisted of 5 days on haloperidol and 2 days on placebo. The prescribed dose of haloperidol was not significantly different between the groups (1.2 mg/day in the continuous group and 1.0 mg/day in the discontinuous group). Treatment response measured by CGI-I (score ≤2) and CGI-S (difference score ≤2) was not statistically significantly different between the groups.

Second generation versus second generation antipsychotics. Marcus et al.[69] evaluated the efficacy of aripiprazole in children and adolescents (aged 6 to 17 years) with irritability associated with autistic disorder based on DSM-IV-TR and ADI-R criteria. Patients were randomized to placebo (n = 52) and three fixed-dose regimens of aripiprazole: 5 mg/day (n = 53), 10 mg/day (n = 59), and 15 mg/day (n = 54). There was no significant difference between the aripiprazole doses for treatment response, suicide-related behaviors, and adherence rate at 8 weeks.

Novaes et al.[113] conducted a retrospective cohort study to evaluate the efficacy of first and second generation antipsychotics in patients with autistic spectrum disorder diagnosed using DSM-IV criteria. Twenty-six patients (aged 4 to 21 years) were included; mental retardation was present in 20. Eighteen patients were treated with risperidone (n = 13) or risperidone in combination with first generation antipsychotics (n = 5). Four patients were treated exclusively with other second generation antipsychotic drugs; one was treated exclusively with first generation antipsychotic drugs, and three were treated with a combination of first and second generation antipsychotics. Response rate (defined by CGI-I score ≤2) was not significantly different between patients treated with risperidone (with or without a first generation

antipsychotic) compared with patients treated with second generation antipsychotics other than risperidone (with or without a first generation antipsychotic).

Second generation antipsychotics versus placebo. Six studies compared second generation antipsychotics with placebo: aripiprazole,[60] olanzapine,[69] and risperidone.[70,73,86,94]

Hollander et al.[60] assessed the efficacy of olanzapine and placebo in children (aged 6 to 14 years) with pervasive developmental disorders. Patients were diagnosed with autism (n = 6), Asperger syndrome (n = 1), or pervasive developmental disorder NOS (n = 4) based on DSM-IV, ADI-R, and Autism Diagnostic Observation Schedule criteria. Eleven patients were randomized to olanzapine (n = 6, mean dose: 10±2 mg/day) or placebo (n = 5) for 8 weeks. Patients with normal cognitive functioning (n = 4) and those with mental retardation were included. Response rate, based on CGI-I and CPRS ratings, was not significantly different between groups.

Marcus et al.[69] compared three doses of aripiprazole with placebo (described previously). Treatment response rate (defined as ≥25 percent reduction in ABC-I and CGI-I ≤2) was significantly greater with 5 mg/day aripiprazole compared with placebo (p = 0.04), but there was no significant difference between the medium- (10 mg/day) and high-dose (15 mg/day) aripiprazole groups versus placebo. One patient in each group showed nonadherence to medication; there were no differences between groups. Suicide-related behaviors were reported by three patients in the placebo group and none in the aripiprazole groups; this result significantly favored the aripiprazole groups (p = 0.04).

An RCT conducted by McCracken et al.[70] evaluated the efficacy of risperidone compared with placebo for the treatment of behavioral disturbances in children (aged 5 to 17 years) with autistic disorder based on the DSM-IV and ADI-R criteria. Participants were randomly assigned to receive risperidone (n = 49) or placebo (n = 52) for 8 weeks. The mean daily dose of risperidone was 1.8±0.7 mg. Patients with borderline (n = 12), mild/moderate (n = 43), and severe (n = 31) mental retardation were included. Patients assigned to the placebo group who did not improve were offered an 8-week open-label trial of risperidone. After a 4-month open-label extension phase for all patients, risperidone responders were randomized to risperidone or placebo substitution for a 2-month discontinuation phase. Response rate (≥25% reduction in ABC-I and CGI-I ≤2) was significantly higher in the risperidone-treated patients compared with placebo (p<0.001) at 8 weeks. One child in the placebo group was nonadherent to the study protocol during the 8 weeks of the study. Cognitive effects were evaluated in a subset of patients, and risperidone showed no detrimental effect on cognitive performance. Compared with placebo, no statistically significant declines for risperidone were noted 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). There were no statistically significant differences in sleep time increases between the treatment groups. In the discontinuation phase of the study, remission rate (≥25 percent increase in ABC-I and CGI-I ≥2 compared with prediscontinuation baseline for 2 consecutive weeks) was significantly higher in the placebo group than in the risperidone group (p = 0.01). Time to relapse was 34 days with placebo versus 57 days with risperidone; the significance of this result was not reported.

Nagaraj et al.[73] conducted an RCT to evaluate the efficacy of risperidone compared with placebo in children (aged 2 to 9 years) diagnosed with autism according to DSM-IV criteria. Forty participants were randomized to risperidone at 1 mg/day (n = 19) or placebo (n = 21) for 6 months. All children had severe language impairment and behavioral complaints (irritability [n = 36], aggression [n = 20], self-injurious behavior [n = 12]); eight patients had seizures. Response rate (>20 percent improvement from baseline on CARS and CGAS) was significantly higher in

the risperidone group compared with placebo ($p<0.01$). Response rate according to improvement on CGI was not significantly different between the groups.

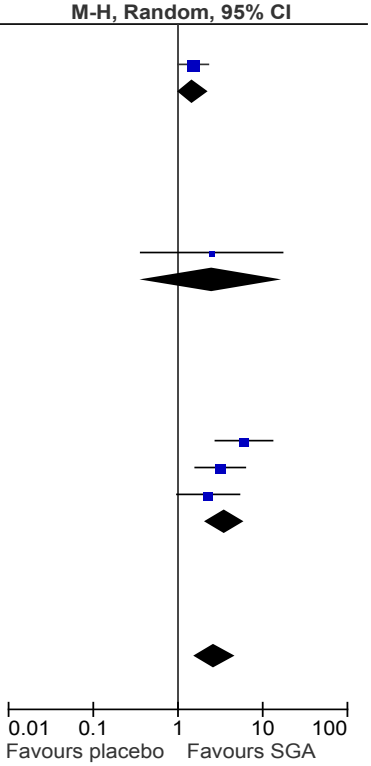
Shea et al.[86] evaluated the efficacy of risperidone for treating behavioral symptoms in children (aged 5 to 12 years) with pervasive developmental disorders based on DSM-IV criteria. Children were randomized to risperidone (n = 41, mean daily dose: 1.2 mg) or placebo (n = 39) for 8 weeks. Patients had the following diagnoses: autistic disorder (n = 55), Asperger syndrome (n = 12), childhood disintegrative disorder (n = 1), and pervasive developmental disorders NOS (n = 11). Mental retardation was present in 27 children. The response rate (≥50 percent reduction in two of five ABC subscales) was significantly higher in children treated with risperidone versus placebo ($p = 0.01$). Composite response (≥25 percent improvement on ABC-I and CGI-I score ≤2) was achieved by significantly more patients given risperidone versus placebo ($p = 0.008$).

Troost et al.[94] evaluated the efficacy of risperidone in children (aged 5 to 17 years) with autism spectrum disorders based on DSM-IV-TR and ADI-R criteria in a discontinuation study. Twenty-four risperidone short-term responders (assessed at 8 weeks) were randomly assigned to continued active treatment (n = 12) or gradual placebo withdrawal (n = 12) consisting of 3 weeks of taper and 5 weeks of placebo alone. Patients had autistic disorder (n = 6), Asperger syndrome (n = 2), and pervasive developmental disorder NOS (n = 16); two patients had mental retardation. The mean daily dose of risperidone before randomization was 1.9±0.7 mg for continued active risperidone group and 1.7±0.5 mg for the placebo group. The risperidone group was superior to the placebo group in preventing relapse (defined as ≥25 percent ABC-I and CGI-I ≥6 for 2 consecutive weeks) ($p = 0.05$). Mean time to relapse was longer in patients in the risperidone group compared with the placebo group ($p = 0.01$). Neuropsychological effects of risperidone as measured by a focused-attention task were not significantly different between the groups.

Five RCTs contributed data on response rate for a comparison of second generation antipsychotics and placebo (Figure 35). Second generation antipsychotics were favored in the one aripiprazole study (RR = 1.51; 95% CI, 1.00 to 2.28)[69] and in a pooled estimate of three risperidone studies (RR = 3.54; 95% CI, 2.06 to 6.10).[70,73,86] One RCT[60] comparing olanzapine and placebo showed no significant difference between groups. Overall, the combined estimate based on all studies showed a significantly higher response rate in patients receiving second generation antipsychotics than placebo (RR = 2.69; 95% CI, 1.52 to 4.74). There was substantial heterogeneity ($p = 0.03$, $I^2 = 64$ percent), which may be attributable to differences in drug comparator and dosing, as well as differences in patient ages.

Figure 35. Second generation antipsychotics versus placebo on response rate in pervasive developmental disorders

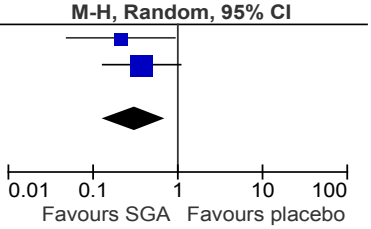
Study or Subgroup	SGA Events	SGA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Aripiprazole						
Marcus 2009	86	164	17	49	29.3%	1.51 [1.00, 2.28]
Subtotal (95% CI)		**164**		**49**	**29.3%**	**1.51 [1.00, 2.28]**
Total events	86		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.97 (P = 0.05)						
6.1.2 Olanzapine versus placebo						
Hollander 2006	3	6	1	5	6.9%	2.50 [0.36, 17.17]
Subtotal (95% CI)		**6**		**5**	**6.9%**	**2.50 [0.36, 17.17]**
Total events	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.93 (P = 0.35)						
6.1.3 Risperidone versus placebo						
McCracken 2002	34	49	6	52	21.0%	6.01 [2.77, 13.06]
Nagaraj 2006	18	19	6	20	23.2%	3.16 [1.60, 6.22]
Shea 2004	14	40	6	39	19.5%	2.27 [0.97, 5.32]
Subtotal (95% CI)		**108**		**111**	**63.7%**	**3.54 [2.06, 6.10]**
Total events	66		18			
Heterogeneity: Tau² = 0.08; Chi² = 3.03, df = 2 (P = 0.22); I² = 34%						
Test for overall effect: Z = 4.57 (P < 0.00001)						
Total (95% CI)		**278**		**165**	**100.0%**	**2.69 [1.52, 4.74]**
Total events	155		36			
Heterogeneity: Tau² = 0.24; Chi² = 10.99, df = 4 (P = 0.03); I² = 64%						
Test for overall effect: Z = 3.42 (P = 0.0006)						
Test for subgroup differences: Not applicable						



Two RCTs[70,94] comparing risperidone with placebo provided data for a meta-analysis on relapse rate. 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 percent).

Figure 36. Second generation antipsychotics versus placebo on relapse rate in pervasive developmental disorders

Study or Subgroup	SGA Events	SGA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
McCracken 2002	2	49	10	52	34.2%	0.21 [0.05, 0.92]
Troost 2005	3	12	8	12	65.8%	0.38 [0.13, 1.08]
Total (95% CI)		**61**		**64**	**100.0%**	**0.31 [0.13, 0.73]**
Total events	5		18			
Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%						
Test for overall effect: Z = 2.68 (P = 0.007)						



Two RCTs comparing aripiprazole[69] and risperidone[70] with placebo were combined in a meta-analysis for adherence rate (Figure 37). There was no statistically significant difference in adherence to study medication (RR = 0.66; 95% CI, 0.11 to 4.11) and no evidence of heterogeneity (p = 0.64, I^2 = 0 percent).

Figure 37. Second generation antipsychotics versus placebo on adherence rate in pervasive developmental disorders

Study or Subgroup	SGA Events	SGA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Marcus 2009	3	164	1	49	66.8%	0.90 [0.10, 8.42]
McCracken 2002	0	49	1	52	33.2%	0.35 [0.01, 8.47]
Total (95% CI)		**213**		**101**	**100.0%**	**0.66 [0.11, 4.11]**
Total events	3		2			

Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%

Test for overall effect: Z = 0.45 (P = 0.65)

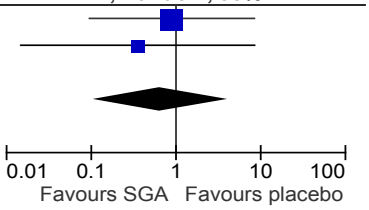


Table 27. Study and patient characteristics for studies examining pervasive developmental disorders

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Hollander, 2006[60] RCT, 8 wk	**G1:** Olanzapine (6), 10±2 mg/day **G2:** Placebo (5)	**G1:** 9.3±2.9 (6-14.8) yr / Male: all / Caucasian: 50% **G2:** 8.9±2.1 (6.1-11) yr / Male: 60% / Caucasian: 80% Comorbidities: MR (mild (5), severe (2))	Asperger syndrome (1), autism (6), PDD NOS (4) NR, NR
Malone, 2001[68] RCT, 6 wk	**G1:** Haloperidol (6), 1.4±0.7 mg/day **G2:** Olanzapine (6), 7.9±2.5 mg/day	**G1:** 7.3±1.9 (5-10.1) yr / Male: 67% / Caucasian: 67% **G2:** 8.5±2.4 (4.9-11.8) yr / Male: 67% / Caucasian: 50% Comorbidities: MR (mild (1), moderate (5), severe (5))	autistic disorder (11), PDD NOS (1) NR, 3
Marcus, 2009[69] RCT, 8 wk	**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% / Caucasian: 70% **G2:** 10.0±3.2 yr / Male: 85% / Caucasian: 70% **G3:** 9.5±3.1 yr / Male: 93% / Caucasian: 78% **G4:** 10.2±3.1 / Male: 92% / 67% Comorbidities: NR	autistic disorder NR, 172
McCracken, 2002[70] RCT, 8 wk (4 mo extension for risperidone responders)	**G1:** Risperidone (49), 1.8±0.7 mg/day **G2:** Placebo (52)	**G1:** NR / Male: 80% / Caucasian: NR **G2:** NR / Male: 83% / Caucasian: NR Comorbidities: MR (borderline (12), mild or moderate (43), severe (31))	autistic disorder NR, 96
Nagaraj, 2006[73] RCT, 6 mo	**G1:** Risperidone (19), 1 mg/day **G2:** Placebo (21)	**G1:** 4.8±1.7 yr / Male: 84% / Caucasian: NR **G2:** 5.3±1.7 yr / Male: 90% / Caucasian: NR Comorbidities: Aggression (20), irritability (36), self-injurious behavior (12), seizures (8)	autistic disorder NR, 31
Novaes, 2008[113] Retrospective cohort, 17 mo (mean)	**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	**G1:** NR / Male: NR / Caucasian: NR **G2:** NR / Male: NR / Caucasian: NR **G3:** NR / Male: NR / Caucasian: NR **G4:** NR / Male: NR / Caucasian: NR Comorbidities: aggression/ agitation (all), MR (20)	NR NR, NR
Perry, 1989[115] RCT, 6 mo	**G1:** Haloperidol (continuous) (34), 1.2 mg/day **G2:** Haloperidol (discontinuous) (36), 1 mg/day	**G1:** NR / Male: NR / Caucasian: NR **G2:** NR / Male: NR / Caucasian: NR Comorbidities: NR	autistic disorder NR, NR

ADHD = attention deficit and hyperactivity disorder; FGA = first generation antipsychotic; G = group; Mg = milligram; Mo = month; MR = mental retardation; N = number; NOS = not otherwise specified; NR = not reported; PDD = pervasive developmental disorder; RCT = randomized controlled trial; SD = standard deviation; wk = week; yr = year

Table 27. Study and patient characteristics for studies examining pervasive developmental disorders (continued)

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Shea, 2004[86] RCT, 8 wk	**G1:** Risperidone (41), 1.2 mg/day **G2:** Placebo (39)	**G1:** 7.6 (5-12) yr / Male: 73% / Caucasian: NR **G2:** 7.3 (5-12) yr / Male: 82% / Caucasian: NR Comorbidities: MR (27)	Asperger syndrome (12), autistic disorder (55), childhood disintegrative disorder (1), PDD NOS (11) NR, NR
Troost, 2005[94] RCT, 6 mo	**G1:** Risperidone (12), 1.9±0.7 mg/day **G2:** Placebo (12)	**G1:** 9.4±3.4 yr / Male: 92% / Caucasian: 100% **G2:** 8.7±1.2 yr / Male: 92% / Caucasian: 83% Comorbidities: MR (2)	Asperger syndrome (2), autistic disorder (6), PDD NOS (16) NR, 23

Table 28. Outcome data for studies assessing pervasive developmental disorders

Author, Year	Intervention (N analyzed)	Outcome	G1: Events (Rate)	G2: Event (Rate)	G3: Events (Rate)	p-value
Hollander, 2006[60]	G1: Olanzapine (6) G2: Placebo (5)	Response	3 (0.5)	1 (0.2)	NA	0.35
Malone, 2001[68]	G1: Haloperidol (6) G2: Olanzapine (6)	Response	3 (0.50)	5 (0.83)	NA	0.25
Marcus, 2009[69]	G1: Aripiprazole, 5 mg/day (52) G2: Aripiprazole, 10 mg/day (59) G3: Aripiprazole, 15 mg/day (53) G4: Placebo (49)	Response	29 (0.56)	29 (0.49)	28 (0.53) G4: 17 (0.35)	G1 vs. G2: 0.49 G1 vs. G3: 0.76 G1 vs. G4: 0.04 G2 vs. G3: 0.70 G2 vs. G4: 0.14 G3 vs. G4: 0.07
		Suicide-related behavior	0 (0)	0 (0)	0 (0) G4: 3 (0.06)	0.04
		Poor/nonadherence	8 wk: 1 (0.02)	8 wk: 1 (0.02)	8 wk: 1 (0.02) G4: 8 wk: 1 (0.02)	all: >0.9
McCracken, 2002[70]	G1: Risperidone (49) G2: Placebo (52) G3: Risperidone responders: risperidone (16) G4: Risperidone responders: placebo (16)	Response	8 wk: 34 (0.69)	8 wk: 6 (0.12)	NA	8 wk: <0.001
		Relapse	G3: 2 (0.13)	G4: 10 (0.63)	NA	0.01
		Time to relapse, days*	G3: 57	G4: 34	NA	NR
		Nonadherence	0	1 (0.02)	NA / G4: NA	NR
	G1: Risperidone (12) G2: Placebo (7)	Cancellation task correct detection*	126.75 (46.9) / 8 wk: 138.5 (59.7)	110.71 (56.3) / 8 wk: 95.29 (59.7)	NA	0.31
		Cancellation task commissions*	6.50 (22.2) / 8 wk: 0.08 (0.3)	2.29 (4.3) / 8 wk: 4.09 (9.7)	NA	0.25
		Cancellation task omissions*	11.75 (22.6) / 8 wk: 10.0 (19.3)	19.0 (20.3) / 8 wk: 27.57 (33.8)	NA	0.42
	G1: Risperidone (8) G2: Placebo (8)	Classroom analogue task, # attempted*	22.88 (14.7) / 8 wk: 24.5 (5.8)	31.63 (11.0) / 8 wk: 32.5 (15.7)	NA	0.91
		Classroom analogue task, # correct*	19.25 (11.4) / 8 wk: 20.50 (6.6)	24.5 (10.5) / 8 wk: 26.63 (18.0)	NA	0.89
	G1: Risperidone (12) G2: Placebo (8)	Verbal learning task, immediate recall*	28.5 (11.9) / 8 wk: 31.92 (11.6)	25.00 (8.8) / 8 wk: 29.88 (8.9)	NA	0.75
	G1: Risperidone (10) G2: Placebo (6)	Verbal learning task, delayed recall*	6.2 (4.6) / 8 wk: 7.4 (2.7)	4.67 (2.9) / 8 wk: 4.83 (2.9)	NA	0.55
	G1: Risperidone (10) G2: Placebo (5)	Verbal learning task, recognition*	77.89 (19.1) / 8 wk: 83.17 (15.4)	81.0 (11.6) / 8 wk: 75.0 (14.0)	NA	0.16

CARS = Childhood Autism Rating Scale ; CGAS = Clinical Global Assessment Scale; CGI–I = Clinical Global Impressions–Improvement; CGI–S = Clinical Global Impressions–Severity; FFQ = Food Frequency Questionnaire; FGA = first generation antipsychotic; G = group; mg = milligram; mcg = microgram; mo = month; ms = millisecond; N = number; NA = not applicable; NR = not reported; SGA = second generation antipsychotic; wk = week

* mean (SD)

Table 28. Outcome data for studies assessing pervasive developmental disorders (continued)

Author, Year	Intervention (N analyzed)	Outcome	G1: Events (Rate)	G2: Event (Rate)	G3: Events (Rate)	p-value
McCracken, 2002 (continued)	G1: Risperidone (17) G2: Placebo (13)	Purdue pegboard, dominant hand insert*	32.76 (17.4) / 8 wk: 34.59 (16.0)	24.08 (10.5) / 8 wk: 28.38 (13.9)	NA	0.64
		Purdue, nondominant hand insert*	26.82 (18.4) / 8 wk: 29.53 (14.7)	22.38 (9.9) / 8 wk: 24.23 (10.3)	NA	0.86
		Purdue, dominant hand drops*	2.35 (1.9) / 8 wk: 4.0 (3.4)	2.77 (2.4) / 8 wk: 3.0 (2.6)	NA	0.17
		Purdue, nondominant hand drops*	3.24 (3.0) / 8 wk: 4.0 (3.0)	2.31 (2.4) / 8 wk: 3.54 (2.9)	NA	0.65
		Purdue, both hands inserts*	59.59 (35.3) / 8 wk: 64.12 (30.0)	46.46 (19.5) / 8 wk: 54.62 (23.2)	NA	0.72
		Purdue, both hands drops*	5.59 (4.0) / 8 wk: 8.0 (5.5)	5.08 (4.3) / 8 wk: 6.54 (4.9)	NA	0.59
	G1: Risperidone (4) G2: Placebo (4)	Dot test, difference*	4.79 (2.0) / 8 wk: 2.44 (2.2)	1.43 (1.5) / 8 wk: 2.38 (2.9)	NA	0.04
	G1: Risperidone (49) G2: Placebo (52)	FFQ vitamin K intake (mcg)*	19 (30)	-16 (37)	NA	<0.05
		Sleep time increase, minutes*	40	17	NA	>0.05
Nagaraj, 2006[73]	G1: Risperidone (19) G2: Placebo (20)	Response (CARS)	6 mo: 12 (0.63)	6 mo: 0 (0)	NA	<0.01
		Response (CGAS)	6 mo: 17 (0.89)	6 mo: 2 (0.1)	NA	0.001
		Response (CGI)	6 mo: 18 (0.95)	6 mo: 6 (0.3)	NA	>0.05
Novaes, 2008[113]	G1: Risperidone (with or without FGA) (18) G2: SGA other than risperidone (with or without FGA) (7)	Response	mean 17 mo: 14 (0.78)	mean 17 mo: 5 (0.71)		>0.05
Perry, 1989[77]	G1: Haloperidol (continuous) (30) G2: Haloperidol (discontinuous) (22)	Response (CGI-I)	7 mo: 18 (0.6)	7 mo: 10 (0.46)	NA	0.32
		Response (CGI-S)	7 mo: 6 (0.29)	7 mo: 6 (0.20)	NA	0.54
Shea, 2004[86]	G1: Risperidone (40) G2: Placebo (39)	Response	27 (0.69)	15 (0.40)	NA	0.01
		Composite response	14 (0.58)	6 (0.21)	NA	0.008
Troost, 2005[94]	G1: Risperidone (12) G2: Placebo (12)	Relapse	3 (0.25)	8 (0.67)	NA	0.05
		Mean time to relapse, wk	7 (1)	6 (1)	NA	0.01
	G1: Risperidone (6) G2: Placebo (6)	Focused attention: reaction time (ms)*	1230.5 (460.3) / 1072.2 (410.9)	1261.7 (363.1) / 1105.8 (290.1)	NA	0.68

ADHD and Disruptive Behavior Disorders

Summary. Eight studies provided data on a variety of short- and long-term outcomes for patients with disruptive behavior disorders. The following is a summary of the results by outcome:

- *Response and remission.* Two RCTs comparing risperidone and placebo reported treatment response rate. One study[41] found a significant difference in response favoring risperidone ($p<0.001$), while another study[43] found no significant difference between the groups. One RCT[79] 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[79] 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 reported on the comparative efficacy of risperidone versus 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 ($p\leq0.05$).[40] Reyes et al.[79] found no difference between groups on verbal learning and continuous performance tasks.
- *Medication adherence and persistence.* A meta-analysis of four studies[41,43,55,89] 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. The strength of evidence was considered low.
- *School performance.* School refusal was assessed in one RCT[48] comparing quetiapine and placebo; no significant difference was found between groups.
- *Patient or parent/care provider reported outcomes.* Social withdrawal was assessed in an RCT[48] comparing quetiapine and placebo; no difference was found between treatment arms. There was insufficient evidence upon which to draw a conclusion.
- *Health-related quality of life.* One RCT[48] assessed patients on the Quality of Life Enjoyment and Satisfaction Questionnaire and found a significant difference favoring treatment with quetiapine over placebo ($p = 0.005$). There was insufficient evidence upon which to draw a conclusion.
- *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.

Results by individual study. Eight RCTs examined the efficacy of second generation antipsychotics for treating symptoms in patients with ADHD with aggression[43] and disruptive behavior disorders[40,41,47,48,55,79,89] on a variety of short- and long-term outcomes. All of the trials compared a second generation antipsychotic with placebo. A meta-analysis was conducted comparing risperidone with placebo for adherence rate. Patient and study characteristics and outcome data are presented in Table 29 and Table 30, respectively.

Second generation antipsychotics versus placebo. One trial evaluated quetiapine[48] and seven RCTs[40,41,43,47,55,79,89] examined risperidone.

An RCT conducted by Connor et al.[48] examined the efficacy of quetiapine compared with placebo for treating conduct disorder based on K-SADS-E in adolescents (aged 12 to 17 years) with moderate to severe aggression. Nineteen patients were randomly assigned to quetiapine (n = 9) or placebo (n = 10) for 6 weeks. The most common comorbid psychiatric diagnoses included oppositional defiant disorder (n = 18) and ADHD (n = 15). The mean dose of quetiapine was 294±78 mg/day. Patients were assessed on school refusal, social withdrawal, and Quality of Life Enjoyment and Satisfaction Questionnaire. 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, there were no statistically significant differences between groups for the other outcomes.

Aman et al.[40] conducted a crossover RCT to assess the efficacy of risperidone compared with placebo in children receiving maintenance therapy. Sixteen children (4 to 14 years) were randomly assigned to an alternating 2-week sequence of risperidone and placebo. Patient diagnoses were based on DSM-IV criteria: ADHD (n = 1), ADHD and conduct disorder (n = 2), ADHD and oppositional defiant disorder (n = 6), autism spectrum disorder (n = 3), conduct disorder (n = 1), and oppositional defiant disorder (n = 3). Intellectual functioning was as follows: average (n = 1), borderline mental retardation (n=10), mild mental retardation (n=4), and moderate mental retardation (n = 1). The mean daily dose of risperidone was 1.7±1.3 mg. Patients were assessed with various cognitive tasks (match-to-sample, short-term recognition memory, continuous performance, and graduated holes 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). No statistically significant differences between groups were found for any other outcomes.

Aman et al.[41] assessed the short- and long-term efficacy of risperidone for severe disruptive behaviors in children (aged 5 to 12 years) with subaverage intelligence. One hundred and nineteen children (1 dropout prior to treatment) were randomized to risperidone (n = 55) or placebo (n = 63) for 6 weeks. All patients were enrolled in a 48-week open-label extension study to evaluate the long-term efficacy of risperidone. Patient diagnoses based on DSM-IV criteria were conduct disorder (n = 21), conduct disorder and ADHD (n = 26), disruptive behavior disorder and ADHD (n = 6), disruptive behavior disorder NOS (n = 2), oppositional defiant disorder (n = 25), and oppositional defiant disorder and ADHD (n = 38). Intellectual disability was borderline (n = 60), mild (n = 38), or moderate (n = 20). The mean daily dosage of risperidone was 1.2±0.6 mg at 6 weeks. Treatment response (very much or much improved on the CGI) was significantly more common for risperidone than placebo ($p<0.001$). Medication nonadherence did not differ between groups.

An RCT conducted by Armenteros et al.[43] evaluated the efficacy of risperidone compared with placebo for treating aggression in stimulant-treated children (aged 7 to 12 years) with ADHD based on DSM-IV and Computerized Diagnostic Interview Schedule for Children criteria. Twenty-five patients were randomly assigned to risperidone augmentation (n = 12) or placebo (n = 13) for 4 weeks. The mean risperidone dose at endpoint was 1.1±0.6 mg/day. Treatment response was assessed using two different scales: ≥30 percent change in CAS (both parent and teacher versions) and a CGI-I score ≤3. Patients in the risperidone group showed greater response according to the CAS parent version measure than did patients in the placebo group ($p<0.05$); however, statistically significant differences were not found using the other scales. Medication nonadherence did not differ between groups.

An RCT conducted by Buitelaar et al.[47] compared risperidone with placebo for the treatment of aggression in hospitalized adolescents (aged 12 to 18 years) with subaverage intelligence and disruptive behavior disorders based on DSM-IV criteria. Patients were randomized to risperidone (n = 19) or placebo (n = 19) for 6 weeks. Principal diagnoses were conduct disorder (n = 30), oppositional defiant disorder (n = 6), and disruptive behavior disorder NOS (n = 2). Comorbidities were ADHD (n = 26), mental retardation (n = 14), and anxiety disorder (n = 3). The mean daily dose of risperidone was 2.9 mg at endpoint. Patient adherence was assessed via plasma serum level; however, a statistical comparison was not reported.

Findling et al.[55] conducted an RCT to compare the efficacy of risperidone and placebo for treating children and adolescents (aged 5 to 15 years) with conduct disorder based on DSM-IV and SADS-E criteria. Patients were randomly assigned to risperidone (n = 10) or placebo (n = 10) for 10 weeks. The mean dose of risperidone at the end of the study was 0.028±0.004 mg/kg/day. Two patients in the placebo group were nonadherent; the difference between groups was not statistically significant.

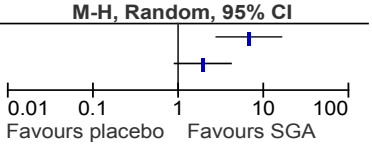
An RCT conducted by Reyes et al.[79] evaluated the efficacy of risperidone maintenance therapy compared with placebo for treating children (aged 5 to 17 years) with disruptive behavior disorders based on DSM-IV and K-SADS-PL criteria. Three hundred thirty-five patients who responded to risperidone treatment were randomized to risperidone (n = 172) or placebo (n = 163) for 6 months. Primary diagnoses were conduct disorder (n = 123), oppositional defiant disorder (n = 204), and disruptive behavior disorder NOS (n = 8); 227 patients had comorbid ADHD (n = 227). The mean daily dose of risperidone was 0.81±0.34 mg for patients <50 kg and 1.22±0.36 mg for patients ≥50 kg. Patients were assessed for symptom recurrence (deterioration in CGI-S ≥2 points or ≥7 points on the conduct problem subscale), time to symptom recurrence in 25 percent of patients, 6-month symptom recurrence, relapse, Tanner stages, verbal learning scores, and continuous performance task. Risperidone was significantly superior to placebo for symptom recurrence, time to symptom recurrence, 6-month recurrence, and relapse ($p \leq 0.002$). There were no statistically significant differences between groups in Tanner stages, verbal learning, or the continuous performance task.

An RCT conducted by Snyder et al.[89] evaluated the short- and long-term efficacy of risperidone in children (aged 5 to 12 years) with subaverage intelligence and disruptive behaviour disorders based on DSM-IV criteria (intelligence quotient: 36 to 84). Participants were randomized to risperidone (n = 53) or placebo (n = 57) for 6 weeks. A 48-week open-label extension study was conducted to evaluate long-term efficacy. Patients were diagnosed with conduct disorder (n = 41) and oppositional defiant disorder (n = 69); 84 patients had comorbid ADHD. The mean daily dose of risperidone was 1.0±0.73 mg at 6 weeks. Nonadherence was reported for two patients in the risperidone group and one in the placebo group; there was no significant difference between the groups.

Two studies[41,43] comparing risperidone versus placebo reported treatment response rates. The results of two studies were not pooled due to substantial heterogeneity ($p = 0.02$, $I^2 = 81$ percent). All patients in one study[41] had mental retardation, and mental retarding was an exclusion criteria in the second study.[43] This may account for the difference in response rates. Aman et al.[41] found a significant difference in favor of risperidone.

Figure 38. Second generation antipsychotics versus placebo on response rate in disruptive behavior disorders

Study or Subgroup	SGA Events	SGA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Aman 2002	28	52	5	63		6.78 [2.82, 16.32]
Armenteros 2007	9	12	5	13		1.95 [0.91, 4.17]



Four studies[41,43,55,89] contributed data for a meta-analysis comparing adherence rate for patients receiving risperidone compared with those receiving placebo (Figure 39). There was no significant difference between the study groups (RR = 1.43; 95% CI, 0.35 to 5.83) and little evidence of heterogeneity between the studies (p = 0.35, I^2 = 9 percent).

Figure 39. Second generation antipsychotics versus placebo on adherence rate in disruptive behavior disorders

Study or Subgroup	SGA Events	SGA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Aman 2002	3	52	0	63	21.2%	8.45 [0.45, 160.01]
Armenteros 2007	1	12	1	13	25.6%	1.08 [0.08, 15.46]
Findling 2000	0	10	2	10	21.5%	0.20 [0.01, 3.70]
Snyder 2002	2	38	1	39	31.7%	2.05 [0.19, 21.71]
Total (95% CI)		**112**		**125**	**100.0%**	**1.43 [0.35, 5.83]**
Total events	6		4			

Heterogeneity: Tau² = 0.18; Chi² = 3.29, df = 3 (P = 0.35); I² = 9%
Test for overall effect: Z = 0.49 (P = 0.62)

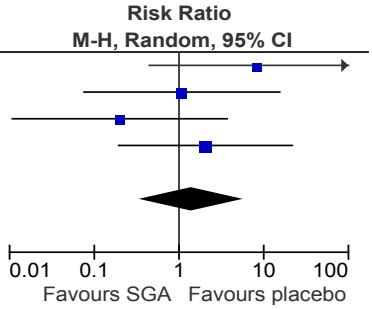


Table 29. Study and patient characteristics for studies examining ADHD and disruptive behavior disorders

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Aman, 2009[40] RCT (crossover), 4 wk	**G1:** Risperidone (16),* 1.7±1.3 mg/day **G2:** Placebo (16)*	**G1:** NR / Male : NR / Caucasian: NR **G2:** NR / Male : NR / Caucasian: NR Comorbidities: MR (borderline (10), mild (4), moderate (1))	ADHD (1), ADHD + CD (2), ADHD + ODD (6), ASD (3), CD (1), ODD (3) NR, NR
Aman, 2002[41] RCT, 6 wk (48 wk extension)	**G1:** Risperidone (55), 1.2±0.6 mg/day **G2:** Placebo (63)	**G1:** 8.7±2.1 yr / Male: 85% / Caucasian: 51% **G2:** 8.1±2.3 yr / Male: 79% / Caucasian: 62% Comorbidities: ADHD (70), MR (borderline (60), mild (38), moderate (20))	CD (21), CD + ADHD (26), DBD (2), DBD + ADHD (6), ODD (25), ODD + ADHD (38) NR, 118
Armenteros, 2007[43] ADHD with aggression RCT, 4 wk	**G1:** Risperidone (12), 1.1±0.6 mg/day **G2:** Placebo (13)	**G1:** 7.3±3.7 yr / Male: 83% / Caucasian: 50% **G2:** 8.8±3.1yr / Male: 92% / Caucasian: 46% Comorbidities: MR (0), generalized anxiety disorder (1), ODD (13), separation anxiety disorder (3)	ADHD (all) NR, 0
Buitelaar, 2001[47] RCT, 6 wk	**G1:** Risperidone (19), 2.9 mg/day **G2:** Placebo (19)	**G1:** 14.0±1.5 (11-18) yr / Male: 90% / Caucasian: NR **G2:** 13.7±2 (11-18) yr / Male: 84% / Caucasian: NR Comorbidities: ADHD (26), aggression (all), anxiety disorder (3), MR (14)	CD (30), DBD NOS (2), ODD (6) NR, 26
Connor, 2008[48] RCT, 6 wk	**G1:** Quetiapine (9), 294±78 mg/day **G2:** Placebo (10)	**G1:** 13.1±1.2 yr / Male: 78% / Caucasian: 78% **G2:** 15±1.4 yr / Male: 70% / Caucasian: 70% Comorbidities: ADHD (15), depression (4), dysthymia (5), generalized anxiety disorder (3), MR (0), OCD (3), ODD (18), panic disorder (1), psychosis (0), PTSD (3), SA (6), separation anxiety (3), social phobia (3)	CD (all) NR, 3
Findling, 2000[55] RCT, 10 wk	**G1:** Risperidone (10), 0.028±0.004 mg/kg/day **G2:** Placebo (10)	**G1:** 10.7±3.4 yr / Male: NR / Caucasian: NR **G2:** 8.2±1.9 yr / Male: NR / Caucasian: NR Comorbidities: NR	CD (all) NR, 19

ADHD = attention deficit hyperactivity disorder; CD = conduct disorder; DBD = disruptive behavior disorder; G = group; 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 = posttraumatic stress disorder; RCT = randomized controlled trial; SA = substance abuse; wk = week
*All patients experienced each of the treatment arms in this crossover study

Table 29. Study and patient characteristics for studies examining ADHD and disruptive behavior disorders (continued)

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Reyes, 2006[79] RCT, 6 mo	**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% / Caucasian: NR **G2:** 10.8±2.9 yr / Male: 91% / Caucasian: NR Comorbidities: ADHD (227)	CD (123), DBD NOS (8), ODD (204) NR, NR
Snyder, 2002[89] RCT, 6 wk (48 wk extension)	**G1:** Risperidone (53), 1±0.73 mg/day **G2:** Placebo (57)	**G1:** 8.6±0.3 (5-12) yr / Male: 77% / Caucasian: 79% **G2:** 8.8±0.3 (5-12) yr / Male: 74% / Caucasian: 74% Comorbidities: ADHD (84), MR (borderline (53), mild (42), moderate (15))	CD (10), CD + ADHD (31), ODD (16), ODD + ADHD (53) NR, NR

Table 30. Outcome data for studies assessing ADHD and disruptive behavior disorders

Author, Year	Intervention (N analyzed)	Outcome	G1: Events (Rate)	G2: Event (Rate)	P-value
Aman, 2009[40]	G1: Risperidone (15) G2: Placebo (15)	MTS: accuracy*	87.1	87.4	0.95
		MTS: response time*	1.75	1.83	0.67
		MTS: longest delay*	7.61	8.11	0.62
		MTS: mean delay*	4.20	4.15	0.93
		MTS: seat movements*	106.6	139.6	0.21
		STRM: accuracy*	69.7	70.0	0.96
		STRM: response time*	2.26	2.68	0.01
		STRM: seat movements*	137.4	240.6	0.05
		CPT: omissions*	1.79	1.71	0.86
		CPT: commissions*	2.61	3.94	0.21
		CPT: response time*	0.54	0.54	0.98
		CPT: seat movement*	250.9	357.7	0.38
		GHT: contacts*	231.7	280.1	0.05
		GHT: error time*	13.8	17.1	0.19
Aman, 2002[41]	G1: Risperidone (52) G2: Placebo (63)	Response	28 (0.54)	5 (0.08)	<0.001
		Nonadherence	3 (0.06)	0 (0)	0.15
Armenteros, 2007[43] ADHD	G1: Risperidone (12) G2: Placebo (13)	Response: CAS–P	12 (1.0)	10 (0.77)	0.08
		Response: CAS–T	3 (0.27)	7 (0.54)	>0.05
		Response: CGI–I	9 (0.75)	5 (0.38)	0.06
		Nonadherence	1 (0.08)	1 (0.08)	NR
Buitelaar, 2001[47]	G1: Risperidone (19) G2: Placebo (19)	Adherence	18 (24) ng/mL	0.0 ng/mL	NR
Connor, 2008[48]	G1: Quetiapine (9) G2: Placebo (10)	Q-LES-Q*	36.9 (8.6) / 6 wk: 48.2 (10.2)	39.3 (9.5) / 6 wk: 35.2 (8.0)	0.005
		School refusal	2 (0.22)	4 (0.40)	>0.05
		Social withdrawal	4 (0.44)	5 (0.50)	>0.05
Findling, 2000[55]	G1: Risperidone (10) G2: Placebo (10)	Nonadherence	0 (0)	2 (0.2)	0.28
Reyes, 2006[79]	G1: Risperidone (172) G2: Placebo (163)	Symptom recurrence	47 (0.27)	69 (0.42)	0.002
		Time to symptom recurrence in 25%*	119 days	37 days	<0.001

ADHD = attention deficit hyperactivity disorder; BL = baseline; CAS = Children's Aggression Scale (Parents or Teachers); CGI-I = Clinical Global Impressions–Improvement; CPT = Continuous Performance Task; G = group; GHT = Graduated Holes task; mL = millilitre; MTS = Match-to-Sample task; MVLT = Modified California Verbal Learning task; N = number; NA = not applicable; NR = not reported; STRM = Short-Term Recognition Memory task; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; wk = week

* mean (SD)

Table 30. Outcome data for studies assessing ADHD and disruptive behavior disorders (continued)

Author, Year	Intervention (N analyzed)	Outcome	G1: Events (Rate)	G2: Event (Rate)	p-value
Reyes, 2006 (continued)		Six-month symptom recurrence	51 (0.30)	77 (0.47)	0.001
		Relapse	48 (0.28)	76 (0.47)	<0.001
	G1: Risperidone (154) G2: Placebo (146)	Tanner stage I	BL: 68 (0.44); 57 (0.37)	BL: 76 (0.47); 63 (0.43)	>0.05
		Tanner stage II	BL: 34 (0.21); 34 (0.22)	BL: 34 (0.21); 26 (0.18)	>0.05
		Tanner stage III	BL: 28 (0.18); 28 (0.18)	BL: 23 (0.14); 28 (0.19)	>0.05
		Tanner stage IV	BL: 19 (0.11); 21 (0.14)	BL: 18 (0.11); 15 (0.11)	>0.05
		Tanner stage V	BL: 10 (0.06); 14 (0.09)	BL: 11 (0.07); 14 (0.10)	>0.05
	G1: Risperidone (138) G2: Placebo (139)	MVLT-15, change (total correct scores)*	-0.3 (3.8)	0.1 (1.7)	>0.05
	G1: Risperidone (9) G2: Placebo (5)	MVLT-10, change*	2.0 (2.1)	4.3 (4.9)	>0.05
	G1: Risperidone (139) G2: Placebo (136)	CPT, change in number of correct hits*	0.1 (0.4)	0.1 (0.4)	>0.05
Snyder, 2002[89]	G1: Risperidone (38) G2: Placebo (39)	Nonadherence (48 wk extension)	2 (0.05)	1 (0.03)	0.55

Bipolar Disorder

Summary. Nine studies provided data on a variety of short- and long-term outcomes for patients with bipolar disorder receiving treatment with second generation antipsychotics. The following is a summary of the results by outcome:

- *Response and remission.* Medication response rate was reported in seven studies. High-dose aripiprazole was favored over low-dose aripiprazole in one RCT,[54] while no difference was observed in a study comparing olanzapine with risperidone[46] and a study comparing low-dose and high-dose risperidone.[57] A meta-analysis of six studies[50,52,54,57,92,93] that compared a second generation antipsychotic with placebo showed a significant difference favoring second generation antipsychotics (RR = 1.79; 95% CO, 1.41 to 2.28). Remission rate was significantly higher for high-dose aripiprazole than low-dose aripiprazole.[54] No differences were observed in a study comparing low-dose and high-dose risperidone.[57] A meta-analysis of five placebo-controlled studies[50,54,57,92,93] examining second generation antipsychotics showed a statistically significant difference favoring antipsychotics (RR = 2.64; 95% CI, 1.45 to 4.79) for remission rate.
- *Cognitive and emotional development.* One RCT comparing ziprasidone with placebo found a lower speed of processing score in patients receiving ziprasidone; however, the level of significance was not reported.
- *Suicide-related behaviors.* Two RCTs found no deaths by suicide[54,57] and no difference in suicidal ideation[51,54,57] and suicide attempts[57] in studies comparing second generation antipsychotics. The strength of evidence supporting no deaths by suicide was low and that supporting no difference in suicide behaviors between second generation antipsychotics and placebo was moderate.
- *Medication adherence and persistence.* One RCT comparing two doses of risperidone found no difference in adherence rate between groups.[57] A meta-analysis of three RCTs[52,57,93] comparing second generation antipsychotics with placebo found a significant difference between groups favoring placebo. There was insufficient evidence to make a conclusion regarding adherence rates for different doses of risperidone and low strength of evidence supporting adherence rates for second generation drugs versus placebo.
- *Other outcomes.* No studies provided data for the following outcome categories: growth and maturation, school performance, work-related functional capacity, patient insight into illness, patient or parent reported outcomes, health-related quality of life, legal system interactions, or health care system utilization.

Results by individual study. Nine RCTs[46,50-52,54,57,75,92,93] assessed a variety of short- and long-term outcomes in patients with bipolar disorder who were treated with first generation and second generation antipsychotics. The number of participants ranged from 30 to 296 (median = 63 [IQR, 32 to 170]). All of the studies included patients with bipolar I disorder; one study[93] also included patients with bipolar II disorder. Second generation antipsychotics were compared other second generation antipsychotics,[46] with another dose of the same antipsychotic,[51,54,57] and with placebo.[50,52,54,57,75,92,93] For the comparison of second generation antipsychotics versus placebo, a meta-analysis was conducted for treatment response, remission, adherence, death by suicide,

suicidal ideation, and suicide attempts. Patient and study characteristics and outcome data are presented in Table 31 and Table 32, respectively.

Second generation versus second generation antipsychotics. One RCT compared olanzapine versus risperidone;[46] three RCTs compared different doses of aripiprazole,[54] risperidone,[57] and ziprasidone.[51]

An RCT conducted by Findling et al.[54] evaluated the efficacy of two doses of aripiprazole to treat adolescents (aged 10 to 17 years) with or without psychosis and with bipolar I disorder based on DSM-IV and K-SADS-PL criteria and. Patients were randomized to aripiprazole 10 mg/day (n = 98), 30 mg/day (n = 99), or placebo (n = 99) for 4 weeks. Current or past comorbid diagnoses were ADHD (n = 153), disruptive behavior disorders (n = 93), or anxiety disorders (n = NR). Participants had a current mixed (n = 119) or manic (n = 125) episode with psychotic features (n = 14). Treatment response was defined by a 50 percent or greater reduction in YMRS score from baseline to endpoint; remission was defined by a YMRS score of ≤12 points and a CGI-BP severity score of ≤2 points at endpoint. The response and remission rates were significantly higher in high-dose aripiprazole compared with low-dose aripiprazole (p = 0.01 and p = 0.002, respectively). Improvement in health-related quality of life was noted on P-QLES-Q score in each group, but no statistically significant differences between the groups were found at 4 weeks. There were no deaths by suicide during the study; however, one patient in the low-dose aripiprazole group reported suicidal ideation.

An RCT conducted by Biederman et al.[46] compared the efficacy of olanzapine and risperidone in children (aged 4 to 6 years) with bipolar disorder based on DSM-IV and K-SADS criteria. Thirty-one patients were randomly assigned to the interventions (15 to olanzapine, 16 to risperidone) and were followed to the endpoint at 8 weeks. The mean drug doses were 6.3±2.3 mg/day and 1.4±0.5 mg/day for the olanzapine and risperidone groups, respectively. Treatment response was defined as a greater than 30 percent reduction in YMRS or CGI-I of ≤2 points. No significant difference for response rate was found between groups.

Haas et al.[57] conducted an RCT to evaluate the efficacy of risperidone in children and adolescents (ages 10 to 17 years) with bipolar I disorder based on DSM-IV and SADS-E criteria. Patients were randomly assigned to risperidone at a daily dose of 0.5 to 2.5 mg (n = 50), 3 to 6 mg (n = 61), or placebo (n = 58) for 3 weeks. Patients had manic (n = 60) and mixed episodes (n = 109); comorbidities were disruptive behavior disorders (n = 101) and ADHD (n = 85). Treatment response was defined as a 50 percent or greater reduction in YMRS score from baseline and remission was defined as ≤12 points and CGI-BP ≤2 points at endpoint. No statistically significant differences were observed between the risperidone groups for response and remission. There were no deaths by suicide during the study. Rates of suicide attempt and suicidal ideation were not significantly different between groups.

An RCT conducted by DelBello et al.[51] compared the efficacy of low- and high-dose ziprasidone in treating children and adolescents (aged 10 to 17 years) with bipolar mania, schizophrenia and schizoaffective disorder based on DSM-IV-TR criteria. Separate analyses were provided for patients with bipolar disorder. Participants were randomly assigned to low- (80 mg/day; 15 participants) or high-dose (160 mg/day; 31 participants) ziprasidone and were followed for 3 weeks. One patient in the high-dose group reported suicidal ideation; it was unclear whether this patient had bipolar disorder or schizophrenia.

Second generation antipsychotics versus placebo. Seven RCTs provided data on five comparisons with placebo: aripiprazole,[54,93] olanzapine,[92] quetiapine,[50,52] risperidone,[57]and ziprasidone.[75]

An RCT conducted by Findling et al.[54] compared two doses of aripiprazole and placebo (described previously). Treatment response was defined as a 50 percent or greater reduction in YMRS score from baseline; remission was defined as a YMRS score of ≤12 points and CGI-BP severity score of ≤2 points. The response and remission rates at endpoint in both aripiprazole treatment groups were significantly higher than in the placebo group (response: 10 mg vs. placebo: $p = 0.007$, 30 mg vs. placebo: $p<0.0001$; remission: 10 mg vs. placebo: $p = 0.0002$, 30 mg vs. placebo: $p<0.0001$). Improvement in health-related quality of life was noted on P-QLES-Q score in each group, but no statistically significant differences between the groups were observed. There were no deaths by suicide, but one patient receiving aripiprazole 10 mg/day reported suicidal ideation.

Tramontina et al.[93] evaluated the efficacy of aripiprazole in children and adolescents (aged 8 to 17 years) with bipolar disorder and ADHD comorbidity based on DSM-IV and K-SADS-E criteria. Patients were randomly assigned to aripiprazole (n = 18) or placebo (n = 25) for 6 weeks. Baseline characteristics of bipolar I (n = 35) and II (n = 8) participants included ADHD combined type (n = 34), psychosis (n = 16), disruptive behavior disorders (n = 35), and anxiety disorders (n = 21). The mean daily dose of aripiprazole was 13.6±5.4 mg. The treatment response rate, defined as 50 percent or greater reduction in YMRS score from baseline, was significantly higher in patients treated with aripiprazole compared with patients treated with placebo ($p = 0.02$). Remission rate, defined as YMRS score of ≤12 points, was higher in the aripiprazole group compared with the placebo group ($p = 0.01$). Rate of medication adherence and suicidal ideation did not differ between groups.

Tohen et al.[92] conducted an RCT to assess the efficacy of olanzapine for the treatment of acute manic or mixed episodes of adolescents (aged 13 to 17 years) with bipolar disorder based on DSM-IV and K-SADS criteria. Patients were randomized to olanzapine 2.5 to 20 mg/day (n = 107) or placebo (n = 54) for 3 weeks. Patients were diagnosed with mixed episodes (n = 86), rapid cycling (n = 30), psychotic features (n = 29), and current or past comorbid diagnosis of ADHD (n = 58), and disruptive behavior disorder (n = 49). The mean dose of olanzapine was 8.9 mg/day. Treatment response was defined as 50 percent or less reduction in YMRS score from baseline; remission was defined as YMRS score ≤12 points at endpoint. Rates of response and remission were significantly higher for patients treated with olanzapine compared with placebo (response: $p = 0.002$, remission: $p = 0.001$). The incidence of switch to depression, defined as a CGI depression score of ≤3 points at baseline and ≤4 points during the study, did not differ significantly between the groups. There were no deaths by suicide during the study; however, one patient in the olanzapine group reported suicidal ideation.

An RCT conducted by DelBello et al.[50] compared the efficacy of quetiapine and placebo in children (aged 12 to 18 years) with bipolar I disorder based on DSM-IV and Washington University in St. Louis K-SADS criteria who were experiencing depressive episodes. Thirty-two patients were randomly assigned to quetiapine (n = 17) or placebo (n = 15) for 8 weeks. The mean dose of quetiapine was 403±133 mg/day. Comorbidities were psychosis (n = 3), ADHD (n = 4), disruptive behavior disorders (n = 8), and anxiety disorders (n = 8). Treatment response was defined as 50 percent or greater reduction in CDRS scores from baseline. Remission was defined as CDRS score ≤28 points and CGI-BP score ≤2 points. Response and remission rates were not statistically significantly different between the groups. One patient receiving quetiapine had a suicide attempt.

An RCT conducted by DelBello et al.[52] compared the efficacy of quetiapine as an adjunct to divalproex (DVP) for the treatment of acute mania in hospitalized adolescents (aged 12 to 18

years) with bipolar disorder based on DSM-IV and Washington University in St. Louis K-SADS criteria. Thirty patients were randomly assigned to combination therapy with quetiapine (n = 15) or with placebo (n = 15) for 6 weeks. Bipolar diagnosis was accompanied by mixed episodes (n = 23), psychosis (n = 14), or ADHD (n = 18). The mean quetiapine dose was 432 mg/day. Treatment response was defined by 50 percent or greater reduction in YMRS score from baseline. Response rate was significantly greater in the quetiapine plus DVP group compared with the placebo plus DVP group (p = 0.05). Nonadherence was observed in three patients in the quetiapine group.

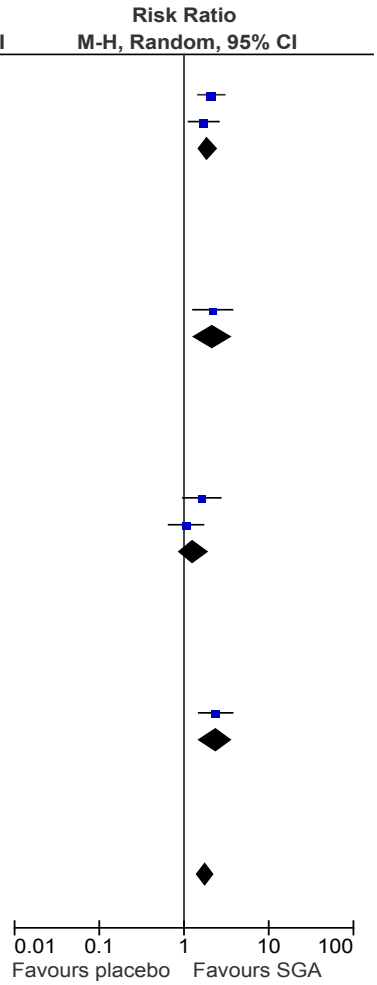
Haas et al.[57] conducted an RCT to evaluate the efficacy of risperidone in children and adolescents (aged 10 to 17 years) with manic and mixed episodes associated with bipolar I disorder based on DSM-IV and K-SADS-PL criteria. Patients were randomly assigned to risperidone at a daily dose of 0.5 to 2.5 mg (n = 50), 3 to 6 mg (n = 61), or placebo (n = 58) for 3 weeks. Patients were diagnosed with mania (n = 60) or mixed episodes (n = 109); comorbidities were disruptive behavior disorders (n = 101) and ADHD (n = 85). Treatment response was defined as 50 percent or greater reduction in YMRS score from baseline; remission was defined as a YMRS score of ≤12 points and CGI-BP of ≤2 points at endpoint. The response and remission rates were significantly higher for both risperidone groups at endpoint compared with placebo (response: p<0.002, remission: p = 0.003). There were no deaths by suicide during the study. The number of suicide attempts (n = 5) and suicidal ideation (n = 6) were not significantly different between groups. One participant randomized to placebo was nonadherent.

An RCT[75] evaluated the efficacy of ziprasidone for treating children and adolescents (aged 10 to 18 years) with manic or mixed bipolar I disorder based on DSM-IV and K-SADS criteria. Patients were randomized to flexible dosing of ziprasidone (n = 149) or placebo (n = 88) for 4 weeks. There were no deaths by suicide during the study and no significant differences in the number of suicide attempts (n = 2), suicidal ideation (n = 6), or self-injurious behavior (n = 1) between the groups. Speed of processing score was lower in patients treated with ziprasidone with placebo; however, level of significance was not reported.

Six RCTs[50,52,54,57,92,93] provided data for a meta-analysis comparing second generation antipsychotics with placebo for treatment response rate (Figure 40). The combined estimate showed a statistically significant difference between treatments favoring second generation antipsychotics (RR = 1.79; 95% CO, 1.41 to 2.28). There was moderate heterogeneity among the pooled studies (p = 0.12, I^2 = 42 percent). The heterogeneity may be attributable to one study[50] that enrolled patients who were older and were currently experiencing a depressive episode.

Figure 40. Second generation antipsychotics versus placebo on response rate in bipolar disorder

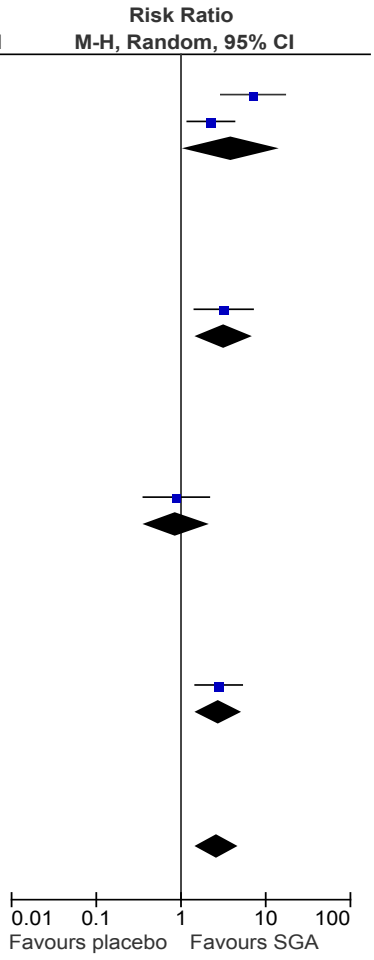
Study or Subgroup	SGA Events	SGA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Aripiprazole versus placebo						
Findling 2009	107	197	25	97	21.2%	2.11 [1.47, 3.02]
Tramontina 2009	16	18	13	25	18.6%	1.71 [1.13, 2.58]
Subtotal (95% CI)		**215**		**122**	**39.8%**	**1.92 [1.47, 2.52]**
Total events	123		38			
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 4.73 (P < 0.00001)						
4.1.2 Olanzapine versus placebo						
Tohen 2007	52	107	12	54	13.5%	2.19 [1.28, 3.74]
Subtotal (95% CI)		**107**		**54**	**13.5%**	**2.19 [1.28, 3.74]**
Total events	52		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.86 (P = 0.004)						
4.1.3 Quetiapine versus placebo						
DelBello 2002	13	15	8	15	14.3%	1.63 [0.97, 2.72]
DelBello 2009	12	17	10	15	15.9%	1.06 [0.66, 1.70]
Subtotal (95% CI)		**32**		**30**	**30.2%**	**1.30 [0.85, 1.97]**
Total events	25		18			
Heterogeneity: Tau² = 0.03; Chi² = 1.45, df = 1 (P = 0.23); I² = 31%						
Test for overall effect: Z = 1.21 (P = 0.23)						
4.1.4 Risperidone versus placebo						
Haas 2009	68	111	15	58	16.4%	2.37 [1.50, 3.75]
Subtotal (95% CI)		**111**		**58**	**16.4%**	**2.37 [1.50, 3.75]**
Total events	68		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.67 (P = 0.0002)						
Total (95% CI)		**465**		**264**	**100.0%**	**1.79 [1.41, 2.28]**
Total events	268		83			
Heterogeneity: Tau² = 0.04; Chi² = 8.63, df = 5 (P = 0.12); I² = 42%						
Test for overall effect: Z = 4.72 (P < 0.00001)						
Test for subgroup differences: Not applicable						



Five RCTs[50,54,57,92,93] provided data for a meta-analysis comparing second generation antipsychotics with placebo for remission rate (Figure 41). The pooled estimate showed a statistically significant difference between treatments favoring second generation antipsychotics over placebo (RR = 2.64; 95% CI, 1.45 to 4.79). There was substantial heterogeneity among the pooled studies (p = 0.01, I^2 = 68 percent), which was mostly a result of one study[50] that included only patients who were currently experiencing a depressive episode.

Figure 41. Second generation antipsychotics versus placebo on remission rate in bipolar disorder

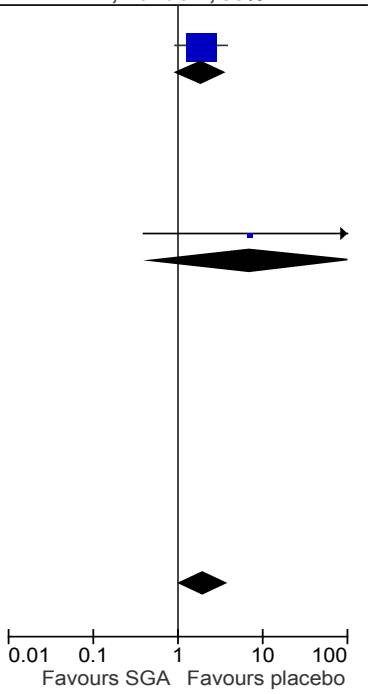
Study or Subgroup	SGA Events	SGA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 Aripiprazole versus placebo						
Findling 2009	72	197	5	97	18.2%	7.09 [2.96, 16.98]
Tramontina 2009	13	18	8	25	22.2%	2.26 [1.19, 4.28]
Subtotal (95% CI)		**215**		**122**	**40.4%**	**3.88 [1.05, 14.36]**
Total events	85		13			
Heterogeneity: Tau² = 0.74; Chi² = 5.86, df = 1 (P = 0.02); I² = 83%						
Test for overall effect: Z = 2.03 (P = 0.04)						
4.2.2 Olanzapine versus placebo						
Tohen 2007	38	107	6	54	19.5%	3.20 [1.44, 7.09]
Subtotal (95% CI)		**107**		**54**	**19.5%**	**3.20 [1.44, 7.09]**
Total events	38		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.86 (P = 0.004)						
4.2.3 Quetiapine versus placebo						
DelBello 2009	6	17	6	15	17.9%	0.88 [0.36, 2.16]
Subtotal (95% CI)		**17**		**15**	**17.9%**	**0.88 [0.36, 2.16]**
Total events	6		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.78)						
4.2.4 Risperidone versus placebo						
Haas 2009	48	111	9	58	22.2%	2.79 [1.47, 5.27]
Subtotal (95% CI)		**111**		**58**	**22.2%**	**2.79 [1.47, 5.27]**
Total events	48		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.15 (P = 0.002)						
Total (95% CI)		**450**		**249**	**100.0%**	**2.64 [1.45, 4.79]**
Total events	177		34			
Heterogeneity: Tau² = 0.31; Chi² = 12.51, df = 4 (P = 0.01); I² = 68%						
Test for overall effect: Z = 3.18 (P = 0.001)						
Test for subgroup differences: Not applicable						



Three RCTs[52,57,93] contributed to a meta-analysis comparing adherence rate for second generation antipsychotics versus placebo (Figure 42). 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 among the studies (p = 0.35, I^2 = 0 percent).

Figure 42. Second generation antipsychotics versus placebo on adherence rate in bipolar disorder

Study or Subgroup	SGA Events	SGA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 Aripiprazole versus placebo						
Tramontina 2009	9	15	8	25	94.3%	1.88 [0.93, 3.80]
Subtotal (95% CI)		**15**		**25**	**94.3%**	**1.88 [0.93, 3.80]**
Total events	9		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.75 (P = 0.08)						
4.3.2 Quetiapine versus placebo						
DelBello 2002	3	15	0	15	5.7%	7.00 [0.39, 124.83]
Subtotal (95% CI)		**15**		**15**	**5.7%**	**7.00 [0.39, 124.83]**
Total events	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.32 (P = 0.19)						
4.3.3 Risperidone versus placebo						
Haas 2009	0	111	0	58		Not estimable
Subtotal (95% CI)		**111**		**58**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**141**		**98**	**100.0%**	**2.02 [1.02, 4.01]**
Total events	12		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 2.01 (P = 0.04)						
Test for subgroup differences: Not applicable						

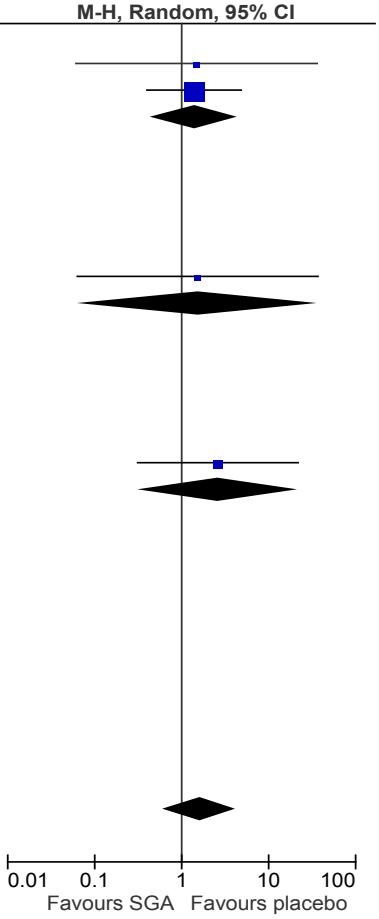


Three RCTs[54,57,75] reported suicide rate for second generation antipsychotics versus placebo comparisons. No deaths by suicide occurred in either of the groups across all studies, so a metagraph was not possible.

Five RCTs[54,57,75,92,93] comparing second generation antipsychotics with placebo reported rate of suicidal ideation (Figure 43). The pooled estimate showed no significant difference between the groups (RR = 1.61; 95% CI, 0.61 to 4.24). There was no evidence of heterogeneity among the studies (p = 0.97, I^2 = 0 percent).

Figure 43. Second generation antipsychotics versus placebo on suicidal ideation in bipolar disorder

Study or Subgroup	SGA Events	SGA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.4.1 Aripiprazole versus placebo						
Findling 2009	1	197	0	97	9.2%	1.48 [0.06, 36.12]
Tramontina 2009	4	18	4	25	60.6%	1.39 [0.40, 4.83]
Subtotal (95% CI)		**215**		**122**	**69.8%**	**1.40 [0.44, 4.47]**
Total events	5		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%						
Test for overall effect: Z = 0.57 (P = 0.57)						
4.4.2 Olanzapine versus placebo						
Tohen 2007	1	107	0	54	9.3%	1.53 [0.06, 36.89]
Subtotal (95% CI)		**107**		**54**	**9.3%**	**1.53 [0.06, 36.89]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.79)						
4.4.3 Risperidone versus placebo						
Haas 2009	5	111	1	58	20.9%	2.61 [0.31, 21.84]
Subtotal (95% CI)		**111**		**58**	**20.9%**	**2.61 [0.31, 21.84]**
Total events	5		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.89 (P = 0.38)						
4.4.4 Ziprasidone versus placebo						
NCT00257166 2008	0	149	0	88		Not estimable
Subtotal (95% CI)		**149**		**88**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**582**		**322**	**100.0%**	**1.61 [0.61, 4.24]**
Total events	11		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 3 (P = 0.97); I² = 0%						
Test for overall effect: Z = 0.96 (P = 0.34)						
Test for subgroup differences: Not applicable						



The suicide attempt rate was combined for four RCTs[50,57,75,92] comparing second generation antipsychotics with placebo (Figure 44). 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 percent).

Figure 44. Second generation antipsychotics versus placebo on suicide attempts in bipolar disorder

Study or Subgroup	SGA Events	SGA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.5.1 Olanzapine versus placebo						
Tohen 2007	0	107	0	54		Not estimable
Subtotal (95% CI)		**107**		**54**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.5.2 Quetiapine versus placebo						
DelBello 2009	1	17	0	15	22.9%	2.67 [0.12, 60.93]
Subtotal (95% CI)		**17**		**15**	**22.9%**	**2.67 [0.12, 60.93]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
4.5.3 Risperidone versus placebo						
Haas 2009	4	111	1	58	47.7%	2.09 [0.24, 18.27]
Subtotal (95% CI)		**111**		**58**	**47.7%**	**2.09 [0.24, 18.27]**
Total events	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.51)						
4.5.4 Ziprasidone versus placebo						
NCT00257166 2008	1	149	1	88	29.4%	0.59 [0.04, 9.32]
Subtotal (95% CI)		**149**		**88**	**29.4%**	**0.59 [0.04, 9.32]**
Total events	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						
Total (95% CI)		**384**		**215**	**100.0%**	**1.52 [0.34, 6.81]**
Total events	6		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 2 (P = 0.72); I² = 0%						
Test for overall effect: Z = 0.55 (P = 0.58)						
Test for subgroup differences: Not applicable						

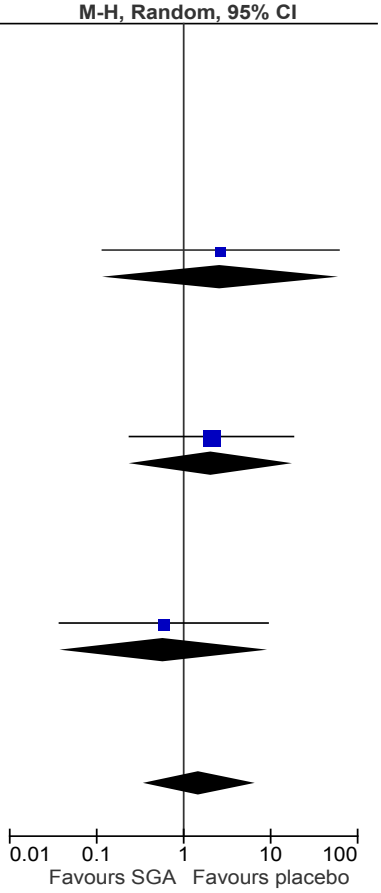


Table 31. Study and patient characteristics for studies examining bipolar disorder

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Biederman, 2005[46] RCT, 8 wk	**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% / Caucasian: 100% **G2:** 5.3±0.8 yr / Male: 75% / Caucasian: 94% Comorbidities: ADHD (19), CD (13), MDD (22)	Bipolar I (27), type not specified (4), mania (all) NR, NR
DelBello, 2009[50] RCT, 8 wk	**G1:** Quetiapine (17), 403±133 mg/day **G2:** Placebo (15)	**G1:** 16.0±2 yr / Male: 29% / Caucasian: 82% **G2:** 15±2 yr / Male: 33% / Caucasian: 80% Comorbidities: ADHD (4), anxiety disorder (8), DBD (8), psychosis (3)	Bipolar I with depressive episode (all) NR, 23
DelBello, 2008[51] RCT, 3 wk (24 wk extension)	**G1:** Ziprasidone (low) (15), target: 80 mg/day **G2:** Ziprasidone (high) (31), target: 160 mg/day	**G1:** 13.2±2.1 yr / Male: 47% / Caucasian: NR **G2:** 13.8±2.4 yr / Male: 77% / Caucasian: NR Comorbidities: MR (0), SA (0)	Bipolar I (all) NR, NR
DelBello, 2002[52] RCT, 6 wk	**G1:** Quetiapine (15), 432 mg/day **G2:** Placebo (15)	**G1:** 14.1±2 yr / Male: 53% / Caucasian: 80% **G2:** 14.5±2 yr / Male: 53% / Caucasian: 87% Comorbidities: ADHD (18), psychosis (14)	Bipolar I (all), mixed episode (23) NR, NR
Findling, 2009[54] RCT, 4 wk	**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% / Caucasian: 66% **G2:** 13.3±2.3 yr / Male: 52% / Caucasian: 69% **G3:** 13.3±2.1 yr / Male: 57% / Caucasian: 61% Comorbidities: ADHD (153), anxiety disorder (NR), DBD (93), psychosis (14)	Bipolar I (all), mania (119), mixed (125), unknown (52) NR, 126
Haas, 2009[57] RCT, 3 wk	**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 (10-17) yr / Male: 56% / Caucasian: 70% **G2:** NR (10-17) yr / Male: 43% / Caucasian: 82% **G3:** NR (10-17) yr / Male: 48% / Caucasian: 78% Comorbidities: ADHD (85), DBD (101)	Bipolar I (all), manic episode (60), mixed episode (109) NR, NR
NCT00257166, 2008[75] RCT, 4 wk	**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 / Caucasian: NR **G2:** 13.7 yr / Male: NR / Caucasian: NR Comorbidities: NR	Bipolar I (all) NR, NR

ADHD = attention deficit hyperactivity disorder; CD = conduct disorder; DBD = disruptive behavior disorder; G = group; kg = kilogram; MDD = major depressive disorder; mg = milligrams; mo = month; MR = mental retardation; N = number; NR = not reported; RCT = randomized controlled trial; SA = substance abuse; SD = standard deviation; wk = week; yr = year

Table 31. Study and patient characteristics for studies examining bipolar disorder (continued)

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Tohen, 2007[92] RCT, 3 wk (6 mo extension)	**G1:** Olanzapine (107), 8.9 mg/day **G2:** Placebo (54)	**G1:** 15.1±1.3 yr / Male: 57% / Caucasian: 66% **G2:** 15.4±1.2 yr / Male: 44% / Caucasian: 76% Comorbidities: ADHD (58), DBD (49)	Bipolar I (all), mixed (86), psychotic features (29), rapid cycling (30) NR, NR
Tramontina, 2009[93] Bipolar with ADHD RCT, 6 wk	**G1:** Aripiprazole (18), 13.6±5.4 mg/day **G2:** Placebo (25)	**G1:** 11.7±2.7 yr / Male: 33% / Caucasian: 83% **G2:** 12.2±2.8 yr / Male: 56% / Caucasian: 96% Comorbidities: ADHD (all), anxiety disorders (21), DBD (35), psychosis (16)	Bipolar type I (35), type II (8) NR, NR

Table 32. Outcome data for studies assessing bipolar disorder

Author, Year	Intervention (N analyzed)	Outcome	G1: Events (Rate)	G2: Event (Rate)	G3: Events (Rate)	p-value
Biederman, 2005[46]	G1: Olanzapine (15) G2: Risperidone (16)	Response	8 (0.53)	11 (0.69)	NA	0.9
DelBello, 2009[50]	G1: Quetiapine (17) G2: Placebo (15)	Response	12 (0.71)	10 (0.67)	NA	1.0
		Remission	6 (0.35)	6 (0.4)	NA	1.0
		Suicide attempt	1 (0.06)	0 (0)	NA	0.54
DelBello, 2008[51]	G1: Ziprasidone, 80 mg (15) G2: Ziprasidone, 160 mg (31)	Suicidal ideation	0 (0)	1 (0.04)	NA	0.73
DelBello, 2002[52]	G1: Quetiapine (15) G2: Placebo (15)	Response	13 (0.87)	8 (0.53)	NA	0.05
		Nonadherent	3 (0.2)	0	NA	0.19
Findling, 2009[54]	G1: Aripiprazole, (98) G2: Aripiprazole, (99) G3: Placebo (97)	Response	44 (0.45)	63 (0.64)	25 (0.26)	G1 vs. G2: 0.01 G1 vs. G3: 0.007 G2 vs. G3: <0.0001
		Remission	25 (0.25)	47 (0.48)	5 (0.05)	G1 vs. G2: 0.002 G1 vs. G3: 0.0002 G2 vs. G3: <0.0001
		Death by suicide	0 (0)	0 (0)	0 (0)	1.0
		Suicidal ideation	1 (0.01)	0 (0)	0 (0)	0.50
Haas, 2009[57]	G1: Risperidone, (50) G2: Risperidone, (61) G3: Placebo (58)	Response	30 (0.60)	38 (0.62)	15 (0.26)	G1 vs. G2: 0.81 G1 vs. G3: 0.002 G2 vs. G3: <0.001
		Remission	22 (0.44)	26 (0.43)	9 (0.16)	G1 vs. G2: 0.88 G1 vs. G3: 0.003 G2 vs. G3: 0.003
		Death by suicide	0	0	0	1.0
		Suicide attempt	2 (0.04)	2 (0.03)	1 (0.02)	G1 vs. G2: 0.84 G1 vs. G3: 0.92 G2 vs. G3: 0.60
		Suicidal ideation	1 (0.02)	4 (0.07)	1 (0.02)	G1 vs. G2: 0.28 G1 vs. G3: 0.92 G2 vs. G3: 0.23
		Nonadherent	0	0	1 (0.02)	0.48

G = group; mg = milligram; N = number; NA = not applicable; NR = not reported; P-QLES-Q = Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire; wk = week

Table 32. Outcome data for studies assessing bipolar disorder (continued)

Author, Year	Intervention (N analyzed)	Outcome	G1: Events (Rate)	G2: Event (Rate)	G3: Events (Rate)	p-value
NCT00257166, 2008[75]	G1: Ziprasidone (149) G2: Placebo (88)	Death by suicide	0	0	NA	1.0
		Suicide attempt	1 (<0.01)	1 (0.01)	NA	0.71
		Suicidal ideation	3 (0.02)	3 (0.03)	NA	0.51
		Self injurious behavior	1 (0.01)	0	NA	0.74
		Speed of processing score, change	NR / 4 wk: -3.5	NR / 4 wk: 0.4	NA	NR
Tohen, 2007[92]	G1: Olanzapine (107) G2: Placebo (54)	Response	52 (0.49)	12 (0.22)	NA	0.002
		Remission	38 (0.36)	6 (0.11)	NA	0.001
		Switch to depression	9 (0.08)	8 (0.14)	NA	0.48
		Suicide attempt / self-injurious behavior	0	0	NA	1.0
		Suicidal ideation	1 (0.01)	0	NA	0.80
Tramontina, 2009[93]	G1: Aripiprazole (18) G2: Placebo (25)	Response	16 (0.89)	13 (0.52)	NA	0.02
		Remission	13 (0.72)	8 (0.32)	NA	0.01
		Suicidal ideation	4 (0.22)	4 (0.16)	NA	0.61
		Patients with any unused pills	9 (0.5)	8 (0.32)	NA	0.34

Schizophrenia and Psychosis

Summary. Twenty-one studies provided data on a variety of short- and long-term outcomes for patients with schizophrenia (n = 17 studies) and psychosis (n = 4 studies). The following is a summary of the results by outcome:

Schizophrenia.

- *Response and remission.* Treatment response was reported in 10 studies and defined variably across the studies.[58,61,63,64,66,72,74,85,87,96] A single RCT[58] comparing low- and high-dose risperidone found a significantly greater response rate in patients receiving high-dose risperidone ($p<0.001$). No other significant differences in response rate were found. One study[53] found a significantly higher remission rate in patients treated with aripiprazole compared with placebo.
- *Suicide-related behaviors.* Two studies[53,87] reported on suicide rate. One death by suicide occurred in the risperidone arm of an RCT comparing olanzapine and risperidone;[87] however, there was no significant difference between groups. Three studies[58,63,80] examining second generation antipsychotics reported that no suicide-related behaviors occurred. Suicidal ideation was also rare in four studies[51,58,76,87] and did not differ between groups. The strength of evidence for this outcome was low.
- *Medication adherence and persistence.* Eight studies[49,58,61,63,78,87,96,97] reported patient adherence to medication. All studies found no significant difference between groups for adherence rate. The strength of evidence for this outcome was low.
- *Patient or parent/care provider reported outcomes.* One RCT[74] found statistically significant improvement for the Caregiver Strain Questionnaire favoring low-dose quetiapine over placebo. No significant difference was observed between high-dose quetiapine and placebo; the evidence was too limited to make conclusions.
- *Health-related quality of life.* One small RCT[49] 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.[53] There was insufficient evidence upon which to base a conclusion.
- *Other outcomes.* No studies provided data for the following outcome categories: growth and maturation, cognitive and emotional development, school performance, work-related functional capacity, patient insight into illness, legal system interactions, or health care system utilization.

Psychosis.

- *Response and remission.* Three RCTs found no significant differences between groups on response rate for the following comparisons: low- versus high-dose quetiapine,[45] haloperidol versus olanzapine versus risperidone,[88] and quetiapine versus risperidone.[91] One study found no difference in remission rate between low- and high-dose quetiapine.[45]

- *Cognitive and emotional development.* An RCT[42] 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.* One RCT[45] comparing low- and high-dose quetiapine reported one death by suicide in the high-dose group; the difference between the groups was not statistically significant.
- *Medication adherence and persistence.* Medication adherence rate was reported in three studies.[42,45,88] There were no significant differences among the groups.
- *Legal/justice system interaction.* One RCT[45] 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.
- *Health care system utilization.* One RCT[45] 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 ($p = 0.005$). Duration of hospital stay did not differ significantly between groups.
- *Other outcomes.* No studies provided data for the following outcomes: growth and maturation, school performance, work-related functional capacity, patient insight into illness, patient or parent reported outcomes, or health-related quality of life.

The strength of evidence was insufficient for all comparisons and outcomes was insufficient to make conclusions.

Results by individual study: Schizophrenia. Seventeen studies[49,51,53,58,61,63,64,66,72,74,76,78,80,85,87,96,97] reported data for a variety of short- and long-term efficacy outcomes in patients with schizophrenia and schizophrenia-related psychosis. The number of participants ranged from 23 to 302 (median = 60 [IQR, 30 to 201]). Two studies compared first generation with second generation antipsychotics,[49,78] 13 studies[51,53,58,61,64,66,72,74,78,80,85,87,96] evaluated two or more second generation antipsychotics, and six studies compared second generation antipsychotics with placebo.[53,63,74,76,80,97] Meta-analyses were conducted comparing clozapine with olanzapine for response, olanzapine with risperidone for response and adherence, and second generation antipsychotics versus placebo for response and adherence. Patient and study characteristics and outcome data are presented in Table 33 and Table 34, respectively.

First generation versus second generation antipsychotics. Two studies (one RCT[49] and one prospective cohort study[78]) compared first generation and second generation antipsychotics. Comparisons were made for haloperidol versus olanzapine[49,78] and haloperidol versus risperidone.[78]

An RCT by de Haan et al.,[49] compared the efficacy of haloperidol and olanzapine in adolescents and young adults (aged 17 to 26 years) with schizophrenia based on DSM-IV criteria. Twenty-four patients were randomly assigned to the interventions (12 to haloperidol, 12 to olanzapine) and patients were followed to the study endpoint at 6 weeks. The mean dose was 2.5 mg/day and 7.5 mg/day for the haloperidol and olanzapine groups, respectively. There were no significant differences between groups for The Subjective Well-being Under Neuroleptics scale and for medication adherence.

A prospective cohort study conducted by Ratzoni et al.[78] compared the efficacy of haloperidol, olanzapine, and risperidone in adolescents (aged 13 to 20 years) with schizophrenia (n = 46), schizoaffective disorder (n = 2), and conduct disorder (n = 2) based on DSM-IV and K-SADS-PL (Hebrew version) criteria and consensus of two child psychiatrists. Fifty patients were received, treated (eight patients on haloperidol, 21 on olanzapine, 21 on risperidone), and 36 patients were followed to the study endpoint at 12 weeks. The mean dosage of the drugs was 7.6±4 mg/day, 12.7±3.1 mg/day, and 3.2±1.1 mg/day for the haloperidol, olanzapine, and risperidone groups, respectively. Nonadherence did not differ significantly among the three intervention groups.

Second generation versus second generation antipsychotics. Thirteen studies evaluated second generation antipsychotics. Dose comparisons were made in five studies for the following drugs: aripiprazole,[53] paliperidone,[80] quetiapine,[74] risperidone,[58] and ziprasidone.[51] Other comparisons included: clozapine versus olanzapine,[64,66,85] olanzapine versus quetiapine,[61] and olanzapine versus risperidone.[72,78,87,96]

Findling et al.[53] conducted an RCT comparing low-dose aripiprazole, high-dose aripiprazole, and placebo in adolescents (aged 13 to 17 years) with schizophrenia based on DSM-IV and K-SADS-PL criteria. A total of 302 patients were randomly assigned to the intervention groups (100 to low-dose aripiprazole, 102 to high-dose aripiprazole, 100 to placebo) and 258 patients were followed to the study endpoint at 6 weeks. The mean dosage of the drugs was 9.8 mg/day and 28.9 mg/day for the low- and high-dose aripiprazole groups, respectively. Remission was defined as a PANSS score <3 for several items. There were no significant differences between the two doses of aripiprazole for remission rate or quality of life. No patients experienced death by suicide.

Kumra et al.[64] conducted an RCT to compare the efficacy of clozapine and olanzapine in adolescents (aged 10 to 18 years) with schizophrenia (n = 25) or schizoaffective disorder (n = 14) based on DSM-IV and K-SADS-PL criteria and a structured interview. Forty patients were randomly assigned to the interventions (19 to clozapine, 21 to olanzapine) and 28 patients were followed to the study endpoint at 12 weeks with a 12-week extension. The mean dosage of the drugs was 403.1±201.8 mg/day and 26.2±6.5 mg/day for the clozapine and olanzapine groups, respectively. Treatment response was defined as a reduction greater than 30 percent in BPRS score and CGI-I <2 points at endpoint. There were significantly more treatment responders in the clozapine group than in the olanzapine group (p = 0.038).

Kumra et al.[66] conducted a prospective cohort study to compare the efficacy of clozapine and olanzapine in patients (aged 6 to 18 years) with schizophrenia based on DSM-III-TR and K-SADS-E criteria. Eleven patients had disorganized schizophrenia, three had paranoid schizophrenia, and nine had undifferentiated schizophrenia. Twenty-three patients received open-label treatment with clozapine (n = 15) or olanzapine (n = 8) for 6 weeks (clozapine group) and 8 weeks (olanzapine group). The mean dosage of the drugs was 317±147 mg/day and 17.5±2.3 mg/day for the clozapine and olanzapine groups, respectively. Rates of response, partial response at 6 weeks and full or partial response at 8 weeks did not differ significantly between groups.

An RCT conducted by Shaw et al.[85] compared the efficacy of clozapine and olanzapine in the treatment of children (aged 7 to 16 years) with schizophrenia based on DSM-IV and K-SADS criteria, medical and school record review, and an interview with the child and parents. ADHD and anxiety disorders were present in seven patients, respectively. Twenty-five patients were randomly assigned to the interventions (12 to clozapine, 13 to olanzapine) and all patients were

followed to the study endpoint at 8 weeks with a 2 year extension. The mean dosage of the drugs was 327±113 mg/day and 18.1±4.3 mg/day for the clozapine and olanzapine groups, respectively. Treatment response was assessed as either full response (20 percent reduction in BPRS-24 score and CGI-S less than 3 or BPRS total score less than 35) or partial response (20 percent reduction in BPRS-24 score). Treatment response rate did not differ significantly between groups.

Jensen et al.[61] conducted an RCT to compare the efficacy of olanzapine, quetiapine, and risperidone in children (aged 10 to 18 years) with schizophrenia-related disorders based on DSM-IV and K-SADS criteria. Sixteen patients had schizophrenia or schizoaffective disorder, five patients had schizophreniform disorder, and nine patients had a psychotic disorder NOS. Thirty patients were randomly assigned to the interventions (10 to each group) and 21 patients were followed to the study endpoint at 12 weeks. The mean dosages of the drugs were 14±4.6 mg/day, 611±253.4 mg/day, and 3.4±1.5 mg/day for the olanzapine, quetiapine, and risperidone groups, respectively. Response (>40 percent reduction in PANSS scores) and medication adherence did not differ significantly among the three treatment groups.

Mozes et al.[72] conducted an RCT comparing olanzapine and risperidone in children (aged 8 to 14 years) with schizophrenia based on DSM-IV and K-SADS criteria. Seven patients had disorganized schizophrenia, six had paranoid schizophrenia, 10 had schizophreniform disorder, and two had unspecified schizophrenia. Eleven patients had additional comorbidities: ADHD (n = 3), OCD (n = 3), epilepsy (n = 2), familial Mediterranean fever (n = 1), tic disorder (n = 1), and neurofibromatosis (n = 1). Twenty-five patients were randomly assigned to the interventions (12 to olanzapine, 13 to risperidone), and 20 patients were followed to endpoint at 12 weeks. The mean dosage of the drugs was 8.2±4.4 mg/day and 1.6±1 mg/day for the olanzapine and risperidone groups, respectively. Patients were assessed using a symptom reduction of 50 percent on both the PANSS and BPRS. There were no statistically significant differences between the two groups for either of these outcomes.

Ratzoni et al.[78] compared the efficacy of olanzapine, risperidone, and haloperidol in a prospective cohort study (described previously). Fifty patients were given the interventions (8 on haloperidol, 21 on olanzapine, 21 on risperidone) and 36 patients were followed to the study endpoint at 12 weeks. The mean dosage of the drugs was 7.6±4 mg/day, 12.7±3.1 mg/day, and 3.2±1.1 mg/day for the haloperidol, olanzapine, and risperidone groups, respectively. Nonadherence did not differ between groups.

Sikich et al.[87] conducted an RCT to compare the efficacy of olanzapine and risperidone in children and adolescents (aged 8 to 19 years) with schizophrenia-related disorders (50 with schizophrenia, 26 with schizoaffective disorder) based on DSM-IV and Childhood disorders form of the Structured Clinical Interview for DSM-IV Disorders criteria. Comorbidities were ADHD (n = 22), anxiety disorder (n = 21), affective disorder (n = 19), disruptive behavior disorders (n = 16), psychosis (n = 10), autism spectrum disorder (n = 5), learning disability (n = 3), and substance abuse (n = 4). Seventy-eight patients were randomly assigned to the interventions (36 to olanzapine, 42 to risperidone) and were followed to the endpoint at 8 weeks with a 44-week extension. The mean dosage of the drugs was 11.4±5 mg/day and 2.8±1.4 mg/day for the olanzapine and risperidone groups, respectively. Rate of treatment response (CGI-I score <2 and reduction in PANSS score >20 percent after 8 weeks of treatment) and nonadherence did not differ significantly between groups. Other criteria for response based on the CGI-I, HAM-D, and YMRS similarly showed no difference between groups. One patient

reported suicidal ideation and one patient died by suicide; both patients were in the risperidone group.

An RCT conducted by van Bruggen et al.[96] compared the efficacy of olanzapine and risperidone in patients (aged 16 to 28 years) with schizophrenia, schizophreniform disorder, or schizoaffective disorder based on DSM-IV criteria. Forty-four patients were randomly assigned to the interventions (18 to olanzapine, 26 to risperidone), and data from 42 patients were analyzed at a mean followup period of 9.8 weeks (olanzapine group) and 6.7 weeks (risperidone group). The mean dosage of the drugs was 15.6±4 mg/day and 4.4±1.5 mg/day for the olanzapine and risperidone groups, respectively. Patient response was defined as a PANSS score of less than mild at endpoint. No statistically significant differences were found between the olanzapine and risperidone groups for any outcomes.

Robb et al.[80] conducted an RCT to compare the efficacy of low-, medium- and high-dose extended release paliperidone and placebo in adolescents (aged 12 to 17 years) with schizophrenia based on DSM-IV and K-SADS-PL criteria. One hundred forty-three patients had a diagnosis of paranoid schizophrenia, and 58 had other diagnoses. Two hundred one patients were randomly assigned to the interventions (54 to low-dose paliperidone, 48 to medium-dose paliperidone, 48 to high-dose paliperidone, 51 to placebo) and 139 patients were followed to the study endpoint at 6 weeks. No patients exhibited suicidal behavior.

One RCT[74] compared the efficacy of low- and high-dose quetiapine and placebo in adolescents (aged 13 to 17 years) with schizophrenia based on DSM-IV and K-SADS-PL criteria. Schizophrenia subtypes identified were paranoid (n = 155), undifferentiated (n = 48), disorganized (n = 16), and residual (n = 1). Two hundred twenty-two patients were randomly assigned to the interventions (73 to low-dose quetiapine, 74 to high-dose quetiapine, 75 to placebo), and all patients were followed to the endpoint at 6 weeks. The mean dosage of the drugs was 400 mg/day and 800 mg/day for the low- and high-dose quetiapine groups, respectively. 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 Caregiver Strain Questionnaire scores.

An RCT conducted by Haas et al.,[58] examined the efficacy of low- and high-dose risperidone in adolescents (aged 13 to 17 years) with schizophrenia based on DSM-IV and K-SADS-PL criteria. Patients had the following schizophrenia subtypes: paranoid (n = 175), undifferentiated (n = 49), disorganized (n = 19), catatonic (n = 7), and residual (n = 7) schizophrenia. Two hundred fifty-seven patients were randomly assigned to the interventions (132 to low-dose risperidone, 125 to high-dose risperidone) and 172 patients were followed to the endpoint at 8 weeks. The mean dosage of the drugs was 0.4 mg/day and 4 mg/day for the low- and high-dose risperidone groups, respectively. Sustained response (time until >20 percent change in PANSS score) was statistically 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 patients receiving high-dose risperidone was nonadherent.

An RCT conducted by DelBello et al.[51] compared the efficacy of low- and high-dose ziprasidone in treating children and adolescents (aged 10 to 17 years) with bipolar mania, schizophrenia, and schizoaffective disorder based on DSM-IV-TR criteria. Separate analyses were provided for patients with schizophrenia. Participants were randomly assigned to low- (80 mg/day; 8 participants) or high-dose (160 mg/day; 9 participants) ziprasidone and were followed for 3 weeks. One patient in the high-dose group reported suicidal ideation; however, it is unclear whether this patient had bipolar disorder or schizophrenia.

Second generation antipsychotics versus placebo. Six placebo-controlled studies evaluated the efficacy of second generation antipsychotics on short- and long-term outcome in patients with schizophrenia. The studies evaluated aripiprazole,[53] olanzapine,[63,97] paliperidone,[80] quetiapine,[74] and ziprasidone.[76]

Findling et al.[53] conducted an RCT to compare the efficacy of low-dose aripiprazole, high-dose aripiprazole, and placebo in adolescents (aged 13 to 17 years) with schizophrenia (described previously). Remission rate (PANSS score <3 for several items) was significantly higher in both the low- and high-dose aripiprazole groups compared with placebo ($p = 0.02$ and $p = 0.003$ for low- and high-dose aripiprazole, respectively). There was no significant difference between aripiprazole and placebo for time to discontinuation and quality of life scores.

An RCT was conducted by Kryzhanovskaya et al.[63] compared olanzapine with placebo in adolescents (aged 13 to 18 years) with schizophrenia based on DSM-IV-TR and K-SADS criteria. One hundred seven patients were randomly assigned to the interventions (72 to olanzapine, 35 to placebo) and patients were followed to the endpoint at 6 weeks with a 6-month extension. The mean dose of olanzapine was 11.1 mg/day. Treatment response (reduction >30 percent in BPRS from baseline and CGI-S <3 at endpoint) and time to response did not differ significantly between groups. There were no reports of suicide-related behaviors in either group and nonadherence did not differ between the olanzapine and placebo groups.

Robb et al.[80] conducted an RCT to compare the efficacy of low-, medium- and high-dose extended release paliperidone and placebo in adolescents (aged 12 to 17 years) with schizophrenia (described previously). None of the patients exhibited suicide-related behaviors.

One RCT[74] compared the efficacy of low- and high-dose quetiapine and placebo in adolescents (aged 13 to 17 years) with schizophrenia (described previously). Compared with the placebo group, scores on the Caregiver Strain Questionnaire showed significantly greater improvement in the low-dose quetiapine group ($p = 0.01$). The groups did not differ significantly on rate of treatment response.

An RCT[76] evaluated the efficacy of ziprasidone compared with placebo in adolescents (aged 13 to 17 years) with schizophrenia based on DSM-IV and Childhood disorders form of the Structured Clinical Interview for DSM-IV Disorders criteria. One hundred eighty-four patients were diagnosed with paranoid type schizophrenia; the subtype was not reported for the remaining patients. Two hundred eighty-four patients were randomly assigned to the interventions and were followed to the study endpoint at 6 weeks. The target dosage for each of the drugs 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 there were no reports in the placebo group; however, this difference was not statistically significant.

An RCT conducted by Woods et al.[97] examined the efficacy of olanzapine in patients (aged 12 to 45 years, mean age: 17.7 years) with prodromal syndromes based on DSM-IV, Criteria of Prodromal Syndromes, and Presence of Psychosis scale criteria. Comorbid marijuana abuse was present in 16 patients and other substance abuse (except nicotine) was present in 11 patients. Sixty patients were randomly assigned to the interventions (31 to olanzapine, 29 to placebo) and 59 patients were followed to the endpoint at 8 weeks with a 1-year extension. The mean dosage of the drugs was 8±3.1 mg/day and 9.3±2.8 mg/day for the olanzapine and placebo groups, respectively. There were no statistically significant differences between the groups for rate of conversion to psychosis or medication adherence.

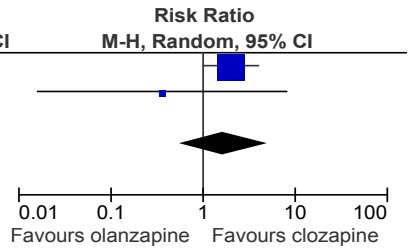
Two RCTs[64,85] provided data for a meta-analysis comparing clozapine and olanzapine for treatment response rate (Figure 45). The pooled estimate of the trials showed no statistically

significant difference between the two second generation antipsychotics (RR = 1.64; 95% CI, 0.55 to 4.93). Heterogeneity among the two studies was minimal (p = 0.28, I^2 = 15 percent).

Figure 45. Clozapine versus olanzapine on response rate in schizophrenia

Study or Subgroup	Clozapine Events	Clozapine Total	Olanzapine Events	Olanzapine Total	Weight	Risk Ratio M-H, Random, 95% CI
Kumra 2008	12	18	7	21	88.6%	2.00 [1.01, 3.98]
Shaw 2006	0	12	1	13	11.4%	0.36 [0.02, 8.05]
Total (95% CI)		**30**		**34**	**100.0%**	**1.64 [0.55, 4.93]**
Total events	12		8			

Heterogeneity: Tau² = 0.23; Chi² = 1.17, df = 1 (P = 0.28); I² = 15%
Test for overall effect: Z = 0.89 (P = 0.37)

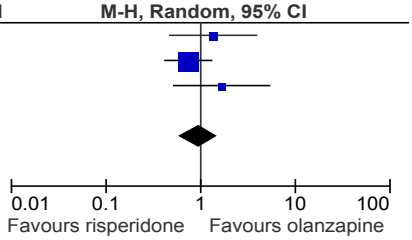


Three RCTs[72,87,96] compared olanzapine and risperidone for treatment response rate (Figure 46). The pooled result showed no difference between the second generation antipsychotics (RR = 0.95; 95% CI, 0.59 to 1.53). Heterogeneity among the studies was negligible (p = 0.35, I^2 = 4 percent).

Figure 46. Olanzapine versus risperidone on response rate in schizophrenia

Study or Subgroup	Olanzapine Events	Olanzapine Total	Risperidone Events	Risperidone Total	Weight	Risk Ratio M-H, Random, 95% CI
Mozes 2006	5	12	4	13	19.8%	1.35 [0.47, 3.89]
Sikich 2008	12	35	19	41	63.9%	0.74 [0.42, 1.30]
van Bruggen 2003	5	18	4	24	16.3%	1.67 [0.52, 5.34]
Total (95% CI)		**65**		**78**	**100.0%**	**0.95 [0.59, 1.53]**
Total events	22		27			

Heterogeneity: Tau² = 0.01; Chi² = 2.09, df = 2 (P = 0.35); I² = 4%
Test for overall effect: Z = 0.20 (P = 0.84)

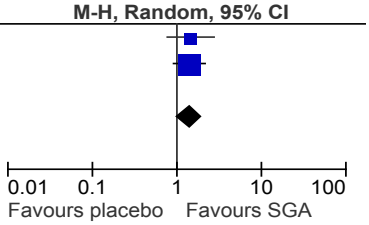


Two RCTs reported response rate for second generation antipsychotics versus placebo (Figure 47).[63,74] One study examined olanzapine[63] and the other examined quetiapine.[74] The pooled result was not statistically significant (RR = 1.42; 95% CI, 0.99 to 2.03) and there was no evidence of heterogeneity (p = 0.92, I^2 = 0 percent).

Figure 47. Second generation antipsychotics versus placebo on response rate in schizophrenia

Study or Subgroup	SGA Events	SGA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Kryzhanovskaya 2009	27	72	9	35	31.3%	1.46 [0.77, 2.76]
NCT00090324 2008	55	147	20	75	68.7%	1.40 [0.91, 2.16]
Total (95% CI)		**219**		**110**	**100.0%**	**1.42 [0.99, 2.03]**
Total events	82		29			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 1.93 (P = 0.05)

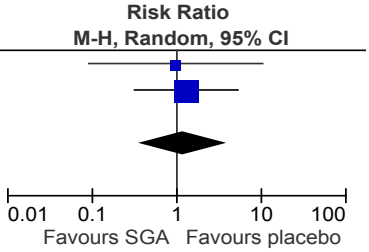


Two RCTs reported medication adherence rate for olanzapine versus placebo (Figure 48).[63,97] There was no significant difference in the proportion of patients who were nonadherent between the groups (RR = 1.20; 95% CI, 0.36 to 4.01) and there was no evidence of heterogeneity (p = 0.84, I^2 = 0 percent).

Figure 48. Olanzapine versus placebo on adherence rate in schizophrenia

Study or Subgroup	SGA Events	SGA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Kryzhanovskaya 2009	2	72	1	35	26.1%	0.97 [0.09, 10.36]
Woods 2003	4	30	3	29	73.9%	1.29 [0.32, 5.26]
Total (95% CI)		**102**		**64**	**100.0%**	**1.20 [0.36, 4.01]**
Total events	6		4			

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.29 (P = 0.77)



Two RCTs provided data on the rate of suicide-related behavior comparing second generation antipsychotics and placebo.[63,80] There were no events reported in either study, so meta-analysis was not possible.

Table 33. Study and patient characteristics for studies examining schizophrenia

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
de Haan, 2003[49] RCT, 6 wk	**G1:** Haloperidol (12), 2.5 mg/day **G2:** Olanzapine (12), 7.5 mg/day	**G1:** 21.0±2.8 (17-26) yr / Male: NR / Caucasian: NR **G2:** 21±2.3 (17–25) yr / Male: NR / Caucasian: NR Comorbidities: MR (0)	disorganized (6), paranoid (13), undifferentiated (5) 20, 0
DelBello, 2008[51] RCT, 3 wk (24 wk extension)	**G1:** Ziprasidone (low) (8), target: 80 mg/day **G2:** Ziprasidone (high) (9), target: 160 mg/day	**G1:** 14.4±2.3 yr / Male: 52% / Caucasian: NR **G2:** 14.7±2.0 yr / Male: 75% / Caucasian: NR Comorbidities: MR (0), SA (0)	NR NR, NR
Findling, 2008[53] RCT, 6 wk	**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% / Caucasian: 54% **G2:** 15.4±1.4 yr / Male: 64% / Caucasian: 61% **G3:** 15.4 ±1.4 yr / Male: 61% / Caucasian: 64% Comorbidities: NR	NR NR, 79
Haas, 2009[58] RCT, 8 wk	**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% / Caucasian: 85% **G2:** 15.6±1.3 (13-17) yr / Male: 52% / Caucasian: 85% Comorbidities: NR	catatonic (7), disorganized (19), paranoid (175), residual (7), undifferentiated (49) NR, NR
Jensen, 2008[61] RCT, 12 wk	**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% / Caucasian: 50% **G2:** 14.8±2.3 yr / Male: 70% / Caucasian: 60% **G3:** 15.6±2.5 yr / Male: 80% / Caucasian: 70% Comorbidities: MR (0), psychosis (all)	psychotic disorder NOS (9), schizophrenia/schizoaffective disorder (16), schizophreniform disorder (5) NR, 23
Kryzhanovskaya, 2009[63] RCT, 6 wk (6 mo extension	**G1:** Olanzapine (72), 11.1 mg/day **G2:** Placebo (35)	**G1:** 16.1±1.3 (13-18) yr / Male: 71% / Caucasian: 72% **G2:** 16.3±1.6 (13.1-18) yr / Male: 69% / Caucasian: 71% Comorbidities: MR (0), SA (0)	NR NR, 26
Kumra, 2008[64] RCT, 12 wk (12 wk extension)	**G1:** Clozapine (19), 403.1±201.8 mg/day **G2:** Olanzapine (21), 26.2±6.5 mg/day	**G1:** 15.8±2.2 yr / Male: 44% / Caucasian: 11% **G2:** 15.5±2.1 yr / Male: 62% / Caucasian: 29% Comorbidities: MR (0)	schizoaffective disorder (14), schizophrenia (25) 0, 0

ADHD = attention deficit hyperactivity disorder; ASD = autism spectrum disorder; CD = conduct disorder; ER = extended release; G = group; mg =milligram; mo = month; MR = mental retardation; N = number; NR = not reported; NRCT = nonrandomized controlled trial; OCD = obsessive-compulsive disorder; PDD = pervasive developmental disorder; RCT = randomized controlled trial; SA = substance abuse; SD = standard deviation; wk = week; yr = year

Table 33. Study and patient characteristics for studies examining schizophrenia (continued)

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Kumra, 1998[66] Prospective cohort, G1: 6 wk, G2: 8 wk	**G1:** Clozapine (15), 317±147 mg/day **G2:** Olanzapine (8), 17.5±2.3 mg/day	**G1:** 13.6±1.5 yr / Male: 53% / Caucasian: NR **G2:** 15.3±2.3 yr / Male: 50% / Caucasian: NR Comorbidities: NR	disorganized (11), paranoid (3), undifferentiated (9) NR, NR
Mozes, 2006[72] RCT, 12 wk	**G1:** Olanzapine (12), 8.2±4.4 mg/day **G2:** Risperidone (13), 1.6±1 mg/day	**G1:** 11.5±1.6 (8.5-14) yr / Male: 42% / Caucasian: NR **G2:** 10.7±1.4 (8.8-13.3) yr / Male: 39% / Caucasian: NR Comorbidities: ADHD (3), epilepsy (2), familial mediterranean fever (1), MR (0), neurofibromatosis (1), OCD (3), tic disorder (1)	disorganized schizophrenia (7), paranoid schizophrenia (6), schizophreniform disorder (10), unspecified schizoprehenia (2) NR, 24
NCT00090324, 2008[74] RCT, 6 wk	**G1:** Quetiapine (low) (73), 400 mg/day **G2:** Quetiapine (high) (74), 800 mg/day **G3:** Placebo (75)	**G1:** 15.5±1.3 (13-17) yr / Male: 59% / Caucasian: 62% **G2:** 15.5±1.3 (13-17) yr / Male: 60% / Caucasian: 60% **G3:** 15.3±1.4 (13-17) yr / Male: 58% / Caucasian: 63% Comorbidities: NR	disorganized (16), paranoid (155), residual (1), undifferentiated (48) NR, NR
NCT00257192, 2010[76] RCT, 6 wk	**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 / Caucasian: NR **G2:** 15.4 yr / Male: NR / Caucasian: NR Comorbidities: NR	paranoid type (184) NR, NR
Ratzoni, 2002[78] Prospective cohort, 12 wk	**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 (15-19) yr / Male: 63% / Caucasian: NR **G2:** 17±1.6 (14-19) yr / Male: 67% / Caucasian: NR **G3:** 17.1±2.1 (13-20.5) yr / Male: 57% / Caucasian: NR Comorbidities: NR	CD (2), schizoaffective disorder (2), schizophrenia (46) NR, 9
Robb, 2009[80] RCT, 6 wk	**G1:** Paliperidone ER (low) (54), NR **G2:** Paliperidone ER (medium) (48), NR **G3:** Paliperidone ER (high) (48), NR **G4:** Placebo (51)	**G1:** NR / Male: NR / Caucasian: NR **G2:** NR / Male: NR / Caucasian: NR **G3:** NR / Male: NR / Caucasian: NR **G4:** NR / Male: NR / Caucasian: NR Comorbidities: NR	paranoid schizophrenia (143), other (58) NR, NR
Shaw, 2006[85] RCT, 8 wk (2 yr extension)	**G1:** Clozapine (12), 327±113 mg/day **G2:** Olanzapine (13), 18.1±4.3 mg/day	**G1:** 11.7±2.3 yr / Male: 67% / Caucasian: 58% **G2:** 12.8±2.4 yr / Male: 54% / Caucasian: 54% Comorbidities: ADHD (7), anxiety disorders (7), MR (0)	NR 0, 0

Table 33. Study and patient characteristics for studies examining schizophrenia (continued)

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Sikich, 2008[87] RCT, 8 wk (44 wk extension)	**G1:** Olanzapine (36), 11.4±5 mg/day **G2:** Rispiradone (42), 2.8±1.4 mg/day	**G1:** NR / Male: 71% / Caucasian: 60% **G2:** NR / Male: 66% / Caucasian: 61% Comorbidities: ADHD (22), affective disorder (19), anxiety disorder (21), ASD (5), DBD (16), learning disability (3), MR (0), psychosis (10), SA (4)	schizoaffective disorder (26), schizophrenia (50) 73, 22
van Bruggen, 2003[96] RCT, olanzapine 9.8 wk, risperidone 6.7 wk	**G1:** Olanzapine (18), 15.6±4 mg/day **G2:** Risperidone (26), 4.4±1.5 mg/day	**G1:** 21±2.8 yr / Male: 72% / Caucasian: NR **G2:** 20.6±3 yr / Male: 85% / Caucasian: NR Comorbidities: NR	NR 38, NR
Woods, 2003[97] RCT, 8 wk (12 mo extension	**G1:** Olanzapine (31), 8±3.1 mg/day **G2:** Placebo (29)	**G1:** 18.2±5.5 yr / Male: 68% / Caucasian: 74% **G2:** 17.2±4 yr / Male: 62% / Caucasian: 59% Comorbidities: SA (marijuana (16), other (11))	NR all, 53

Table 34. Outcome data for studies assessing schizophrenia

Author, Year	Intervention (N analyzed)	Outcome	G1: Events (Rate)	G2: Event (Rate)	G3: Events (Rate)	p-value
de Haan, 2003[49]	G1: Haloperidol (10) G2: Olanzapine (9)	Subjective Well-being under Neuroleptics scale, change	158.0 (35.9) / 6 wk: 11.7 (10.2)	154.0 (21.1) / 6 wk: 4.7 (15.6)	NA	0.26
		Adherence	10 (1.0)	9 (1.0)	NA	1.0
DelBello, 2008[51]	G1: Ziprasidone, 40 mg BID (8) G2: Ziprasidone, 80 mg BID (9)	Suicidal ideation	0 (0)	1 (0.04)	NA	0.73
Findling, 2008[53]	G1: Aripiprazole, 10 mg/day (99) G2: Aripiprazole, 30 mg/day (97) G3: Placebo (98)	Remission	53 (0.54)	56 (0.58)	35 (0.36)	G1 vs. G2: 0.55 G1 vs. G3: 0.02 G2 vs. G3: 0.003
		Time to discontinuation	NR	NR	NR	G1 vs. G2: NR G1 vs. G3: 0.20 G2 vs. G3: 0.11
		PQLESQ	43.9 (90.5) / 6 wk: 5.2 (8.9)	44.3 (89.6) / 6 wk: 5.9 (8.9)	44.3 (94.0) / 6 wk: 4.5 (8.9)	G1 vs. G2: 0.98 G1 vs. G3: 0.55 G2 vs. G3: 0.26
		Death by suicide	0 (0)	0 (0)	NA	1.0
Haas, 2009[58]	G1: Risperidone, 0.15–0.6 mg/day (131) G2: Risperidone, 1.5 to 6.0 mg/day (124)	Sustained response	52 (0.40)	80 (0.65)	NA	<0.001
		Suicide attempt	0 (0)	0 (0)	NA	1.0
		Suicidal ideation	2 (0.02)	0 (0)	NA	0.31
		Nonadherent	0 (0)	1 (0.01)	NA	0.48
Jensen, 2008[61]	G1: Olanzapine (10) G2: Quetiapine (10) G3: Risperidone (10)	Response	5 (0.50)	3 (0.30)	7 (0.70)	0.65
		Nonadherent	1 (0.1)	0 (0)	0 (0)	G1 vs. G2 / G1 vs. G3: 0.49 G2 vs. G3: 1.0
Kryzhanovskaya, 2009[63]	G1: Olanzapine (72) G2: Placebo (35)	Response	27 (0.38)	9 (0.26)	NA	0.28
		Time to response	NR	NR	NA	>0.05
		Suicide-related behaviors	0 (0)	0 (0)	NA	1.0
		Nonadherence	2 (0.03)	1 (0.03)	NA	0.98

BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impressions–Severity; DB = double blind; G = group; mo = month; HAM-D = Hamilton Depression Scale; N = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Symptom Scale; PQLESQ = Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire; SD = standard deviation; wk = week; YMRS = Young Mania Rating Scale

Table 34. Outcome data for studies assessing schizophrenia (continued)

Author, Year	Intervention (N analyzed)	Outcome	G1: Events (Rate)	G2: Event (Rate)	G3: Events (Rate)	p-value
Kumra, 2008[64]	G1: Clozapine (18) G2: Olanzapine (21)	Response	12 (0.66)	7 (0.33)	NA	0.038
Kumra, 1998[66]	G1: Clozapine (15) G2: Olanzapine (8)	Response	8 (0.53)	0 (0)	NA	0.11
		Partial response at wk 6	1 (0.07)	1 (0.13)	NA	0.58
		Full or partial response at wk 8	2 (0.25)	1 (0.13)	NA	0.96
Mozes, 2006[72]	G1: Olanzapine (12) G2: Risperidone (13)	Reduction of 50%, PANSS	5 (0.42)	4 (0.31)	NA	0.57
		Reduction of 50%, BPRS	4 (0.33)	3 (0.23)	NA	0.57
NCT00090324, 2008[74]	G1: Quetiapine, 400 mg/day (73) G2: Quetiapine, 800 mg/day (74) G3: Placebo (75)	Response	28 (0.38)	27 (0.37)	20 (0.26)	G1 vs. G2: 0.81 G1 vs. G3: 0.11 G2 vs. G3: 0.19
		Caregiver Strain Questionnaire, change	-0.47	-0.30	-0.17	G1 vs. G3: 0.01 (favors G1); G2 vs. G3: 0.25
NCT00257192, 2008[76]	G1: Ziprasidone (189) G2: Placebo (87)	Suicidal ideation	3 (0.02)	0 (0)	NA	0.44
Ratzoni, 2002[78]	G1: Haloperidol (8) G2: Olanzapine (21) G3: Risperidone (21)	Nonadherence	0 (0)	1 (0.05)	1 (0.05)	G1 vs. G2 / G1 vs. G3: 0.91 G2 vs. G3: 1.0
Robb, 2009[80]	G1: Paliperidone, low (NR) G2: Paliperidone, medium (NR) G3: Paliperidone, high (NR) G4: Placebo (NR)	Suicide-related behaviors	0 (0)	0 (0)	0 (0) 0 (0)	NA
Shaw, 2006[85]	G1: Clozapine (12) G2: Olanzapine (13)	Full response	0 (0)	1 (0.08)	NA	0.52
		Partial response	4 (0.31)	2 (0.15)	NA	0.31
		Non-response	8 (0.67)	10 (0.77)	NA	0.67
Sikich, 2008[87]	G1: Olanzapine (35) G2: Risperidone (41)	Response	12 (0.34)	19 (0.46)	NA	0.30
		Death by suicide	0 (0)	1 (0.02)	NA	0.56
		Suicidal ideation	0 (0)	1 (0.02)	NA	0.56
		Nonadherence, DB acute phase	7 (0.2)	4 (0.10)	NA	0.21
		Nonadherence	0 (0)	0 (0)	2 (0.11)	0.323
		Response: BPRS	3 wk: 6 (0.55) / 6 wk: 6 (0.55)	3 wk: 4 (0.36) / 6 wk: 5 (0.46)	NA	3 wk: 0.67 6 wk: 1.0

Table 34. Outcome data for studies assessing schizophrenia (continued)

Author, Year	Intervention (N analyzed)	Outcome	G1: Events (Rate)	G2: Event (Rate)	G3: Events (Rate)	p-value
Sikitch, 2008 (continued)		Response: CGI-S	3 wk: 3 (0.27) / 6 wk: 5 (0.46)	3 wk: 3 (0.27) / 6 wk: 6 (0.55)	NA	3 wk: 1.0 6 wk: 1.0
		Response: HAM-D	3 wk: 6 (0.6) / 6 wk: 5 (0.50)	3 wk: 6 (0.6) / 6 wk: 7 (0.7)	NA	3 wk: 1.0 6 wk: 0.65
		Response: YMRS	3 wk: 8 (0.73) / 6 wk: 7 (0.64)	3 wk: 8 (0.73) / 6 wk: 10 (0.91)	NA	3 wk: 1.0 6 wk: 0.311
van Bruggen, 2003[96]	G1: Olanzapine (18) G2: Risperidone (24)	Response	wk 6: 3 (0.17); wk 10: 5 (0.28)	wk 6: 4 (0.17); wk 10: 4 (0.17)	NA	wk 6: >0.05; wk 10: >0.05
		Time to response	NR	NR	NA	0.46
		Time to non-response	NR	NR	NA	0.36
		Adherent	16 (0.88)	21 (0.88)	NA	0.89
Woods, 2003[97]	G1: Olanzapine (30) G2: Placebo (29)	Conversion to psychosis rate	12 mo: 5 (0.16) / 24 mo: 3/9 (0.33)	12 mo: 11 (0.38) / 24 mo: 2/8 (0.25)	NA	12 mo: 0.08; 24 mo: 1.0
		Adherence, % (SD)	87.8 (14.8)	89.3 % (11.4)	NA	0.66

Results by individual study: Psychosis. Four RCTs examined the efficacy of antipsychotics on short- and long-term outcomes in patients experiencing a first episode of psychosis.[42,45,88,91] The number of participants ranged from 22 to 141 (median = 50 [IQR, 43 to 73]. One study[88] compared a first generation antipsychotic with two second generation antipsychotics and four studies compared various second generation antipsychotics.[42,45,88,91] Outcomes could not be pooled in a meta-analysis because studies examined different comparisons. Patient and study characteristics and outcome data are presented in Table 35 and Table 36, respectively.

First generation versus second generation antipsychotics. Sikich et al.[88] conducted an RCT comparing the efficacy of haloperidol, olanzapine, and risperidone in children (aged 8 to 19 years) with affective disorders (n = 24) and schizophrenia spectrum disorder (n = 26) based on DSM-IV and K-SADS present episode version criteria. Fifty patients were randomly assigned to the interventions (15 to haloperidol, 16 to olanzapine, 19 to risperidone) and 32 patients were followed to the endpoint at 8 weeks. The mean dosage of the drugs was 5±2 mg/day, 12.3±3.5 mg/day, and 4±1.2 mg/day for the haloperidol, olanzapine, and risperidone groups, respectively. Patients were assessed for treatment response (CGI-I score of 2 and a reduction of ≥20 percent on the BPRS-C total score) and nonadherence; there were no statistically significant differences between the three groups on these measures.

Second generation versus second generation antipsychotics. Four RCTs including patients with first episode psychosis compared the efficacy of various second generation antipsychotics: olanzapine versus quetiapine,[42] olanzapine versus risperidone,[88] low- versus high-dose quetiapine,[45] and quetiapine versus risperidone.[91]

An RCT conducted by Arango et al.[42] compared the efficacy of olanzapine and quetiapine in adolescents (ages 12 to 18 years) with psychosis based on DSM-IV and K-SADS-PL criteria. Fifty patients were randomly assigned to the interventions (26 to olanzapine, 24 to quetiapine) for 6 months. Thirteen patients had bipolar disorder, 17 had schizophrenia, and 20 had other psychoses: major depressive episode with psychotic features (five patients), schizoaffective disorder (five patients), schizophreniform disorder (four patients), and psychosis NOS (six patients). The mean dosage 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 statistically significant differences between the olanzapine and quetiapine groups were found for any of the outcomes.

Sikich et al.[88] conducted an RCT to compare the efficacy of olanzapine, risperidone, and haloperidol (described previously). There were no significant differences between olanzapine and risperidone for response or nonadherence.

Berger et al.[45] conducted an RCT to compare the efficacy of low- and high-dose quetiapine in patients (aged 15 to 25 years) with first episode psychosis based on DSM-IV and Clinical interview for DSM-IV-TR Axis I Disorders-Patient Edition criteria. No patients had comorbid mental retardation; 58 had problems with substance abuse. One hundred forty-one patients were randomly assigned to the interventions (69 to low-dose quetiapine, 72 to high-dose quetiapine) and were followed to the study endpoint at 4 weeks. The mean dosage of the drugs was 200 mg/day and 400 mg/day for the low- and high-dose groups, respectively. Treatment response (BPRS psychotic subscales score less than 3 and a CGI-I score less than 2) and remission (BPRS psychotic subscales score <3, CGI-S score <3, and a CGI-I score <2) did not differ between groups. Hospital admission rate was significantly lower in the high-dose group (p = 0.005).

There were no statistically significant differences between group on the number of deaths by suicide, imprisonments, days in hospital, or medication adherence.

An RCT conducted by Swadi et al.[91] evaluated the efficacy of quetiapine and risperidone in adolescents (aged <19 years) with first onset psychosis based on DSM-IV criteria. Twenty-two patients were randomized to receive quetiapine (n = 11) or risperidone (n = 11) for 6 weeks. The mean daily dosage was 607 mg/day and 2.9 mg/day for quetiapine and risperidone, respectively. 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, HAM-D, and YMRS. No statistically significant difference was found between the quetiapine and risperidone groups for treatment response or medication adherence.

Table 35. Study and patient characteristics for studies examining psychosis

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Arango, 2009[42] RCT, 6 mo	**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% / Caucasian: 77% **G2:** 16.3±1.1 yr / Male: 79% / Caucasian: 88% Comorbidities: NR	Bipolar disorder (13), schizophrenia (17), other psychoses (20) [MDD with psychotic features (5), psychosis NOS (6), schizoaffective disorder (5), schizophreniform disorder (4)] all, 25
Berger, 2008[45] RCT, 4 wk (8 wk extension)	**G1:** Quetiapine (low) (69), 200 mg/day **G2:** Quetiapine (high) (72), 400 mg/day	**G1:** 19.7±2.6 (15-24) yr / Male: 71% / Caucasian: NR **G2:** 19±2.9 (15-24) yr / Male: 64% / Caucasian: NR Comorbidities: MR (0), psychosis (all), SA (58)	NR all, 47
Sikich, 2004[88] RCT, 8 wk (12 wk extension)	**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% / Caucasian: 73% **G2:** 14.6±3.1 yr / Male: 56% / Caucasian: 63% **G3:** 14.6±2.9 yr / Male: 68% / Caucasian: 47% Comorbidities: NR	Affective disorders (24), schizophrenia spectrum (26) 39, 18
Swadi, 2010[91] RCT, 6 wk	**G1:** Quetiapine (11), 607 mg/day **G2:** Risperidone (11), 2.9 mg/day	**G1:** NR / Male: 55% / Caucasian: NR **G2:** NR / Male: 64% / Caucasian: NR Comorbidities: NR	NR NR, NR

G = group; MDD = major depressive disorder; mg = milligram; mo = month; MR = mental retardation; N = number; NOS = not otherwise specified; NR = not reported; RCT = randomized controlled trial; SA = substance abuse; SD = standard deviation; wk = week; yr = year

Table 36. Outcome data for studies assessing psychosis

Author, Year	Intervention (N analyzed)	Outcome	G1: Events (Rate)	G2: Event (Rate)	G3: Events (Rate)	p-value
Arango, 2009[42]	G1: Olanzapine (25) G2: Quetiapine (24)	Nonadherence	0 (0)	1 (0.04)	NA	0.48
	G1: Olanzapine (16) G2: Quetiapine (16)	Cognitive Domain: Attention	BL: –0.24 (0.91); 6 mo: 0.05 (0.45)	BL: 0.32 (0.63); 6 mo: 0.39 (0.51)	NA	0.12
		Cognitive Domain: Working Memory	BL: –0.27 (0.77); 6 mo: –0.18 (0.63)	BL: 0.49 (1.01); 6 mo: 0.43 (1.18)	NA	0.08
		Cognitive Domain: Learning and Memory	BL: 0.28 (0.77); 6 mo: 0.58 (1.12)	BL: 0.22 (0.90); 6 mo: 0.53 (1.02)	NA	0.68
		Cognitive Domain: Executive Functions	BL: –0.13 (0.64); 6 mo: –0.07 (0.76)	BL: 0.17 (0.70); 6 mo: 0.34 (0.70)	NA	0.29
Berger, 2008[45]	G1: Quetiapine, 200 mg/day (69) G2: Quetiapine, 400 mg/day (72)	Death by suicide	0 (0)	1 (0.01)	NA	0.52
		Imprisoned	0 (0)	1 (0.01)	NA	0.52
	G1: Quetiapine, 200 mg/day (62) G2: Quetiapine, 400 mg/day (64)	Response	wk 1–4: 38 (0.61); wk 5–12: 29 (0.46)	wk 1–4: 30 (0.47); wk 5–12: 37 (0.58)	NA	wk 1–4: 0.10; wk 5–12: 0.33
		Remission	wk 1–4: 9 (0.15); wk 5–12: 15 (0.23)	wk 1–4: 15 (0.23); wk 5–12: 20 (0.32)	NA	wk 1–4: 0.20; wk 5–12: 0.36
		Hospital admission rate	31 (0.51)	17 (0.27)	NA	0.005
	G1: Quetiapine, 200 mg/day (46) G2: Quetiapine, 400 mg/day (45)	Remained on medication	41 (0.90)	35 (0.78)	NA	0.14
	G1: Quetiapine, 200 mg/day (20) G2: Quetiapine, 400 mg/day (7)	No. days in hospital	17.4 (17.8)	9.6 (7.8)	NA	0.26
Sikich, 2004[88]	G1: Haloperidol (15) G2: Olanzapine (16) G3: Risperidone (19)	Response	8 (0.53)	14 (0.88)	14 (0.74)	0.12
		Nonadherence	0 (0)	0 (0)	2 (0.11)	0.323

BL = baseline; G = group; mg = milligram; mo = month; NA = not applicable; No. = number; wk = week

Table 36. Outcome data for studies assessing psychosis (continued)

Author, Year	Intervention (N analyzed)	Outcome	G1: Events (Rate)	G2: Event (Rate)	G3: Events (Rate)	p-value
Swadi, 2010[91]	G1: Quetiapine (11) G2: Risperidone (11)	Response: PANSS	3 wk: 5 (0.46) / 6 wk: 6 (0.55)	3 wk: 4 (0.36) / 6 wk: 8 (0.73)	NA	3 wk: 1.0 6 wk: 0.66
		Response: BPRS	3 wk: 6 (0.55) / 6 wk: 6 (0.55)	3 wk: 4 (0.36) / 6 wk: 5 (0.46)	NA	3 wk: 0.67 6 wk: 1.0
		Response: CGI-S	3 wk: 3 (0.27) / 6 wk: 5 (0.46)	3 wk: 3 (0.27) / 6 wk: 6 (0.55)	NA	3 wk: 1.0 6 wk: 1.0
		Response: HAM-D	3 wk: 6 (0.6) / 6 wk: 5 (0.50)	3 wk: 6 (0.6) / 6 wk: 7 (0.7)	NA	3 wk: 1.0 6 wk: 0.65
		Response: YMRS	3 wk: 8 (0.73) / 6 wk: 7 (0.64)	3 wk: 8 (0.73) / 6 wk: 10 (0.91)	NA	3 wk: 1.0 6 wk: 0.311

Tourette Syndrome

Summary. Four RCTs making four comparisons assessed the efficacy of antipsychotics for treating a variety of short- and long-term outcomes in patients with Tourette syndrome. The following is a summary of the results by outcome:

- *Response and remission.* Treatment response rate was reported in two RCTs. One[81] found no significant difference in response rate between haloperidol and pimozide; the second[84] found a significantly greater response rate in patients treated with risperidone compared with placebo. One RCT[111] 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.[83] There were no significant differences in reaction time between groups.
- *Medication adherence and persistence.* Adherence was assessed in one RCT[81] comparing haloperidol, pimozide, and placebo. Patients in all groups adhered to treatment; there was no difference between groups.
- There was insufficient evidence to make conclusions for any comparisons or outcomes.
- *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 or parent reported outcomes, health-related quality of life, legal system interactions, or health care system utilization.

Results by individual study. Four RCTs[81,83,84,111] examined the efficacy of antipsychotics on other short- and long-term outcomes. The number of participants ranged from 10 to 41 (median = 24 [IQR, 19 to 30]). Three RCTs compared the efficacy of two first generation antipsychotics: haloperidol versus pimozide[81,83] and short- pimozide versus long-term treatment with pimozide.[111] Haloperidol and pimozide were compared with placebo in one study.[81] One RCT compared risperidone with placebo.[84] No studies could be combined in a meta-analysis because the studies examined different comparisons. Patient and study characteristics and outcome data are presented in Table 37 and Table 38, respectively.

First generation versus first generation antipsychotics. A placebo-controlled crossover RCT by Sallee et al.[81] compared haloperidol, pimozide, and placebo in children (aged 7 to 16 years) with Tourette syndrome based on DSM-III-TR and K-SADS present episode version criteria. Comorbidities were ADHD (n = 13) and OCD (n = 5). Twenty-two patients were randomly assigned to an intervention sequence, which comprised 6 weeks of each treatment with an intervening 2-week placebo washout period. All patients were followed to the endpoint at 24 months. The mean daily dosage was 3.5±2.2 mg and 3.4±1.6 mg for the haloperidol and pimozide groups, respectively. 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.

Sallee et al.[83] evaluated the relative effects of haloperidol versus pimozide on cognition in patients (aged 7 to 16 years) diagnosed using the DSM-III-TR and Tourette Syndrome Global

Scale criteria. Thirteen patients had comorbid ADHD. Forty-one patients were randomly assigned to the interventions (17 to haloperidol, 24 to pimozide) and all patients were followed to the endpoint at 6 weeks. The mean daily dosage was 1.5±0.6 mg for haloperidol and 3.7±1.4 mg for pimozide. 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.

In a placebo-withdrawal study, Sehgal et al.[111] compared the efficacy of short- and long-term treatment with pimozide in patients (aged 7 to 13 years) diagnosed using the DSM-III-TR criteria. Ten patients were randomly assigned to continue on pimozide (n = 6) or gradual placebo withdrawal (n = 4) for 8 months or until a dose increase was required. The mean dosage was 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 compared with short-term pimozide ($p = 0.02$).

First generation antipsychotics versus placebo. One RCT[81] compared haloperidol, pimozide, and placebo for response rate and adherence (described previously). Response rate was significantly higher in both the haloperidol and pimozide groups compared with placebo ($p = 0.003$ and $p = 0.002$, respectively). Patients in all groups adhered to treatment protocol.

Second generation antipsychotics versus placebo. One RCT[84] evaluated the efficacy of risperidone in 34 patients (aged 7 to 65 years) diagnosed using DSM-IV criteria and a joint parent and child interview. Data were provided separately for 26 pediatric patients (mean age: 11.1±2.2 years). Comorbities were ADHD (n = 11) and OCD (n = 4). Twenty-six patients were randomly assigned to the interventions (12 to risperidone, 14 to placebo), and all patients were analyzed at the endpoint at 8 weeks. The mean dose of risperidone was 2.5±0.9 mg/day. A CGI-I score ≤2 points was regarded as a positive therapeutic response. The treatment response rate was statistically significantly higher in the risperidone group compared with the placebo group ($p<0.003$).

Table 37. Study and patient characteristics for studies examining Tourette syndrome

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Sallee, 1997[81] RCT (crossover), 24 wk	**G1:** Haloperidol (22)*, 3.5±2.2 mg/day **G2:** Pimozide (22)*, 3.4±1.6 mg/day **G3:** Placebo (22)*	**G1:** NR / Male: NR / Caucasian: NR **G2:** NR / Male: NR / Caucasian: NR Comorbidities: ADHD (13), OCD (5)	NR NR, NR
Sallee, 1994[83] RCT, 6 wk (3 wk extension)	**G1:** Haloperidol (17), 1.5±0.6 mg/day **G2:** Pimozide (24), 3.7±1.4 mg/day	**G1:** 10.4 yr / Male: NR / Caucasian: NR **G2:** 10.8 yr / Male: NR / Caucasian: NR Comorbidities: ADHD (13)	NR NR, NR
Scahill, 2003[84] RCT, 8 wk	**G1:** Risperidone (12), 2.5±0.9 mg/day **G2:** Placebo (14)	**G1:** NR / Male: NR / Caucasian: NR **G2:** NR / Male: NR / Caucasian: NR Comorbidities: ADHD (11), OCD (4)	NR NR, 24
Sehgal, 1999[111] RCT, 8 mo	**G1:** Pimozide (short-term) (4), 3.8 mg/day **G2:** Pimozide (long-term) (6), 3.5 mg/day	**G1:** NR / Male: NR / Caucasian: NR **G2:** NR / Male: NR / Caucasian: NR Comorbidities: NR	NR NR, all

ADHD = attention deficit hyperactivity disorder; CD = conduct disorder; DBD = disruptive behavior disorder; G = group; mg = milligrams; mo = month; N = number; NR = not reported; OCD = obsessive-compulsive disorder; ODD = oppositional defiant disorder; RCT = randomized controlled trial; SD = standard deviation; wk = week
*All patients received each of the treatment arms in this crossover study; 11 patients had haloperidol before pimozide and 11 patients had pimozide before haloperidol

Table 38. Outcome data for studies assessing Tourette syndrome

Author, Year	Intervention (N analyzed)	Outcome	G1: Events (Rate)	G2: Event (Rate)	G3: Events (Rate)	p-value
Sallee, 1997[81]	G1: Haloperidol (22) G2: Pimozide (22) G3: Placebo (22)	Response	17 (0.65)	18 (0.69)	5 (0.23)	G1 vs. G2: 0.77 G1 vs. G3: 0.003 G2 vs. G3: 0.002
		Nonadherence	0 (0)	0 (0)	0 (0)	1.0
Sallee, 1994[83]	G1: Haloperidol (16) G2: Pimozide (22)	CPT errors: omissions	5.3 (6.9)	4.0 (4.6)	NA	<0.05
		CPT errors: commissions	5.3 (7.1)	1.5 (3.1)	NA	<0.05
		MST: reaction time at highest memory load	1.38 (0.39)	1.30 (0.44)	NA	>0.05
Scahill, 2003[84]	G1: Risperidone (12) G2: Placebo (14)	Response	9 (0.78)	1 (0.07)	NA	0.003
Sehgal, 1999[111]	G1: Pimozide, short-term (4) G2: Pimozide, long-term (6)	Time to dose increase due to tic exacerbation	37 days	231 days	NA	0.02

CPT = continuous performance task; G = group; MST = memory search task; N = number; NA = not applicable; NR = not reported

Behavioral symptoms

Summary. Two retrospective cohort studies examined the relative effectiveness of different second generation antipsychotics for treating patients with behavioral disturbances on various short- and long-term measures. A study[44] 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.[62] The evidence for all comparisons and outcomes was insufficient to make conclusions.

Results by individual study. Two retrospective cohort studies[44,62] examined the efficacy of second generation antipsychotics on other short- and long-term outcomes. Comparisons included aripiprazole versus ziprasidone[44] and olanzapine versus ziprasidone.[62] No outcome data could be pooled in a meta-analysis because the studies examined different comparisons. Patient and study characteristics and outcome data are presented in Table 39 and Table 40, respectively.

Second generation versus second generation antipsychotics. Bastiaens[44] compared the efficacy of aripiprazole and ziprasidone in children and adolescents (aged 6 to 17 years) with aggressive behaviour in a retrospective cohort study. Forty-six patients treated with aripiprazole (n = 24) or ziprasidone (n = 22) were assessed using the Health and Life Functioning scale. Patients were diagnosed with bipolar disorder (n = 12), conduct disorder (n = 14), depressive disorder (n = 6), mood disorder NOS (n = 8), pervasive developmental disorder (n = 2), and psychotic disorder (n = 4) based on DSM-IV criteria and Mini International Neuropsychiatric Interview for Children and Child/Adolescent Symptom Inventory. Mean daily dose was 4.5±2.3 mg and 42.9±18 mg for aripiprazole and ziprasidone, respectively. After 2 months of treatment, quality of life improved in both groups; however, there was no statistically significant difference between the groups.

Khan et al.[62] conducted a retrospective cohort study comparing the efficacy of olanzapine and ziprasidone for treating aggression in youth (aged <18 years). Intramuscular olanzapine (n = 50) or intramuscular ziprasidone (n = 50) was used to treat agitation or aggression in psychiatric inpatients. The mean daily dose was 8.2±2.4 mg for olanzapine and 19.1±2.6 mg for ziprasidone. The mean duration of treatment was 3.7±2.4 weeks (olanzapine group) and 4.9±3.4 weeks (ziprasidone group). 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.

Table 39. Study and patient characteristics for studies examining behavioral symptoms

Author, Year Study design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / Caucasian (%) Comorbidities	Diagnosis Breakdown (n) First Episode Psychosis (n), Treatment naïve (n)
Bastiaens, 2009[44] Aggression Retrospective cohort, 2 mo	**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% / Caucasian: NR **G2:** 12.1±2.9 yr / Male: 91% / Caucasian: NR Comorbidities: NR	Bipolar (12), CD (14), depressive disorder (6), mood disorder NOS (8), PDD (2), psychotic disorder (4) NR, 34
Khan, 2006[62] Agitation & aggression Retrospective cohort, 1 mo	**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% / Caucasian: 60% **G2:** 14.6±2.1 yr / Male: 32% / Caucasian: 68% Comorbidities: MR (0), PTSD (18), SA (27)	Psychosis (34) NR, NR

CD = conduct disorder; G = group; mg = milligrams; mo = month; MR = mental retardation; N = number; NOS = not otherwise specified; NR = not reported; PDD = pervasive developmental disorder; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; SA = substance abuse; SD = standard deviation

Table 40. Outcome data for studies assessing behavioral symptoms

Author, Year	Intervention (N analyzed)	Outcome	G1: Mean (SD)	G2: Mean (SD)	p-value
Bastiaens, 2009[44]	G1: Aripiprazole (20) G2: Ziprasidone (14)	Health and life functioning scale	10.0 (2.9) / 2 mo: 13.1 (4.0)	8.7 (3.8) / 2 mo: 11.6 (3.6)	0.43
Khan, 2006[62]	G1: Olanzapine (50) G2: Ziprasidone (50)	Length of hospital stay (days)	26 (17)	34 (24)	0.053
		Mean number of restrains within 4 hr after medication	0.32	0.44	0.56
		Mean time in restrain after medication (min)	41	38	0.218

G = group; Hr = hour; min = minute; mo = month; N = number; NA = not applicable; SD = standard deviation

Question 4: Subpopulations

Summary. Overall, 32 of the 74 studies examined patient outcomes across various subpopulations. The following is a summary of the results for eight subgroups identified a priori:

- *Gender:* The effect of gender on various outcomes was reported in 17 studies. No impact of gender was found for aggression, mania scores, response rate, and time and number of physical restraints. Findings for the associations between gender and prolactin levels and weight were inconsistent across studies.
- *Age:* The impact of age was examined in 16 studies. Younger patients had greater improvement in symptom scores, had lower prolactin levels, and showed more irritability compared with older patients (one study each). Studies found no impact of age on psychiatric symptoms as measured by the CPRS, treatment response, illness relapse, conversion to psychosis, symptom recurrence, mania, ADHD symptoms, time and number of physical restraints, total adverse events and rate of study completion. The effect of age on aggression, clinical impressions, and weight gain was varied across the studies.
- *Race:* Four studies evaluated the impact of race on various outcomes. One study found that race (African American) predicted conversion to psychosis. Race had no impact on determining the mania scores, on increase in BMI, or study completion rate (one study each).
- *Comorbidities:* Seven studies reported the effect of comorbidities on outcomes. Mental retardation was associated with poorer treatment response rate in two studies. Patients with ADHD made significantly more errors on a continuous performance task than patients without ADHD in one study. No effect was found for mood disorders on response rate (one study), mental retardation, ADHD, secondary diagnosis of disruptive behavior disorders on conduct problem (one study), and ADHD and bipolar subtypes on mania and clinical impression scores (one study). Substance abuse and presence of psychosis were not related to weight gain or risk of adverse health outcome, but psychosis was related to drug dose (one study each).
- *Cotreatment:* The effect of cotreatment on various outcomes was reported in seven studies. One study found a higher response rate in patients who received at least one nonpharmacological intervention in addition to antipsychotic treatment. Cotreatment with antidepressants resulted in significantly less weight gain, while other cotreatments (not specified) had no effect on weight gain (one study). There was no impact of cotreatment with psychostimulant on conduct problem, weight gain, or mania scores (one study). No effect was found for anti-seizure medication, mood stabilizers, or antidepressants on response rate, and for various cotreatments on risk for adverse health outcomes (one study each).
- *History of psychosis:* One study found that patients with first episode psychosis had greater impairment on neurocognitive function tests compared with people at risk for psychosis. No studies evaluated the impact of first episode of psychosis versus recurrent episodes of psychosis on outcomes.

- *Duration of illness:* Three studies reported no effect of duration of illness on global clinical judgments, neurocognitive performance, or weight gain (one study each).
- *Treatment history:* Five studies compared outcomes for treatment-naïve patients versus patients with previous use of antipsychotics. One study found that risperidone-naïve patients had lower conduct problem scores, lower prolactin levels, and more sedation compared with patients previously treated with risperidone. Prior treatment had no impact on symptom severity (one study), risk of adverse health outcome (one study), or weight gain (four studies).

Pervasive Developmental Disorders

Of the 11 studies examining first generation and second generation antipsychotics in patients with pervasive developmental disorder, three studies conducted an analysis of patient outcomes in different subpopulations. Studies used regression analysis[70] or subgroup analysis.[77,113]

One study[70] found no impact of gender on weight gain. Three studies found no significant effect of age on various outcomes, including weight gain,[70] BMI,[70] response,[113] and relapse.[70,77] One study[113] 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 antipsychotic therapy.

ADHD and Disruptive Behavior Disorders

Five of seven studies examining antipsychotics in patients with ADHD and disruptive behavioral disorders conducted an analysis of patient outcomes in different subpopulations. Studies used regression analysis[55,89] and subgroup analysis.[41,47,79] Two studies assessed the impact of gender on prolactin levels: Females experienced a greater increase in prolactin levels compared with males in one study,[79] while a second study found males but not females to experience a significant increase in prolactin levels while on risperidone.[41] Two studies found no effect of age on Rating of Aggression Against People and/or Property scale,[55] CPRS,[55] total adverse events,[79] rate of study completion,[55] and risk of symptom recurrence.[79] However, weight gain was more frequent in children younger than 12 years compared with children older than 12 years (nonsignificant).[79] In one study, race was not significantly different in patients who completed the study compared with those who did not.[55] Comorbidities, including mental retardation, ADHD, and secondary diagnosis of disruptive behavior disorders, had no effect on NCBRF conduct problem subscale in one study.[89]

Snyder et al.[89] found no impact of cotreatment with psychostimulants on NCBRF conduct problem subscale and weight gain. Two studies examined the effect of previous treatment on ABC,[47] CGI-S,[47] NCBRF conduct problem subscale,[89] weight gain,[89] prolactin levels,[89] and sedation.[89] Prior treatment had no impact on symptoms severity[47] or weight gain.[89] Risperidone-naïve patients had lower NCBRF conduct problem scores, lower prolactin levels, and reported sedation more frequently than patients who were previously treated with risperidone.[89]

Bipolar Disorder

Of the eight studies examining antipsychotics in patients with bipolar disorder, four studies conducted an analysis of patient outcomes in different subpopulations. Studies used regression analysis[92,93] or subgroup analysis.[54,57] Three studies investigated the effect of gender on YMRS[57] and prolactin levels.[54,92] Gender had no impact on YMRS scores.[57] Prolactin level were lower in males than females in one study,[54] while greater prolactin changes were reported in males than females in a second study.[92] Two studies found no impact of age on mania as measured on the YMRS,[57,93] ADHD symptoms on the Swanson, Nolan and Pelham Scale,[93] total adverse events,[57] and weight gain measures.[93] Race had no statistically significant impact on YMRS.[57] Another study[92] examined the impact of comorbidities and bipolar subtypes on CGI-BP and YMRS. Diagnosis of comorbid ADHD and bipolar diagnostic subtypes did not alter treatment outcome.[92] In addition, concomitant use of psychostimulants had no effect on YMRS scores.[92]

Schizophrenia and First Episode Psychosis

Eight studies examining efficacy of antipsychotics in patients with schizophrenia and first episode psychosis conducted an analysis of patient outcomes in different subpopulations. Studies used regression analysis,[78] subgroup analysis,[58,63,74,90,102,112] or both.[97] Four studies assessed the effect of gender on outcomes including weight gain,[78,102] BMI,[78] or prolactin levels.[58,112] Girls experienced higher weight and BMI increases compared with boys in one study.[78] In another study, weight gain greater than seven percent from baseline occurred more frequently in males than in females.[102] Findings in both studies were not statistically significant. Prolactin levels were significantly higher in females compared with males in patients given clozapine[112] or risperidone.[58] Three studies examined the impact of age on global clinical judgements rating,[90] treatment response,[88] and conversion to psychosis.[97] Younger patients experienced only mild or moderate improvement on the global clinical judgements rating scale compared with older patients.[90] Age had no impact on response rate or conversion to psychosis. One study[97] found that race (African American) predicted conversion to psychosis.

One study[88] 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. Woods et al.[97] analyzed the effect of history of psychosis and duration of prodromal symptoms on neurocognitive performance. Patients with first episode psychosis were significantly more impaired on neurocognitive function test compared with patients at risk for psychosis. Three studies found no impact of illness duration on global clinical judgements rating,[90] weight gain,[78] or neurocognitive performance.[97] One study[78] evaluated the effect of previous antipsychotic use on weight gain and no association was found.

Tourette Syndrome

Three studies on Tourette syndrome conducted an analysis of patient outcomes in different subpopulations. Studies used regression analysis[83] or subgroup analysis.[81,100] One crossover RCT[81] found no statistically significant difference in prolactin levels by gender. One study[100] investigated the effect on age on weight gain and on various condition specific and nonspecific outcomes (i.e., CGI, GAF, Hamilton Anxiety Rating Scale, PGI, Tourette's Symptom Severity Scale, and Yale-Brown Obsessive Compulsive Scale). Patients younger than 18 years of age had

better efficacy scores at endpoint and experienced more weight gain compared with patients older than 18 years, but the differences were not statistically significant. Patients with comorbid ADHD had a significantly higher error rate on continuous performance tasks compared with patient without ADHD.[83]

Behavioral Symptoms

Of the four studies examining antipsychotics in patients with behavioral symptoms, three studies conducted an analysis of patient outcomes in different subpopulations. Studies used subgroup analysis[44,59] or subgroup analysis and regression analysis.[62] Three studies investigated the effect of gender on outcomes including OAS,[44] response,[59] and number of restraints and time in restraints.[62] Aggression decreased more in males than females as measured using OAS, but the difference was not statistically significant. Gender was not a significant predictor of response or number of restrains and time in restraints. Three studies investigated the effect of age on ABC-I,[59] OAS,[44] weight gain,[59] prolactin levels,[59] response,[59] dose required for symptom reduction,[62] and number of restraints and time in restraints.[62] Children experienced more irritability (measured on ABC-I), greater weight gain, and lower prolactin levels compared with adolescents and adults.[59] In addition, children younger than 11 years showed decreased aggression compared with patients older than 12 years.[44] In another study, adolescents required a significantly higher dosage of olanzapine for symptom reduction; however, age had no impact on number of restrains or time in restraints in this study.[62] One study[59] also investigated the impact of comorbid mental retardation, mood disorder, and cotreatment with antiseizure medications on response. Patients with severe mental retardation showed poor response compared with patients with mild mental retardation, while mood disorders and concomitant antiseizure medications were not significant predictors of response.

Multiple Conditions

Four studies examining patients with a variety of psychiatric or behavioral diagnoses conducted an analysis of outcomes in different subpopulations. Studies used regression analysis[104] or subgroup analysis.[101,105,106] The effect of gender was assessed on weight gain,[104,105] BMI,[104,105] neuroleptic-inducted movement disorders,[106] and risk for adverse health outcomes.[105] Males gained more weight than females in one study, but the difference was not statistically significant.[105] Gender had no impact on substantial weight gain in two studies[104,105] or BMI in one study.[105] All patients who developed neuroleptic-induced movement disorders were female.[106] Males tended to be at risk of adverse health outcome more frequently compared with females.[105] Two studies found no effect of age on weight gain measures, including BMI.[104,105] As well, race had no impact on BMI increases in one study.[105] The study also examined the effect of comorbidities, including psychosis and substance abuse, on weight gain, risk for adverse health outcome. These outcomes were not related to presence of psychosis, length of inpatient treatment, tobacco use, alcohol abuse, or cannabis abuse.[105] One study found psychosis to be associated with high drug dose.[106]

Cotreatment with antidepressants resulted in significantly less weight gain than monotherapy in one study,[105] while a second study found no effect of comedications on weight gain.[104] Risk for adverse health outcomes was not affected by cotreatments.[105] Two studies assessed the effect of previous antipsychotic treatment on weight gain[104,105] and risk of adverse health outcome;[105] no significant effect was observed.

Table 41. Differences between patient subpopulations on treatment outcomes

Author, Year Comparison	Type of analysis	Outcome	Authors' conclusions
Pervasive developmental disorder			
McCracken, 2002[70] *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, gender, IQ, site, Tanner stage, and the following at baseline: ABC, Child Symptom Inventory, CYBOCS, 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[113] *FGA vs. risperidone vs. other SGA vs. FGA+SGA*	Subgroup analysis by age, comorbidity (MR), cotreatment (non-pharmacological), duration of treatment, health-care setting	Response (CGI-I ≤2)	Patients with no MR had a statistically significant greater response compared with 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 statistically significant improvements were observed as a function of age, health-care clinic, or duration of treatment.
Perry, 1989[77] *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 anti-psychotic withdrawal regimen showed statistically significant deterioration compared with patients without these variables. All other variables did not predict deterioration.
ADHD and disruptive behavior disorder			
Aman, 2002[41] *Risperidone vs. placebo*	Subgroup analysis by gender	Prolactin	Males had a significantly greater increase in prolactin levels on risperidone compared with placebo, while increase in mean prolactin levels was not statistically significant for females.
Buitelaar, 2001[47] *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.

ABC = Aberrant Behavior Checklist; ADHD = attention deficit hyperactivity disorder; AE = Adverse Event; BMI = body mass index; CD = conduct disorder; CGI-BP = Clinical Global Impression-bipolar; CGI-I = Clinical Global Impressions-Improvement; CGI-S = Clinical Global Impressions-Severity; CPRS = Children's Psychiatric Rating Scale; day = day(s); CPT = Continuous performance task; CVLT = California Verbal Learning Test; DBD = disruptive behavior disorder; GAF = Global Assessment of Functioning; HAM-A = Hamilton Anxiety Rating Scale; IQ = intelligence quotient; MR = mental retardation; NCBRF = Nisonger Child Behavior Rating Form; NOS = not otherwise specified; OAS = Overt Aggression Scale; ODD = oppositional defiant disorder; PGI = Patient Global Impressions; RAAPP = Rating of Aggression Against People and/or Property; SNAP-IV = Swanson, Nolan and Pelham Scale-Version IV; TSSS = Tourette's Symptom Severity Scale; (C)YBOCS = (Children's); Yale-Brown Obsessive Compulsive Scale; YMRS = Young Mania Rating Scale; WAIS-R = Wechsler Adult Intelligence Scale revised

Table 41. Differences between patient subpopulations on treatment outcomes (continued)

Author, Year Comparison	Type of analysis	Outcome	Authors' conclusions
ADHD and disruptive behavior disorder (continued)			
Findling, 2000[55] *Risperidone vs. placebo*	Regression analysis by age, race, and baseline RAAPP & CGI-S scores	Completion of study	Age, race, baseline RAAPP score, and baseline CGI-S score was not significantly different between completers and non-completers.
		RAAPP, CPRS	When an adjustment for age was made, no alteration in rating scales scores were observed
Reyes, 2006[79] *Risperidone vs. placebo*	Subgroup analysis by gender, age, diagnosis, disease severity	Risk for symptom recurrence	Gender, age, diagnosis and baseline disruptive behavior severity did not affect risk for symptom recurrence.
	Subgroup analysis by age	Weight and AE	Weight gain was reported more frequently in children < 12 years of age than those ≥12 years; however this trend was not statistically significant. Other AEs were comparable between age groups.
	Subgroup analysis by gender	Prolactin	Females experienced greater increase in prolactin levels compared with males.
Snyder, 2002[89] *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 compared with those previously treated with risperidone at extension study entry.
		Sedation	Sedation increased among risperidone-naïve patients, but not among previously treated patients.
Bipolar disorder			
DelBello, 2009[50] *Quetiapine vs. placebo*	Subgroup analysis by inpatient status, site	Symptomatology (rating scales)	There was no difference in the change scores on rating scales between inpatient and outpatient participants, and study center.
Findling, 2009[54] *Low- vs. high-dose aripiprazoleipiprazole high-dose vs. placebo*	Subgroup analysis by gender	Prolactin	Decreases in prolactin levels were more pronounced for males than for females.
Haas, 2009[57] *Low- vs. high-dose risperidone vs. placebo*	Subgroup analysis by age	YMRS	Both age groups (≤12 or >12 years) experienced significant improvements with risperidone compared with 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.

Table 41. Differences between patient subpopulations on treatment outcomes (continued)

Author, Year Comparison	Type of analysis	Outcome	Authors' conclusions
Bipolar disorder (continued)			
Haas, 2009 (continued)	Subgroup analysis by gender, race, diagnostic subgroup, or hospitalization	YMRS	Risperidone was consistently more effective than placebo regardless or sex, race, diagnosis, or hospitalization at screening.
Tohen, 2007[92] *Olanzapine vs. placebo*	Regression analysis controlling for comorbidities, cotreatment, bipolar subtypes, age of onset, gender	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 compared with females.
Tramontina, 2009[93] *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.
Schizophrenia			
Crocq, 2007[102] *Olanzapine ODT vs. SOT vs. risperidone*	Subgroup analysis by gender	Weight	Weight and BMI increase was consistently but not statistically greater in girls than boys in all treatment groups.
Haas, 2009[58] *Low- vs. high-dose risperidone*	Subgroup analysis by gender	Prolactin	Mean increases in prolactin levels were greater in females compared with males.
Kryzhanovskaya, 2009[63] *Olanzapine vs. placebo*	Subgroup analysis by country	Response	The response rate did not differ significantly by country.
NCT00090324, 2008[74] *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[78] *Haloperidol vs. olanzapine vs. risperidone*	Regression analysis by gender, 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 patient subpopulations on treatment outcomes (continued)

Author, Year Comparison	Type of analysis	Outcome	Authors' conclusions
Schizophrenia (continued)			
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[97] *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	Neurocognitive 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[112] *Clozapine vs. haloperidol vs. olanzapine*	Subgroup analysis by gender	Prolactin	In patients receiving clozapine, females had significantly elevated prolactin levels compared with males. There was no significant gender difference in patients receiving haloperidol or olanzapine.
Psychosis			
Sikich, 2003[88] *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 anti-psychotic, treated with either concomitant anti-depressant or mood-stabilizer, or both concomitant anti-depressant and mood-stabilizer.
Tourette syndrome			
Bruggeman, 2001[100] *Pimoide 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 compared with 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 statistically significant. Weight gain was comparable across age groups in the pimozide-treated patients.
Sallee, 1997[81] *Haloperidol vs. pimozide vs. placebo*	Subgroup analysis by gender, Tanner score	Prolactin	There were no significant differences in prolactin levels by gender or Tanner scores.

Table 41. Differences between patient subpopulations on treatment outcomes (continued)

Author, Year Comparison	Type of analysis	Outcome	Authors' conclusions
Tourette syndrome (continued)			
Sallee, 1994[83] *Haloperidol vs. pimozide*	Regression analysis by comorbidity	CPT task commission and omission errors	Patients with ADHD had significantly higher commission and omission errors compared with patients without ADHD.
Behavioral symptoms			
Bastiaens, 2009[44] *Aripiprazole vs. ziprasidone*	Subgroup analysis by gender, age	OAS	Males improved more than females, and patients ≤11 years improved more than patients 12 years or older; however neither trend was statistically significant.
Hellings, 2006[59] *Low- vs. high-dose risperidone*	Subgroup analysis by age	ABC irritability	Irritability scores were significantly higher in children compared with adolescents and adults. There was no significant difference between adolescents and adults.
	Subgroup analysis for gender, 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. Gender, concomitant anti-seizure 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 statistically significant.
		Prolactin	Adults had a greater acute increased in prolactin levels compared with children/ adolescents. Prolactin levels were significantly higher for adults compared with children/adolescents in the acute phase but not during maintenance.
Khan, 2006[62] *Olanzapine vs. ziprasidone*	Subgroup analysis for age	Dose required for symptom reduction	Adolescents (13-17 years) required a significantly higher dose of olanzapine compared with children (≤12 years). There was no difference between age groups for ziprasidone.
	Regression analysis controlling for gender and age	Number of restraints Time in restraint after drug	Age and gender had no impact on differences between the groups for number of restraints or time in restraint after receiving the study medications.
Multiple condition categories			
Correll, 2009[101] *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[104] *Clozapine vs. olanzapine vs. risperidone*	Regression analysis by gender, 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 gender and extreme weight gain was found. No significant correlation was found between age, drug history status (naïve vs. previous use), co-medications or dieting history and weight measures.

Table 41. Differences between patient subpopulations on treatment outcomes (continued)

Author, Year Comparison	Type of analysis	Outcome	Authors' conclusions
Multiple condition categories (continued)			
Fraguas, 2008[105] *Olanzapine vs. quetiapine vs. risperidone*	Subgroup analysis by gender, age, race, comorbidities, cotreatment, duration of inpatient treatment, treatment history	Weight	Males gained more weight than females, but this trend was not statistically significant. BMI increases were not related to race, age, presence of psychosis, alcohol abuse, cannabis abuse or length of inpatient treatment.
		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 gender, 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 anti-psychotic 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[106] *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 gender	Neuroleptic-induced movement disorders	All patients who developed neuroleptic-induced movement disorders were female.

Chapter 4. Discussion

Summary of Findings

This report provides a comprehensive synthesis of the evidence on the comparative efficacy of first generation and second generation antipsychotics for the treatment of various psychiatric and behavioral conditions in children and young adults (aged ≤24 years). The strength of the body of evidence for key efficacy and safety outcomes is summarized by condition in Table 42 and Table 43. For the majority of outcomes, data on the relative efficacy of treatments were sparse and precluded making firm conclusions. Patient-important outcomes were rarely assessed in the studies, including health-related quality of life, social and occupational functioning, and legal interactions, thus limiting potential applicability to children, youth, and their families who are affected by this clinical topic. Disorder-specific symptoms and clinical global impressions were reported more consistently across the studies making study outcomes relevant for clinicians. Data were provided primarily from RCTs; however, in our quality assessment, nearly all of the trials were found to be at high risk of bias due to industry funding. Sample sizes varied considerably, with an overall median of 41 enrolled patients per study (IQR: 24 to 100). Overall, there were few significant differences of clinical importance between active drug comparisons. First and second generation antipsychotics 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.

KQ1: Disorder specific and nonspecific symptoms. Fifty-nine studies evaluated the efficacy of antipsychotics for treating symptoms, including 10 for pervasive developmental disorders, eight for ADHD and disruptive behavior disorders, nine for bipolar disorder, 24 for schizophrenia and schizophrenia-related psychosis, five for Tourette syndrome, and four for behavioral symptoms (one study examined two conditions). For ADHD and disruptive behavior disorders, a moderate level of evidence shows second generation antipsychotics to be superior to placebo for behavior symptoms and clinical impressions; the effect of second generation antipsychotics may be greater for treating disruptive behavior disorder than ADHD. A moderate level of evidence from five RCTs shows second generation antipsychotics to be favored over placebo for clinical impressions in both bipolar disorder and schizophrenia, and for positive and negative symptoms in schizophrenia. For bipolar disorder, all second generation antipsychotics except for quetiapine showed improvement over placebo for clinical global impression and mania. There was a low level of evidence showing no difference between olanzapine and risperidone for clinical global impression and positive and negative symptoms in schizophrenia. A significant effect of second generation antipsychotics over placebo for reducing tic severity in Tourette syndrome was supported by a moderate level of evidence from two RCTs. The strength of evidence for the relative efficacy was low or insufficient (due to sparseness of data) for the remaining comparisons and outcomes, including all outcomes for pervasive developmental disorders. Similarly, no conclusions could be made for first episode psychosis due to insufficient evidence.

KQ2: Adverse events. Seventy-one studies provided data for at least one adverse event. The evidence for all outcomes for head-to-head comparisons of first versus second generation and first versus first generation antipsychotics, was rated as low or insufficient. Several of the outcomes were supported by a moderate level of evidence when second generation antipsychotics were compared with each other. These included a significant effect favoring

risperidone over olanzapine for dyslipidemia (five studies), favoring olanzapine over risperidone for prolactin-related adverse events (10 studies), and favoring quetiapine and risperidone over olanzapine for less increase in weight/body composition (4 studies and 13 studies, respectively). The evidence for all other outcomes for various second generation antipsychotic comparisons was graded as low or insufficient.

There was insufficient evidence for outcomes regarding first generation antipsychotics versus placebo. There was a moderate level of evidence favoring placebo over various second generation antipsychotics for dyslipidemia (quetiapine [two studies]), extrapyramidal symptoms (aripiprazole [four studies] and risperidone [14 studies]), prolactin-related adverse events (olanzapine [two studies] and risperidone [eight studies]), sedation (risperidone [12 studies] and ziprasidone [three studies]), and less increase in weight/body composition (aripiprazole, olanzapine, and quetiapine [four studies each]; risperidone [12 studies]). A moderate level of evidence from three studies favored aripiprazole over placebo for prolactin-related adverse events.

KQ3: Other short- and long-term outcomes. Fifty-two studies examined the efficacy of antipsychotics for other short- and long-term outcomes. Data were provided for pervasive developmental disorders (nine studies), ADHD and disruptive behavior disorders (eight studies), bipolar disorder (nine studies), schizophrenia (17 studies), psychosis (four studies), Tourette syndrome (four studies), and behavioral symptoms (two studies), with one study providing data for two conditions. There was no effect of second generation antipsychotics for suicide-related behaviors in bipolar disorder (moderate level of evidence) and schizophrenia (low level of evidence). A low level of evidence showed no difference in medication adherence for first generation versus second generation antipsychotics (schizophrenia), olanzapine versus risperidone (schizophrenia), or second generation antipsychotics versus placebo (pervasive developmental disorder, disruptive behavior disorders and schizophrenia). Two studies examining bipolar disorder provided a low level of evidence showing significantly poorer medication adherence for second generation antipsychotics compared with placebo.

KQ4: Subpopulations. A total of 32 studies compared outcomes for various patient subpopulations. Gender and age were examined most frequently; the remaining subpopulations of interest were examined in only a few studies. Few associations between the patient or clinical variables and outcomes were supported by more than one study. The majority of subpopulations were found to have no impact on the outcomes. Two studies reported low intelligence to be associated with less response to second generation antipsychotics. Four studies found greater increases in prolactin level in females than males during treatment with second generation antipsychotics; however, this result was not consistent across studies.

Table 42. Summary of the strength of evidence for efficacy outcomes

Outcome	Comparison (# studies)	Strength of evidence	Summary
Pervasive developmental disorder			
Aggression	None	Insufficient	No data
Anxiety	SGA vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Autistic symptoms	FGA vs. SGA (2 RCTs)	Low	No significant difference.
	Low-dose vs. medium-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (6 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 impressions	FGA vs. SGA (2 RCTs)	Insufficient	The evidence was too limited to make a conclusion.
	Continuous vs. discontinuous haloperidol (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. medium-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (3 RCTs)	Low	No significant difference.
OC symptoms	Low-dose vs. medium-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (3 RCTs)	Low	Significant effect in favor of SGA (MD = -1.7; 95% CI: -3.2, -0.3)
Social/occupational functioning	None	Insufficient	No data
HRQL	None	Insufficient	No data
Legal interactions	None	Insufficient	No data
Medication adherence	Low-dose vs. medium-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (2 RCTs)	Low	No significant difference.
Patient/parent-reported outcomes	SGA vs. placebo (1 RCT) for sleep and food frequency questionnaire	Insufficient	The evidence was too limited to make a conclusion.
Suicide-related behaviors	Low-dose vs. medium-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
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 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)
OC symptoms	None	Insufficient	No data
Social/occupational functioning	None	Insufficient	No data
HRQL	SGA vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Legal interactions	None	Insufficient	No data

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; HRQL = health-related quality of life; MD = mean difference; NCBRF = Nisonger Child Behavior Rating Scale; NR = not reported; OC = obsessive-compulsive; PCS = prospective cohort study; RCS = retrospective cohort study; RCT = randomized controlled trial; RR = relative risk; SGA = second generation antipsychotic

Table 42. Summary of the strength of evidence for efficacy outcomes (continued)

Outcome	Comparison (# studies)	Strength of evidence	Summary
ADHD and disruptive behavior disorder (continued)			
Medication adherence	SGA vs. placebo (5 RCTs)	Low	No significant difference.
Patient/parent-reported outcomes	None	Insufficient	No data
Suicide-related behaviors	None	Insufficient	No data
Bipolar disorder			
Aggression	SGA vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Clinical impressions	Low-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose ziprasidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (5 RCTs)	Moderate	Significant effect in favor of SGA (MD = -0.7; 95% CI: -0.9, -0.5)
Depression	Olanzapine vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (4 RCTs)	Low	No significant difference.
Manic symptoms	Olanzapine vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose ziprasidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (7 RCTs)	Low	All except one study significantly favored SGA (studies not pooled due to high heterogeneity)
OC symptoms	None	Insufficient	No data
Positive and negative symptoms	None	Insufficient	No data
Social/occupational functioning	None	Insufficient	No data
HRQL	None	Insufficient	No data
Legal interactions	None	Insufficient	No data
Medication adherence	Low-dose vs. high-dose risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (2 RCTs)	Low	Significant effect in favor of placebo (RR = 2.0; 95% CI: 1.0, 4.0)
Patient/parent-reported outcomes	SGA vs. placebo (1 RCT) for switch to depression	Insufficient	The evidence was too limited to make a conclusion.
Suicide-related behaviors	Low-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose ziprasidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (6 RCTs)	Moderate	No significant difference for suicide-related deaths, attempts, or ideation.

Table 42. Summary of the strength of evidence for efficacy outcomes (continued)

Outcome	Comparison (# studies)	Strength of evidence	Summary
Schizophrenia			
Aggression	SGA vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Clinical impressions	FGA vs. SGA (2 RCTs)	Low	Significant effect in favor of SGA (MD = -0.86; 95% CI: -1.6, -0.08)
	Clozapine vs. olanzapine (2 RCTs)	Low	No significant difference.
	Olanzapine vs. quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. risperidone (2 RCTs)	Low	No significant difference.
	Low-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose paliperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose risperidone (1 RCT)	Low	Significant effect in favor of high-dose risperidone (MD = 0.6; 95% CI: 0.3, 0.9)
	Low-dose ziprasidone vs. high-dose ziprasidone	Insufficient	The evidence was too limited to make a conclusion.
Clinical impressions (continued)	Haloperidol vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (5 RCTs)	Moderate	Significant effect in favor of SGA (MD = -0.4; 95% CI: -0.6, -0.3)
Depression	None	Insufficient	No data
Manic symptoms	SGA vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
OC symptoms	None	Insufficient	No data
Positive and negative symptoms	FGA vs. SGA (3 RCTs, 1 PCS)	Low	No significant difference.
	Clozapine vs. risperidone (2 RCTs, 1 PCS)	Low	No significant difference.
	Olanzapine vs. risperidone (3 RCTs, 1 PCS)	Low	No significant difference.
	Low-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose paliperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose risperidone (1 RCT)	Low	Significant effect in favor of high-dose risperidone (MD = 0.6; 95% CI: 0.3, 0.9)
	Low-dose vs. high-dose ziprasidone	Insufficient	The evidence was too limited to make a conclusion.
	Haloperidol vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (5 RCTs)	Moderate	Significant effect in favor of SGA (MD = -0.4; 95% CI: -0.6, -0.3)
Social/occupational functioning	None	Insufficient	No data
HRQL	FGA vs. SGA (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Legal interactions	None	Insufficient	No data
Medication adherence	FGA vs. SGA (1 RCT, 1 PCS)	Low	No significant difference
	Olanzapine vs. quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. risperidone (3 RCTs, 1 PCS)	Low	No significant difference

Table 42. Summary of the strength of evidence for efficacy outcomes (continued)

Outcome	Comparison (# studies)	Strength of evidence	Summary
Schizophrenia (continued)			
	Low-dose vs. high-dose risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (2 RCTs)	Low	No significant difference.
Patient/parent-reported outcomes	Low-dose vs. high-dose quetiapine (1 RCT) for caregiver strain	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (1 RCT) for caregiver strain	Insufficient	The evidence was too limited to make a conclusion.
Suicide-related behaviors	Olanzapine vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose aripiprazole (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose paliperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose ziprasidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (4 RCTs)	Low	No significant difference.
Psychosis			
Aggression	None	Insufficient	No data
Anxiety	None	Insufficient	No data
Clinical impressions	FGA vs. SGA (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Depression	None	Insufficient	No data
Manic symptoms	Olanzapine vs. quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
OC symptoms	None	Insufficient	No data
Positive and negative symptoms	Olanzapine vs. quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Quetiapine vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose quetiapine vs. high-dose quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Social/occupational functioning	Low-dose vs. high-dose quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
HRQL	None	Insufficient	No data
Legal interactions	Low-dose vs. high-dose quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Medication adherence	FGA vs. SGA (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Low-dose vs. high-dose quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Patient/parent-reported outcomes	None	Insufficient	No data
Suicide-related behaviors	Low-dose vs. high-dose quetiapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.

Table 42. Summary of the strength of evidence for efficacy outcomes (continued)

Outcome	Comparison (# studies)	Strength of evidence	Summary
Tourette syndrome			
Aggression	None	Insufficient	No data
Anxiety	None	Insufficient	No data
Clinical impressions	Pimozide vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Haloperidol vs. pimozide (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	FGA vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (2 RCTs)	Insufficient	The evidence was too limited to make a conclusion.
OC symptoms	SGA vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Social/occupational functioning	Haloperidol vs. pimozide (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Tics	Pimozide vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	SGA vs. placebo (2 RCTs)	Moderate	Significant effect in favor of SGA (MD = -6.98 (95% CI: -10.3, -3.6)
HRQL	None	Insufficient	No data
Legal interactions	None	Insufficient	No data
Medication adherence	Haloperidol vs. pimozide (1 RCT)	Insufficient	No data
	FGA vs. placebo (1 RCT)	Insufficient	No data
Patient/parent-reported outcomes	Short-term vs. long-term pimozide (1 RCT) for time to dose increase due to tic exacerbation	Insufficient	The evidence was too limited to make a conclusion.
Suicide-related behaviors	None	Insufficient	No data
Behavioral symptoms			
Aggression	Aripiprazole vs. ziprasidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. ziprasidone	Insufficient	The evidence was too limited to make a conclusion.
Anxiety	None	Insufficient	No data
Autistic symptoms	Low-dose vs. high-dose risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	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
Clinical impressions	Aripiprazole vs. ziprasidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Risperidone vs. placebo	Insufficient	The evidence was too limited to make a conclusion.
Depression	None	Insufficient	No data
Manic symptoms	Aripiprazole vs. ziprasidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
OC symptoms	None	Insufficient	No data
Positive and negative symptoms	None	Insufficient	No data
Social/occupational functioning	None	Insufficient	No data
Tics	None	Insufficient	No data
HRQL	Aripiprazole vs. ziprasidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
Legal interactions	None	Insufficient	No data
Medication adherence	None	Insufficient	No data
Patient/parent-reported outcomes	None	Insufficient	No data
Suicide-related behaviors	None	Insufficient	No data

Table 43. Summary of the strength of evidence for adverse events

Outcome	Comparison (# studies)	Strength of evidence	Summary
First vs. second generation antipsychotic			
Dyslipidemia	Haloperidol vs. olanzapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Haloperidol vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
EPS	Haloperidol vs. clozapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Haloperidol vs. olanzapine (2 RCTs, 1 PCS)	Low	Significant effect in favor of olanzapine (MD = 3.53, 95% CI:1.14, 10.93)
	Haloperidol vs. risperidone (2 RCTs, 1 PCS)	Insufficient	The evidence was too limited to make a conclusion.
Insulin resistance	Haloperidol vs. olanzapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Haloperidol vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Prolactin-related and sexual AE	FGAs vs. clozapine (1 NRCT)	Insufficient	The evidence was too limited to make a conclusion.
	Haloperidol vs. clozapine	Insufficient	The evidence was too limited to make a conclusion.
	Haloperidol vs. olanzapine (1 RCT, 1 PCS)	Low	No significant difference.
	Haloperidol vs. risperidone (2 RCTs)	Low	No significant difference.
Sedation	Haloperidol vs. clozapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	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. clozapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Haloperidol vs. olanzapine (2 RCTs, 2 PCS)	Low	Significant effect in favor of haloperidol (MD = -5.79, 95% CI: -8.6, -2.98)
	Haloperidol vs. risperidone (2 RCTs, 1 PCS)	Low	No significant difference.
	Pimozide vs. risperidone (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
First vs. first generation antipsychotic			
Dyslipidemia	None	Insufficient	No data
EPS	Haloperidol vs. pimozide (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Insulin resistance	None	Insufficient	No data
Prolactin-related and sexual AE	Haloperidol vs. pimozide (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Sedation	None	Insufficient	No data
Weight/ body composition	Haloperidol vs. pimozide (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Second vs. second generation antipsychotic			
Dyslipidemia	Aripiprazole vs. olanzapine (1 PCS)	Low	Significant effect in favor of aripiprazole (MD = -11.9, 95% CI, -23.4, -0.3).
	Aripiprazole vs. quetiapine (1 PCS)	Low	Significant effect in favor of aripiprazole (MD = -39.4, 95% CI, -71.3, -7.4).
	Aripiprazole vs. risperidone (1 PCS)	Insufficient	The evidence was too limited to make a conclusion.
	Clozapine vs. olanzapine (2 RCTs)	Low	No significant difference.
	Olanzapine vs. quetiapine (2 PCSs)	Low	No significant difference.

Table 43. Summary of the strength of evidence for adverse events (continued)

Outcome	Comparison (# studies)	Strength of evidence	Summary
Second vs. second generation antipsychotic (continued)			
Dyslipidemia (continued)	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 PCS)	Low	No significant difference.
EPS	Aripiprazole vs. ziprasidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Clozapine vs. olanzapine (1 RCT, 1 PCS, 1 RCS)	Low	No significant difference.
	Clozapine vs. quetiapine (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	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 PCS, 3 RCS)	Low	No significant difference
	Olanzapine vs. ziprasidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Quetiapine vs. risperidone (3 RCTs)	Low	No significant difference.
Insulin resistance	Aripiprazole vs. olanzapine (1 PCS)	Insufficient	The evidence was too limited to make a conclusion.
	Aripiprazole vs. quetiapine (1 PCS)	Insufficient	The evidence was too limited to make a conclusion.
	Aripiprazole vs. risperidone (1 PCS)	Insufficient	The evidence was too limited to make a conclusion.
	Clozapine vs. olanzapine (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. quetiapine (2 PCS)	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)
	Clozapine vs. quetiapine (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Clozapine vs. risperidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. quetiapine (1 RCT, 1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. risperidone (7 RCTs, 3 PCSs)	Moderate	Significant effect in favor of olanzapine (MD = -18.7, 95% CI, -30.2, -7.2)
	Quetiapine vs. risperidone (3 RCTs)	Low	No significant difference.

Table 43. Summary of the strength of evidence for adverse events (continued)

Outcome	Comparison (# studies)	Strength of evidence	Summary
Second vs. second generation antipsychotic (continued)			
Sedation	Aripiprazole vs. ziprasidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Clozapine vs. olanzapine (1 RCT, 1 PCS, 1 RCS)	Low	No significant difference.
	Clozapine vs. quetiapine (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Clozapine vs. risperidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Olanzapine vs. quetiapine (2 RCTs, 1 RCS)	Low	No significant difference.
	Olanzapine vs. risperidone (5 RCTs, 2 PCS, 2 RCS)	Low	No significant difference.
	Olanzapine vs. ziprasidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	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)	Insufficient	The evidence was too limited to make a conclusion.
	Aripiprazole vs. risperidone (1 PCS)	Insufficient	The evidence was too limited to make a conclusion.
	Aripiprazole vs. ziprasidone (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Clozapine vs. olanzapine (2 RCTs, 2 PCS, 1 RCS)	Low	No significant difference.
	Clozapine vs. quetiapine (1 RCS)	Insufficient	The evidence was too limited to make a conclusion.
	Clozapine vs. risperidone (1 RCS, 1 PCS)	Low	No significant difference.
	Olanzapine vs. quetiapine (2 RCTs, 2 PCSs)	Moderate	Significant effect in favor of quetiapine (MD = 6.8, 95% CI: 1.4, 12.2).
	Olanzapine vs. risperidone (7 RCTs, 1 NRCT, 4 PCSs, 1 RCS)	Moderate	Significant effect in favor of risperidone (MD = 2.4, 95% CI: 1.3, 3.4)
	Quetiapine vs. risperidone (3 RCTs, 2 PCSs)	Low	No significant difference.
First generation antipsychotic vs. placebo			
Dyslipidemia	None	Insufficient	No data
EPS	Haloperidol and pimozide vs. placebo	Insufficient	The evidence was too limited to make a conclusion.
Insulin resistance	None	Insufficient	No data
Prolactin-related and sexual AE	Haloperidol and pimozide vs. placebo	Insufficient	The evidence was too limited to make a conclusion.
Sedation	Haloperidol vs. placebo	Insufficient	The evidence was too limited to make a conclusion.
Weight/ body composition	Haloperidol and pimozide vs. placebo	Insufficient	The evidence was too limited to make a conclusion.

Table 43. Summary of the strength of evidence for adverse events (continued)

Outcome	Comparison (# studies)	Strength of evidence	Summary
Second generation antipsychotic vs. placebo			
Dyslipidemia	Aripiprazole vs. placebo (2 RCTs)	Low	Significant effect in favor of placebo (MD = 2.5, 95% CI: 1.4, 4.4).
	Olanzapine vs. placebo (2 RCTs)	Low	Significant effect in favor of placebo (MD = 2.4, 95% CI: 1.2, 4.9).
	Quetiapine vs. placebo (2 RCTs)	Moderate	Significant effect in favor of placebo (MD = 29.1, 95% CI: 7.3, 50.9).
	Risperidone vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
EPS	Aripiprazole vs. placebo (4 RCTs)	Moderate	Significant effect in favor of placebo (MD = 4.6, 95% CI: 2.4, 9.1)
	Olanzapine vs. placebo (3 RCTs)	Low	No significant difference.
	Quetiapine vs. placebo (3 RCTs)	Low	No significant difference.
	Risperidone vs. placebo (14 RCTs)	Moderate	Significant effect in favor of placebo (MD = 2.7, 95% CI: 1.4, 4.9).
	Ziprasidone vs. placebo (3 RCTs)	Low	Significant effect in favor of placebo (MD = 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.
	Paliperidone vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Quetiapine vs. placebo (2 RCTs)	Insufficient	The evidence was too limited to make a conclusion.
	Risperidone vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
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 (4 RCTs)	Low	No significant difference.
	Risperidone vs. placebo (8 RCTs)	Moderate	Significant effect in favor of placebo (MD = 21.9, 95% CI: 8.9, 35.0).
	Ziprasidone vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
Sedation	Aripiprazole vs. placebo (4 RCTs)	Low	Significant effect in favor of placebo (MD = 2.7, 95% CI: 1.1, 6.5)
	Olanzapine vs. placebo (3 RCTs)	Low	No significant difference.
	Quetiapine vs. placebo (4 RCTs)	Low	No significant difference.
	Risperidone vs. placebo (12 RCTs)	Moderate	Significant effect in favor of placebo (MD = 2.9, 95% CI: 1.5, 5.5)
	Ziprasidone vs. placebo (3 RCTs)	Moderate	Significant effect in favor of placebo (MD = 2.98, 95% CI: 1.7, 5.2)
Weight/ body composition	Aripiprazole vs. placebo (4 RCTs)	Moderate	Significant effect in favor of placebo (MD = 0.77, 95% CI: 0.40, 1.15)
	Olanzapine vs. placebo (4 RCTs)	Moderate	Significant effect in favor of placebo (MD = 4.6, 95% CI: 3.1, 6.1).
	Paliperidone vs. placebo (1 RCT)	Insufficient	The evidence was too limited to make a conclusion.
	Quetiapine vs. placebo (4 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.

Applicability

The majority of the studies included in this body of evidence were small to moderate-sized RCTs that examined the efficacy of two or more intervention groups. Study populations generally excluded patients with diagnoses of other 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 in the studies 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 from participation in the double-blind treatment phase. Since 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 safety of antipsychotics.

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

Another factor that restricts the applicability of the studies is the limited duration of followup. In particular, the median study duration of 8 weeks may have been 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 precisions 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 for assessing risk of bias developed by The Cochrane Collaboration. 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. Blinding through use of matched placebo tablets that appear and taste similar to the study medication may reduce the risk that knowledge of which intervention was received, rather than the active drug itself, affected outcomes. Since many of the outcomes, such as improvement on symptom scales, were assessed by physicians, blinding should extend beyond patients to include all outcome assessors. Incomplete outcome data was a problem in half of the

trials due to loss to followup and inadequate handling of missing data in the reporting and/or analysis, 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 pharmaceutical company sponsorship to be strongly associated with study findings that favor the sponsors by overestimating treatment effects.[116]

Fifteen cohort studies were included in the review. Since these studies did not employ randomization, they are particularly vulnerable to bias resulting from 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 analysis.

Lack of consistency and precision of results across studies also contributed to the low strength of evidence rating for the majority of outcomes. Consistency was often unknown due to the few studies comparing the same interventions. In addition, lack of consistency may also be 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 clinically important differences. 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 ages, gender ratio, and dose of antipsychotics.

Consensus is needed in this field regarding the selection of outcomes and measures used to assess outcomes. Over 60 outcome scales were used to assess efficacy outcomes across the studies. While some outcomes and scales were assessed fairly consistently for some conditions, such as the YMRS for bipolar disorder and the PANSS for schizophrenia, there was great diversity in the scales used in studies for conditions such as pervasive developmental disorder, disruptive behavior disorder, and Tourette syndrome. Further, response and remission were based on different outcome measures and criteria across studies. This heterogeneity makes comparisons across studies and interventions challenging. Discussion and consensus are also needed on what differences in outcome measures are clinically important. 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 contributed to inconsistency.

Several key outcomes identified to be clinically important were rarely evaluated: health-related quality of life, social and occupational functioning, legal interactions, and patient- or parent-reported outcomes. Since the duration of followup was brief in the majority of studies, with a median of 8 weeks (IQR, 6 to 12 weeks), longer-term data is needed to assess the impact of antipsychotic use of these patient-important outcomes. Similarly, longer followup is needed to determine the association of acute adverse effects, such as neuroleptic-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. While many of the studies included open-label extension phases to assess efficacy and/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 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 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 statistically significant), limiting the conclusions that could be made. 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., gender, age) on key outcomes (e.g., prolactin levels, weight gain) are needed.

Future Research

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

- 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. In addition, independent/investigator driven research efforts are needed to reduce the potential for overestimated treatment effects associated with industry-funded research.
- Studies examining the long-term efficacy and, particularly, the safety of antipsychotics over the course of several years are needed.
- Consensus on clinically and patient-important 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.
- Future studies should evaluate patient-important outcomes which have rarely been assessed, including health-related quality of life, school performance, and legal interactions.
- Studies examining associations between important outcomes and key patient subpopulations are needed to inform clinical practice.
- Large-scale effectiveness studies that use inclusive patient selection criteria and closely match typical clinical practice are needed to achieve greater generalizability of results.

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[117] and STROBE[118] statement helpful in designing and reporting on randomized controlled trials and cohort studies, respectively.

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 a first or second generation antipsychotic with only placebo and no active comparator. Based on the finding of this report, antipsychotics can be considered to have superior symptom improvement and inferior adverse event profiles than does placebo. There was insufficient evidence 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.

Continued incorporation of an additional placebo group is also encouraged, as this provides opportunities for data to be statistically compared through use of network meta-analysis.

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 developing individuals.[36] While 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[119] or a simplified version of this scale[120] 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.[36] Future cohort studies that examine the long-term comparative safety of drugs are also needed. Correll et al.[101] provides a good example of a well designed and conducted cohort study in this field.

While 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 pervasive developmental disorders or disruptive behavior disorders 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.

Conclusions

The efficacy and safety of first and second generation antipsychotics have been studied in children and young adults (aged ≤24 years) for the following conditions: pervasive developmental disorders, ADHD and disruptive behaviour disorders, bipolar disorder, schizophrenia, Tourette syndrome and behavioral problems. Overall, data for head-to-head comparisons (first versus second generation, first versus first generation, and second versus second generation antipsychotics) were generally of low level of evidence; therefore, few conclusions regarding the relative efficacy and safety of antipsychotics could be made. However, evidence consistently showed that second generation antipsychotics resulted in greater symptom improvement and a poorer safety profile compared with placebo. There was sparse evidence for several patient important outcomes, such as health-related quality of life, legal interactions, and school performance and few studies reported long-term data.

Treatment benefit and risks were examined most frequently for schizophrenia, with fewer studies examining conditions such as pervasive developmental disorders, ADHD and disruptive behaviour disorders, and Tourette syndrome. In addition, there were no studies for OCD, PTSD, or anorexia nervosa that met our inclusion criteria. The majority of the evidence also examined adolescents and young adults; preschool and school aged children were included in the studies less frequently. Additional research is needed to assess the treatment efficacy, and particularly, the safety of antipsychotics in these populations.

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 clinically and patient-important outcomes, as well as minimum

clinically-important differences. Consistency across studies is needed in choice of outcomes and measurement tools. Standardized assessment of adverse events, and analysis and comprehensive reporting of subpopulations in future studies will allow for more accurate iterpretation of findings across studies as well as greater understanding with respect to the applicability of the findings.

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Abbreviations

ABC	Aberrant Behavior Checklist
ADHD	Attention deficit hyperactivity disorder
ADI-R	Autism Diagnostic Interview-Revised
AHRQ	Agency for Healthcare Research and Quality
ALT	Alanine transaminase
AST	Aspartate amino transferase
BMI	Body mass index
BPI	Behavior Problem Inventory
BPRS	Brief Psychiatric Rating Scale
CARS	Childhood Autism Rating Scale
CDRS	Children's Depression Rating Scale
CGAS	Children's Global Assessment Scale
CGI-BP	Clinical Global Impressions-Bipolar
CGI-I	Clinical Global Impressions-Improvement
CGI-S	Clinical Global Impressions-Severity
CPRS	Children's Psychiatric Rating Scale
CYBOCS	Children's Yale-Brown Obsessive Compulsive Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
DVP	Divalproex
IQR	Interquartile range
K-SADS	Kiddie-Schedule for Affective Disorders and Schizophrenia
K-SADS-E	Kiddie-Schedule for Affective Disorders and Schizophrenia (Epidemiological Version)
K-SADS-PL	Kiddie-Schedule for Affective Disorders and Schizophrenia (Present and Lifetime Version)
KQ	Key question
Mg	Milligram
N	Number
NCBRF	Nisonger Child Behavior Rating Form
NOS	Not otherwise specified
NRCT	Non-randomized controlled trial
OAS	Overt Aggression Scale
PANSS	Positive and Negative Syndrome Scale
PTSD	Post-traumatic stress disorder
RCT	Randomized controlled trial
SANS	Scale for the Assessment of Negative Symptoms
VAS	Visual analog scale
YGTSS	Yale Global Tic Severity Scale
YMRS	Young Mania Rating Scale