Comparative Effectiveness Review
Number 184

First- and Second-Generation Antipsychotics in Children and Young Adults: Systematic Review Update

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This report is based on research conducted by the University of Alberta Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00001-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

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Errata

In the original version of this report there was an error with respect to review findings for gains in weight and body mass index (BMI) from the trial on lurasidone for the treatment of irritability associated with autistic disorder (Loebel et al. J Autism Dev Disord 2016;46:1153-63). We thank Sunovion Pharmaceuticals for bringing this to our attention. Our original report used data for the mean change in percentile instead of the mean change in raw measure of kilograms (kg) and $kg \cdot m^{-2}$, which led to higher values used for between-group differences in weight and BMI: mean weight change for lurasidone (doses pooled) versus placebo was 0.45 kg not 2.67 kg, and mean change in BMI was 0.15 $kg \cdot m^{-2}$ rather than 2.92 $kg \cdot m^{-2}$.

We updated the following analyses for Key Question 2 about the effect of olanzapine compared with lurasidone on weight gain and BMI: network meta-analysis for body composition outcomes across all conditions; analysis for SGA vs. placebo; and analysis for between- and within study subgroup effects. Based on the updated data this changed our original conclusion that olanzapine did not appear to cause greater weight gain or higher BMI than lurasidone. We now find that olanzapine appears to cause greater weight gain or higher BMI than other SGAs, including lurasidone. Our main conclusion that the most robust findings were of olanzapine being worse for weight gain and BMI than risperidone, ziprasidone, and aripiprazole (because of precision in findings for these drugs) remains the same.

We have revised the relevant parts of this report with the updated data.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

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 can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. 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 email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officers named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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First- and Second-Generation Antipsychotics in Children and Young Adults: Systematic Review Update

Structured Abstract

Objectives. To review the evidence on first- and second-generation antipsychotics (FGAs and SGAs) for the treatment of various psychiatric and behavioral conditions in children, adolescents, and young adults (ages ≤ 24 years).
Data sources. Eight electronic databases, gray literature, trial registries, and reference lists.
Methods. Two reviewers conducted study selection and risk of bias assessment independently, and resolved discrepancies by consensus. One reviewer extracted and a second verified the data. We conducted meta-analyses when appropriate and network meta-analysis across conditions for changes to body composition. We rated strength of evidence for prespecified outcomes.
Results: One hundred thirty-five studies (95 trials and 40 observational studies) were included. None of the evidence was rated as high strength of evidence; results having moderate strength (i.e., probably an accurate effect) are presented (with n studies) below.
Schizophrenia and related psychoses (n = 39): Compared with placebo, SGAs as a class probably increase response rates, decrease slightly (not clinically significant for many patients) negative and positive symptoms, and improve slightly global impressions of improvement, severity, and functioning. There is likely little or no difference between high and low doses of quetiapine for clinical severity and functioning. Many outcomes for individual drug comparisons were of low or insufficient strength of evidence.
Bipolar disorder (n = 19): Compared with placebo, SGAs probably decrease mania, decrease depression symptoms slightly, and improve symptom severity and global functioning to a small extent. SGAs (and aripiprazole alone) probably increase response and remission rates versus placebo for manic/mixed phases. Quetiapine likely makes little or no difference in depression.
Autism spectrum disorders (n = 23): Compared with placebo, SGAs as a class probably decrease irritability, and decrease slightly lethargy/social withdrawal, stereotypy, and inappropriate speech; they likely increase response rates and (slightly) clinical severity. It is likely that aripiprazole and risperidone decrease irritability.
Attention deficit hyperacvtivity disorder (ADHD) and disruptive, impulse-control, and conduct disorders (n = 13): Compared with placebo, SGAs as a class (and risperidone individually) probably decrease conduct problems and aggression. Risperidone alone likely decreases hyperactivity in children with a primary diagnosis of conduct disorders or with ADHD but not responding to stimulants.
Other conditions: All outcomes had low or insufficient strength of evidence for tic disorders (n = 12), obsessive-compulsive disorder (n = 1), depression (n = 1), eating disorders (n = 3), and behavioral issues (n = 2).
Harms across conditions: From network meta-analysis, olanzapine was more harmful for gains in weight and body mass index (BMI) than other SGAs except for clozapine; results were most robust for relative harm over aripiprazole, quetiapine, and risperidone, and most applicable to the short term. Findings from pairwise meta-analysis between different SGAs were similar, except for showing longer term benefit for quetiapine and risperidone versus olanzapine, and little or no short-term differences between risperidone and quetiapine, or between different doses of aripiprazole, asenapine, or quetiapine. FGAs probably cause slightly less harm for weight and

BMI compared with SGAs. There is probably little or no difference in risk for somnolence between different doses of asenapine or quetiapine. There is likely little or no difference in risk for mortality or prolonged QT interval in the short term for SGAs as a class. SGAs versus placebo/no treatment probably increase short-term risk for high triglyceride levels, extrapyramidal symptoms, sedation, and somnolence.

Conclusion. SGAs probably improve to some extent key intermediate outcomes for which they are usually prescribed, but they have a poorer harms profile than placebo or no antipsychotic treatment, particularly for body composition and somnolence. Data for head-to-head comparisons within and between classes were generally limited and rated as insufficient or low strength of evidence. Evidence was sparse for patient-important outcomes (e.g., health-related quality of life) and outcomes for young children (<8 years). Key priorities for research are long-term comparative effectiveness and development of systems for monitoring harms.

Contents

Tables

Figures

Appendixes

Executive Summary

Introduction

The use of psychotropic medications, including antipsychotics, in children, adolescents, and young adults has risen over the past 20 years,[1-6] and use of antipsychotics in children with public health insurance[2] and living in foster homes[4] is greater than for those with private health insurance in the United States. During 2010, the percentages of young people filling prescriptions for antipsychotics in the United States was 0.11 percent (younger children), 0.8 percent (older children) 1.19 percent (adolescents), and 0.84 percent (young adults).[5] Antipsychotic medications are commonly categorized into two classes. First-generation antipsychotics (FGAs) were developed in the 1950s, while second-generation antipsychotics (SGAs) emerged in the 1980s. Each class is considered to have a distinct side-effect profile, although there is considerable overlap between them. FGAs are mainly associated with dry mouth, sedation, and extrapyramidal symptoms, which are movement disorders characterized by repetitive, involuntary muscle movements, restlessness, or an inability to initiate movement. Neuroleptic malignant syndrome is a rare but serious adverse effect. In the United States there has been a near disappearance of the use of FGAs over the last two decades.[7] A shift towards SGAs was partly driven by the lower risk of extrapyramidal symptoms with their use, and other adverse events caused by the persistent dopamine receptor blockade by FGAs. The pharmacology of SGAs is diverse (based on action at several types of receptors) with associated heterogeneity in effects and harms; nevertheless, this class seems more prone than FGAs to adverse effects such as weight gain, elevated lipid and prolactin levels, and development of metabolic syndrome.[8-10] This risk profile has led to great concern, because of the known associations between weight gain and obesity with diabetes, dyslipidemia, and hypertension, all of which are leading risk factors for future cardiovascular morbidity and mortality.[11] This risk profile necessitates safety monitoring and prescription choices based on benefit-risk assessments.

For most FGAs and SGAs, the U.S. Food and Drug Administration (FDA)–approved indications for children (≤ 18 years of age) are restricted to the treatment of schizophrenia and bipolar mania. Other pediatric indications approved by the FDA include treatment of irritability associated with autism in children 5 years or older (risperidone in 2006 and aripiprazole in 2009) and of Tourette's syndrome in children aged 6-18 (aripiprazole in 2014) or over 8 years (pimozide). Off-label use of antipsychotics is common in children and adults.[1,12] Twenty-four to 31 percent of antipsychotic-treated children have attention deficit hyperactivity disorder (ADHD),[1,13] and 34.5 percent of antipsychotic-treated young adults have depression.[5] In Medicaid-enrolled children, ADHD accounted for 50 percent of total antipsychotic use in 2007;[12] ADHD and mood disorders not otherwise specified were the most common uses (32% and 37.2%, respectively) for antipsychotics in a sample of Medicaid-insured children in Vermont during 2012.[12] In these cases or other conditions such as conduct disorders, antipsychotics are usually given for adjunctive treatment of severe behavioral symptoms (e.g., aggression), rather than for psychoses.[5-14] They may also be prescribed for mood instability or relatively minor symptomatology (e.g., insomnia) of a condition, or even outside the context of a condition;[12] these uses are accompanied by considerable controversy because of concerns regarding the balance of benefits and harms. This is particularly relevant when other treatment options exist for many conditions; for instance, fewer than half of very young, privately insured children taking antipsychotics received formal mental health services in 2007.[1]

Because of the marked increase in FDA-approved and off-label use of antipsychotics, prescribing practices have been under ongoing scrutiny (including use of prior authorization by Medicaid in many U.S. States),[15] and there is a need for ongoing investigation into the comparative effectiveness and harms of available medications. Practice parameters for antipsychotic use produced by the American Academy of Child and Adolescent Psychiatry (AACAP) are referred to when assessing practice for pediatrics in the United States,[16] but these parameters may be considered outdated (all studies cited in the parameters were published prior to 2012) for providing the best evidence. The purpose of the systematic review is to provide a comprehensive synthesis of the evidence examining the benefits and harms associated with the use of FDA-approved FGAs and SGAs in children, adolescents, and young adults ≤24 years of age. This systematic review covers many psychiatric conditions, as well as behavioral issues, for which antipsychotics are being prescribed as mono- or adjunctive therapy, such that a diverse range of stakeholders can be provided with evidence on the relative benefits and harms of antipsychotics to make informed decisions.

This is an update of Comparative Effectiveness Review (CER) No. 39 published in 2012.[17] The scope of this update has remained quite similar, with key changes being the addition of (1) three newly approved SGAs (i.e., brexpiprazole, asenapine, lurasidone) and the previously discontinued FGA molindone, (2) some conditions of interest (i.e., anxiety, depression, substance use), and (3) modification to some key outcomes to be more specific to symptoms targeted by clinicians when prescribing antipsychotics.

Scope of Review and Key Questions

Conditions of Interest

- Schizophrenia and schizophrenia-related psychoses, including schizoaffective disorder and prodromic (ultra high-risk) psychosis.
- Autism spectrum disorders, including pervasive developmental disorder, autism, Rett's disorder, childhood disintegrative disorder, Asperger's disorder, and pervasive developmental disorder not otherwise specified.
- Bipolar disorder.
- Attention deficit hyperactivity disorder, or disruptive, impulse-control, and conduct disorders
- Obsessive-compulsive disorder.
- Substance use disorder.
- Major and persistent depressive disorders, or disruptive mood dysregulation disorder.
- Anxiety disorders.
- Posttraumatic stress disorder.
- Eating disorders (i.e., anorexia nervosa, bulimia nervosa, binge-eating disorder).
- Tic disorders (e.g., Tourette’s syndrome).
- Behavioral issues outside the context of a mental disorder, including aggression, agitation, behavioral dyscontrol, irritability, self-injurious behaviors, and insomnia.

Key Questions

Key Question 1. For each condition of interest, what are the benefits, in terms of intermediate and effectiveness outcomes, of first and second generation antipsychotics—at the level of individual antipsychotics and across each class—in comparisons with placebo, different doses of the same antipsychotic, or different antipsychotics in children and young adults (≤24 years)?

a. Do the benefits vary with respect to patient characteristics, such as age, sex, race/ethnicity, medical comorbidities, phase or features of disorder, and antipsychotic treatment history?

b. Do the benefits vary with respect to clinical characteristics such as dose of antipsychotic or cotreatments including other antipsychotics, other medications, or nonpharmacologic therapy?

Key Question 2. Across all conditions of interest, what are the harms of first and second generation antipsychotics—at the level of individual antipsychotics and across each class—in comparisons with placebo, different doses of the same antipsychotic, or different antipsychotics in children and young adults (≤24 years)?

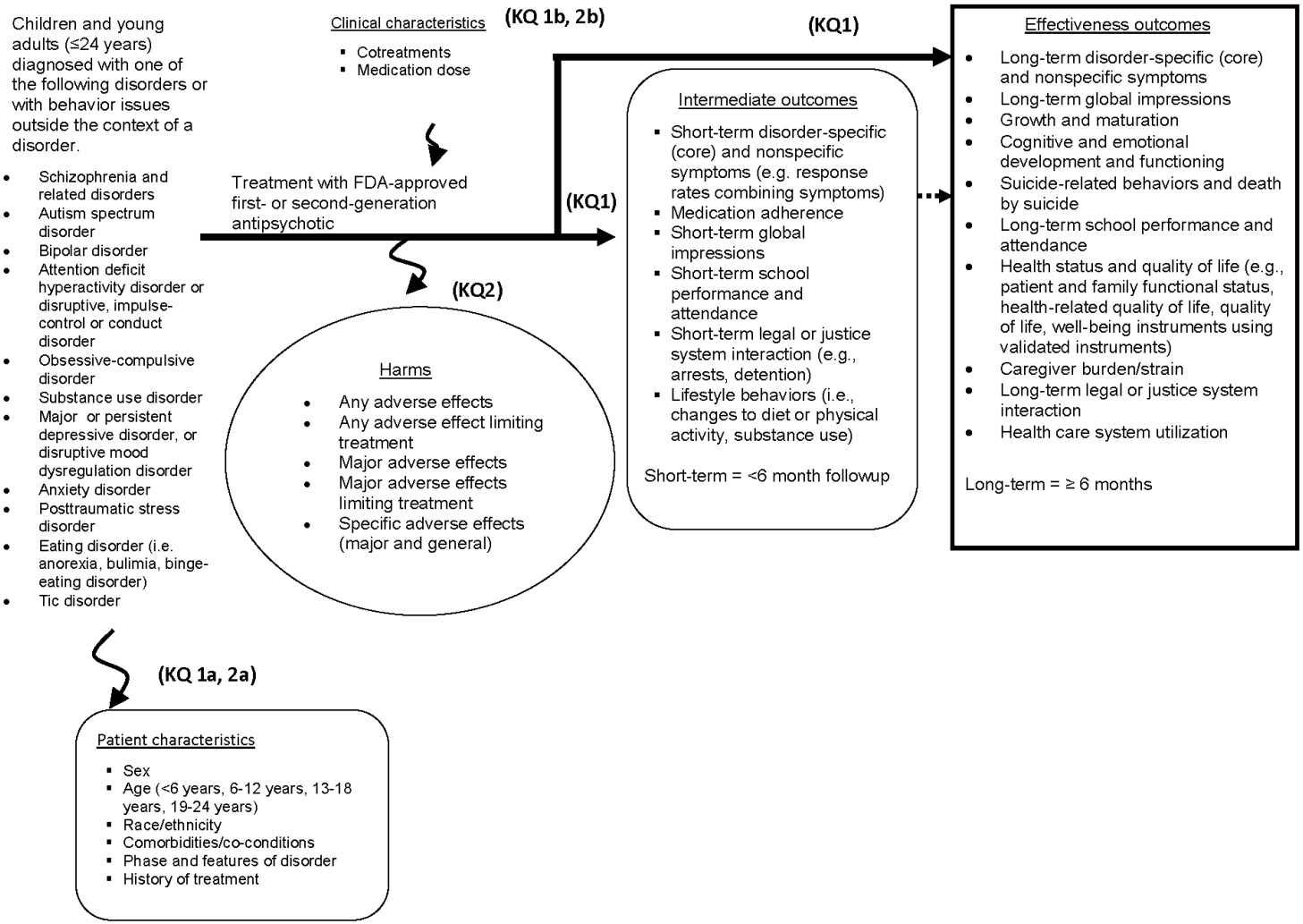
a. Do the harms vary with respect to patient characteristics, such as age, sex, race/ethnicity, diagnosis, medical comorbidities, phase of disorder, and prior exposure to antipsychotics?

b. Do the harms vary with respect to clinical characteristics such as dose of antipsychotic or cotreatments including other antipsychotics, other medications, or nonpharmacologic therapy?

Analytic Framework

Figure A is an analytic framework that depicts the structure used to address the Key Questions (KQs) for evaluating the benefits and harms of FGAs and SGAs in children and young adults (≤24 years of age). We examined the benefits and harms of FDA-approved FGAs and SGAs in a population of children and young adults (≤ 24 years) diagnosed with one of the psychiatric conditions identified, or experiencing behavioral issues outside the context of a psychiatric diagnosis (e.g., sleep difficulties, agitation, aggression). In KQ1, benefit was determined (by condition) for intermediate outcomes (e.g., disorder-specific and nonspecific symptoms, medication adherence, and lifestyle behaviors from short-term treatment durations), and effectiveness outcomes (e.g., symptoms over long-term treatment, growth and maturation, health status and quality of life, caregiver burden/strain). In KQ2, we assessed harms across conditions in terms of adverse effects (AEs) categorized as major (e.g., mortality, development of diabetes) and general (e.g., extrapyramidal effects, weight gain, hyperprolactinemia). Within each KQ, we assessed outcomes for subgroups of patients or studies based on patient and clinical/treatment characteristics.

Figure A. Analytic framework for the Key Questions evaluating the comparative effectiveness of FDA-approved first- and second generation antipsychotics in children and young adults 24 years old and under



FDA = Food and Drug Administration; KQ = Key Question

Methods

The methods for this review of antipsychotics in children and young adults are based on the methods specified in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (Methods Guide).[18] We provide here a summary of the methods outlined in detail in the protocol and full report.[19]

Inclusion/Exclusion Criteria

We used the eligibility criteria in terms of the population, intervention(s), comparator(s), outcome(s), timing (of followup), setting, and design of study (PICOTS-D) as presented in Table A; details specific to our key outcomes follow. The primary focus in KQ2 was harms across all conditions, rather than within each condition, because adverse events associated with an antipsychotic are likely to be consistent regardless of the indication for which a drug is being taken; the difference in harms between conditions was treated as a subgroup of interest. We defined nonrandomized controlled trials (NRCTs) as *experimental trials without random allocation but where intervention(s) are introduced, standardized, and allocated objectively [e.g., by date of birth, but not using subjective means such as patient or clinician preferences] by investigators and blinding of participants is typically possible.*

Table A. PICOTS (population, interventions, comparators, outcomes, timing, setting)

Category	Criteria
Population	Children and young adults (≤24 years) with one or more of the following conditions/issues: AD, ADHD/DICD, ASD, BD, DD, ED, OCD, PTSD, SUD, SZ, TD, or behavioral issues outside the context of a disorder (e.g., insomnia). KQ1: For each condition category, inclusion of studies enrolling ≥90 percent of patients diagnosed with the specific condition (s). KQ2: Across all conditions, inclusion of studies enrolling patients within a single or within multiple/mixed condition categories. Subpopulations based on patient characteristics: sex; age; race/ethnicity; comorbidities/co-conditions; history of treatment; phase and features of disorder.
Interventions	Any FDA-approved FGA (chlorpromazine, droperidol, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide, prochlorperazine, thiothixene, thioridazine, trifluoperazine) Any FDA-approved SGA (aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone) All formulations and doses eligible. Subpopulations as per clinical characteristics: presence of cotreatments (e.g., other medication, nonpharmacological therapy, as reported); medication dose.
Comparators	Placebo/no treatment, any other antipsychotic, or same antipsychotic at different dose. Exclusion of non-antipsychotic medications as comparator.
Outcomes	KQ1: intermediate and effectiveness outcomes (see following list of outcomes). KQ2: any AE and any major AEs; any or major AE limiting treatment (e.g., withdrawal due to AE); specific AEs (i.e., individual major or general AEs; see following list of outcomes)
Timing	No minimum followup duration Short term: <6 months Long term: ≥6 months-<12 months; 12 months+
Setting	Any setting
Design	Clinical trials (RCTs and NRCTs), controlled cohort studies (prospective or retrospective), controlled before-after studies (e.g., open-label extensions with comparator group, pooled analyses of individual patient-level data from one or a combination of similar trials).
Language	English

AD = anxiety disorders; ADHD/DICD = attention-deficit/hyperactivity disorder, or disruptive, impulse-control, or conduct disorders; AE = adverse effect; ASD = autism spectrum disorders; BD = bipolar disorder; DD = depressive disorders, ED = eating disorder; FDA = Food and Drug Administration; FGA = first-generation antipsychotic; KQ = Key Question; NRCT = nonrandomized controlled trial; OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; SGA = second-generation antipsychotic; SUD = substance use disorder; SZ = schizophrenia and related psychosis; TD = tic disorders

Outcomes

The key intermediate and effectiveness outcomes of interest to this review are listed below, followed by the harms. We accounted for duration of response, that is, short- (< 6 months) and long-term (≥ 6 months - < 12 months; ≥ 12 months).

Key Intermediate Outcomes

- Short-term (in terms of followup) disorder-specific (core) symptoms:
  - Schizophrenia and related psychoses: positive and negative symptoms;
  - Autism spectrum disorders: irritability, qualitative impairment in social interactions, communication, restricted repetitive and stereotyped behaviors;
  - Bipolar disorder: severity of mania, depression, psychotic features;
  - Attention deficit hyperactivity disorder or disruptive, impulse-control, and conduct disorders: aggression, externalizing behaviors, impulsivity;
  - Obsessive compulsive disorder: obsessive thoughts, compulsive behavior;
  - Substance use disorder: cravings, abstinence/substance use days;
  - Major or persistent depressive disorder: depression, irritability, psychotic features;
  - Anxiety disorder: anxiety, irritability;
  - Posttraumatic stress disorder: hyperarousal, avoidance behaviors, intrusion;
  - Eating disorders: weight, eating disorder attitudes and beliefs;
  - Tic disorders: motor and vocal tic frequency and severity;
  - Behavioral issues outside the context of disorder or illness: aggression, agitation, irritability, mood lability, self-injurious behaviors, and sleep latency and duration.
- Short-term nonspecific or associated symptoms
  - Response rates (other symptoms as reported were included but not considered key outcomes)
- Short-term global impressions and functioning

Key Effectiveness (Patient- and Family-Important) Outcomes

- Long-term disorder-specific symptoms (see list above)
- Long-term nonspecific or associated symptoms (see above)
- Long-term (≥ 6 month followup) global impressions and functioning
- Cognitive and emotional development and functioning
- Suicide-related ideations or behaviors, or death by suicide
- Generic and specific health status and quality of life (including patient and family functional status, well-being) using validated instruments
- Long-term (≥ 6 month followup) legal or justice system interaction

Key Harms: Major Adverse Effects

- Mortality, cerebrovascular disease-related events, development of diabetes mellitus, diabetic ketoacidosis, neuroleptic malignant syndrome, seizures, tardive dyskinesia, cardiomyopathies, cardiac arrhythmias, agranulocytosis and related (e.g., neutropenia)

Key Harms: General Adverse Effects

- Neuromotor effects: extrapyramidal symptoms including dystonia, akinesia, akathisia
- Metabolic effects: metabolic syndrome, change in body composition, fasting glucose, insulin sensitivity/resistance, dyslipidemia, blood pressure
- Prolactin-related effects and sexual dysfunction (e.g., hyperprolactinemia, AEs related to prolactin elevations [e.g., galactorrhea/bloody galactorrhea, hypogonadism], erectile dysfunction, infertility, oligo/amenorrhea, precocious puberty)
- Somnolence

Literature Search Strategy

We comprehensively searched the following electronic databases: Ovid MEDLINE and Ovid MEDLINE® In-Process & Other Non-Indexed Citations (1946 to Present), Cochrane Central Register of Controlled Trials via Wiley Cochrane Library (1991 to Present), EMBASE® via Ovid (1980 to 2016 Week 15), CINAHL Plus with Full Text via EBSCOhost (1937 to Present), PsycINFO® via Ovid (1987 to October Week 1, 2016), ProQuest® Dissertations and Theses Global (1861 to Present), and TOXLINE via The U.S. National Library of Medicine (1840s to Present). The original searches from October 2015 were updated in April 2016. Several other sources were used to obtain studies or additional data, including reference lists of relevant systematic reviews and guidelines, ClinicalTrials.gov, and World Health Organization's International Clinical Trials Registry Platform. Drug manufacturers and other relevant stakeholders were notified of the opportunity to submit scientific information relevant to the interventions of this systematic review. We handsearched the Journal of Child and Adolescent Psychopharmacology, and the Journal of the American Academy of Child and Adolescent Psychiatry (2014-2015). We searched Drugs@FDA for Medical/Clinical and Statistical review documents containing harm data for patients 18 years of age or younger.

Study Selection

For the database searches, two reviewers independently screened the titles and abstracts (when available) using broad inclusion/exclusion criteria. One reviewer conducted all other searches outlined in the above section. Disagreements on final inclusion of all studies were resolved through consensus or third party adjudication.

Data Abstraction

One review team member extracted data for each study, and a senior level team member verified all data. A wide variety of checklists and scales were used to assess symptomatology in patients. In various instances (e.g., hyperactivity, aggression) we used subscale items on one or more questionnaires, rather than their overall composite scores, to capture the outcomes of interest with more specificity. Data on within-study subgroup analysis was collected.

Assessment of Methodological Quality of Individual Studies

Two experienced reviewers independently assessed the methodological quality of all original and new studies and resolved discrepancies through consensus. We re-assessed original studies because of changes to guidance in the Evidence-based Practice Center (EPC) program made subsequent to the original review. For randomized controlled trials (RCTs) and NRCTs we used the Cochrane Collaboration Risk of Bias tool,[20] with some modification based on EPC Methods guidance.[18] For cohort studies, we used the Newcastle-Ottawa Quality Assessment Scale.[21] Ratings reflect risk of bias (ROB: high, medium, low) such that the methodological quality is opposing (e.g., high ROB represents low quality).

Data Synthesis

For each KQ, we synthesized data in the following order based on type of drug comparison (as possible depending on data): aggregate (across class) data for FGAs versus SGAs, individual FGAs versus SGAs, within-class comparisons between individual FGAs and individual SGAs (other drug or dose), and then individual and aggregate data for FGAs versus placebo/no treatment and SGAs versus placebo/no treatment.

For pairwise meta-analyses, we employed a Bayesian random effects model.[22, 23] We used this approach when more than two studies reported on the same outcome and comparison. When different outcomes were considered to measure the same construct (e.g., different subscores of hyperactivity) we combined the results (at followup) of multiple scores using a standardized mean difference (SMD); in this way we were able to use as many studies as possible to capture effect estimates for our outcomes. When the SMD was not used because of reporting by multiple studies using the same measurement scale (enabling calculation of a mean difference [MD]), change scores were preferred over followup scores and we combined these two when necessary. We report MDs, SMDs, or risk ratios (RRs) with corresponding 95% credible intervals (95% CrI; Bayesian approaches provide variances using credible rather than confidence intervals, interpretable as the range of values within which there is a 95% chance of finding the true value of the effect). We often started with combining all studies within a condition category and then used our a priori defined list of patient and intervention subgroups (listed in Figure A as patient and clinical characteristics) to explore the heterogeneity. For intermediate and effectiveness outcomes we considered combining results from RCTs with NRCTS, but not with cohort studies. For harm outcomes we combined data from all study designs for the following reasons: 1) empirical evidence has found no difference in estimates of harms between meta-analyses of RCT and cohort study designs;[24] 2) a major contributor to bias on harms from observational studies is confounding by indication (e.g., differential prescriptions based on beliefs/knowledge about factors related to development of harms) which we did not believe was an important threat in studies examining mostly unanticipated harms in treatment naïve children; and 3) cohort studies are commonly recognized as contributing valuable, relatively high-quality evidence on harms applicable to real-world settings. To avoid making conclusions from these analyses without carefully considering possible biases, we identified important potential confounders on which to assess the findings for heterogeneity and also extracted data from all studies that reported within-study subgroup analysis for possible patient and clinical treatment modifiers. In the event that results from studies were not combined, the findings of each study are reported with statistical precision indicated with confidence intervals (95% CIs).

For commonly reported key harm outcomes (weight and body mass index [BMI]), we employed a network meta-analysis to simultaneously evaluate a suite of comparisons including

indirect comparisons (e.g., incorporation of placebo/no treatment-controlled and head-to-head trial data) while still preserving the within-study randomization. Results are presented in terms of a placebo referent, to rank the drugs based on a common comparator, but data from head-to-head comparisons (e.g., risperidone versus olanzapine) were incorporated in the analysis. An appendix to the report contains the methods and results including those for every possible comparison between the individual drugs. Findings from the network meta-analyses are considered fairly observational in nature and were compared with other more direct findings from the pairwise meta-analyses.

Our primary approach to answer each KQ's parts (a) and (b) on subgroup effects (i.e., variation in effect based on patient and clinical characteristics) was to record any within-study subgroup analyses performed by study investigators using individual patient data; these results preserved the within-study randomization. Because these results are often based on diverse methodology and may be difficult to interpret across the body of evidence, we also performed our own subgroup analyses using study-level data, where possible. For the benefit outcomes (for which we usually had fewer than 6-10 studies) we performed sensitivity analyses on the results of the pairwise meta-analyses by subgroup variables, such as treatment phase, and/or made observations of the data about possible modification to effect sizes or heterogeneity specific to the subgroup variables of interest. We employed univariate Bayesian meta-regression analyses for four key harm outcomes (weight, weight gain of greater than 7%, somnolence, incidence of any extrapyramidal symptoms) in terms of patient age, sex, antipsychotic treatment history (i.e., % treatment naïve), and treatment duration. We also performed adjusted network meta-analyses using treatment duration (found statistically significant in the metaregression for weight gain) as a study-level variable. These analyses relied on study-level data (e.g., average age in study), such that the results should be considered observational in nature.

Grading the Strength of the Body of Evidence

We followed the Methods Guide and updated guidance[25] to evaluate the strength of the body of evidence for the key outcomes and comparisons. The strength of evidence (SOE) was graded by one reviewer, and reviewed by a second reviewer. Disagreements were resolved through discussion or by consulting with a third reviewer, as needed. Tables of findings were generated for all outcomes and comparisons that had greater than insufficient SOE. We assessed SOE based on five core domains: study limitations, consistency, directness, precision, and reporting bias. For rare events (≤ 5% of patients in both groups having event) we considered 2000 patients sufficient to offer adequate power to detect a difference and therefore provide precise results. For continuous outcomes, more than 400 total enrolled patients are generally considered to offer precise data based on adequate power to detect a 0.2 standardized effect size;[26] we estimated that studies having as few as 200 patients could offer precise estimates of effect. When a confidence interval around an effect estimate was not statistically significant (suggesting no difference) but included values that may be clinically significant for some patients, we could not rule out the possibility of a benefit or harm for this outcome and therefore rated down for precision.

Interpretations of Findings

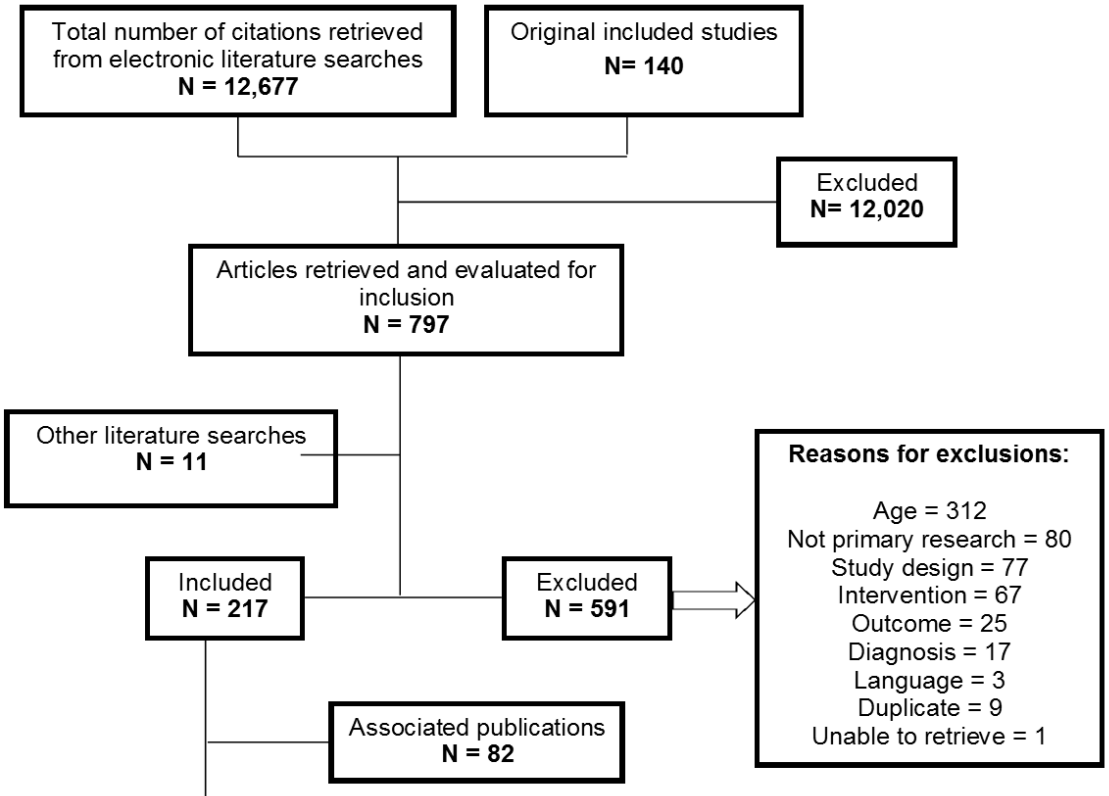
We chose to use standard wording to describe our interpretations of the SOE and of the magnitude of the effects.[27] For findings supported by high, moderate, low, and insufficient SOE (for which we have similar confidence in the results) we use "will", "probably/likely", "may/appears to", and "not known" in our textual descriptions of the results. Related to

magnitude of effects, when the evidence showed effects that would be considered by many patients and practitioners to be clinically important or small, we use “increase/improve/decrease/worsen” (as suitable) or “slightly increase/improve/decrease/worsen”, respectively; when there appears to be no difference in effect, we use “makes little or no difference.”

Results and Discussion

Our database searches identified 12,677 citations, and 11 additional records were identified from other sources. In total, we included 57 new studies in addition to 78 from the original review (N = 135). Figure B describes the flow of literature through the screening.

Figure B. Flow of literature through study search and selection process



Schizophrenia and Related Psychoses	39[a]
Autism Spectrum Disorders	23
Bipolar Disorder	19[a]
ADHD and Disruptive, Impulse-Control, and Conduct Disorders	13
Obsessive Compulsive Disorder	1
Depressive Disdorders	1
Eating Disorders	3
Tic Disorders	12
Behavioral Issues	2
Multiple/Mixed Conditions[b]	23
Total	**135**

ADHD = attention deficit hyperactivity disorder

[a] One study provided separate data for both bipolar disorder and schizophrenia; [b]Studies with populations having multiple primary diagnosis were included for key question 2 on harms only.

A total of 100 studies (74%) examined antipsychotics for intermediate and effectiveness outcomes (KQ1). Harms (KQ2) were reported in 126 studies (93%). Of the 135 studies, 89 (66%) were RCTs, 6 (4%) were NRCTs, and 40 (30%) were observational studies.

The number of enrolled/examined participants ranged from 8 to 4140 (median = 59; IQR [interquartile range], 30 to 119). The mean age of study participants ranged from 4 to 22 years

(median, 13; IQR, 9.8 to 15.35); studies of schizophrenia generally enrolled older patients (mean 15.8, range 8.86 to 22 years) than those of other conditions (mean 11.34, range 4-19 years). The mean age was lower than 12 years in 52 studies (39%). One hundred and one (75%) studies reported on followup durations of < 6 months, 10 reported on both short- and long-term followup, and 24 reported only on longer-term followup.

Overall, 113 studies provided one or more head-to-head comparisons of individual FGAs or SGAs. A total of 20 studies compared different doses of the same antipsychotic, and 56 studies compared one antipsychotic with placebo. Only five studies included arms with patients taking a variety of SGAs or FGAs.

For subjective outcomes in trials, the overall ROB was rated as high for 60 percent of studies; only eight were assessed as low ROB. The ROB was slightly lower when considering objective outcomes (high for 55% of studies). The main contributor to ROB was incomplete outcome data. Overall, the observational studies were of quite high quality; of 40 studies, 4 (10%) were rated as having high ROB, 12 (30%) as having medium ROB, and 24 (60%) as low ROB. Despite this, the observational studies are still considered of poorer quality (i.e., providing less validity) than the RCTs, because of their inability to completely account for confounding by patient characteristics. Almost half of the studies did not account in some way for variables of confounding considered important (i.e., treatment history, duration/stage of illness).

Key Findings of Intermediate and Effectiveness Outcomes (Key Question 1)

The findings for key intermediate and effectiveness outcomes are summarized below. With the exception of studies examining schizophrenia, the evidence comparing FGAs with SGAs and different antipsychotics within each class was limited. For most conditions, the majority of the findings focused on the comparison of SGA versus placebo. Summary of findings tables contain the findings having at least low SOE.

Schizophrenia and Related Psychoses

Twenty-eight studies reported on intermediate outcomes and 14 reported on effectiveness outcomes for use of FGAs and SGAs in schizophrenia and related psychosis. The average age of patients across the studies was 15.8 years (range 8.9-22). Sexes were fairly equally represented across the studies (60.1% male). Most studies had treatment durations between 4 and 12 weeks; nine studies were 6 months or longer. Table B summarizes the findings.

There may be little or no difference between FGAs and SGAs for the key outcomes of negative symptoms, positive symptoms, response rates, and global impressions of illness severity. The effects for depression symptoms or global impressions of improvement are not known.

Six studies comparing olanzapine with risperidone found that there may be little or no difference in their effects for negative and positive symptoms, response rates, and global impressions of severity. There appears to be little or no difference between low- and high-dose asenapine for response rates or global impressions of severity in the short-term. Between high and low doses of quetiapine, there is probably little or no difference in clinician impressions of severity or global functioning, and there may be little or no difference in reduction in negative symptoms or improvements in response rates. The effects between different doses of other antipsychotics are not known.

Compared with placebo, SGAs as a class likely increase response rates, decrease slightly (not clinically significant) negative and positive symptoms, and improve slightly global impressions of improvement, severity, and functioning. They may make little or no difference in depression symptoms. The only outcome which appeared to result in substantial clinical benefit was response rates (RR, 1.52; 95% CrI, 1.15 to 2.02); the effect estimates for all other outcomes were of a small magnitude, which appears to be influenced by a substantial placebo effect in many cases. Sensitivity analysis by removing the study examining maintenance, rather than acute, treatment with aripiprazole did not affect overall findings to any meaningful extent; results were similar when applying sensitivity analysis for the prodrome phase of psychosis. There appears to be little or no difference between SGAs and placebo for suicide attempts, completed suicide, suicide ideations, or suicide behaviors in short-term studies.

Table B. Summary of findings for schizophrenia and related psychosis: Key intermediate and effectiveness outcomes having at least low strength of evidence

Comparison, Category of Outcome	Outcome (N Studies, N Patients)	Findings,[a] Measurement Tool With Possible Range of Values, if Applicable	Strength of Evidence; Conclusions
SGAs vs. FGAs Intermediate outcomes	Negative symptoms (RCTs: 5, 217)	4 RCTs: SMD, 0.0; 95% CrI, -0.55 to 0.50 1 RCT: No difference (p value NR)	Low; may make little or no difference[b]
	Positive symptoms (RCTs: 5, 217)	4 RCTs: SMD, -0.25; 95% CrI, -0.92 to 0.29 1 RCT: No difference (p value NR)	Low; may make little or no difference[b]
	Response rates (RCTs: 2, 188)	RR, 1.06; 95% CrI, 0.53 to 2.25	Low; may make little or no difference[b]
	Global impressions of severity using CGI-S[c] (RCTs: 2, 124)	MD, -0.21; 95% CrI, -1.19 to 0.67	Low; may make little or no difference[d]
Olanzapine vs. risperidone Intermediate outcomes	Negative symptoms (RCTs: 5, 198)	4 RCTs: SMD, -0.09; 95% CrI, -0.76 to 0.53 1 RCT: No difference p = 0.19	Low; may make little or no difference[b]
	Positive symptoms (RCTs: 5, 198)	4 RCTs: SMD, -0.11; 95% CrI, -0.76 to 0.40 1 RCT: No difference p = 0.10	Low; may make little or no difference[b]
	Response rates (RCTs: 4, 156)	RR, 1.01; 95% CrI, 0.51 to 1.9	Low; may make little or no difference[b]
	Global impressions of severity using CGI-S (RCTs: 3, 131)	1 RCT: MD, 0.30; 95% CI, -0.53 to 1.13 1 RCT: MD, 0.30; 95% CI, -0.41 to 1.01 1 RCT: No difference p = 0.33	Low; may make little or no difference[d]
Asenapine high vs. low	Response rate (RCTs: 1, 204)	1 RCT: RR, 1.00; 95% CI, 0.75 to 1.32	Low; may make little or no difference[e]
	Global impressions of severity using CGI-S (RCTs: 1, 204)	1 RCT: MD, 0.20; 95% CI, -0.05 to 0.45	Low; may make little or no difference[e]
Quetiapine high vs. low dose Intermediate outcomes	Negative symptoms (RCTs: 2, 238)	1 RCT: MD, 1.6; 95% CI, -4.79 to 7.99 (SANS; range 0-25) 1 RCT: MD, 0.14; 95% CI, -1.81 to 2.09 (PANSS; range 7-49)	Low; may make little or no difference[b]
	Response rates (RCTs: 2, 273)	1 RCT: RR, 0.73; 95% CI, 0.41 to 1.29 1 RCT: RR, 1.05; 95% CI, 0.69 to 1.60	Low; may make little or no difference[b]
	Global impressions of severity using CGI-S (RCTs: 2, 238)	1 RCT: MD, 0.00; 95% CI, -0.35 to 0.35 1 RCT: MD, -0.13; 95% CI, -0.47 to 0.21	Moderate; probably makes little or no difference[f]
	Global impressions of functioning (RCTs: 2, 238)	1 RCT: MD, -3.5; 95% CI, -8.37 to 1.37 (GAF; range 1-100) 1 RCT: MD, 1.9; 95% CI, -2.35 to 6.15 (C-GAS; range 1-100)	Moderate; probably makes little or no difference[f]

Comparison, Category of Outcome	Outcome (N Studies, N Patients)	Findings,[a] Measurement Tool With Possible Range of Values, if Applicable	Strength of Evidence; Conclusions
All SGAs vs. placebo Intermediate outcomes	Negative symptoms (RCTs: 9, 1788)	MD, -1.31; 95% CrI, -2.05 to -0.58 (PANSS Negative; range 7-49)	Moderate; SGAs probably decrease slightly[f]
	Positive symptoms (RCTs: 9, 1788)	MD, -2.20; 95% CrI, -2.98 to -1.48 (PANSS Positive; range 7-49)	Moderate; SGAs probably decrease slightly[f]
	Depression symptoms (RCTs: 2, 420)	1 RCT: MD, -0.59; 95% CI, -1.46 to 0.28 1 RCT: MD, -0.59; 95% CI, -1.45 to 0.27 (PANSS Depression)	Low; may make little or no difference[f]
	Response rates (RCTs: 5, 993)	RR, 1.52; 95% CrI, 1.15 to 2.02	Moderate; SGAs probably increase[f]
	Global impressions of improvement using CGI-I (RCTs: 6, 1202)	MD, -0.54; 95% CrI, -1.07 to -0.14	Moderate; SGAs probably improve slightly[f]
	Global impressions of severity using CGI-S (RCTs: 9, 1788)	MD, -0.36; 95% CrI, -0.51 to -0.22	Moderate; SGAs probably improve slightly[f]
	Global impressions of functioning (RCTs: 7, 1339)	MD, 4.15; 95% CrI, 2.03 to 6.59 (C-GAS; range 0-100)	Moderate; SGAs probably improve slightly[f]
All SGAs vs. placebo Effectiveness Outcomes	Short-term suicide attempts/suicides (RCTs: 7, 1463)	Attempts: 2 in 693 SGA and 2 in 318 placebo patients Suicides: 0 in 447 SGA vs. 0 in 227 placebo patients	Low; may make little or no difference[g]
	Short-term suicide ideations or behaviors (RCTs: 4, 758)	Ideations: 3 in 340 SGA and 1 in 165 placebo patients Behaviors: 1 in 170 SGA and 1 in 83 placebo patients	Low; may make little or no difference[g]

C-GAS = Global Assessment Scale for Children; CGI-I = Clinical Global Impressions of Improvement; CGI-S = Clinical Global Impressions of Severity; CI = confidence interval; CrI = credible interval (used with Bayesian meta-analysis); FGA = first-generation antipsychotic; GAF = Global Assessment of Functioning; MD = mean difference; N = number; NR = not reported; PANSS; Positive and Negative Syndrome Scale; RCT: randomized controlled trial; ROB = risk of bias; RR = risk ratio; SANS = Scale for the Assessment of Negative Symptoms; SGA = second-generation antipsychotics; SMD = standardized mean difference

[a] When the findings are not representative of the total number of studies identified in the outcome column, we included the number of studies for each finding; we did not pool data from 1 or 2 studies so these results are always presented separately. All values except Response and Global Impressions of Functioning are favorable for group 1 (G1) when there is a negative effect estimate; the larger the magnitude of the number the larger the effect. SMDs provide results in standard deviation units, and are used when the results from different measurement tools are combined in meta-analysis; as a general rule, 0.2 represents a small effect size, 0.5 a moderate one, and 0.8 a large one.

[b] Downgraded for ROB and imprecision, because credible interval includes a clinically significant value (e.g., SMD $\geq \pm 0.50$, CGI-I or CGI-S $\geq \pm 2$ points [7 point scales]) such that we could not rule out benefit even though effect estimate appears to be of no difference.

[c] CGI-S and CGI-I scores range from 0-6.

[d] Downgraded for ROB and imprecision because of small sample size, typically < 200 patients in total.

[e] Downgraded for inconsitnecy and imprecision.

[f] Downgraded for ROB.

[g] Downgraded for ROB and imprecision because of small event rates; confidence intervals of relative risks ranged between 0.02 to 5.0, to 0.06 to 48.1).

Bipolar Disorder

Of 19 studies examining treatment of bipolar disorder, 15 reported on intermediate and 11 on effectiveness outcomes. The average age of patients was 12.8 years. Both sexes were equally represented across the studies (56% male). Sixteen trials had followup periods ranging from 3 to 12 weeks. One trial had a controlled extension phase of 30 weeks, one trial had a placebo-

controlled maintenance treatment duration of 72 weeks, and an observational study reviewed charts for between 7 to 8 months. Table C contains a summary of the findings.

There may be a slightly greater reduction in manic symptoms from high- (10mg/day) versus low-dose (5 mg/day) asenapine; dose of asenapine may make little or no difference for global impressions of severity or for depression.

Compared with placebo, SGAs likely reduce manic symptoms and probably decrease slightly depression symptoms. SGAs probably increase response and remission rates versus placebo in studies of patients experiencing manic/mixed phases; clinical and statistical heterogeneity was introduced when including two RCTs examining quetiapine for patients with depressive episodes (showing less response). Moderate SOE exists showing that SGAs probably decrease symptom severity to a small extent and increase global functioning slightly compared with placebo.

When examining individual SGAs versus placebo, the findings for aripiprazole were similar to those across all SGAs, with the exception of depression symptoms where use of this SGA may make little or no difference. Quetiapine probably reduces manic symptoms, likely makes little or no difference for depression symptoms, and appears to make no difference for response in studies of patients experiencing manic/mixed episodes; the results of little to no difference for response rates (often focused on manic symptoms) were imprecise showing that many patients may have clinically relevant response. The effects of quetiapine versus placebo for remission rates and for global impressions of severity are not known.

A study enrolling patients with prodromal bipolar disorder reported similar efficacy to the other studies of patients with manic symptoms. A study exclusively enrolling patients having comorbid ADHD did not appear to differ in effect for several outcomes to other similar studies assessing SGAs in manic or mixed episodes. Several within-study subgroup analyses showed that concomitant use of psychostimulants had no significant effect on manic symptoms; comorbid diagnosis of ADHD or a disruptive, impulse-control, or conduct disorder did not significantly affect results either for mania or depression.

For effectiveness outcomes, SGAs may make little or no difference over placebo for suicide ideations and attempts.

Table C. Summary of findings for bipolar disorder: Key intermediate and effectiveness outcomes having at least low strength of evidence

Comparison, Outcome Category	Outcome (N Studies; N Patients)	Findings,[a] Tool With Range of Values, if Applicable	Strength of Evidence; Conclusions
Asenapine high (10 mg/day) vs. low (5 mg/day) dose	Manic symptoms (1, 199)	MD, -2.80; 95% CI -0.64 to -4.96 (YMRS; range 0-60)	Low; High-dose asenapine may decrease slightly manic symptoms[b]
	Global impressions of severity (1, 199)	MD, -0.10, 95% CI -0.29 to 0.49	Low; may make little or no difference[b]
	Depression (1, 199)	MD, 0.80; 95% CI -1.87 to 3.47 (CDRS; range 0-113)	Low; may make little or no difference[b]
All SGAs vs. placebo Intermediate Outcomes	Manic symptoms (11, 1639)	MD, -6.42; 95% CrI, -7.88 to -5.26 (YMRS; range 0-60)	Moderate; SGAs probably decrease[c]
	Depression symptoms (9, 1622)	MD, -1.65; 95% CrI, -2.78 to -0.48 (CDRS; range 0-113)	Moderate; SGAs probably decrease slightly[c]
	Response (10, 1664) (Manic/mixed phases)[d]	RR, 1.97; 95% CrI, 1.66 to 2.34 (40-50% reduction in YMRS from baseline)	Moderate; SGAs probably increase for manic/mixed phases[c]

Comparison, Outcome Category	Outcome (N Studies; N Patients)	Findings,[a] Tool With Range of Values, if Applicable	Strength of Evidence; Conclusions
	Remission (5, 944) (Manic/Mixed phases)[d]	RR, 2.84; 95% CrI, 1.67 to 5.55	Moderate; SGAs probably increase for manic/mixed phases[c]
	Global impressions of severity using CGI-S[e] (9, 1778)	MD, -0.65; 95% CI, -0.80 to -0.49	Moderate; SGAs probably slightly decrease[c]
	Global impressions of functioning (4, 1188)	MD, 6.64; 95% CrI, 2.45 to 10.95 (C-GAS; range 1-100)	Moderate; SGAs probably slightly increase[c]
All SGAs vs. placebo Effectiveness Outcomes	Suicide ideation (8, 1782)	RR, 1.12; 95% CrI, 0.58 to 2.26	Low; SGAs may make little or no difference[f]
	Suicide attempts (6, 1285)	RR, 1.71; 95% CrI, 0.39 to 7.38	Low; SGAs may make little or no difference[f]
Aripiprazole vs. placebo Intermediate Outcomes	Manic symptoms (3, 387)	MD, -7.08; 95% CrI, -10.96 to -3.24 (YMRS; range 0-60)	Moderate; Aripiprazole probably decreases[c]
	Depression symptoms (2, 311)	1 RCT: MD, -1.74; 95% CI, -3.92 to 0.44 1 RCT: MD, -2.29; 95% CI, -10.62 to 6.04 (CDRS-R; range 17-113)	Low; Aripiprazole may make little or no difference[g]
	Response rates (2, 311)	1 RCT: RR, 2.11; 95% CI, 1.47 to 3.02 1 RCT: RR, 1.71; 95% CI, 1.13 to 2.58	Moderate; Aripiprazole probably increases[c]
	Remission (2, 311)	1 RCT: RR, 7.09; 95% CI, 2.96 to 16.99 1 RCT: RR, 2.26; 95% CI, 1.19 to 4.28	Moderate; Aripiprazole probably increases[c]
	Global impressions of severity using CGI-S (2, 328)[e]	1 RCT: MD, -1.00; 95% CI, -1.34 to -0.67 1 RCT: MD, -0.41; 95% CI, -0.80 to -0.02	Moderate; Aripiprazole probably slightly decreases[c]
Quetiapine vs. placebo Intermediate Outcomes	Manic symptoms (3, 339)	MD, -5.34; 95% CrI, -9.92 to -0.44 (YMRS; range 0-60)	Moderate; Quetiapine probably decreases[c]
	Depression symptoms (3, 501)	MD, -1.87; 95% CrI, -4.71 to 1.11 (CDRS-R; range 17-113)	Moderate; Quetiapine probably makes little or no difference[c]
	Response (2, 307) (Manic/mixed)	1 RCT: RR, 1.36; 95% CI, 0.97 to 2.72 1 RCT: RR, 1.97; 95% CI, 1.38 to 2.81	Low; Quetiaipine may make little or no difference[g]

CDRS-R = Children's Depression Rating Scale-Revised; C-GAS = Global Assessment Scale for Children; CGI-S = Clinical Global Impressions of Severity; CrI = credible interval (used with Bayesian meta-analysis); MD = mean difference; N = number; RCT: randomized controlled trial; RR = risk ratio; SGA = second-generation antipsychotics; YMRS = Young Mania Rating Scale

[a] When the findings are not representative of the total number of studies identified in the outcome column, we included the number of studies for each finding; we did not pool data from 1 or 2 studies so these results are always presented separately. All values except Response, Remission, and Global Impressions of Functioning are favorable for the SGA when there is a negative effect estimate; the larger the magnitude of the number the larger the effect.

[b] Dowgraded for imprecision.

[c] Downgraded for ROB.

[d] When two studies examining the depressive phase were included the heterogeneity has substantial.

[e] CGI-S scores range from 0-6.

[f] Downgraded for ROB and imprecision due to small samples for this rare outcome.

[g] Downgraded for ROB and imprecision due to CI including clinically relevant benefit for SGAs.

Autism Spectrum Disorders

Twenty-three studies examined the effectiveness of FGAs and SGAs in autism spectrum disorders. The average age of patients was 9.1 years, and patients were predominantly male (average 83%). Treatment duration varied widely across studies (range, 4 weeks to 2.3 years). For the studies (n = 18) we considered short-term (< 6 months duration), average duration was 8.9 weeks. Table D summarizes the findings.

At least low SOE was only found for intermediate outcomes in comparisons between SGA and placebo. SGAs probably decrease irritability, and probably slightly decrease lethargy/social withdrawal, stereotypy, and inappropriate speech. SGAs likely increase response rates and (slightly) clinical severity. They may increase global impressions of improvement. Maintenance treatment with an SGA appears to decrease relapse rates.

When examining studies of aripiprazole and risperidone, the findings were similar for irritability and (with aripiprazole) for stereotypy. For lethargy, inappropriate speech, and response rates (with risperidone) conclusions were that these SGAs may make little or no difference; smaller sample sizes contributing to the SOE for each drug likely affected the ability to obtain a significant finding for most outcomes (e.g., response rates), with the exception of irritability which overall had the larger magnitude of effect.

Table D. Summary of findings for autism spectrum disorders: Key intermediate outcomes having at least low strength of evidence

Comparison	Outcome (N Studies; N Patients)	Findings,[a] Tool With Range of Values, if Applicable	Strength of Evidence; Conclusion
SGAs vs. placebo	Irritability (8, 809)	MD, -6.38; 95% CrI, -8.94 to -3.83 (ABC subscale; range 0-45)	Moderate; SGAs probably decrease[b]
	Lethargy/social withdrawal (7, 743)	MD, -1.67; 95% CrI, -3.05 to -0.28 (ABC subscale; range 0-48)	Moderate; SGAs probably decrease slightly[b]
	Stereotypy (5, 634)	MD, -1.73; 95% CrI, -3.16 to -0.05 (ABC subscale; range 0-21)	Moderate; SGAs probably decrease slightly[b]
	Inappropriate speech (7, 743)	MD, -1.04; 95% CrI, -1.83 to -0.26 (ABC subscale; range 0-12)	Moderate; SGAs probably decrease slightly [b]
	Response rates (7, 716)	RR, 2.22; 95% CrI, 1.29 to 4.17	Moderate; SGAs probably increase[b]
	Relapse rates (3, 141) (Maintenance phase only)	RR, 0.30; 95% CrI, 0.07 to 0.84	Low; SGAs may decrease during maintenance treatment[c]
	Global impressions of improvement on CGI-I[d] (6, 635)	4 RCTs: MD, -1.00, 95% CrI, -2.34 to 0.07 3 RCTs: RR 4.5 and 6.5; both p < 0.01 (proportion scoring as at least "much improved")	Low; SGAs may increase[b]
	Global impressions of severity on CGI-S[d] (4, 522)	3 RCTs: MD, -0.61; 95% CrI, -1.04 to -0.15	Moderate; SGAs probably slightly decrease[b]
Aripiprazole vs. placebo	Irritability (3, 393)	MD, -5.74; 95% CrI, -9.34 to -2.15 (ABC subscale; range 0-45)	Moderate; Aripiprazole probably decreases[b]
	Lethargy/social withdrawal (3, 393)	MD, -1.41; 95% CrI, -4.19 to 1.35 (ABC subscale; range 0-48)	Low; Aripiprazole may make little or no difference[e]
	Stereotypy (3, 393)	MD, -2.51; 95% CrI, -4.68 to -0.33 (ABC subscale; range 0-21)	Moderate; Aripiprazole probably decreases slightly[b]
	Inappropriate speech (3, 393)	MD, -1.49; 95% CrI, -3.02 to 0.06 (ABC subscale; range 0-12)	Low; Aripiprazole may make little or no difference[e]
Risperidone vs. placebo	Irritability (4, 268)	MD, -8.28; 95% CrI, -12.59 to -3.64 (ABC subscale; range 0-45)	Moderate; Risperidone probably decreases[b]
	Lethargy/social withdrawal (3, 202)	MD, -2.51; 95% CrI, -5.67 to 1.02 (ABC subscale; range 0-48)	Low; Risperidone may make little or no difference[e]

Comparison	Outcome (N Studies; N Patients)	Findings,[a] Tool With Range of Values, if Applicable	Strength of Evidence; Conclusion
	Stereotypy (2, 178) (Acute phase only)	1 RCT: -3.10; 95% CI, -4.93 to -1.27 1 RCT: -1.90; 95% CI, -3.64 to -0.16 (ABC subscale; range 0-21)	Low; Risperidone may decrease slightly in acute treatment[c]
	Inappropriate speech (3, 202)	MD, -1.06; 95% CrI, -2.66 to 0.59 (ABC subscale; range 0-12)	Low; Risperidone may make little or no difference[e]
	Response rate (3, 246)	RR, 2.75; 95% CrI, 0.92 to 9.77	Low; Risperidone may make little or no difference[e]

ABC = Aberrant Behavior Checklist; CB-YOCS = Children's Yale-Brown Obsessive Compulsive Scale; CGI-I = Clinical Global Impressions of Improvement; CGI-S = Clinical Global Impressions of Severity; CI = confidence interval; CrI = credible interval (used with Bayesian meta-analysis); MD = mean difference; N = number; RCT: randomized controlled trial; RR = risk ratio; SGA = second-generation antipsychotics

[a] When the findings are not representative of the total number of studies identified in the outcome column, we included the number of studies for each finding; we did not pool data from 1 or 2 studies so these results are always presented separately. All values except Response are favorable for SGAs when there is a negative MD, or a RR < 1.0 (i.e., relapse); the larger the magnitude of effect, the larger the effect.

[b] Downgraded for ROB.

[c] Downgraded for ROB and imprecision because of small sample size, typically < 200 patients in total.

[d] CGI-S and CGI-I scores range from 0-6.

[e] Downgraded for ROB and imprecision, because credible interval includes a clinically significant value (e.g., lower boundary value considered clinically meaningful reduction) such that we could not rule out benefit even though effect estimate appears to be of no difference.

ADHD and Disruptive, Impulse-Control, or Conduct Disorders

Thirteen studies examined ADHD and/or disruptive, impulse-control, or conduct disorders (DICD). Patients had an average age of 9.9 years and were predominantly male (83%); apart from two RCTs enrolling adolescents, the age of participants was typically below 12 years and close to 9-10 years (no study had a mean age below 8 years). Most RCTs were examining acute phase treatment in patients either naïve to or not taking antipsychotics upon enrollment; one RCT enrolled children maintained on risperidone for 1 year and examined placebo-controlled discontinuation of the antipsychotic. All children were taking stimulants in three RCTs, variable numbers were taking stimulants in five RCTS, and stimulants were prohibited in three RCTs. We summarize the findings in Table E. All evidence graded as having at least low SOE was for outcomes between SGAs and placebo.

Compared with placebo, SGAs as a class (and risperidone alone) probably reduce conduct problems and aggression in children with ADHD and/or DICD. Results for clinical impressions of improvement showed little or no difference, although results were imprecise and indicated that many patients may possibly improve. Risperidone likely decreases hyperactivity, although this level of confidence is specific to studies where not all patients are taking, or are not responding to, stimulant medications. SGAs (and risperidone) appear to reduce clinical severity, and they probably reduce severity more for patients with a primary diagnosis of DICD rather than ADHD. Studies found that SGAs may make little or no difference compared with placebo for global impression of improvement. From two RCTs of patients with primarily ADHD and aggression, risperidone appears to make little or no difference for response rates.

From between-study observations, risperidone may preferentially reduce illness severity, and increase global improvement ratings, for primary diagnosis of DICD compared with ADHD particularly when used for ADHD as adjunctive treatment. Our meta-analysis favored

risperidone over placebo for hyperactivity, although the data came from studies where not all patients were taking stimulants, or to the situation of nonresponse to stimulants; a study with children responding to stimulants found no benefit for risperidone on hyperactivity. Sensitivity analyses for the small study enrolling children with a history of response to risperidone did not affect the results. We did not find any evidence to suggest a differential treatment effect based on patients' intellectual functioning.

Five studies of ADHD and DICD conducted analyses of outcomes in different subpopulations. Two studies found no effect of age for effects of risperidone on aggression or risk of symptom recurrence. One RCT found no impact of comorbidities (including global developmental delay, ADHD, and secondary diagnosis of disruptive behavior disorders) or cotreatment with psychostimulants on conduct problems. A pooled analysis of two similar RCTs found no indication that the effects of risperidone on conduct problems or hyperactivity varied with stimulant use. Risperidone-naïve patients had lower conduct problem scores in one study, whereas prior treatment had no impact on symptom severity in another study.

Table E. Summary of findings for ADHD and disruptive, impulse-control, or conduct disorders: Key intermediate outcomes having at least low strength of evidence

Comparison	Outcome (N Studies; N Patients)	Findings[a]	Strength of Evidence; Conclusion
SGAs vs. placebo	Conduct problems (6, 462)	SMD, -0.77; 95% CrI, -1.34 to -0.17	Moderate; SGAs probably decrease[b]
	Aggression (7, 495)	SMD, -0.43; 95% CrI, -0.67 to -0.14	Moderate; SGAs probably decrease[b]
	Global impressions of improvement using CGI-I[c] (7, 482)	5 RCTs: RR, 2.13; 95% CrI, 0.87 to 6.46 (proportion at least "improved") 1 RCT: MD, -0.50; 95% CI, -1.99 to 0.99 1 RCT: MD, -1.80; 95% CI, -2.89 to -0.71	Low; SGAs may make little or no difference[d]
	Global impressions of severity using CGI-S (3, 75) (Studies of primary treatment in DICD)	MD, -1.98; 95% CrI, -3.18 to -0.93	Low; SGAs may reduce in DICD[e]
Risperidone vs. placebo	Conduct problems (5,443)	SMD, -0.84; 95% CrI, -1.54 to -0.18	Moderate; Risperidone probably decreases[b]
	Aggression (6, 476)	SMD, -0.44; 95% CrI, -0.72 to -0.13	Moderate; Risperidone probably decreases[b]
	Hyperactivity (6, 468) (Specific to primary diagnosis of DICD and study of those with ADHD not responding to stimulants)	5 RCTs: SMD, -0.39; 95% CrI, -0.76 to -0.07 1 RCT: No difference p > 0.05 (All patients taking stimulants)	Moderate; Risperidone probably decreases for those with primary diagnosis of DICD or ADHD if not responding to stimulants[b]

Comparison	Outcome (N Studies; N Patients)	Findings[a]	Strength of Evidence; Conclusion
	Global impressions of improvement using CGI-I (6, 463)	4 RCTs: RR, 1.85; 95% CrI, 0.64 to 5.58 (proportion at least "improved") 1 RCT: MD, -0.50; 95% CI, -1.99 to 0.99 1 RCT: MD, -1.80; 95% CI, -2.89 to -0.71	Low; Risperidone may make little or no difference[d]
	Global impressions of severity using CGI-S (2, 56) (Studies of primary treatment in DICD)	1 RCT: MD, -1.80; 95% CI, -2.54 to -1.06 1 RCT: MD, -2.50; 95% CI, -4.11 to -0.89	Low; Risperidone may decrease in DICD[e]
	Global impressions of severity using CGI-S (2, 193) (Studies of stimulant augmentation in ADHD)	1 RCT: MD, 0.0; 95% CI, -1.65 to 1.65 1 RCT: RR, 1.2; 95% CI, 0.95 to 1.5 (proportion rated as "normal/borderline/mildly ill")	Low; Risperidone may make little or no difference in ADHD treatment augmented with risperidone[d]
	Response rate (2, 193) (Patients with primarily ADHD and aggression)	1 RCT: RR, 1.12; 95% CI, 0.94 to 1.34 1 RCT: RR, 1.28; 95% CI, 0.93 to 1.77	Low; Risperidone may make little or no difference in patients with primary diagnosis of ADHD and aggression[d]

ADHD = attention-deficit/hyperactivity disorder; CGI-S = Clinical Global Impressions of Severity; CI = confidence interval; CrI = credible interval (used with Bayesian meta-analysis); DICD = disruptive, impulse-control, and conduct disorders; MD = mean difference; N = number; RCT: randomized controlled trial; RR = risk ratio; SGA = second-generation antipsychotics

[a] When the findings are not representative of the total number of studies identified in the outcome column, we included the number of studies for each finding; we did not pool data from 1 or 2 studies so these results are always presented separately. All effect estimates reported as MD or SMD values favor SGAs when they are negative (larger magnitude greater effect); a RR >1.0 favor SGAs. SMDs provide results in standard deviation units, and are used when the results from different measurement tools are combined in meta-analysis; as a general rule, an absolute magnitude of 0.2 represents a small effect size, 0.5 a moderate one, and 0.8 a large one.

[b] Downgraded for ROB.

[c] CGI-S and CGI-I scores range from 0-6.

[d] Downgraded for ROB and imprecision, because credible interval includes a clinically significant value (e.g., RR ≤0.75 or ≥1.25) such that we could not rule out benefit even though effect estimate appears to be of no difference.

[e] Downgraded for ROB and impression due to small sample size

Obsessive-Compulsive Disorder

One 12-week RCT with 79 patients examined augmentation with risperidone or aripiprazole in patients with obsessive-compulsive disorder (OCD) who failed to respond to at least 12 weeks of treatment with selective serotonin reuptake inhibitors. No significant differences were found between risperidone and aripiprazole for nonspecific symptoms (i.e., response rates were 51.4% and 61.8% for risperidone and aripiprazole, respectively), and global impressions of severity and functioning. Results for core symptoms of obsessions and compulsions were not reported by the authors. All patients had comorbid tic disorders; response to tic symptomatology was similar with 68 percent in both groups responding. Because of insufficient SOE, the effects of risperidone or aripiprazole augmentation of SSRIs in OCD is not known.

Depression

One observational study examined a subgroup of 35 patients aged ≤ 25 years in a pooled analysis of data from two RCTs of placebo-controlled adjuvant aripiprazole (2-20 mg/day) for patients with major depressive disorder who failed to respond to 8 weeks of antidepressant treatment. The focus of the report was on suicidality. Findings suggested no differences in suicidality between placebo and aripiprazole for adjuvant treatment of SSRIs, but we have no confidence in these findings (insufficient SOE).

Eating Disorders

Two RCTs and one retrospective cohort study examined SGAs versus placebo for adjunctive treatment in eating disorders. All three studies enrolled females (average ages 14-18) with anorexia nervosa or eating disorders not-otherwise specified (allowing for persistence of menstruation), who were also receiving multidisciplinary, tailored care within eating disorder programs. Trials of olanzapine and risperidone compared with placebo failed to demonstrate any benefit from these SGAs in terms of increased body weight (favorable for this condition) or reduced eating disorder symptomatology. Findings from the observational study were substantially confounded by a greater illness severity and overall resource use by the olanzapine group. Speculated changes in resting energy expenditure were not realized. The SOE was graded as insufficient for all key outcomes (i.e., weight) of relevance. The studies did not report any effectiveness outcomes.

Tic Disorders

Twelve trials studies tic disorders. All but one study enrolled patients with Tourette's syndrome. Patients enrolled in the studies had an average age of 10.7 years and were predominantly male (84%). Patients had a variety of comorbidities, including ADHD (34%); obsessive-compulsive disorder (23%); and disruptive, impulse-control, and conduct disorders (5%). Only one study permitted concomitant psychotropic medications including stimulants. Table F summarizes the findings for outcomes having at least low SOE.

Tic severity may be reduced in patients receiving SGAs (aripiprazole, risperidone, and ziprasidone). A 6-point reduction in tic severity using the Yale Global Tic Severity Scale's total tic score has empirical evidence of clinical significance.[28]

Table F. Summary of findings for tic disorders: Key intermediate outcomes having at least low strength of evidence

Comparison	Outcome (N studies; N patients)	Findings,[a] Tool With Range of Values	Strength of Evidence; Conclusion
SGAs vs. placebo	Tic severity (3, 114)	MD, -6.26; 95% CrI, -10.05 to -2.54 YGTSS Total Tic score (range 0-50)	Low; SGAs may decrease[b]

CrI = credible interval; N = number; MD = mean difference; ROB = risk of bias; SGA = second-generation antipsychotic; YGTSS = Yale Global Tic Severity Scale.

[a] A negative MD score favors the SGAs.

[b] Downgraded for ROB and imprecision because of small sample size (typically < 200 patients).

Behavioral Issues

Two 4-week RCTs compared risperidone with placebo for treatment of behavioral issues in children without psychiatric diagnoses within this review's condition categories. The inclusion

criteria in one study (N = 13) were persistent behavioral disturbances (e.g., hostility, aggressiveness, irritability, agitation) in children with intellectual impairment living in residential homes. Compared with placebo, risperidone significantly reduced symptoms of irritability and hyperactivity, but not lethargy, stereotypic behavior, or inappropriate speech; ratings of clinical improvement were also superior for risperidone.

The other study (N = 90) focused on children diagnosed clinically as having a masturbation problem. Risperidone reduced the frequency of masturbation compared with no medication.

All key outcomes were assessed as having insufficient SOE, therefore the effects in all cases are not known.

Key Findings for Harms Across Conditions (Key Question 2)

This section presents the evidence from analyses across all comparisons for the outcomes of weight and BMI, and then for all key outcomes for head-to-head and then placebo-controlled comparisons. Within each comparison, we begin with findings for major adverse effects (AEs) followed by general AEs. Limited evidence was provided for FGAs. The majority of the findings focused on the comparison of SGA versus placebo. The section ends with findings from subgroup analyses.

All Comparisons: Network Meta-Analyses for Body Composition Outcomes

We conducted network meta-analyses for the outcomes of weight and BMI. These outcomes represent two of the key outcomes that were reported by the most studies (weight, n = 71; BMI, n = 35). We used data regardless of followup duration and (for those with multiple timepoints) from each study's longest term followup; 14 studies for weight and 11 for BMI reported data for treatment durations 6 months or longer. Findings from our analyses are presented in Figures C and D. Results are presented in terms of a placebo referent, to rank the drugs based on a common comparator, but data from head-to-head comparisons were incorporated in the analysis. An appendix to the full report contains the results for every possible comparison between the individual drugs.

Results showed that patients taking most antipsychotics gain more weight than patients taking placebo or not receiving antipsychotics. Molindone and ziprasidone may cause less weight gain on average whereas those receiving olanzapine may gain as much as 5 kilograms more weight during treatment durations of a relatively short timeframe (81% of studies for this analysis were short-term which was often 6-12 weeks duration). Not all SGAs appear to contribute to more weight gain than FGAs. Results for olanzapine clearly separated this SGA as more harmful than most other SGAs. Some of the antipsychotics (e.g., pimozide, molindone, lurasidone) had few patients contributing to the findings which resulted in wide credible intervals. The relative harm from olanzapine is most robust compared with aripiprazole, quetiapine, and risperidone because of the precision in these estimates from larger sample sizes.

For BMI, olanzapine and clozapine were worst for average effect, although the results for clozapine are considerably imprecise because of small samples. Seventy-one percent of studies had short-term treatment durations.

Figure C. Plot of network meta-analysis results for weight gain compared with reference standard (placebo/no treatment)

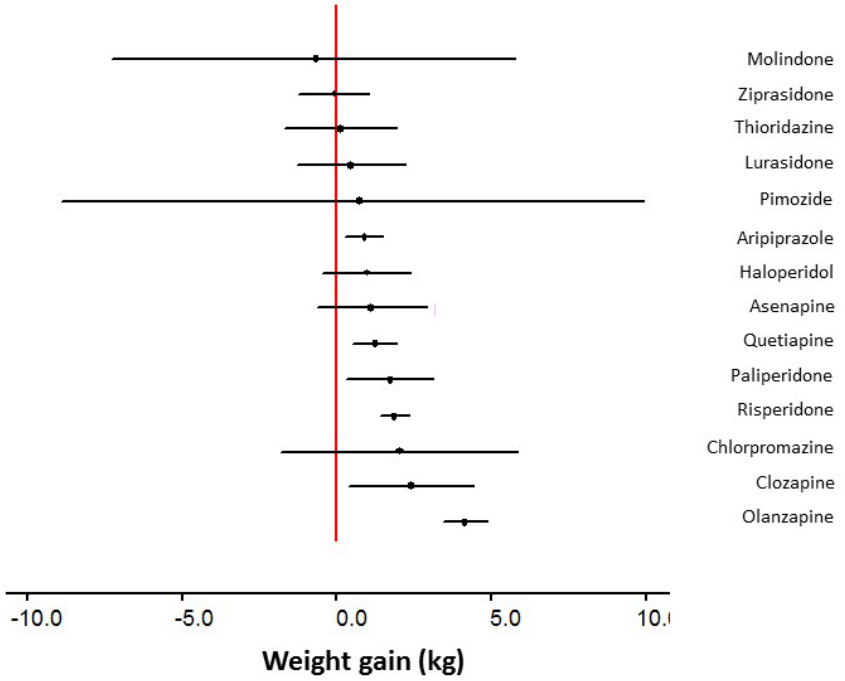
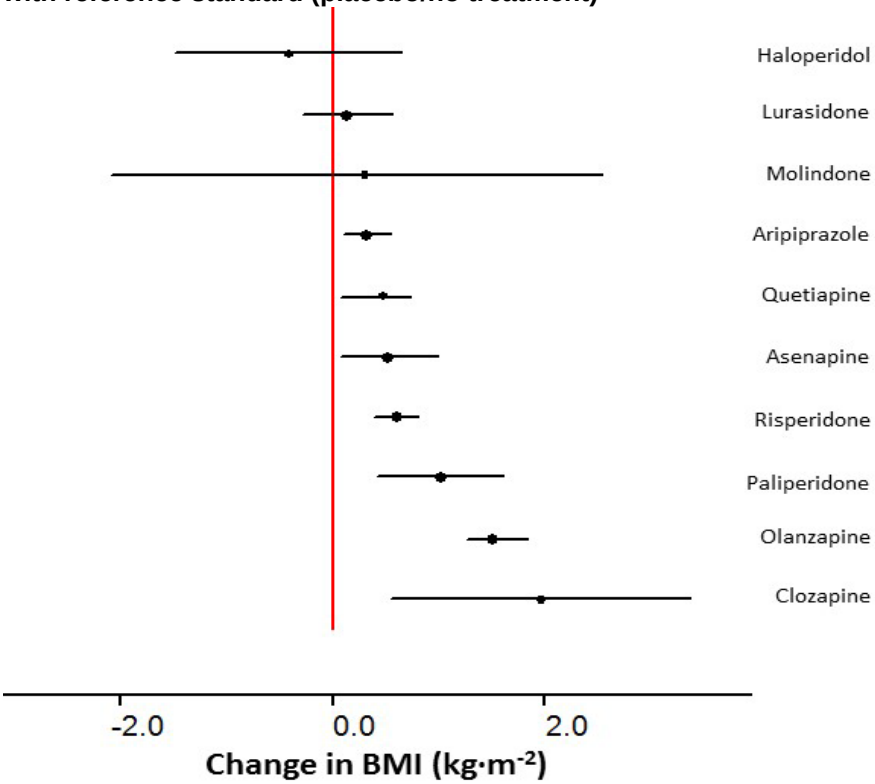


Figure D. Plot of network meta-analysis results for increase in body mass index (BMI) compared with reference standard (placebo/no treatment)



These plots show the findings from network meta-analyses combining placebo-controlled and head-to-head comparisons of first-generation antipsychotics and second-generation antipsychotics within one analysis. The effects shown represent the mean difference and credible intervals of each drug relative to placebo which was used as the reference standard.

FGAs Versus SGAs

Nine studies reported on major (4 long-term duration) and 16 reported on general AEs (2 long-term). Few studies having small sample sizes reported on major AEs which were often rare outcomes. The difference in effects between SGAs and FGAS for all major AEs are not known (insufficient SOE). Table G contains a summary of our key findings for general AEs which are limited to findings of short treatment durations.

Compared with FGAs, SGAs may decrease the risk for experiencing any extrapyramidal symptom (EPS). FGAs probably cause lower gains in weight and BMI. There may be little or no difference between classes for sedation. Evidence was insufficient for other outcomes (e.g., akathisia, dystonia, hyperprolactinemia).

Table G. Summary of findings for general adverse effects: Short-term durations of FGAs versus SGAs

Outcome	N Studies, N Patients	FGA Events	FGA N	SGA Events	SGA N	Relative Effects[a]	Strength of Evidence; Conclusion
Any EPS	4, 110	16	37	13	73	RR, 2.59; 95% CrI, 1.00 to 7.00	Low; SGAs may decrease risk[b]
Weight (kg)	14, 506	-	190	-	316	MD, -2.62; 95% CrI, -4.35 to -0.86	Moderate; FGAs probably better[c]
BMI ($kg \cdot m^{-2}$)	7, 236	-	73	-	163	MD, -1.57; 95% CrI, -2.49 to -0.53	Moderate; FGAs probably better[c]
Sedation	7, 345	70	160	79	185	RR, 1.04; 95% CrI, 0.86 to 1.37	Low; may be little or no difference[d]

AE = adverse effect; BMI = body mass index; CrI = credible interval; FGA = first-generation antipsychotic; G = group; kg = kilogram; m = meter; MD = mean difference; N = number; RR = risk ratio; SGA = second-generation antipsychotic

[a]Risk ratios above 1.0 and positive MD favor SGAs.

[b]Downgraded for ROB and imprecision, based on small sample size.

[c]Downgraded for ROB.

[d]Downgraded for ROB and imprecision, because CrI includes possibility for clinically relevant benefit for SGAs.

FGAs Versus FGAs

Two short-term RCTs reported on major AEs and provided insufficient SOE for all outcomes. No findings for general AEs in comparisons of FGAs versus FGAs, or between different doses of FGAs, were rated as at least low SOE.

SGAs Versus SGAs: Comparison of Different Drugs

Sixteen (5 long-term) and 37 (13 long-term) studies reported on major and general AEs, respectively. Table H presents the key findings for general AEs in comparisons between different SGAs.

Major AEs. Over the long term, aripiprazole appears to increase the risk for developing diabetes compared with risperidone. One large retrospective review of a Medicaid database found that patients newly initiating antipsychotics (compared with propensity-score matched controls not on antipsychotics) were at higher risk ($p < 0.0001$) for developing diabetes after >1 year followup if taking aripiprazole (HR 7.72, 95% CI 3.70 to 16.12) compared with risperidone (HR 2.20, 95% CI 1.14 to 4.26). These results were inconsistent with another small long-term study of 47

patients on various SGAs that only found one incidence of diabetes in a patient taking clozapine. Findings on other major AE outcomes were rated as insufficient SOE.

General AEs. To summarize the findings on general SAEs—

- **Body composition**. Risperidone probably decreases gains in weight (short-term) and BMI (short-and long-term) to a small extent compared with olanzapine; similar findings were found for quetiapine versus olanzapine over the long- but not short-term where there may be little or no difference. There appears to be little or no difference between weight gains caused by olanzapine and clozapine over short-term treatment. Quetiapine and risperidone are probably of little or no difference for short-term changes in BMI and 7 percent or greater increase in weight, and may be of little or no difference for BMI changes or weight gain over the long-term. For 7 percent or greater gain in body weight, there appears to be little or no difference between olanzapine and quetiapine, or olanzapine and risperidone.
- **Hyperprolactinemia**. Quetiapine may decrease the risk for hyperprolactinemia compared with risperidone.
- **Sedation**. There may be little or no difference between olanzapine and risperidone for risk of sedation.

All findings for clozapine versus risperidone and aripiprazole versus risperidone, and most findings for clozapine versus olanzapine, were rated as insufficient SOE, mainly due to imprecision but also because of risk of bias and inconsistency.

Table H. Summary of findings for general adverse effects: Short- and long-term findings of comparisons between different SGAs

Comparison (G1 vs. G2), Timeframe	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects[a]	Strength of Evidence, Conclusions
Clozapine vs. Olanzapine Short-term	Weight (kg)	5 (136)	-	62	-	74	MD, -1.56; 95% CrI, -5.12 to 1.57	Low; may make little or no difference[b]
Olanzapine vs. Quetiapine Short-term	Weight (kg)	3 (232)	-	116	-	116	MD, 4.00; 95% CrI, -1.67 to 10.79	Low; may make little or no difference[c]
	BMI ($kg \cdot m^{-2}$)	3 (232)	-	116	-	116	MD, 1.36; 95% CrI, -0.29 to 3.40	Low; may make little or no difference[c]
	≥ 7% increase in weight	3 (192)	72	99	47	93	RR: 1.41; 95% CI, 0.65 to 2.83	Low; may make little or no difference[c]
Olanzapine vs. Quetiapine Long-term	Weight (kg), 6 to <12months	3 (185)	-	90	-	95	MD, 7.91; 95% CrI, 3.65 to 12.29	Moderate; Quetiapine probably better[d]
	BMI ($kg \cdot m^{-2}$), 6 to <12months	4 (203)	-	99	-	104	MD, 2.68; 95% CrI, 0.96 to 4.27	Moderate; Quetiapine probably better[d]
Olanzapine vs. Risperidone Short-term	Weight (kg)	13 (936)	-	331	-	605	MD, 2.18; 95% CrI, 1.13 to 3.25	Moderate; Risperidone probably slightly better[d]
	BMI ($kg \cdot m^{-2}$)	9 (737)	-	244	-	493	MD, 0.94; 95% CrI, 0.64 to 1.30	Moderate; Risperidone

Comparison (G1 vs. G2), Timeframe	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects[a]	Strength of Evidence, Conclusions
								probably slightly better[d]
	≥ 7% increase in weight	6 (504)	107	150	188	354	RR, 1.36; 95% CrI, 0.93 to 2.04	Low; may make little or no difference[c]
	Sedation	7 (321)	35	133	36	188	RR, 1.19; 95% CrI, 0.73 to 2.35	Low; may make little or no difference[c]
Olanzapine vs. Risperidone Long-term	Weight (kg), 6 to <12months	4 (295)	-	85	-	210	MD, 4.40; 95% CrI, -0.54 to 9.86	Low; may make little or no difference[c]
	BMI ($kg \cdot m^{-2}$), 6 to <12months	5 (328)	-	94	-	234	MD, 1.66; 95% CrI, 0.19 to 3.42	Moderate; Risperidone probably slightly better[d]
	≥ 7% increase in weight, 6 to <12 months	3 (264)	28	64	64	200	RR: 1.44; 95% CI, 0.55 to 5.50}	Low; may make little or no difference[c]
Quetiapine vs. Risperidone Short-term	Weight (kg)	3 (463)	-	116	-	347	MD, 0.08; 95% CrI, -3.77 to 3.14	Low; may make little or no difference[f]
	BMI ($kg \cdot m^{-2}$)	3 (463)	-	116	-	347	MD, 0.04; 95% CrI, -1.34 to 1.20	Moderate; probably makes little or no difference[d]
	≥ 7% increase in weight	4 (417)	55	104	176	313	RR: 0.91; 95% CI, 0.56 to 1.44	Moderate; probably makes little or no difference[d]
	Hyper-prolactinemia	4 (118)	4	31	45	87	RR, 0.20; 95% CrI, 0.06 to 0.73	Low; Quetiapine may decrease risk[e]
Quetiapine vs. Risperidone Long-term	Weight (kg), 6 to <12months	3 (295)	-	93	-	202	MD, -1.48; 95% CrI, -4.16 to 1.18	Low; may make little or no difference[e]
	BMI ($kg \cdot m^{-2}$), 6 to <12months	4 (328)	-	102	-	226	MD, -0.32; 95% CrI, -1.56 to 1.12	Low; may make little or no difference[e]

BMI=body mass index; CrI = credible interval; kg = kilogram; m = meters; MD = mean difference; N=number; RR = risk ratio

[a] Positive MDs favor group 2; RR above 1.0 favor group 2

[b]Downgraded for ROB and imprecision, because CrI includes possibility for clinically relevant benefit for group 1.

cDowngraded for ROB and imprecision, because CrI includes possibility for clinically relevant benefit for group 2.

[d]Downgraded for ROB.

[e]Downgraded for ROB and imprecision, based on small sample size.

[f]Downgraded for ROB and inconsistency.

SGAs Versus SGAs: Dose Comparisons

The effects between different doses of SGAs in terms of major AEs during short-term treatment are mostly unknown (insufficient SOE). There may be no difference between 5 mg/day and 10 mg/day asenapine for risk of developing diabetes over 8 weeks of treatment (low SOE); both groups (n = 98, n = 102) had 7 percent incidence of possible new-onset diabetes (compared with 4% in placebo group).

Table I includes the findings for general AEs; the doses considered are identified for each drug. The findings for each drug are summarized below.

- **Aripiprazole**. Different doses of aripiprazole are probably of little or no difference in the extent of weight gain they cause over the short-term. There may be little or no difference between doses for any EPS symptoms, BMI, the proportion gaining 7 percent or more weight, and somnolence (all short-term); for these outcomes the 95% CIs included values favoring the low dose. There appears to be little or no difference in risk for hypertriglyceridemia or high total cholesterol.
- **Asenapine**. There is probably little or no difference in the short-term between low and high doses of asenapine for weight gain, proportion of patients gaining 7 percent or more weight, risk of somnolence, or risk of hyperprolactinemia.
- **Quetiapine.** Low and high doses of quetiapine are likely of little or no difference for risk of gaining greater than 7 percent weight, somnolence, or sedation over the short-term.
- **Risperidone**. Risks for somnolence and EPS symptoms may be of little or no difference for low- versus high-dose risperidone during short-term treatment.

Table I. Summary of findings for general adverse effects: Short-term findings from comparisons between different doses of SGAs

Comparison	Outcome	High Dose Events	High Dose N	Low Dose Events	Low Dose N	Relative Effects[a]	Strength of Evidence; Conclusions
Aripiprazole High (15/30mg/day) vs. Low (10mg/day)	Any EPS	39 12	99 54	23 13	98 59	RR, 1.68; 95% CI, 1.09 to 2.59 RR, 1.01; 95% CI, 0.50 to 2.02	Low; may make little or no difference[b]
	Weight (kg)	-	229	-	234	MD, 0.22; 95% CrI, -0.64 to 1.09	Moderate; probably makes little or no difference[c]
	BMI ($kg \cdot m^{-2}$)	-	223	-	233	MD, 0.14; 95% CrI, -0.47 to 5.86	Low; may make little or no difference[b]
	≥ 7% weight increase	37	250	24	256	RR, 1.62; 95% CrI, 0.47 to 5.86	Low; may make little or no difference[b]
	High cholesterol	28 0	65 54	27 0	64 59	RR, 1.02; 95% CI, 0.68 to 1.52 Not estimable	Low; may make little or no difference[d]
	High triglycerides	22 2	65 54	22 6	65 59	RR, 1.00; 95% CI, 0.62 to 1.62 RR: 0.36; 95% CI, 0.08 to 1.73	Low; may make little or no difference[d]
	Somnolence	62	255	47	257	RR, 1.31; 95% CrI, 0.46 to 3.80	Low; may make little or no difference[b]
Asenapine High (10mg/day) vs. Low (5mg/day)	BMI ($kg \cdot m^{-2}$)	--	-	-	-	MD, 0.03; 95% CI, -0.04 to 0.10	Low; may make little or no difference[e]
	≥ 7% weight increase	10 8	99 90	9 11	95 92	RR, 1.07; 95% CI, 0.45 to 2.51 RR, 0.74; 95% CI, 0.31 to 1.76	Moderate; probably makes little or no difference[e]
	Somnolence	31 52	106 99	24 49	98 104	RR, 1.19; 95% CI, 0.76 to 1.89	Moderate; probably makes

						RR, 1.11; 95% CI, 0.85 to 1.47	little or no difference[e]
	Hyperprolactinemia	20	106	23	98	RR, 1.24; 95% CI, 0.73 to 2.12	Low; may make little or no difference[e]
Quetiapine High (600/800 mg/day) vs. Low (400 mg/day)	≥ 7% weight increase	14 10	74 98	17 14	73 95	RR, 0.81; 95% CI, 0.43 to 1.52 RR, 0.69; 95% CI, 0.32 to 1.48	Moderate; probably makes little or no difference[c]
	Somnolence	22 31	74 98	20 27	73 95	RR, 1.09; 95% CI, 0.65 to 1.81 RR, 1.11; 95% CI, 0.72 to 1.71	Moderate; probably makes little or no difference[c]
	Sedation	4 25	74 98	4 22	73 95	RR, 0.99; 95% CI, 0.26 to 3.80 RR, 1.10; 95% CI, 0.67 to 1.81	Moderate; probably makes little or no difference[c]
Risperidone High (3-6mg/day) vs. Low (0.5-3mg/day)	Any EPS	20 15	51 61	18 4	55 50	RR, 1.20; 95% CI, 0.72 to 2.00 RR, 3.07; 95% CI, 1.09 to 8.68	Low; may make little or no difference[b]
	Somnolence	6 34	51 61	13 21	55 50	RR, 0.50; 95% CI, 0.20 to 1.21 RR, 1.33; 95% CI, 0.89 to 1.97	Low; may makie little or no difference[f]

AE = adverse effect; BMI=body mass index; CI = confidence interval; CrI = credible interval; EPS = extrapyramidal symptoms; kg = kilogram; m = meter; mg = milligrams; MD = mean difference; N=number; RR = risk ratio

[a] Positive MDs and RRs above 1.0 favor the low dose group. Effects are shown for each study contributing data (we did not pool data from only 2 studies).

[b]Downgraded for ROB and imprecision, because CIs include possibility for clinically relevant benefit for the low dose group.

[c]Downgraded for ROB.

[d]Downgraded for ROB and imprecision due to small sample sizes.

[e] Downgraded for imprecision, because CIs include possibility for clinically relevant benefit for the low dose group.

[f] Downgraded for ROB and imprecision, because of inconsistency between studies.

FGAs Versus Placebo

No findings for major or general AEs in comparisons between FGAs and placebo offered greater than insufficient SOE. Four small studies reported on AEs to a varying extent with most outcomes having imprecise data from one small study having medium or higher ROB.

SGAs Versus Placebo

Findings for major and general AEs in comparisons between SGAs and placebo are presented below.

Major AEs

There is probably little or no difference in the short-term across all SGAs compared with placebo for mortality (13 studies, 2447 patients; 0 events) or for having a pathologically prolonged QT interval (14 studies, 2425 patients; events in 19 of 1490 in SGA and 9 of 935 in placebo).

Compared with no antipsychotic treatment, SGAs may increase the risk for developing diabetes over the long-term. A large retrospective cohort study compared incidence of type 2 diabetes in patients newly initiated on antipsychotics compared with matched patients not taking antipsychotics for at least 1 year; taking SGAs was associated with an increased risk (HR 2.89, 95% CI 1.64 to 5.10; 25.3 vs. 7.8 cases per 10,000 person-years followup).

Other outcomes were rated as having insufficient SOE due to rare events (≤ 5% of patients) occurring in samples too small to offer adequate power to detect a difference (N < 2000).

General AEs

Tables J and K summarize findings for general AEs having at least low SOE during short- and long-term studies, respectively. A summary of the key points is included below for findings across SGAs and for individual drugs, respectively.

- **All SGAs versus placebo**. SGAs as a class are probably worse than placebo/no antipsychotic treatment for seven outcomes: EPS symptoms, changes to body composition (weight, BMI, and ≥7% weight gain), high triglycerides, sedation, and somnolence. They appear to be worse for risk of high total cholesterol, and there may be little or no difference in risk for akathisia. In the longer term, few studies provided insufficient SOE.
- **Individual SGAs versus placebo**.
    - Aripiprazole is probably slightly worse than placebo/no treatment for gains in weight and BMI, and may increase risk for any EPS, ≥7 percent weight gain, and somnolence.
    - Compared with placebo, olanzapine likely increases weight gain and BMI, and may increase risk for ≥7 percent weight gain and hyperprolactinemia.
    - Quetiapine probably increases weight gain slightly, and may make little or no difference in risk for sedation and somnolence.
    - Risperidone probably increases weight gain and BMI to a small extent, and probably increases risk for somnolence. It may increase risk for any EPS symptoms. In long-term studies, there may be little or no difference over placebo in changes in weight and BMI.
    - Ziprasidone probably makes little or no difference for weight gain, and appears to make little or no difference for somnolence.

Table J. Summary of findings for general adverse effects: Short- and long-term durations of comparisons between SGAs and placebo

Comparison	Outcome	N Studies, N Patients	SGA Events	SGA N	Placebo Events	Placebo N	Relative Effects[a]	Strength of Evidence; Conclusions
All SGAs vs. placebo	Any EPS	15, 2730	233	1757	40	973	RR, 2.94; 95% CI, 2.02 to 4.27	Moderate; SGAs probably increase risk[b]
		2, 32	0	17	0	15	Not estimable	
	Akathisia	21, 3638	151	2433	56	1205	RR, 1.29; 95% CrI, 0.81 to 2.27	Low; SGAs may make little or no difference[c]
	Weight (kg)	37, 3919	-	2384	-	1535	MD, 1.48; 95% CI, 1.06 to 1.91	Moderate; SGAs probably increase slightly[b]
	BMI ($kg \cdot m^{-2}$)	16, 2462	-	1582	-	880	MD, 0.61; 95% CI, 0.38 to 0.85	Moderate; SGAs probably increase slightly[b]
	≥ 7% increase in weight	17, 3057	337	2023	42	1034	RR, 3.53; 95% CrI, 2.49 to 5.23	Moderate; SGAs probably increase risk[b]

Comparison	Outcome	N Studies, N Patients	SGA Events	SGA N	Placebo Events	Placebo N	Relative Effects[a]	Strength of Evidence; Conclusions
	Increased total cholesterol	6, 643 1, 218	92 0	410 52	13 0	233 166	RR, 3.17; 95% CrI, 1.29 to 9.13 Not estimable	Low; SGAs may increase risk[d]
	Increased triglycerides	10, 1383	130	897	38	486	RR, 1.64; 95% CrI, 1.09 to 2.63	Moderate; SGAs probably increase risk[b]
	Sedation	21, 2710	288	1696	79	1014	RR, 2.19; 95% CrI, 1.50 to 3.41	Moderate; SGAs probably increase risk[b]
	Somnolence	26, 3942	560	2481	119	1461	RR, 2.91; 95% CrI, 2.27 to 3.86	Moderate; SGAs probably increase risk[b]
Aripiprazole vs. placebo	Any EPS	6, 1000	117	655	17	345	RR, 3.10; 95% CrI, 1.26 to 7.01	Low; Aripiprazole may increase risk[e]
	Weight (kg)	7, 1042	-	647	-	395	MD, 0.98; 95% CrI, 0.54 to 1.48	Moderate; Aripiprazole probably increases slightly[b]
	BMI ($kg \cdot m^{-2}$)	5, 881	-	587	-	294	MD, 0.33; 95% CI, 0.07 to 0.67	Moderate; Aripiprazole probably increases slightly[b]
	≥ 7% increase in weight	5, 991	93	647	15	344	RR, 3.01; 95% CrI, 1.33 to 7.10	Low; Aripiprazole may increase risk[e]
	Somnolence	6, 1012	119	661	29	351	RR, 2.73; 95% CrI, 1.24 to 7.65	Low; Aripiprazole may increase risk[e]
Olanzapine vs. placebo	Weight (kg)	4, 337	-	215	-	122	MD, 3.96; 95% CI, 2.31 to 6.34	Moderate; Olanzapine probably increases[b]
	BMI ($kg \cdot m^{-2}$)	2, 267	- -	107 72	- -	54 34	MD, 1.16; 95% CI, 0.93 to 1.39 MD, 1.50; 95% CI, 1.06 to 1.94	Moderate; Olanzapine probably increases[b]
	≥ 7% increase in weight	4, 337	99	215	8	122	RR, 6.08; 95% CrI, 1.84 to 27.06	Low; Olanzapine may increase risk[e]
	Hyper-prolactinemia	2, 268	50 58	107 72	1 6	54 35	RR, 25.53; 95% CI, 3.58 to 177.76 RR, 4.70; 95% CI, 2.25 to 9.82	Low; Olanzapine may increase risk[e]
Quetiapine vs. placebo	Weight (kg)	6, 778	-	473	-	305	MD, 1.44; 95% CI, 0.60 to 2.31	Moderate; Quetiapine probably increases slightly[b]
	Sedation	6, 778	90	473	32	305	RR, 1.67; 95% CrI, 0.77 to 3.87	Low; may make little or no difference[c]
	Somnolence	3, 697	106	432	18	265	RR, 2.95; 95% CrI, 0.92 to 8.62	Low; may make little or no difference[c]
Risperidone vs. placebo	Any EPS	5, 636	52	365	13	271	RR, 2.78; 95% CrI, 1.27 to 6.50	Low; Risperidone may increase risk[e]
	Weight (kg)	14, 929	-	522	-	475	MD, 1.52; 95% CI, 0.78 to 2.29	Moderate; Risperidone

Comparison	Outcome	N Studies, N Patients	SGA Events	SGA N	Placebo Events	Placebo N	Relative Effects[a]	Strength of Evidence; Conclusions
								probably increases slightly[b]
	BMI ($kg \cdot m^{-2}$)	6, 730	-	397	-	333	MD, 0.68; 95% CI, 0.27 to 1.18	Moderate; Risperidone probably increases slightly[b]
	Somnolence	9, 862	163	473	43	389	RR, 3.25; 95% CrI, 1.96 to 5.94	Moderate; Risperidone probably increases risk[b]
Ziprasidone vs. placebo	Weight (kg)	3, 360	-	246	-	114	MD, -0.10; 95% CI, -1.34 to 1.13	Moderate; Ziprasidone probably makes little or no difference[b]
	Somnolence	3, 548	76	358	13	190	RR, 2.97; 95% CrI, 0.84 to 9.96	Low; Ziprasidone may make little or no difference[c]

AE = adverse effect; BMI = body mass index; CI = confidence interval; CrI = credible interval; kg = kilogram; m = meter; MD = mean difference; N = number; RR = risk ratio; SGA = second-generation antipsychotic

[a]Risk ratios above 1.0 and positive MD favor placebo.

[b]Downgraded for ROB.

[c]Downgraded for ROB and imprecision because point estimate and CrI includes clinically significant favor for placebo.

[d]Downgraded for ROB and inconsistency.

[e]Downgraded for ROB and imprecision, based on small sample size.

Table K. Summary of findings for general adverse effects: Long-term durations of SGAs versus placebo

Comparison	Outcome, Duration	N Studies, N Patients	Relative Effects[a]	Strength of Evidence; Conclusions
Risperidone vs. placebo	Weight (kg), 6 to <12months	4, 467	MD, 2.86; 95% CrI, -1.22 to 7.42	Low; Risperidone may make little or no difference[b]
	BMI ($kg \cdot m^{-2}$), 6 to <12months	2, 405	MD, 0.70; 95% CI, 0.49 to 0.91 MD, 1.80; 95% CI, -0.61 to 4.21	Low; Risperidone may make little or no difference[b]

BMI = body mass index; CI = confidence interval; CrI = credible interval; kg = kilogram; m = meter; MD = mean difference; N = number; RR = risk ratio; SGA = second-generation antipsychotic

[a]Positive MD favors placebo.

[b] Downgraded for ROB and imprecision because CrI includes clinically significant favor for placebo.

Between- and Within-Study Subgroup Effects

Bayesian univariate meta-regression analyses were conducted to determine if effects on four outcomes (weight change, proportion gaining 7% or more weight, somnolence, and EPS symptoms) were influenced by four subgroup variables (mean age, % male, % treatment naïve, and treatment duration). We used data from longest followup duration from SGA-placebo/no treatment comparisons. For the outcome of EPS symptoms, we included data from findings on (in hierarchical order) akathisia, dystonia, and any EPS. The only analysis with statistically significant findings was for treatment duration on weight change; age and proportion being treatment naïve were not found to significantly modify effects. The model predicted small

increments in weight gain over longer treatment durations (0.043 kg per week; 95% CrI, 0.015 to 0.072). Because of these findings, we ran adjusted network meta-analyses for weight and BMI using the study-level variable of treatment duration; athough this variable was shown to statistically modify effects, the results of the network meta-analysis were not changed to any meaningful extent.

Observations based on diagnostic condition did not indicate any moderating effect in terms of the four harm outcomes evaluated; harms appeared to occur to a similar magnitude in different conditions regardless of the typical dose used.

Twenty-six studies reported on subgroup analyses. Findings were often inconsistent on whether there are any moderating effects by various subgroup variables on harms. Several studies found no significant differences in harms for different age groups. Body composition, fasting glucose, and prolactin elevations do not appear to differ in patients taking SGAs based on concurrent use of psychostimulants. Dose of SGAs—particularly when considering cumulative doses—was found in two large observational studies to increase the risk for metabolic effects including increased glucose levels and development of diabetes. Risperidone appears to increase serum prolactin more in females than males; few studies reported on other subgroup variables for this harm. Findings for effect moderation on risk for somnolence and neuromotor effects were mainly from single studies.

Applicability of Findings

Study populations seem moderately applicable to general practice in terms of age, gender and existence of common comorbid diagnoses (e.g., ADHD comorbidity within primary diagnosis of bipolar or tic disorders) within each condition category. Findings will not be as applicable in terms of patients having complex clinical diagnoses, medical comorbidity, less-than-moderate symptom severity, and (with the exception of studies of clozapine in schizophrenia) a history of poor response to antipsychotics.

The majority of the studies in this review did not enroll young adults; therefore, the results may have limited applicability to this population. Nor was the mean age in any condition below 8 years. Exclusion of patients with comorbidities, a history of various adverse events, and/or less-than-moderate symptom severity at baseline may have overestimated the estimates of the efficacy and underestimated the harms of antipsychotics.

Another factor that restricts the applicability of the studies is the short duration of followup (75% of studies had treatment durations < 6 months). Adequate trials of antipsychotic treatment to assess response can be considered within 4 to 6 weeks,[16] which supports applicability for these outcomes from the evaluated studies; nevertheless, issues impacting longterm treatment success, such as treatment compliance and resistance, were not accounted for in many studies. Data on most effectiveness outcomes were deficient, and few studies allowed for conclusions on major adverse effects—especially those often arising with longterm treatment (e.g., tardive dyskinesias, diabetes). Adverse effects may have been underestimated due to the short followup periods; not all effects are likely to become evident in all patients within the 1-2 month treatment phase commonly investigated.

Applicability may also be limited due to monitoring practices within the trial settings to ensure treatment adherence as well as perform dose adjustments based on response and tolerability assessments. In typical practice settings, it is likely that will patients have lower rates of medication adherence—and therefore less symptom improvement—and may have higher rates of AEs because of poor monitoring. Although comprehensive and individualized monitoring for

AEs has been recommended for several years,[12,16,29] there is evidence from Medicaid claims data[30-32] and clinician self-reports[33] that these practices remain inadequate. Guidelines for screening and monitoring have been developed, especially in the area of schizophrenia where antipsychotics are the primary treatment, although there has been some critique of their degree of rigor (e.g., use of systematic reviews of the evidence), stakeholder involvement, and efforts to make recommendations on organizational aspects.[34]

Implications for Clinical and Policy Decisionmakers

There are some conclusions which can support clinician decisionmaking despite at best moderate SOE. SGAs showed benefit over placebo for manic and mixed states in bipolar disorder, irritability and other symptoms in autism, and aggression and conduct problems in children with DICD with or without comorbid ADHD. It is not known whether antipsychotics improve clinical impressions of severity and hyperactivity in youth who have previously responded to psychostimulant medications. Moderate evidence for clinical benefit in these symptoms is present only for those for whom stimulant medications have not produced clinically significant reductions in ADHD symptoms, or for whom DICD is the primary diagnosis. Interestingly, comorbid ADHD did not impact the treatment effect across many conditions, and there was a significant placebo effect for treatment of positive and negative symptoms of schizophrenia. Limited evidence suggests that SGAs are effective for reduction in tic severity. The effect on depressive symptoms may be small and possibly nonsignificant for schizophrenia and bipolar disorder. Reliance on findings from placebo-controlled studies for schizophrenia may not offer great help to those needing to choose between different antipsychotics for this condition which often relies on this treatment. In general, the small number of comparions between different antipsychotics is a limitation in the evidence base. Some of the findings for harms are quite considerable in light of the short-term duration of treatment of many of the studies contributing data. Nevertheless, some findings on harms—such as the low impact on weight suggested by studies of molindone—may provide some assistance when choosing between treatment alternatives. Continued guidance related to ongoing benefit-harm assessments for individual patients, regardless of which antipsychotic is prescribed, seems prudent.

Consistent with the role of systematic reviewers, we did not incorporate contextual considerations in our assessment of the SOE as would guideline developers.[26] For example, our assessment of precision in findings should be interpreted in view of our confidence in the direction and magnitude of the average effect and an estimated threshold rather than having a (possibly greater) threshold based on various benefit-harm considerations. Several of the findings for intermediate outcomes only support small effects, although the placebo effect in several studies (especially for schizophrenia) was substantial which makes some findings difficult to interpret in light of real-world practice. Likewise, we did not downgrade any evidence for lack of directness related to the comparability of study populations with those treated in clinical practice, for which there may be important differences. The main reasons we downgraded the SOE was for risk of bias (largely from incomplete data due to study withdrawals) and imprecision from small samples or when the results included possibility of substantial benefit or harm when insignificant findings were found (i.e., limiting confidence in findings of no difference). It should be recognized that attaining high SOE from trials of antipsychotics in children with psychiatric conditions is likely very difficult and the overall evidence reviewed should not be interpreted as lacking in credibility.

Systematic reviews may become outdated, at least in part, if new studies are published that change some or all of their conclusions. Although our comprehensive search was only undertaken to April 2016, we are quite confident there has been no evidence as of September 2016 which would change our findings in such a manner (e.g., to moderate or higher SOE for any outcome). A search update in Medline for April to September 8, 2016 identified three RCTs[35-37] and one retrospective cohort study;[38] assessment of these studies for their ability to potentially change the SOE indicated no change for the relevant comparators and outcomes. The studies, though, appear to represent a trend for more comparative research between different SGAs, if not also between SGAs and FGAs as suggested from our findings.

Research Gaps

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

- Studies examining long-term effectiveness and, particularly, safety of antipsychotics (and differences between different antipsychotics) over the course of several years are needed. Future research should evaluate long-term developmental outcomes, such as growth, maturation, and cognitive and emotional development.
- Future studies should evaluate outcomes that are important to patients and parents, including health-related quality of life, school performance, and involvement with the legal system.
- Studies examining the impact of key patient subpopulations on important outcomes are needed to inform clinical practice. In particular, subgroup analyses examining young adults would be helpful in guiding clinical decisions due to the unique issues associated with this population.
- Consensus on outcomes and outcome measures is needed to ensure consistency and comparability across future studies. Moreover, consensus on minimal clinically important differences is needed to guide study design and interpretation of results.
- Large-scale effectiveness studies that use inclusive patient-selection criteria and closely match typical clinical practice are needed to achieve greater applicability of results. Data on the real-world benefits and harms across groups defined by race/ethnicity, socioeconomic status, and geographical region would be informative.
- Studies incorporating therapeutic drug monitoring over long-term periods in naturalistic settings should be encouraged to help create quality standards and provide insight into operational considerations to inform recommendations for monitoring.
- Considering antipsychotics are recommended for use as adjunctive, or add-on, treatment for many conditions/symptoms, more studies examining these approaches (e.g., behavioral/family interventions with and without antipsychotics for hyperactivity or irritability) may help practitioners create guidance on when to start a trial of antipsychotics

Conclusions

The efficacy and safety of FGAs and SGAs have been studied in children, adolescents, and young adults (ages ≤ 24 years) for a wide array of psychiatric conditions. Overall, data for head-to-head comparisons (FGAs vs. SGAs, FGAs vs. FGAs, and SGAs vs. SGAs) were generally of insufficient or low SOE; therefore, few conclusions regarding the relative benefits and harms of

antipsychotics could be drawn. For schizophrenia, there appears to be little or no difference between FGAs and SGAs for negative symptoms, positive symptoms, response rates, and global impressions of illness severity; deciding on which antipsychotic to use for this condition likely relies on close examination of the relative harms including considerations of their tolerance, management, and reversibility. Many conclusions for intermediate outcomes of SGAs relative to placebo showed small magnitudes of effect, and this together with some confidence that SGAs increase the risk for several adverse effects with potentially long-term health consequences lends towards a fine balance of benefits and harms particularly in cases where alternatives exist. Evidence was sparse for several patient- and family-important outcomes, such as health-related quality of life, involvement with the legal system, and school performance. Our confidence in the findings from studies reporting most long-term data was poor.

Treatment benefit and harms were examined most frequently for schizophrenia. Fewer studies examined other conditions; only one study was eligible for each of depression and obsessive-compulsive disorder, and there were no eligible studies exclusively examining posttraumatic stress disorder, anxiety disorders, or substance use disorder. Young adults were rarely examined, particularly for conditions other than schizophrenia; there were also few studies of young children. Additional research is needed to assess the treatment efficacy, and particularly the harms, of antipsychotics in these populations.

This review identified several areas for which the evidence is sparse and which are priorities for future research. One of the greatest priorities for future research is the systematic evaluation of harms. Studies incorporating therapeutic drug monitoring over long-term periods in naturalistic settings could help create a more accurate picture of the comparative harms between the diverse number of antipsychotics. They may also help define quality standards and provide insight into operational considerations to inform recommendations for monitoring implementation. Comprehensive comparative effectiveness reviews such as this one, combined with active involvement of patients, families, and multidisciplinary practitioners may improve the applicability and usefulness of guidelines and help ensure their recommendations can be attained.

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Introduction

Background

The use of psychotropic medications, including antipsychotics, in children, adolescents, and young adults has risen over the past 20 years,[1-5] and use of antipsychotics in children with public health insurance[2] and living in foster homes[4] is greater than in those with private health insurance in the United States. During 2010, the percentages of young people filling prescriptions for antipsychotics in the United States was 0.11 percent (younger children), 0.8 percent (older children) 1.19 percent (adolescents), and 0.84 percent (young adults).[5] Annual sales of the newer class ("second generation") of antipsychotics (see below) in 2010 were $16.1 billion, growing by $1.4 billion since the previous year.[6] This drug class had also become the most costly within the Medicaid program, far exceeding the costs of any other drug class.[7]

Antipsychotic medications are commonly categorized into two classes. First-generation antipsychotics (FGAs) were developed in the 1950s, while second-generation antipsychotics (SGAs) emerged in the 1980s. Each class is considered to have a distinct side-effect profile, although there is considerable overlap between them. FGAs are mainly associated with dry mouth, sedation, and extrapyramidal symptoms, which are movement disorders characterized by repetitive, involuntary muscle movements, restlessness, or an inability to initiate movement. Neuroleptic malignant syndrome is a rare but serious adverse effect. In the United States there has been a near disappearance of the use of FGAs over the last two decades.[8] A shift towards SGAs was partly driven by the lower risk of extrapyramidal symptoms with their use, and other adverse events caused by the persistent dopamine receptor blockade by FGAs. The pharmacology of SGAs is diverse (based on action at several types of receptors) with associated heterogeneity in effects and harms; nevertheless, this class is thought as more prone than FGAs to adverse effects such as weight gain, elevated lipid and prolactin levels, and development of metabolic syndrome.[9-11] This risk profile has led to great concern, because of the known associations between weight gain and obesity with diabetes, dyslipidemia, and hypertension, all of which are leading risk factors for future cardiovascular morbidity and mortality.[12] This risk profile necessitates safety monitoring and prescription choices based on benefit-risk assessments.

For most FGAs and SGAs, the U.S. Food and Drug Administration (FDA)–approved indications for children (≤ 18 years of age) are restricted to the treatment of schizophrenia and bipolar mania. Other pediatric indications approved by the FDA include treatment of irritability associated with autism in children 5 years or older (risperidone in 2006 and aripiprazole in 2009) and of Tourette's syndrome in children aged 6-18 (aripiprazole in 2014) or over 8 years (pimozide). Off-label use of antipsychotics is common in children and adults.[13] Twenty-four to 31 percent of antipsychotic-treated children have attention deficit hyperactivity disorder (ADHD),[1,14] and 34.5 percent of antipsychotic-treated young adults have depression.[5] In Medicaid-enrolled children, ADHD accounted for 50 percent of total antipsychotic use in 2007, and ADHD together with mood disorders not otherwise specified were the most common uses (32% and 37.2%, respectively) for antipsychotics in a sample of Medicaid-insured children in Vermont during 2012.[13] In these cases or other conditions such as conduct disorders or depression, antipsychotics are usually given for adjunctive treatment of severe behavioral symptoms (e.g., aggression), rather than for psychoses.[5,7] They may also be prescribed for mood instability or relatively minor symptomatology (e.g., insomnia) of a condition, or even outside the context of a condition;[13] these uses are accompanied by considerable controversy because of concerns regarding the balance of benefits and harms. This is particularly relevant when other

treatment options exist for many conditions; for instance, fewer than half of very young, privately insured children taking antipsychotics received formal mental health services in 2007.[1]

Because of the marked increase in FDA-approved and off-label use of antipsychotics, prescribing practices have been under ongoing scrutiny (including use of prior authorization by Medicaid in many U.S. States),[15] and there is a need for ongoing investigation into the comparative effectiveness and harms of available medications. Practice parameters for antipsychotic use produced by the American Academy of Child and Adolescent Psychiatry (AACAP) are referred to when assessing practice for pediatrics in the United States,[16] but these parameters may be considered outdated (all studies cited in the parameters were published prior to 2012) for providing the best evidence. This Comparative Effectiveness Review (CER) covers many psychiatric conditions, as well as behavioral issues, for which antipsychotics are being prescribed as mono- or adjunctive therapy, such that a diverse range of stakeholders can be provided with evidence on the relative benefits and harms of antipsychotics to make informed decisions.

Use of Antipsychotics

The following sections describe the main features and uses of antipsychotics in the conditions covered by this CER.

Schizophrenia and Schizophrenia-Related Psychosis

Schizophrenia and schizophrenia-related psychosis are grouped together because psychotic symptoms are prominent features of both conditions. The category includes schizophrenia, schizoaffective disorder, substance/medication-induced psychotic disorder, or prodromal phase (ultra high-risk). Schizophrenia and related psychoses are uncommon in preadolescent children; the prevalence of childhood-onset schizophrenia is approximately 1 in 40,000.[17] In adolescents, the prevalence is estimated to be 0.1 percent, and about twice as many boys are affected as girls.[18] The onset of the condition is usually insidious, with symptoms gradually becoming apparent over an extended period of time. Typically, psychotic symptoms are classed as either being positive (e.g., hallucinations or delusions) or negative (e.g., anhedonia or lack of motivation). Treatment of psychotic disorders or psychotic features includes long-term use of antipsychotic medications.

Bipolar Disorder

Bipolar disorder is characterized by unstable mood. There are several types of bipolar disorder: bipolar type I (manic episodes and depressive episodes occur independently), bipolar type II (hypomanic episodes and depressive episodes occur independently), cyclothymic disorder (episodes not meeting criteria for bipolar I or II), and (most prevalent) other or unspecific bipolar disorder (not meeting criteria for mania or hypomanic episodes in duration).[19] The latter disorder appears to be the most prevalent (3% of children in the community); Bipolar I and bipolar II disorders are less common (approximately 1% and 0.5% prevalence, respectively) but are associated with higher morbidity.[20] Children with bipolar disorders of any type often have multiple co-occurring mental health problems. Antipsychotics may be used as the first-line medication, primarily for mania, even when psychosis is not present.

Autism Spectrum Disorders

Autism spectrum disorders (ASD) include autism, pervasive developmental disorders, Asperger's disorder, and pervasive developmental disorders not otherwise specified.[19] These disorders are characterized by: 1) deficits in social communication and social interaction and 2) restricted repetitive patterns of behavior, interests, and activities. The median prevalence of childhood autistic spectrum disorders (e.g., autism, Asperger's disorder, pervasive developmental disorders not otherwise specified) across many studies is 13 in 10,000.[21, 22] The U.S. National Health Interview Survey data indicated a prevalence of 1 in 88 children and nearly a four-fold increase in autism from 1997-1999 to 2006-2008.[23] This rising trend may be due to broadening diagnostic criteria, better ascertainment, and/or increased incidence.[24] Antipsychotics have been used to manage irritability or aggressive outbursts, reduce hyperactivity or repetitive behaviors, or promote sleep onset and continuity.[25]

Attention Deficit Hyperactivity Disorder and Disruptive, Impulse-Control, and Conduct Disorders

Attention deficit hyperactivity disorder (ADHD) and disruptive, impulse-control, and conduct disorders 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. Based on parent reports of healthcare provider diagnosis, the 2011/12 U.S. National Survey of Children's Health estimates that 11 percent of school-aged children have received a diagnosis of ADHD; this represents a 42 percent increase from 2003.[26] Smaller prevalence estimates (4.6% in 2007) have been reported for oppositional defiant disorder; the prevalence of conduct disorder may be slightly lower.[27] The rates of disorder vary by age and sex, but the most marked difference is the 6 to 1 ratio of boys to girls with ADHD prior to puberty. Antipsychotics may be used to manage impulsive aggression and other conduct problems; they may also be used to reduce hyperactivity or help regulate negative emotions, or (in small doses) to promote somnolence (an intended side effect), as many people with ADHD have sleep disturbance.

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) is a chronic condition characterized by obsessions (repetitive thoughts) or compulsions (repetitive behaviors) that cause distress and/or interfere with functioning. More than 90 percent of lifetime OCD diagnoses met the criteria for another psychiatric disorder including anxiety disorders (75.8%), followed by mood disorders (63.3%), impulse-control disorders (55.9%), and substance abuse disorders (38.6%).[28] Because of failure for many patients in response to first-line treatment with antidepressants and other therapies, treatment is often augmented with antipsychotics.[29]

Substance Use Disorder

The essential feature of a substance use disorder is a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems.[19] Dopamine-related behaviors, including impulsivity, aggression, and sensation seeking, have been shown to limit effectiveness of intensive outpatient therapies. Because of their blockade of dopamine transmission, antipsychotics may be used to reduce the reinforcing properties of certain substances (e.g., cocaine and psychostimulants).[30]

The use of antipsychotics in other cases, such as for alcohol use disorders, may in part rely on the dopamine-enhancing properties of some of these medications.[31]

Major and Persistent Depressive Disorders, and Disruptive Mood Dysregulation Disorder

Of the depressive disorders, major depressive disorder (MDD) represents the classic condition. It is characterized by discrete episodes of at least 2 weeks duration, involving changes in affect, cognition, and neurovegetative functions (i.e., sleep, appetite). Persistent depressive disorder requires symptoms of at least one year (two in adults). To address concerns about potential overdiagnosis and overtreatment of bipolar disorder in children, a new diagnosis, disruptive mood dysregulation disorder, is included for children up to age 18 years who exhibit persistent irritability and frequent episodes of extreme behavioral dyscontrol.[19] Antipsychotics are often used as adjunctive therapy for depressive disorders (i.e., aripiprazole, quetiapine, and olanzapine are indicated for treatment for major depression in adults), and have been shown to result in improvements in core symptoms of the condition for adults.[32]

Anxiety Disorders

Anxiety may occur in the course of another condition (e.g., bipolar, posttraumatic stress, OCD), but there are also several primary anxiety disorders (DSM-V does not classify OCD or posttraumatic stress disorder [PTSD] as anxiety disorders).[19] Prevalence rates of anxiety disorders (excluding rates for OCD and PTSD) in adolescence and in 18 to 29 year olds are substantial (21-25% from the National Comorbidity Surveys). When onset is before adolescence, some disorders such as separation anxiety are more common; despite this, generalized anxiety disorder occurs in children and has a 12-month prevalence of 0.9 percent in the United States.[19] The median age of onset of anxiety disorders in children has been reported to be six years of age. Apart from anxiety symptoms, irritability and sleep disturbances are examples of symptoms which may be treated with antipsychotics.[33]

Posttraumatic Stress Disorder

Posttraumatic stress disorder develops following a reaction of intense fear, helplessness, or horror resulting from a traumatic event.[34, 35] Symptoms of PTSD include a persistent re-experience of the traumatic event (i.e., intrusions, flashbacks), persistent avoidance of stimuli associated with the trauma, numbing of general responsiveness, and persistent symptoms of increased arousal.[19] Individuals with PTSD may also experience psychotic symptoms such as paranoia, agitation, and delusional beliefs.[36] Median age of onset for a representative sample of adults in the United States' National Comorbidity Surveys was 23 years.[37] A national sample of adolescents (12–17 years old) indicated that 3.7 percent of male and 6.3 percent of female adolescents met full diagnostic criteria for PTSD.[38]Antipsychotics have been studied for use as monotherapy or adjunctive treatment (with antidepressants) for various symptoms in adults with PTSD.[39, 40]

Eating Disorders

Eating disorders are characterized by a persistent disturbance of eating or eating-related behavior that results in the altered consumption or absorption of food and that significantly impairs physical health or psychosocial functioning.[19] The prevalence of anorexia is reported to

be approximately 0.13 percent in females aged 15 to 20. In males, it is approximately one-tenth of that.[19] The incidence of anorexia nervosa appears to have increased in recent decades.

SGAs have been prescribed off-label as an adjunctive to treatment for agitation, anxiety and ruminations.[41] Use may also reflect an attempt to promote weight gain in boys and girls who are underweight as a result of their disorder.

Tic Disorders

Tics are involuntary motor movements or vocalizations. Although some individuals have only motor or verbal tics, those with Tourette's syndrome have both types. The U.S. prevalence was estimated in 2007 at 0.3 percent of children aged 6-17, with two times as many boys affected as girls.[23] For a diagnosis of Tourette syndrome, the onset of symptoms must occur before age 18. In most cases, Tourette's syndrome is associated with co-morbid neuropsychiatric disorders—most commonly OCD or ADHD.[23, 42] Medications that inhibit dopamine reuptake, such as antipsychotics, generally help to reduce tics, but may induce tics in some cases. Antipsychotics may also have a beneficial impact on comorbid conditions.

Objectives

In February 2012, the Agency of Healthcare Research and Quality (AHRQ) published the results of Comparative Effectiveness Review (CER) No. 39, "First- and Second-Generation Antipsychotics for Children and Young Adults," prepared by the University of Alberta Evidence-based Practice Center (EPC).[43] CER No. 39 examined evidence on benefits and harms for comparisons within and between classes of FGAs and SGAs across a broad range of conditions. The only findings having a moderate strength of evidence included: (1) olanzapine caused more dyslipidemia and weight gain, but fewer prolactin-related events, than risperidone, (2) olanzapine caused more weight gain than quetiapine, and (3) compared with placebo, SGAs improved clinical global impressions (schizophrenia, bipolar, and ADHD/disruptive behavior disorders) and diminished positive and negative symptoms (schizophrenia), behavior symptoms (disruptive behavior disorders), and tics (Tourette syndrome). The large majority of comparisons between and within classes of antipsychotics offered low or insufficient evidence about comparative effectiveness or harms.

Due to the popularity, potential impact, and use in clinical practice guidelines of reviews on this topic, in August, 2014, AHRQ's Comparative Effectiveness Review Surveillance Program[44] assessed the need for CER No. 39 to be updated. Many of the newer studies identified had the potential to change several of the conclusions in the review, or add results for conditions (e.g., eating disorders) and antipsychotics not previously studied (e.g., lurasidone, asenapine). The scope of this review is quite similar to CER No. 39, with key changes being the addition of (1) three newly approved SGAs (i.e., brexpiprazole, asenapine, lurasidone) and the previously discontinued FGA molindone, (2) some conditions of interest (i.e., anxiety, depression, substance use), and (3) modification to some key outcomes to be more specific to symptoms targeted by clinicians when prescribing antipsychotics. A detailed explanation of all changes made for this systematic review is included in Appendix A.

The purpose of this systematic review is to provide a comprehensive synthesis of the evidence examining the benefits and harms associated with the use of FDA-approved FGAs and SGAs in children, adolescents, and young adults ≤24 years of age. The findings from this update will be useful for multiple stakeholders, and inform efforts by professional societies to develop

evidence-based recommendations and clinical practice guidelines to guide appropriate use in practice.

Scope of Review and Key Questions

Conditions of Interest

- Schizophrenia and schizophrenia-related psychoses, including schizoaffective disorder and substance/medication-induced psychotic disorder, and prodromic (ultra high-risk) psychosis.
- Autism spectrum disorders, including pervasive developmental disorder, autism, Rett's disorder, childhood disintegrative disorder, Asperger's disorder, and pervasive developmental disorder not otherwise specified.
- Bipolar disorder.
- Attention deficit hyperactivity disorder, or disruptive, impulse-control, and conduct disorders, including conduct disorder, oppositional defiant disorder, intermittent explosive disorder, and other specified/unspecified disruptive, impulse-control, or conduct disorders.
- Obsessive-compulsive disorder.
- Substance use disorder.
- Major and persistent depressive disorders, or disruptive mood dysregulation disorder.
- Anxiety disorders.
- Posttraumatic stress disorder.
- Eating disorders (i.e., anorexia nervosa, bulimia nervosa, binge-eating disorder).
- Tic disorders (e.g., Tourette's syndrome).
- Behavioral issues outside the context of a mental disorder, including aggression, agitation, anxiety, behavioral dyscontrol, irritability, mood lability, self-injurious behaviors, and insomnia.

Key Questions

For Each Condition of Interest:

Key Question 1. What are the benefits, in terms of intermediate and effectiveness outcomes, of first and second generation antipsychotics—at the level of individual antipsychotics and across each class—in comparisons with placebo, different doses of the same antipsychotic, or different antipsychotics in children and young adults (≤24 years)?

a. Do the benefits vary with respect to patient characteristics, such as age, sex, race/ethnicity, medical comorbidities, phase or features of disorder, and antipsychotic treatment history?

b. Do the benefits vary with respect to clinical characteristics such as dose of antipsychotic or cotreatments including other antipsychotics, other medications, or nonpharmacologic therapy?

Across All Conditions:

Key Question 2. Across all conditions of interest, what are the harms of first and second generation antipsychotics—at the level of individual antipsychotics and across each class—in comparisons with placebo, different doses of the same antipsychotic, or different antipsychotics in children and young adults (≤24 years)?

a. Do the harms vary with respect to patient characteristics, such as age, sex, race/ethnicity, diagnosis, medical comorbidities, phase of disorder, and prior exposure to antipsychotics?

b. Do the harms vary with respect to clinical characteristics such as dose of antipsychotic or cotreatments including other antipsychotics, other medications, or nonpharmacologic therapy?

Analytic Framework

Figure 1 is an analytic framework that depicts the structure used to address the Key Questions (KQs) for evaluating the benefits and harms of FGAs and SGAs in children and young adults (≤24 years of age). We examined the benefits and harms of FDA-approved FGAs and SGAs in a population of children and young adults (≤ 24 years) diagnosed with one of the psychiatric conditions identified, or experiencing behavioral issues outside the context of a psychiatric diagnosis (e.g., sleep difficulties, agitation, aggression). In KQ1, benefit was determined (by condition) for intermediate outcomes (e.g., short-term disorder-specific and nonspecific symptoms, short-term medication adherence, lifestyle behaviors), and effectiveness outcomes (e.g., long-term symptoms, growth and maturation, health status and quality of life, caregiver burden/strain). In KQ2, we assessed harms across conditions in terms of medication-associated adverse effects categorized as major (e.g., mortality, development of diabetes) and general (e.g., extrapyramidal effects, weight gain, hyperprolactinemia). Within each KQ, we assessed outcomes for subgroups of patients or studies based on patient and clinical/treatment characteristics.

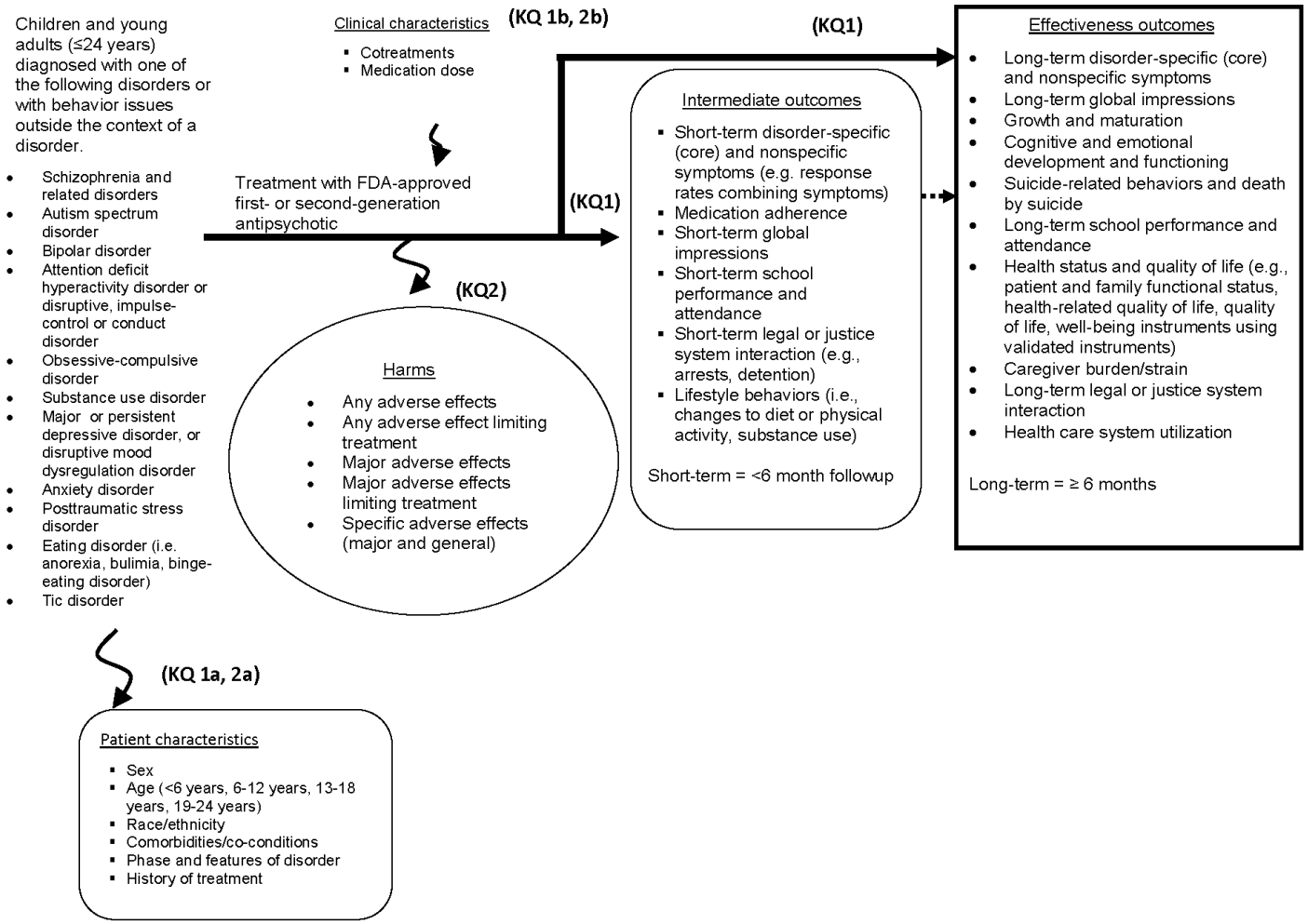
Organization of This Report

The remainder of the report describes our methods in detail and presents the results of our synthesis of the evidence with key points, detailed syntheses, and our assessment of the strength of evidence for our key outcomes. The first part of the results, evaluating benefit outcomes, is organized by condition; the second part focuses on harms with findings reported across all conditions. The results are divided to specifically address the different types of comparisons of interest (as possible depending on data): aggregate (across class) data for FGAs versus SGAs, within-class comparisons between individual FGAs and individual SGAs (other drug or dose), and then aggregate and individual data for FGAs versus placebo, and SGAs versus placebo. The discussion section offers our conclusions, summarizes our findings, and provides other information relevant to the interpretation of this work for clinical practice and future research. References and a list of abbreviations and acronyms follow the discussion section.

The report includes a number of appendices to provide further detail on our methods, the studies assessed, the quality assessments for individual studies, and findings not presented in the main body of the report. The appendixes are as follows:

Appendix A: Changes From Original Review
Appendix B: Literature Search Strategies
Appendix C: Quality Assessment Ratings
Appendix D: Study Characteristics
Appendix E: Associated Publications
Appendix F: Excluded Studies
Appendix G: Analytical Models and Code, and Additional Results for Key Question 2 From Network Meta-Analysis and for General Adverse Effects

Figure 1. Analytic framework for the Key Questions evaluating the comparative effectiveness of FDA-approved first- and second-generation antipsychotics in children and young adults 24 years old and under



FDA = Food and Drug Administration; KQ = Key Question

Methods

The methods for this review of antipsychotics in children and young adults are based on the methods specified in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (Methods Guide).[45] The main sections in this chapter reflect the elements of the protocol established for the review;[46] this report provides a summary of the methods outlined in detail in the protocol. The methods and analyses were determined a priori, except where otherwise specified.

Topic Refinement and Review Protocol

The American Academy of Child and Adolescent Psychiatry (AACAP) is a partner with AHRQ for this systematic review. During the topic development and refinement processes, we developed draft versions of the analytic frameworks, Key Questions (KQs), and inclusion/exclusion criteria in the form of PICOTS (populations, interventions, comparators, outcomes, timing, settings). The processes were guided by the information provided by original CER No. 39, a scan of the literature, and discussions with methods and contents experts, and Key Informants (KIs); we worked with six KIs during topic refinement. Subsequently, the analytic frameworks, KQs, and PICOTs were posted for public comment on AHRQ's Effective Health Care Web site from June 9 through June 29, 2015. After consultation with AHRQ and responding to the public comments, we engaged a Technical Expert Panel (TEP)—including two of the KIs—to develop the systematic review protocol. The final protocol was posted on AHRQ's Effective Healthcare Web site on December 4, 2015.[46] The protocol was registered with the PROSPERO database (No. CRD 42016032943) on January 5, 2016. The KIs and TEP members will be identified in the front matter of the final report.

Inclusion/Exclusion Criteria

We used the eligibility criteria outlined in the PICOTS-D as presented in Table 1. Additional details for the inclusion and exclusion criteria related to the PICOTS-D elements, including FDA-regulatory status and indications for each antipsychotic, are described in the published protocol. We provide details here for the outcomes of interest, including those considered key outcomes for assessing the strength of the body of evidence. The primary focus in KQ2 was harms across all conditions because adverse events associated with an antipsychotic are likely to be consistent regardless of the indication for which a drug is being taken; the difference in harms between conditions was treated as a subgroup of interest. We defined nonrandomized controlled trials (NRCTs) as *experimental trials without random allocation but where intervention(s) are introduced, standardized, and allocated objectively [e.g., by date of birth, but not using subjective means such as patient or clinician preferences] by investigators and blinding of participants is typically possible.*

Table 1. PICOTS (population, interventions, comparators, outcomes, timing, setting)

Category	Criteria
Population	Children and young adults (≤24 years) with one or more of the following conditions/issues: AD, ADHD/DICD, ASD, BD, DD, ED, OCD, PTSD, SUD, SZ, TD, or behavioral issues outside the context of a disorder (e.g., insomnia). KQ1: For each condition category, inclusion of studies enrolling ≥90 percent of patients diagnosed with the specific condition (s). KQ2: Across all conditions, inclusion of studies enrolling patients within a single or within multiple/mixed condition categories. Subpopulations based on patient characteristics: sex; age (<6 years, 6-12 years, 13-18 years, 19-24 years); race/ethnicity (i.e., % nonwhite); comorbidities/co-conditions (e.g., ADHD); history of treatment (e.g., naïve, refractory); phase and features of disorder (e.g., acute mania vs. maintenance treatment [bipolar disorder], first-episode psychosis versus treatment in context of prior episodes [schizophrenia], presence of psychosis [disorders other than schizophrenia]).
Interventions	Any FDA-approved FGA (chlorpromazine, droperidol, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide, prochlorperazine, thiothixene, thioridazine, trifluoperazine) Any FDA-approved SGA (aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone) All formulations and doses eligible. Subpopulations as per clinical characteristics: presence of cotreatments (e.g., other medication, nonpharmacological therapy, as reported); medication dose.
Comparators	Placebo/no treatment, any other antipsychotic, or same antipsychotic at different dose. Exclusion of non-antipsychotic medications as comparator.
Outcomes	KQ1: intermediate and effectiveness outcomes (see following list of outcomes). KQ2: any AE and any major AEs; any or major AE limiting treatment (e.g., withdrawal due to AE); specific AEs (i.e., individual major or general AEs; see following list of outcomes)
Timing	No minimum followup duration Short term: <6 months Long term: ≥6 months-<12 months; 12 months+
Setting	Any setting
Design	Clinical trials (RCTs and NRCTs), controlled cohort studies (prospective or retrospective), controlled before-after studies (e.g., open-label extensions with comparator group, pooled analyses of individual patient-level data from one or a combination of similar trials).
Language	English

AD = anxiety disorders; ADHD/DICD = attention deficit hyperactivity disorder, or disruptive, impulse-control, or conduct disorders; AE = adverse effect; ASD = autism spectrum disorders; BD = bipolar disorder; DD = depressive disorders, ED = eating disorder; FDA = Food and Drug Adminsitration; FGA = first-generation antipsychotic; KQ = key question; NRCT = nonrandomized controlled trial; OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; SGA = second-generation antipsychotic; SUD = substance use disorder; SZ = schizophrenia and related psychosis; TD = tic disorders

Outcomes

The intermediate and effectiveness outcomes of interest to this review are listed below, followed by the harms. We accounted for duration of response, that is, short- (< 6 months) and long-term (≥ 6 months - < 12 months; ≥ 12 months). Key outcomes assessed for the strength of the body of evidence and considered when assessing subgroup analyses are indicated by an asterisk (*); these key outcomes were chosen—using input from KIs our TEP—because they reflect outcomes most targeted by treatment with antipsychotics and are of relatively high importance to patients, their families, and clinicians.

Intermediate Outcomes

- Short-term disorder-specific (core) symptoms:
  - Schizophrenia and related psychoses: positive* and negative symptoms*, disorganized behavior, impaired thought process, mood symptoms;
  - Autism spectrum disorders: irritability (i.e., aggression, deliberate self-injury, and temper tantrums)*, qualitative impairment in social interactions*, communication*, restricted repetitive and stereotyped behaviors*, interests, and activities;
  - Bipolar disorder: severity of mania*, anxiety, depression*, mood symptoms, psychotic features*;
  - Attention deficit hyperactivity disorder (ADHD) or disruptive, impulse-control, and conduct disorders (DICD): aggression*, negativistic, hostile and defiant behavior, externalizing behaviors*, impulsivity*;
  - Obsessive compulsive disorder (OCD): obsessive thoughts*, compulsive behavior*;
  - Substance use disorder: cravings, abstinence/substance use days*;
  - Major or persistent depressive disorder: depression*, irritability*, psychotic features (e.g., positive and negative symptoms)*;
  - Anxiety disorder: anxiety*, irritability*;
  - Posttraumatic stress disorder: hyperarousal*, avoidance behaviors*, intrusion*;
  - Eating disorders: weight*, body mass index, cognitive distortions, eating disorder attitudes and beliefs;
  - Tic disorders: motor and vocal tic frequency* and severity*;
  - Behavioral issues outside the context of disorder or illness: aggression, agitation, anxiety, behavioral dyscontrol, irritability, mood lability, self-injurious behaviors, and sleep latency and duration.
- Short-term nonspecific or associated symptoms
  - Various (often composite or associated) psychiatric behaviors or symptoms (e.g., response rates*, anxiety in OCD, depression in tic disorders, sleep disorders, overall behaviors/symptoms in autism), and not including global assessments
- Short-term global impressions and functioning*
- Medication adherence
- Short-term school performance and attendance
- Short-term legal or justice system interaction (e.g., arrests, detention)
- Lifestyle behaviors (i.e., changes to diet or physical activity)

Effectiveness (Patient- and Family-Important) Outcomes

- Long-term (≥ 6 month followup) disorder-specific symptoms (see list above under Intermediate Outcomes)*
- Long-term (≥ 6 month followup) nonspecific or associated symptoms
  - Various (often composite or associated) psychiatric behaviors or symptoms (e.g., response rates*, anxiety in OCD, depression in tic disorders, sleep disorders, overall behaviors/symptoms in autism), and not including global assessments
- Long-term (≥ 6 month followup) global impressions and functioning*
- Growth and maturation
- Cognitive and emotional development and functioning*
- Suicide-related ideations or behaviors, or death by suicide*

- Long-term (≥ 6 month followup) school performance and attendance
- Occupational functional capacity
- Generic and specific health status and quality of life (i.e., patient and family functional status [e.g., social or relationship success, development of autonomy, and others tied to developmental level and family function], health-related quality of life, quality of life, well-being) using validated instruments*
- Caregiver burden/strain
- Long-term (≥ 6 month followup) legal or justice system interaction*
- Health care system utilization

Harms

Adverse effects (AEs) were examined across all conditions (KQ2). In addition to describing findings for each AE specified below, we analyzed AEs in terms of: 1) any adverse event (AE) and any AE limiting treatment (i.e., non-compliance/withdrawal rates due to AEs), and 2) major AEs and major AEs limiting treatment.

Major Adverse Effects*

- Mortality
- Cerebrovascular disease-related events
- Development of diabetes mellitus
- Diabetic ketoacidosis
- Neuroleptic malignant syndrome
- Seizures
- Tardive dyskinesia
- Cardiomyopathies
- Cardiac arrhythmias
- Agranulocytosis

General Adverse Effects

- Neuromotor effects (e.g., extrapyramidal symptoms including dystonia, akinesia, akathisia)*
- Metabolic effects (e.g., metabolic syndrome, change in body composition [weight, BMI], fasting glucose, insulin sensitivity/resistance, dyslipidemia [total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides], blood pressure)*
- Prolactin-related effects and sexual dysfunction (e.g., hyperprolactinemia, AEs related to prolactin elevations [e.g., galactorrhea/bloody galactorrhea, hypogonadism], erectile dysfunction, infertility, oligo/amenorrhea, precocious puberty)*
- Agitation
- Constipation
- Somnolence* and fatigue
- Elevated transaminases
- Exercise intolerance
- Discontinuation syndrome (including symptoms related to motor [e.g., withdrawal-induced dyskinesias, dystonias], autonomic (e.g., disturbed temperature regulation, nausea] and psychoses [e.g., rebound psychosis]

Literature Search Strategy

The research librarian, in collaboration with the investigative team, revised and implemented the original search strategy to incorporate the changes to the conditions of interest. Because of the addition of several conditions, we re-ran all searches back to 1987 rather than 2010 as suggested for update searches.

We comprehensively searched the following electronic databases: Ovid MEDLINE and Ovid MEDLINE® In-Process & Other Non-Indexed Citations (1946 to Present), Cochrane Central Register of Controlled Trials via Wiley Cochrane Library (1991 to Present), EMBASE® via Ovid (1980 to 2016 Week 15), CINAHL Plus with Full Text via EBSCOhost (1937 to Present), PsycINFO® via Ovid (1987 to April Week 1 2016), ProQuest® Dissertations and Theses Global (1861 to Present), and TOXLINE via The U.S. National Library of Medicine (1840s to Present). Searches were conducted between October 15th and October 22nd, 2015 and were restricted to English language studies published since 1987. The searches of the first five databases were updated in April 2016. Using a combination of controlled vocabulary and keywords, search filters for RCTs, NRCTs, and observational studies were applied (where applicable) to the search results retrieved from the above listed databases.[47] The search strategies for each database are located in Appendix B; the MEDLINE strategy was peer reviewed by a second librarian and adapted to accommodate the controlled vocabularies and search languages of the other databases.

Several other sources were used to obtain data from reports of studies. Reference lists of relevant systematic reviews and guidelines (identified when searching bibliographic databases), and of included studies were screened to identify potentially relevant (published or unpublished) studies. On October 26th and 27th, 2015, we searched ClinicalTrials.gov, and the World Health Organization's International Clinical Trials Registry Platform. We handsearched the Journal of Child and Adolescent Psychopharmacology, and the Journal of the American Academy of Child and Adolescent Psychiatry (2014-2015). Drug manufacturers and other relevant stakeholders (via AHRQ's Scientific Resource Center) were notified of the opportunity to submit scientific information relevant to the interventions of this systematic review. We searched Drugs@FDA for Medical/Clinical and Statistical review documents; as with the original CER, we only searched regulatory documents containing harm data for patients 18 years of age or younger.

All results of the database searches were imported into an EndNote® database (Thomson Reuters, New York, NY). Results from other searches were documented in a Microsoft Excel database (Microsoft Corp., Redmond, WA). We tracked the screening and selection results in EndNote.

Study Selection

For the database searches, two reviewers independently screened the titles and abstracts (when available) using broad inclusion/exclusion criteria. One reviewer conducted all other searches outlined in the above section. The full text of all studies classified as "include/unsure" or identified after screening the reference citations were retrieved for full review; two reviewers independently assessed eligibility using a standard form that outlined the inclusion and exclusion criteria. Disagreements on final inclusion of all studies were resolved through consensus or third party adjudication.

Data Abstraction and Data Management

One review team member extracted data for each study, and a senior level team member verified all data. Data was extracted on elements relevant to the Key Questions, including population characteristics, study characteristics (including funding source), descriptions of the intervention(s) and comparator(s)—including dose, route of administration, etcetera—analytic details including subgroup analysis on treatment modification, and outcomes including outcome type, timing and definitions. As done for the original CER, when there were multiple publications associated with a study we considered the earliest report of the main (primary) outcome data to be the primary data source. We extracted data from the primary source first and then add outcome data reported in the secondary/associated publications and data sources (e.g., FDA reports). We referenced the primary source throughout the evidence report; all associated literature was tabulated for reference.

Benefit and harm data were extracted as reported by study authors; for example, we included relevant author-defined outcomes (such as percentage of participants gaining ≥7% body weight, remission, relapse, withdrawal due to lack of efficacy/response) as long as these accounted for benefit and harm outcomes of interest. A wide variety of checklists and scales were used to assess symptomatology in patients. In various instances (e.g., hyperactivity, aggression) we used subscale items on one or more questionnaires, rather than their overall composite scores, to capture the outcomes of interest with more specificity. For harms, we focused on outcome metrics most likely to be relevant to decision making; for example, we focused on reports of abnormal serum lipids rather than mean changes in serum levels which may not reflect a clinically relevant degree of harm.

We recorded intention-to-treat results, if possible. For continuous outcomes measures, we extracted (by arm) the mean baseline and endpoint or change scores, standard deviations (SD) or other measure of variability, and number analyzed. If necessary, we approximated means by medians. If SD were not given, they were computed from p-values, 95% confidence intervals (95% CIs), z-statistics, or t-statistics. If computation was not possible they were estimated from upper bound p-values, ranges, inter-quartile ranges, or (as a last resort) by imputation using the largest reported SD from the other studies in the same meta-analysis. When computing SDs for change from baseline values, we assumed a correlation of 0.5. For dichotomous outcomes, we reported counts or proportions, and sample size, by study arm. When there was data for more than one timepoint within each of our followup strata (e.g., results for 1- and 3-month followup were both within our 0 to <6-month stratum) we used the longest followup duration.

Only numerical data for AEs was extracted; that is, we made no assumptions on lack or presence of an AE if it was not reported. We extracted data (taking care to avoid duplication with other study reports) on harms from trial registries and regulatory agency reports of pediatric trials. For each major AE, we reported the number of studies that provided data for the AE. We also reported summary totals of the number of individuals in the medication groups who were reported to have experienced the event and the total number of patients in the medication groups in relevant trials.

Data on within-study subgroup analysis was collected, including: subgroups (independent variables), the type of analysis (e.g., subgroup/stratified or regression analysis), the outcomes assessed (dependent variables), and the authors' conclusions. We collected data suitable for all patient and clinical characteristics for performing our own subgroup analyses based on study-level data.

Assessment of Methodological Quality of Individual Studies

Two experienced reviewers independently assessed the methodological quality of all original and new studies and resolved discrepancies through consensus. We re-assessed original studies because of changes to guidance in the EPC program made subsequent to the original CER. For RCTs and NRCTs we used the Cochrane Collaboration Risk of Bias tool,[48] with some modification based on EPC Methods guidance.[45] We did not assess selective outcome reporting at the study level, since this was considered within the reporting bias domain of our assessment of the strength of evidence (SOE) for individual outcomes across studies.[49] The "other" domain included considerations of baseline imbalances between study groups and whether the study protocol included a wash-out period for patients who were not drug naïve. 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 considered low only if all components were rated as having a low risk of bias. The risk of bias for all other studies was rated as medium. Information was collected for each study on the source of funding.

For cohort studies, we used the Newcastle-Ottawa Quality Assessment Scale.[50] The scale comprises of seven items that evaluate three domains of quality/risk of bias: sample selection, comparability of cohorts, and assessment of outcomes. Each item that is adequately addressed is awarded one star, except for the "comparability of cohorts" item, for which a maximum of two stars can be given. We considered a total score of 6 to 8 stars to indicate high quality/low risk of bias, 4 or 5 stars to indicate moderate quality/medium risk of bias, and 3 or fewer stars to indicate poor quality/high risk of bias.

Data Synthesis

For each condition we summarized the characteristics of included studies qualitatively and present important features of the study populations, study designs, interventions, comparators, and reported outcomes in summary tables. For each KQ, we synthesized data in the following order based on type of comparison (as possible depending on data): aggregate (across drug class) data for FGAs versus SGAs, individual FGAs versus SGAs, within-class comparisons between individual FGAs and individual SGAs (other drug or dose), and then individual and aggregate data for FGAs versus placebo and SGAs versus placebo.

Various approaches to synthesizing the evidence are available including direct pairwise meta-analysis and methods that combine direct and indirect evidence (i.e., network meta-analysis or mixed treatment comparisons).[51-52] The summary effect from direct comparisons (e.g., an SGA vs. placebo, one SGA or FGA vs. another SGA or FGA) for one outcome at a similar timepoint is meaningful as a first approach. However, such an approach does not allow for comparisons between drugs that may not have much direct evidence (e.g., drug A was compared to drug B and C, but drugs B and C were not been directly compared). Where feasible, we conducted network meta-analyses, as described below.

In the event that results from studies were not combined using meta-analysis, a narrative summary of the results is presented and precision is indicated using 95% CIs from the individual studies.

Pairwise and Network Meta-Analyses

For pairwise meta-analyses, we employed a Bayesian random effects model using WinBUGs software.[53] This approach models uncertainty in between-study variability and was used in place of the more traditionally employed Der Simonian-Laird approach, which has been shown to result in a high number of statistically significant results (falsely high precision) especially in the face of heterogeneity and few studies.[54] We used this approach when more than two studies reported on the same outcome and comparisons; when two studies are combined using this model the precision in the effect estimate is very often too wide to provide, in our opinion, any benefit from the analysis. When different outcomes were considered to measure the same construct (e.g., different subscores of hyperactivity) we combined the results (at followup) of multiple scores using a standardized mean difference (SMD); in this way we were able to use as many studies as possible to capture effect estimates for our outcomes. When the SMD was not used because of reporting by multiple studies using the same measurement scale (enabling calculation of a mean difference [MD]), change scores were preferred over followup scores and we combined these two when necessary.We reported MD, SMD, or relative risks/risk ratios (RR) with corresponding 95 percent credible intervals (95% CrI; Bayesian approaches provide variances using credible rather than confidence intervals, interpretable as the range of values within which there is a 95% chance of finding the true value of the effect). Non-informative priors were selected for estimated parameters. A Markov chain Monte Carlo (MCMC) simulation was then run, using a burn in sample of 20,000 iterations (which were discarded) followed by 200,000 iterations which were used to estimate the model parameters. A description of the model and code is included in Appendix G.

In general, we combined results from studies when there was sufficient clinical (i.e., population characteristics, interventions, outcome ascertainments) and methodological (i.e., study design, conduct and quality) similarities. We often started with combing all studies within a condition category and then used our a priori defined list of patient and intervention subgroups to explore the heterogeneity. For intermediate and effectiveness outcomes we considered combining results from RCTs with NRCTS, but not with cohort studies. For harm outcomes we combined data from all study designs, for the following reasons: 1) empirical evidence has found no difference in estimates of harms between meta-analyses of RCT and cohort study designs;[55] 2) a major contributor to bias on harms from observational studies is confounding by indication (e.g., differential prescriptions based on beliefs/knowledge about factors related to development of harms) which we did not believe was an important threat in studies examining unanticipated harms in (mostly) treatment naïve children; and 3) cohort studies are commonly recognized as contributing valuable, relatively high-quality evidence applicable to real-world settings. To avoid making conclusions from these analyses without carefully considering possible biases, we identified important potential confounders on which to assess the findings for heterogeneity and also extracted data from all studies on their own subgroup analysis for patient and clinical treatment modifiers. Where there are at least eight studies in a meta-analysis, we analyzed publication bias both visually using the funnel plot and quantitatively using Egger's test.[56]

Since we were interested in comparisons within and across classes of FGAs and SGAs, approaches that considered inferences from indirect data were suitable. Rather than providing a simple pair-wise analysis of similar comparisons (e.g., SGAs vs. placebo) through standard meta-analysis, a network meta-analysis allows for simultaneous evaluation of a suite of comparisons while still preserving the within-study randomization. A network of different comparisons is constructed (with "nodes" representing the different medications) to consider

both direct evidence from comparisons of similar interventions/nodes and indirect evidence from comparisons where one intervention is in common, but not all (e.g., intervention A vs. placebo, and intervention B vs. placebo infer knowledge about intervention A vs. intervention B). This analysis was conducted for the outcomes of weight and body mass index; other outcomes were often only reported by a single study within a particular comparison, such that the validity of using this approach for these was questionable.

When using this Bayesian network meta-analysis approach, all unknown parameters were given non-informative prior distributions and were estimated using MCMC methods in WinBUGS software. The model was run for 220,000 iterations, with the first 20,000 samples conservatively discarded as burn-in, leaving 200,000 for inference. We conducted convergence diagnostics (i.e., convergence verified using autocorrelation, paying particular attention to prior distributions on between study variance parameter) and assessed the fit of the models by monitoring the deviance parameters; the analyses were also checked for consistency by contrasting direct and indirect estimates in every closed loop of the networks with a display of the results in plots.[57] We obtained estimates of the treatment effects and rank probabilities for each treatment strategy (e.g., probability that a particular drug is the "worst" for the particular outcome). Findings from the network meta-analysis are considered fairly observational in nature and were compared with other more direct findings. The model structure and code are included in Appendix G.

In addition to multiple comparisons, meta-analytical approaches have been developed to incorporate multiple outcomes even within a network meta-analysis.[58] One example is when most, but not all, studies report on a set of specific measurement tools or values but others only report a subset of the values. A multivariate approach can allow for the borrowing of strength across the entire set of relevant studies, and enable the correlation between outcomes (both within and between studies) to be directly estimated. We had anticipated this approach may have been suitable for enhancing our ability to report on some outcomes, particularly on harms, which are not reported on by all studies. The only outcomes that were reported on by enough studies to have missing data for a minority were weight and BMI, but since these variables are mathematically correlated (i.e., BMI is function of weight and height) it would not be appropriate to include them in such a model.[59] Other groups of outcomes (e.g., dyslipidemia, fasting glucose) were not all reported by enough studies or by enough different comparisons (i.e., mostly through placebo-controlled studies) to enable a valid model.

Analysis of Subgroups

Our primary approach to answer parts (a) and (b) of each KQ was to record any within-study subgroup analyses performed by study investigators using individual patient data; these results preserved the within-study randomization. Because these results are often based on diverse methodology and may be difficult to interpret across the body of evidence, we also performed our own "across study" subgroup analyses using study-level data on our variables of interest (e.g., phase of treatment, treatment history of participants), where possible. For the benefit outcomes, the number of studies within any given comparison was too few to perform formal statistical approaches such as meta-regression; for these outcomes we performed sensitivity analysis of the results of the pairwise meta-analyses by subgroup variables, and/or commented on observations about the differences in effects and heterogeneity between studies based on subgroup variables of interest. Since there were more studies for KQ2 on several harm outcomes, we employed univariate Bayesian meta-regression analyses for four key harm outcomes (weight,

weight gain of greater than 7%, somnolence, incidence of any extrapyramidal symptoms) in terms of each study's mean patient age, sex, antipsychotic treatment history (i.e., % treatment naïve), and treatment duration. These analyses relied on study-level data, such that the results should be considered observational in nature. We used the same prior distributions (adding a non-informative uniform prior for the regression coefficient), burn in iterations, and estimate iterations as were used in the primary meta-analyses (Appendix G contains details). Because of the finding that treatment duration was a statistically significant modifier for weight gain, we also performed adjusted network meta-analyses for weight and BMI using this study-level variable.

Grading the Strength of the Body of Evidence

We followed the Methods Guide and updated guidance[50] to evaluate the strength of the body of evidence (SOE) for the key outcomes and comparisons. The body of evidence was graded by one reviewer, and reviewed by a second reviewer. Disagreements were resolved through discussion or by consulting with a third reviewer, as needed. Tables of findings were generated for all outcomes and comparisons that had greater than insufficient SOE.

Trials and observational evidence were graded separately for each outcome-comparison pair, with the overall SOE incorporating both study designs, if applicable. We assessed the SOE based on five core domains: study limitations, consistency, directness, precision, and reporting bias. Our protocol contains details for these assessments and we only expand on our assessments of precision here to provide explanation for many of our decisions. We assessed *precision* (precise or imprecise) first on the basis of sample size. For continuous outcomes, more than 400 total enrolled patients are generally considered to offer precise data based on adequate power to detect a 0.2 standardized effect size;[60] we estimated that studies having as few as 200 patients could offer precise estimates of effect supporting a particular direction (but not magnitude) of effect. For binary data with our harm outcomes, the sufficiency of the sample size was based on event rates in the control group.[60] That is, when fewer than 5 percent of patients experienced the event we required more than 2000 patients to represent adequate power to detect a difference between groups. When sample size was considered adequate, we further assessed precision based on the magnitude of the effects represented by the effect estimate and limits of the credible/confidence intervals. For outcomes where thresholds of clinically significant values were found in the literature, or estimated using the study reports or by our clinical investigators, we downgraded the precision domain if the 95% CrI (or the 95% CI in cases where results were not combined) crossed both no difference (0 MD or 1.0 RR) and the threshold; if a 95% CrI was very wide we downgraded the imprecision domain twice. In other words, when a CrI/CI around an effect estimate was not statistically significant but included values that may be clinically significant for many patients, we cannot rule out the possibility of a benefit for this outcome and therefore rated down for precision.

We rated the body of evidence for each outcome and comparison using four SOE grades which indicate our level of confidence that the evidence reflects the true (direction of) effect for the major comparisons of interest:

High	**We are very confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.

Moderate	**We are moderately confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	**We have limited confidence that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	**We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome**. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Interpretations Throughout Report

We chose to use standard wording to describe how we interpreted the SOE and the magnitude of the effects for key outcomes;[61] our Key Points and tables of the strength of evidence (results chapter) and discussion relay these interpretations, while our Detailed Findings sections provide the exact fidnings regardless of their strength of evidence. For findings supported by high, moderate, low, and insufficient SOE (for which we similar confidence in the results) we use "will", "probably/likely", "may/appears to", and "not known" in our textual descriptions of the results. Related to magnitude of effects, when the evidence showed effects that would be considered by many patients and practitioners to be either clinically important or small, we use "increase/improve/decrease/worsen" (as suitable) or "increase/improve/decrease/worsen *slightly/a small extent*", respectively; when there appears to be no difference in effect, we use "makes little or no difference."

Applicability

We assessed the applicability of the findings with respect to our PICOTS elements. We summarized common features of the study populations and documented diagnoses. We considered patient ages, treatment histories, co-occurring diagnoses, and symptom severity reported in the included studies and the degree to which the populations studied reflect the target populations for practice.

Peer Review and Public Commentary

Apart from review by members of our TEP, experts in psychiatry, developmental and behavioral health, and statistics, and individuals representing stakeholder and user communities were invited to provide external peer review of this report; AHRQ and an EPC Associate Editor also provided comments. The draft report was posted on AHRQ's Effective Healthcare website for 4 weeks to elicit public comment. We addressed all reviewer comments, revising the text as appropriate, and documented everything in a disposition of comments report that will be made available 3 months after the Agency posts the final report on the AHRQ Effective Healthcare website.

Results

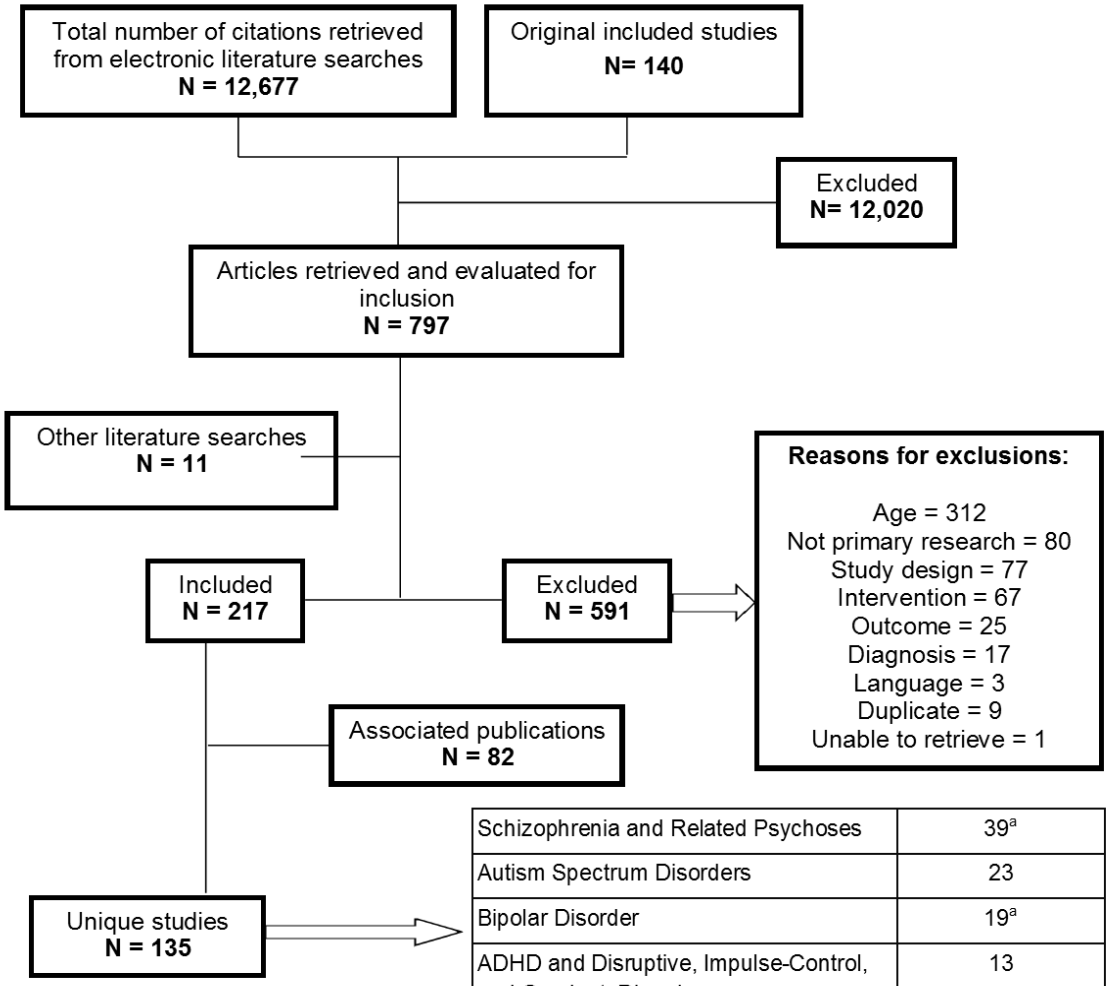
This chapter begins with a summary of our literature search and selection. A description of the characteristics and methodological quality of the studies follows. We then present the findings for intermediate and effectiveness outcomes (Key Question [KQ] 1) using separate sections for each condition category. Findings for harms across all conditions (KQ2) follow. Within each section we present a general description of the included studies followed by the findings for the various comparisons examined in the evidence base. Metagraphs and tables reporting the strength of evidence (SOE) for key outcomes are available within each applicable section. As per our methods, precision in effect estimates from meta-analyses (pair-wise and network) is reported using credible intervals (95% CrI), while that from single study results is indicated by a confidence interval (95% CI). Moreover, the wording used when interpreting findings is standardized with "will", "probably/likely", "may/appears to", and "not known" for cases of high, moderate, low, and insufficient SOE, respectively; the magnitude of effects are stated as "increase/improve/decrease/ worsen" (as suitable) or "increase/improve/decrease/worsen *slightly/to a small extent*", for effects that are probably clinically important for at least some patients or small, respectively. When there appears to be no difference in effect, we use "makes little or no difference". Throughout this report, a "significant" result refers to a finding that is statistically significant. We do not infer that statistically significant results are necessarily clinically meaningful.

Several appendixes provide supporting information to the findings presented in this section. Appendix C provides the quality assessment ratings by domain for each study. Appendix D contains detailed evidence tables describing the study, participant, and treatment characteristics, outcomes for each study. A table citing all associated publications is included in Appendix E, and a list of citations for the excluded and unobtained studies is available in Appendix F. Appendix G contains findings for our network meta-analysis and general adverse effects (AEs) that are not included in the main body of the report.

Literature Search and Screening

Our database searches identified 12,677 citations, and 11 additional records were identified from other sources including reference lists of systematic reviews and included studies, handsearching of journal websites, and our search of regulatory documents. In total, we included 57 new studies in addition to 78 from the original comparative effectiveness review (CER) (N = 135). Three previously included studies were excluded; two were reported in insufficient formats (e.g., abstract)[62, 63] and another had a large proportion of drugs within its first-generation antipsychotic (FGA) group not currently approved by the FDA.[64] We included several studies published during the timeframe of the original CER, largely reflecting our inclusion of pooled analyses of trial data and the expanded number of conditions of interest; some observational studies were previously excluded because of a relatively high proportion of patients having conditions within our newly included categories of depression, anxiety, and substance use disorders. Figure 2 describes the flow of literature through the screening process and the number of studies included by condition. Appendix F provides a complete list of articles excluded at the full-text screening stage, with reasons for exclusion.

Figure 2. Flow of literature through study search and selection process



Schizophrenia and Related Psychoses	39[a]
Autism Spectrum Disorders	23
Bipolar Disorder	19[a]
ADHD and Disruptive, Impulse-Control, and Conduct Disorders	13
Obsessive Compulsive Disorder	1
Depressive Disdorders	1
Eating Disorders	3
Tic Disorders	12
Behavioral Issues	2
Multiple/Mixed Conditions[b]	23
Total	**135**

ADHD = attention deficit hyperactivity disorder

[a] One study provided separate data for both bipolar disorder and schizophrenia; [b]Studies with populations having multiple primary diagnosis were included for key question 2 on harms only.

Description of Included Studies

A total of 135 unique studies met the eligibility criteria for this review. Evidence tables in Appendix D describe the characteristics of the studies. The studies were published between 1989 and 2016 (median = 2008 [interquartile range (IQR), 2004 to 2012]). Most of the studies (98%) were reported in peer-reviewed publications. Studies were conducted in the United States (52%), Europe (16%), Israel (3%), Canada (4%), other regions (13%), or in multiple countries (12%).

A total of 100 studies (74%) examined antipsychotics for intermediate and effectiveness outcomes (KQ 1). Harms (KQ 2) were reported in 126 studies (93%). Of the 135 studies, 89 (66%) were randomized controlled trials (RCTs) and 6 were nonrandomized controlled trials (NRCTs) (4%). Most of the trials had a parallel design and two treatment arms. Eight trials used a crossover design; 20 trials had three or four arms. A total of 40 observational studies were included.

The studies examined the following conditions: schizophrenia or schizophrenia-related psychosis (39 studies); autism spectrum disorders (ASD) (23 studies); bipolar disorder (19 studies); attention deficit hyperactivity disorder (ADHD) or disruptive, impulse control, or conduct disorders (DICD; 13 studies); obsessive-compulsive disorder (OCD) (1 study); depression (1 study); eating disorders (3 studies); tic disorders (12 studies); behavioral issues outside the context of a disorder (2 studies); and patients diagnosed with various psychiatric and behavioral conditions ("mixed conditions" contributing to harms data only; 23 studies). One study provided separate data for both pediatric bipolar disorder and schizophrenia.[65] Another study of first-episode psychotic mania included a mixed sample of patients initially diagnosed with bipolar or schizoaffective disorder; because the primary focus was on mania and considering the diagnostic instability in these conditions, clinicians suggested we included this study in the section on bipolar disorders.[66] None of the included studies exclusively examined anxiety disorders, posttraumatic stress disorder, or substance use disorder.

The number of enrolled/examined participants ranged from 8 to 4140 (median = 60; IQR, 30 to 119). The mean age of study participants ranged from 4 to 22 years (median, 13; IQR, 9.9.8 to 15.35). The mean age was lower than 12 years in 52 studies (39%). One hundred and one (75%) studies reported on followup durations of < 6 months, 10 reported on both short- and long-term followup, and 24 reported only on longer-term followup.

Overall, 113 studies provided one or more head-to-head comparisons of different FGAs or second-generation antipsychotics (SGAs) (Table 2). A total of 21 studies compared different doses of the same antipsychotic, and 56 studies compared one antipsychotic with placebo (risperidone N= 22, aripiprazole N = 10, olanzapine N = 6, quetiapine and ziprasidone N = 4, haloperidol N = 3, others N < 3).

Table 2. Head-to-head comparisons examined in the review

Comparison	Number of Studies	Comparison	Number of Studies
FGAs vs. FGAs	**2**	**SGAs vs. SGAs**	**84**
Haloperidol vs. pimozide	2	*Aripiprazole vs. olanzapine*	3
		Aripiprazole vs. paliperidone	1
FGAs vs. SGAs	**27**	*Aripiprazole vs. quetiapine*	3
Chlorpromazine vs olanzapine	1	*Aripiprazole vs. risperidone*	8
Haloperidol vs. aripiprazole	1	*Aripiprazole vs. various SGAs*	1
Haloperidol vs. clozapine	3	*Aripiprazole vs. ziprasidone*	3
Haloperidol vs. olanzapine	8	*Clozapine vs. olanzapine*	7
Haloperidol vs. risperidone	5	*Clozapine vs. quetiapine*	1
Molindone vs. olanzapine	1	*Clozapine vs. risperidone*	3
Molindone vs. risperidone	1	*Olanzapine vs. quetiapine*	11
Pimozide vs. aripiprazole	2	*Olanzapine vs. risperidone*	22
Pimozide vs. risperidone	2	*Olanzapine vs. ziprasidone*	3
Various FGAs vs. various SGAs	3	*Quetiapine vs. risperidone*	13
		Quetiapine vs. ziprasidone	2
		Risperidone vs various SGAs	2
		Risperidone vs. ziprasidone	1

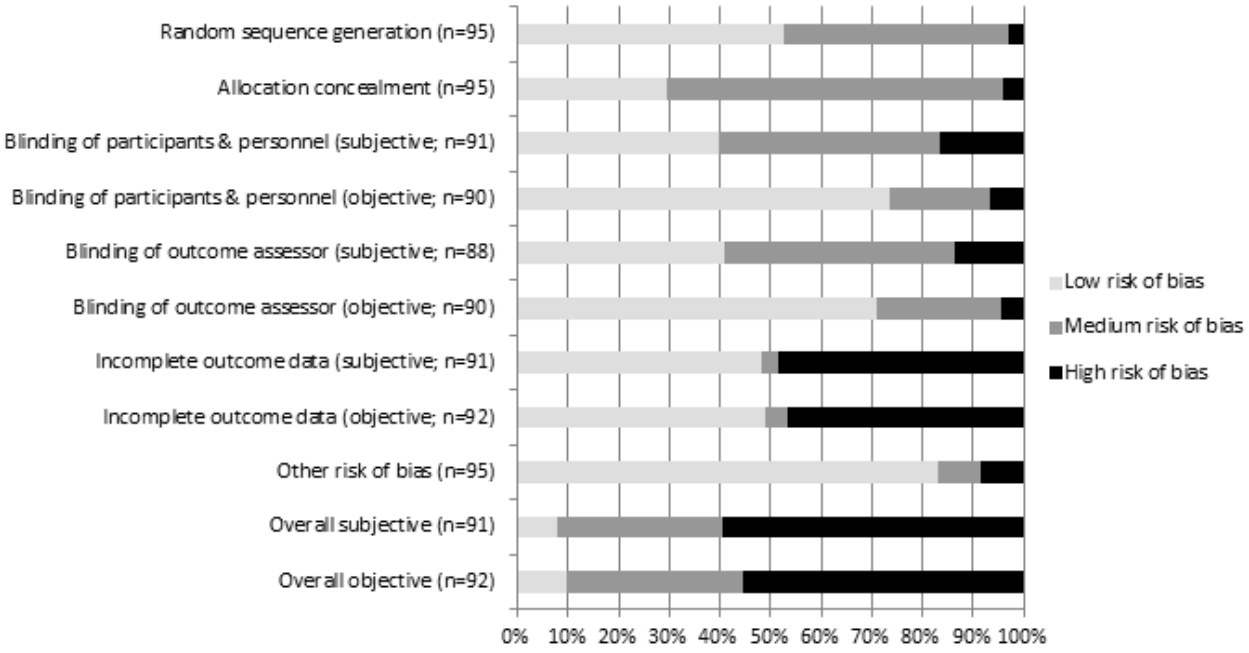
FGA = first-generation antipsychotic; SGA = second-generation antipsychotic

Methodological Quality of Included Studies

The methodological quality of each study was assessed by two independent reviewers and consensus was reached for final assessments. Figures 3 and 4 contain a summary of the quality assessments for trials and observational studies, respectively. The consensus ratings for each study and domain are presented in Appendix C, Tables C1 and C2.

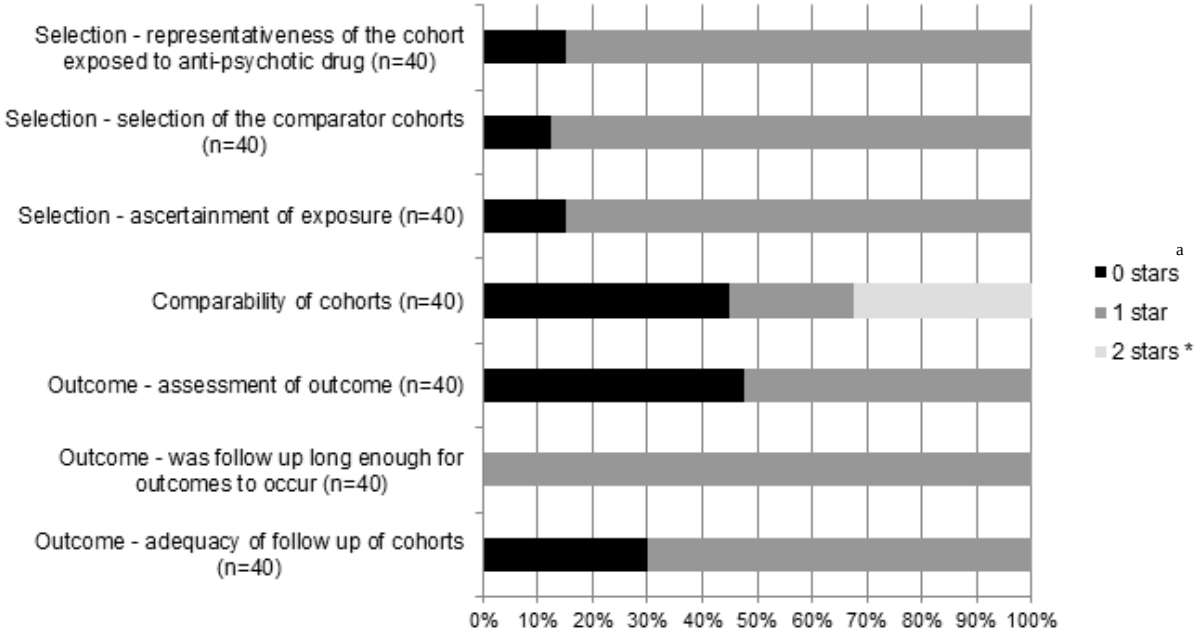
For subjective outcomes in trials, the overall ROB was rated as high for 60 percent; only eight were assessed as low ROB. The ROB reduced to a small extent for objective outcomes. The main contributor to ROB was incomplete outcome data, which has rated as high ROB when drop-out/incompletion rates were ≥ 30 percent, or when differences between study groups in numbers and reasons for withdrawal were considered substantial. Overall, the observational studies were of quite high quality; of 40 studies, 4 (10%) were rated as having poor quality/high ROB (3 stars out of 8), 12 (30%) as having moderate quality/medium ROB, and 24 (60%) as high quality/low ROB. Despite this, the observational studies are still considered of poorer quality (i.e., providing less validity) than the RCTs, because of their inability to completely account for confounding by patient characteristics. Almost half of the studies did not account in some way for variables of confounding considered potentially important (i.e., treatment history, duration/stage of illness).

Figure 3. Risk of bias summary for trials of first- and second-generation antipsychotics in children and young adults



n = number of studies

Figure 4. Summary of ratings of methodological quality for observational studies of first- and second-generation antipsychotics in children and young adults



n = number of studies

[a] The question on comparability of cohorts is the only one that has a possible score of 2 stars.

Key Question 1: Intermediate and Effectiveness Outcomes

This section reviews the evidence of the effect of antipsychotics on intermediate and effectiveness outcomes (KQ 1). For each condition of interest, we describe the studies that provided data for this review and present the results either within figures or narratively. Each section is organized by comparison, with head-to-head data preceding placebo comparisons.

Schizophrenia and Related Psychoses: Overview

Thirty-nine studies examined patients with schizophrenia and schizophrenia-related psychosis; 30 were trials [65, 67-95] and nine were observational studies.[96-104] Three publications were identified for studies which in the original CER only had unpublished data.[71, 72, 90] Tables 3 and 4 highlight key characteristics of the trials and observational studies, respectively. The tables include all studies for this condition, even though six studies only reported on harms and not any intermediate outcomes described in this section.[69, 89, 96, 97, 100, 103] Individual studies are presented in order of drug comparison, with head-to-head evidence preceding placebo comparisons. Several studies included both head-to-head comparisons and a placebo control; these studies are classified under the head-to-head category. Detailed evidence tables are available in Appendix D.

The average age of patients across the studies was 15.8 years (range 8.9-22). Sexes were fairly equally represented across the studies (60.1% male). Among the 22 studies that reported race/ethnicity, the majority (average 65.4%) of patients were white, with the exception of one study of African Americans.[78] Five studies [67, 68, 84, 101, 103] examined patients experiencing a first episode of psychosis; five other studies had a large proportion (>75%) of patients having their first episode.[70, 81, 82, 85, 97] Childhood- or early-onset schizophrenia was examined in eight studies.[77, 79-81, 83, 98, 100, 104] Two trials only enrolled patients at ultra-high risk (i.e., prodromal phase) for schizophrenia.[86, 93] Six studies enrolled patients with affective (e.g., presenting within primary diagnosis of bipolar disorder) and nonaffective (i.e., schizophrenia spectrum) psychosis;[67, 68, 82, 84, 91, 101] one study included patients with bipolar disorder (not specific to the presence of psychosis) or schizophrenia, although reported data separately for those with schizophrenia.[65] All other patients had a disorder along the schizophrenia spectrum. A large majority of studies excluded patients with substance-induced psychosis and/or mental retardation. Of 24 studies reporting on the proportion of patients who were antipsychotic-treatment naïve, the average percentage of patients who were naïve was 41 (range 0-100); six studies focused on first treatment[84, 86, 91, 93, 103, 104] (two of which studied the prodrome phase)[86, 93] and six focused on patients having prior exposure to antipsychotics.[70, 78, 80, 87, 90, 95]

Haloperidol was compared with various SGAs (clozapine, olanzapine, and risperidone) in five RCTs and four observational studies, molindone was compared with olanzapine and risperidone in one RCT, and one observational study compared a mixture of FGAs with SGAs. Eighteen RCTs and four observational studies compared SGAs. Of these, 13 studies compared different SGAs and nine compared two doses of the same SGA. Haloperidol was compared with placebo in one study. SGAs were compared with placebo in 10 studies. Most studies allowed for variable dosing—often adjusted by clinicians based on tolerability and response—although seven used a fixed dose of medication.[68, 70, 76, 88-90, 92] Studies not examining treatment naïve patients typically reported wash-out periods of between 1-3 weeks; one study was designed as a maintenance study whereby patients stabilized (duration not reported) on 10 to 30 mg/day of aripiprazole were randomized to maintenance on aripiprazole or discontinuation with replacement by placebo for up to 52 weeks.[95]

Most studies had treatment durations between 4 and 12 weeks; nine studies were 6 months or longer,[67, 81, 86, 93-95, 101, 102, 104] and four of these long-term studies reported both short- and long-term outcomes.[81, 86, 94, 95] The majority (70%) of the trials had high risk of bias; the most common source of potential bias was incomplete outcome data (i.e., ≥30% withdrawal or significant imbalance between groups for reasons for withdrawal), although several also failed to incorporate blinding of patients or providers. Three trials had low ROB.[68, 81, 92] Of the nine observational studies, three were in each of the high,[100, 101, 104] moderate,[97, 98, 102] and poor[96, 99, 103] quality categories.

Table 3. Characteristics of trials examining schizophrenia and related psychosis

First Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n), History of Treatment, Quality Rating
FGAs vs. SGAs			
Kumra, 1996[77] 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% / White: NR **G2:** 14.4±2.9 yr / Male: 50% / White: NR Comorbidities: NR	disorganized (10), paranoid (1), undifferentiated (10) History of treatment: 100% resistant to FGAs ROB: High (subjective), High (objective)
de Haan, 2003[70] RCT, 6 wk	**G1:** Haloperidol (12), 2.5 mg/day **G2:** Olanzapine (12), 7.5 mg/day	**G1:** 21.0±2.8 yr / Male: NR / White: NR **G2:** 21±2.3 yr / Male: NR / White: NR Comorbidities: NR	disorganized (6), paranoid (13), undifferentiated (5) History of treatment: 0% drug naïve ROB: High (subjective), High (objective)
Buchsbaum, 2007[91] RCT, 8 wk	**G1:** Haloperidol (7), up to 20 mg/day **G2:** Olanzapione (12), up to 20 mg/day	**G1:** 16.2±2.0yr / Male: 53% / White: NR **G2:** see group 1 Comorbidities: NR	schizophrenia (14), schizoaffective disorder (2), bipolar affective (4) History of treatment: 100% drug naïve ROB: Medium (subjective), NA (objective)
Sikich, 2004[82] RCT, 8 wk	**G1:** Haloperidol (15), 5±2 mg/day **G2:** Olanzapine (16), 12.3±3.5 mg/day **G3:** Risperidone (19), 4±1.2 mg/day	**G1:** 15.4±2.2 yr / Male: 53% / White: 73% **G2:** 14.6±3.1 yr / Male: 56% / White: 63% **G3:** 14.6±2.9 yr / Male: 68% / White: 47% Comorbidities: NR	affective disorders (24), schizophrenia spectrum (26) History of treatment: 26% drug naïve ROB: High (subjective), High (objective)

First Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n), History of Treatment, Quality Rating
Yen, 2004[87] 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 / White: NR **G2:** 20.7 yr / Male: 67% / White: NR Comorbidities: NR	schizophrenia (8) History of treatment: 0% drug naïve ROB: High (subjective), High (objective)
Sikich, 2008[81] RCT, 8 wk (44 wk extension)	**G1:** Molindone (41), 59.9±33.5 mg/kg **G2:** Olanzapine (36), 11.4±5 mg/day **G3:** Risperidone (42), 2.8±1.4 mg/day	**G1:** NR / Male: 58% / White: 70% **G2:** NR / Male: 71% / White: 60% **G3:** NR / Male: 66% / White: 61% Comorbidities: ADHD (22), affective disorder (19), anxiety disorder (21), ASD (5), DBD (16), learning disability (3), psychosis (10), SA (4)	schizoaffective disorder (26), schizophrenia (50) History of treatment: 33% drug naïve ROB: Low (subjective), Low (objective)
SGAs vs. SGAs			
Findling, 2015a[92] RCT, 8 wk	**G1:** Asenapine (106), 5mg bid **G2:** Asenapine (98), 2.5mg bid **G3:** Placebo (102)	**G1:** 15.4±1.5yr / Male: 63% / White: 52% **G2**: 15.2±1.5yr / Male: 63% / White: 55% **G3:** 15.4±1.4yr / Male: 61% / White: 56% Comorbidities: NRI	schizophrenia (306) History of treatment: 32% drug naïve ROB: Low (subjective), Low (objective)
Findling, 2008a[73] 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% / White: 54% **G2:** 15.4±1.4 yr / Male: 64% / White: 61% **G3:** 15.4 ±1.4 yr / Male: 61% / White: 64% Comorbidities: NR	schizophrenia (302) History of treatment: 26% drug naïve ROB: Medium (subjective), Medium (objective)
Kumra, 2008[78] RCT, 12 wk	**G1:** Clozapine (18), 403.1±201.8 mg/day **G2:** Olanzapine (21), 26.2±6.5 mg/day	**G1:** 15.8±2.2 yr / Male: 44% / White: 11% **G2:** 15.5±2.1 yr / Male: 62% / White: 29% Comorbidities: NR	schizoaffective disorder (14), schizophrenia (25) History of treatment: 100% resistant to ≥2 antipsychotic trials ROB: High (subjective), High (objective)

First Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n), History of Treatment, Quality Rating
Shaw, 2006[80] RCT, 8 wk	**G1:** Clozapine (12), 327±113 mg/day **G2:** Olanzapine (13), 18.1±4.3 mg/day	**G1:** 11.7±2.3 yr / Male: 67% / White: 58% **G2:** 12.8±2.4 yr / Male: 54% / White: 54% Comorbidities: ADHD/ODD/CD (7), anxiety disorders (7)	Childhood-onset schizophrenia (25) History of treatment: 100% resistant to ≥2 different antipsychotics ROB: Medium (subjective), Medium (objective)
Arango, 2009[67] 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% / White: 77% **G2:** 16.3±1.1 yr / Male: 79% / White: 88% Comorbidities: NR	BD (13), schizophrenia (17), other psychoses (20) History of treatment: 50% drug naïve ROB: High (subjective), High (objective)
Jensen, 2008[75] 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% / White: 50% **G2:** 14.8±2.3 yr / Male: 70% / White: 60% **G3:** 15.6±2.5 yr / Male: 80% / White: 70% Comorbidities: NR	psychotic disorder NOS (9), schizophrenia/ schizoaffective disorder (16), schizophreniform disorder (5) History of treatment: 77% drug naïve ROB: High (subjective), High (objective)
Mozes, 2006[79] 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 yr / Male: 42% / White: NR **G2:** 10.7±1.4 yr / Male: 39% / White: NR Comorbidities: ADHD (3), epilepsy (2), familial mediterranean fever (1), neurofibromatosis (1), OCD (3), tic disorder (1)	disorganized schizophrenia (7), paranoid schizophrenia (6), schizophreniform disorder (10), unspecified schizoprehenia (2) History of treatment: 96% drug naïve ROB: High (subjective), High (objective)

First Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n), History of Treatment, Quality Rating
van Bruggen, 2003[85] 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% / White: NR **G2:** 20.6±3 yr / Male: 85% / White: NR Comorbidities: NR	NR History of treatment: NR ROB: High (subjective), High (objective)
Crocq, 2007[69] NRCT, 12 wk Harms	**G1:** Olanzapine (16), 16.6±4.4 mg/day (oral disintegrating) **G2:** Olanzapine, (10) 18.0±4.2 mg/day (standard oral tablet) **G3:** Risperidone (26), 2.8±1.2 mg/day	**G1:** 16.5±1.7 yr / Male: 31.3% / White: 100% **G2:** 17.0±1.3yr / Male: 60% / White: 100% **G3:** 15.2±1.4 yr / Male: 57.7% / White: 100% Comorbidities: NR	schizophreniform disorder (52) History of treatment: 75% drug naïve ROB: NA (subjective), High (objective)
Singh, 2011[90] RCT, 6 wk	**G1:** Paliperidone ER (low) (54), 1.5 mg/day **G2:** Paliperidone ER (medium) (48), 3 (<51 kg), 6 (≥51 kg) **G3**: Paliperidone ER (high) (48), 6 (<51 kg), 12 (≥51 kg **G4:** Placebo (51)	**G1:** 15.1±1.5 yr / Male: 56% / White 65% **G2:** 15.3±1.6yr / Male: 65% / White71% **G3:** 15.5±1.6 yr / Male: 70% / White 68% **G4:** 15.7±1.4 yr / Male: 55% / White 69% Comorbidities: BD (0), MDD (0), MR (0), SUD (0), ASD (0), diabetes (0)	paranoid schizophrenia (143), other (58) History of treatment: 10% drug naïve ROB: High (subjective), Medium (objective)
Johnson & Johnson Pharmaceutical Research and Development , 2011[89] RCT, 1 wk Harms	**G1:** Paliperidone ER (8), 0.086 mg/kg/day **G2:** Paliperidone ER (9), 0.129 mg/kg/day **G3:** Paliperidone ER (8), 0.171 mg/kg/day	**All groups:** 14.6±2.2yr / Male: 72% / White: 56% Comorbidities: NR	schizophreniform disorder (8), schizoaffective disorder (7), paranoid (6), undifferentiated (3), disorganized (1) History of treatment: NR ROB: High (subjective), High (objective)
Savitz, 2015[94] RCT, 8 wk (18 wk extension)	**G1:** Paliperidone ER (112), 6.75±1.8 mg/day **G2:** Aripiprazole (114), 11.6±3.0 mg/day	**G1:** 15.2±1.5yr / Male: 65% / White: 75% **G2:** 15.4±1.5yr / Male: 67% / White: 77% Comorbidities: NR	schizophrenia (226) History of treatment: 10.6% drug naïve ROB: Medium (subjective), Medium (objective)

First Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n), History of Treatment, Quality Rating
Berger, 2008[68] RCT, 4 wk	**G1:** Quetiapine (low) (69), 200 mg/day **G2:** Quetiapine (high) (72), 400 mg/day	**G1:** 19.7±2.6 yr / Male: 71% / White: NR **G2:** 19±2.9 yr / Male: 64% / White: NR Comorbidities: SA (58)	nonaffective psychosis (95), affective psychosis (31) History of treatment: 33% drug naïve ROB: Low (subjective), Low (objective)
Findling, 2012a[72] 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 yr / Male: 59% / White: 62% **G2:** 15.5±1.3 yr / Male: 60% / White: 60% **G3:** 15.3±1.4 yr / Male: 58% / White: 63% Comorbidities: NR	disorganized (16), paranoid (155), residual (1), undifferentiated (48) History of treatment: NR ROB: High (subjective), High (objective)
Swadi, 2010[84] RCT, 6 wk	**G1:** Quetiapine (11), 607 mg/day **G2:** Risperidone (11), 2.9 mg/day	**G1:** NR / Male: 55% / White: NR **G2:** NR / Male: 64% / White: NR Comorbidities: NR	first onset psychotic disorder or a mood disorder with psychotic features History of treatment: 100% drug naïve ROB: High (subjective), High (objective)
Haas, 2009a[74] RCT, 8 wk	**G1:** Risperidone (low) (132), 0.4 mg/day **G2:** Risperidone (high) (125), 4 mg/day	**G1:** 15.6±1.3 yr / Male: 61% / White: 85% **G2:** 15.7±1.3 yr / Male: 52% / White: 85% Comorbidities: NR	catatonic (7), disorganized (19), paranoid (175), residual (7), undifferentiated (49) History of treatment: NR ROB: High (subjective), High (objective)
Haas, 2009b[88] RCT, 6 wk	**G1:** Risperidone, 1–3 mg/day (54) **G2:** Risperidone, 4–6 mg/day (50) **G3:** Placebo (54)	**G1:** 15.7±1.3 yr / Male: 55% / White: 60% **G2:** 15.6±1.3 yr / Male: 73% / White: 47% **G3:** 15.5±1.4 yr / Male: 65% / White: 50% Comorbidities: NR	paranoid (110), undifferentiated (33), disorganized (15), catatonic (1), residual (1) History of treatment: NR ROB: High (subjective), High (objective)

First Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n), History of Treatment, Quality Rating
DelBello, 2008[65] RCT, 3 wk	**G1:** Ziprasidone (low) (8), target: 80 mg/day **G2:** Ziprasidone (high) (9), target: 160 mg/day	**G1:** 14.4±2.3 yr / Male: 52% / White: NR **G2:** 14.7±2.0 yr / Male: 75% / White: NR Comorbidities: NR	bipolar I disorder (46), schizophrenia or schizoaffective disorder (17) History of treatment: 25% drug naïve ROB: High (subjective), High (objective)
FGAs vs. Placebo			
Spencer, 1994[83] RCT (cross-over), 8 wk	**G1:** Haloperidol (16),[a] 2 mg/day **G2:** Placebo (16)[a]	**All groups:** NR (5-11 yr) / Male: NR / White: NR Comorbidities: Prior diagnoses: atypical PDD (5), atypical psychosis (3), borderline personality disorder (1), CD (1), pica (1)	schizophrenia History of treatment: NR ROB: Medium (subjective), Medium (objective)
SGAs vs. Placebo			
NCT01149655[95] RCT, 52 wk maintenance study	**G1:** Aripiprazole (98), 10-30 mg/day **G2:** Placebo (48)	**G1:** 15.3±1.3yr / Male: 63.3% / White: NR **G2:** 15.6±1.1yr / Male: 70.8% / White: NR Comorbidities: NR	schizophrenia (146) History of treatment: 0% drug naïve; 100% stabilized on aripiprazole ROB: High (subjective), High (objective)
McGorry, 2013[93] RCT, 52 wk	**G1:** Cognitive therapy and risperidone (43), up to 2mg/day **G2:** Cognitive therapy and placebo (44)	**G1:** 17.6±3.0yr / Male: 35% / White: NR **G2:** 18.0±2.7yr / Male: 39% / White: NR Comorbidities: NR	ultra-high risk (87) History of treatment: 100% drug naïve ROB: High (subjective), High (objective)
Kryzhanovskaya, 2009[76] RCT, 6 wk	**G1:** Olanzapine (72), 11.1 mg/day **G2:** Placebo (35)	**G1:** 16.1±1.3 yr / Male: 71% / White: 72% **G2:** 16.3±1.6 yr / Male: 69% / White: 71% Comorbidities: NR	NR History of treatment: 24% drug naïve ROB: High (subjective), High (objective)
Woods, 2003[86] 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% / White: 74% **G2:** 17.2±4 yr / Male: 62% / White: 59% Comorbidities: SA (marijuana (16), other (11))	prodromal psychosis (60) History of treatment: 90% drug naïve ROB: High (subjective), High (objective)

First Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n), History of Treatment, Quality Rating
Findling, 2013a[71] RCT, 6 wk	**G1:** Ziprasidone (193), 67.8 mg/day (<45 kg), target 120–160 mg/day (≥45 kg) **G2:** Placebo (90)	**G1:** 15.3 yr / Male: 56% / White: 59% **G2:** 15.4 yr / Male: 69% / White: 67% Comorbidities: NR	schizophrenia (284), paranoid 65% History of treatment: NR ROB: High (subjective), High (objective)

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

[a]All patients received each of the treatments in this cross-over study.

Table 4. Characteristics of observational studies examining schizophrenia and related psychosis

First Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
FGAs vs. SGAs			
Cianchetti, 2011[102] Prospective cohort, 3-11 yr	All groups: 47 enrolled at 3 yr; 41 at 5 yr (analysis accounts for medication not subjects) **G1**: Haloperidol: (29) mean months treatment 9.4±14.3 **G2**: Risperidone: (33) mean months of treatment 19.6±17.9 **G3**: Olanzapine: (12) mean months of treatment 11.7±9.2 **G4**: Clozapine: (28) mean months of treatment 31.5±916.3	**All groups**: 15.5 (range 10-17) / Males: 45% / White: 100% Comorbidities: NR	schizophrenia (29), schizoaffective disorder (18) History of treatment: 100% drug naive 5/8 stars
Wudarsky, 1999[100] Prospective cohort, 6 wk Harms	**G1:** Haloperidol (15), 15.3±8.2 mg/day **G2:** Clozapine (22), 325.4±211 mg/day **G3:** Olanzapine (10), 17.0±3.5 mg/day	**G1:** 13.7±1.5 yr / Male: 60% / White NR **G2**: 14.7±2.3 yr / Male: 73% / White: NR **G3**: 14.2±2.9 yr / Male: 70% / White: NR Comorbidities: NR	childhood-onset schizophrenia (32), psychosis NOS (3) History of treatment: NR 7/8 stars
Gothelf, 2002[96] Prospective cohort, 4 wk Harms	**G1:** Haloperidol (10), 6.5±3.5 mg/day **G2:** Olanzapine (10), 14.0±4.1 mg/day	G1: 17.0±1.6yr / Male: 100% / White NR G2: 17.0±1.6yr / Male: 100% / White: NR Comorbidities: NR	schizophrenia (100) History of treatment: 5% drug naïve ROB: 3/8 stars

First Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
Ratzoni, 2002[99] 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 yr / Male: 63% / White: NR **G2:** 17±1.6 yr / Male: 67% / White: NR **G3:** 17.1±2.1 yr / Male: 57% / White: NR Comorbidities: NR	CD (2), schizoaffective disorder (2), schizophrenia (46) History of treatment: 18% drug naïve 3/8 stars
Hrdlicka, 2009[97] Retrospective cohort, 6 wk Harms	**G1:** Haloperidol 6.8±1.1, Perphenazine 12±6.9, Sulpiride 450±409.3 mg/day **G2**: Clozapine 247.5±118, Olanzapine 15±6.1, Risperidone 2.7±1.3, Ziprasidone 80±0 mg/day	**G1**: 15.8±1.6yr (all) / Male: 48% (all) / White: NR **G2**: see above Comorbidities: NR	schizophrenia (56), schizoaffective disorder (15), other schizophrenic disorders (38) History of treatment: NR 5/8 stars
SGAs vs. SGAs			
Olfson, 2012[104] Retrospective cohort, 6 mo	**G1:** Risperidone (805), dose NR **G2**: Olanzapine (382), dose NR **G3:** Quetiapine (260), dose NR **G4:** Aripiprazole (173), dose NR **G5**: Ziprasidone (125), dose NR	**All groups:** Age NR (13-17 yr) **G1**: Males: 62% / White: 38% **G2**: Males: 69% / White: 38% **G3:** Males: 52% / White: 42% **G4**: Males: 55% / White: 42% **G5**: Males: 57% / White: 44% (White includes American Indians and Pacific Islanders) Comorbidities: DBD (27-35%), SUD (0-4%), MDD (24-32%), anxiety (8-13%), PDD/MR (0-5%)	schizophrenia (850), schizophreniform (170), schizoaffective (680) History of treatment: 100% drug naïve 7/8 stars
O'Donoghue, 2014[103] Prospective cohort, 31 wk Harms	**G1**: Olanzapine & quetiapine (16), dose NR **G2**: Risperidone (20), dose NR	All groups: 15.9±1.2yr / Males: 58% / White: NR Comorbidities: NR	schizophrenia (32), schizoaffective disorder (2), schizophreniform (2) History of treatment: 100% drug naïve 3/8 stars
Castro-Fornieles, 2007[101] Prospective cohort, 24 mo	**G1:** Risperidone (31), 2.8±1.2mg/day **G2:** Quetiapine (15), 626.8±526 mg/day **G3:** Olanzapine (14), 11.7±7.0 mg/day	**G1**: 15.1±2.1yr / Male: 68% / White: 86% (all) **G2:** 16.4±1.1yr / Male: 67% / White: NR **G3:** 15.7±1.2yr / Male: 71% / White: NR Comorbidities: NR	psychosis NOS (28), schizophrenia (49), MDD with psychotic symptoms (6), BD (manic with psychosis)(14) (All patients in cohort, n=110) History of treatment: 49.1% drug naïve 6/8 stars

First Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
Kumra, 1998[98] Controlled before-after, 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% / White: NR **G2:** 15.3±2.3 yr / Male: 50% / White: NR Comorbidities: NR	disorganized (11), paranoid (3), undifferentiated (9) History of treatment: NR 5/8 stars

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

Schizophrenia and Related Psychoses: Intermediate Outcomes

Twenty-eight studies reported on intermediate outcomes for use of FGAs and SGAs in schizophrenia and related psychosis. A summary of the key findings, and for observations on subgroup effects, by comparison is provided below. Table 5 contains the findings and SOE assessments for the key outcomes assessed as having at least low SOE; the reason for each SOE decision is included in the table footnotes. A detailed analysis for all comparisons follows.

Key Points

- **FGAs versus SGAs** (six RCTs[70, 77, 81, 82, 87, 91] and one prospective cohort study[99]): There may be little or no difference between FGAs and SGAs for negative symptoms, positive symptoms, response rates, and global impressions of illness severity. We did not have enough confidence to make any conclusions for depression symptoms or global impressions of improvement, because of high ROB and imprecision (e.g., confidence intervals including clinically meaningful estimates despite nonsignificant findings). ***Observations on between-study subgroup effects***: (a) clozapine may have greater relative efficacy over other SGAs in comparisons with FGAs,[77] (b) SGAs appear to have greater benefit over haloperidol than over molindone.
- **Olanzapine versus risperidone** (five RCTs[75, 79, 81, 82, 85] and one prospective cohort[99]): There may be little or no difference between olanzapine and risperidone for negative and positive symptoms, response rates, and global impressions of severity. The SOE was insufficient for global functioning due to high ROB, unknown consistency, and imprecision from a small sample. Possible subgroup effects based on medication dose or treatment history appear conflicting
- **Other SGA-SGA comparisons**: The comparative effects are not known for several outcomes in comparisons between aripiprazole and paliperidone[94], clozapine and olanzapine[78, 80, 98], olanzapine and quetiapine[74], and quetiapine and risperidone[75,84] (all insufficient SOE). ***Observations on between-study subgroup effects***: clozapine's apparent benefit (though not statistically significant) over olanzapine was diminished when high-dose olanzapine was the comparator;[78] the relative efficacy of clozapine and olanzapine is limited to studies of treatment resistance.
- **SGAs—Dose comparisons** (aripiprazole,[73] asenapine,[92] paliperidone,[90] quetiapine,[68, 72] risperidone,[74, 88] and ziprasidone[65]): There may be little or no difference between low-

and high-dose asenapine for response rates or global impressions of severity in the short-term. Between high and low doses of quetiapine, there appears to be little or no difference for their effects on negative symptoms or response rates; there is probably little or no difference between the doses for global impressions of severity or functioning. The comparative effects between different doses of other SGAs are not known.

- **Haloperidol versus placebo** (one RCT[83]): Findings from studies in this review's time period were rated as insufficient SOE.
- **SGAs versus placebo** (aripiprazole,[73, 95] asenapine,[92] olanzapine,[76, 86] paliperidone,[90] quetiapine,[72] risperidone,[88] and ziprasidone[71]): Compared with placebo, SGAs probably decrease slightly negative and positive symptoms, increase response rates, and improve slightly global impressions of improvement, severity, and functioning. SGAs may make little or no difference for depression symptoms. The only outcome which appeared to result in a substantial magnitude of clinical benefit was response rates (RR, 1.52; 95% CrI, 1.15 to 2.02); the small magnitude for other outcomes appears to be influenced by a substantial placebo effect in many cases. ***Observations on between-study subgroup effects***: (a) maintenance, rather than acute, treatment with aripiprazole did not appear to affect findings; (b) olanzapine may be similarly effective in treatment of schizophrenia and the prodrome phase of psychosis.

Table 5. Strength of evidence for schizophrenia and related psychosis: Key intermediate outcomes having at least low strength of evidence

Comparison	Outcome (N Studies, N Patients)	Findings,[a] Studies, Measurement Tool With Range of Values, if Applicable	Strength of Evidence; Conclusions
SGAs vs. FGAs	Negative symptoms (RCTs: 5, 217)	4 RCTs:[77, 81, 82, 87] SMD, 0.0; 95% CrI, -0.55 to 0.50 1 RCT:[91] No difference (p value NR)	Low; may make little or no difference[b]
	Positive symptoms (RCTs: 5, 217)	4 RCTs:[77, 81, 82, 87] SMD, -0.25; 95% CrI, -0.92 to 0.29 1 RCT:[91] No difference (p value NR)	Low; may make little or no difference[b]
	Response rates (RCTs: 2, 188)	RR, 1.06; 95% CrI, 0.53 to 2.25[81, 82]	Low; may make little or no difference [b]
	Global impressions of severity using CGI-S[d] (RCTs: 2, 124)	MD, -0.21; 95% CrI, -1.19 to 0.67[81, 82]	Low; may make little or no difference [c]
Olanzapine vs. risperidone	Negative symptoms (RCTs: 5, 198)	4 RCTs:[79, 81, 82, 85] SMD, -0.09; 95% CrI, -0.76 to 0.53 1 RCT:[75] No difference p = 0.19	Low; may make little or no difference [b]
	Positive symptoms (RCTs: 5, 198)	4 RCTs:[79, 81, 82, 85] SMD, -0.11; 95% CrI, -0.76 to 0.40 1 RCT:[75] No difference p = 0.10	Low; may make little or no difference [b]
	Response rates (RCTs: 4, 156)	RR, 1.01; 95% CrI, 0.51 to 1.9[75, 79, 81, 82]	Low; may make little or no difference [b]
	Global impressions of severity using CGI-S (RCTs: 3, 131)	1 RCT:[82] MD, 0.30; 95% CI, -0.53 to 1.13 1 RCT:[81] MD, 0.30; 95% CI, -0.41 to 1.01 1 RCT:[75] No difference p = 0.33	Low; may make little or no difference [c]
Asenapine high vs. low dose	Response rate (RCTs: 1, 204)	1 RCT:[92] RR, 1.00; 95% CI, 0.75 to 1.32	Low; may make little or no difference
	Global impressions of severity using CGI-S (RCTs: 1, 204)	1 RCT:[92] MD, 0.20; 95% CI, -0.05 to 0.45	Low; may make little or no difference
Quetiapine high vs. low dose	Negative symptoms (RCTs: 2, 238)	1 RCT:[68] MD, 1.6; 95% CI, -4.79 to 7.99 (SANS; range 0-25) 1 RCT:[72] MD, 0.14; 95% CI, -1.81 to 2.09 (PANSS; range 7-49)	Low; may make little or no difference [b]
	Response rates (RCTs: 2, 273)	1 RCT:[68] RR, 0.73; 95% CI, 0.41 to 1.29 1 RCT:[72] RR, 1.05; 95% CI, 0.69 to 1.60	Low; may make little or no difference [b]
	Global impressions of severity using CGI-S (RCTs: 2, 238)	1 RCT:[68]MD, 0.00; 95% CI, -0.35 to 0.35 1 RCT:[72]MD, -0.13; 95% CI, -0.47 to 0.21	Moderate; probably makes little or no difference [e]
	Global impressions of functioning (RCTs: 2, 238)	1 RCT:[68] MD, -3.5; 95% CI, -8.37 to 1.37 (GAF; range 1-100) 1 RCT:[72] MD, 1.9; 95% CI, -2.35 to 6.15 (C-GAS; range 1-100)	Moderate; probably makes little or no difference [e]
SGAs vs. placebo	Negative symptoms (RCTs: 9, 1788)	MD, -1.31; 95% CrI, -2.05 to -0.58 (PANSS Negative; range 7-49)[71-73, 76, 86, 88, 90, 92, 95]	Moderate; SGAs probably decrease slightly[e]
	Positive symptoms (RCTs: 9, 1788)	MD, -2.20; 95% CrI, -2.98 to -1.48 (PANSS Positive; range 7-49)[71-73, 76, 86, 88, 90, 92, 95]	Moderate; SGAs probably decrease slightly[e]
	Depression symptoms (RCTs: 2, 420)	1 RCT:[90] MD, -0.59; 95% CI, -1.46 to 0.28 1 RCT:[72] MD, -0.59; 95% CI, -1.45 to 0.27 (PANSS Depression)	Low; may make little or no difference [e]
	Response rates (RCTs: 5, 993)	RR, 1.52; 95% CrI, 1.15 to 2.02[72, 76, 88, 90, 92]	Moderate; SGAs probably increase[e]
	Global impressions of improvement using CGI-I (RCTs: 6, 1202)	MD, -0.54; 95% CrI, -1.07 to -0.14[71-73, 76, 88, 95]	Moderate; SGAs probably improve slightly[e]

Comparison	Outcome (N Studies, N Patients)	Findings,[a] Studies, Measurement Tool With Range of Values, if Applicable	Strength of Evidence; Conclusions
	Global impressions of severity using CGI-S (RCTs: 9, 1788)	MD, -0.36; 95% CrI, -0.51 to -0.22[71-73, 76, 86, 88, 90, 92, 95]	Moderate; SGAs probably improve slightly SGAs[e]
	Global impressions of functioning (RCTs: 7, 1339)	MD, 4.15; 95% CrI, 2.03 to 6.59 (C-GAS; range 0-100)[71-73, 86, 88, 90, 95]	Moderate; SGAs probably improve slightly[e]

C-GAS = Global Assessment Scale for Children; CGI-I = Clinical Global Impressions of Improvement; CGI-S = Clinical Global Impressions of Severity; CI = confidence interval; CrI = credible interval (used with Bayesian meta-analysis); FGA = first-generation antipsychotic; GAF = Global Assessment of Functioning; MD = mean difference; N = number; NR = not reported; PANSS; Positive and Negative Syndrome Scale; RCT: randomized controlled trial; ROB = risk of bias; RR = risk ratio; SANS = Scale for the Assessment of Negative Symptoms; SGA = second-generation antipsychotics; SMD = standardized mean difference

[a] When the findings are not representative of the total number of studies identified in the outcome column, we included the number of studies for each finding; we did not pool data from 1 or 2 studies so these results are always presented separately. All values except Response and Global Impressions of Functioning are favorable for group 1 (G1) when there is a negative effect estimate; the larger the magnitude of the number the larger the effect. SMDs provide results in standard deviation units, and are used when the results from different measurement tools are combined in meta-analysis; as a general rule, 0.2 represents a small effect size, 0.5 a moderate one, and 0.8 a large one.

[b] Downgraded for ROB and imprecision, because credible interval includes a clinically significant value (e.g., SMD $\geq \pm 0.50$, RR ≤ 0.75 or ≥ 1.25, CGI-I or CGI-S $\geq \pm 2$ points [0-7 point scales]) such that we could not rule out benefit even though effect estimate appears to be of no difference.

[c] Downgraded for ROB and imprecision because of small sample size, typically < 200 patients in total.

[d] CGI-S and CGI-I scores range from 0-6.

[e] Downgraded for ROB.

Detailed Analysis

This section is organized by comparison, beginning with head-to-head evidence (FGAs vs. SGAs and SGAs vs. SGAs) and followed by placebo comparisons for FGAs and SGAs.

FGAs Versus SGAs

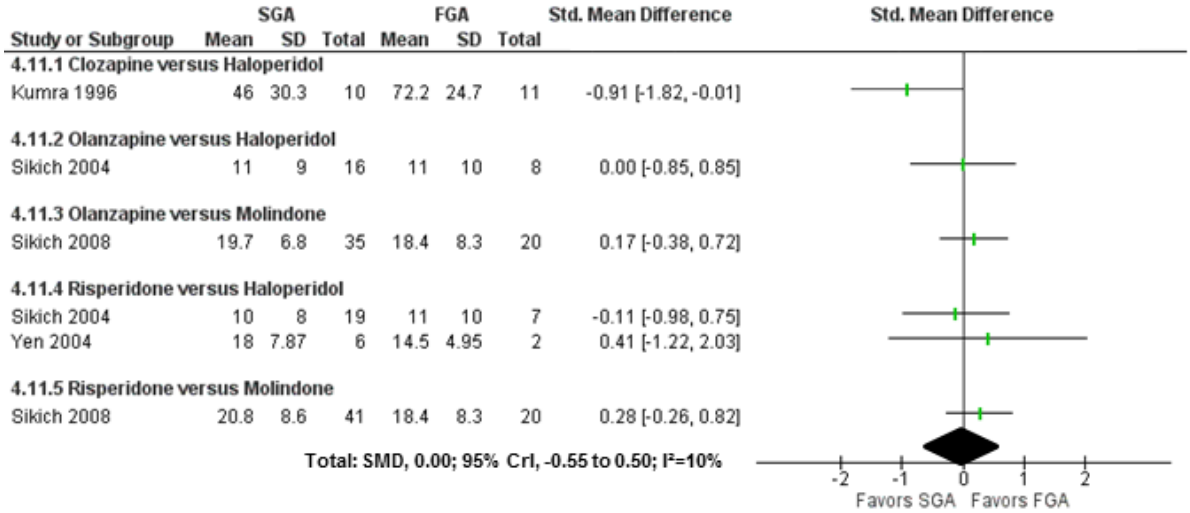
Seven studies provided data on intermediate outcomes for the following FGA versus SGA comparisons: haloperidol versus clozapine,[77] haloperidol versus olanzapine,[70, 82, 91, 99] haloperidol versus risperidone,[82, 87, 99] molindone versus olanzapine,[81] and molindone versus risperidone.[81] The comparisons between SGAs and molindone from one study[81] were not included in the original CER because this drug was not available in the United States at that time. Average treatment duration was 10 weeks (range 6 to 19.2 weeks). The average age of the patients was 17.5 years, including one study enrolling eight young adults.[87] In total, 299 patients were enrolled in the trials. Most patients had a diagnosis of schizophrenia; two studies enrolled some patients having schizoaffective disorder,[81, 99] and another enrolled patients (45%) having psychoses associated with affective disorders.[82]

Meta-Analyses Comparing FGAs Versus SGAs

We performed meta-analysis when three or more studies (or comparisons within studies) reported on the same outcome. Meta-analyses were conducted to compare FGAs and SGAs for the short-term core symptoms of negative symptoms and positive symptoms. They were also conducted for short-term nonspecific symptoms—captured by the Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS) total, response rates, and rates of discontinuation for lack of efficacy—and for global impressions of improvement and severity (Clinical Global Impressions of Improvement [CGI-I] and Severity [CGI-S]).

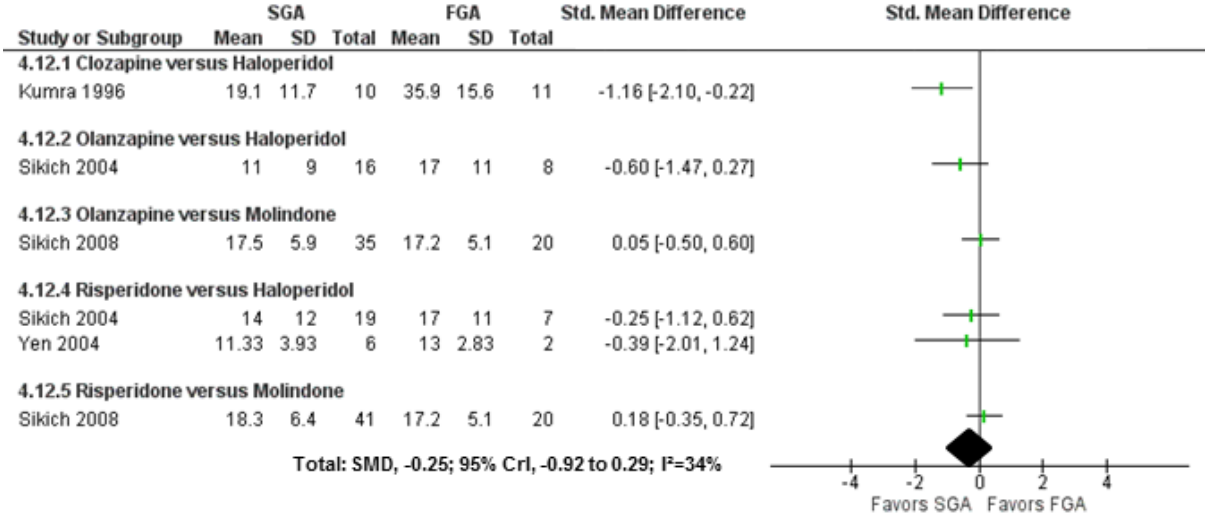
Short-term core symptoms. Two meta-analyses of four studies found no significant differences between SGAs and FGAs on the negative (SMD, 0.0; 95% CrI, -0.55 to 0.50) or positive (SMD, -0.25; 95% CrI, -0.92 to 0.29) symptom scores of the PANSS, CPRS, and Scale for the Assessment of Negative Symptoms (SANS) (Figures 5 and 6).[77, 81, 82, 87] Findings of no significant differences between groups in studies not used in the meta-analysis agree with the results.[91, 99] Clozapine was more effective than haloperidol for these symptoms in the one small study of treatment-resistant patients.[77]

Figure 5. FGAs versus SGAs on negative symptoms in schizophrenia and related psychosis



CrI = credible interval; FGA = first-generation antipsychotic; SD = standard deviation; SGA = second-generation antipsychotic: SMD = standardized mean difference

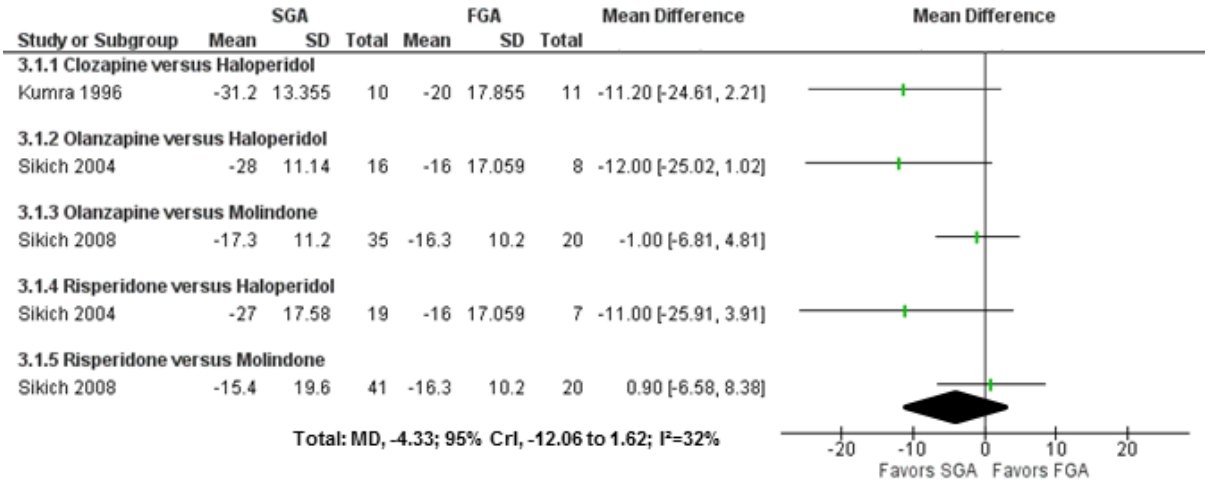
Figure 6. FGAs versus SGAs on positive symptoms in schizophrenia and related psychosis



CrI = credible interval; FGA = first-generation antipsychotic; SD = standard deviation; SGA = second-generation antipsychotic: SMD = standardized mean difference

Short-term nonspecific symptoms. A meta-analysis of three studies providing data for five comparisons found no significant difference between SGAs and FGAs for overall psychiatric symptoms as measured by the BPRS total score (MD, -4.33; 95% CrI, -12.06 to 1.62) (Figure 7).[77, 81, 82] The authors of one study did not report data for use in any meta-analysis; no significant difference was found between groups in the total symptom score on the BPRS scale.[91] The relative effect of SGAs for this outcome appears greater in comparisons with haloperidol than with molindone.

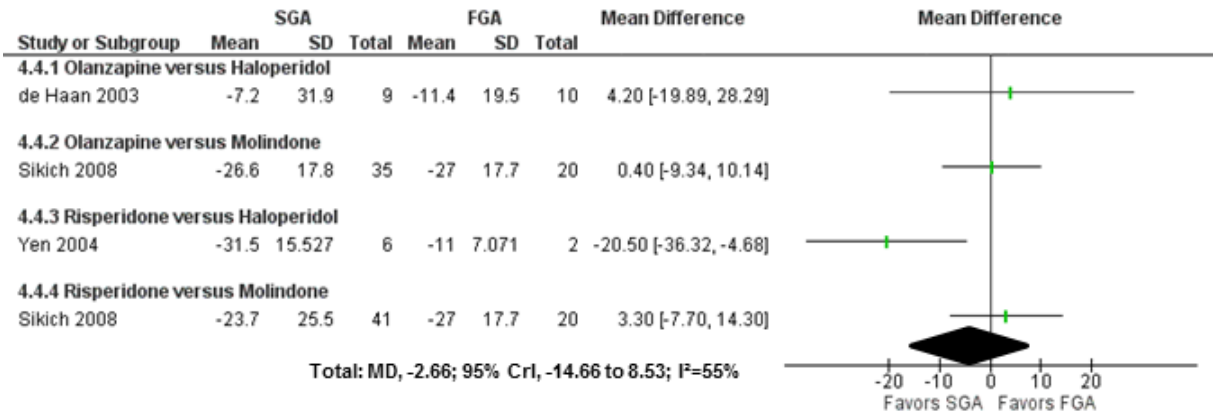
Figure 7. FGAs versus SGAs for psychiatric symptoms on BPRS in schizophrenia and related psychosis



BPRS = Brief Psychiatric Rating Scale; CrI = credible interval; FGA = first-generation antipsychotic; MD = mean difference; SD = standard deviation; SGA = second-generation antipsychotic

Three RCTs provided data for a meta-analysis on the efficacy of FGAs versus SGAs on overall schizophrenia symptoms as measured by the PANSS total score (Figure 8).[70, 81, 87] There was no significant difference between groups (MD, -2.66; 95% CrI, -14.66 to 8.53). The patients in the studies evaluating haloperidol appeared to be quite similar in terms of age and clinical characteristics; the dose of haloperidol in the study of de Haan et al.[70] (2.5 mg/day) was lower than that used by Yen et al.[87] (11.2 mg/day), but showed a relatively greater response. The difference may be explained by the difference in SGA. Results of no difference for this outcome were also found in the observational study not used in the meta-analysis.[99]

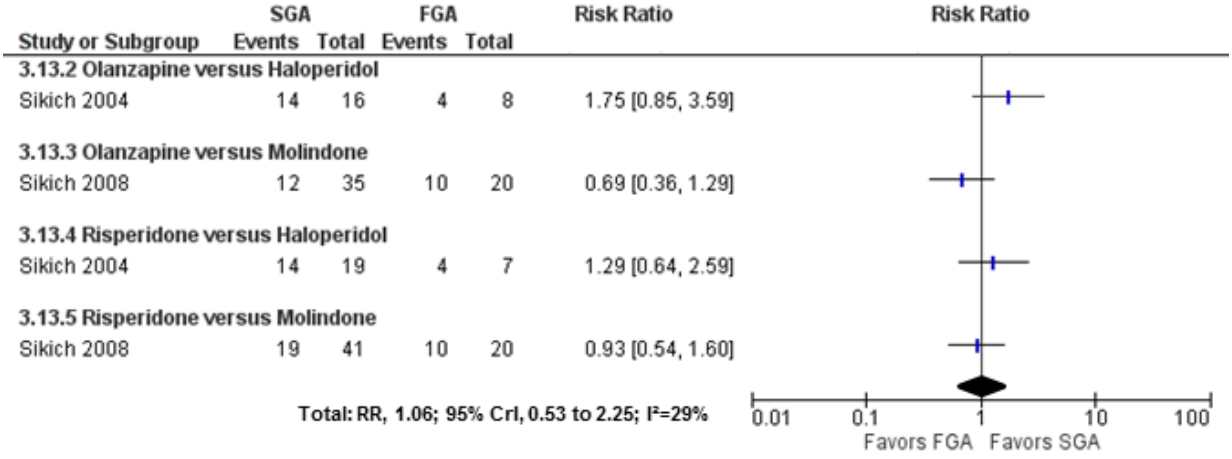
Figure 8. FGAs versus SGAs for schizophrenia symptoms using PANSS total score in schizophrenia and related psychosis



PANSS = Positive and Negative Syndrome Scale; CrI = credible interval; FGA = first-generation antipsychotic; MD = mean difference; SD = standard deviation; SGA = second-generation antipsychotic

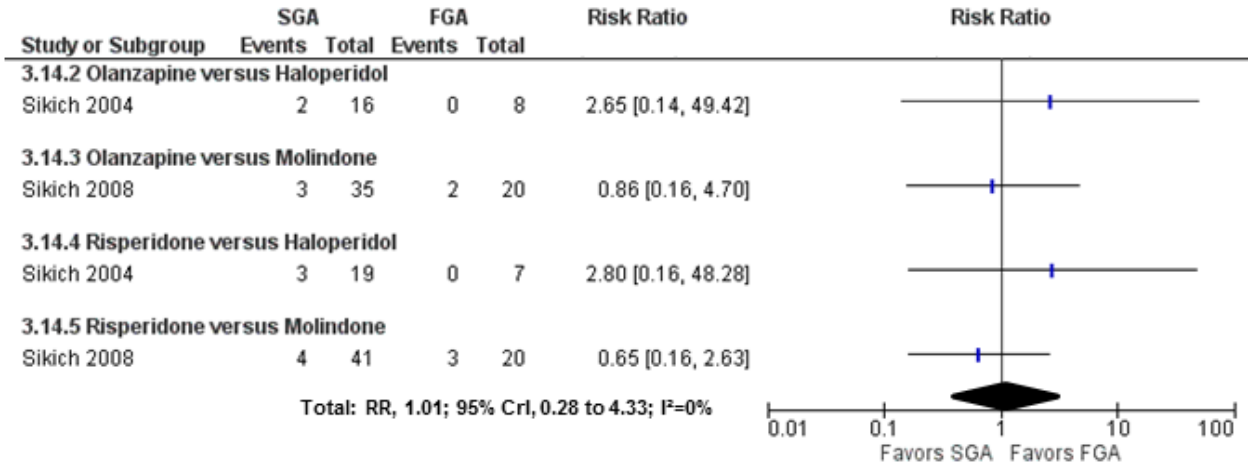
A meta-analysis was performed using data from four comparisons in two trials comparing response rates for SGAs and FGAs (Figure 9).[81, 82] No difference was found (RR, 1.10; 95% CrI, 0.53 to 2.27). Another meta-analysis pooled data on discontinuations due to lack of efficacy from the same two trials, and also found no difference (RR, 0.99; 95% CrI, 0.31 to 4.01) (Figure 10).

Figure 9. FGAs versus SGAs for response rates in schizophrenia and related psychosis



CrI = credible interval; FGA = first-generation antipsychotic; RR = risk ratio; SGA = second-generation antipsychotic

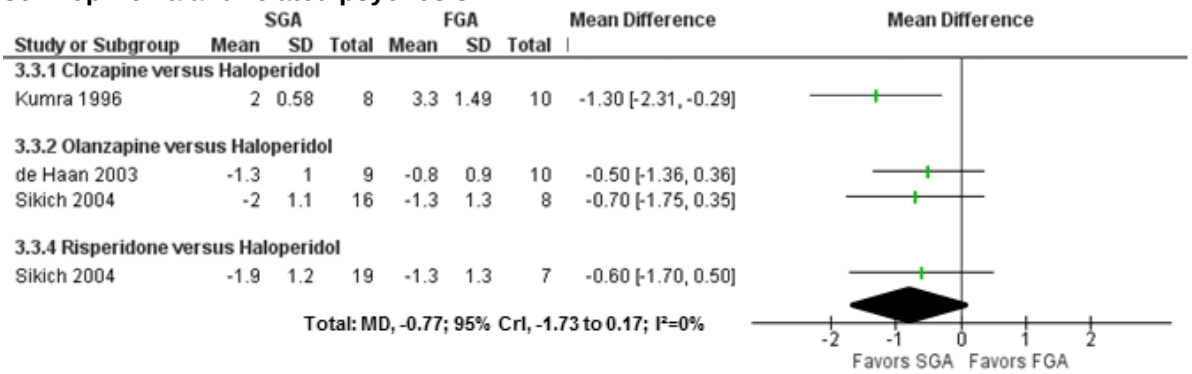
Figure 10. FGAs versus SGAs for discontinuation due to lack of efficacy in schizophrenia and related psychosis



CrI = credible interval; FGA = first-generation antipsychotic; RR = risk ratio; SGA = second-generation antipsychotic

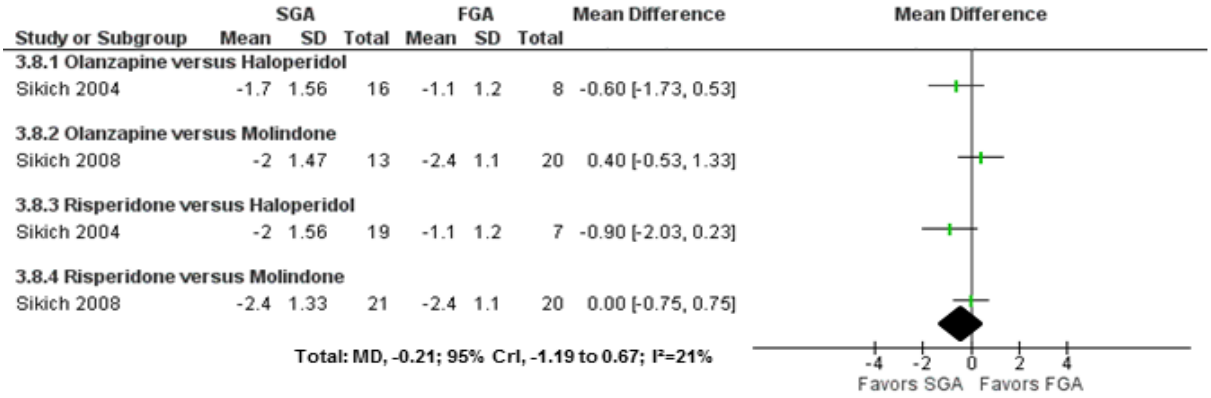
Short-term global impressions. Three RCTs provided data for a meta-analysis on the efficacy of FGAs versus SGAs on global impressions of improvement using the CGI–I (Figure 11).[70, 77, 82] The pooled estimate was not significant for any difference (MD, -0.77; 95% CrI, -1.73 to 0.17). Two RCTs with four comparisons provided data for a meta-analysis on the efficacy of FGAs versus SGAs on global impressions of severity using the CGI–S (Figure 12).[81, 82] No difference between SGAs and FGAs was found for this outcome (MD, -0.21; 95% CrI, -1.19 to 0.67).

Figure 11. FGAs versus SGAs for global impressions of improvement using CGI–I in schizophrenia and related psychosis



CGI–I = Clinical Global Impressions–Improvement; CrI = credible interval; FGA = first-generation antipsychotic; MD = mean difference; SD = standard deviation; SGA = second-generation antipsychotic

Figure 12. FGAs versus SGAs for global impressions of severity using CGI–S in schizophrenia and related psychosis

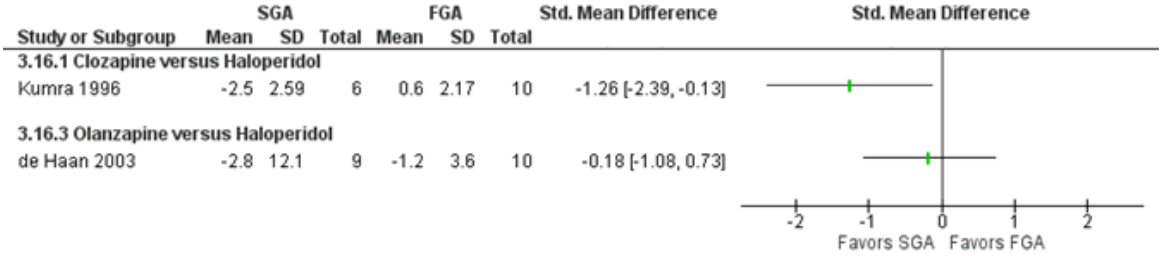


CGI–S = Clinical Global Impressions–Severity; CrI = credible interval; FGA = first-generation antipsychotic; MD = mean difference; SD = standard deviation; SGA = second-generation antipsychotic

Additional Findings

Four studies reported on outcomes for which we did not perform meta-analysis.[70, 77, 81, 82] Two studies reported on SGAs versus haloperidol for depression symptoms as measured by the Montgomery-Åsperg Depression Rating Scale[70] and the BPRS[77] (Figure 13). Clozapine had a favorable effect over haloperidol in the study of treatment-resistance conducted by Kumra et al.[77]

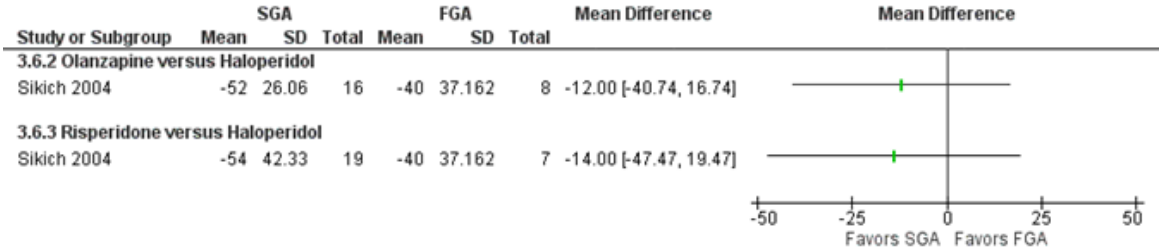
Figure 13. FGAs versus SGAs on depression symptoms in schizophrenia and related psychosis



FGA = first-generation antipsychotic; SD = standard deviation; SGA = second-generation antipsychotic

Two comparisons within one study assessed the relative efficacy for psychiatric symptoms between two SGAs, olanzapine and risperidone, and haloperidol using the CPRS.[82] No difference was found between SGAs and haloperidol for this outcome (Figure 14).

Figure 14. FGAs versus SGAs for psychiatric symptoms using CPRS total score in schizophrenia and related psychosis



CPRS = Conner's Parent Rating Scale; FGA = first-generation antipsychotic; SD = standard deviation; SGA = second-generation antipsychotic

Exploratory analyses in one trial showed olanzapine to produce a shorter time to response (1.6±1.3 vs. 2.4±1.3 weeks; $p < 0.045$ using multiple treatment comparisons) than haloperidol.[82] There were improvements for both SGAs (olanzapine and risperidone) and molindone (range 32 to 47 percent) in functional assessment using the Children and Adolescent Functional Assessment Scale, but no differences were found between groups (p values not reported).[81]

Observations on Between-Study Subgroup Effects

Clozapine appears to have greater relative efficacy over other SGAs in comparisons with FGAs. This is particularly noteworthy when considering the dose of haloperidol in the study examining clozapine [77] was considerably higher than in the other studies (16 mg/day vs. 2.5[70] to 11.2[87] mg/day) comparing other SGAs to haloperidol.

From the results of two studies having similar patient populations (in terms of illness severity and treatment history) comparing SGAs olanzapine and risperidone with haloperidol[82] and molindone,[81] it appears that these SGAs have less relative benefit over molindone; this finding may be in part explained by the lower doses of SGAs prescribed in the study of molindone than those evaluating haloperidol (olanzapine 11.4 vs. 12.3 mg/day; risperidone 2.8 vs 4.0 mg/day).

SGAs Versus SGAs

Fifteen RCTs and two observational studies compared SGAs in terms of intermediate outcomes. Of these, ten studies compared different SGAs and eight compared two doses of the same SGA. Depending on the number of studies within a comparison reporting on an outcome, findings are either presented narratively or in metagraphs with or without results from meta-analyses which were conducted when data was available for three or more studies.

Aripiprazole Versus Paliperidone

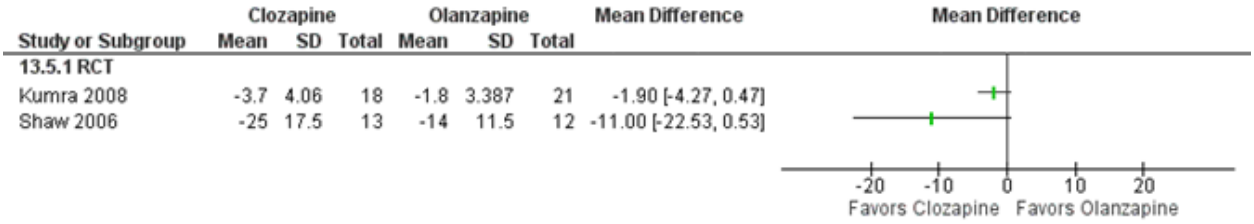
An RCT with an 8-week acute phase and 18-week extension phase compared once-daily paliperidone extended release with aripiprazole.[94] At 8 weeks, both groups had a similar reduction in the primary outcome of overall schizophrenia symptoms (PANSS total reduced by 19 points). There was no difference between groups for other outcomes including negative and positive symptoms, rates of response and remission, and global impressions of severity.

Clozapine Versus Olanzapine

Three studies (N = 88) compared clozapine with olanzapine for short-term core symptoms, nonspecific symptoms, and global impressions in treatment-resistant schizophrenia.[78, 80, 98] The duration of the studies were 6,[98] 8,[80] and 12[78] weeks. Patients were on average 14.1 years of age.

Short-term core symptoms. Two RCTs provided data on negative symptoms, measured using the SANS (Figure 15).[78, 80] Although clozapine appeared favorable, neither study found a significant difference between the two SGAs on improvement in negative symptoms. Positive symptoms were measured by one study, with no difference between groups at study endpoint ($p = 0.38$).[80] An observational study reported that its clozapine group showed a greater change from baseline for negative and positive symptoms; however, statistical comparisons between the groups were not reported.[98]

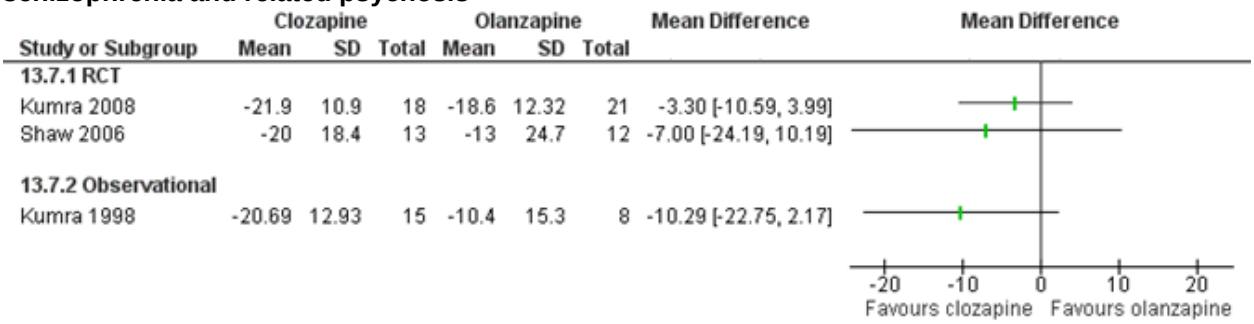
Figure 15. Clozapine versus olanzapine for negative symptoms on SANS in schizophrenia and related psychosis



SANS = Scale for the Assessment of Negative Symptoms; SD = standard deviation; RCT = randomized controlled trial

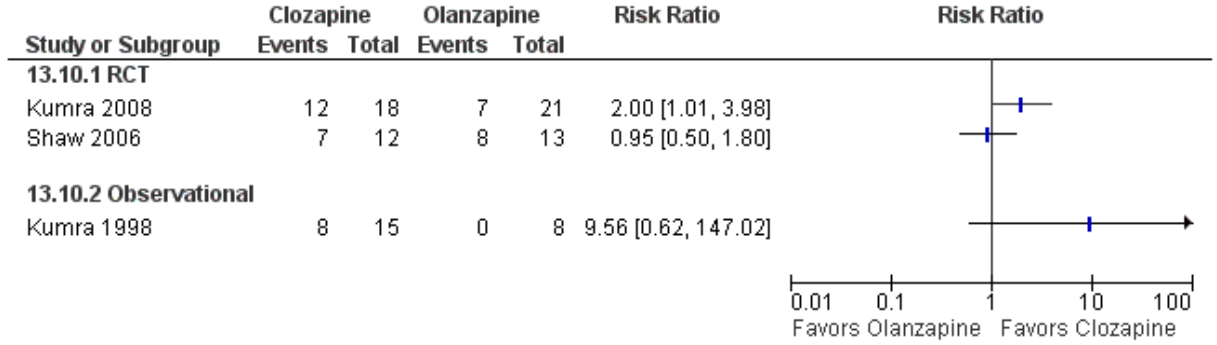
Short-term nonspecific symptoms. All three studies comparing clozapine with olanzapine reported on nonspecific symptom reduction for overall psychiatric symptoms (BPRS) and for response rates (Figures 16 and 17).[78, 80, 98] No significant differences between the drugs were found when using the BPRS (p = 0.38,[78] 0.42,[80] and 0.11[98]). Kumra et al.[78] found clozapine favorable for response rates, but the other two studies did not.

Figure 16. Clozapine versus olanzapine on overall psychiatric symptoms using the BPRS in schizophrenia and related psychosis



BPRS = Brief Psychiatric Rating Scale; RCT = randomized controlled trial; SD = standard deviation

Figure 17. Clozapine versus olanzapine for response rates in schizophrenia and related psychosis

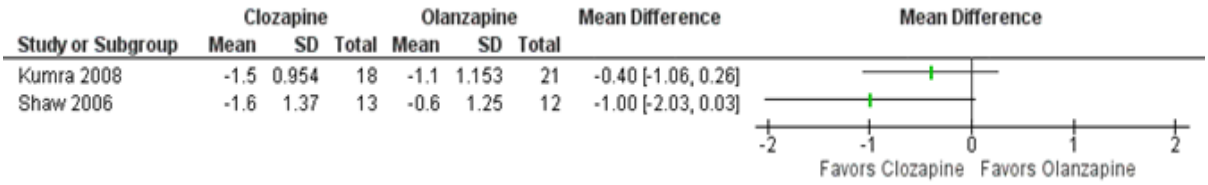


RCT = randomized controlled trial

Short-term global impressions. In terms of global impressions of severity, the two trials reported data on CGI–S scores (Figure 18).[78, 80] The mean between-group effects favored clozapine for reduction in symptom severity, however neither finding was statistically significant (p = 0.24[78] and 0.06[80]). Global assessment of functioning (Global Assessment Scale for Children

[C-GAS]) showed improvement of approximately 20 points for both groups in one study without any differences between drugs (p = 0.91).[78]

Figure 18. Clozapine versus olanzapine on global impressions of severity (CGI–S) in schizophrenia and related psychosis



CGI–S = Clinical Global Impressions–Severity; SD = standard deviation

Observations on between-study subgroup effects. The relatively small effects in the study by Kumra et al.[78] may stem from the higher dose of olanzapine in this study than that reported by Shaw et al. (26.3 mg/day vs. 18.1 mg/day, respectively). When comparing clozapine to olanzapine, the effect sizes for all outcomes are numerically (if not statistically) favorable for clozapine despite a relatively high dose of olanzapine (up to 26.2 mg/day). Common for this drug, this study was targeting treatment-resistant children and it is unclear if clozapine would have even higher relative effect when used in other contexts.

Olanzapine Versus Quetiapine

One 12-week RCT compared olanzapine with quetiapine for intermediate outcomes.[75] On intention-to-treat analysis, no differences were found between groups for negative (p = 0.1) and positive (p = 0.19) symptoms, overall schizophrenia symptoms (p = 0.06), response rates (p = 0.65), and global impressions of severity (p = 0.33) and functioning (p = 0.24).

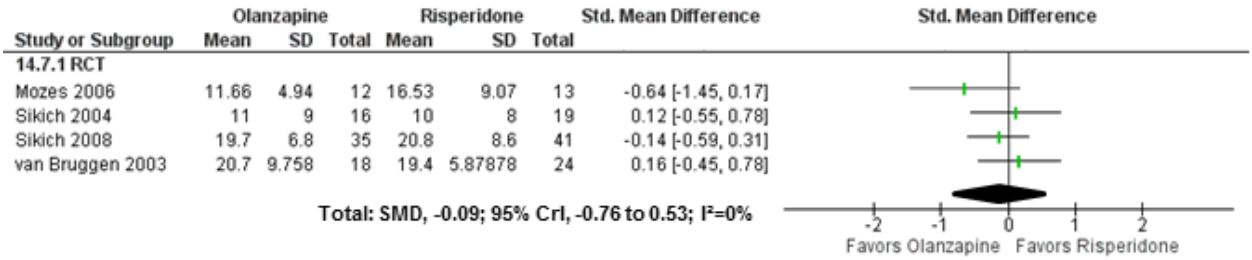
Olanzapine Versus Risperidone

Olanzapine was compared with risperidone in six studies (N = 242) having durations between 7 and 12 weeks.[75, 79, 81, 82, 85, 99] Patients were on average 15.8 years of age. Most studies assessed adolescents with disorders in the schizophrenia spectrum; one study enrolled patients with affective disorders who experienced psychotic symptoms (45%).[82]

Meta-analyses for olanzapine versus risperidone. Four studies provided data for meta-analyses on intermediate outcomes. Data from the RCT by Jensen et al.[75] were only used in two of the meta-analysis.

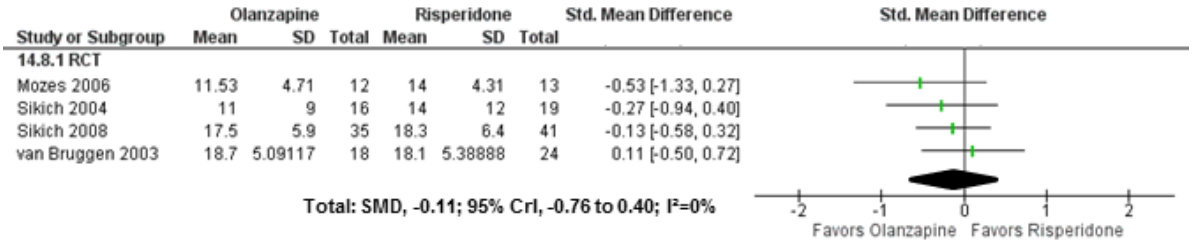
***Short-term core symptoms*.** Two meta-analyses were conducted for negative and positive symptoms; SMDs were generated for these outcomes using data from PANSS and CPRS measures (Figures 19 and 20).[79, 81, 82, 85] Results found no difference between olanzapine and risperidone for these outcomes (negative symptoms: SMD, -0.09; 95% CrI, -0.76 to 0.53 and positive symptoms: SMD, -0.11; 95% CrI, -0.76 to 0.40). The results from the studies not used in the meta-analysis were also of no difference.[75, 99]

Figure 19. Olanzapine versus risperidone for negative symptoms in schizophrenia and related psychosis



CrI = credible interval; RCT = randomized controlled trial; SD = standard deviation; SMD = standardized mean difference

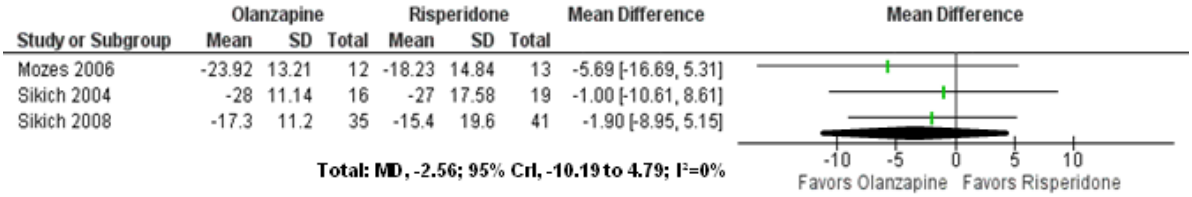
Figure 20. Olanzapine versus risperidone for positive symptoms in schizophrenia and related psychosis



CrI = credible interval; RCT = randomized controlled trial; SD = standard deviation; SMD = standardized mean difference

Short-term nonspecific symptoms. Three studies[79, 81, 82] comparing olanzapine with risperidone reported data for psychiatric symptoms using the BPRS total score (Figure 21). The meta-analysis showed no significant difference between the two SGAs (MD, -2.56; 95% CrI, -10.19 to 4.79).

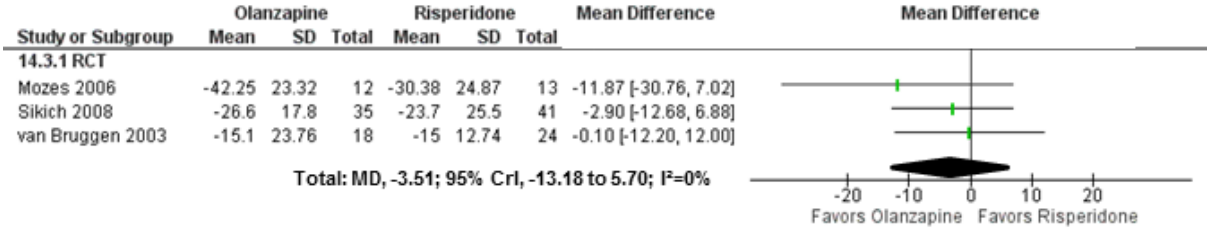
Figure 21. Olanzapine versus risperidone for psychiatric symptoms on BPRS in schizophrenia and related psychosis



BPRS = Brief Psychiatric Rating Scale; CrI = credible interval; MD = mean difference; SD = standard deviation

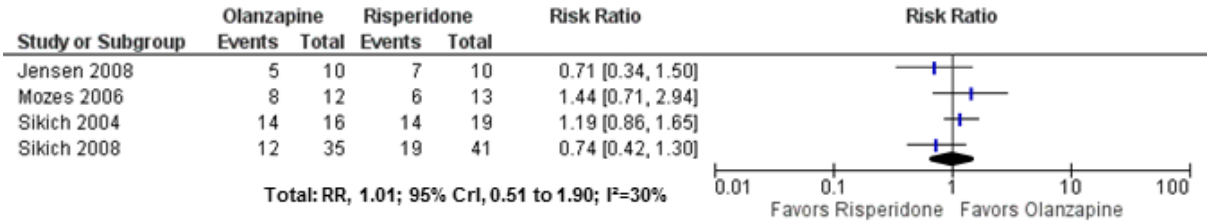
Three meta-analyses were generated for outcomes of schizophrenia symptoms (PANSS total score), response rates, and discontinuation due to lack of efficacy (Figures 22-24). There were no differences between these SGAs for these nonspecific outcomes. Data from the RCT by Jensen et al.[75] was not sufficient for adding to the meta-analysis on PANSS total score; this study found risperidone numerically but not statistically favorable to olanzapine (p = 0.06). An observational study[99] also found no difference between olanzapine and risperidone groups (p = 0.14).

Figure 22. Olanzapine versus risperidone for schizophrenia symptoms on PANSS total score in schizophrenia and related psychosis



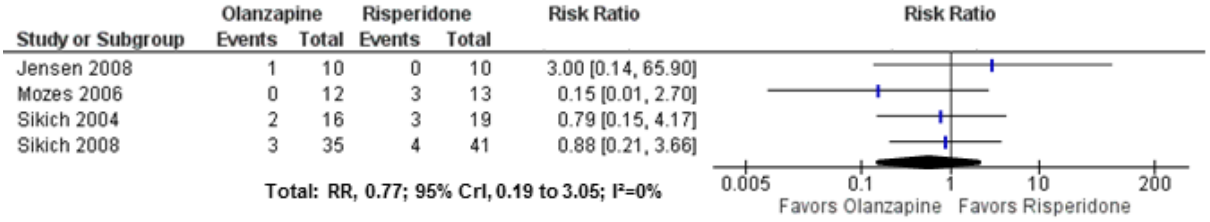
CrI = credible interval; MD = mean difference; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SD = standard deviation

Figure 23. Olanzapine versus risperidone for response rates in schizophrenia and related psychosis



CrI = credible interval; RR = risk ratio

Figure 24. Olanzapine versus risperidone for discontinuation for lack of efficacy in schizophrenia and related psychosis

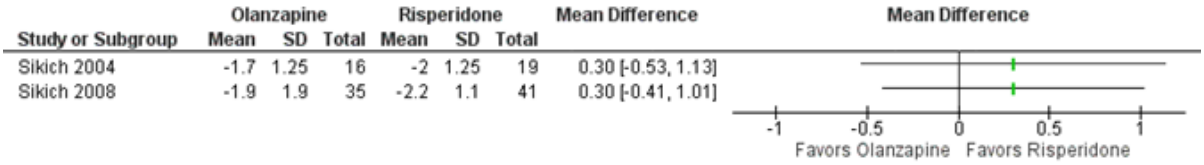


CrI = credible interval; RR = risk ratio

Additional findings. One RCT found no difference between olanzapine and risperidone for overall psychiatric symptoms using the CPRS (p = 0.86).[82] There was no difference between groups in one RCT for outcomes of medication adherence and remission.[85] Nonadherence did not differ between the two treatment groups in the observational study.[99]

Two RCTs provided scores for global impressions of severity using the CGI–S score (Figure 25).[81, 82] Both studies found no difference between olanzapine and risperidone. Jensen et al.[75] reported the proportion of patients who attained a certain CGI–S threshold instead of the change scores; the results of this study showed no difference between drugs. Global impressions of functioning, measured by C-GAS, did not differ by groups at study end point in the studies of Mozes et al. (p = 0.44),[79] and Jensen et al. (p = 0.24).[75]

Figure 25. Olanzapine versus risperidone for global severity using CGI–S in schizophrenia and related psychosis



CGI–S = Clinical Global Impressions–Severity; SD = standard deviation

Observations on between-study subgroup effects. Possible influences of treatment effect based on dose or treatment history appear conflicting. The study by Mozes et al.[79] appears to be an outlier favoring olanzapine; although the dose of olanzapine was relatively low in this study (8.2 mg/day), 96 percent of the patient population was treatment naïve. A trend favoring olanzapine for treatment naïve patients was not found by the study by Jensen et al.[75] having a largely treatment naïve (77%) population, in which PANSS total scores and response rates numerically favored risperidone (PANSS, p = 0.06; response rates, 70% vs. 50%).

Quetiapine Versus Risperidone

Two RCTs compared quetiapine with risperidone for intermediate outcomes in mainly (>75%) treatment naïve patient populations. A 6-week RCT[84] (N = 22) found no significant differences between the risperidone and quetiapine groups for the primary outcomes of 30 percent or more reduction in PANSS (p = 0.66), BPRS (p = 1.0), CGI-S (p = 1.0), or the Hamilton Depression Rating Scale (HAM-D; p = 0.64). Some benefit favoring risperidone over quetiapine was found when comparing percentage of patients improving by at least one level on the CGI-S (72.7% vs. 45.5%), or by at least 10 points on the HAM-D (50% vs. 20%). No significant difference was found between the groups for medication adherence.

A 12-week RCT comparing olanzapine, quetiapine, and risperidone found no differences between groups for negative (p = 0.1) and positive (p = 0.19) symptoms, overall schizophrenia symptoms (p = 0.06), response rates (p = 0.65), and global impressions of severity (p = 0.33) and functioning (p = 0.24).[75]

Data by treatment group was not provided by one study[75] to enable presentation of findings for most outcomes from both studies in metagraphs. Results for response rates and for discontinuation due to lack of efficacy are presented in Figures 26 and 27.

Figure 26. Quetiapine versus risperidone on response rates in schizophrenia and related psychosis

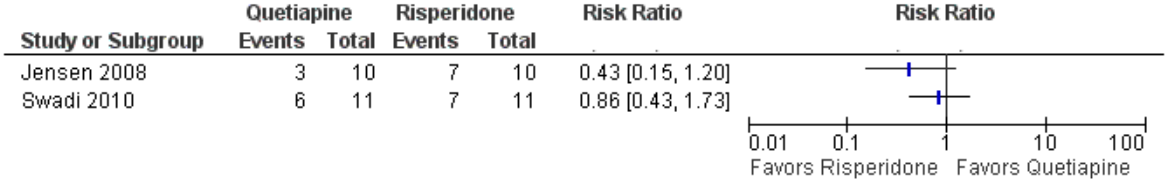
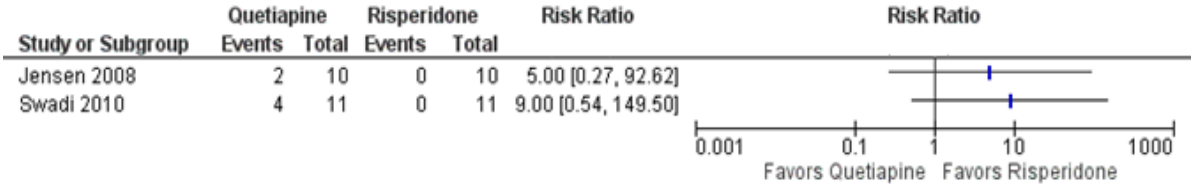


Figure 27. Quetiapine versus risperidone on discontinuation due to lack of efficacy in schizophrenia and related psychosis



Aripiprazole—Low- versus high-dose. A 6-week RCT enrolled 302 adolescents with schizophrenia to compare low- or high-dose aripiprazole with placebo.[73] Twenty-six percent of patients were treatment naïve. No significant differences occurred between the low- and high-dose aripiprazole groups for negative ($p = 0.72$), positive ($p = 0.56$), and general psychotic symptoms ($p = 0.37$), and for global impression of improvement ($p = 0.16$), severity ($p = 0.48$), and functioning ($p = 0.96$).

Asenapine—Low versus high-dose. An 8-week RCT (N = 306) compared asenapine 2.5 mg twice daily, asenapine 5.0 mg twice daily, and placebo.[92] Approximately 68 percent had previous antipsychotic exposure, although none had been on clozapine. There was no difference between the two doses of asenapine for the PANSS total score ($p = 0.83$), CGI-S scores ($p = 0.2$), or response based on ≥30 percent reduction in PANSS total score ($p = 0.99$).

Paliperidone–Low- versus medium- versus high-dose. Singh et al.[90] compared three doses of extended-release paliperidone and placebo in a 6-week RCT (N = 201). There were no differences between doses for negative symptoms ($p > 0.10$). Compared with the low dose group, the medium, but not high, dose achieved greater reduction in positive symptoms (3 points on PANSS; $p = 0.01$) and overall schizophrenia symptoms (7.5 points on PANSS; $p = 0.03$), and a higher response rate (64.6% vs. 38.9%; $p = 0.001$). Both medium and high doses reduced illness severity (1 point on CGI-S; $p < 0.001$ for medium and $p = 0.02$ for high) and improved global functioning (> 4 points on C-GAS; $p < 0.05$) compared with the low dose.

Quetiapine–Low- versus high-dose. Two RCTs compared two doses of quetiapine. Berger et al.[67] examined 141 drug-naïve patients with first-episode psychosis in a 4-week RCT comparing quetiapine doses of 200 and 400 mg/day. There was no difference between groups noted for negative symptoms ($p = 0.62$), overall psychiatric symptoms ($p = 0.15$), or global impressions of severity ($p = 1.00$) or functioning ($p = 0.12$).

A 6-week placebo-controlled RCT (N = 222) examined the efficacy of low- (400 mg/day) and high-dose (800 mg/day) quetiapine.[71] No significant differences were found between the low- and high-dose groups for outcomes of core and general symptoms ($p > 0.40$); depression/anxiety ($p = 0.65$); response rates ($p = 0.81$); or global impressions of severity ($p = 0.46$), improvement ($p = 0.38$), or functioning ($p = 0.38$). Medication adherence rates were also similar (> 96%).

Risperidone–Low- versus high-dose. An 8-week RCT compared the efficacy of low- (0.4 mg/day) and high-dose (4 mg/day) risperidone in 275 adolescents.[74] The high-dose risperidone group showed greater improvement than the low-dose group for negative, positive, and overall schizophrenia symptoms; response rates; and for global impressions of improvement and severity ($p < 0.005$ for all).

A 6-week placebo-controlled RCT (N = 158) compared the efficacy of low- (1–3 mg/day) and high-dose (4–6 mg/day) risperidone.[88] No significant differences were observed between the two dosing groups for negative, positive and overall schizophrenia symptoms ($p > 0.6$ for all);

rates of response or discontinuation for lack of efficacy ($p > 0.4$); and for global impressions of improvement ($p = 0.74$), severity ($p = 0.24$), and functioning ($p = 0.56$).

Ziprasidone–Low- versus high-dose. DelBello et al.[65] conducted a 3-week RCT comparing the efficacy of low- (80 mg/day) and high-dose (160 mg/day) ziprasidone for treating bipolar mania, schizophrenia, and schizoaffective disorder. Separate analyses were provided for the 17 patients with schizophrenia. No significant differences were found between the low- and high-dose groups for overall psychiatric symptoms ($p = 0.21$), or global impressions of severity ($p = 0.8$).

FGAs Versus Placebo

An 8-week crossover RCT (N = 16) compared haloperidol with placebo in children ages 5 to 11 with schizophrenia.[83] Both the positive and negative syndrome scores on the CPRS improved significantly in the haloperidol group compared with the placebo group ($p < 0.01$). Statistical comparisons between the two groups were not possible (no variances reported) for overall psychiatric symptoms, or global improvement and severity.

SGAs Versus Placebo

Nine RCTs (N = 1788) compared an SGA with placebo for intermediate outcomes: aripiprazole,[72, 95] asenapine,[92] olanzapine,[76, 86] paliperidone,[90] quetiapine,[72] risperidone,[88] and ziprasidone.[71] The average age of patients across studies was 15.8 years and 62 percent were males; 7 studies reporting on race/ethnicity enrolled 39.2 percent minorities. Studies were either 6 or 8 weeks' duration, with the exception of the unpublished study[95] from which we extracted 24-week followup data. The only study that reported a large proportion (90%) of the study population as being treatment naïve was that examining the prodromal phase.[86]

Meta-Analyses Comparing Various SGAs With Placebo

Meta-analyses were conducted to compare various SGAs versus placebo for the short-term core symptoms of negative symptoms, positive symptoms, and depression. They were also conducted for short-term nonspecific symptoms—captured by the BPRS, PANSS total, response rates, and rates of discontinuation for lack of efficacy—and for global impressions of improvement (CGI-I), severity (CGI-S), and functioning (C-GAS, Global Assessment of Functioning [GAF]). Four studies also contributed to a meta-analysis for medication adherence.

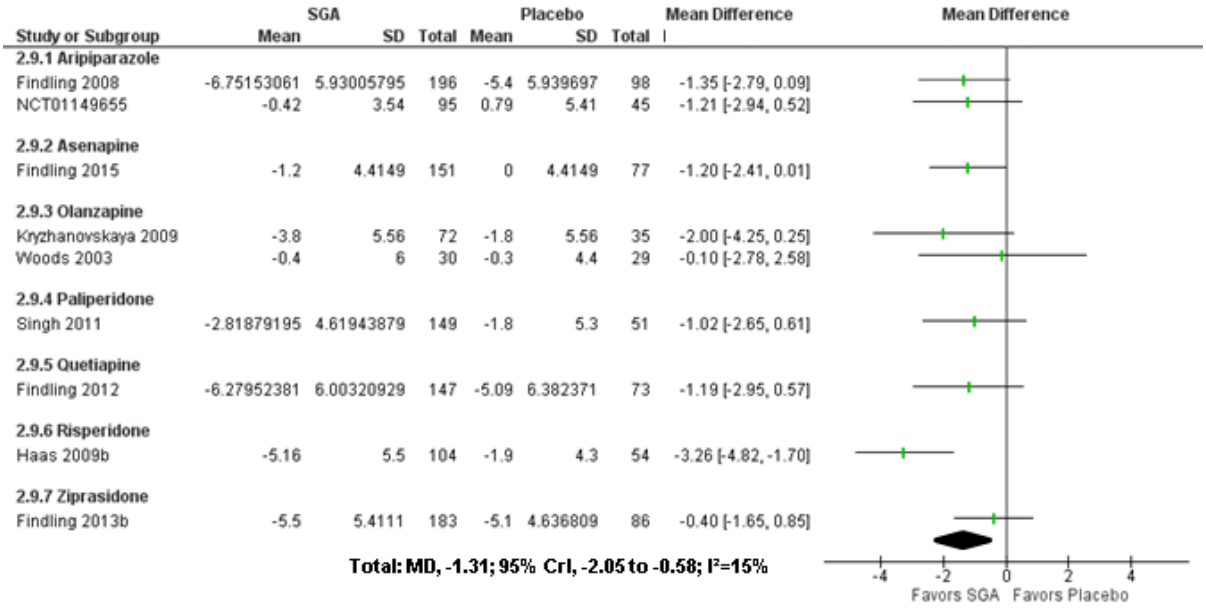
When a study had two or more arms with patients taking different doses of the same drug, we combined data from all arms; the studies in general did not report any difference in effect between doses of the same drug. We realize this strategy may mask a greater or lesser effect when prescribing lower or higher doses to individual patients.

We conducted sensitivity analysis for some analyses, because of clinical heterogeneity related to a priori specified factors of phase of illness and treatment history. The study reported by Woods et al.[86] on use of olanzapine in the prodromal phase of psychosis, and the trial examining discontinuation of aripiprazole in patients stabilized on this drug[95] were removed from several analyses to examine whether results differed.

Short-term core symptoms. Nine RCTs contributed data for meta-analyses for negative (Figure 28) and positive (Figure 29) symptoms measured using the PANSS.[71-73, 76, 86, 88, 90, 92, 95] Both results showed statistically significant differences between SGAs and placebo (negative symptoms: MD, -1.31; 95% CrI, -2.05 to -0.58, and positive symptoms: MD, -2.20; 95% CrI, -2.98 to -1.48). Sensitivity analyses removing the studies examining the prodromal phase (Woods et al.[86]) and the maintenance after stabilization on the SGA (NCT01149655[95]) did not change the

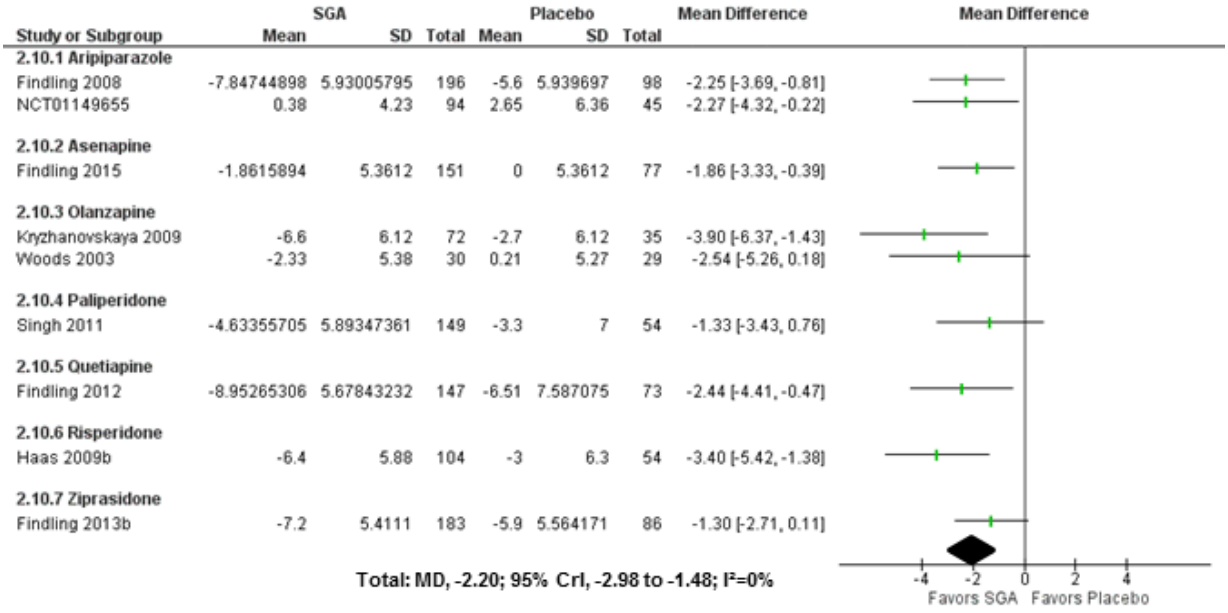
results in a meaningful manner for negative or positive symptoms (MD, -1.41; 95% CrI, -2.38 to -0.51 and MD, -2.19; 95% CrI, -3.18 to -1.31, respectively).

Figure 28. SGAs versus placebo for negative symptoms on PANSS in schizophrenia and related psychosis



CrI = credible interval; MD = mean difference; PANSS = Positive and Negative Syndrome; SD = standard deviation; SGA = second generation antipsychotic

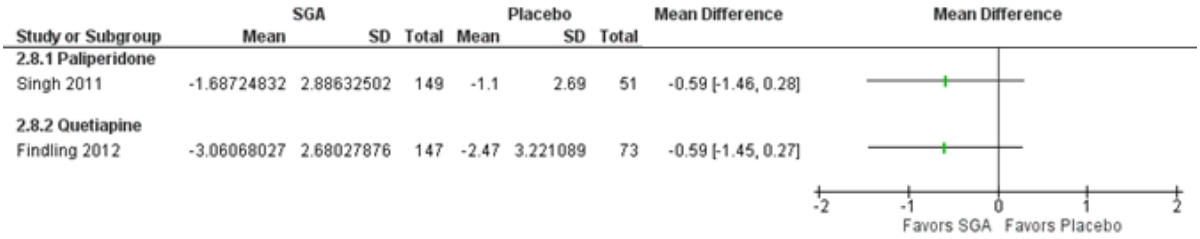
Figure 29. SGAs versus placebo for positive symptoms on PANSS in schizophrenia and related psychosis



CrI = credible interval; SD = standard deviation; MD = mean difference; PANSS = Positive and Negative Syndrome Scale; SGA = second generation antipsychotic

Two RCTs contributed data on depression symptoms from the PANSS (Figure 30).[72, 90] No difference was shown between the SGAs paliperidone (p = 0.19) or quetiapine (p = 0.18) and placebo.

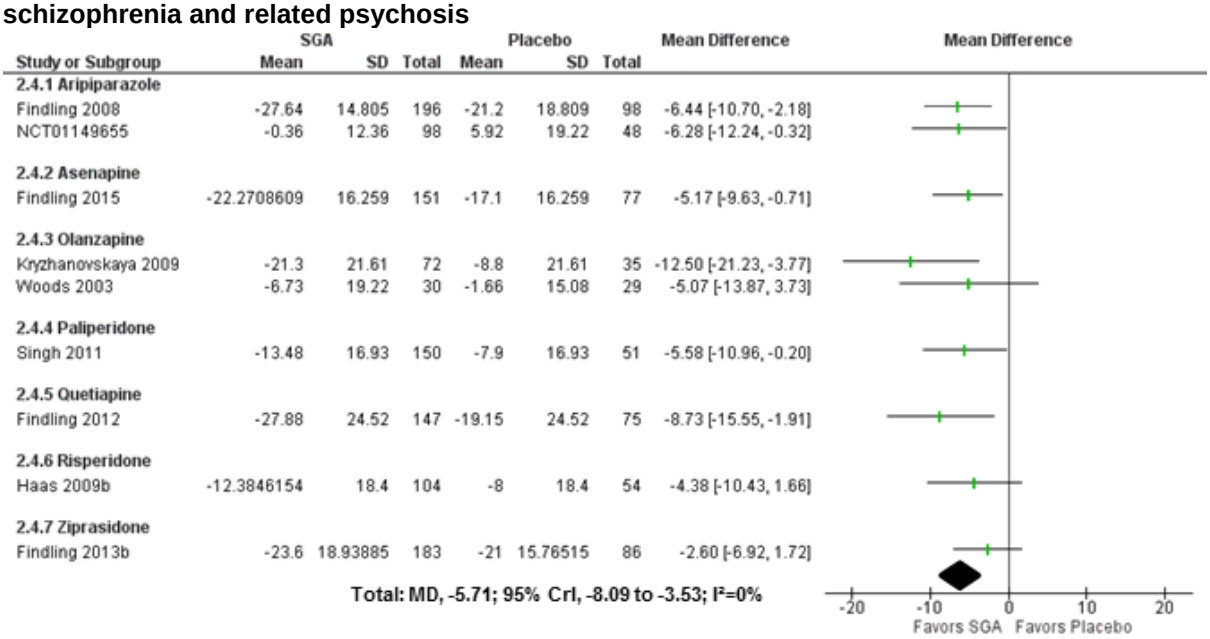
Figure 30. SGAs versus placebo for depressive symptoms on PANSS in schizophrenia and related psychosis



PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; SGA = second generation antipsychotic

Short-term nonspecific symptoms. All nine RCTs[71-73, 76, 86, 88, 90, 92, 95] reported overall symptoms of schizophrenia using the PANSS total score and were combined in a meta-analysis (Figure 31). The pooled estimate found SGAs to be superior to placebo in reducing overall schizophrenia symptoms (MD, -5,71; 95% CrI, -8.09 to -3.53); no effect was seen on sensitivity analysis. The effect size of approximately a 6-point reduction is lower than most reports defining a clinically meaningful value of at least 10 points or ≥ 20 percent reduction; many studies had inclusion criteria of baseline PANSS total scores in the 60-80 range. The placebo groups in several studies experienced clinically relevant improvements.

Figure 31. SGAs versus placebo for overall schizophrenia symptoms using PANSS Total score in schizophrenia and related psychosis

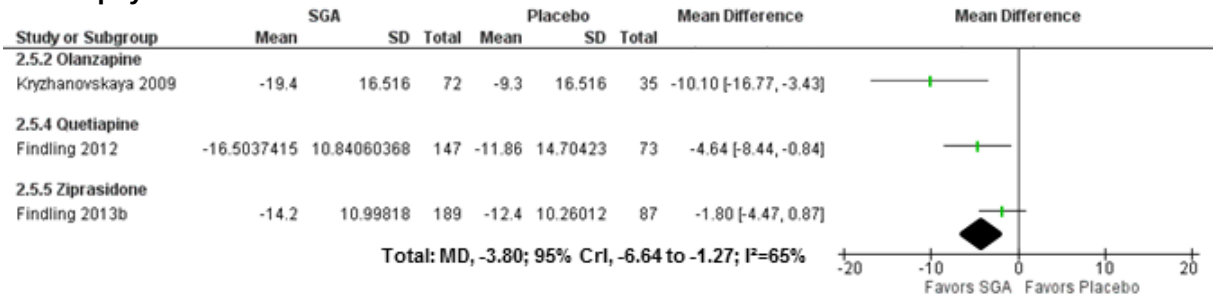


CrI = credible interval; MD = mean difference; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; SGA = second generation antipsychotic

Three RCTs compared SGAs (olanzapine,[76] ziprasidone,[71] and quetiapine[72]) with placebo for overall psychiatric symptoms using BPRS scores (Figure 32). These drugs reduced symptoms to

a greater extent than placebo (MD, -3.80; 95% CrI, -6.64 to -1.27). There was moderate heterogeneity (I^2 = 65%) in the analysis which may be in part due to the different SGAs.

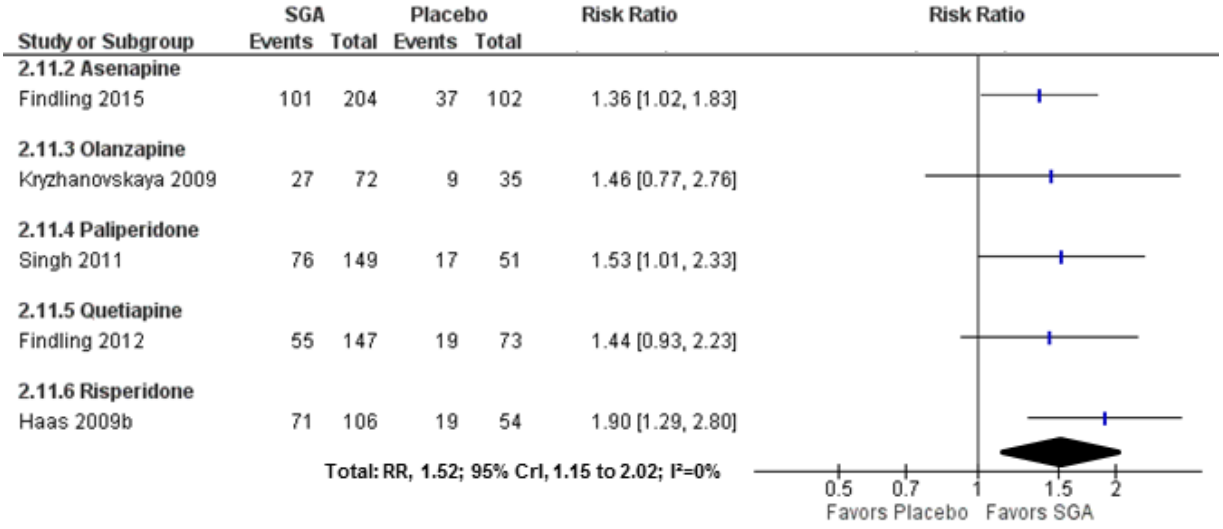
Figure 32. SGAs versus placebo for overall psychiatric symptoms on BPRS in schizophrenia and related psychosis



BPRS = Brief Psychiatric Rating Scale; CrI = credible interval; MD = mean difference; SD = standard deviation; SGA = second generation antipsychotic

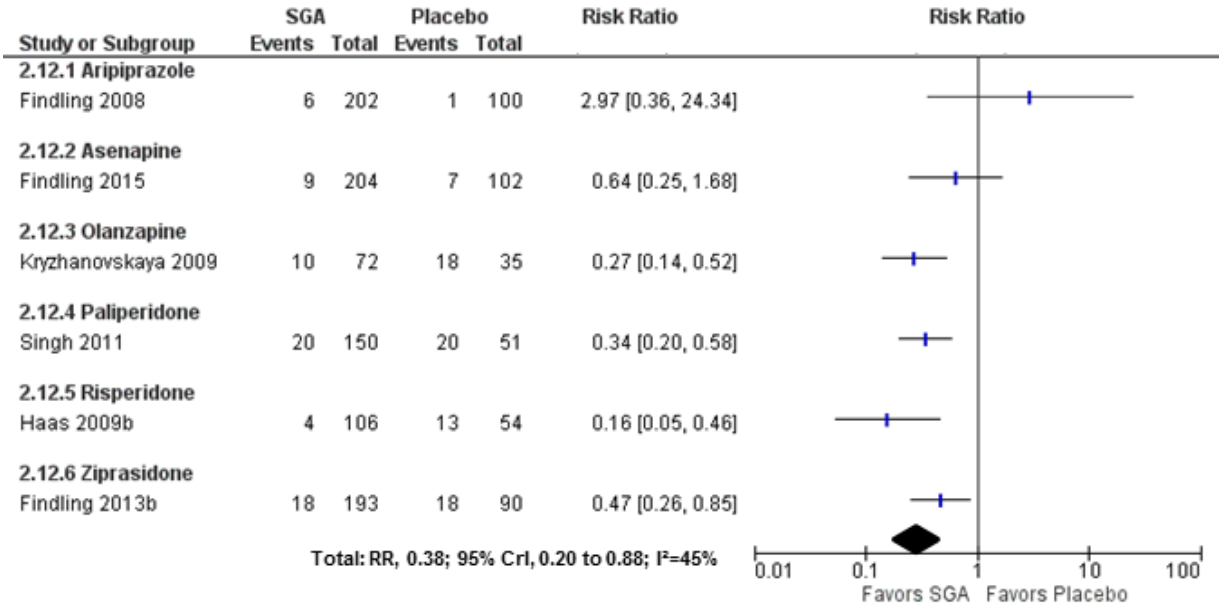
Five RCTs reported response rates for SGAs versus placebo (Figure 33).[72, 76, 88, 90, 92] The estimated RR was 1.52 (95% CrI, 1.15 to 2.02) showing greater response for SGAs compared with placebo. Data from six RCTs also found the SGAs favorable over placebo for having lower rates of discontinuation for lack of efficacy (RR, 0.38; 95% CrI, 0.20 to 0.88) (Figure 34).[71, 73, 76, 88, 90, 92]

Figure 33. SGAs versus placebo for response rates in schizophrenia and related psychosis



CrI = credible interval; RR = risk ratio; SGA = second generation antipsychotic

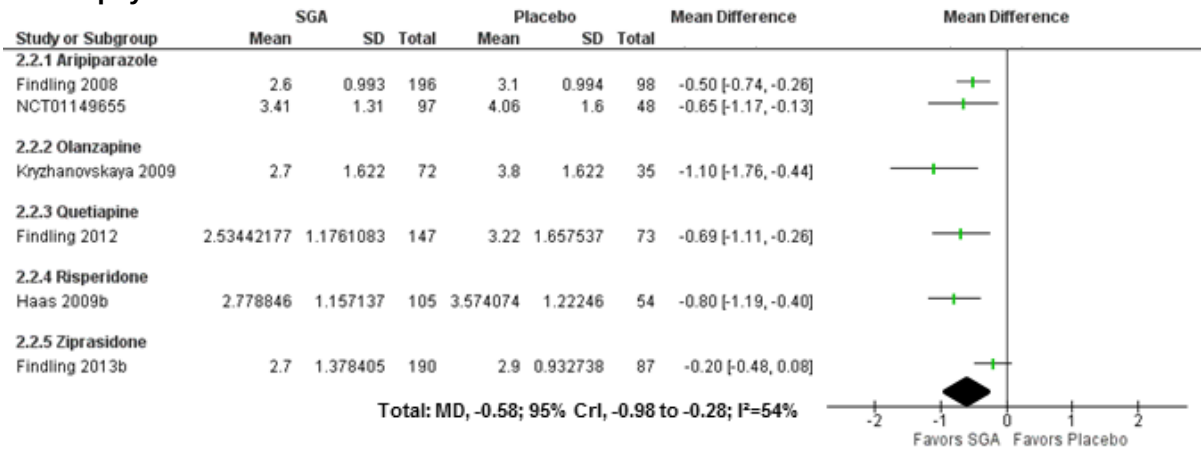
Figure 34. SGAs versus placebo for discontinuation due to lack of efficacy in schizophrenia and related psychosis



CrI = credible interval; RR = risk ratio; SGA = second generation antipsychotic

Short-term global impressions. Six RCTs comparing aripiprazole,[73, 95] olanzapine,[76] risperidone,[88] quetiapine,[72] and ziprasidone[71] with placebo reported on global impressions of improvement using CGI–I scores (Figure 35). The pooled estimate significantly favored SGAs over placebo (MD, -0.54; 95% CrI, -1.07 to -0.14). Removing the maintenance study (NCT01149655[95]) did not affect the effect estimate although broadened the credible interval slightly (-1.28 to -0.07). There was moderate statistical heterogeneity between the studies (I^2 = 64%), which may have been driven by differences between the SGA comparators.

Figure 35. SGAs versus placebo for symptom improvement using the CGI–I in schizophrenia and related psychosis

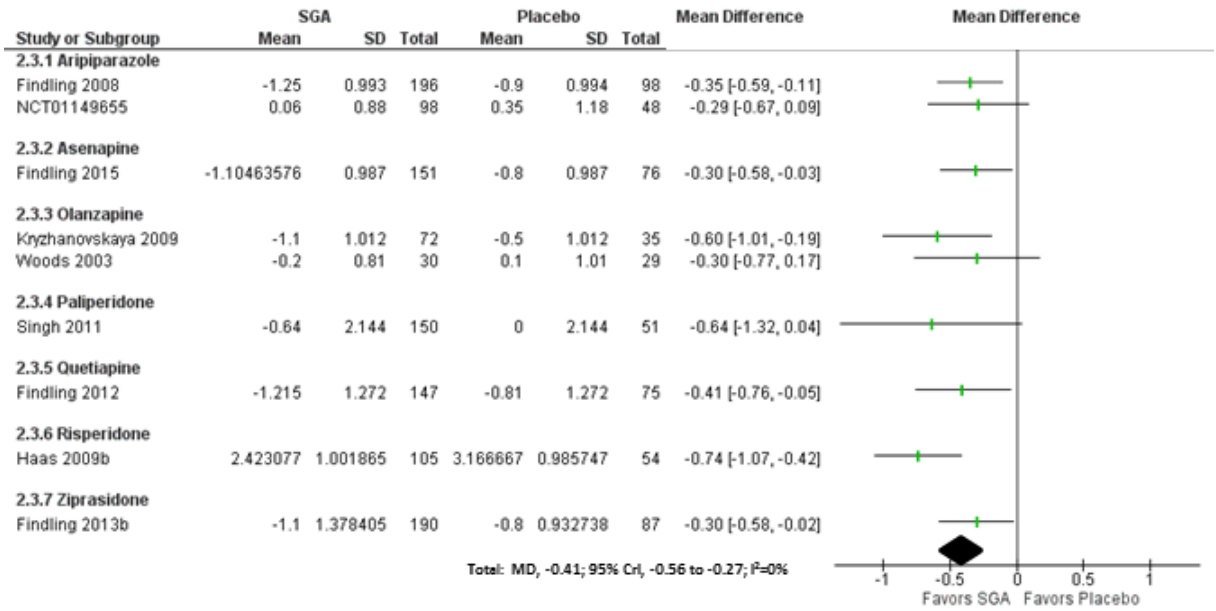


CGI-I = Clinical Global Impression of Improvement; CrI = credible interval; MD = mean difference; SD = standard deviation; SGA = second generation antipsychotic

All nine studies provided data for a meta-analysis comparing SGAs with placebo for global impression of severity (CGI-S) (Figure 36). Patients treated with SGAs had a greater reduction in

illness severity than those receiving placebo (MD, -0.36; 95% CrI, -0.51 to -0.22). Sensitivity analysis removing the two studies having clinical heterogeneity (Woods[86] and NCT01149655[95]) did not affect the results appreciably (MD, -0.38; 95% CrI, -0.58 to -0.21).

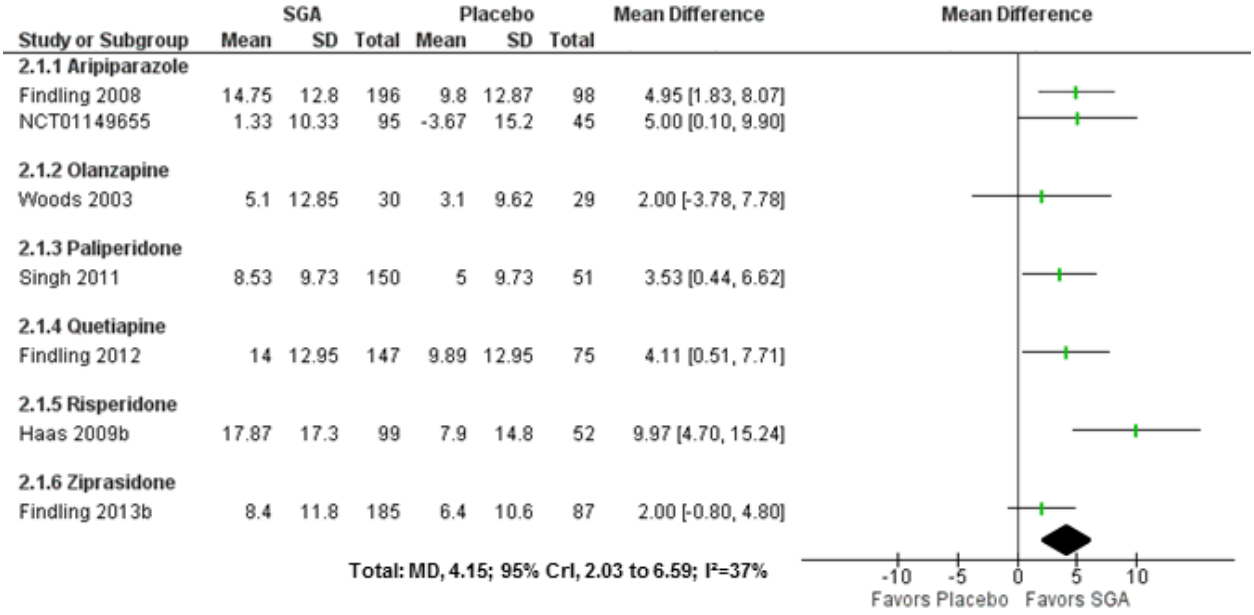
Figure 36. SGAs versus placebo for symptom severity using the CGI–S in schizophrenia and related psychosis



CGI-S = Clinical Global Impression of Severity; CrI = credible interval; MD = mean difference; SGA = second generation antipsychotic; SD = standard deviation

Seven RCTs[71-73, 86, 88, 90, 95] contributed data to a meta-analysis comparing SGAs with placebo for global impressions of function measured by the C-GAS (Figure 37). With the exception of two studies examining olanzapine,[86] and ziprasidone[71] all trials significantly favored the SGAs. The pooled estimate showed a significant improvement in functioning for SGAs compared with placebo (MD, 4.15; 95% CrI, 2.03 to 6.59). Our sensitivity analysis showed minimal changes when removing the Woods et al. and NCT01149655 trials[86, 95] (MD, 4.32; 95% CrI, 1.28 to 8.06).

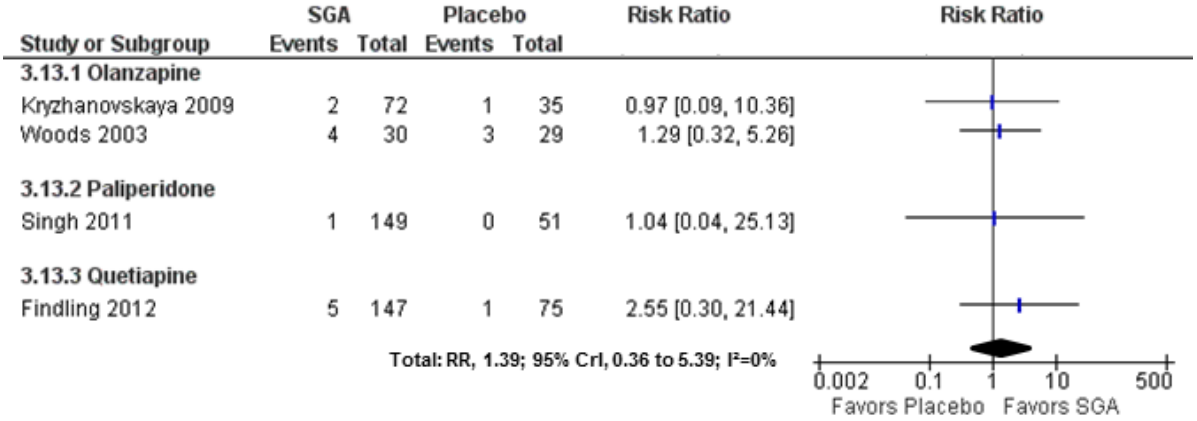
Figure 37. SGAs versus placebo for global functioning using the C-GAS in schizophrenia and related psychosis



C-GAS = Children's Global Assessment Scale; CrI = credible interval; SD = standard deviation; SGA = second-generation antipsychotic; MD = mean difference

Medication adherence. Four RCTs examining olanzapine,[76, 86] paliperidone,[90] and quetiapine[72] provided data on medication adherence (Figure 38). No difference between the SGAs and placebo in terms of poor adherence rates was found (RR, 1.39; 95% CrI, 0.36 to 5.39).

Figure 38. SGAs versus placebo on poor medication adherence in schizophrenia and related psychosis

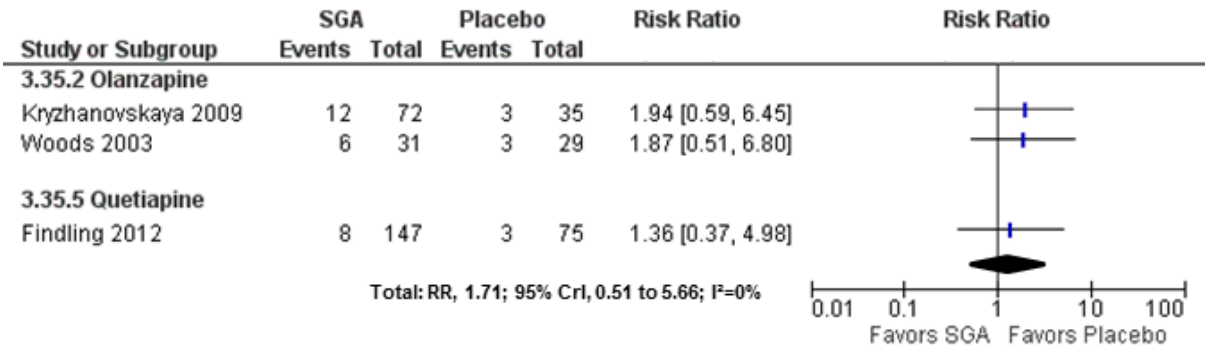


CrI = credible interval; RR = risk ratio; SGA = second-generation antipsychotic

Lifestyle behaviors. Three RCTs[72, 76, 86] reported on the number of patients experiencing an increase in appetite; because of the concerns about excessive weight gain for children taking antipsychotics we considered an increase in appetite to be a negative finding for SGAs. Figure 39 displays the findings for our analysis which showed no statistically significant difference between SGAs and placebo (RR, 1.71; 95% CrI, 0.51 to 5.66). Although the relative effect was

not statistically significant, in all studies there were more patients in the treatment than placebo group experiencing increased appetite.

Figure 39. SGAs versus placebo for increased appetite in schizophrenia and related disorders



CrI= credible interval; RR = risk ratio; SGA = second-generation antipsychotic

Observations on Between-Study Subgroup Effects

One study randomized patients to maintenance or discontinuation of aripiprazole after treatment stabilization; inclusion criteria was response to aripiprazole.[95] Patients starting a trial with less severity of illness than patients in other studies may limit the degree of potential change, even relative to placebo. As per protocol, we extracted data from this study's results at 24 weeks which was the longest followup within this short-term stratum of 0 to <6 months; these longer term results may have increased the relative effects between treatment and placebo. Sensitivity analyses in the meta-analyses including data from this trial did not change the results.

Combining results from studies enrolling severely ill patients with schizophrenia with those enrolling high-risk, but undiagnosed, outpatients may confound results. We performed sensitivity analyses for the meta-analysis including data from the trial investigating the prodromal phase (Woods et al.[86]) the difference in results was negligible.

Schizophrenia and Related Psychoses: Effectiveness Outcomes

Fourteen studies reported on effectiveness outcomes for treating schizophrenia and related psychosis. A summary of the key findings by comparison is provided below. Table 6 contains the findings and SOE ratings for the key outcomes assessed as having at least low SOE; the reason for each SOE decision is included in the table footnotes. A detailed analysis follows.

Key Points

- **FGAs versus SGAs** (two RCTs[70, 81] and one prospective cohort[102]): The effects are not known for several effectiveness outcomes in studies between FGAs and SGAs (insufficient SOE). Apart from long-term symptom scores, only two studies reported on other effectiveness outcome including global functioning, suicide and subjective wellbeing
- **Different SGAs:** aripiprazole versus paliperidone (one RCT[94]), olanzapine versus quetiapine (one RCT[67]), olanzapine versus risperidone (one RCT[81] and three observational studies[101, 102, 104]), risperidone versus quetiapine (two observational studies[101, 104]), clozapine versus other SGAs (one prospective cohort[102]). It is not known

whether there is any difference between various SGAs for effectiveness outcomes, including long-term core and nonspecific outcomes, global impressions, personal and social performance, suicide ideations, occupational functioning and functioning in the family, and inpatient psychiatric admissions.

- **SGAs—Dose comparisons** (aripiprazole,[73] quetiapine,[68, 72] and risperidone[88]): The comparative effects between different doses are not known for outcomes of quality of life, caregiver strain, social and occupational functioning, hospital admission rates, imprisonments, suicide ideations/behaviors, or deaths by suicide.
- **SGAs versus placebo** (five RCTs[72, 73, 86, 93, 95]): There may be little or no difference between SGAs and placebo for suicide attempts, completed suicide, suicide ideations, or suicide behaviors in short-term studies.[71-73, 76, 88, 90, 92, 95] The effects from long-term maintenance on aripiprazole are not known for positive symptoms, relapse rates, response and remission rates, global impressions of improvement, changes in illness severity or functioning, or suicide behaviors. For patients experiencing the prodrome phase, the effects are not known for long-term negative, positive, or depression symptoms; rates of 12-month transition to psychosis; global impression of severity or functioning; or for quality of life. SOE was insufficient because of high ROB and imprecision from small samples and confidence intervals including possibility for substantial benefit for either group. The effects on caregiver strain are not known for patients taking low- or high-dose quetiapine.[72]

Table 6. Strength of evidence for schizophrenia and related psychosis: Key effectiveness outcomes having at least low strength of evidence

Comparison	Outcome (N Studies; N Patients)	Findings[a] and Studies	Strength of Evidence; Conclusions
SGAs vs. placebo	Short-term suicide attempts/suicides (7, 1463)	Attempts: 2 in 693 SGA and 2 in 318 placebo patients [71, 72, 90, 92] Suicides: 0 in 447 SGA vs. 0 in 227 placebo patients[72, 73, 88]	Low; may make little or no difference [b]
	Short-term suicide ideations or behaviors (4, 758)	Ideations: 3 in 340 SGA and 1 in 165 placebo patients[71, 72] Behaviors: 1 in 170 SGA and 1 in 83 placebo patients[76, 95]	Low; may make little or no difference [b]

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

[a] There were no meta-analyses conducted for these findings because of 0 events in some studies; there were no outcomes with ≥ 3 studies having events.

[b] Downgraded for ROB and imprecision because of small event rates; confidence intervals of relative risks ranged between 0.02 to 5.0, to 0.06 to 48.1).

Detailed Analysis

FGAs Versus SGAs

Three studies reported on effectiveness outcomes when comparing FGAs with SGAs.[70, 81, 102] A brief description of the long-term studies is presented before summarizing the effectiveness outcomes by category.

Description of Long-Term Studies

Haloperidol versus olanzapine, risperidone, and clozapine. A prospective cohort study evaluated long-term efficacy and safety of an FGA (haloperidol) and SGAs (olanzapine,

risperidone, clozapine) in patients (N = 47) with early-onset psychosis who were followed between 3 and 11 years.[102] Patients were treated using a clinical algorithm, whereby haloperidol was first-line treatment during 1990 and 1999 before risperidone or olanzapine were preferred between 2000 and 2005.

Molindone versus risperidone and olanzapine. A 44-week double-blind extension (N = 54) of the 8-week study by Sikich et al.[81] maintained patients showing improvement during the 8-week acute phase on flexibly dosed molindone, risperidone, or olanzapine.

Results on Effectiveness Outcomes From Short- and Long-Term Studies

Long-term core symptoms. Over 3 year followup, patients taking haloperidol and SGAs all showed clinical improvement but clozapine was more effective for negative and positive symptoms than haloperidol ($p < 0.0001$) and risperidone was favored over haloperidol for positive symptoms ($p < 0.03$).[102] Similar to the RCT's acute phase, 52-week followup found no differences between molindone, olanzapine, and risperidone for negative and positive symptoms;[81] significant differences seen in responders at 8-weeks remained stable over the long-term.

Long-term nonspecific symptoms. Clozapine and risperidone were more effective than haloperidol for overall symptoms measured using the PANSS scale (p values < 0.0001 and 0.03, respectively).[102] Clozapine was more effective than haloperidol for response rates ($p < 0.001$); all three SGAs were superior to haloperidol for rates of discontinuation due to lack of efficacy ($p < 0.003$).[102] The RCT comparing molindone to SGAs found no differences between drugs for long-term overall schizophrenia symptoms;[81] no group achieved more than a 7-point reduction in the PANSS total score.

Long-term global impressions. Global impressions of illness severity (CGI-S) were no different between molindone, risperidone, and olanzapine at 52-week followup;[81] the changes of about 2 points reduction seen at 8-weeks were maintained in this subgroup of patients. Global functioning measured using the Child and Adolescent Functional Assessment Scale was worse for the risperidone group than the molindone group ($p = 0.025$).[81] In the observational study, clozapine was favored over haloperidol in terms of overall functioning measured using the GAF or C-GAS ($p < 0.01$).[102]

Suicide-related ideations and behaviors. One RCT reported on suicide ideation, with no patients reporting these in any group.[81]

Occupational functional capacity. No findings specific to FGA-SGA comparisons were reported; at 5-year followup 6 of 19 patients on clozapine and 5 of 20 patients on other antipsychotics (including haloperidol) had completed school and were able to work.[102]

Quality of life. A 6-week RCT comparing haloperidol with olanzapine assessed patients for wellbeing using the Subjective Well-Being Under Neuroleptics Scale.[70] This outcome improved from baseline to endpoint in both groups; however, there was no significant difference ($p = 0.26$) between the groups.

SGAs Versus SGAs

Six studies (3 RCTs[67, 81, 94] and 3 observational studies[101, 102, 104]) compared different SGAs for effectiveness outcomes. Three RCTs compared different doses of an SGA;[72, 73, 75] none of these dose comparisons reported on long-term symptom or global impression outcomes (≥ 6 months) but they reported on other effectiveness outcomes (e.g., quality of life, cognitive effects).

Aripiprazole versus paliperidone. An RCT with an 8-week acute phase and 18-week extension phase compared once-daily paliperidone extended release with aripiprazole in patients with prior exposure to antipsychotics.[94] At 26 weeks, both groups had a similar reduction ($p = 0.877$) in the primary outcome of overall schizophrenia symptoms (PANSS total reduced by 26 points). More than 50 percent of patients in both groups remained clinically stable ($p = 0.30$). There was no difference between groups for other long-term outcomes including negative ($p = 0.7$) and positive ($p = 0.4$) symptoms, global impressions of severity ($p = 0.91$), and personal and social performance ($p = 0.71$). Two patients in the paliperidone group had suicide ideations and attempted suicide; four patients in the paliperidone group and two in the aripiprazole group had suicide related events.

Olanzapine versus quetiapine. A 6-month RCT (N = 50) enrolled adolescents experiencing a first episode of psychosis.[67] There was a significant difference between the groups favoring olanzapine for Strengths and Difficulties Questionnaire as rated by patients ($p = 0.03$); the results for the ratings by parents and teachers were not significant. No differences were found for the negative ($p = 0.34$), positive ($p = 0.12$), and overall symptoms ($p = 0.4$); depression symptoms ($p = 0.66$); or global impressions of severity ($p = 0.6$) or functioning ($p = 0.12$). Results for adherence and performance on various cognitive domains (attention, working memory, learning and memory, and executive functions) were also of no difference.

Olanzapine versus risperidone. A 44-week double-blind extension (N = 54) of the study by Sikich et al.[81] maintained patients showing improvement during the 8-week acute phase on flexibly dosed molindone, risperidone, or olanzapine. No differences between groups were found for changes in clinical outcomes from baseline to 52 weeks; changes in global functioning as measured using the Child and Adolescent Functional Assessment Scale were worse for the risperidone group than the olanzapine group during the maintenance phase ($p = 0.025$). In the risperidone group, one patient reported suicidal ideation, and one patient died by suicide.

Olanzapine versus risperidone versus clozapine. A prospective cohort study evaluated the 3- to 11- year efficacy and safety of haloperidol, olanzapine, risperidone, and clozapine.[102] For negative, positive, and overall symptoms measured using the PANSS scale, clozapine was more effective than the other SGAs ($p < 0.0001$). Similar results occurred for response rates, measured via ≥ 20 percent reduction in PANSS total scores and being "improved" or "very improved" on the CGI-I, and for discontinuation due to lack of efficacy. Clozapine was also favored over the other drugs in terms of overall functioning measured using the GAF or CGAS ($p < 0.01$).

Risperidone versus quetiapine versus olanzapine. A 24-month prospective cohort study recruited 110 consecutive children and adolescents having first-episode psychotic disorder (23 percent with affective psychoses).[101] Patients were assessed for negative, positive and overall psychotic symptoms (PANSS); global impressions of improvement, severity, and functioning (CGI and GAF); and for occupational functioning and functioning in the family and social environments (World Health Organization Disability Assessment Schedule). When looking at patients who only received one antipsychotic for 6 months (N = 60), all had significantly improved responses on all scales ($p < 0.005$) with the exception of those taking risperidone who did not improve in terms of negative symptoms ($p = 0.530$). There were no differences between groups for any outcome (p values ranging from 0.07 for functioning and disability to > 0.2 for core and nonspecific symptoms). Overall rates and reasons for discontinuation over the 24 months were not different between groups; 71 percent of patients discontinued their first antipsychotic treatment. Insufficient response was the most frequent reason for discontinuation at all timepoints.

Risperidone versus olanzapine, quetiapine, aripiprazole, and ziprasidone. A 6-month retrospective cohort study (N = 1745) using a 45-state Medicaid Claims database examined patients having early-onset schizophrenia prescribed antipsychotic monotherapy with an SGA between 2011-2005.[104] Most (71% for quetiapine to 77% for aripiprazole) youth discontinued their medication within the first 6 months of treatment. Compared with risperidone, the adjusted hazards of antipsychotic discontinuation did not significantly differ for any comparator. Inpatient psychiatric treatment ranged from 7.19 percent (aripiprazole) to 9.89 percent (quetiapine), although there were no treatment differences between risperidone and the other SGAs (p = 0.94).
Aripiprazole—Low- versus high-dose. Findings for quality of life measured using the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire were similar between the low- and high-dose aripiprazole groups in one 6-week RCT.[73]
Quetiapine–Low- versus high-dose. Two RCTs examined patients for effectiveness outcomes from taking different doses of quetiapine. Measurement using the Social and Occupational Functioning Assessment Scale showed significantly greater improvement in one low-dose (200 mg/day) group although this group started at a lower level of baseline functioning.[68] Hospital admission rate was significantly lower in the high-dose (400 mg/day) group (p = 0.005); days in hospital did not differ between groups. There was also no difference in imprisonments or deaths by suicide. In the other RCT, there was significantly greater reduction in scores on the Caregiver Strain Questionnaire for the low-dose (400 mg/day) but not high-dose (600 mg/day) quetiapine group compared with placebo (p = 0.008).[72]
Risperidone–Low- versus high-dose. In an 8-week RCT comparing the efficacy of low- (0.4 mg/day) and high-dose (4 mg/day) risperidone, no patient attempted suicide; however, two patients in the low-dose risperidone group reported suicidal ideation.[79]

FGAs Versus Placebo

An 8-week crossover RCT (N = 16) comparing haloperidol (2 mg/day) with placebo in children ages 5 to 11 years with schizophrenia did not report on any effectiveness outcomes.[83]

SGAs Versus Placebo

Five RCTs examined effectiveness outcomes for SGAs compared with placebo.[72, 73, 86, 93, 95] Three of these studies reported long-term outcomes.[86, 93, 95]

Description of Long-Term Studies

Aripiprazole versus placebo. A 52-week RCT (N = 146) examined maintenance with aripiprazole (10-30 mg/day) compared with placebo in adolescent patients who were previously stabilized on aripiprazole (previously described).[95]
Olanzapine versus placebo. An RCT (N = 60) comparing olanzapine (8±3.1 mg/day) with placebo in patients (ages 12 to 45 years, mean age of 17.7 years) with prodromal syndrome included data for 8 and 52 weeks.[86]
Risperidone versus placebo. A 12-month RCT examined the addition of risperidone (n = 43) or placebo (n = 44) to cognitive behavioral therapy in patients ages 14-30 (mean ages 17.6 ±3.0 and 18.0±2.7, respectively) experiencing the prodromal phase of psychosis.[93]

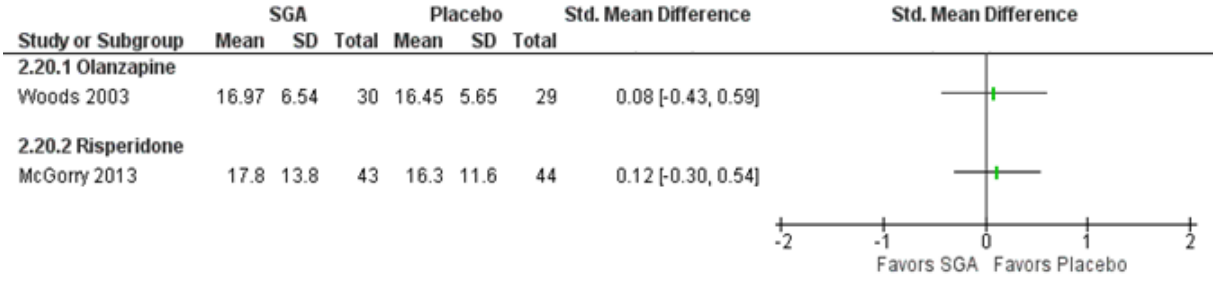
Results on Effectiveness Outcomes From Short- and Long-Term Studies

Long-term core symptoms. Comparing maintenance aripiprazole to placebo, both groups experienced more positive symptoms at 12 months, although the aripiprazole group less so

(0.16±4.6 vs. 2.31±6.8 increase in PANSS positive score; $p < 0.05$).[95] Between-group changes for negative symptoms were not significant in this study ($p = 0.22$).

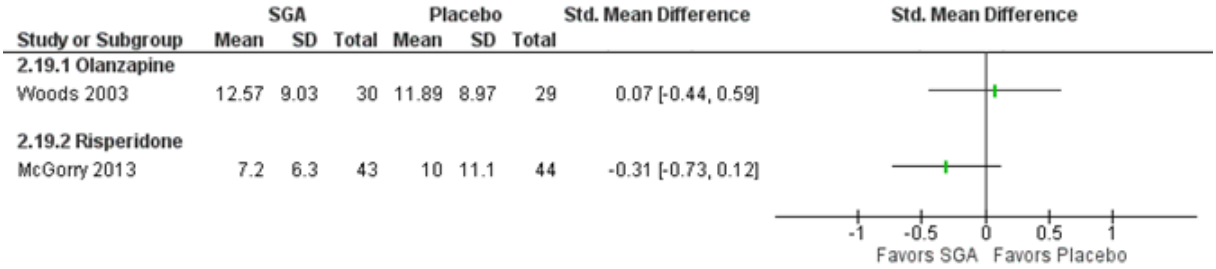
There were no differences between olanzapine and placebo groups for changes in positive symptoms in patients experiencing prodrome ($p = 0.44$).[86] Figures 40 and 41 present data on negative (PANNS and SANS) and depression (Hamilton Depression Rating Scale and Montgomery-Asberg Depression Rating Scale) symptoms from the two 12-month RCTs enrolling patients at high-risk for schizophrenia.[86, 93]

Figure 40. SGAs versus placebo for negative symptoms at 12 months in schizophrenia and related psychosis



SD = standard deviation; SGA = second-generation antipsychotic

Figure 41. SGAs versus placebo for depression symptoms at 12 months in schizophrenia and related psychosis

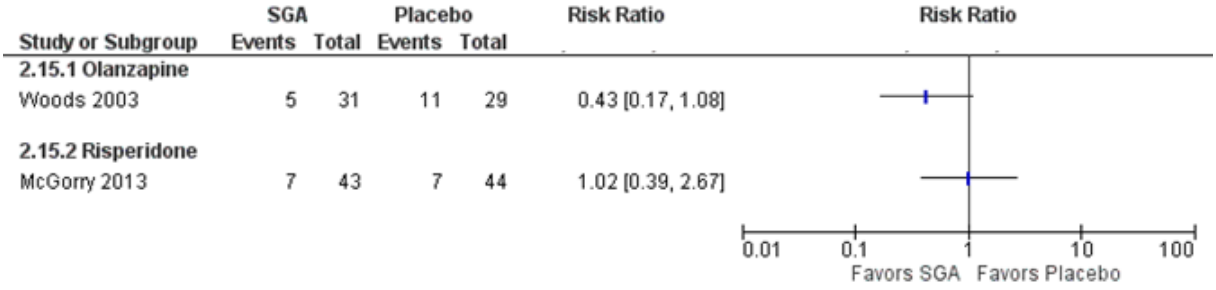


SD = standard deviation; SGA = second-generation antipsychotic

Long-term nonspecific symptoms. Patients maintained on aripiprazole had significantly lower overall schizophrenia symptoms at 1-year than those on placebo (-1.3 vs. 4.8 points on PANSS total; $p = 0.06$).[95] Overall relapse rate (CGI-I ≥5 and ≥20% increase in PANSS total) was lower for those maintained on aripiprazole than placebo (19.4% vs. 37.5%; $p = 0.0161$).[95] Response and remission rates did not differ between these groups ($p = 0.1$ and 0.9, respectively).

For 12-month transition to psychosis disorder (Figure 42), olanzapine appeared favorable over placebo (16.1% vs. 37.9% conversion) but the result did not reach statistical significance ($p = 0.08$).[86]

Figure 42. SGAs versus placebo for transition to psychosis at 12 months in schizophrenia and related psychosis

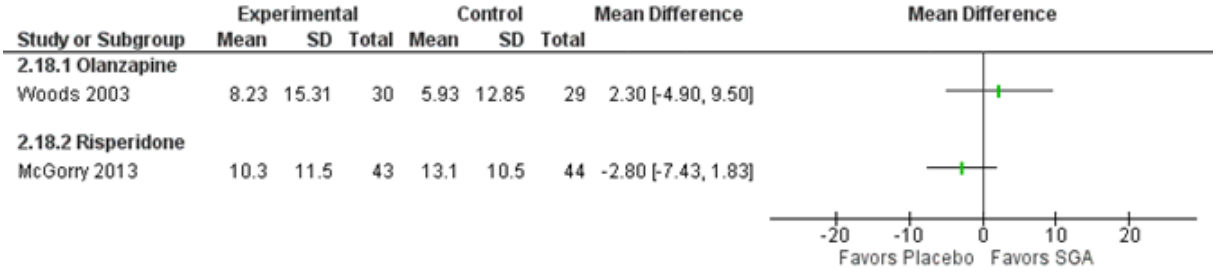


SGA = second-generation antipsychotic

Long-term global impressions. Maintenance treatment with aripiprazole was not significantly different than with placebo for long-term scores in global impressions of improvement (3.42 vs. 3.92 on CGI-I, respectively; p = 0.08), or changes from baseline in illness severity (0.05 vs. 0.29 on CGI-S; p = 0.23) or global functioning (2.35 vs. -2.25 on C-GAS; p = 0.09).[95]

Patients experiencing prodrome psychosis did not benefit more from olanzapine than from placebo for global impressions of severity (p = 0.51) at 12 months.[86] Figure 43 shows the results for global impressions of functioning using GAF in schizophrenia prodrome. There was no difference between the SGAs and placebo for this outcome in either RCT.[86, 93]

Figure 43. SGAs versus placebo for 12-month global impressions of functioning in schizophrenia and related psychosis



SGA = second-generation antipsychotic; SD = standard deviation

Suicide-related ideations or behaviors. Four short-term RCTs reporting on suicide attempts did not find any differences between groups;[71, 72, 90, 92] all had either no or one attempt in any group. Three short-term RCTs reported no suicides.[72, 73, 88] Two RCTs reported on suicide behaviors; no behaviors in either group were reported in the study of olanzapine,[76] while one patient in each arm exhibited behaviors in the study of aripiprazole.[95] Suicide ideations were no different between placebo and ziprasidone[71] or quetiapine[72] groups; two or fewer patients in either arm had suicide ideations.

Quality of life. Using the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire; neither low- (p = 0.55) or high-dose (p = 0.26) aripiprazole groups were favorable over placebo for this outcome at 6-weeks.[73] There was no difference in the Quality of Life Scale scores

between risperidone and placebo groups at 12 months for patients experiencing the prodrome phase ($p = 0.14$).[93]

Caregiver burden/strain. Parents of those in the lower (400 mg/day) and higher (800 mg/day) quetiapine dose groups experienced significantly greater reduction than placebo in scores on the Caregiver Strain Questionnaire ($p = 0.008$).[72]

Schizophrenia and Related Psychoses: Within-Study Subgroup Effects

Table 7 summarizes the within-study analysis for subgroups of interest. Four studies examined the impact of age on total PANSS scores,[94] global clinical judgments rating,[83] treatment response,[82] and conversion to psychosis.[86] Patients experiencing only mild or moderate improvement on the global clinical judgments rating scale on haloperidol tended to be younger than those rated as more improved.[83] A greater-than–two point difference in change in total PANSS scores was observed between 12-to-14 and 15-to-17 age groups in one study, although it is unclear which group received more benefit.[94] Age had no impact on response rate or conversion to psychosis. One study found that race (African American) predicted conversion to psychosis.[86]

Savitz et al.[94] found no differences between paliperidone and aripiprazole in change in total PANSS scores for groups differing by weight category, previous antipsychotic exposure, or duration of illness. One study investigated the effect of antipsychotic monotherapy compared with treatment with an antipsychotic plus concomitant antidepressant and/or mood stabilizers on response rate.[82] The study found no significant difference in response rate between subgroups in patients given haloperidol, olanzapine, or risperidone. Woods et al.[86] analyzed the effect of history of psychosis and duration of prodromal symptoms on neurocognitive performance in olanzapine-treated patients. Patients with first-episode psychosis were significantly more impaired on neurocognitive function test than patients at risk for psychosis.[83] Two studies found no impact of illness duration on global clinical judgments rating or neurocognitive performance.[86]

Table 7. Within-study analyses for subgroups of interest for schizophrenia and related psychoses

First Author, Year Comparison	Type of Analysis	Outcome	Authors' Conclusions
Savitz, 2015[94] *Paliperidone ER vs aripiprazole*	Subgroup analysis by age, previous antipsychotic exposure, illness duration	PANSS	Changes in PANSS total score were comparable regardless of age group, weight category, region, number of previous antipsychotic medications (<3 vs. ≥3) and duration of schizophrenic illness (<3 vs. ≥3 yr), except in the 12 to 14 year age group (between-group difference was >2 points).
Sikich, 2004[82] *Haloperidol vs. olanzapine vs. risperidone*	Subgroup analysis by age, cotreatment, treatment history, diagnosis, baseline symptom severity	Response	No significant relationship between response status and age, diagnosis, prior antipsychotic exposure or baseline severity of symptoms. Also, there was no significant difference in response rate between patients treated exclusively with antipsychotic, treated with either concomitant antidepressant or mood stabilizer, or both concomitant antidepressant and mood stabilizer.
Spencer, 1994[83] *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[86] 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 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, digit symbol, working memory and verbal fluency measures. Cognitive performance was not significantly correlated with length of manifestation of prodromal symptoms.

CPT = continuous performance task; CVLT = continuous verbal learning test; IQ = intelligence quotient; PANSS = Positive and Negative Syndrome Scale

Bipolar Disorder: Overview

Nineteen studies compared SGAs with other drugs of the same class or with placebo in children and adolescents with bipolar disorder.[65, 66, 105-121] Tables 8 and 9 provide selected information on the characteristics of the individual trials and the one observational study,[107] respectively. Studies that include both head-to-head and placebo comparisons are listed under the head-to-head category. Head-to-head drug comparisons were made in three studies comparing chlorpromazine with olanzapine,[66] and risperidone with olanzapine[113] and quetiapine.[112] Different doses of the same SGA were compared in five trials.[65, 108, 117-119] Fourteen RCTs compared one or more doses of an SGA to placebo.[105, 106, 108-111, 114-121] Most studies had flexible-dosing protocols; three used fixed doses when comparing two or three doses of the same SGA.[65, 108, 119] Detailed evidence tables are available in Appendix D.

The average age of patients was 12.8 years. Both sexes were equally represented across the studies (56% male). The majority of patients (range 65-100%) reported a White race/ethnicity.

Diagnosis of bipolar disorder was established using the DSM–IV or DSM–IV–TR. Most studies enrolled patients having bipolar I disorder. Three studies had a mixture of bipolar I and bipolar II disorder,[107, 109, 121] and three others included patients with bipolar disorder not-otherwise-specified (NOS).[107, 110, 113] One study only enrolled patients with bipolar NOS or cyclothymia,[106] and another only enrolled patients with psychotic features.[66] Most studies focused on treatment for mania or mixed phases of bipolar disorder; two studies focused on patients having depressive episodes within bipolar I or II disorder.[109, 114] As noted earlier, the diagnosis of bipolar disorder in children is controversial, particularly in young children (e.g., preschoolers in Biederman et al.[113]). A majority of studies enrolled many (> 40%) children with secondary diagnoses, including ADHD; disruptive, impulse-control, or conduct disorders; and/or anxiety disorders. All of the patients in one study had comorbid ADHD.[121] Several studies included patients who experienced psychoses.

Sixteen of the trials had followup periods ranging from 3 to 12 weeks. One trial had a controlled extension phase of 30 weeks,[117] one trial had a placebo-controlled maintenance treatment duration of 72 weeks,[110] and the observational study reviewed charts for between 7 to 8 months.[107] Sixty-seven percent of RCTs had high ROB; the most common source of potential bias was incomplete outcome data although some studies[65, 66 112, 113] did not blind participants or providers. The observational study was of high quality (6 of 8 stars).[107]

Table 8. Characteristics of trials examining bipolar disorder

First Author, Year Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
FGAs vs SGAs			
Conus et al., 2015[66] RCT, 8wk	**G1:** Chlorpromazine (41), 185.9±126.7 mg/day **G2:** Olanzapine (42), 12.2±7.8 mg/day	**G1:** 22±3 yr / Male: 63.9% / White: NR **G2:** 21.1±2.7 / Male: 71.1% / White: NR	Psychotic features within bipolar I (61) or schizoaffective disorder (22) History of treatment: NR ROB: High (subjective), High (objective)
SGAs vs. SGAs			
Findling, 2009[117] 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% / White: 66% **G2:** 13.3±2.3 yr / Male: 52% / White: 69% **G3:** 13.3±2.1 yr / Male: 57% / White: 61% Comorbidities: ADHD (153), DBD (93), psychosis (14)	bipolar I (all), mania (119), mixed (125), unknown (52) ROB: Medium (subjective), Medium (objective)
Findling, 2015b[108] RCT, 3 wk	**G1:** Asenapine (104), 2.5 mg/day **G2:** Asenapine (99), 5 mg/day **G3:** Asenapine (99), 10 mg/day **G4:** Placebo (101)	**G1:** 13.7±2.1 yr / Male: 50% / White: 72.1% **G2:** 13.8±2.0 yr / Male: 44% / White: 67.7% **G3:** 13.9±2.1 yr / Male: 58.6% / White: 65.7% **G4:** 13.7±2.0 yr / Male: 37.6% / White: 67.3% Comorbidities: ADHD (220)	manic (171), mixed (232) ROB: Low (subjective), Low (objective)

First Author, Year Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
Biederman, 2005[113] 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% / White: 100% **G2:** 5.3±0.8 yr / Male: 75% / White: 94% Comorbidities: ADHD (19), CD (13), MDD (22)	bipolar I (27), bipolar NOS (4), mania (all) ROB: High (subjective), High (objective)
Pathak, 2013[119] RCT, 3 wk	**G1:** Quetiapine, low dose (93), 400 mg/day **G2:** Quetiapine. high dose (95), 600 mg/day **G3:** Placebo (89)	**G1:** 13.1±2.2 yr / Male: 51% / White: 79% **G2:** 13.2±2.2 yr / Male: 58% / White: 77% **G3:** 13.3±2.1 yr / Male: 61% / White: 75% Comorbidities: ADHD (124)	bipolar I, manic (272), mixed (5) ROB: High (subjective), High (objective)
Masi, 2015[112] RCT, 12 wk	**G1:** Quetiapine (12), 163.3±55.2 mg/day **G2:** Risperidone (10), 1.90±0.60 mg/day	**G1:** 14.9±1.1 yr / Male: 71.4% / White: 100% **G2:** 15.1±1.8 yr / Male: 42.9% / White: 100% Comorbidities: ADHD (5), anxiety disorders (5), substance use disorder (3), eating disorder NOS (2)	hypomanic (all) ROB: High (subjective), High (objective)
Haas, 2009c[118] 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 / Male: 56% / White: 70% **G2:** NR / Male: 43% / White: 82% **G3:** NR / Male: 48% / White: 78% Comorbidities: ADHD (85), DBD (101)	bipolar I (all), manic episode (60), mixed episode (109) ROB: High (subjective), High (objective)
DelBello, 2008[65] RCT, 3 wk	**G1:** Ziprasidone (low) (15), target: 80 mg/day **G2:** Ziprasidone (high) (31), target: 160 mg/day	**G1:** 13.2±2.1 yr / Male: 47% / White: NR **G2:** 13.8±2.4 yr / Male: 77% / White: NR Comorbidities: NR	bipolar I (all) ROB: High (subjective), High (objective)
SGA vs. Placebo			
Tramontina, 2009[121] RCT, 6 wk	**G1:** Aripiprazole (18), 13.6±5.4 mg/day **G2:** Placebo (25)	**G1:** 11.7±2.7 yr / Male: 33% / White: 83% **G2:** 12.2±2.8 yr / Male: 56% / White: 96% Comorbidities: ADHD (all), anxiety disorders (21), DBD (35), psychosis (16)	bipolar I (35), bipolar II (8) ROB: Low (subjective), Low (objective)
Findling, 2012b[110] RCT, 72 wk	**G1:** Aripiprazole (30), 0.23±0.07 mg/kg/day (at randomization), 0.26±0.11 (end of study) **G2:** Placebo (30)	**G1:** 7.1±1.5 yr / Male: 63% / White: NR **G2:** 6.7±1.7 yr / Male: 77% / White: NR Comorbidities: DBD (11), ADHD (54), any anxiety disorder (2)	bipolar disorder NOS (33), bipolar I disorder (21), cyclothymia (6) ROB: High (subjective), High (objective)

First Author, Year Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
NCT00194012[106] RCT, 12 wk	**G1:** Aripiprazole (30), 2-15 mg/day **G2:** Placebo (29)	**G1: 5**-17 yr / Male: 66.7% / White: NR **G2:** 5-17yr / Male: 51.7% / White: NR Comorbidities: NR (ASD & MR exclusion criteria)	bipolar NOS or cyclothymia ROB: High (subjective), High (objective)
Tohen, 2007[120] RCT, 3 wk	**G1:** Olanzapine (107), 8.9 mg/day **G2:** Placebo (54)	**G1:** 15.1±1.3 yr / Male: 57% / White: 66% **G2:** 15.4±1.2 yr / Male: 44% / White: 76% Comorbidities: ADHD (58), DBD (49)	bipolar I (all), mixed (86), psychotic features (29), rapid cycling (30) ROB: Medium (subjective), Medium (objective)
DelBello, 2002[115] RCT, 6 wk	**G1:** Quetiapine (15), 432 mg/day **G2:** Placebo (15)	**G1:** 14.1±2 yr / Male: 53% / White: 80% **G2:** 14.5±2 yr / Male: 53% / White: 87% Comorbidities: ADHD (18), psychosis (14)	bipolar I (all), mixed episode (23) ROB: Medium (subjective), Medium (objective)
DelBello, 2009[114] RCT, 8 wk	**G1:** Quetiapine (17), 403±133 mg/day **G2:** Placebo (15)	**G1:** 16.0±2 yr / Male: 29% / White: 82% **G2:** 15±2 yr / Male: 33% / White: 80% Comorbidities: ADHD (4), anxiety disorder (8), DBD (8), psychosis (3)	bipolar I with depressive episode (32) ROB: High (subjective), High (objective)
Findling, 2014a[109] RCT, 8 wk	**G1:** Quetiapine (92), mean modal dose: 204.9 mg/day **G2:** Placebo (100)	**G1:** 13.9±2.2 yr / Male: 48.9% / White: 70.7% **G2:** 14.0±2.1 yr / Male: 52% / White: 60% Comorbidities: ADHD (84)	bipolar I or II with depression ROB: High (subjective), High (objective)
Kowatch, 2015[111] RCT, 6 wk	**G1:** Risperidone (18), 0.5 (0.5-0.75) mg/day **G2:** Placebo (7)	**G1:** 5.31±1.3 yr / Male: 61% / White: 61% **G2:** 5.19±1.0 yr / Male: 71% / White: 71% Comorbidities G1/G2: ADHD (37/15.2%), ODD (4.3/0%), GAD (8.7/6.5%)	manic, hypomanic, mixed ROB: Medium (subjective), Medium (objective)
Findling, 2013b[116] 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 / White: NR **G2:** 13.7 yr / Male: NR / White: NR Comorbidities: NR	bipolar I (237) ROB: High (subjective), High (objective)
Schneider, 2012[105] RCT, 4 wk	**G1:** Ziprasidone (14), 20 mg/day **G2:** Placebo (9)	**G1:** 14.7±2.3 yr/ Male: 64% / White: 86% **G2:** 14.5±2.2 yr / Male: 22% / White: 89% Comorbidities: ADHD (10)	bipolar I mixed (18), manic (NR) ROB: High (subjective), High (objective)

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

Table 9. Characteristics of observational studies examining bipolar disorder

First Author, Year Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
SGAs vs. SGAs			
Oh, 2013[107] Retrospective cohort, 7-8 mo	**G1:** Aripiprazole (62), 9.58±5.38 mg/day **G2:** Others (65), 1.46±1.08 mg/day (risperidone), 207.46±200.53 mg/day (quetiapine), 4.50±2.12 mg/day (paliperidone)	**G1:** 13.16±2.80 yr / Male: 66.1% / White: NR **G2:** 11.46±3.95 yr / Male: 76.9% / White: NR Comorbidities: ADHD (50), tic related disorders (17), conduct disorders and ODD (5), autism spectrum disorder (12)	Bipolar I, II, NOS (NR) 6/8 stars

ADHD = attention deficit hyperactivity disorder; G = group; mg = milligram; mo = month; N = number; NOS = not otherwise specified; NR = not reported; ODD = oppositional defiant disorder; SD = standard deviation; SGA = second-generation antipsychotic; wk = week; yr = year

Bipolar Disorder: Intermediate Outcomes

Sixteen RCTs reported on intermediate outcomes for treating bipolar disorder. A summary of the key findings is provided below; some observations related to possible subgroup effects are provided for SGA-placebo comparisons. Table 10 contains the findings and SOE ratings for the key outcomes assessed as having at least low SOE; the reason for each SOE decision is included in the table footnotes. The remainder of this section provides a detailed analysis of the findings by comparison and outcome category.

Key Points

- **Chlorpromazine versus olanzapine**:[66] The differences between these two antipsychotics are not known for symptoms of mania, depression, or psychosis, or for response, remission, or global impressions of severtity.
- **Risperidone versus olanzapine**[113] **and quetiapine**[112]: The effects between risperidone and olanzapine are not known for manic or depression symptoms. Comparative effects of quetiapine and risperidone are not known for outcomes of anxiety, manic or depression symptoms, or global impressions of severity or functioning.
- **SGAs—Dose comparisons** (aripiprazole,[117] asenapine,[108] quetiapine,[119] risperidone,[118] ziprasidone[65]): There may be a slightly greater reduction in manic symptoms from high- (10mg/day) versus low-dose (5 mg/day) asenapine; dose of asenapine may make little or no difference for global impressions of severity or for depression. The effects are not known for comparisons between different doses of other SGAs for manic symptoms, remission and response rates, depression, global impressions of severity, or global functioning.
- **SGAs versus placebo** (aripiprazole,[106, 117, 121] asenapine,[108] olanzapine,[120] quetiapine,[109, 114, 115, 119, 120] risperidone,[111, 118] ziprasidone[105, 116]): SGAs probably decrease manic symptoms and decrease slightly depression symptoms. They probably increase response and remission rates for patients experiencing manic/mixed phases; clinical and statistical heterogeneity was introduced when including two RCTs[109, 114] examining quetiapine for patients with depressive episodes. SGAs likely improve symptom severity and global functioning slightly. When examining individual SGAs versus placebo, the findings for aripiprazole were similar to those across all SGAs, with the exception of depression

symptoms where use of this SGA may make little or no difference. Quetiapine probably reduces manic symptoms, likely makes little or no difference for depression symptoms, and may make no difference for response in studies of patients experiencing manic/mixed episodes; the results of little or no difference for response rates (often focused on manic symptoms) were imprecise showing that many patients may have clinically relevant response. The effects of quetiapine versus placebo for remission rates and for global impressions of severity are not known. ***Observations on between-study subgroup effects***: (a) two RCTs focused on patients experiencing depressive episodes,[109, 114] for whom it appears the efficacy of SGAs for response and remission rates are lower; (b) a study[106] enrolling patients with prodromal bipolar disorder reported similar efficacy to the other studies of patients with manic symptoms; and (c) a study exclusively enrolling patients having comorbid ADHD[121] did not appear to differ in effect for several outcomes to other similar studies assessing SGAs in manic or mixed episodes.

Table 10. Strength of evidence for bipolar disorder: Key intermediate outcomes having at least low strength of evidence

Comparison	Outcome (N Studies; N Patients)	Findings,[a] Studies, Tool With Range of Values, if Applicable	Strength of Evidence; Conclusions
Asenapine high (10 mg/day) vs. low (5 mg/day) dose	Manic symptoms (1, 199)	MD, -2.80; 95% CI -0.64 to -4.96 (YMRS; range 0-60)[108]	Low; High-dose asenapine may decrease slightly manic symptoms
	Global impressions of severity (1, 199)	MD, -0.10, 95% CI -0.29 to 0.49[108]	Low; may make little or no difference
	Depression (1, 199)	MD, 0.80; 95% CI -1.87 to 3.47 (CDRS; range 0-113)[108]	Low; may make little or no difference
SGAs vs. placebo	Manic symptoms (11, 1639)	MD, -6.42; 95% CrI, -7.88 to -5.26 (YMRS; range 0-60)[106, 108, 111, 114-121]	Moderate; SGAs probably decrease[b]
	Depression symptoms (9, 1622)	MD, -1.65; 95% CrI, -2.78 to -0.48 (CDRS; range 0-113)[108, 109, 111, 114, 116, 117, 119-121]	Moderate; SGAs probably decrease slightly[b]
	Response (10, 1664) (Manic/mixed phases)[c]	RR, 1.97; 95% CrI, 1.66 to 2.34 (40-50% reduction in YMRS from baseline) [105, 108, 111, 115-121]	Moderate; SGAs probably increase for manic/mixed phases[b]
	Remission (5, 944) (Manic/Mixed phases)[c]	RR, 2.84; 95% CrI, 1.67 to 5.55[117-121]	Moderate; SGAs probably increase for manic/mixed phases[b]
	Global impressions of severity using CGI-S[d] (9, 1778)	MD, -0.65; 95% CI, -0.80 to -0.49[108, 109, 114, 116-121]	Moderate; SGAs probably improve slightly[b]
	Global impressions of functioning (4, 1188)	MD, 6.64; 95% CrI, 2.45 to 10.95 (C-GAS; range 1-100)[108, 116, 117, 119]	Moderate; SGAs probably improve slightly[b]
Aripiprazole vs. placebo	Manic symptoms (3, 387)	MD, -7.08; 95% CrI, -10.96 to -3.24 (YMRS; range 0-60)[106, 117, 121]	Moderate; Aripiprazole probably decreases[b]
	Depression symptoms (2, 311)	1 RCT: MD, -1.74; 95% CI, -3.92 to 0.44[117] 1 RCT: MD, -2.29; 95% CI, -10.62 to 6.04[121] (CDRS-R; range 17-113)	Low; Aripiprazole may make little or no difference [e]
	Response rates (2, 311)	1 RCT: RR, 2.11; 95% CI, 1.47 to 3.02[117] 1 RCT: RR, 1.71; 95% CI, 1.13 to 2.58[121]	Moderate; Aripiprazole probably increases[b]
	Remission (2, 311)	1 RCT: RR, 7.09; 95% CI, 2.96 to 16.99[117] 1 RCT: RR, 2.26; 95% CI, 1.19 to 4.28[121]	Moderate; Aripiprazole probably increases[b]
	Global impressions of severity using CGI-S (2, 328)	1 RCT: MD, -1.00; 95% CI, -1.34 to -0.67[117] 1 RCT: MD, -0.41; 95% CI, -0.80 to -0.02[121]	Moderate; Aripiprazole probably improves slightly[b]
Quetiapine vs. placebo	Manic symptoms (3, 339)	MD, -5.34; 95% CrI, -9.92 to -0.44 (YMRS; range 0-60)[114, 115, 119]	Moderate; Quetiapine probably decreases [b]
	Depression symptoms (3, 501)	MD, -1.87; 95% CrI, -4.71 to 1.11 (CDRS-R; range 17-113)[109, 114, 119]	Moderate; Quetiapine probably makes little or no difference [b]
	Response (2, 307) (Manic/mixed)	1 RCT: RR, 1.36; 95% CI, 0.97 to 2.72[115] 1 RCT: RR, 1.97; 95% CI, 1.38 to 2.81[119]	Low; Quetiapine may make little or no difference [e]

CDRS-R = Children's Depression Rating Scale-Revised; C-GAS = Global Assessment Scale for Children; CGI-S = Clinical Global Impressions of Severity; CrI = credible interval (used with Bayesian meta-analysis); MD = mean difference; N = number; RCT: randomized controlled trial; RR = risk ratio; SGA = second-generation antipsychotics; YMRS = Young Mania Rating Scale

[a] When the findings are not representative of the total number of studies identified in the outcome column, we included the number of studies for each finding; we did not pool data from 1 or 2 studies so these results are always presented separately. All values except Response, Remission, and Global Impressions of Functioning are favorable for the SGA when there is a negative effect estimate; the larger the magnitude of the number the larger the effect.

[b] Downgraded for ROB.

[c] When two studies examining the depressive phase were included the heterogeneity has substantial.

[d] CGI-S and CGI-I scores range from 0-6.
[e] Downgraded for ROB and imprecision due to CI including clinically relevant benefit for SGAs.

Detailed Analysis

FGAs Versus SGAs

One RCT compared olanzapine with chlorpromazine as adjunct treatment to lithium for intermediate outcomes in first episode psychotic mania. Eighty-three patients (average age 21.5 years) with either bipolar I or schizoaffective disorder were treated for 8 weeks. Patients taking olanzapine were more likely to achieve remission of mania (YMRS score < 12; p = 0.032) at 8 weeks. No significant differences were found for changes in manic or depressive symptoms, reponse (p = 0.121) rates, severity of illness, or positive psychotic symptoms at 8 weeks.[66]

SGAs Versus SGAs

Seven RCTs compared either different SGAs[112, 113] or different doses of the same SGA.[65, 108, 117-119]

Olanzapine versus risperidone. An 8-week RCT compared olanzapine with risperidone in children ages 4 to 6.[113] Risperdone lowered manic symptoms to a greater extent (6.7 points on the Young Mania Rating Scale [YMRS]; p = 0.04) than olanzapine. The numerical values favored risperidone for change in depression (4.4 points greater reduction on Children's Depression Rating Scale-Revised [CDRS-R]) but the difference was not significant (p > 0.30).

Quetiapine versus risperidone. A 12-week RCT compared quetiapine with risperidone in treatment naïve adolescents with bipolar II disorder comorbid with conduct disorder.[112] All outcomes improved for both groups at study endpoint (p < 0.001 for time effects), although there was similar efficacy between groups in manic symptoms (p = 0.34), depression (p = 0.24), aggression (p = 0.62), global clinical severity (p = 0.58), and functional impairment (p = 0.06). Quetiapine was favored for reducing anxiety symptoms (p = 0.03). Responder status was similar between groups (50 and 60 percent for quetiapine and risperidone).

Aripiprazole–Low- versus high-dose. A 4-week RCT randomized 296 children ages 10 to 17 to two doses of aripiprazole (10 mg/day and 30 mg/day) and placebo.[117] Both dosing groups significantly improved on most outcomes compared with placebo. No significant differences were observed between the two aripiprazole doses for manic symptoms (p = 0.07; high-dose numerically favorable), depression (p = 0.38), or global impression of functioning (p = 0.22). Remission and response rates were higher for the high-dose (47.5% and 63.6%) versus low-dose (25% and 44.8%) group (p = 0.009).

Asenapine-Low- versus medium- versus high-dose. A 3-week placebo-controlled RCT compared three doses (2.5, 5, and 10 mg twice daily) of asenapine.[108] All three doses offered significant improvement over placebo for manic symptoms, response rates, and global impressions of severity and functioning. The results suggest a dose-response relationship for the outcomes of manic symptoms and response rates (both related to YMRS scores; p values < 0.5, < 0.001, and < 0.0001, respectively), although not for depression or for global impressions of severity or functioning. Only the 10 mg twice daily group was favored over placebo for depression scores on the CDRS.

Quetiapine–Low- versus high-dose. A 3-week placebo-controlled RCT compared the efficacy of low-dose (400 mg/day) and high-dose (600 mg/day) quetiapine.[119] No significant differences were observed between the two quetiapine dose regimens for manic symptoms (p = 0.16),

depression (p = 0.39), response or remission (p > 0.4), or global impressions of severity or functioning (p = 0.51). Both groups showed high medication adherence.

Risperidone–Low- versus high-dose. A 3-week placebo-controlled RCT compared the effectiveness of low-dose (0.5–2.5 mg/day) and high-dose (3–6 mg/day) risperidone.[118] The following outcomes showed no significant differences between the low- and high-dose groups: mania (p = 0.30), time to onset of improvement of mania, response rates (i.e., >50% reduction in YMRS), overall psychiatric symptoms (p = 0.55), and global clinical impressions of severity (p = 0.40).

Ziprasidone–Low- versus high-dose. Children ages 10 to 17 years with bipolar disorder or schizophrenia were randomized to low-dose (80 mg/day) and high-dose (160 mg/day) ziprasidone in a 3-week RCT.[65] Separate analyses were provided for patients with bipolar disorder (N = 46). No significant differences were found between the two doses for global impressions of severity (p = 0.65) or manic symptoms (p = 0.21).

SGAs Versus Placebo

Thirteen RCTs compared various SGAs with placebo for intermediate outcomes in bipolar disorder: aripiprazole,[106, 117, 121] asenapine,[108] olanzapine,[120] quetiapine,[109, 114, 115, 119] risperidone,[111, 118] and ziprasidone.[105, 116] Average treatment duration was 5.5 weeks (range 3-12 weeks). The average age of patients was 13.1 years, which included one study of children ages 3 to 7.[111] A total of 1,958 patients were enrolled in the trials. Most patients had a diagnosis of bipolar I disorder with the exception of three trials: two trials had approximately 20 percent patients with bipolar II,[109, 121] and one trial enrolled patients only with bipolar NOS or cyclothymia ("prodromal").[106] The most clinical heterogeneity was suspected from two RCTs focusing on treatment of depressive episodes.[108, 114]

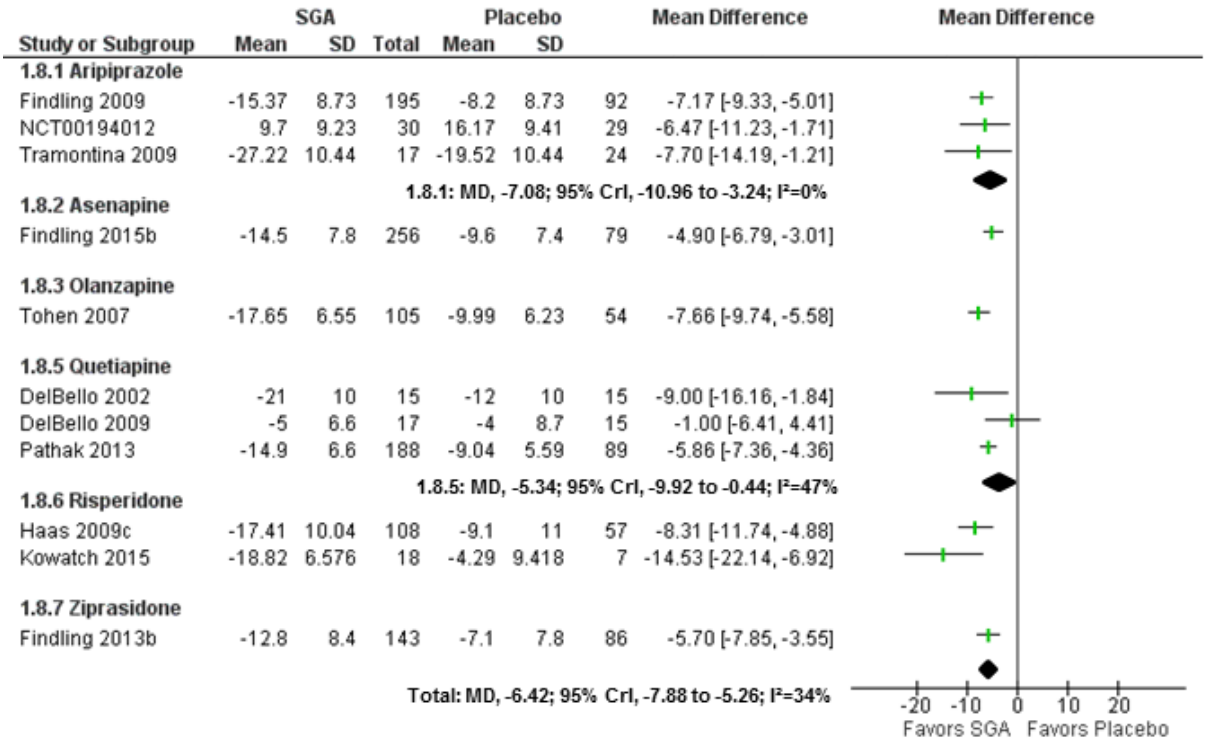
Meta-Analysis for SGAs Versus Placebo in Bipolar Disorder

Meta-analyses were conducted to compare SGAs with placebo for the short-term core symptoms of mania (YMRS) and depression (CDRS-R). They were also conducted for short-term nonspecific symptoms of response rate, remission, and discontinuation for lack of efficacy, and for global impressions of severity (CGI-Bipolar for severity) and functioning (C-GAS). To examine any effects based on clinical heterogeneity, sensitivity analyses were conducted by removing the studies examining depressive episodes.[109, 114]

Short-term core symptoms. Eleven RCTs[106, 108, 111, 114-121] evaluated the efficacy of SGAs versus placebo for manic symptoms, as measured by the YMRS (Figure 44). The results favored the SGAs (MD, -6.42; 95% CrI, -7.88 to -5.26; I^2 = 34%). Sensitivity analysis was conducted by removing the DelBello et al. study of patients experiencing depressive episodes;[114] results were similar (MD, -6.60; 95% CrI, -8.14 to -5.50; I^2 = 21%).

Meta-analysis of three studies[106, 117, 121] comparing aripiprazole with placebo showed a significant difference favoring aripiprazole (MD, -7.08; 95% CrI, -10.96 to -3.24); there was no evidence of statistical heterogeneity (I^2 = 0%) although the unpublished study examined patients with prodromal bipolar disorder (NCT00194012[106]) The three studies[114, 115, 119] of quetiapine were also meta-analyzed (MD, -5.34; 95% CrI, -9.92 to -0.44; I^2 = 47%), with results showing moderate statistical heterogeneity which may be related to the relatively lower extent of baseline mania symptoms in the 2009 study by DelBello of depression episodes.

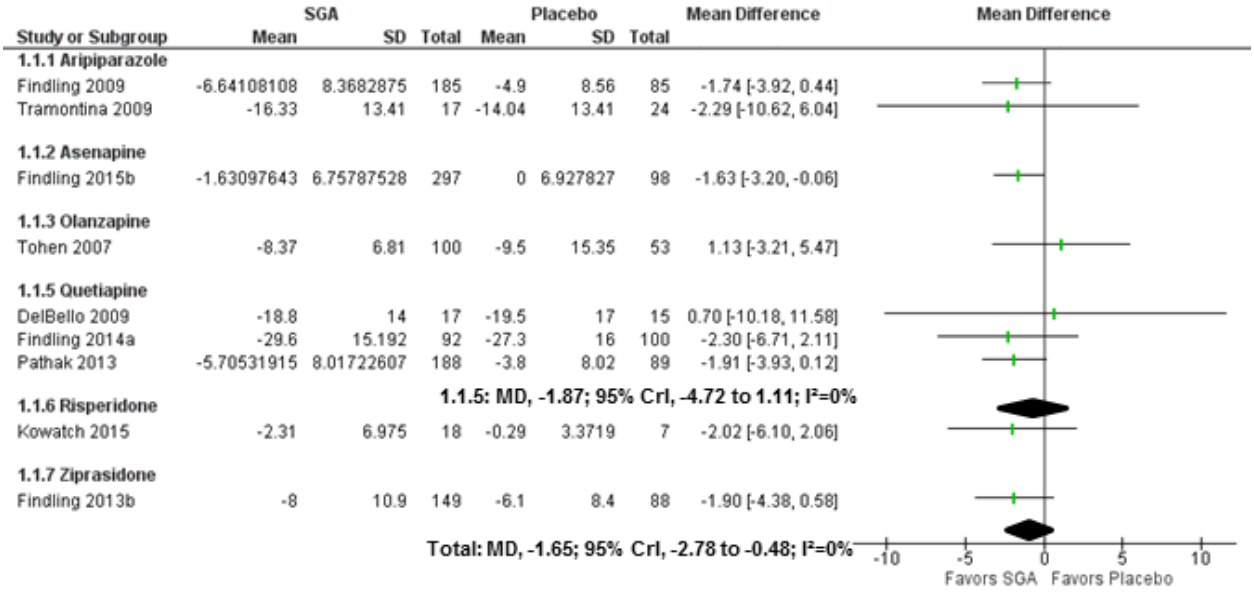
Figure 44. SGAs versus placebo for manic symptoms using YMRS in bipolar disorder



CrI = credible interval; MD = mean difference; SD = standard deviation; SGA = second-generation antipsychotic

Nine RCTs[108, 109, 111, 114, 116, 117, 119-121] compared various SGAs versus placebo for depression symptoms using the CDRS-R (Figure 45). Only one study found a statistically significant difference, favoring asenapine over placebo.[108] Results of the meta-analysis across all studies found a significant difference favoring SGAs (MD, -1.65; 95% CrI, -2.78 to -0.48; I^2 = 0%). Because of the lack of any statistical heterogeneity and focus on depression symptoms, we did not undertake sensitivity analysis by removing the two studies (DelBello 2009 and Findling 2014a) with patients having depression episodes.[109, 114] Meta-analysis of data from three RCTs[109, 114, 119] found no difference between quetiapine and placebo for depression symptoms (MD, -1.87; 95% CrI, -4.71 to 1.11; I^2 = 0%). Neither of the two studies[109, 114] focusing on the depressive phase found quetiapine beneficial for these symptoms.

Figure 45. SGAs versus placebo for depression using CDRS-R in bipolar disorder



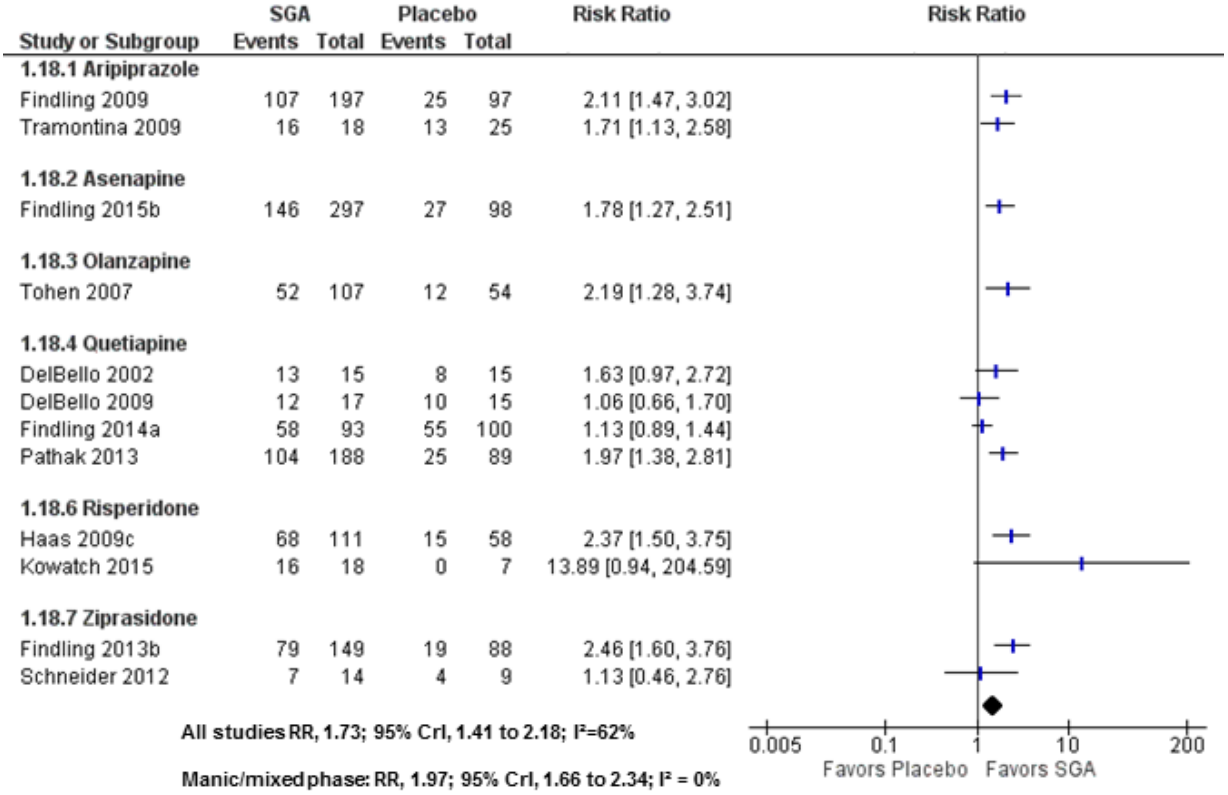
CDRS-R = Children's Depression Rating Scale-Revised; CrI = credible interval; MD = mean difference; SD = standard deviation; SGA = second-generation antipsychotic

Short-term nonspecific symptoms. Twelve studies reported on response rates for comparisons of SGAs with placebo (Figure 46).[108, 109, 114-121] Apart from the studies (DelBello 2009 and Findling 2014a) examining depression (using CDRS-R scores for response), the response rates were based on 40 to 50 percent reduction in YMRS at endpoint. Results favored SGAs for higher response, showing a RR of 1.73 (95% CrI, 1.41 to 2.18). Sensitivity analysis removing the studies of depression resulted in a higher RR of 1.97 (95% CrI, 1.66 to 2.34) and reduced the heterogeneity (I^2 = 0% from 62%).

Rates of remission were reported by seven trials (Figure 47).[109, 114, 117-121] Higher remission rates were found for patients taking SGAs compared with placebo (RR, 2.22; 95% CrI, 1.26 to 4.12). Removing the studies of patients experiencing depression found higher rates of remission for patients taking SGAs for manic/mixed episodes (RR, 2.84; 95% CrI, 1.67 to 5.55); the statistical heterogeneity (I^2) was reduced from 72 percent to 42 percent.

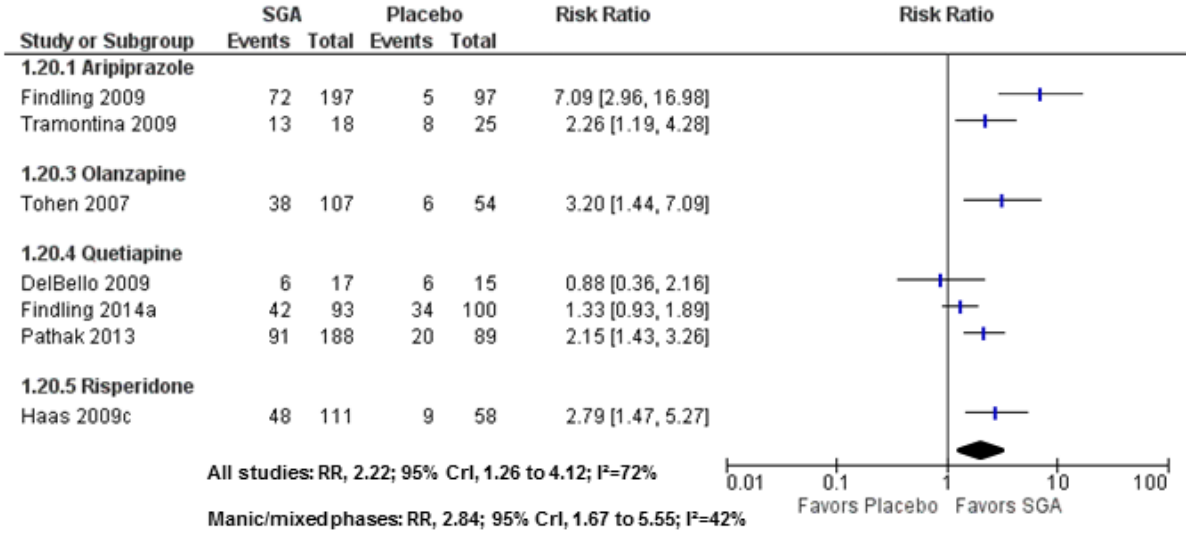
Nine studies provided data for meta-analysis of discontinuation due to lack of efficacy (Figure 48). Results favored SGAs over placebo (RR, 0.37; 95% CrI, 0.23 to 0.61; I^2 = 0%); there was no effect from removing the DelBello[114] and Findling[109] studies. Individual meta-analysis for aripiprazole[106, 117, 121] and quetiapine[109, 114, 115] failed to show significant benefit for these SGAs (aripiprazole: RR, 0.36; 95% CrI, 0.09 to 1.35, and quetiapine: RR, 0.55; 95% CrI, 0.13 to 2.65).

Figure 46. SGAs versus placebo for response rates in bipolar disorder



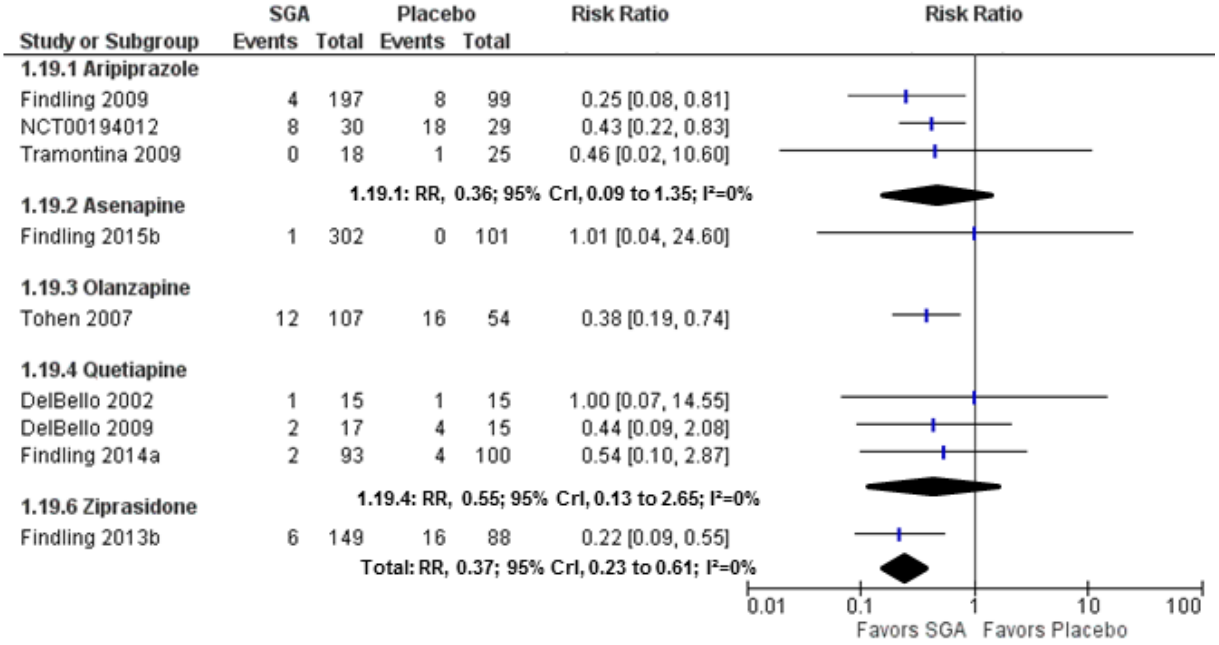
CrI = credible interval; RR = risk ratio; SGA = second-generation antipsychotic

Figure 47. SGAs versus placebo for rates of remission in bipolar disorder



CrI = credible interval; RR = risk ratio; SGA = second-generation antipsychotic

Figure 48. SGAs versus placebo for discontinuation due to lack of efficacy in bipolar disorder

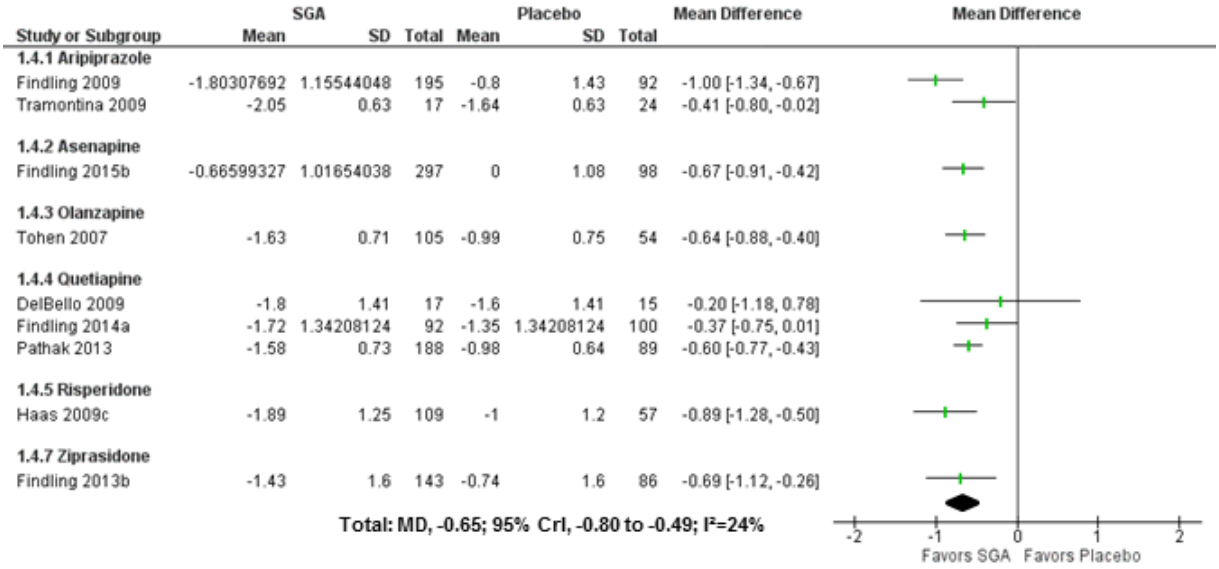


CrI = credible interval; RR = risk ratio; SGA = second-generation antipsychotic

Short-term global impressions. Nine RCTs[108, 109, 114, 116-121] provided data for a meta-analysis of the efficacy of SGAs versus placebo for global impressions of severity (Figure 49). Two studies used the CGI–S,[116, 121] and seven studies used the CGI–Bipolar Version for Severity. The combined estimate favored SGAs (MD, -0.65; 95% CI, -0.80 to -0.49; I^2 = 24%). Removing the two studies enrolling patients in the depressive episode[109, 114] did not affect the results (MD, -0.68; 95% CrI, -0.86 to -0.52; I^2 = 20%).

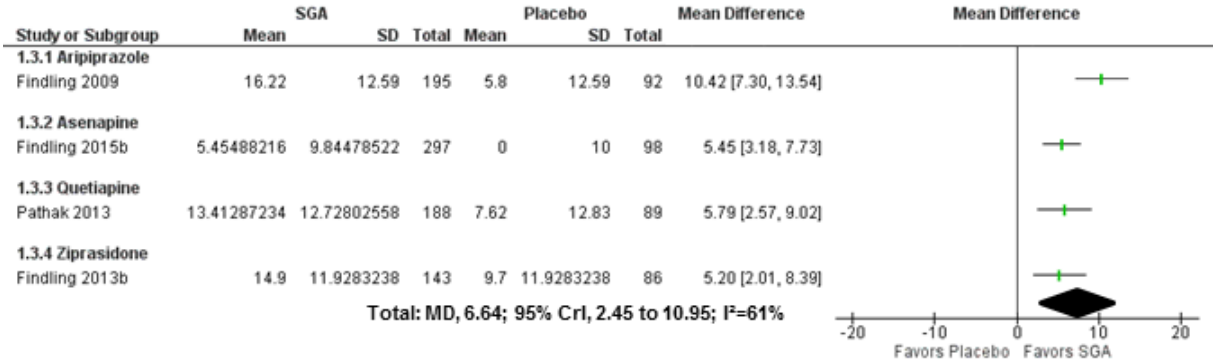
Four studies provided data for SGAs versus placebo on global impressions of functioning, measured using the C-GAS (Figure 50).[108, 116, 117, 119] The SGAs were favorable over placebo for improving overall functioning (MD, 6.64; 95% CrI, 2.45 to 10.95). There was moderate statistical heterogeneity (I^2 = 61%) which may in part relate to the higher relative dose of SGA used in one of the aripiprazole groups in the Findling 2009 study.[117]

Figure 49. SGAs versus placebo for global impression of severity using CGI-S/CGI-BP in bipolar disorder



CGI-S = Clinical Global Impressions of Severity; CGI-BP = Clinical Global Impressions for Bipolar Illness; CrI = credible interval; MD = mean difference; SD = standard deviation; SGA = second-generation antipsychotic

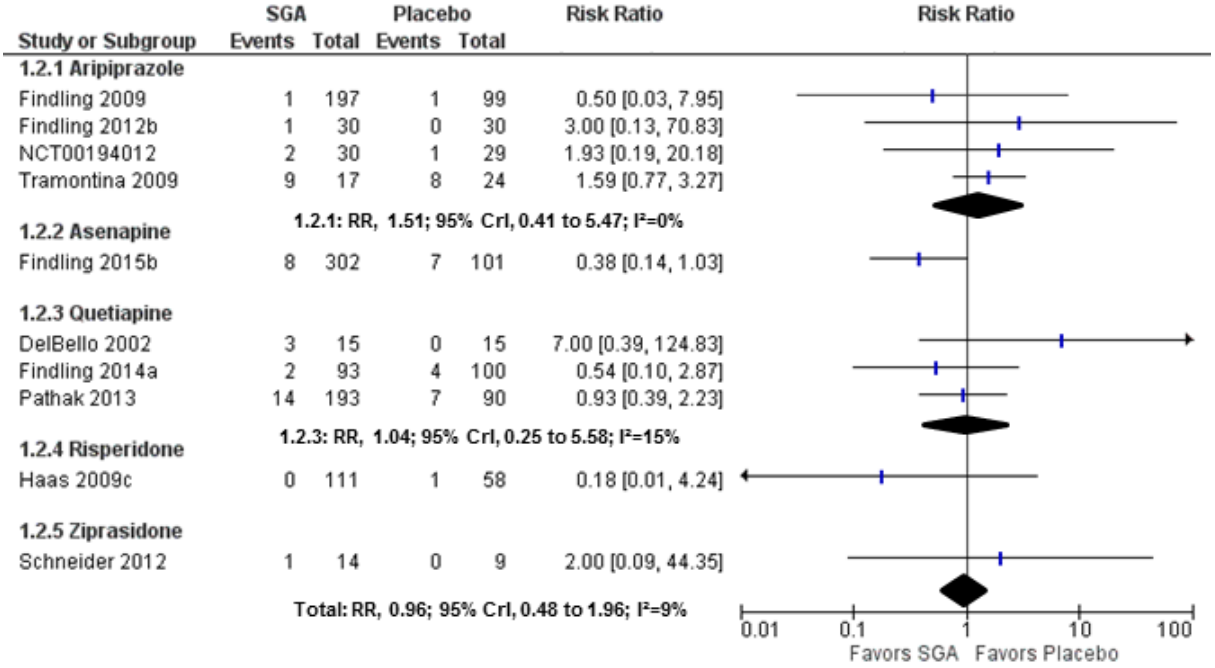
Figure 50. SGAs versus placebo for global impression of functioning using C-GAS in bipolar disorder



C-GAS = Children's Global Assessment Scale; CrI = credible interval; MD = mean difference; SD = standard deviation; SGA = second-generation antipsychotic

Medication adherence. Ten RCTs contributed to a meta-analysis comparing poor adherence rates (often discontinuation for poor treatment compliance) for SGAs versus placebo (Figure 51).[105, 106, 108-110, 115, 117-118, 121] The only drug that approached statistical significance for better adherence over placebo was asenapine;[108] the relatively short (3-week) treatment duration may have influenced these results. The pooled results for all comparisons showed no significant difference between groups (RR, 0.96; 95% CrI, 0.48 to 1.96). Meta-analysis was conducted for aripiprazole (RR, 1.51; 95% CrI, 0.41 to 5.47)[106, 110, 117, 121] and quetiapine (RR, 1.04; 95% CrI, 0.25 to 5.58),[109, 114, 119] with similar results of no difference.

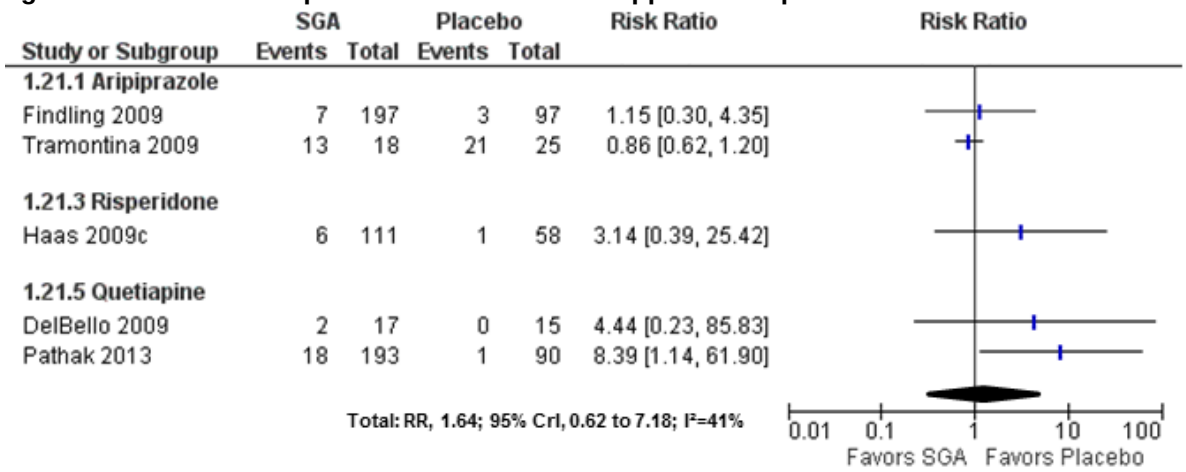
Figure 51. SGAs versus placebo for poor medication compliance in bipolar disorder



CrI = credible interval; MD = mean difference; SGA = second-generation antipsychotic

Lifestyle behaviors. Data provided by five RCTs[114, 117-119, 121] on increases in appetite as reported by patients found no difference between SGAs and placebo (RR, 1.64; 95% CrI, 0.62 to 7.18) (Figure 52). Two studies having treatment durations of 6 months or longer found similar results. In one study,[117] 6 versus 0 percent (p = 0.13) of patients taking aripiprazole or placebo, respectively, reported increased appetite after 12 months of treatment. In the other study,[110] of 12-month placebo-controlled aripiprazole maintenance treatment, 30 versus 43 percent taking aripiprazole or placebo reported increases.

Figure 52. SGAs versus placebo for increases in appetite in bipolar disorder



CrI = credible interval; RR = risk ratio; SGA = second-generation antipsychotic

Additional Findings

Few studies reported on psychotic symptoms, despite many enrolling patients with this symptomatology; one study on quetiapine reported no between-group differences ($p = 0.8$) in positive symptoms using the PANSS. The incidence of switch to depression (CGI depression score ≤3 at baseline and ≥4 points at any time during the double-blind phase) did not differ significantly between olanzapine and placebo.[120] A single study favored aripiprazole over placebo on the General Behavior Inventory ($p < 0.0001$).[117] Patients using olanzapine showed significantly greater ($p = 0.002$) improvement in aggression on the OAS than patients on placebo.[120] There was no significant difference ($p = 0.76$) between quetiapine and placebo groups on the Hamilton Anxiety Rating Scale in another study.[114] Risperidone was favored ($p = 0.004$) over placebo for general psychiatric symptoms on the BPRS.[118] Taking ziprasidone improved global impressions on the CGI-I in one study (MD, -0.76; $p = 0.002$).[116]

Observations on Between-Study Subgroup Effects

The trials examining SGAs versus placebo were fairly similar in terms of patient populations, protocols, and duration. There was some heterogeneity in terms of phase of illness (e.g., manic or mixed vs. depressive) and relative number of patients having comorbidities. Apart from the studies examining depressive episodes which marginally impacted (reduced) effects on response and remission rates,[109, 114] the study enrolling patients with prodromal bipolar disorder[106] reported similar efficacy to the other studies of patients with manic symptoms. The study by Tramontina et al.[121] exclusively enrolling patients having comorbid ADHD did not appear to differ in effect for several outcomes to other similar studies assessing SGAs in manic or mixed episodes. These authors also stated that there were no between group differences in ADHD symptoms.

Bipolar Disorder: Effectiveness Outcomes

Eleven studies reported on effectiveness outcomes when treating children for bipolar disorder. With the exception of the observational study comparing various SGAs,[107] all studies reported on SGAs versus placebo. A summary of the findings on key outcomes by comparison is provided below. Table 11 contains the findings and SOE grades the key outcomes assessed as having at least low SOE; the reason for each SOE decision is included in the table footnotes. A detailed analysis for all relevant outcomes follows.

Key Points

- **SGAs versus SGAs** (one retrospective cohort[107]): The comparative effectiveness of risperidone, quetiapine, and aripiprazole for global impressions of improvement or severity after 4- to 6-month followup are not known.
- **SGAs versus placebo** (10 RCTs: aripiprazole,[110, 117, 121] asenapine,[108] olanzapine,[118] quetiapine,[109, 114, 119] risperidone,[118] ziprasidone[116]): There may be little or no difference between SGAs and placebo for suicide ideations and attempts. Studies examining long-term aripiprazole for acute and maintenance treatment with placebo reported on outcomes of manic and depression symptoms, global impressions of severity and functioning, response, and quality of life; all effects are considered unknown. Effects of ziprasidone on speed of processing are unknown, nor are the effects of olanzapine for psychosocial, behavior, family activities, and mental health scores. Besides suicide attempts and

ideations, conclusions were of unknown effect (insufficient SOE) due to ROB and inconsistency (or unknown consistency) and/or imprecision.

Table 11. Strength of evidence for bipolar disorder: Key effectiveness outcomes having at least low strength of evidence

Comparison	Outcome (N Studies; N Patients)	Findings[a]	Strength of Evidence; Conclusion
SGAs vs. placebo	Suicide ideation (8, 1782)	RR, 1.12; 95% CrI, 0.58 to 2.26[108, 109, 116-121]	Low; may make little or no difference [b]
	Suicide attempts (6, 1285)	RR, 1.71; 95% CrI, 0.39 to 7.38[108, 114, 116, 118-120]	Low; may make little or no difference [b]

CrI = credible interval (used with Bayesian meta-analysis); RR = risk ratio; SGA = second-generation antipsychotics.
[a] Positive RR represents benefit for placebo group.
[b] Downgraded for ROB and imprecision because CrI included values favoring either group to clinically meaningful extent (i.e., RR ≤0.75 or ≥1.25).

Detailed Analysis

Description of Long-Term Studies

Aripiprazole versus risperidone, quetiapine, and paliperidone. A retrospective cohort study examined charts of 125 outpatients with bipolar I, II or NOS ages 4 to 18 years attending a psychiatric clinic over a period of five visits (7.9±5.3 months).[107] Aripiprazole, risperidone, and quetiapine were administered to 62, 52, and 11 patients, respectively; the dose of aripiprazole was higher in terms of chloropromazine-equivalent doses.

Aripiprazole–Low- versus high-dose. A 4-week RCT (N = 296) comparing two doses of aripiprazole (10 mg/day and 30 mg/day) and placebo added a 26-week extension phase for acute treatment completers (n = 210 although results for intention-to-treat of whole sample).[117]

Aripiprazole versus placebo. A 72-week RCT (N = 60) was undertaken to compare aripiprazole with placebo for maintenance in children ages 4 to 9 with bipolar disorder I, II, NOS, or cylcothymia and stable for >12 weeks on aripiprazole (6.4±2.1 mg/day).[110]

Results on Effectiveness Outcomes From Short- and Long-term Studies

Long-term core symptoms. At 30 weeks, groups receiving low and high doses of aripiprazole had lower YMRS scores than placebo when considering the whole study population or only those in the extension phase (6.5 and 7 point reductions, respectively; $p < 0.001$);[117] very similar responses were found between doses. Neither dose of aripiprazole helped reduce depression symptoms compared with placebo. In the 72-week maintenance study of aripiprazole versus placebo, no significant between-group treatment effects were found for core symptoms of mania (YMRS) or depression (CDRS) ($p > 0.05$).[110]

Long-term nonspecific symptoms. Most patients discontinued treatment from the aripiprazole and placebo arms of the 72-week maintenance study (73% vs. 97%; $p = 0.06$).[110] Time until discontinuation as a result of a mood event was significantly longer for the aripiprazole group (25.93±31.8 vs. 3.10±1.0 weeks; $p = 0.005$). In the 30-week study of Findling et al.,[117] more patients were discontinued from the placebo (48.4%) compared with aripiprazole groups (22.7 and 14.1 for low- and high-dose groups) for lack of efficacy. Time to discontinuation in this

study significantly favored aripiprazole (low-dose $p < 0.001$; high-dose $p < 0.05$), but the results were not specific to lack of efficacy.

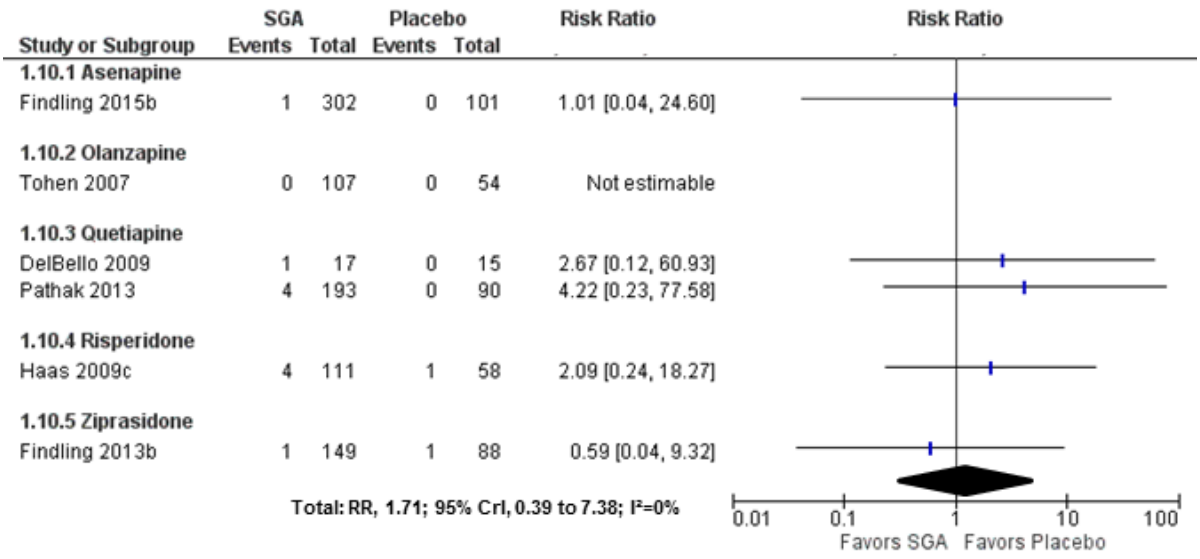
Long-term global impressions and functioning. Low and high doses of aripiprazole significantly favored placebo for global impressions of severity (CGI-BP overall illness; $p < 0.05$) and functioning (CGAS; $p < 0.05$).[117] For aripiprazole versus risperidone and quetiapine, no between group differences were seen between groups in terms of global impression of improvement or severity at 4 to 6 months followup;[107] all groups improved on these outcomes over baseline.

Cognitive functioning. Speed of processing score was lower in patients treated for 4-weeks with ziprasidone than with placebo; however, the level of significance was not reported.[116]

Suicide-related ideations or behaviors, or death by suicide. The suicide attempt rate was pooled for five short-term RCTs[108, 114, 116, 118, 119] comparing SGAs with placebo (Figure 53); one additional study reported no suicide attempts in either group.[120] There was no significant difference between the groups (RR, 1.71; 95% CrI, 0.39 to 7.38). Three short-term RCTs[116-118] reported suicide rates for SGAs versus placebo comparisons. No deaths by suicide occurred in either of the groups across all studies; therefore, a meta-analysis could not be conducted.

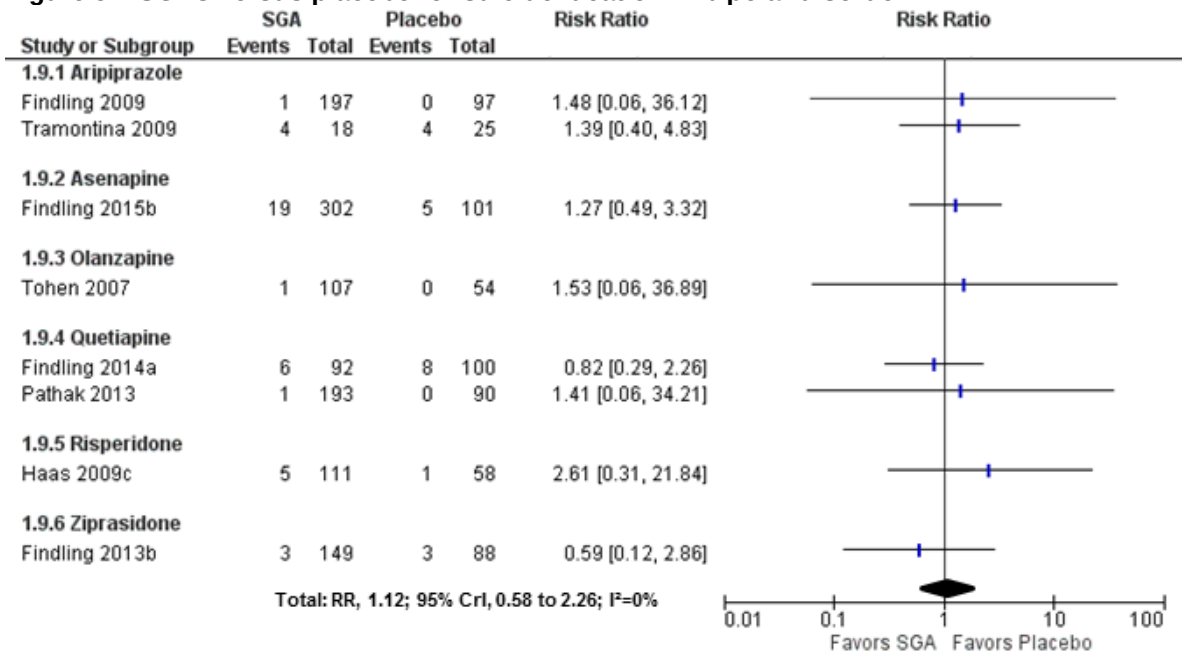
Eight short-term RCTs[108, 109, 116-121] comparing SGAs with placebo reported rates of suicidal ideation (Figure 54). The pooled estimate showed no significant difference between the groups (RR, 1.12; 95% CrI, 0.58 to 2.26). One study found no difference between ziprasidone and placebo for self-injurious behavior.[116]

Figure 53. SGAs versus placebo for suicide attempts in bipolar disorder



CrI = credible interval; RR = risk ratio; SGA = second-generation antipsychotic

Figure 54. SGAs versus placebo for suicide ideation in bipolar disorder



CrI = credible interval; RR = risk ratio; SD = standard deviation; SGA = second-generation antipsychotic

Quality of life/wellbeing. The Child Health Questionnaire (CHQ-PF50) was completed by parents in a 3-week study of adolescents taking olanzapine or placebo.[120] The olanzapine group improved to a greater extent than the placebo group in the Psychosocial summary score (10.7 vs. 6.5 points change, $p = 0.03$). The Behavior, Family activities, and Mental health subscales also showed significantly greater improvement in mean scores in the olanzapine group than the placebo group ($p < 0.05$). In both the acute (4-week) and long-term (30-week) phases in a trial comparing low- and high-dose aripiprazole with placebo, there was no difference between groups in quality of life measured by the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire.[117]

Caregiver burden/strain. One 3-week RCT found no significant difference between quetiapine and placebo in relieving caregiver burden, as assessed by the Caregiver Strain Questionnaire.[119]

Bipolar Disorder: Within-Study Subgroup Effects

Seven studies examining bipolar disorder conducted an analysis of patient outcomes in different subpopulations (Table 12).[108, 109, 116-120] All studies were placebo-controlled and evaluated SGAs.

The benefits of SGAs versus placebo for reducing manic[117-119] and depression[109] symptoms appear to be similar for children and adolescents (analyses using a cut-off around 12 years). Sex and race had no significant impact on YMRS scores in one placebo-controlled RCT comparing risperidone dosing regimens.[118] Another study[120] examined the impact of bipolar subtypes on CGI–BP and YMRS in patients treated with olanzapine. Diagnosis of bipolar diagnostic subtypes did not alter treatment outcomes.[120] Concomitant use of psychostimulants had no effect on YMRS scores;[108, 109, 119, 120] comorbid diagnosis of ADHD or a disruptive, impulse-control, or conduct disorder did not effect results either for mania[108, 116, 117, 119, 120] or depression.[109]

Table 12. Within-study analyses for subgroups of interest in bipolar disorder

First Author, Year Comparison	Type of Analysis	Outcome	Authors' Conclusions
Findling, 2015[108] *2.5mg vs. 5mg vs. 10 mg asenapine vs. placebo*	Subgroup analysis by comorbidity, cotreatment, onset, sex	YMRS	There was no significant difference in YMRS total score from baseline to day 21 between patients with/without ADHD, with/without concomitant stimulant use, onset of bipolar I disorder ≤11 yr or >11 yr, and gender.
Findling , 2009[117] *Aripiprazole vs. placebo*	Subgroup analysis by age, prior treatment, comorbidities	YMRS	Significant findings for YMRS remained for 10-12 and 13-17 yr olds, those with and without prior bipolar treatment, and for those with or without ADHD, ODD
Findling, 2014b[109] *Quetiapine vs. placebo*	Subgroup analysis by phase of disorder, bipolar subtypes, age, comorbidities, cotreatment	CDRS-R	No significant mean change in CDRS-R total score (baseline to 8 wk) found for patients with/without rapid cycling, with bipolar I or II disorder, 10-12yr or 13-17yr, patients with comorbid ADHD, patients with comorbid ADHD with/without concomitant psychostimulants
Findling, 2013b[116] *Ziprasidone vs. placebo*	Subgroup analysis by comorbidity, key symptoms	YMRS	Ziprasidone was efficacious in subjects who had the key symptoms elation/euphoria or grandiosity. Significant least squares mean difference in comorbid ADHD patients treated with ziprasidone vs. placebo.
Haas, 2009c[118] *Low- vs. high-dose risperidone vs. placebo*	Subgroup analysis by age	YMRS	Patients ≤12 and >12 years had significantly more improvement with risperidone than placebo.
	Subgroup analysis by sex, race, diagnosis, or hospitalization	YMRS	Risperidone was consistently more effective than placebo regardless or sex, race, diagnosis, or hospitalization at screening.
Pathak, 2013[119] *Low- vs. high dose quetiapine vs. placebo*	Subgroup analysis by age, sex, comorbidity, cotreatment	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 (10-12 vs.13-17 yr). Concomitant use of psychostimulants did not differentially affect YMRS scores.

First Author, Year Comparison	Type of Analysis	Outcome	Authors' Conclusions
Tohen, 2007[120] *Olanzapine versus placebo*	Subgroup analysis for comorbidities, bipolar subtypes, use of stimulants	CGI–BP and YMRS	Diagnosis of comorbid ADHD and bipolar diagnostic subtypes did not alter treatment outcomes. Concomitant use of psychostimulants had no effect on YMRS scores.

ADHD = attention deficit hyperactivity disorder; CDRS-R = Children's Depression rating Scale-Revised; CGI-BP = Clinical Global Impressions of Severity Bipolar; ODD = oppositional defiant disorder; YMRS = Young Mania rating Scale; yr = year

Autism Spectrum Disorders: Overview

Twenty-three studies examined the effectiveness of FGAs and SGAs in treating patients with autism spectrum disorders (ASD): nineteen RCTs,[122-140] two controlled before-after studies,[139, 140] and two retrospective cohort studies.[143, 144] The majority of the studies reported on intermediate and/or effectiveness outcomes; one RCT only provided data on harms specific to the patients within our age range.[125] Tables 13 and 14 provide selected information on the characteristics of the individual trials and observational studies, respectively. The studies are grouped according to the drug class comparisons. Studies that include both head-to-head and placebo comparisons are listed under the head-to-head category. Within each comparison, studies are listed alphabetically by the specific drugs compared. Detailed evidence tables are available in Appendix D.

Overall, the average age of patients was 9.1 years. Patients were predominantly male (average 83%) and White (72%; not reported in 11 studies). All studies included patients with ASD, with varying numbers specific to categories of pervasive developmental disorder, Asperger Syndrome, etcetera. In four studies, all enrolled patients had behavioral issues, such as tantrums, aggression, or self-injury. [131, 132, 140, 143] Global developmental delay was present in 24 percent of all patients across the studies.

Two studies provided head-to-head evidence for comparisons of an FGA (haloperidol) with SGAs (olanzapine or risperidone).[130, 133] One RCT[136] compared the long-term effectiveness of continuous (daily) versus discontinuous (5 days per week) administration of haloperidol. Two studies compared two SGAs (aripiprazole and risperidone),[124, 144] one compared risperidone to other SGAs,[143] and 13 compared an SGA (N = 8 for risperidone) with placebo.[123,125-129, 131, 132, 134, 135, 138-140,] Four RCTs compared different doses of SGAs,[125, 127, 128, 131] although one of them only for harms outcomes.

Treatment duration varied widely across studies (range, 4 weeks to 2.3 years). For the studies we considered short-term (< 6 month duration), average duration was 8.9 weeks. Four other studies provided 6-month data,[129, 133, 134, 136] and two provided data for longer than 12 months.[143, 144] Eight of 18 trials (44 percent) had a high ROB, mainly due to incomplete outcome data and unclear allocation concealment. Two of the four observational studies were of high quality/low ROB, one had moderate and another had poor quality.

Table 13. Characteristics of trials examining autism spectrum disorders

First Author, Year Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
FGAs vs. SGAs			
Malone, 2001[130] 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 yr / Male: 67% / White: 67% **G2:** 8.5±2.4 yr / Male: 67% / White: 50% Comorbidities: MR (mild (1), moderate (5), severe (5))	autism (11), PDD NOS (1) ROB: High (subjective), Medium (objective)
Miral, 2008[133] 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 yr / Male: 87% / White: NR **G2:** 10.0±2.7 yr / Male: 73% / White: NR Comorbidities: NR	autism (all) ROB: Medium (subjective), Medium (objective)
FGAs vs. FGAs			
Perry, 1989[136] RCT, 6 mo	**G1:** Haloperidol (continuous) (34), 1.2 mg/day **G2:** Haloperidol (discontinuous) (36), 1 mg/day	**G1 and G2:** 2.3–7.9 yr / Male: 69 / White: NR Comorbidities: NR	autism (all) ROB: High (subjective), High (objective)
SGAs vs. SGAs			
Ghanizadeh, 2014a[124] RCT, 8 wk	**G1:** Aripiprazole (29), 5.5 mg/day **G2:** Risperidone (30), 1.12mg/day	**G1:** 9.6±3.3 yr / Male: 86.2% / White: NR **G2:** 9.5±4.6 yr / Male: 76.6% / White: NR Comorbidities: NR	autism (38), asperger disorder (8), PDD-NOS (9), childhood disruptive behavior disorder (1) ROB: Medium (subjective), Medium (objective)
Hellings, 2006[125] RCT (cross-over), 6 wk Harms	**G1:** Risperidone (low) (26), NR **G2:** Risperidone (high) (26), 2 (1.2-2.9) **G3:** Placebo (26)	**All groups (G1-G3):** NR/ Male: NR / White: NR Comorbidities: MR (Mild (8), moderate (6), severe (8), profound (4)), PDD-NOS (NR)	NR ROB: High (subjective), High (objective)
Kent, 2013[128] RCT, 6 wk	**G1:** Risperidone (low) (30), 0.125–0.175 mg/day **G2:** Risperidone (high) (31), 1.25–1.75 mg/day **G3:** Placebo (35)	**All groups:** Age NR / Male: 88% **G1:** White: 70% **G2:** White: 81% **G2:** White: 57% Comorbidities: NR	autism (all) ROB: Medium (subjective), Medium (objective)
Loebel et al., 2016[127] RCT, 6 wk	**G1:** Lurasidone (low)(48), 20 mg/day **G2:** Lurasidone (high)(51), 60 mg/day **G3:** Placebo (49)	**G1:** 10.5±3 yr / Male: 79.2% / White: 79.2% **G2:** 10.5±3 / Male: 84.3% / White: 74.5% **G3:** 11±3 / Male: 81.6% / White: 81.6% Comorbidities: NR	autistic disorder (all) ROB: Medium (subjective), Medium (objective)

First Author, Year Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
Marcus, 2009[131] 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% / White: 70% **G2:** 10.0±3.2 yr / Male: 85% / White: 70% **G3:** 9.5±3.1 yr / Male: 93% / White: 78% **G4:** 10.2±3.1 yr / Male: 92% / 67% Comorbidities: behavior issues (e.g., tantrums, aggression, self-injury; all)	autism (all) ROB: High (subjective), High (objective)
SGA vs. Placebo			
Findling, 2014b[123] RCT, 16 wk (after 13-26 wk stabilization)	**G1:** Aripiprazole (41), 2-15 mg/day **G2:** Placebo (44)	**G1:** 10.1±2.8 yr / Male: 73.2% / White: 75.6% **G2:** 10.8±2.8 yr / Male: 86.4% / White: 63.6% Comorbidities: NR	autistic disorder (all) ROB: High (subjective), High (objective)
Hollander, 2006[126] RCT, 8 wk	**G1:** Olanzapine (6), 10±2 mg/day **G2:** Placebo (5)	**G1:** 9.3±2.9 yr / Male: all / White: 50% **G2:** 8.9±2.1 yr / Male: 60% / White: 80% Comorbidities: MR (mild (5), severe (2))	asperger syndrome (1), autism (6), PDD NOS (4) ROB: High (subjective), High (objective)
Luby, 2006[129] RCT, 6 mo	**G1:** Risperidone (12), 1.1±0.3 mg/day **G2:** Placebo (12)	**G1:** 4.1±0.9 yr / Male: 75% / White: 91% **G2:** 4.0±1.1 yr / Male: 67% / White: 92% Comorbidities: NR	autistic disorder (NR), PDD NOS (NR) ROB: Medium (subjective), Low (objective)
McCracken, 2002[132] RCT, 8 wk	**G1:** Risperidone (49), 1.8±0.7 mg/day **G2:** Placebo (52)	**G1:** NR / Male: 80% / White: NR **G2:** NR / Male: 83% / White: NR Comorbidities: MR (borderline (12), mild or moderate (43), severe (31)), serious behavior issues (all)	autistic disorder (all) ROB: Medium (subjective), Medium (objective)
Nagaraj, 2006[134] RCT, 6 mo	**G1:** Risperidone (19), 1 mg/day **G2:** Placebo (21)	**G1:** 4.8±1.7 yr / Male: 84% / White: NR **G2:** 5.3±1.7 yr / Male: 90% / White: NR Comorbidities: Aggression (20), irritability (36), self-injurious behavior (12), seizures (8)	autistic disorder (all) ROB: Low (subjective), Low (objective)
Owen, 2009[135] RCT, 8 wk	**G1:** Aripiprazole (47), NR **G2:** Placebo (51)	**G1:** 9.7±3.2 yr / Male: 89.4% / White: 68.1% **G2:** 8.8±2.6yr / Male: 86.3% / White: 80.4% Comorbidities: NR	NR ROB: Medium (subjective), low (objective)

First Author, Year Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
RUPP, 2005[138] RCT, 8 wk (after 4 mo stabilization)	**G1:** Risperidone (16), 3.5 (15-45 kg), 4.5 (>45 kg) **G2:** Placebo (16)	**All groups (G1-G2):** 9.0±2.5 yr / Male: 86.8% / White: 60.5% Comorbidities: IQ average (2), IQ borderline (5), MR (27)	autistic disorder (all) ROB: Medium (subjective), Medium (objective)
Shea, 2004[139] RCT, 8 wk	**G1:** Risperidone (41), 1.2 mg/day **G2:** Placebo (39)	**G1:** 7.6 yr / Male: 73% / White: NR **G2:** 7.3 yr / Male: 82% / White: NR Comorbidities: MR (27)	asperger syndrome (12), autistic disorder (55), childhood disintegrative disorder (1), PDD NOS (11) ROB: Medium (subjective), Medium (objective)
Troost, 2005[140] RCT, 8 wk (after 24 wk stabilization)	**G1:** Risperidone (12), 1.9±0.7 mg/day **G2:** Placebo (12)	**G1:** 9.4±3.4 yr / Male: 92% / White: 100% **G2:** 8.7±1.2 yr / Male: 92% / White: 83% Comorbidities: behavior issues (e.g., tantrums, aggression, or self-injury; all), MR (2)	asperger syndrome (2), autistic disorder (6), PDD NOS (16) ROB: Low (subjective), Low (objective)
FGA vs. Placebo			
Anderson, 1989[122] RCT (cross-over), 4 wk	**G1:** Haloperidol, Placebo, Placebo (14), 0.84±0.57 mg/day **G2:** Placebo, Haloperidol, Placebo (14), 0.84±0.57 mg/day **G2:** Placebo, Placebo, Haloperidol (14), 0.84±0.57 mg/day	**All groups:** 4.49±1.16 yr / Male: 77.8% / White: NR Comorbidities: mild/low level MR (42), of these, profoundly or severely MR (29)	austistic disorder (all) ROB: High (subjective), Medium (objective)
Remington, 2001[137] RCT (cross-over), 7 wk	**G1:** Chlomipramine-Placebo-Haloperidol (CPH), PHC, HCP (33), 1-1.5 mg/day	**G1:** 16.3 (10–36) yr / Male: 83.3% / White: NR Comorbidities: NR	austistic disorder (all) ROB: High (subjective), High (objective)

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

Table 14. Characteristics of observational studies examining autism spectrum disorders

First Author, Year Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
SGAs vs. SGAs			
Novaes, 2008[143] Retrospective cohort, 17 mo	**G1:** Risperidone or risperidone and FGA (13 and 5), NR **G2:** Other SGA with or without FGA (8), NR	**All patients:** 4–21 yr / Male: 89 / White: NR Comorbidities: aggression/ agitation (all), MR (20)	autistic disorder (all) 8/8 stars
Wink, 2014[144] Retrospective cohort, 1.5 (aripiprazole) – 2.4 (risperidone) yr	**G1:** Risperidone (72), 2.23±1.30 mg/day **G2:** Aripiprazole (70), 11.85±7.23 mg/day	**G1:** 8.41±3.59 yr / Male: 83.3% / White: 77.8% **G2:** 9.74±3.46 yr / Male: 80% / White: 75.7% Comorbidities: intellectual disability (64)	autistic disorder (84), PDD-NOS (48), asperger's disorder (10) 7/8 stars
SGA vs. Placebo/No treatment			
NCT00619190[141] Controlled before-after, 12 wk	**G1:** Aripiprazole (21), 1-30 mg/day **G2:** No treatment as per parental desire (9)	**G1:** 8.3±3.8 yr / Male: 90% / White: NR **G2:** 11.1±4.5 yr / Male: 89% / White: NR Comorbidities: NR	autism spectrum disorders (30) 4/8 stars
Mankoski, 2013[142] Retrospective (pooled analysis), see Marcus 2009 & Owen 2009 Subgroup analysis for harms	**G1:** Aripiprazole (antipsychotic naïve, 176), NR **G2:** Placebo (naive, 80), NR **G3:** Aripiprazole (prior antipsychotic exposure, 36), NR **G4:** Placebo (prior exposure, 21), NR	**All groups:** mean (9.4-10) yr / Male: NR / White: NR Comorbidities: NR	NR 6/8 stars

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

Autism Spectrum Disorders: Intermediate Outcomes

Seventeen studies reported on intermediate outcomes for treating ASD. A summary of the key findings by comparison is provided below. Table 15 contains the findings and SOE ratings for key outcomes assessed as having at least low SOE; the reason for each SOE decision is included in the table footnotes. A detailed analysis follows for the findings, organized by comparison.

Key Points

- **FGAs versus SGAs** (two RCTs[130, 133]): The comparative effectiveness is not known for outcomes of anger, hyperactivity, or global impressions of improvement or severity.
- **Aripiprazole versus risperidone** (one RCT[124]): For reported outcomes of irritability, inappropriate speech, lethargy, social withdrawal, hyperactivity, and stereotypy, the comparative effects of aripiprazole and risperidone are not known.

- **SGAs—Dose comparisons** (aripiprazole[131] , lurasidone [127] and risperidone[128]): Different doses of aripiprazole,lurasidone, or risperidone have unknown effects on irritability, lethargy/social withdrawal, stereotypic behavior, speech impairment, conduct problems, and global impressions of improvement.
- **SGAs versus placebo** (ten RCTs [aripiprazole,[123, 131, 134] lurasidone, [127] olanzapine,[126] and risperidone.[128, 132, 138-140]] and one controlled before-after study[141]): SGAs probably decrease irritability, and decrease slightly lethargy/social withdrawal, stereotypy, inappropriate speech, and compulsions. They probably increase response rates and improve slightly illness severity. They may increase global impressions of improvement. Maintenance treatment with an SGA may decrease relapse rates. When examining studies of aripiprazole and risperidone separately, these SGAs probably decrease irritability, but there may be little or no difference for lethargy/social withdrawal and inappropriate speech. The smaller sample sizes contributing to the SOE for each drug likely affected the ability to obtain a significant finding for most outcomes (e.g., response rates), with the exception of irritability which overall had the larger magnitude of effect.
  Observations of between-study subgroup effects: (a) findings suggested that the relative effect between SGAs and placebo are reduced to a small extent in patients previously stabilized on the SGA; (b) the dose of SGAs was fairly similar between studies examining the same drug—for risperidone, one of the acute phase RCTs administered a slightly larger dose (1.8 mg/day[132] vs. 1.2[139] and 1.25-1.75[128] mg/day) than the others and this appeared to heighten its effect for several outcomes.

Table 15. Strength of evidence for autism spectrum disorders: Key intermediate outcomes having at least low strength of evidence

Comparison	Outcome (N Studies; N Patients)	Findings,[a] Studies, and Tool With Range of Values, if Applicable	Strength of Evidence; Conclusions
SGAs vs. placebo	Irritability (8, 809)	MD, -6.38; 95% CrI, -8.94 to -3.83 (ABC subscale; range 0-45)[123, 127, 128, 131, 132, 135, 139, 140]	Moderate; SGAs probably decrease[b]
	Lethargy/social withdrawal (7, 743)	MD, -1.67; 95% CrI, -3.05 to -0.28 (ABC subscale; range 0-48)[123, 127, 131, 132, 135, 139, 140]	Moderate; SGAs probably decrease slightly[b]
	Stereotypy (5, 634)	MD, -1.73; 95% CrI, -3.16 to -0.05 (ABC subscale; range 0-21) [127,131, 132, 135, 139]	Moderate; SGAs probably decrease slightly[b]
	Inappropriate speech (7, 743)	MD, -1.04; 95% CrI, -1.83 to -0.26 (ABC subscale; range 0-12)[123, 127, 131, 132, 135, 139, 140]	Moderate; SGAs probably decrease slightly[b]
	Response rates (7, 716)	RR, 2.22; 95% CrI, 1.29 to 4.17[126, 127, 128, 131, 132, 133, 137]	Moderate; SGAs probably increase[b]
	Relapse rates (3, 141) (Maintenance phase only)	RR, 0.30; 95% CrI, 0.07 to 0.84[123, 138, 140]	Low; SGAs may decrease in maintenance phase[c]
	Global impressions of improvement on CGI-I[d] (6, 635)	4 RCTs: MD, -1.00, 95% CrI, -2.34 to -0.07[126, 127, 131, 135] 2 RCTs: RR 4.5[128] and 6.5[132]; both p < 0.01 (proportion scoring as at least "much improved")	Low; SGAs may increase[e]
	Global impressions of severity on CGI-S[d] (4, 522)	4 RCTs: MD, -0.61; 95% CrI, -1.04 to -0.15 [127, 128, 131, 135]	Moderate; SGAs probably decrease slightly[b]

Comparison	Outcome (N Studies; N Patients)	Findings,[a] Studies, and Tool With Range of Values, if Applicable	Strength of Evidence; Conclusions
Aripiprazole vs. placebo	Irritability (3, 393)	MD, -5.74; 95% CrI, -9.34 to -2.15 (ABC subscale; range 0-45)[123, 1231, 135]	Moderate; Aripiprazole probably decreases[b]
	Lethargy/social withdrawal (3, 393)	MD, -1.41; 95% CrI, -4.19 to 1.35 (ABC subscale; range 0-48)[123, 131, 135]	Low; Aripiprazole may make little or no difference[e]
	Stereotypy (3, 393)	MD, -2.51; 95% CrI, -4.68 to -0.33 (ABC subscale; range 0-21)[123, 131, 135]	Moderate; Aripiprazole probably decreases slightly[b]
	Inappropriate speech (3, 393)	MD, -1.49; 95% CrI, -3.02 to 0.06 (ABC subscale; range 0-12)[123, 131, 135]	Low; Aripiprazole may make little or no difference[e]
Risperidone vs. placebo	Irritability (4, 268)	MD, -8.28; 95% CrI, -12.59 to -3.64 (ABC subscale; range 0-45)[128, 132, 139, 140]	Moderate; Risperidone probably decreases[b]
	Lethargy/social withdrawal (3, 202)	MD, -2.51; 95% CrI, -5.67 to 1.02 (ABC subscale; range 0-48)[132, 139, 140]	Low; Risperidone may make little or no difference[e]
	Stereotypy (2, 178) (Acute phase only)	1 RCT: -3.10; 95% CI, -4.93 to -1.27[132] 1 RCT: -1.90; 95% CI, -3.64 to -0.16[139] (ABC subscale; range 0-21)	Low; Risperidone may decrease slightly for acute treatment[c]
	Inappropriate speech (3, 202)	MD, -1.06; 95% CrI, -2.66 to 0.59 (ABC subscale; range 0-12)[132, 139, 140]	Low; Risperidone may make little or no difference[e]
	Response rate (3, 246)	RR, 2.75; 95% CrI, 0.92 to 9.77[128, 1302 139]	Low; Risperidone may make little or no difference[e]

ABC = Aberrant Behavior Checklist; CB-YOCS = Children's Yale-Brown Obsessive Compulsive Scale; CGI-I = Clinical Global Impressions of Improvement; CGI-S = Clinical Global Impressions of Severity; CI = confidence interval; CrI = credible interval (used with Bayesian meta-analysis); MD = mean difference; N = number; RCT: randomized controlled trial; RR = risk ratio; SGA = second-generation antipsychotics

[a] When the findings are not representative of the total number of studies identified in the outcome column, we included the number of studies for each finding; we did not pool data from 1 or 2 studies so these results are always presented separately. All values except Response are favorable for SGAs when there is a negative MD, or a RR < 1.0 (i.e., relapse); the larger the magnitude of effect, the larger the effect.

[b] Downgraded for ROB.

[c] Downgraded for ROB and imprecision because of small sample size, typically < 200 patients in total.

[d] CGI-S and CGI-I scores range from 0-6.

[e] Downgraded for ROB and imprecision, because credible interval includes a clinically significant value (e.g., lower boundary value considered clinically meaningful reduction) such that we could not rule out benefit even though effect estimate appears to be of no difference.

Detailed Analysis

FGAs Versus SGAs

Two RCTs compared FGAs versus SGAs for intermediate outcomes.[130, 133]

Haloperidol versus olanzapine. A 6-week RCT compared haloperidol with olanzapine in children ages 5 to 17 years.[130] Using factors on the CPRS sensitive to antipsychotic treatment of autism, patients on olanzapine showed significantly greater improvement for anger and hyperactivity (p = 0.05 and p = 0.01, respectively), but not for the autism factor (p = 0.56) or the speech deviance factors. Global impressions of severity (p = 0.08) and improvement (p = 0.25) did not significantly differ between groups.

Haloperidol versus risperidone. A 12-week RCT assessed the comparative effectiveness of haloperidol and risperidone in children ages 8 to 18 years.[133] Risperidone led to significantly

greater improvement in nonspecific symptoms measured by the Aberrant Behavior Checklist (ABC) total score ($p = 0.006$). On the Ritvo-Freeman Real Life Rating Score, the risperidone group had improvement ($p < 0.01$) in all five subscales (sensory-motor, social, affect, sensory, language) while haloperidol failed to offer significant improvement in the sensory ($p = 0.21$) and language ($p = 0.051$) subscales.

SGAs Versus SGAs

One RCT compared two SGAs[124] and three RCTs[127, 128, 131] compared different doses of SGAs for intermediate outcomes.

Aripiprazole versus risperidone. An 8-week RCT compared aripiprazole with risperidone for their safety and efficacy on irritability.[124] There were no differences between groups for changes in symptoms of irritability ($p = 0.06$; aripiprazole numerically favorable), inappropriate speech ($p = 0.3$), lethargy/social withdrawal ($p = 0.5$), hyperactivity ($p = 0.5$), or stereotypy ($p = 0.6$) measured using ABC subscales. There was also no difference between groups for number of patients showing at least "much improvement" in global impressions of improvement ($p = 0.3$).

Aripiprazole–Low- versus medium- versus high-dose. An 8-week, placebo-controlled RCT evaluated the efficacy of daily fixed-dose regimens of aripiprazole at 5 mg, 10 mg, and 15 mg on irritability associated with autistic disorder.[131] The high-dose aripiprazole group had significantly greater improvement for lethargy/social withdrawal symptoms (ABC subscale) than the medium-dose group ($p = 0.05$). No differences were found between any groups for other ABC scores (i.e., irritability, speech impairment) (all $p > 0.3$), conduct problems (Children's Yale-Brown Obsessive Compulsive Scale [CY-BOCS]; all $p > 0.2$), or for global impressions of improvement (all $p > 0.65$) or severity (all $p > 0.5$).

Lurasidone – Low-versus high-dose. A 6-week, placebo-controlled RCT compared low-dose 20 mg/day and high-dose 60 mg/day lurasidone and found no differences between groups for irritability, global impressions of improvement, hyperactivity, stereotypic behavior, inappropriate speech, lethargy/withdrawal, or for compulsion.[127]

Risperidone–Low- versus medium- versus high-dose. A 6-week, placebo-controlled RCT compared low-dose (0.125–0.175 mg/day) and high-dose (1.25–1.75 mg/day) risperidone.[128] The high-dose group was superior to placebo for symptoms of irritability ($p < 0.001$) and compulsions ($p = 0.003$), response rates ($p = 0.004$), and global impressions of improvement ($p < 0.001$), but not for inappropriate speech or social withdrawal (both $p > 0.5$). The low dose group showed no benefit over placebo for all outcomes.

SGAs Versus Placebo

Ten RCTs compared SGAs with placebo for intermediate outcomes: aripiprazole,[123, 131, 135] lurasidone,[127] olanzapine,[126] and risperidone.[128, 132, 138-140] A 12-week controlled before-after study[141] compared a group taking open-label aripiprazole with another withheld from antipsychotic treatment as per parental desire. A total of 997 patients with an average age of 9.3 years were enrolled in the studies. The average treatment duration was 10 weeks. The majority of patients were males (84.9%) and white (72%). Six of the RCTs examined SGAs in the context of acute treatment in patients either naïve (> 80% in those reporting on previous exposure)[128, 131, 132, 135] to or not taking antipsychotics; three RCTs[123, 138, 140] studied the effects of placebo-controlled discontinuation of an SGA after stabilization on the SGA.

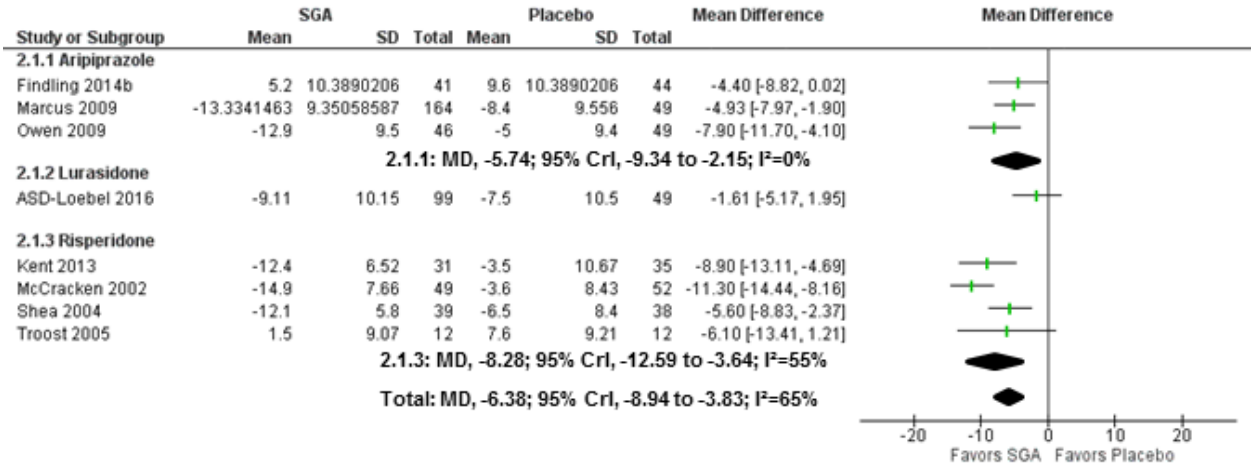
Meta-Analysis for SGAs Versus Placebo in Autism Spectrum Disorders

Meta-analyses were conducted to compare SGAs with placebo for short-term symptoms of irritability, lethargy/social withdrawal, stereotypy, inappropriate speech, and compulsions. Nonspecific symptoms that were examined using meta-analysis include response rates, relapse rates, and discontinuations due to lack of efficacy; data on global impression of illness severity and improvement were also pooled across studies. Because of clinical heterogeneity, sensitivity analyses were conducted for several outcomes when there was some indication of statistical heterogeneity (I^2 >20%) and studies examining placebo-controlled maintenance treatment were included (Findling 2014b[123], RUPP 2005[138], and Troost 2005[140]). There were three studies comparing multiple doses of an SGA with placebo; we combined the results for the three doses (5, 10, and 15 mg/day) of aripiprazole[131] and two doses of lurasidone (20 and 60 mg/day),[127] but for the other study[128] we did not use data for the low-dose (0.125-0.175 mg/day) risperidone group which was found inferior to the higher dose for all outcomes and was considerably lower than approved by the FDA (1-3 mg/day).

Short-term core symptoms. Data were reported for all subscales of the ABC by seven RCTs[123, 127, 131, 132, 135, 139, 145]; one RCT[128] only provided sufficient data for the irritability subscale. Each subscale has a different range of possible values (lower scores better) which is important for interpretation: irritability (0-45), lethargy/social withdrawal (0-48), stereotypy (0-21), inappropriate speech (0-12) were used for short-term symptoms.

Results for irritability indicated significantly greater reductions for the SGAs (MD, -6.38; 95% CrI, -8.94 to -3.83; I^2 = 65%) (Figure 55). Removing two studies of maintenance (Findling 2014b[123] and Troost 2005[140]) increased the magnitude of the effect estimate slightly although did not reduce the statistical heterogeneity (MD, -6.68; 95% CrI, -9.75 to -3.61; I^2 = 74%). When pooling the results for each drug, there was a larger effect estimate for risperidone although considerable heterogeneity (risperidone: MD, -8.28; 95% CrI, -12.59 to -3.64; I^2 = 55%, and aripiprazole: MD, -5.74; 95% CrI, -9.34 to -2.15; I^2 = 0%). In the controlled before-after study,[141] the aripiprazole group had higher irritability scores (7.6 points) at study endpoint over baseline, while the no treatment control group has a slight reduction (-0.6 points) (between-group p value = 0.0002).

Figure 55. SGAs versus placebo for irritability using ABC in autism spectrum disorders



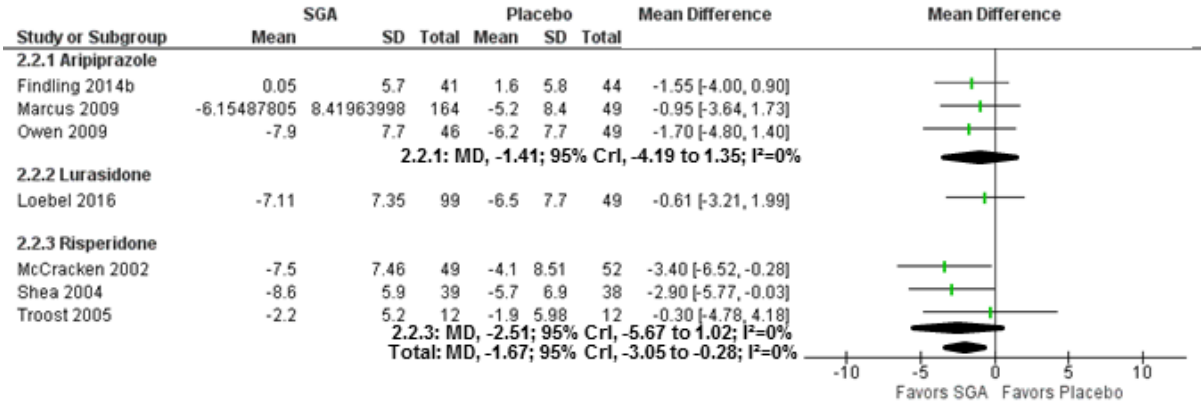
ABC = Aberrant Behavior Checklist; CrI = credible interval; SD = standard deviation; SGA = second-generation antipsychotic; MD = mean difference

SGAs were also favorable over placebo for lethargy/social withdrawal (MD, -1.67; 95% CrI, -3.05 to -0.28; I^2 = 0%) (Figure 56). No sensitivity analysis was conducted for the maintenance studies.[123, 140] Separate meta-analyses for risperidone (MD, -2.51; 95% CrI, -5.67 to 1.02) and aripiprazole (MD, -1.41; 95% CrI, -4.19 to 1.35) showed no difference from placebo for either SGA. The controlled before-after study of aripiprazole versus no treatment[141] found greater reduction in lethargy/social withdrawal scores for the aripiprazole compared with no treatment group (4.2 points lower; p = 0.01).

Results for stereotypy indicated significantly greater reductions for the SGAs (MD, -1.73; 95% CrI, -3.16 to -0.05; I^2 = 62%) (Figure 57). Sensitivity analysis by removing two studies of maintenance increased the magnitude of the effect estimate slightly but did not reduce the statistical heterogeneity (MD, -2.09; 95% CrI, -3.84 to -0.38; I^2 = 54%). We pooled the results for aripiprazole and found similar results in favor of this SGA (MD, -2.51; 95% CrI, -4.68 to -0.33). We did not pool the results for risperidone because of the influence on heterogeneity from the maintenance study by Troost and colleagues.[140]

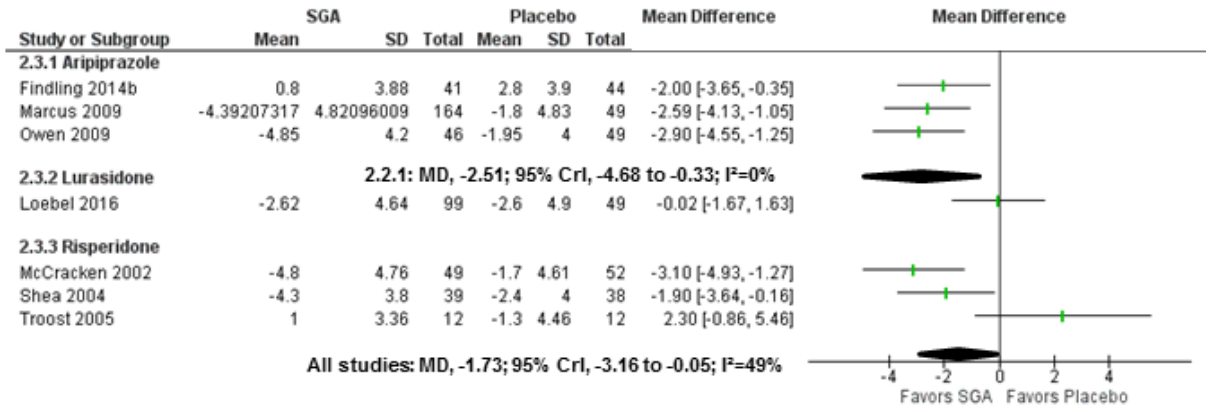
The symptom of inappropriate speech was reduced significantly (MD, -1.04; 95% CrI, -1.83 to -0.26; I^2 = 39%) (Figure 58). Separate meta-analyses for aripiprazole and risperidone failed to show significant benefit for the individual SGAs (aripiprazole: MD, -1.49; 95% CrI, -3.02 to 0.06, and risperidone: MD, -1.06; 95% CrI, -2.66 to 0.59); these results are likely due to the imprecision resulting from analyzing few studies.

Figure 56. SGAs versus placebo for lethargy/social withdrawal using ABC in autism spectrum disorders



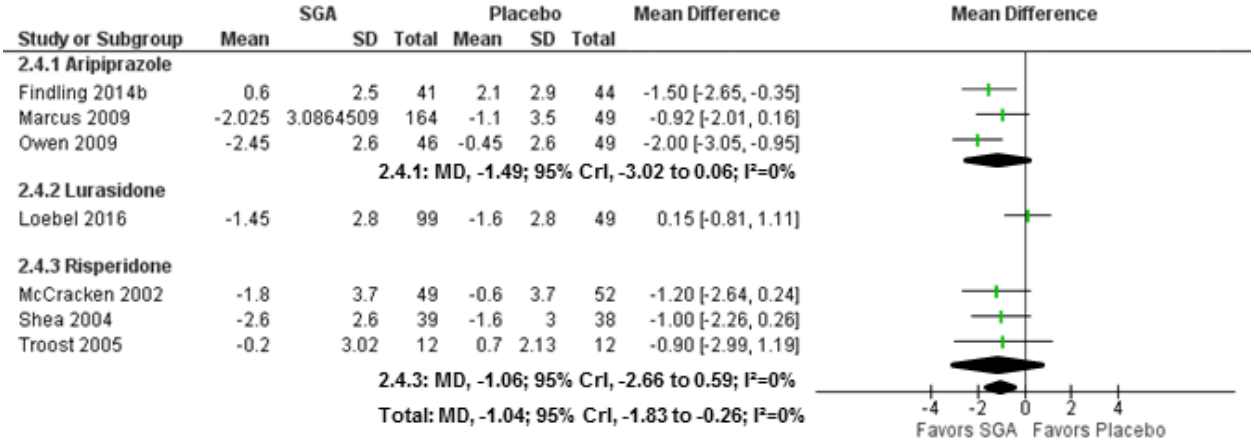
ABC = Aberrant Behavior Checklist; CrI = credible interval; MD = mean difference; SD = standard deviation; SGA = second-generation antipsychotic

Figure 57. SGAs versus placebo for stereotypy using ABC in autism spectrum disorders



ABC = Aberrant Behavior Checklist; CrI = credible interval; MD = mean difference; SD = standard deviation; SGA = second-generation antipsychotic

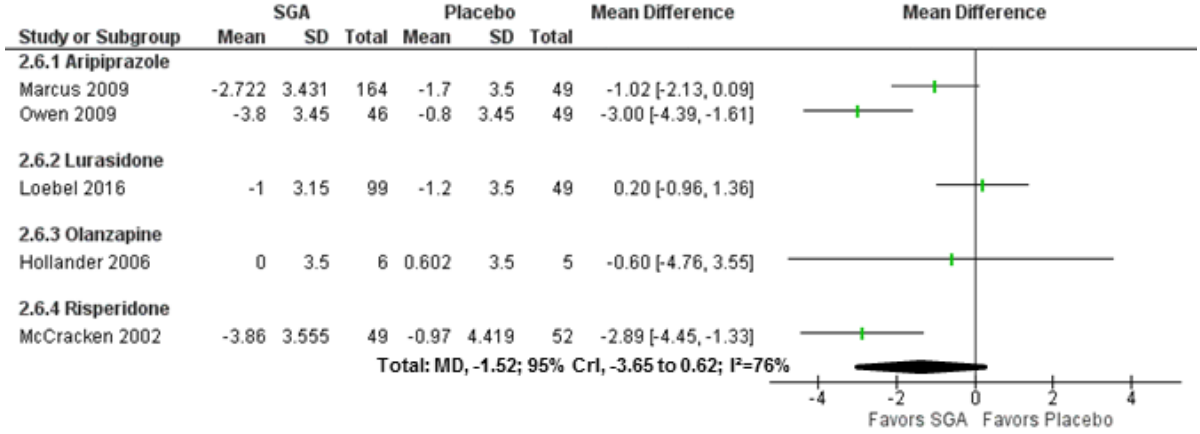
Figure 58. SGAs versus placebo for inappropriate speech using ABC in autism spectrum disorders



ABC = Aberrant Behavior Checklist; CrI = credible interval; MD = mean difference; SD = standard deviation; SGA = second-generation antipsychotic

A meta-analysis of five RCTs[126, 127, 131, 132, 135] examining compulsions using the CY-BOCS compared SGAs to placebo (Figure 59). The pooled estimate indicated no significant improvement for patients taking SGAs (MD, -1.52; 95% CrI, -3.65 to 0.62). We did not conduct meta-analysis for any individual drug.

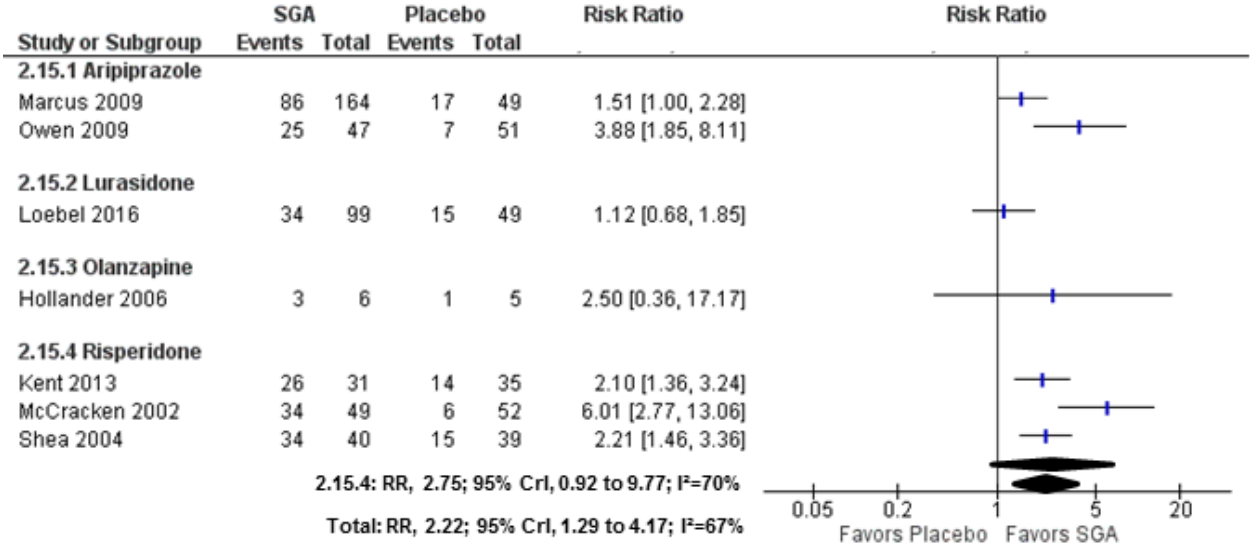
Figure 59. SGAs versus placebo for compulsions using CY-BOCS in autism spectrum disorders



CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale; CrI = credible interval; MD = mean difference; SD = standard deviation; SGA = second-generation antipsychotic

Short-term nonspecific symptoms. Meta-analyses were conducted to compare SGAs with placebo for response rates, relapse rates, and discontinuations for lack of efficacy (Figures 60-62). Patients taking SGAs showed more than twice the response than those taking placebo (RR, 2.22; 95% CrI, 1.29 to 4.17). The average doses of the two RCTs of aripiprazole were quite similar.[131, 135] The estimated RR for the three risperidone studies[128, 132, 139] was 2.75, and it was not significant (95% CrI, 0.92 to 9.77); the statistical heterogeneity may in part relate to the slightly higher dose of risperidone in one of the studies (McCracken 2002)[132] than the others.[128, 139]

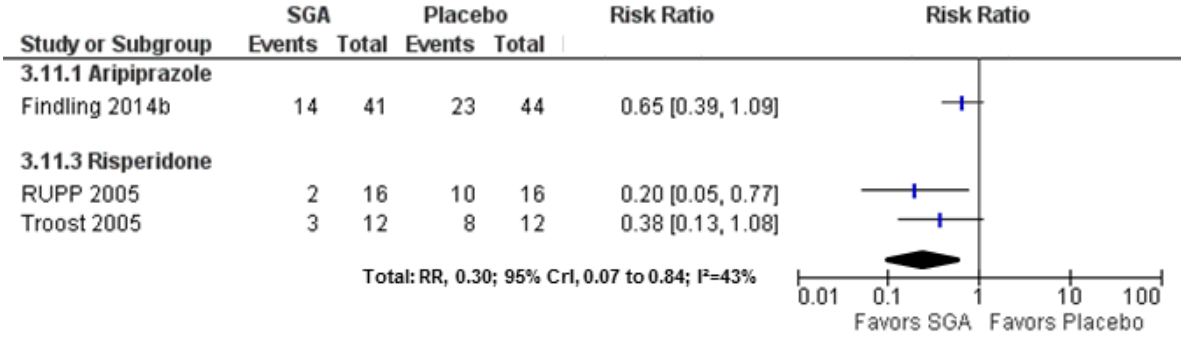
Figure 60. SGAs versus placebo for response rates in autism spectrum disorders



CrI = credible interval; RR = risk ratio; SGA = second-generation antipsychotic

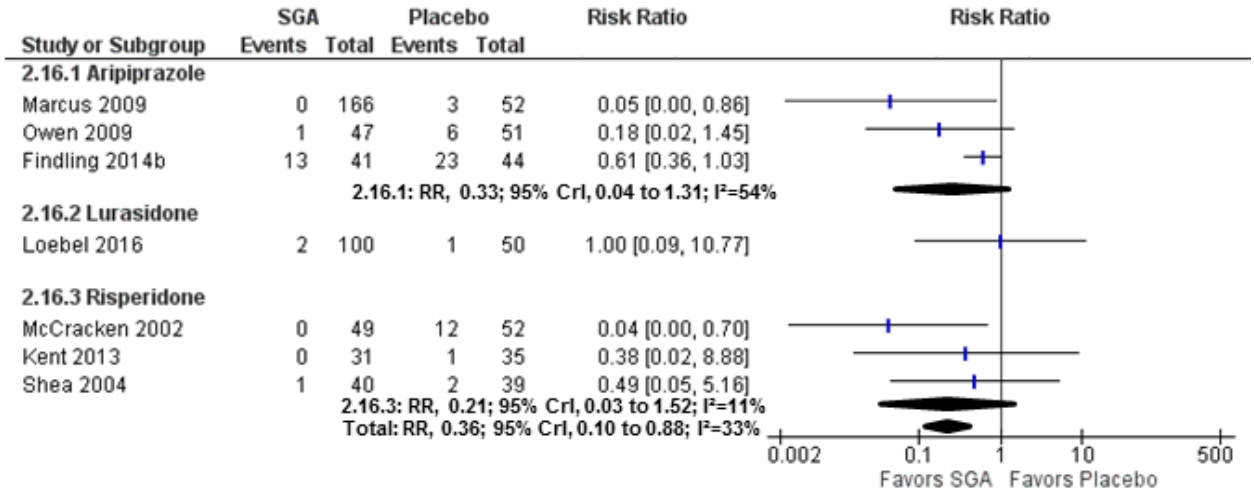
Meta-analysis of relapse rates (based on irritability symptoms and overall clinical impressions) for three RCTs[123, 138, 140] examining placebo-controlled maintenance of SGAs in patients with ASD found a significant effect favoring maintenance on a SGA compared with placebo (RR, 0.30; 95% CrI, 0.07 to 0.84) (Figure 61). Discontinuation due to lack of efficacy was lower for treatment groups across seven RCTs comparing SGAs with placebo (RR, 0.36; 95% CrI, 0.10 to 0.88; I^2 = 33%) (Figure 62). When pooling data for only those studies examining the acute phase of treatment, the results favored the SGAs even more (RR, 0.22; 95% CrI, 0.06 to 0.81).

Figure 61. SGAs versus placebo for relapse rates in autism spectrum disorders



CrI = credible interval; RR = risk ratio; SD = standard deviation; SGA = second-generation antipsychotic

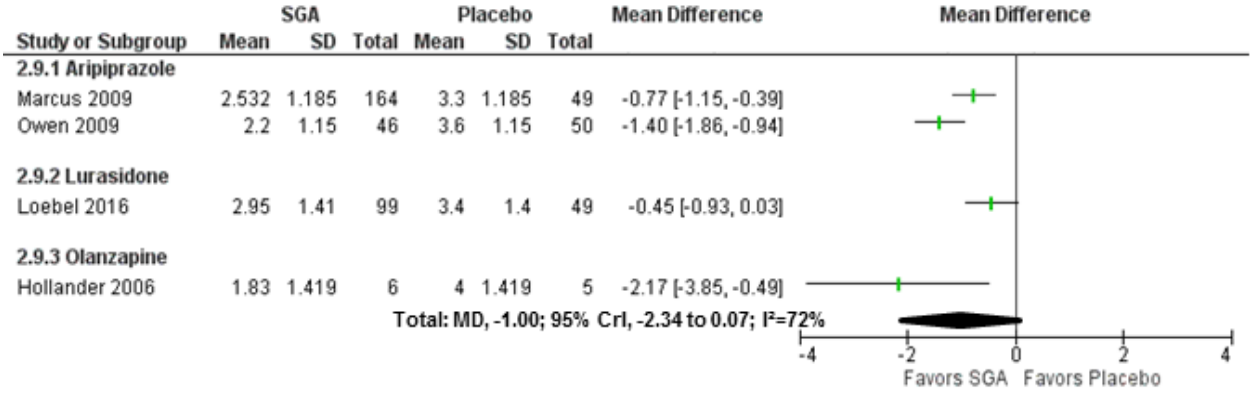
Figure 62. SGAs versus placebo for discontinuation due to lack of efficacy in autism spectrum disorders



CrI = credible interval; RR = risk ratio; SGA = second-generation antipsychotic

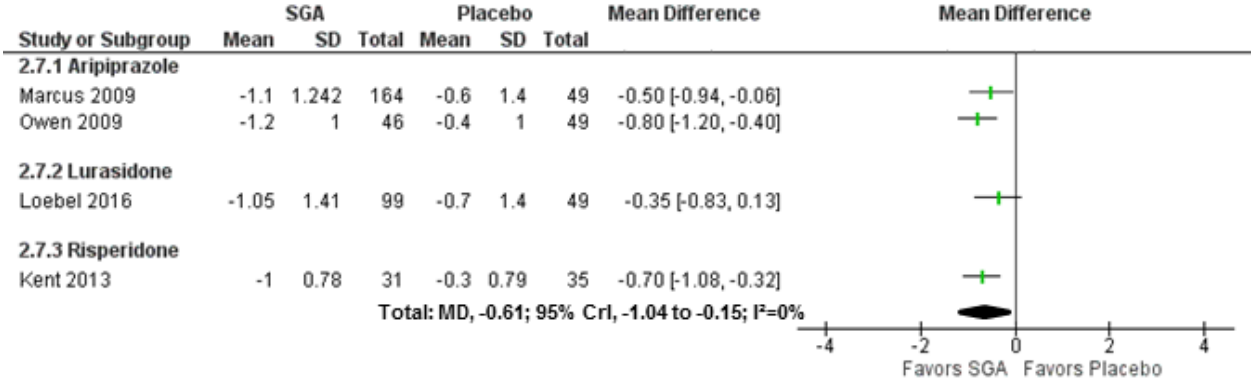
Short-term global impressions. Four RCTs provided data for meta-analyses of SGAs versus placebo for global impressions of improvement[126, 127, 131, 135] (Figure 63) and severity (Figure 64).[127, 128, 131, 135] Results found no difference for global improvement (MD, -1.00, 95% CrI, -2.34 to 0.07; I^2 = 72%) but showed significant improvement for global severity (MD, -0.61; 95% CrI, -1.04 to -0.15; I^2 =0%). There was considerable heterogeneity in the results for global improvement likely resulting from the Hollander[126] study which was small and enrolled a high proportion of patients with mild or moderate mental retardation. Results were different for studies of risperidone providing data for the proportion of patients scored as at least "much improved" on the CGI-I (RR, 4.5[128] and 6.5[132]; both $p < 0.01$). The controlled before-after study of aripiprazole versus no treatment found lower CGI-S scores for (therefore favoring) the no treatment group at study endpoint (0.85 points lower; $p = 0.01$).[141]

Figure 63. SGAs versus placebo for global impressions of improvement in autism spectrum disorders



CGI-I = Clinical Global Impression of Improvement; CrI = credible interval; MD = mean difference; SD = standard deviation; SGA = second-generation antipsychotic

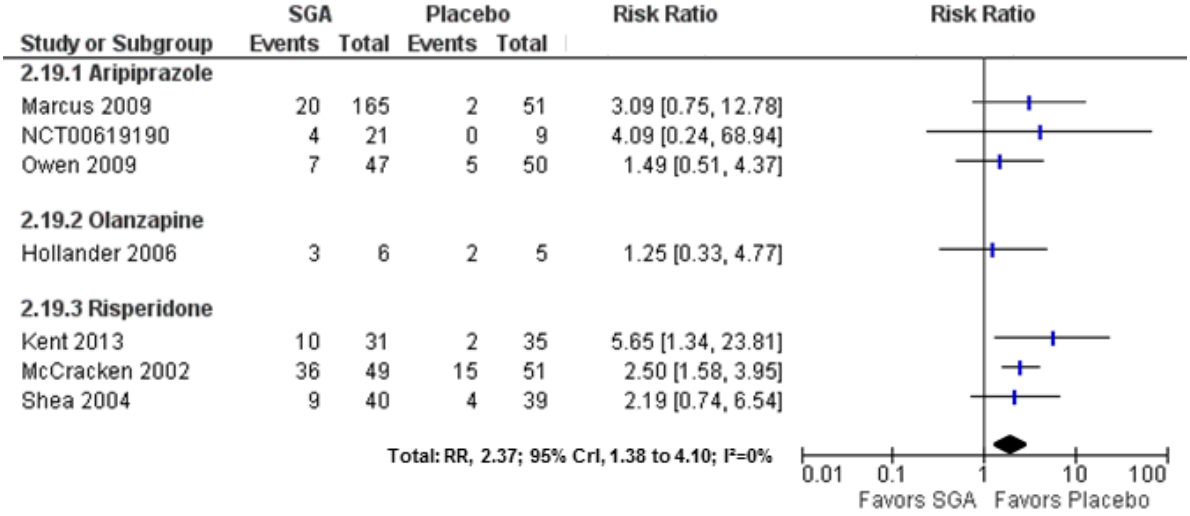
Figure 64. SGAs versus placebo for global impressions of severity in autism spectrum disorders



CGI-S = Clinical Global Impressions of Severity; CrI = credible interval; MD = mean difference; SD = standard deviation; SGA = second-generation antipsychotic

Lifestyle behaviors. Seven RCTs[126, 128, 131, 132, 135, 139, 141] provided data for a meta-analysis on increases in appetite for children in comparisons between SGAs and placebo (Figure 65). Because increased appetite may contribute to increased weight which is considered a potential harm for these drugs, the results are considered to significantly favor placebo (RR, 2.37; 95% CrI, 1.38 to 4.10). A 6-month study[129] (N = 23) of risperidone versus placebo found 55 and 25 percent, respectively, of children stated they had an increase in appetite (p = 0.15).

Figure 65. SGAs versus placebo for increases in appetite in autism spectrum disorders



CrI = credible interval; RR = risk ratio; SGA = second-generation antipsychotic

Additional Findings

Individual studies found that risperidone improved symptoms more than placebo for the following measures: the conduct problem, hyperactive, insecure, and overly sensitive subscales of the Nisonger Child Behavior Rating Form (NCBRF) parent version ($p < 0.05$),[139] Ritvo-Freeman Real Life Rating Score ($p < 0.001$),[132] Vineland Adaptive Behavior Scale–maladaptive subscale ($p < 0.001$),[132] and Visual Analog Scale of the most troublesome symptom ($p \leq 0.05$).[139]

Observations on Between-Study Subgroup Effects

Apart from type of SGA, the primary difference between the studies comparing SGAs with placebo was the treatment history of the patients. We performed sensitivity analyses in cases showing some statistical heterogeneity, to examine the influence on the results. Our findings suggested that the relative effect between SGAs and placebo are reduced to a small extent in patients previously stabilized on the SGA. The response to the SGAs appears greater for patients when they are first prescribed the drug.

The dose of SGAs was fairly similar between studies. For risperidone, one of the acute phase RCTs administered a slightly larger dose (1.8 mg/day[132] vs. 1.2[139] and 1.25-1.75[128] mg/day) than the others which appeared to heighten its effect for several outcomes.

Autism Spectrum Disorders: Effectiveness Outcomes

Ten studies reported on effectiveness outcomes in ASD. Four RCTs[129, 133, 134, 136] and two observational studies[143, 144] provided treatment durations of 6 months or longer. A summary of the findings on key outcomes is provided below. The SOE for all key outcomes was assessed as insufficient due to ROB, unknown consistency (most outcomes), and imprecision. A brief description of the long-term studies is provided, followed by details on findings by outcome category.

Key Points

- **FGAs versus SGAs** (one RCT[133]): Global improvement and language was examined between risperidone and haloperidol, but the effects are unknown due to insufficient SOE.
- **FGAs versus FGAs** (one RCT[136]): The evidence was insufficient to determine if a difference in effect exists for clinical impressions of improvement and symptom severity between groups taking continuous or discontinuous (5 days per week) haloperidol for 6 months.
- **SGAs versus SGAs** (two retrospective cohort studies[143, 144]): Studies examined risperidone versus aripiprazole for global improvement scores at end of greater than 1.5 year followup,[144] and risperidone versus other SGAs[143] for global improvement, but we had no confidence to make any conclusions on effects.
- **SGAs versus placebo** (six RCTs[127,129, 131, 132, 134, 140]): Compared with placebo, the effects from risperidone for language or socialization skills, [129] 6-month global functioning, [134] and cognitive tasks[132] are not known. The comparative effects of two doses of lurasidone[127] and three doses of aripiprazole[131] versus placebo on suicide-related behaviors are not known.

Detailed Analysis

Description of Long-Term Studies

FGAs versus SGAs. A 12-week RCT with a 12-week extension assessed the comparative effectiveness of haloperidol and risperidone.[133]

FGA versus FGAs. A 6-month RCT randomized children to continuous or discontinuous drug administration of haloperidol.[136] The discontinuous drug schedule consisted of 5 days on haloperidol with 2 days on placebo. The prescribed dose of haloperidol was similar between the groups (1.2 mg/day in the continuous group, and 1.0 mg/day in the discontinuous group).

SGAs versus SGAs. A retrospective cohort study compared risperidone with aripiprazole after mean treatment durations 2.4 and 1.5 years, respectively.[144] Another retrospective study compared effects on agitation and aggression of risperidone compared with other SGAs (quetiapine, aripiprazole, and olanzapine); both groups in this analysis had patients taking concomitant FGAs.[143]

SGAs versus placebo. Two 6-month RCTs compared risperidone with placebo in young children with ASD.[129, 134] The children in one of these RCTs[129] were also receiving intensive behavioral therapy (Applied Behavioral Analysis).

Results on Effectiveness Outcomes From Short- and Long-Term Studies

Long-term core symptoms. Risperidone led to significantly greater improvement than haloperidol for the language subscale of the Ritvo-Freeman Real Life Rating Score ($p = 0.04$).[133] No difference was found in one RCT[129] for language or socialization skills when comparing risperidone with placebo.

Long-term nonspecific symptoms. Two RCTs comparing risperidone with placebo assessed children for overall autism symptoms using the Childhood Autism Rating Scale.[129, 134] Luby et al.[129] found no difference between groups ($p = 0.14$), while Nagaraj et al.[134] found that risperidone was favored significantly with 6 points greater reduction ($p < 0.0001$) and 12 of 19 versus 0 of 20 showing 20 percent or greater improvement in total Childhood Autism Rating Scale scores. The difference between studies may relate to the intensive behavioral therapy provided to all children in the study by Luby et al.[129]

Long-term global impressions and functioning. The proportion of patients improving by at least two points of the CGI-I or CGI-S did not differ between groups taking continuous or discontinuous haloperidol for 6 months ($p = 0.32$ and 0.48).[136] Risperidone was favored over haloperidol for CGI-I scores at 24 weeks ($p = 0.02$).[133] In studies comparing different SGAs, groups taking risperidone and aripiprazole did not differ in global improvement scores at end of 1.5 years or greater followup ($p = 0.32$),[144] and there was no difference between groups taking risperidone and other SGAs in the proportion of patients attaining one or two points improvement on the CGI-I ($p = 0.75$).[143] Global functioning was improved significantly more for children taking risperidone than placebo in one 6-month RCT;[134] 17 of 19 versus 2 of 20 children improved by at least 20 percent on the C-GAS ($p = 0.035$).

Cognitive functioning. Two short-term RCTs[132, 140] 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.[132] Similarly, reaction time did not differ between groups.[140]

Suicide-related ideations or behaviors, or death by suicide. In an 8-week RCT[131] comparing three doses of aripiprazole with placebo, three patients in the placebo group (N = 52) displayed suicide-related behaviors compared to no patients in the aripiprazole groups (N =166). In a 6-week RCT comparing two doses of lurasidone with placebo, one patient in the 60 mg group (N=51) had suicidal ideation leading to study discontinuation compared with no patients in the 20 mg group (N=49) and placebo group (N=49).

Autism Spectrum Disorders: Within-Study Subgroup Effects

Five studies of autism spectrum disorders conducted an analysis of outcomes in different subpopulations (Table 16).[123, 132, 136, 138, 143]

Four studies found no significant effect of age on response[141] or relapse[123, 132, 136] after treatment with a variety of FGAs and SGAs, including aripiprazole, risperidone, and haloperidol. Race/ethnicity did not moderate response for irritability in one study of risperidone;[132] another study found aripiprazole to lower relapse rates in white but not non-white patients.[123]

Table 16. Within-study analysis for subgroup effects

First Author, Year Comparison	Type of Analysis	Outcome	Authors' Conclusions
McCracken, 2002[132] *Risperidone vs. placebo*	Moderator analyses for sex, age, ethnicity, income, IQ	ABC-I	None of the variables were a significant moderator of response to risperidone.
	Mediator analyses for dose	ABC-I	Dose had a strong and significant point bi-serial correlation with treatment; children taking risperidone were likely to receive lower doses than children randomized to placebo.
Findling, 2014b[123] *Aripiprazole vs. placebo*	Subgroup analysis by race, age	Relapse	Aripiprazole treatment resulted in significantly lower relapse rate among white patients; non-significant results for non-white patients. No significant age interaction observed between the 2 groups (aripiprazole vs. placebo).
RUPP, 2005[138] *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.
Perry, 1989[136] *Continuous haloperidol vs. discontinuous haloperidol*	Subgroup analysis by age, developmental quotient, baseline rating scores	Severe deterioration (CGI–I difference)	Patients with high baseline CPRS Conduct Problem Factor scores and patients with significant improvement before the antipsychotic withdrawal regimen showed significant deterioration than patients without these variables. All other variables did not predict deterioration.

ABC-I = Aberrant Behavior Checklist Irritability subscale; CGI-I = Clinical Global Impressions of Improvement; CPRS = Conner's Parent Rating Scale; IQ = intelligence quotient

ADHD and Disruptive, Impulse-Control, or Conduct Disorders: Overview

Thirteen studies examined the effectiveness of antipsychotics for treating patients with ADHD and/or DICD.[146-158] Tables 17 and 18 provide selected information on the characteristics of the individual studies. Studies are organized within their respective comparison (head-to-head then placebo-controlled), and then alphabetically by drug name and then by author. There was only one head-to-head drug comparison. Both observational studies were pooled analyses of two of the included RCTs;[146, 149] one provided data for subgroup effects for patients using stimulants,

and the other provided data for cognitive function. Detailed evidence tables are available in Appendix D.

Patients had an average age of 9.9 years and were predominantly male (83%); apart from two RCTs enrolling adolescents,[154, 155] the age of participants was typically below 12 years. Among 11 studies that reported race/ethnicity, the majority (62%) of patients self-reported as being white. Across the eleven RCTs, children had a primary diagnosis of ADHD in four[147, 148, 150, 153] and of DICD in 7;[151, 152, 154-158] all trials except one[156] had a large proportion of children with comorbid diagnoses of either DICD or ADHD, respectively. Patients were required to have aggression to be included in five of the trials.[147, 153-156] Common comorbidities apart from ADHD and DICD were global developmental delay and anxiety disorders.

Most RCTs examined acute phase treatment in patients either naïve to or not taking antipsychotics upon enrollment; one RCT enrolled children maintained on risperidone for 1 year and examined placebo-controlled discontinuation of the antipsychotic.[152] All children were taking stimulants in three RCTs,[147, 148, 153] variable numbers were taking stimulants in five RCTs,[1451, 152, 154, 157, 158] and stimulants were prohibited in three RCTs.[150, 155, 156]

The duration of treatment ranged from 2 weeks[152] to 6 months[157]. For the 10 RCTs lasting less than 6 months, the duration of treatment was on average 6.8 weeks. Six of 11 RCTs had a high ROB; in all cases the high risk was from incomplete outcome data, that is, ≥ 30 percent withdrawals or significant imbalance in reasons for withdrawals between groups.

Table 17. Characteristics of trials examining ADHD and disruptive, impulse-control, or conduct disorders

First Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n), Quality Rating
FGAs vs. FGAs			
Stocks, 2012[148] RCT, 8-11 wk	**G1:** Molindone (20), <30 kg: 5 mg/day; ≥ 30 kg: 10 mg/day **G2:** Molindone (19), <30 kg: 10 mg/day; ≥ 30 kg: 20 mg/day **G3:** Molindone (19), <30 kg: 15 mg/day; ≥ 30 kg: 30 mg/day **G4:** Molindone (20), <30 kg: 20 mg/day; ≥ 30 kg: 40 mg/day	**G1:** 8.5±1.88 yr / Male: 95% / White: 55% **G2:** 9.4±1.98 yr / Male: 84.2% / White: 57.9% **G3:** 8.8±2.12 yr / Male: 68.4% / White: 42.1% **G4:** 8.8±2.00 yr / Male: 95% / White: 65% Comorbidities: Asthma (13), CD (8), Eczema (6), Enuresis (12), Environmental allergies (4), Insomnia (5), ODD (26), Seasonal allergies (5)	ADHD (78) ROB: High (subjective), High (objective)
SGAs vs. Placebo			
Aman, 2014[147] RCT (parallel), 6 wk	**G1:** Risperidone + stimulant + parent training (84), 1.7±0.75 mg/day **G2:** Placebo + stimulant + parent training (84), 1.9±0.72 mg/day	**G1:** 9.03±2.05 yr / Male: 77.4% / White: 57.1% **G2:** 8.75±1.98 yr / Male: 76.2% / White: 48.8% Comorbidities: CD (44), ODD (124)	ADHD (168) ROB: Medium (subjective), Medium (objective)

First Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n), Quality Rating
Aman, 2009[152] RCT (cross-over), 2 wk (after 1 yr treatment duration)	**G1:** Risperidone (16),* 1.7±1.3 mg/day **G2:** Placebo (16)*	**All groups:** 8.6±2.6 yr / Male : 88% / White: 81% Comorbidities: MR (borderline (10), mild (4), moderate (1))	ADHD with CD (2), ADHD with ODD (6), ADHD only (1), ASD (3), CD (1), ODD (3) ROB: Medium (subjective), Medium (objective)
Aman, 2002[151] RCT, 6 wk	**G1:** Risperidone (55), 1.2±0.6 mg/day **G2:** Placebo (63)	**G1:** 8.7±2.1 yr / Male: 85% / White: 51% **G2:** 8.1±2.3 yr / Male: 79% / White: 62% Comorbidities: ADHD (70), MR (all; borderline (60), mild (38), moderate (20))	CD (47), DBD (8), ODD (63) ROB: High (subjective), High (objective)
Armenteros, 2007[153] RCT, 4 wk	**G1:** Risperidone (12), 1.1±0.6 mg/day **G2:** Placebo (13)	**G1:** 7.3±3.7 yr / Male: 83% / White: 50% **G2:** 8.8±3.1 yr / Male: 92% / White: 46% Comorbidities: GAD (1), ODD (13), separation anxiety disorder (3)	ADHD with aggression (all) ROB: Medium (subjective), Medium (objective)
Buitelaar, 2001[154] RCT, 6 wk	**G1:** Risperidone (19), 2.9 mg/day **G2:** Placebo (19)	**G1:** 14.0±1.5 yr / Male: 90% / White: NR **G2:** 13.7±2 yr / Male: 84% / White: NR Comorbidities: ADHD (26), anxiety disorder (3), MR (14)	CD (30), DBD NOS (2), ODD (6), aggression (all) ROB: Medium (subjective), Medium (objective)
Findling, 2000[156] RCT, 10 wk	**G1:** Risperidone (10), 0.028±0.004 mg/kg/day **G2:** Placebo (10)	**G1:** 10.7±3.4 yr / Male: NR / White: NR **G2:** 8.2±1.9 yr / Male: NR / White: NR Comorbidities: ADHD (0)	CD with aggression (all) ROB: High (subjective), High (objective)
Reyes, 2006[157] 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% / White: NR **G2:** 10.8±2.9 yr / Male: 91% / White: NR Comorbidities: ADHD (227)	CD (123), DBD NOS (8), ODD (204) ROB: High (subjective), High (objective)
Snyder, 2002[158] RCT, 6 wk	**G1:** Risperidone (53), 1±0.73 mg/day **G2:** Placebo (57)	**G1**: 8.6±0.3 yr / Male: 77% / White: 79% **G2:** 8.8±0.3 yr / Male: 74% / White: 74% Comorbidities: ADHD (84), MR (all; borderline (53), mild (42), moderate (15))	CD (41), ODD (69) ROB: High (subjective), High (objective)

First Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n), Quality Rating
Connor, 2008[155] RCT, 6 wk	**G1:** Quetiapine (9), 294±78 mg/day **G2:** Placebo (10)	**G1:** 13.1±1.2 yr / Male: 78% / White: 78% **G2:** 15±1.4 yr / Male: 70% / White: 70% Comorbidities: ADHD (15), depression (4), dysthymia (5), GAD (3), OCD (3), ODD (18), panic disorder (1), PTSD (3), SA (6), separation anxiety (3), social phobia (3)	CD with moderate to severe aggression (all) ROB: High (subjective), High (objective)
FGAs vs Placebo			
Aman, 1991[150] RCT (cross-over), 3 wk	**G1:** Thioridazine (30)*, 1.75 mg/kg/day **G2:** Placebo (30)*	**All groups:** 10.0 (4.1-16.5) yr / Male: 83% / White: 70% Comorbidities: Significantly subnormal IQ(<76) (27), PDD (1)	ADHD (24), ADD (4), ADD Residual type (1), CD (3) ROB: Medium (subjective), Medium (objective)

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

Table 18. Characteristics of observational studies examining ADHD and disruptive, impulse-control, or conduct disorders

First Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
SGAs vs. Placebo			
Aman, 2004[149] Observational (pooled analysis, see Aman 2002 and Snyder 2002), 6 wk Subgroup data only	**G1:** Risperidone (43), 1.11 mg/day **G2:** Risperidone + stimulant (35), 1.07 mg/day **G3:** Placebo (39) **G4:** Placebo + stimulant (38)	**G1:** 8.6±2.1 yr / Male: 81.4% / White: 55.8% **G2:** 9.0±1.7 yr / Male: 85.7% / White: 65.7% **G3:** 8.3±2.2 yr / Male: 74.4% / White: 56.4% **G4:** 8.9±2.1 yr / Male: 92.1% / White: 73.7% Comorbidities: ADHD (all)	CD/ODD/DBD-NOS (breakdown not provided) 7/8 stars
Pandina, 2007[146] Observational (pooled analysis, see Aman 2002 and Snyder 2002), 6 wk	**G1:** Risperidone (108), 1.3±0.7 mg/day **G2:** Placebo (88)	**G1:** 8.6 yr / Male: 81% / White: 64% **G2:** 8.4 yr / Male: 77% / White: 68% Comorbidities: ADHD (155)	CD (88), ODD (59), Axis 1 (71), BD NOS (10) 6/8 stars

ADHD = attention deficit hyperactivity disorder; CD = conduct disorder; DBD = disruptive behavior disorder; G = group; mg = milligrams; mo = month; N = number; NOS = not otherwise specified; ODD = oppositional defiant disorder; SD = standard deviation; wk = week

ADHD and Disruptive, Impulse-Control, or Conduct Disorders: Intermediate Outcomes

Ten studies reported on intermediate outcomes for using FGAs and SGAs in the treatment of ADHD and DICD. A summary of the findings for our key outcomes is provided below, followed by the results on the SOE for those outcomes assessed as having at least low SOE (Table 19). The section ends with a detailed analysis of the findings by comparison.

Key Points

- **FGAs—Dose comparison** (one RCT[148]): The SOE was insufficient from an RCT examining four doses of molindone for conduct problems, inattention, hyperactivity/impulsivity, or global impression of severity.
- **SGAs versus placebo** (eight RCTs [risperidone[147, 151-154, 156, 158] and quetiapine[155]]): SGAs as a class, and risperidone alone, likely reduce conduct problems and aggression in children with ADHD and/or DICD. Results for clinical impressions of improvement showed little or no difference, although results were imprecise and indicated that many patients may possibly improve. Risperidone likely reduces hyperactivity, although this conclusion is specific to studies where not all patients were taking stimulants, or to the situation of nonresponse to stimulants. Clinical severity may be reduced by SGAs and risperidone individually; the results for risperidone do not apply to the study of risperidone augmentation of stimulants and parent training. Risperidone may make little or no difference over placebo for global impressions of improvement. For patients with a primary diagnosis of ADHD and exhibiting aggression, risperidone may make little or no difference for response. ***Observations on between-study subgroup effects***: (a) risperidone may preferentially reduce illness severity, and increase global improvement ratings, for DICD compared with ADHD particularly when used for ADHD as adjunctive treatment; (b) our meta-analysis favored SGAs for hyperactivity, although the data came from studies that did not enroll children responding to stimulants as did another study[153] that found no benefit for risperidone on hyperactivity; (c) sensitivity analyses by removing the small study enrolling children with a long-term history of response to risperidone did not affect the results;[152] and (d) we did not find any evidence to suggest a differential treatment effect between studies having different inclusion criteria related to intellectual functioning.
- **FGAs versus placebo** (one RCT[150]): The effects of thioridazine versus placebo for conduct problems, hyperactivity, anxiety, and global functioning are not known.

Table 19. Strength of evidence findings for ADHD and disruptive, impulse-control, or conduct disorders: Key intermediate outcomes having at least low strength of evidence

Comparison	Outcome (N Studies; N Patients)	Findings,[a] Studies	Strength of Evidence; Conclusions
SGAs vs. placebo	Conduct problems (6, 462)	SMD, -0.77; 95% CrI, -1.34 to -0.17[147, 151, 152, 155, 154, 156]	Moderate; SGAs probably decrease [b]
	Aggression (7, 495)	SMD, -0.43; 95% CrI, -0.67 to -0.14[145, 149, 151-154, 156]	Moderate; SGAs probably decrease[b]
	Global impressions of improvement using CGI-I[c] (7, 482)	5 RCTs: RR, 2.13; 95% CrI, 0.87 to 6.46 (proportion at least "improved")[147, 151, 153, 1, 158] 1 RCT: MD, -0.50; 95% CI, -1.99 to 0.99[153] 1 RCT: MD, -1.80; 95% CI, -2.89 to -0.71[156]	Low; SGAs may make little or no difference[d]
	Global impressions of severity using CGI-S (3, 75) (Studies of primary treatment in DICD)	3 RCTs: MD, -1.98; 95% CrI, -3.18 to -0.93[153-156]	Low; SGAs may decrease in DICD[e]
Risperidone vs. placebo	Conduct problems (5,443)	SMD, -0.84; 95% CrI, -1.54 to -0.18[145, 149, 150, 154, 156]	Moderate; Risperidone probably decreases[b]
	Aggression (6, 476)	SMD, -0.44; 95% CrI, -0.72 to -0.13[147, 151, 153, 154, 156, 158]	Moderate; Risperidone probably decreases[b]
	Hyperactivity (6, 468)	SMD, -0.39; 95% CrI, -0.76 to -0.07[147, 151, 152, 156, 158] 1 RCT: No difference p > 0.05[151]	Moderate; Risperidone probably decreases in children not on, or responding to, stimulants[b]
	Global impressions of improvement using CGI-I (6, 463)	4 RCTs: RR, 1.85; 95% CrI, 0.64 to 5.58 (proportion at least "improved")[147, 151, 153, 158] 1 RCT: MD, -0.50; 95% CI, -1.99 to 0.99[153] 1 RCT: MD, -1.80; 95% CI, -2.89 to -0.71[156]	Low; Risperidone may make little or no difference[d]
	Global impressions of severity using CGI-S (2, 56) (Studies of primary treatment in DICD)	1 RCT: MD, -1.80; 95% CI, -2.54 to -1.06[154] 1 RCT: MD, -2.50; 95% CI, -4.11 to -0.89[156]	Low; Risperidone may improve in DICD[e]
	Global impressions of severity using CGI-S (2, 193) (Studies of stimulant augmentation in ADHD)	1 RCT: MD, 0.0; 95% CI, -1.65 to 1.65[153] 1 RCT: RR, 1.2; 95% CI, 0.95 to 1.5 (proportion rated as "normal/borderline/mildly ill")[147]	Low; Risperidone may make little or no difference in ADHD treatment augmented with risperidone[d]
	Response rate (2, 193) (Patients with primarily ADHD and aggression)	1 RCT:[147] RR, 1.12; 95% CI, 0.94 to 1.34 1 RCT:[153] RR, 1.28; 95% CI, 0.93 to 1.77	Low; Risperidone may make little or no difference[d]

CGI-S = Clinical Global Impressions of Severity; CI = confidence interval; CrI = credible interval (used with Bayesian meta-analysis); DICD = disruptive, impulse-control, and conduct disorders; MD = mean difference; N = number; RCT: randomized controlled trial; RR = risk ratio; SGA = second-generation antipsychotics

[a] When the findings are not representative of the total number of studies identified in the outcome column, we included the number of studies for each finding; we did not pool data from 1 or 2 studies so these results are always presented separately. All effect estimates reported as MD or SMD values favor SGAs when they are negative (larger magnitude greater effect); a RR >1.0 favor SGAs. SMDs provide results in standard deviation units, and are used when the results from different measurement tools are combined in meta-analysis; as a general rule, an absolute magnitude of 0.2 represents a small effect size, 0.5 a moderate one, and 0.8 a large one.

[b] Downgraded for ROB.

[c] CGI-S and CGI-I scores range from 0-6.

[d] Downgraded for ROB and imprecision, because credible interval includes a clinically significant value (e.g., RR ≤0.75 or ≥1.25) such that we could not rule out benefit even though effect estimate appears to be of no difference.

[e] Downgraded for ROB and impression due to small sample size

Detailed Analysis

FGAs Versus FGAs

Molindone—Four-dose comparison. A 9- to 12-week RCT compared four doses of molindone in children with ADHD and persistent conduct problems.[148] No differences (p = 0.58) were found between doses for conduct problems measured using the NCBRF conduct problem subscale; although not significant, changes from baseline for the high-dose (40 mg/day; 20 mg/day if < 30 kg body weight) group were approximately 6 points greater than for the other doses between 10 and 30 mg/day (14.3 points vs. 7.0 to 8.7 points). Similar results were found using the Swanson, Nolan, and Pelham rating scale (SNAP-IV) for inattention (8.15 vs. 4.4 to 6.8 points) and hyperactivity/impulsivity (8.5 vs. 5.42 to 5.8 points), and for global impressions of severity on the CGI-S (1.7 vs. 1.0 to 1.26 points).

SGAs Versus Placebo

Quetiapine versus placebo. A 6-week, placebo-controlled RCT assessed the effectiveness of quetiapine for treating adolescents with conduct disorder and aggression.[155]

Risperidone versus placebo. Seven RCTs compared risperidone and placebo for intermediate outcomes.[147, 151-154, 156, 158] Treatment durations were between 2 and 10 weeks (average 6 weeks). Overall, 606 children and adolescents ranging from age 4 to 17 years participated in the trials. The average age of participants was between 8 and 10 years, with the exception of one study with an average age around 14 years.[154] Mean daily risperidone doses ranged from 0.8 to 2.9 mg/day, with the higher doses administered to older participants. Most studies examined acute treatment; one enrolled patients responding to risperidone and is considered a maintenance study.[152]

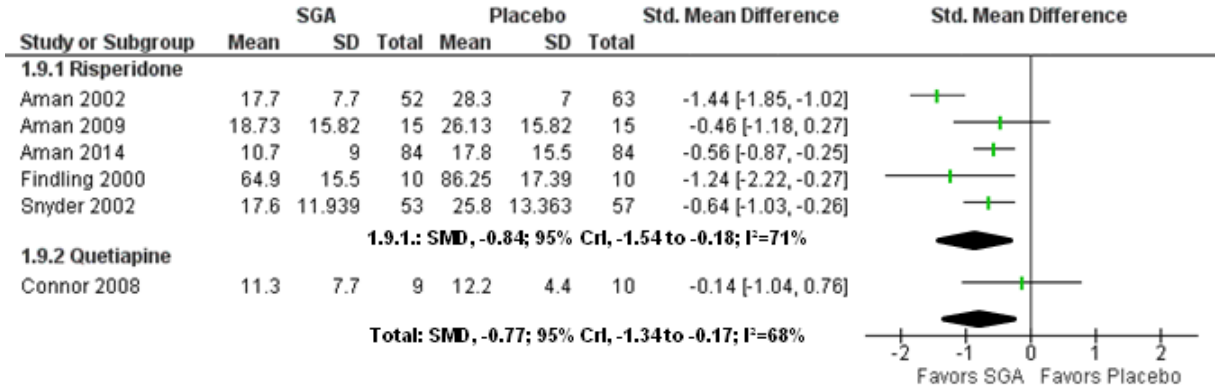
Meta-Analysis for SGAs Versus Placebo in ADHD and/or DICD

Meta-analyses were conducted to compare SGAs with placebo for the short-term core symptoms of conduct problems, aggression, and hyperactivity. Data was pooled for the short-term nonspecific outcomes of aberrant behaviors using the ABC total and hyperactivity/ noncompliance subscale scores, and for the rate of discontinuation due to lack of efficacy. Short-term global impressions of improvement and severity were also captured.

Where applicable, we conducted meta-analysis for quetiapine and risperidone separately as well as together. Sensitivity analysis was considered for the risperidone studies, in cases where statistical heterogeneity existed (> 20%) and clinical heterogeneity was related to either the diagnostic composition or treatment history of the patients.

Short-term core symptoms. Six RCTs provided data for the outcome of conduct problems (Figure 66).[147, 151, 152, 155, 156, 158] We used data from three different subscales to generate an SMD for this outcome: the NCBRF conduct problem subscale,[151, 152, 158] the NCBRF Typical IQ version conduct and oppositional behaviors scores (D-total subscale),[147] and the CPRS conduct problem subscale.[155, 156] For SGAs overall, there was a significant beneficial effect for treatment over placebo (SMD, -0.77; 95% CrI, -1.34 to -0.17). Assessing risperidone by itself resulted in a slightly larger magnitude of effect (SMD, -0.84; 95% CrI, -1.54 to -0.18). There was moderate statistical heterogeneity and removing the maintenance study (Aman 2009)[152] did not change the results or degree of heterogeneity.

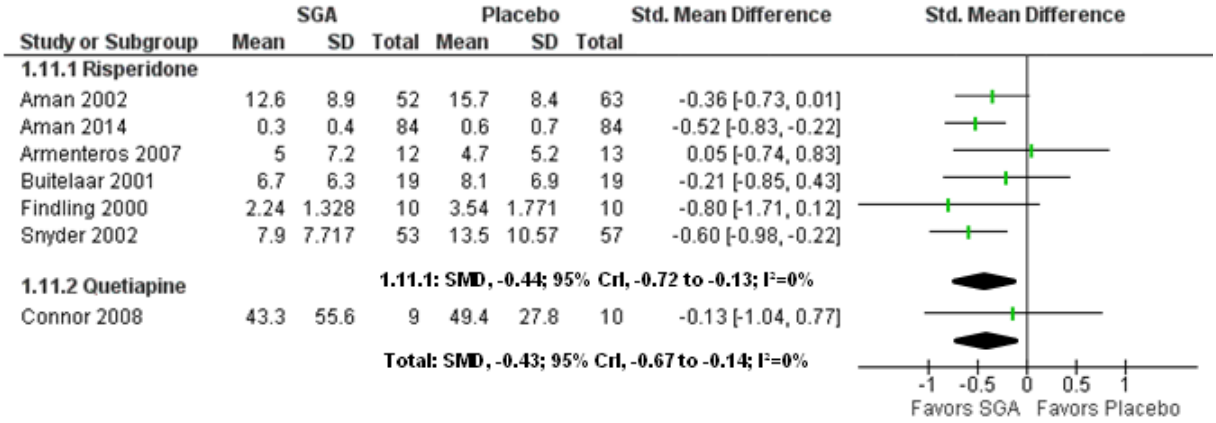
Figure 66. SGAs versus placebo for conduct problems in ADHD and/or disruptive, impulse-control, or conduct disorders



ADHD = attention deficit hyperactivity disorder; CrI = credible interval; SD = standard deviation; SGA = second-generation antipsychotic; SMD = standardized mean difference

For meta-analysis of aggression, we used data from total scores on the Overt Aggression Scale,[154] Rating of Aggression Against People and/or Property scale,[156] and Children's Aggression Scale-Parent version,[153] and aggression scores from the ADHD Symptom Checklist version 4 (ADHD-SC4),[147] and the Behavior Problems Inventory (Figure 67).[151, 158] The pooled results favored SGAs with no statistical heterogeneity (SMD, -0.43; 95% CrI, -0.67 to -0.14). For risperidone alone, the effect estimate was very similar with an SMD of -0.44 (95% CrI, -0.72 to -0.13).

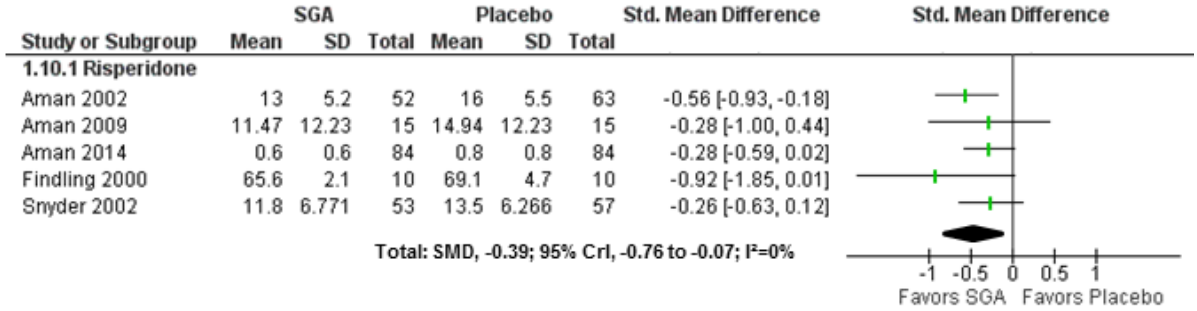
Figure 67. SGAs versus placebo for aggression in ADHD and/or disruptive, impulse-control, or conduct disorders



ADHD = attention deficit hyperactivity disorder; CrI = credible interval; SD = standard deviation; SGA = second-generation antipsychotic; SMD = standardized mean difference

Data from five RCTs [147, 151, 152, 156, 158] that compared risperidone to placebo were pooled to provide an estimate of the effect for the core symptom of hyperactivity (Figure 68). An SMD was generated using data from hyperactivity subscores of the CPRS,[156] NCBRF Problem Behaviors,[151, 152, 158] and ADHD-SC4[147] scales. Only the Aman 2002 study[151] found a significant reduction in hyperactivity. The pooled result across all studies found that risperidone significantly reduced hyperactivity when compared with placebo (SMD, -0.39; 95% CrI, -0.76 to -0.07; $I^2 = 0\%$). An additional study assessing risperidone in children with ADHD and aggression (Armenteros)[153] found no difference (data not provided) between risperidone and placebo for hyperactivity using the CPRS. All of the patients in this study were also taking stimulants which may have confounded the results compared with the other trials; the Aman 2014 study[147] administered placebo-controlled risperidone as adjunct treatment, although patients having good response to the "basic" stimulant and parent training were not eligible.

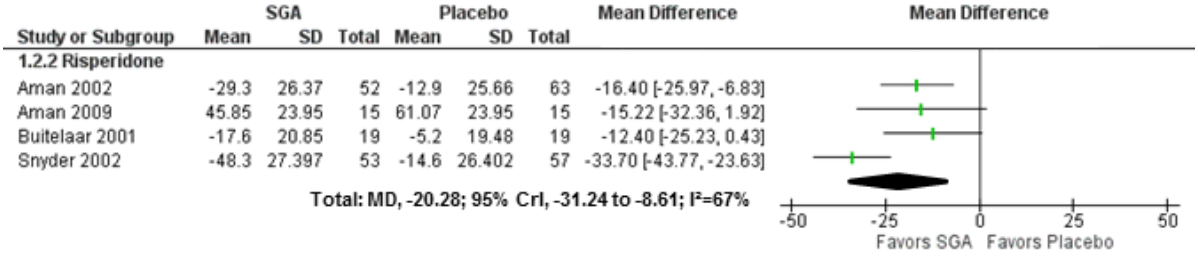
Figure 68. SGAs versus placebo for hyperactivity in ADHD and/or disruptive, impulse-control, or conduct disorders



ADHD = attention deficit hyperactivity disorder; CrI = credible interval; SD = standard deviation; SGA = second-generation antipsychotic; SMD = standardized mean difference

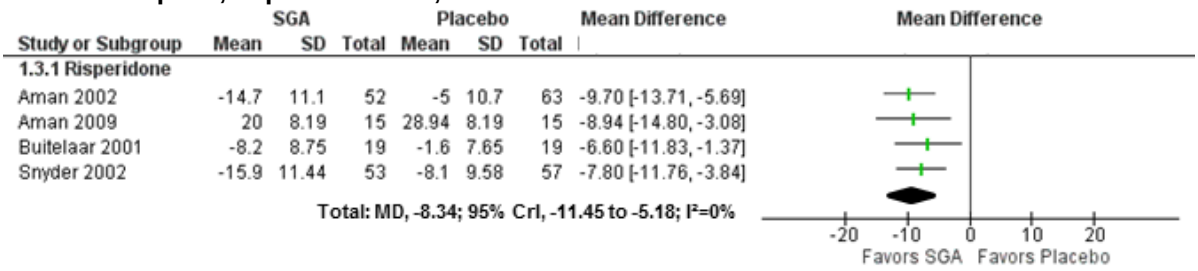
Short-term nonspecific symptoms. Four RCTs[151, 152, 154, 158] provided data for meta-analyses for aberrant behaviors (Figure 69) and for a combination of hyperactivity and noncompliance symptoms (Figure 70); both were assessed on the ABC using total (range 0-147) and hyperactivity/noncompliance (range 0-48) subscales, respectively. Over the short-term, risperidone significantly reduced aberrant behaviors compared with placebo (MD, -20.28; 95% CrI, -31.24, -8.61; $I^2 = 67\%$). Sensitivity analysis, with removal of the data from the maintenance study by Aman et al.,[152] increased the effect estimate slightly but did not reduce the heterogeneity (MD, -21.31; 95% CrI, -34.26 to -7.98; $I^2 = 77\%$). The effect estimate for hyperactivity/noncompliance was also favorable towards risperidone (MD, -8.34; 95% CrI, -11.45 to -5.18; $I^2 = 0\%$) and did not have heterogeneity.

Figure 69. SGAs versus placebo for aberrant behaviors using ABC total score in ADHD and/or disruptive, impulse-control, or conduct disorders



ABC = Aberrant Behavior Checklist; ADHD = attention deficit hyperactivity disorder; CrI = credible interval; MD = mean difference; SD; standard deviation; SGA = second-generation antipsychotic

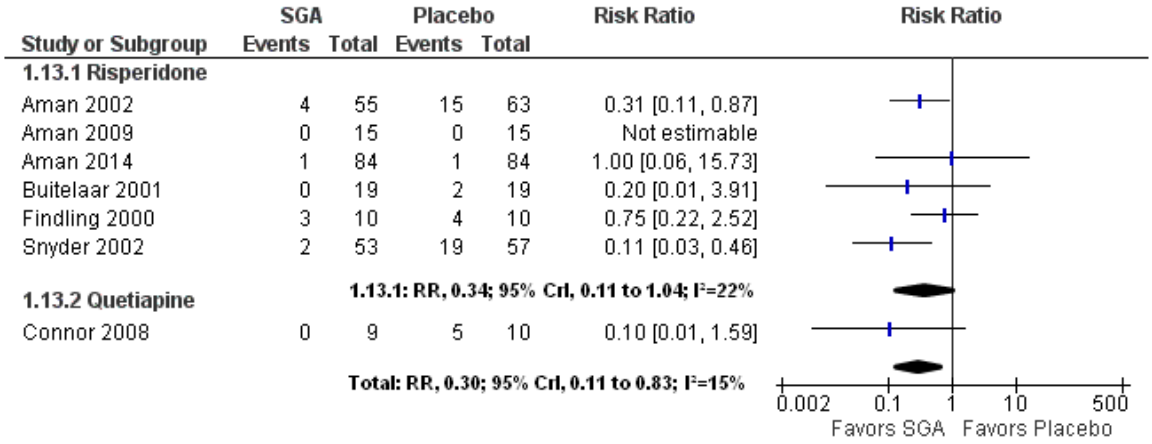
Figure 70. SGAs versus placebo for hyperactivity/noncompliance using ABC subscale in ADHD and/or disruptive, impulse-control, or conduct disorders



ABC = Aberrant Behavior Checklist; ADHD = attention deficit hyperactivity disorder; CrI = credible interval; MD = mean difference; SD; standard deviation; SGA = second-generation antipsychotic

Meta-analysis of data from seven RCTs[147, 151, 152, 154-156, 158] found SGAs superior to placebo (RR, 0.30; 95% CrI, 0.11 to 0.83) for rates of discontinuation due to lack of efficacy (Figure 71). None of the patients in the 2-week (Aman 2009) trial[152] discontinued for lack of efficacy so the data from this study was not included in the pooled estimate. The magnitude of the pooled RR for risperidone was similar although it failed to reach statistical significance (RR, 0.34; 95% CrI, 0.11 to 1.04).

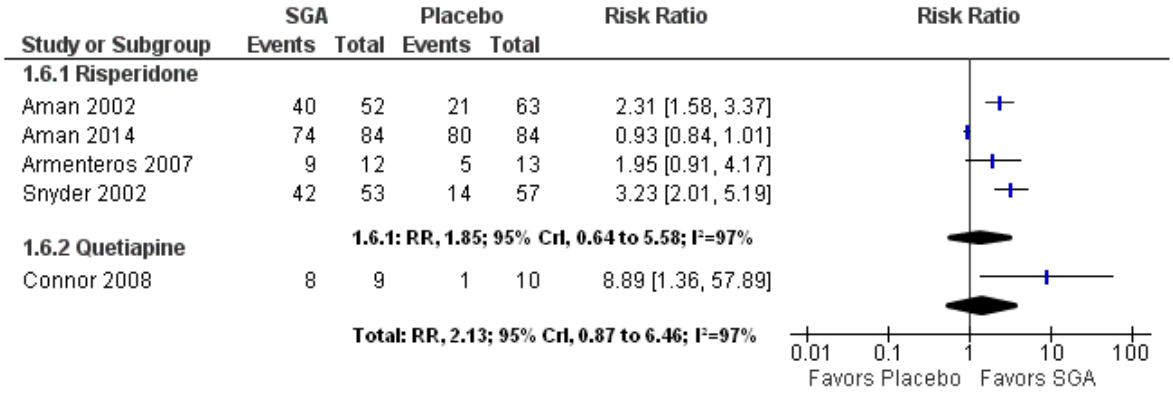
Figure 71. SGAs versus placebo for rates of discontinuation due to lack of efficacy in ADHD and/or disruptive, impulse-control, or conduct disorders



ADHD = attention deficit hyperactivity disorder; CrI = credible interval; RR = risk ratio; SGA = second-generation antipsychotic

Short-term global impressions. Meta-analysis of data from five RCTs[147, 151, 153, 155, 158] that compared SGAs with placebo found no difference for the proportion of patients scored as at least "improved" on the CGI-I (RR, 2.13; 95% CrI, 0.87 to 6.46; I^2 = 97%) (Figure 72). The high degree of heterogeneity may relate to the differences in primary diagnosis, which was ADHD for the two studies (Armenteros 2007 and Aman 2014)[147, 153] showing nonsignificant effects and conduct disorders for the other three.[151, 155, 158] Specific to risperidone, the result was similar (RR, 1.85; 95% CrI, 0.64 to 5.58; I^2 = 97%). Two RCTs reported results for CGI-I using mean scores; one found a significant benefit for risperidone in children with conduct disorders and no concomitant ADHD (1.8-point reduction; p = 0.001),[156] while the other one found no difference for children having ADHD with aggression (p = 0.51).[153]

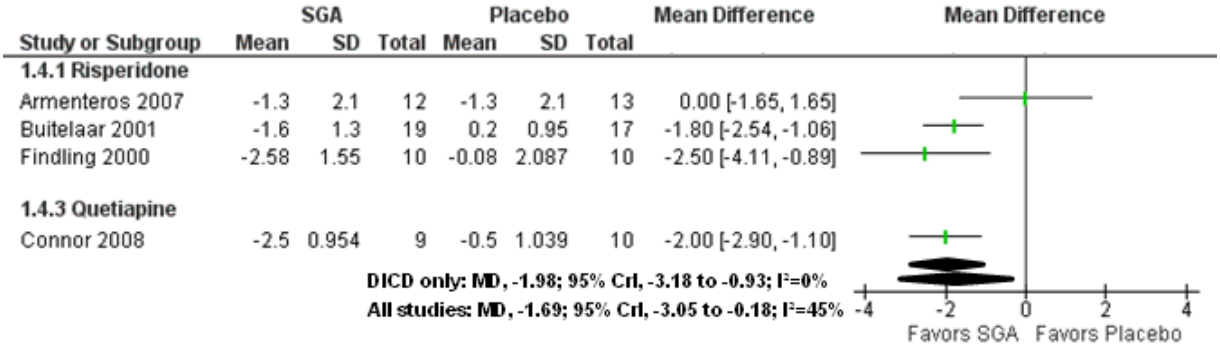
Figure 72. SGAs versus placebo for global impression of improvement in ADHD and/or disruptive, impulse-control, or conduct disorders



ADHD = attention deficit hyperactivity disorder; CrI = credible interval; RR = risk ratio; SGA = second-generation antipsychotic

Four RCTs[153-156] reported data for global impressions of severity using mean scores from the CGI-S (Figure 73). Meta-analysis of the data estimated the pooled effect as significant in favor of SGAs (MD, -1.69; 95% CrI, -3.05 to -0.18; I^2 = 45%); removing the study of Armenteros et al.[153] which focused on risperidone augmentation in ADHD rather than primary treatment of conduct disorders reduced the heterogeneity and increased the precision (MD, -1.99; 95% CrI, -3.18 to -0.93; I^2 = 0%). We did not pool the studies of risperidone due to heterogeneity. One additional trial[147] reported the proportion of patients rated at study endpoint as "normal/borderline/mildly ill" using the CGI-S; there was no difference between patients receiving stimulants and parent training and those having the same augmented by risperidone (59 versus 72 percent; p = 0.10). These findings of no difference for stimulant augmentation agree with those of Armenteros et al.[153]

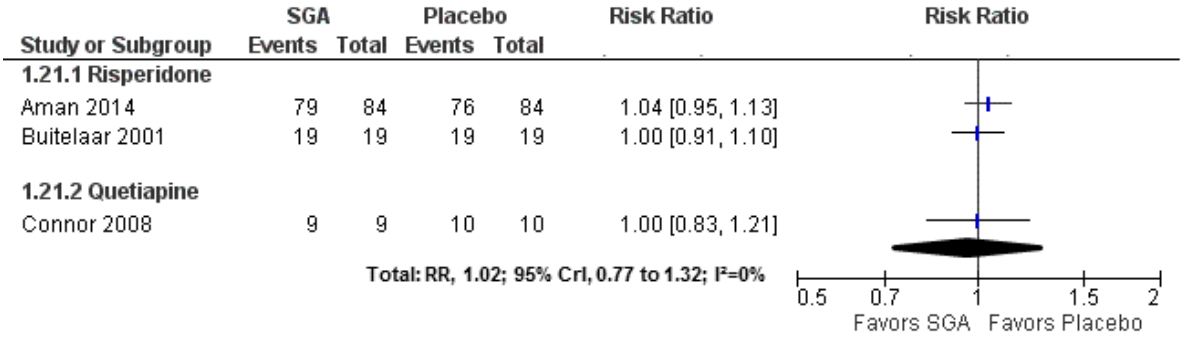
Figure 73. SGAs versus placebo for global impressions of severity in ADHD and/or disruptive, impulse-control, or conduct disorders



ADHD = attention deficit hyperactivity disorder; CrI = credible interval; DICD = disruptive, impulse-control, or conduct disorders; MD = mean difference; SD; standard deviation; SGA = second-generation antipsychotic

Medication adherence. Meta-analysis from three RCTs[147, 154, 155] providing data on medication adherence found no difference between SGAs and placebo (RR, 1.02; 95% CrI, 0.77 to 1.32) (Figure 74). The results of the two studies of risperidone were not pooled although both found no difference between groups. One study[154] reported treatment adherence using plasma samples. The mean plasma concentration of risperidone in the treatment group was 18±24 ng/mL; no risperidone was detected in patients in the placebo group.

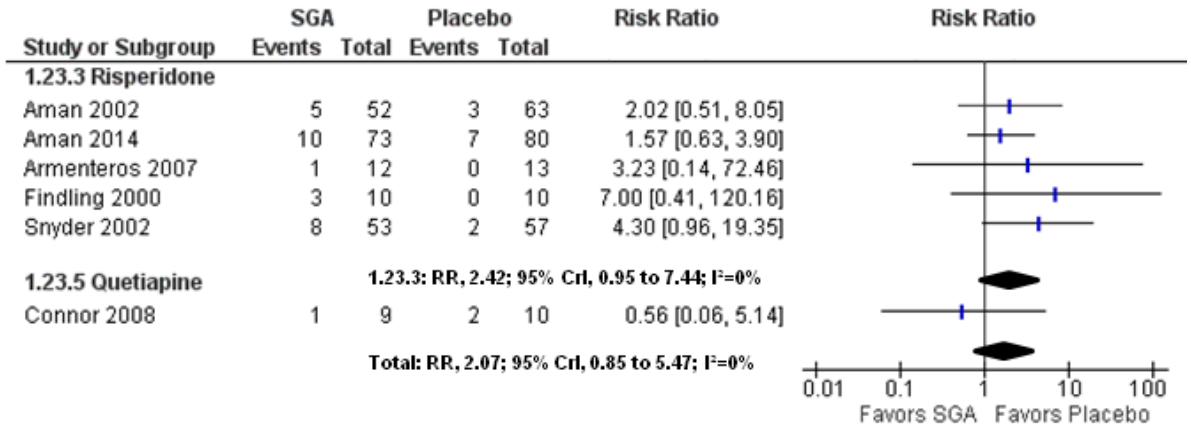
Figure 74. SGAs versus placebo for medication adherence in ADHD and/or disruptive, impulse-control, or conduct disorders



ADHD = attention deficit hyperactivity disorder; CrI = credible interval; RR = risk ratio; SGA = second-generation antipsychotic

Lifestyle behaviors. Increased appetite was reported by six RCTs[147, 151, 153, 155, 156, 158] and meta-analysis found no difference between SGAs and placebo (RR, 2.07; 95% CrI, 0.85 to 5.47) (Figure 75). The results for risperidone were similar (RR, 2.42; 95% CrI, 0.95 to 7.44). A 6-month RCT[157] of risperidone versus placebo had few reports of increased appetite by either the risperidone (4 of 172) or placebo groups (0 of 163) (p = 0.15). Although the relative risk was not statistically significant, in every study of risperidone there were more patients in the treatment than placebo group experiencing increased appetite.

Figure 75. SGAs versus placebo for increased appetite in ADHD and/or disruptive, impulse-control, or conduct disorders



ADHD = attention deficit hyperactivity disorder; CrI = credible interval; RR = risk ratio; SGA = second-generation antipsychotic

Additional Findings

Response rates. Two RCTs comparing risperidone and placebo reported treatment response rate in patients with ADHD and aggression. One study[153] defined response by ≥ 30 percent reduction in aggression, and found no significant difference between the groups (p = 0.13). The other trial's[147] response criteria were ≥ 25 percent reduction in NCBRF Typical IQ disruptive behavior score and at least "much improved" on the CGI-I; this study also found no difference between groups (p = 0.22).

Mood symptoms. Two RCTs assessed mood symptoms. Anxiety as measured using the CPRS did not differ between risperidone and placebo group at study endpoint in one study (p = 0.52).[156] From parent ratings on the Child and Adolescent Symptom Inventory-4R (CASI-4R), risperidone augmentation of stimulants and parent training did not reduce depression symptoms (p = 0.98) or anxiety (p = 0.26) compared with placebo-augmentation.[147] When teachers completed the CASI-4R in this study, there was a significant reduction in anxiety (p = 0.013) but not depression symptoms (p = 0.18).

Short-term school performance and attendance. Short-term classroom functioning (tests/quizzes, homework, class participation) was rated by teachers as improving with risperidone augmentation of stimulant and parent training, although the results did not reach statistical significance (p = 0.07).[147] In a 6-week RCT[155] comparing quetiapine with placebo, no significant differences (p = 0.42) between groups were found for school refusal when captured by an adverse event questionnaire.

Observations on Between-Study Subgroup Effects

Clinical and methodological heterogeneity existed between the trials. Although the primary diagnosis differed between studies—in two it was ADHD[147, 153] and the rest it was DICD[151, 152, 154-156, 158], most studies enrolled a large proportion of children with DICD or ADHD comorbidities, respectively. Examining the findings for each outcome, there was the suggestion for global impressions of severity that risperidone may preferentially reduce illness severity for conduct disorders compared with ADHD. The metagraphs for other outcomes do not provide any clear support for this observation. The findings of our meta-analysis favored risperidone over placebo for hyperactivity, although the data came from studies that did not enroll children

responding to stimulants as with another study[153] that found no benefit for risperidone on hyperactivity.

In one small trial,[152] the children all had a long-term history of response to risperidone; removing this study using sensitivity analyses did not affect the results.

Inclusion criterion related to intellectual functioning differed between studies. Three trials[151, 152, 158] comparing risperidone with placebo limited inclusion to children with subaverage intelligence quotients (IQ 36-84); the children enrolled in other studies of this comparison had higher functioning on average.[147, 153-156] We did not find any clear evidence of a differential treatment effect between these two groups of studies.

FGAs Versus Placebo

A cross-over RCT[150] assigned children with subaverage intelligence to 3 weeks of methylphenidate, thioridazine, and placebo in random order. Children were assessed using teacher and parent rating scales for multiple symptoms including conduct problems, hyperactivity, anxiety, as well as for global functioning. Teachers' ratings showed significant improvement for thioridazine compared with placebo for conduct problems ($p < 0.01$) and hyperactivity ($p < 0.001$), but no other outcome. Parent ratings failed to find any difference for any outcome between these groups.

ADHD and Disruptive, Impulse-Control, or Conduct Disorders: Effectiveness Outcomes

Eight studies comparing SGAs with placebo reported on effectiveness outcomes. Key findings are highlighted below, followed by a detailed analysis by comparison and outcome category.

Key Points

- **SGAs versus placebo** (four RCTs[147, 152, 155, 157] and one observational study[146]): Long-term effectiveness of risperidone compared with placebo is not known for the following outcomes: conduct problems, hyperactivity, relapse, symptom recurrence, time-to-symptom recurrence, and global impressions of severity and functioning.[157] Growth and maturation,[157] cognitive tasks,[152,157] attention,[146] and quality of life (risperidone and quetiapine)[147,155] were also examined. The SOE for all outcomes was determined to be insufficient, because of ROB, unknown consistency (for several outcomes) and imprecision due to small samples.
- **FGAs versus placebo** (one RCT[150]): Cognitive effects of thioridazine versus placebo are unknown due to insufficient SOE.

Detailed Analysis

SGAs Versus Placebo

Five studies reported on effectiveness outcomes for SGAs versus placebo; the one observational study[146] was a pooled analysis of data from two RCTs.[151, 158] One long-term RCT[157] was conducted in children with DICD (67% with comorbid ADHD) assigned to 6-month maintenance or withdrawal of risperidone treatment after response to 12 weeks of treatment.

Results on Effectiveness Outcomes From Short- and Long-Term Studies

Long-term core symptoms. Using the NCBRF, conduct problems (3.3 points; $p < 0.001$) and hyperactivity (1.6 points; $p = 0.007$) were reduced significantly more by risperidone than placebo during 6-months maintenance.[157]

Long-term nonspecific symptoms. The 6-month RCT[157] found risperidone to be significantly superior to placebo for relapse, symptom recurrence, and time-to-symptom recurrence ($p \leq 0.002$).

Long-term global impressions. Global impressions of severity (CGI-S) was reduced to a greater extent with maintenance treatment on risperidone (0.6 points; $p < 0.001$).[157] Global functioning (C-GAS) was reduced significantly less (3.5 vs. 10.2 points; $p < 0.001$) for maintenance treatment on risperidone versus placebo.[157]

Growth and maturation. One RCT[157] compared changes in Tanner stages from baseline for patients treated with risperidone or placebo for 6-month maintenance treatment. No group differences in the distribution of stages were observed.

Cognitive and emotional development. Three RCTs and one observational study compared SGAs and placebo for performance on cognitive tasks or adverse effects related to cognition. 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 in one short-term, cross-over trial in children having prolonged response to risperidone ($p \leq 0.05$).[152] A pooled analysis[146] of patient data from the 6-week trials of Aman[151] and Snyder[158] examined results for attention (Continuous Performance Task) and short- and long-term auditory verbal memory (Verbal Learning Test for Children). There was no significant decline in attention for either the risperidone or placebo group; the only treatment group difference was for total commission errors which favored risperidone ($p = 0.027$). There were no treatment group effects for short- or long-term memory. The longer-term study on maintenance treatment by Reyes et al.[157] found no difference between groups for verbal learning and attention (Continuous Performance Tasks). The RCT[155] comparing quetiapine with placebo found significantly fewer adolescent reports of decreased mental alertness for the quetiapine group ($p = 0.01$).

Quality of life. Risperidone augmentation of stimulants and parent training was shown effective in one short-term study for improving social competence using the NCBRF positive social subscale ($p = 0.0049$).[147] In a 6-week RCT[155] comparing quetiapine with placebo, scores on the Quality of Life Enjoyment and Satisfaction Questionnaire improved significantly in the quetiapine group (by 8 points) compared with the placebo group who worsened by 4 points ($p = 0.005$). Social withdrawal was assessed in the same RCT;[155] no difference was found between treatment arms ($p = 0.81$).

FGAs Versus Placebo

One cross-over RCT[150] with children receiving 3 weeks of methylphenidate, thioridazine, and placebo in random order evaluated cognition using various tests. No differences were found between thioridazine and placebo for tests on IQ performance with reinforcement, breadth of attention, matching-to-sample, short-term memory, attention span (using Continuous Performance Task), seat activity, or for the graduated holes task.

ADHD and Disruptive, Impulse-Control, or Conduct Disorders: Within-Study Subgroup Effects

Five studies of ADHD and disruptive behavior disorders conducted an analysis of outcomes in different subpopulations (Table 20).[149, 154, 156-158] All five compared risperidone with placebo.

Two studies found no effect of age for effects of risperidone on aggression,[156] CPRS,[156] rate of study completion,[156] and risk of symptom recurrence.[157] In one study, race was not significantly different in patients who completed the study than those who did not.[156] Snyder et al.[158] found no impact of comorbidities (including global developmental delay, ADHD, and secondary diagnosis of disruptive behavior disorders) or cotreatment with psychostimulants on NCBRF conduct problem subscale. Pooled analysis[149] of the 6-week Snyder[158] and Aman[151] trials found no indication that the effects of risperidone on conduct problems or hyperactivity varied with stimulant use. Two studies examined the effect of previous treatment on ABC,[154] CGI–S,[154] and NCBRF conduct problem subscale.[158] Risperidone-naïve patients had lower NCBRF conduct problem scores in one study,[158] whereas prior treatment had no impact on symptom severity (ABC, CGI–S) in another study.[154]

Table 20. Within-study analyses for subgroups of interest in ADHD and disruptive, impulse-control, or conduct disorders

First Author, Year Comparison	Type of Analysis	Outcome	Authors' Conclusions
Aman, 2004[149] *Risperidone vs placebo*	Subgroup analysis by cotreatment (stimulant vs no stimulant) Additionally, all subjects in this group selected because they have comorbid ADHD	Conduct problems and hyperactivity (NCBRF subscales)	Reduction in conduct problems: 47.2 % (with stimulants) vs. 44.2% (without stimulants), vs placebo 17.6%; patients on stimulants and placebo showed less improvement than those one placebo only. Reduction in hyperactivity improved for risperidone regardless of stimulant use ($p < 0.011$); addition of risperdione to stimulant significantly improved reduction in hyperactivity ($p = 0.0013$). No indication that the effects of risperidone varied with stimulant use.
Buitelaar, 2001[154] *Risperidone vs. placebo*	Subgroup analysis by IQ and use of prior medication	CGI–S, ABC (school)	No significant difference in rating scale change scores between IQ strata (60–69, 70–79, 80–90) or previous use of medication.
Findling, 2000[156] *Risperidone vs. placebo*	Regression analysis by age, race, and baseline RAAPP and CGI–S scores	Completion of study	Age, race, baseline RAAPP score, and baseline CGI–S score was not significantly different between completers and noncompleters.
		RAAPP, CPRS	When an adjustment for age was made, no alteration in rating scales scores were observed
Reyes, 2006[157] *Risperidone vs. placebo*	Subgroup analysis by somnolence	CPT	There were no significant difference in the change in any CPT values based on present or absence of somnolence.
Snyder, 2002[158] *Risperidone vs. placebo*	Regression analysis by comorbidity, cotreatment, treatment history, condition, gender	NCBRF conduct problem	The efficacy of risperidone was not affected by level of developmental delay, 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. For the CD subgroup, the NCBRF Conduct Problem subscale showed a significant drug effect ($p < 0.002$) from week 1 to week 6 and at end point. For the "other disorders" subgroup, the NCBRF Conduct Problem subscale showed a significant effect for risperidone ($p < .01$).

ABC = Aberrant Behavior Checklist; ADHD = attention deficit hyperactivity disorder; CD = conduct disorder; CGI–S = Clinical Global Impressions–Severity; CPRS = Connor's Parent Rating Scale; CPT = Continuous Performance Task; DBD = disruptive behavior disorder; IQ = intelligence quotient; NCBRF = Nisonger Child Behavior Rating Form; NOS = not otherwise specified; ODD = oppositional defiant disorder; RAAPP = Rating of Aggression Against People and/or Property

Obsessive-Compulsive Disorder: Overview

One 12-week RCT[159] examined augmentation with risperidone or aripiprazole in patients with obsessive-compulsive disorder (OCD) who failed to respond to at least 12 weeks of treatment with selective serotonin reuptake inhibitors (SSRIs). Patients were mainly male (90%) and had early-onset (average age of onset 8.6 years) OCD. Almost half (49.3%) also received cognitive-behavioral therapy during the study. All had comorbid tic disorders. Details of the study are included in Table 21 and Appendix D. Although differences between groups in comorbidities overall did not reach statistical significance, more patients in the risperidone group had anxiety and phobia disorders, while more patients receiving aripiprazole had comorbid ADHD.

Table 21. Characteristics of studies examining obsessive-compulsive disorder

First Author, Year Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
SGAs vs. SGAs			
Masi, 2013[159] NRCT, ≥12 wk	G1: Risperidone (35), 1.7±0.8 (0.5-3) mg/day G2: Aripiprazole (34), 8.9±3.1 (2.5-12.5) mg/day	G1: 13.3±2.2 yr / Males: 94.3% / White: NR G2: 13.9±2.5 yr / Males: 85.3% / White: NR	OCD with comorbid tic disorders (69) ROB: High (subjective), Medium (objective)

Mg = milligram; N = number; NR = not reported; NRCT = nonrandomized controlled trial; OCD = obsessive-compulsive disorder; ROB: risk of bias; SD = standard deviation; SGA = second-generation antipsychotic; wk = week

Obsessive-Compulsive Disorder: Intermediate Outcomes

Below we highlight the key points and provide details for the one study's findings. The SOE for intermediate and effectiveness outcomes in OCD was deemed insufficient.

Key Points

- **SGAs versus SGAs** (one RCT[159]): We are very uncertain of the comparative effects of SSRI augmentation with risperidone and aripiprazole over 12 weeks of treatment for nonspecific symptoms (i.e., response rate) and global impressions of severity and functioning. Results for core symptoms of obsessions and compulsions were not reported by the authors.

Detailed Analysis

One RCT[159] of SGA-augmentation of SSRIs reported on short-term response rates, and on global impressions of improvement, severity, and functioning in terms of OCD symptomatology. Both risperidone and aripiprazole improved all measures over the 12 weeks of treatment. Severity of symptoms (CGI-S) and functioning (C-GAS) improved on average by 2.4 and 13.5 points, respectively ($p < 0.0001$ for all patients). Response rates were 51.4 and 61.8 percent for risperidone and aripiprazole, respectively. There were no significant differences between risperidone and aripiprazole for severity ($p = 0.07$), functioning ($p = .51$), or response rates ($p = 0.53$). Response to tic symptomatology was similar with 68 percent in both groups responding. Although this study examined patients using the Yale-Brown Obsessive-Compulsive Scale symptom checklist after diagnosis, the authors did not use this data for assessment of treatment effectiveness. No effectiveness outcomes were reported for this study.

Depression: Overview

One observational study[160] examined a subgroup of patients aged ≤ 25 years in a pooled analysis of data from two RCTs of placebo-controlled adjuvant aripiprazole (2-20 mg/day) for patients with major depressive disorder who failed to respond to 8 weeks of antidepressant treatment. No details were provided on patient characteristics for the subsample, therefore a table describing study characteristics is not presented.

Depression: Effectiveness Outcomes

Below we highlight the key points and provide details for the findings from the one study.

Key Points

- For SGAs in treatment-resistant depression, we are very uncertain of the effects for intermediate (not reported) and effectiveness outcomes related to suicide; SOE was insufficient because of ROB, unknown consistency, and imprecision (n = 35). No other outcomes were reported.

Detailed Analysis

SGAs Versus Placebo

One observational study[160] examined suicide-related adverse events and suicide ideation from placebo-controlled adjuvant aripiprazole in a pooled analysis of two RCTs of adults; separate findings were reported for patients ages ≤ 25 years. Suicide ideation was evaluated using item 10 (suicidality) of the Montgomery-Åsberg Depression Rating Scale (MADRS) and item 18 (suicidality) on the Inventory of Depressive Symptomatology (IDS). No suicides were reported for the entire study population in patients ages 18 to 65. Only 35 patients were aged ≤ 25 years. Three patients experienced worsening on item 10 of the MADRS; one on placebo and one on aripiprazole experienced a 2-point increase on the 7-point scale, and one on placebo experienced a 1-point increase. By comparison, 7 patients on placebo and 7 patients taking aripiprazole experienced 1- or 2-point decreases (improvements) on this item. On the 4-point IDS, one patient (aripiprazole) experienced worsening by 1 point, while three patients in each group experienced a 1- or 2-point decrease (improvement) on this item. No statistical comparisons were made due to the small sample size. Findings for depressive symptomatology were not reported.

Eating Disorders: Overview

Two RCTs[161, 162] and one retrospective cohort study[163] examined SGAs versus placebo for adjunctive treatment in eating disorders. All three studies enrolled females (average ages 14-18) with anorexia nervosa or eating disorders not-otherwise specified (allowing for persistence of menstruation), who were also receiving multidisciplinary, tailored care within eating disorder programs. Details of the studies are reported in Tables 22 and 23, and in Appendix D. The trials were assessed as having medium risk of bias, and the observational study was of good quality.

Table 22. Study characteristics of trials examining eating disorders

First Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
SGAs vs. Placebo			
Hagman, 2011[161] RCT, 11 wk	**G1:** Risperidone (18), 2.5±1.2mg/day **G2:** Placebo (22)	**G1:** 16.2±2.5 yr / Male: 0 / White: NR **G2:** 18.1±2.0 yr / Male: 0 / White: NR Comorbidities: depression (NR), obsessive-compulsive disorder (NR), anxiety disorder (NR), bulimia nervosa (NR)	Anorexia nervosa (40) ROB: Medium (subjective), Medium (objective)
Kafantaris, 2011[162] RCT, 10 wk	**G1:** Olanzapine (10), target 10 mg/day **G2:** Placebo (10)	**G1:** 16.2±2.5 yr / Male: 0 / White: Overall (80) **G2:** 15.8±2.3 yr / Male: 0 / White: see G1 Comorbidities: NR	Anorexia nervosa-restricting type ROB: Medium (subjective), Medium (objective)

wk = week; mg = milligram; N = number; NR = not reported; RCT = randomized controlled trial; ROB = risk of bias; SD = standard deviation

Table 23. Characteristics of observational studies examining eating disorders

First Author, Year, Study Design, Duration	Intervention (N enrolled), Dosage (mg/day) mean±SD	Age, mean±SD (range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
SGAs vs. Placebo			
Norris, 2011[163] Retrospective cohort	**G1:** Olanzapine (43), 5.0 (3.75-7.5) [median (IQR)] **G2:** No antipsychotic treatment (43) Comparisons between groups for weight, n =11/group	**G1:** 14.4±1.9 yr / Male: 0 / White: NR **G2:** 14.8±1.6 yr / Male: 0 / White: NR Comorbidities: Anxiety (42), depression (41), obsessive compulsive disorder (4)	Anorexia nervosa-restricting type (58), anorexia nervosa binge-purge subtype (4), eting disorder NOS (24) ROB: 7/8 stars

IQR = interquartile range; mg = milligram; N = number; NOS = not otherwise specified; NR = not reported; RCT = randomized controlled trial; ROB = risk of bias; SD = standard deviation; wk = week.

Eating Disorders: Intermediate Outcomes

All studies examining eating disorders compared SGAs with placebo.[161-163] A summary of the key findings is presented below, followed by a detailed analysis.

Key Points

- **SGAs versus placebo** (olanzapine[162, 163] and risperidone[161]): We had very little confidence in the effects for all key outcomes (i.e., weight) of relevance; failure to provide data by group (for determining consistency and precision) and the small sample sizes (imprecision) were the main reasons. The studies did not report any effectiveness outcomes.
- Findings from the observational study were substantially confounded by a greater illness severity and overall resource use by the olanzapine group. Speculated changes in resting energy expenditure were not realized.

Detailed Analysis

SGAs Versus Placebo

Olanzapine versus placebo. A 10-week RCT[162] examined olanzapine versus placebo for core symptoms of body weight gain and eating disorder symptoms, and for general psychiatric symptoms including depression. Eating disorder symptoms were measured using the Eating Disorder Examination and the Yale-Brown-Cornell Eating Disorder Scale. No difference was found between groups for changes in percent mean body weight ($p = 0.88$), eating disordered behaviors and attitudes, depression, or general psychiatric symptoms (BPRS). The study only reported data by group for percentage mean body weight. There were also no differences between groups for numbers reporting increased appetite, or for changes in resting energy expenditure.

A retrospective cohort study[163] attempted to match a group of patients receiving olanzapine with a group not receiving antipsychotics. The authors found that patients treated with olanzapine had significantly greater illness severity (e.g., more comorbidities, more inpatient days, longer treatment course), which greatly confounded their ability to compare these patients with a group not receiving treatment. To minimize confounding, a subgroup of inpatients was analyzed with those in the olanzapine group having received treatment for at least 2 weeks after assessment. Compared to the no treatment group, the olanzapine group had significantly greater weight gain and BMI at discharge, although when examined by rate of weight gain (kg/week) there was no significant differences ($p = 0.068$). More patients treated with olanzapine were admitted to an intensive treatment program and were treated for longer periods of time than those in the no treatment group.

Risperidone versus placebo. An 11-week RCT[161]compared risperidone with placebo for outcomes of weight (time to reach 90 percent of ideal body weight), eating disorder symptomatology (drive for thinness, body dissatisfaction, body image distortion), anxiety symptoms, and resting energy expenditure. The authors defined five possible endpoints for the study, and timepoints for analyses were 7 and 11 weeks. Risperidone was favored significantly over placebo at 7 weeks ($p = 0.002$) but not 11 weeks ($p = 0.13$) on the Drive for Thinness scale on the Eating Disorder Inventory 2. No other significant findings were found for eating disorder symptomatology. Changes over time for anxiety symptoms were not significantly different ($p = 0.44$); the groups did not differ in changes in percentage of ideal body weight or body mass index (p values not provided). Resting energy expenditure was no different between groups either ($p = 0.34$).

Tic Disorders: Overview

Twelve studies (9 RCTs[164-172] and 3 NRCTs[173-175]) assessed antipsychotics for treating children with tic disorders. Three studies only reported on harm data.[164, 173, 174] Table 24 provides selected information on the characteristics of the individual studies. The studies are grouped according to the drug class comparisons. Studies that included both head-to-head and placebo comparisons are listed under the head-to-head category. Within each comparison, studies are listed alphabetically by the specific drugs compared. Detailed study characteristic tables are available in Appendix D.

Patients enrolled in the studies had an average age of 10.7 years and were predominantly male (84 percent). The distribution of patient ethnicity was not reported in any of the studies. All but one study[175] enrolled patients with Tourette's syndrome. Patients had a variety of

comorbidities, including ADHD (34%); OCD (23%); and DICD (5%). Only one study permitted concomitant psychotropic medications including stimulants.[165]

Two studies examining benefit outcomes compared an FGA with an SGA: pimozide versus risperidone,[166] and haloperidol versus aripiprazole.[175] Three other studies reporting on harms only compared pimozide with risperidone[164] and with aripiprazole.[173, 174] One RCT[165] compared an SGA (risperidone) with another SGA (aripiprazole). Two studies[168, 169] provided data on the comparative effectiveness of two FGAs, haloperidol and pimozide. A placebo-controlled withdrawal study compared short-term and long-term outcomes of treatment with pimozide.[171] Two trials compared SGAs risperidone[170] and ziprasidone[167] with placebo.

Two of the RCTs had a cross-over design.[166, 168] Three studies examined treatment durations of longer than 6 months.[171, 173, 174] Of the short-term studies, average duration of treatment was 7.7 weeks (range 4 to 11.2 weeks). Fifty percent of studies had high risk of bias, mainly due to incomplete outcome data (RCTs) or lack of randomization and blinding (NRCTs).

Table 24. Characteristics of trials examining tic disorders

First Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities (n)	Diagnosis Breakdown (n) Quality Rating
FGAs vs. SGAs			
Yoo, 2011[175] NRCT, 8 wk	**G1:** Haloperidol (17), 1.9±1.1 (0.75-4.5) mg/day **G2:** Aripiprazole (31), 10.6±5.2 (2.5-20) mg/day	**G1:** 8.6±2.9 (6-16) yr / Male: 64.7% / White: NR **G2:** 11.2±3.5 (6-18) yr / Male: 71% / White: NR Comorbidities: ADHD (15), ODD (2), OCD (3)	Tourette syndrome (26), chronic motor and vocal tic disorder (11), transient tic disorder (11) ROB: High (subjective), High (objective)
Gulizano, 2011[173] NRCT, 24 mo Harms	**G1:** Pimozide (25), 4.4±1.5 mg/day **G2:** Aripiprazole (25), 5.3±2.4 mg/day	**G1:** 9.1±2.9 yr / Male: 88% / White: NR **G2:** 13.1±2.3 yr / Male: 84% / White: NR Comorbidities: ADHD (28), OCD (24)	Tourette syndrome (50) ROB: NA (subjective), Medium (objective)
Rizzo, 2012[174] NRCT, 24 mo Harms	**G1:** Pimozide (25), 1-4 mg/day **G2:** Aripiprazole (25), 1.25-15 mg/day **G3:** No medication (25)	**G1:** 11.2±3.1 yr / Male: 92% / White: NR **G2:** 11.6 ±2.2 yr / Male: 88% / White: NR **G3:** 10.2±2.8 yr / Male: 88% / White: NR Comorbidities: ADHD (10), OCD (20)	Tourette syndrome (75) ROB: High (subjective), High (objective)
Bruggeman, 2001[164] RCT, 12 wk Harms	**G1:** Pimozide (24), 2.9 (1-6) mg/day **G2:** Risperidone (26), 3.8 (0.5-6) mg/day	**G1:** NR (11-18) / Male: 87.5% / White: NR **G2:** NR (11-18) / Male: 88.5% / White: NR Comorbidities: ADHD (2), GAD (3), OCD (23)	Tourette syndrome (50) ROB: NA (subjective), Medium (objective)
Gilbert, 2004[166] RCT (cross-over*), 4 wk	**G1:** Pimozide (7), 2.4 mg/day **G2:** Risperidone (12), 2.5 mg/day	**All groups:** NR / Male: NR / White: NR Comorbidities: ADHD (7), CD (1), learning disorder (3), OCD (2), ODD (2)	Chronic tic disorder (3), Tourette syndrome (16) ROB: High (subjective), High (objective)
SGAs vs. SGAs			

First Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities (n)	Diagnosis Breakdown (n) Quality Rating
Ghanizadeh, 2014b[165] RCT, 8 wk	**G1:** Aripiprazole (31), 4.0±2.4 mg/day **G2:** Risperidone (29), 0.6±0.2 mg/day	**G1:** 11.12±3.3 yr / Male: 82.8% / White: NR **G2:** 10.22±2.3 yr / Male: 86.2% / White: NR Comorbidities: ADHD (4)	Tic disorder (60) ROB: High (subjective), High (objective)
FGAs vs. FGAs			
Sallee, 1997[168] RCT (cross-over), 6 wk	**G1:** Haloperidol (22)*, 3.5±2.2 mg/day **G2:** Pimozide (22)*, 3.4±1.6 mg/day **G3:** Placebo (22)*	**All groups:** 10.2±2.5 yr / Male: 77% / White: NR Comorbidities: ADHD (13), OCD (5)	Tourette's syndrome (22) ROB: High (subjective), High (objective)
Sallee, 1994[169] RCT, 6 wk	**G1:** Haloperidol (17), 1.5±0.6 mg/day **G2:** Pimozide (24), 3.7±1.4 mg/day **G3:** No medication (25)	**G1:** 10.4 yr / Male: 90% / White: NR **G2:** 10.8 yr / Male: 90% / White: NR **G3:** 10.8 yr / Male: 90% / White: NR Comorbidities: ADHD (22)	Tourettte's syndrome (66) ROB: Medium (subjective), Medium (objective)
FGAs vs. Placebo			
Sehgal, 1999[171] RCT, 8 mo	**G1:** Pimozide (6), 3.5 mg/day **G2:** Placebo (4)	**All groups:** 10 yr / Male: 80% / White: NR Comorbidities: NR	Tourette's syndrome (10) ROB: Medium (subjective), NA (objective)
SGAs vs. Placebo			
Yoo, 2013[172] RCT, 10 wk	**G1:** Aripiprazole (32), 11.0±6.1 mg/day **G2:** Placebo (29)	**G1:** 11±2.5 yr / Male: 93.8% / White: NR **G2:** 10.9±3.0 yr / Male: 79.3% / White: NR Comorbidities: ADHD (6), ODD (3), anxiety disorder (1)	Tourette's syndrome (61) ROB: High (subjective), High (objective)
Scahill, 2003[170] RCT, 8 wk	**G1:** Risperidone (12), 2.5±0.9 mg/day **G2:** Placebo (14)	**All groups:** 11.1±2.2 / Male: 96% / White: NR Comorbidities: ADHD (11), OCD (4)	Tourette's syndrome (26) ROB: Medium (subjective), Medium (objective)
Sallee, 2000[167] RCT, 8 wk	**G1:** Ziprasidone (16), 28.2±9.6 mg/day **G2:** Placebo (12)	**G1:** 11.3 yr / Male: 87.5% / White: NR **G2:** 11.8 yr / Male: 66.7% / White: NR Comorbidities: ADHD (15), DBD (5), learning disability (2), OCD (10)	Tourette's syndrome (27) ROB: Medium (subjective), Medium (objective)

ADHD = attention deficit hyperactivity disorder; CD = conduct disorder; DBD = disruptive behavior disorder; FGA = first-generation antipsychotic; G = group; mg = milligrams; mo = month; N = number; NR = not reported; NRCT = nonrandomized controlled trial; OCD = obsessive-compulsive disorder; ODD = oppositional defiant disorder; RCT = randomized controlled trial; ROB = risk of bias; SD = standard deviation; SGA = second-generation antipsychotic; wk = week
*All patients experienced each of the treatment arms in this cross-over study

Tic Disorders: Intermediate Outcomes

Eight studies reported on the effects of FGAs and SGAs on treating intermediate outcomes of children with tic disorders.[165-170, 172, 175] A summary of the key points by comparison is presented below. Strength of evidence grades for all key outcomes that were graded as having at least low SOE are provided in Table 25.

Key Points

- **FGAs versus SGAs** (one RCT[166] and one NRCT[175]): Tic severity and clinician ratings of global improvement were examined for risperidone versus pimozide[166] and aripiprazole versus haloperidol;[175] the aripiprazole comparison also reported on global impressions of severity. Because of ROB and imprecision, we had no confidence in the findings to support any conclusions.
- **Haloperidol versus pimozide** (two RCTs[168, 169]): The effects between haloperidol and pimozide are not known in terms of tic severity, global impressions of severity or functioning,[168] or school performance.[169]
- **Risperidone versus aripiprazole** (one RCT[165]): It is not known if there is any difference between risperidone and aripiprazole for tic severity, response rates, or school performance.
- **FGAs versus placebo/no treatment** (two RCTs[168, 169]): Our confidence was very low for making any conclusions on effects of haloperidol or pimozide versus placebo for tic severity, response rates, or ratings on global improvement and functioning.[168] The effects of pimozide and haloperidol versus no treatment for school performance, learning, and total academic function are not known.[169]
- **SGAs versus placebo** (three RCTs [aripiprazole,[172] risperidone,[170] ziprasidone[167]]): Tic severity may be reduced in patients receiving SGAs. Effects for response, using global impression ratings, from risperidone and aripiprazole are unknown. In terms of overall tic disorder severity (rated using CGI-I scores), the effects from studies of aripiprazole and ziprasidone provided us with too little confidence to make conclusions. The SOE for response rates and global impression of severity scores was considered insufficient due to ROB, inconsistency (response), and imprecision (response and severity). ***Observations on between-study subgroup effects***: (a) the study enrolling the fewest patients with comorbid ADHD was that of aripiprazole,[172] although there is no suggestion of a differential effect in this study from the others, (b) observations related to concomitant stimulant use cannot be drawn; only one study[165] allowed for concomitant stimulant medication and the rate of stimulant use was low (2 patients per group).

Table 25. Strength of evidence for tic disorders: Key intermediate outcomes having at least low strength of evidence

Comparison	Outcome (N Studies; N Patients)	Findings,[a] Studies, and Tool With Range of Values	Strength of Evidence; Conclusions
SGAs vs. placebo	Tic severity (3, 114)	MD, -6.26; 95% CrI, -10.05 to -2.54[167, 170, 172] YGTSS Total Tic score (range 0-50)	Low; SGAs may decrease[b]

CrI = credible interval; N = number; MD = mean difference; ROB = risk of bias; SGA = second-generation antipsychotic; YGTSS = Yale Global Tic Severity Scale.

[a] A negative MD score favors the SGAs. This MD of 6 points is considered clinically meaningful.

[b] Downgraded for ROB and imprecision because of small sample size (typically < 200 patients).

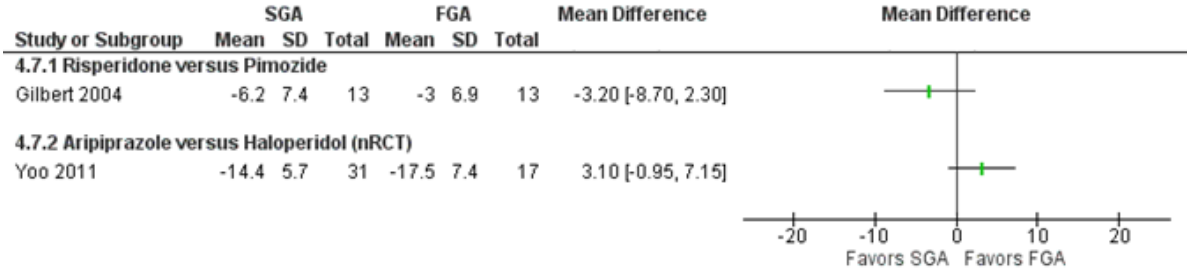
Detailed Analysis

FGAs Versus SGAs

Pimozide versus risperidone. A crossover RCT compared the effectiveness of pimozide and risperidone in children ages 7 to 17 years.[166] The study duration was 8 weeks, and patients received each drug for 4 weeks. Risperidone was significantly more effective than pimozide at reducing the total score (p = 0.05), but not the total tic subscale (p = 0.25; Figure 76), on the Yale Global Tic Severity Scale (YGTSS); risperidone appeared favorable to pimozide for parent reports of tic severity on the Tic Symptom Self-Report but the difference did not reach statistical significance (p = 0.06). No significant differences between the groups were observed for global impressions of improvement on the CGI-I (p = 0.43).

Haloperidol versus aripiprazole. An 8-week NRCT comparing haloperidol with aripiprazole found no difference between groups for tic severity using the total tic score on the YGTSS (Figure 76).[175] The proportion of patients with scores of 1 ("very much improved") or 2 ("much improved") on the CGI-I for global impressions of improvement did not differ between groups (p = 0.42); no difference was found between groups for global impressions of severity on the CGI-S (data not reported). One patient in each group reported an increase in appetite.

Figure 76. FGAs versus SGAs for tic severity using YGTSS Total Tic score in tic disorders



FGA = first-generation antipsychotic; SD = standard deviation; SGA = second-generation antipsychotic; YGTSS = Yale Global Tic Severity Score

FGAs Versus FGAs

Haloperidol versus pimozide. Two RCTs compared the effect of haloperidol and pimozide for intermediate outcomes in children ages 7 to 16 with Tourette syndrome. In a cross-over study with 6 weeks of treatment with each medication, Sallee et al.[168] found no significant differences between groups for tic severity using the tic subscales on the Tourette Syndrome Global Scale (TSGS) (p = 0.4) or the Tourette's Syndrome Symptom List (p = 0.64), or for global impressions of severity (CGI–S; p = 1.0) or functioning (C-GAS; p = 0.51). Treatment adherence was high in both groups, with no significant difference.

A second RCT by Sallee et al.[169] randomized patients to haloperidol, pimozide, or no medication for 8 weeks. Patients were assessed using the school performance, working hard, learning, and function subscales of the Child Behavior Checklist–Teacher Report Form. The pimozide group showed significantly greater improvement on the working hard subscale compared with the haloperidol group (p < 0.05). No significant differences were found between the groups for any of the other subscales.

SGAs Versus SGAs

An 8-week RCT[165] compared risperidone and aripiprazole for intermediate outcomes. No differences were found between groups for tic severity (YGTSS Total Tic score; p = 0.5), response rates (79.3% vs. 90.3%; p = 0.2), or for school performance using parent reports on educational functioning via the Pediatric Quality of Life Inventory (p = 0.67). Eight patients in each group (N = 29 and 31) reported an increase in appetite.

FGAs Versus Placebo/No Treatment

In the crossover RCT comparing haloperidol and pimozide with placebo,[168] tic severity on the TSGS significantly improved compared with placebo for the pimozide (p = 0.005) but not haloperidol (p = 0.07) group. Both groups had a better response rate (70% reduction in tic severity) than did the placebo group (haloperidol, p = 0.02; pimozide, p = 0.009). Both FGAs were superior to placebo for global impressions of severity (CGI-S, p = 0.01) and functioning (C-GAS, p < 0.05).

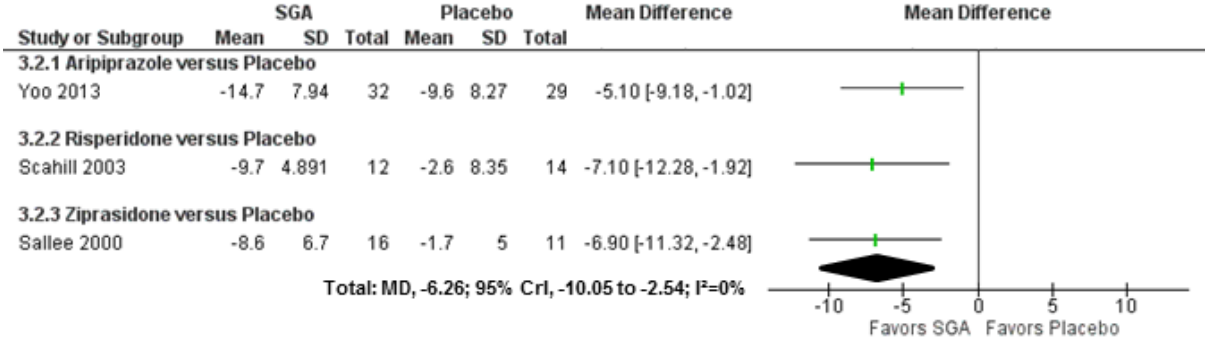
In the RCT[169] comparing haloperidol, pimozide, and no medication, pimozide was similar but haloperidol was inferior to the no medication group on the subscales of working hard, learning, and total academic function (all p < 0.05) using the Child Behavior Checklist–Teacher Report Form.

SGAs Versus Placebo

Three placebo-controlled RCTs evaluated SGAs: aripiprazole,[172] risperidone,[170] and ziprasidone.[167] The trials were between 8 and 10 weeks duration, and studied patients about 11 years of age with Tourette's Syndrome.

Short-term core symptoms. A meta-analysis was conducted using data from all three RCTs on tic severity using the YGTSS Total Tic subscale (Figure 77). Tic severity was significantly reduced by SGAs compared with placebo (MD, -6.26; 95% CrI, -10.05 to -2.54); the magnitude of the mean difference is considered clinically meaningful.[176]

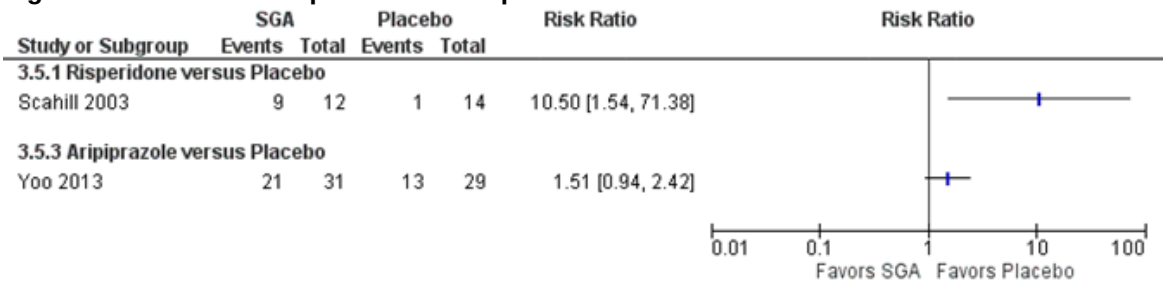
Figure 77. SGAs versus placebo for tic severity using YGTSS Total Tic score in tic disorders



CrI = credible interval; MD = mean difference; SD = standard deviation; SGA = second-generation antipsychotic; YGTSS = Yale Global Tic Severity Scale

Short-term nonspecific symptoms. Obsessive-compulsive symptoms improved significantly in the ziprasidone group compared with placebo (CY-BOCS, p = 0.0003).[167] Response rates were reported by two RCTs (Figure 78).[170, 172] Using final scores of 1 or 2 on the Tourette's Syndrome CGI-I scale, aripiprazole did not differ from placebo for response (66 vs. 45 percent; p = 0.09).[172] Using similar scoring on the generic CGI-I, Scahill et al.[170] found greater response for risperidone versus placebo (75% vs. 7%; p = 0.02).

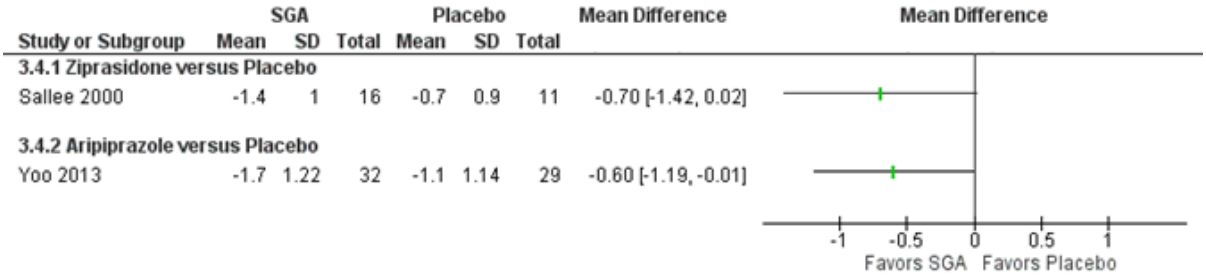
Figure 78. SGAs versus placebo for response rates in tic disorders



SGA = second-generation antipsychotic

Short-term global impressions. Two RCTs[167, 172] measured global impressions of severity using the Tourette's Syndrome CGI-S scale; both aripiprazole (p = 0.03)[172] and ziprasidone (p = 0.1)[167] reduced severity relative to placebo by about 0.7 points, although only the finding for aripiprazole was statistically significant (Figure 79).

Figure 79. SGAs versus placebo for global impressions of severity using Tourette's Syndrome CGI-S in tic disorders



CGI-S = Clinical Global Impressions of Severity; SD = standard deviation; SGA = second-generation antipsychotic

Lifestyle behaviors. One RCT[172] comparing aripiprazole with placebo reported on lifestyle behaviors in terms of appetite increase. Two of 32 patients receiving aripiprazole versus zero of 28 patients on placebo reported increases in appetite (p = 0.33).

Observations on Between-Study Subgroup Effects

All comparisons had few studies making any observations of differential effects for certain subgroups difficult. The two RCTs[165, 172] having the fewest patients with comorbid ADHD both studied aripiprazole, although the effects of this antipsychotic do not seem to differ from others. Observations related to concomitant stimulant use cannot be drawn; only one study[165] allowed for concomitant stimulant medication and the rate of stimulant use was low (2 patients per group).

Tic Disorders: Effectiveness Outcomes

Three RCTs[165, 169, 171] assessed the use of antipsychotics for treating effectiveness outcomes in tic disorders. One RCT[171] examined long-term effectiveness of placebo-controlled discontinuation of pimozide for exacerbation of tics. Below is a summary of the key findings by outcome. Strength of evidence was insufficient to draw conclusions for any comparisons or outcomes.

Key Points

- **FGAs versus FGAs** (one RCT[169]): The effects of pimozide compared with haloperidol for cognitive effects are not known.[169]
- **SGAs versus FGAs** (one RCT[165]): It is not known if risperidone and aripiprazole differ in their effects on social, emotional, or physical functioning.
- **FGAs versus placebo** (one RCT[171]): For long-term treatment with pimozide versus placebo, the relative effects on response are unknown.

Detailed Analysis

Long-term nonspecific symptoms. One RCT[171] compared 8-month treatment with pimozide with discontinuation using placebo after at least 6 weeks of response on pimozide. Patients receiving long-term treatment had a longer time until dose increases were required to treat tic exacerbation (231 vs. 37 days; p = 0.02).

Cognitive and emotional development. One RCT comparing haloperidol and pimozide with a no medication treatment control group found significantly fewer commission errors on a continuous performance task in the pimozide compared with haloperidol and no medication groups.[169] Results for omission errors and memory processing efficiency (memory search task) were no different between groups.

Quality of life. Ghanizadeh et al.[165] compared aripiprazole with risperidone for measures of quality of life using a Farsi version of the parent-rated Children's Quality of Life Inventory. The group receiving risperidone experienced greater increases in social functioning than did the aripiprazole group (p = 0.03), although their baseline scores were lower. No differences between groups were found for the domains of emotional or physical functioning.

Tic Disorders: Within-Study Subgroup Effects

Only one study performed relevant subgroup analysis (Table 26). Sallee et al.[169] found that the preferential effect by pimozide versus haloperidol for reducing commission errors was only present in the sample of patients having comorbid ADHD. In this subsample, haloperidol was associated with significantly higher commission errors. The authors comment on the relatively low doses of pimozide in their study compared with other studies, which may have improved the beneficial effect on cognition.

Table 26. Within-study analysis for subgroup effects in tic disorders

Author, Year, Comparison	Type of Analysis	Outcome	Authors' Conclusions
Sallee, 1994[169] *Haloperidol vs. pimozide*	Regression analysis by comorbidity	CPT task commission and omission errors	Patients with ADHD had significantly higher commission and omission errors than patients without ADHD.

ADHD = attention deficit hyperactivity disorder; CPT = continuous performance task

Behavioral Issues: Overview

Two 4-week RCTs[177, 178] compared risperidone with placebo for treatment of behavioral issues in children without psychiatric diagnoses within the categories of this review. The inclusion criteria in one study[178]were persistent behavioral disturbances (e.g., hostility, aggressiveness, irritability, agitation) in children with intellectual impairment and living in residential homes. The other study[177] focused on children diagnosed clinically with a masturbation problem. Table 27 and Appendix D contain details on the study characteristics.

Table 27. Characteristics of trials examining behavioral issues

First Author, Year Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Quality Rating
SGAs vs. Placebo			
Van Bellinghen, 2001[178] RCT, 4 wk	**G1:** Risperidone (6), 1.2 mg/day **G2:** Placebo (7)	**G1:** 6-14 yrs / Male: 33% / White: NR **G2:** 6-14 yrs / Male: 43% / White: NR Comorbidities: NR	Behavioral disturbances and borderline intellectual functioning ROB: Medium (subjective), Medium (objective)
Omranifard, 2013[177] RCT, 4 wk	**G1:** Risperidone (44), 0.25 - 1 mg/day **G2:** No medication (46)	**G1:** 5.3±1.1 yr / Male: 52% / White: NR **G2:** 4.9±1.1 yr / Male: 58% / White: NR Comorbidities: NR	Habitual behavior (masturbation) ROB: High (subjective), NA (objective)

G = group; N = number; NA = not applicable; NR = not reported; SD = standard deviation; wk = week; yr = year

Behavioral Issues: Intermediate Outcomes

Two RCTs[177, 178] examined intermediate outcomes in children experiencing behavioral issues outside the context of a psychiatric disorder. A summary of findings for key outcomes is followed by details for all outcomes.

Key Points

- Risperidone versus placebo (one RCT[178]): All key outcomes were assessed as having insufficient SOE because of risk of bias, inconsistency, and imprecision.

Detailed Analysis

Risperidone Versus Placebo/No Medication

Van Bellinghen et al.[178] found risperidone to significantly reduce symptoms of irritability ($p < 0.05$) and hyperactivity ($p < 0.01$), but not those of lethargy, stereotypic behavior, or inappropriate speech using the ABC. For global impressions, scores on the CGI-I improved by 2 points more for the risperidone group ($p < 0.05$), and 5 of 6 versus 0 of 6 patients were rated as "much or very much improved" by taking risperidone or placebo, respectively.

Risperidone reduced the frequency of masturbation compared with no medication in the study by Omranifard and colleagues[177] (mean reduction by 1.6 vs. 1.2 times/day, $p = 0.01$).

Key Question 2: Harms

This section reviews the evidence on harms for antipsychotic use in children and young adults (KQ2). The section begins by describing the studies not previously included in the sections for KQ1 on each condition; studies of patients having a variety of primary diagnoses (i.e., "mixed condition" studies) were included for data on harms but not for intermediate or effectiveness outcomes. We then describe findings on harms by comparison, beginning with findings across all comparisons, and followed by head-to-head and then placebo-controlled comparisons. Within each comparison, we begin with findings for major adverse effects (AEs) followed by general AEs, including our assessments of the SOE for key harms having at least low SOE. The section ends with findings from subgroup analyses.

There was a wide variety of possible harms on which to report. We made some decisions regarding which data to report and/or analyze for this report, based on harm category and clinical relevance. All data on our predefined major AEs are presented. For general AEs, we chose outcomes best aligning with our key harm outcomes (e.g., hypertriglyceridemia versus serum triglycerides to represent one feature of dyslipidemia). Also for general AEs, we only present data in the main report for findings on AEs limiting treatment (not undergoing SOE assessments but considered clinically relevant), and on other outcomes assessed as having at least low SOE. Insufficient SOE was often the result of ROB of the studies contributing data, and imprecision due to small sample sizes and/or confidence intervals (or credible intervals if meta-analysis was conducted) included clinically relevant effects despite an effect estimate of no difference. For rare outcomes (i.e., < 5%), the SOE was generally considered insufficient unless the sample size was large enough (2000 at minimum) to offer adequate prognostic balance to detect at least a small difference.[61] Appendix G contains additional findings from the network meta-analysis (star plots, inconsistency tables, results for all possible comparisons), and all findings (absolute and relative effects) for general AEs.

Mixed Condition Studies: Overview

Harms were reported in 126 studies (93%) included in this review. Of these, 1 trial[179]and 22 observational studies (11 prospective[180-190] and 11 retrospective[191-201]) reported on harms data for

children and young adults with mixed primary diagnoses. Table 28 provides details for the studies of mixed conditions; the studies enrolling patients having a primary diagnosis in one of our condition categories are described in the sections on KQ 1 for intermediate and effectiveness outcomes. Twelve of the mixed studies reported on harms after short-term (< 6 months) treatment (range 3 weeks to 3 months); eleven reported on treatment durations ≥ 6 months. Five of these studies focused exclusively on patients naïve to antipsychotic treatment. The average age of patients was 13.5 years, and 67 percent were male; of those reporting on race/ethnicity (N = 14), 66 percent of patients were reported as being white. Nineteen studies examined head-to-head comparisons between various SGAs, while four compared an SGA to a control group not receiving antipsychotics. The NRCT[179] had high risk of bias. Of the observational studies, thirteen eceived a ROB rating of low (6-8 of 8 stars), 8 were of moderate ROB (4-5 stars), and one was considered of high ROB (3 stars).

Table 28. Characteristics of studies reporting on harms for mixed conditions

Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Clinical Context Quality Rating
SGAs vs. SGAs			
Alacqua, 2008[191] Retrospective cohort, 3 mo	**G1:** Clozapine (2), 150±0.7mg/day **G2:** Olanzapine (24), 7.1±4.4mg/day **G3:** Quetiapine (2) 375±318.2mg/day **G4:** Risperidone (45), 2.0±1.3mg/day	**G1:** 15.5±0.7yr / Males: 50% / White: NR **G2:** 14.7±2.3yr / Males: 42% / White: NR **G3:** 16.5±1.5yr / Males: 100 / White: NR **G4:** 13±3.9yr / Males: 80 / White: NR Comorbidities: NR	ASD (15), CD (8), ADHD (1), psychosis (19), schizophrenia (5), TD (2), MR (11), anxiety (6) Incident treatment with atypical antipsychotics; outpatient/community History of treatment: 100% drug naive 6/8 stars
Arango, 2014[181] Prospective cohort, 6 mo	**G1:** Risperidone (157), NR **G2:** Olanzapine (44), NR **G3:** Quetiapine (47), NR	**G1:** 14.0±3.3yr / Males: 64.3% / White: 84.7 **G2:** 15.4±1.8yr / Males: 63.6% / White: 93.2 **G3:** 15.7±1.6yr / Males: 53.2% / White: 89.4% Comorbidities: NR	Schizophrenia spectrum (84), mood spectrum disorders (72), behavioral disorders (47), other diagnosis (38) Inpatient/ outpatient History of treatment: 39% drug naive 5/8 stars
Bastiaens, 2009[192] Retrospective cohort, 2 mo	**G1:** Aripiprazole (24), 4.5±2.3mg/day **G2:** Ziprasidone (22), 42.9±18mg/day	**G1:** 11.7±2.4 yr / Male: 83% / White: NR **G2:** 12.1±2.9 yr / Male: 91% / White: NR Comorbidities: NR	BD (12), CD (14), depressive disorder (6), mood disorder NOS (8), PDD (2), psychotic disorder (4) Clinically significant aggressive behavior, outpatient/community History of treatment: 74% drug naive 6/8 stars

Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Clinical Context Quality Rating
Calarge, 2014[182] Prospective cohort, 6 mo follow up of 1.5 yr study	**G1:** Risperidone continued (74), 0.03±0.02 mg/kg/day **G2:** SGA continued (9), NR **G3:** SGA discontinued (18), NR	**G1**: 13.3±2.7 yr / Males: 95% / White: 80% **G2**: 12.3±2.6 yr / Males: 89% / White: 67% **G3:** 13.1±2.3 yr / Males: 89% / White: 94% Comorbidities: NR	DBD (89), ADHD (89), anxiety disorder (31), depressive disorder (5), ASD (19), tic disorder (25) History of treatment: 0% drug naïve 5/8 stars
Correll, 2009[183] Prospective cohort, 2.8 mo	**G1:** Aripiprazole (47), NR **G2:** Olanzapine (52), NR **G3:** Quetiapine (45), NR **G4:** Risperidone (168), NR	**G1**: 13.4±3.1 (7–19.7) yr / Males: 56% / White: 62.5% **G2**: 14.7±3.2 (6.6–18.6) yr / Males: 64% / White: 46.7% **G3**: 14±3.1 (6.1–19.4) yr / Males: 36% / White: 50% **G4**: 13.6±4 (4.3–19.9) yr / Males: 62% / White: 46.3% Comorbidities: NR	ASD (21), CD/ODD (37), BD (44), MDD (49), mood disorder NOS (37), schizophrenia/schizoaffective (27), psychosis NOS (53) History of treatment: 100% drugnaïve 8/8 stars
Cuerda, 2011[184] Prospective cohort, 1 yr	**G1:** Risperidone (18), NR **G2:** Olanzapine (12), NR **G3:** Quetiapine (16), NR	**G1**: 16.1±1.9 yr / Males: 83.3% / White: 72.2% **G2**: 16.1±1.3 yr / Males: 66.7% / White: 91.7% **G3:** 16.6±0.7 yr / Males: 62.5% / White: 81.3% Comorbidities: NR	BD (7), brief psychosis/schizophrenia (10), CD (4), depression with psychotic symptoms (3), OCD (3), psychosis NOS (11), schizophrenia (4), scholar phobia (1), depression (1), intellectual disability (1), personality disorder (1) History of treatment: 33% drugnaïve 6/8 stars
Findling, 2008b[185] Prospective cohort, 3-4 wk	**G1:** Aripiprazole (8), low (20 mg/day fixed) **G2:** Aripiprazole (7) medium (25 mg/day fixed) **G3:** Aripiprazole (6) high (30 mg/day fixed)	All groups 10-17 yr (mean NR), Males: NR / White: NR Comorbidities: MR (0)	BD, DBD, OCD, ASD, schizophrenia, Tourette syndrome History of treatment: 100% drugnaïve 5/8 stars
Findling, 2015[179] NRCT, 3 wk	**G1:** Lurasidone (20), 20mg/day **G2:** Lurasidone (25), 40mg/day **G3:** Lurasidone (19), 80mg/day **G4:** Lurasidone (25), 120mg/day **G5:** Lurasidone (16), 160mg/day	All groups 12.7 yr mean age, Males: 65% / White: 78% Comorbidities: NR	ADHD (78), BP (19), Schizophrenia (5), Tourette's (2), ASD (1). Outpatient: History of treatment: NR drug naive ROB: NA (subjective), High (objective)

Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Clinical Context Quality Rating
Fleischhaker, 2006[186] Prospective cohort, 7.4 wk	**G1:** Clozapine (16) 321.9±156.5 (125–600) mg/day **G2:** Olanzapine (16), 16.6±7.1 (7.5–30) mg/day **G3:** Risperidone (19), 3.9±1.7 (1–6) mg/day	**G1**: 17.2±1.8 (14.4–21.3) yr / Males: 69% / White: NR **G2**: 15.8±1.4 (12.8–17.8) yr / Males: 56% / White: NR **G3:** 15.6±2.6 (9.7–19) yr / Males: 68% / White: NR Comorbidities: NR	anorexia nervosa, DBD, OCD, ASD, schizophrenia, Tourette syndrome Inpatient History of treatment: NR drug naive 3/8 stars
Fraguas, 2008[187] Prospective cohort, 6 mo	**G1:** Olanzapine (25), 9.8±5.6mg/day **G2:** Quetiapine (29), 390.8±321.2mg/day **G3:** Risperidone (38), 3.5±3.1mg/day	**G1:** 15.9±1.5 (12–17) yr / Males: 65% / White: 90% **G2:** 16.3±1.3 (13–18) yr / Males: 58% / White 96% **G3:** 13.4±4 (4–17) yr / Males: 77% / White: 82% Comorbidities: NR	BD, DBD, ASD, schizophrenia History of drug treatment: 24% drugnaïve 6/8 stars
Friedlander, 2001[195] Retrospective cohort, 6 wk	**G1:** Olanzapine (14), NR **G2: :** Risperidone (41), NR	All groups: 13-24 yr (mean NR) / males: NR / White: NR Comorbidities: Addison's disease (1), hypothyroidism (4), MR (borderline (1), mild (17), moderate (15), severe (9)), Neurodevelopmental syndrome (15), Seizure disorder (9)	BD, DBD, OCD, ASD, schizophrenia-related, Tourette syndrome Developmental disabilities and complex psychiatric problems History of treatment: 0% drug naive 4/8 stars
Germano, 2014[188] Prospective cohort, 2 mo	**G1:** Aripiprazole (29), 7.4±3.1mg/day **G2:** Risperidone (31), 1.5±1.0mg/day	All groups (G1-G2): 10.2±2.6 yr / Male: 91.6% / White: NR Comorbidities: NR	PDD (22), ODD (12), ADHD (21), MR with psychotic disorder (11), Tourette syndrome and other tic disorders (9) Subjects attending programs in a University Polyclinic History of treatment: 23% drug naive 5/8 stars

Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Clinical Context Quality Rating
Jerrell, 2008[196] Retrospective cohort, ≥9 mo	**G1:** Antipsychotics cohort (4140), 7.4±3.1mg/day Multiple logistic regressions with olanzapine (N = 326) as comparator, with aripiprazole (N = 38), ziprasidone (N = 87), quetiapine (N = 266), risperidone (N = 1634), multiple SGAs or SGA and FGA (N = 1756)	All groups: NR / Male: 68% / White: 42% Psychiatric comorbidities: SUD (489), ADHD (3259), CD (2269), neurotic, phobic or personality disorders (1668) Other comorbidities: Epilepsy (954), CNS disorders (919), organic brain syndrome or severe MR (704), congenital heart defects (146), endocrine disorder (168), preexisting obesity (680), preexisting type II diabetes mellitus or dyslipidemia (404), preexisting cardiovascular disorder (246)	Schizophrenia or other psychotic disorders (1507), major affective disorders (2261) Inpatient/ outpatient History of treatment: NR drug naive 6/8 stars
Khan, 2006[198] Retrospective cohort, 3.7-4.9 wk	**G1:** Olanzapine (50), total 8.2±2.4 mg/day, children 6±2.2 mg/day, adolescents 9.20±1.8 mg/day **G2:** Ziprasidone (50), total 19.1±2.7 mg/day, children 15.7±4.4 mg/day, adolescents 19.5±2.1 mg/day	**G1**: 13.7±2.4 yr / Males: 68% / White: 60% **G2**: 14.6±2.1 yr / Male: 32% / White: 68% Comorbidities: substance abuse/ dependence (27), PTSD (18)	BD (57), mood disorder NOS (18), psychosis NOS (15). Agitation or aggression; inpatient History of treatment: NR drug naive 4/8 stars
Khan, 2009[197] Retrospective cohort, olanzapine 27±12 d, risperidone 26±13 d	**G1:** Olanzapine (25), 12.5 (range 5-25 mg/day) **G2:** Risperidone (24), 2.6 (range 1-7 mg/day)	**G1:** 13.0±3.5 yr / Males: 64% / White: 72 **G2:** 13.0±3.5 yr / Males: 83% / White: 58 Comorbidities: SUD (14), ADHD (8)	BD (NR), mood disorder NOS (NR), major depressive disorder (NR), schizoaffective disorder, schizophrenia, and schizophreniform disorder (7) Inpatient History of treatment: NR drug naive 6/8 stars
Migliardi, 2009[200] Retrospective cohort, 12 mo	**G1:** Olanzapine (13), 8.1mg/day **G2:** Risperidone (29), 1.8mg/day	**G1:** 14.1 yr / Males: 54% / White: NR **G2:** 10.7yr / Males: 79% / White: NR Comorbidities: NR	ASD, DBD, schizophrenia, bipolar, OCD, tic disorder Outpatient/community History of treatment: 100% drug naive 7/8 stars

Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Clinical Context Quality Rating
Pogge, 2005[189] Prospective cohort, 10 (3-18) mo	**G1:** Olanzapine (43), NR **G2:** Risperidone (43), NR	All groups (G1-G2): 14.9±1.3 yr / Male: 41.9% / White: 65.1% Comorbidities: NR	Psychotic (11), affective (30), anxiety (23), disruptive (57), PDD/MR (18), polysubstance (2), eating disorder Inpatient History of treatment: 0% drug naive 6/8 stars
Ronsley, 2015[180] Prospective cohort, 12 mo	**G1:** Quetiapine (17), NR **G2:** Risperidone (20), NR	G1: 14.1 yr / Male: 47.1% / White: 52.9% G2: 14 yr / Male: 50% / White: 40% Comorbidites: NR	Psychotic disorders (9), mood disorder (4), depressive disorder (8), BD (6), ADHD(8), ODD(4), PDD (1), anxiety disorder(13), adjustment disorder(1), reactive attachment disorder (2) mental retardation or personality disorder(2) Outpatient History of treatment: 100% drug naive 4/8 Stars
Saito, 2004[190] Prospective cohort, 11.2 wk	**G1:** Olanzapine (13), 7.8±4.2mg/day **G2**: Quetiapine (6), 283.3±222.9mg/day **G3**: Risperidone (21), 2.2±2mg/day	All groups: 13.4±3.4 (5–18) yr / Males: NR / White: NR Comorbidities: NR	schizophrenia or other psychosis (14), mood disorders (14), DBD (9), intermittent explosive disorder (1), PDD NOS (1), eating disorder NOS (1) History of treatment: NR drug naive 6/8 stars
SGAs vs. No Antipsychotic			
Bobo, 2013[193] Retrospective cohort, ≥1 yr	**G1:** Aripiprazole 5 (5-10) mg/day, olanzapine 5 (4.84-9) mg/day, quetiapine 53.57(50-100) mg/day, risperidone 0.75 (0.50-1) mg/day, perphenazine 4(2-6) mg/day, thioridazine 30 (20-50) mg/day, other/multiple 20 (2-50) mg/day (28858) **G2:** Controls not on antipsychotic for >365 days (14429), NR	**G1:** 14.5 yr / Male: 56% / White: 72.8% **G2:** 14.5 yr / Male: 55.9% / White: 73.5% Comorbidities: Menstruation absent or infrequent (1629), menstruation disorder (1486), diagnosed obesity (1658), metabolic disorder (909), blood chemistry panel with glucose (10154), hypertension (1110), other diagnosed cardiovascular disease (1904)	BD (7935), depression (8382), other mood disorder (14298), ADHD (16751), CD (10893), anxiety (8815), alcohol use (1370), other substance use (3909) Subjects enrolled in Medicaid; recent initiators of antipsychotics History of treatment: 0% drug naive 8/8 stars

Author, Year, Study Design, Duration	Intervention (N Enrolled), Dosage (mg/day) Mean±SD	Age, Mean±SD (Range) / Males (%) / White (%) Comorbidities	Diagnosis Breakdown (n) Clinical Context Quality Rating
Ebert, 2014[194] Retrospective cohort, 4-53 wk (G1: 17±10.9 wk; G2: 9.7±6.1 wk)	**G1:** SGAs (32), NR **G2:** Controls with antipsychotic treatment (24), NR	**G1:** 9.6±1.6 yr / Male: 91.7% / White: NR **G2:** 9.3±1.8 yr/ Male: 87.5% / White: NR Comorbidities: Anemia (1), ichthyosis (1), Epilepsy (1), central precocious puberty (1)	Psychotic spectrum disorder (15), BD (4), DBD (29), ADHD (26), anxiety spectrum disorder (8), depression disorder (13), PDD (5), MR (3), OCD (1), adjustment disorder (2), eating disorder (1), tic disorder (2) Inpatient History of treatment: NR drug naive 5/8 stars
Martin, 2000[199] Retrospective cohort, ≥6 mo	**G1:** Risperidone (37), 2.8±1.9 mg/day **G2:** No SGA exposure (33), NR	**G1:** 12.5±2.4 yr / Male: 76% / White: 64 **G2:** 13.5±2.9 yr / Male: 49% / White: 61% Comorbidities: NR	Depressive disorder (37), mood disorder NOS (17), SUD (15), DBD (15), psychotic disorder (12), anxiety disorder (12), BP (10), ADHD (7), eating disorder (2) Inpatient History of treatment: NR drug naive 6/8 stars
Wonodi, 2007[201] Retrospective cohort, ≥6 mo	**G1:** SGAs treatment ≥ 6mo (81), NR **G2:** No antipsychotic (80), NR	**G1:** 11.9±2.8 yr / Male: 77.1% / White: 44.1% **G2:** 10.7±3.9 yr / Male: 72.5% / White: 28.8% Comorbidities: NR	Mood disorder NOS (170), ADHD (123) Inpatient/outpatient History of treatment: 19% drug naïve 8/8 stars

ADHD = attention deficit hyperactivity disorder; ASD = autism spectrum disorder; BD = bipolar disorder; CD = conduct disorder; d = days; DBD = disruptive behavior disorder; G = group; FGA = first-generation antipsychotic; mg = milligram; mo = month; MR = mental retardation; N = number; NOS = not otherwise specified; NR = not reported; NRCT: nonrandomized controlled trial; OCD = obsessive-compulsive disorder; ODD = oppositional defiant disorder; PDD = pervasive developmental disorder; SUD= substance use disorder; SD = standard deviation; SGA = second-generation antipsychotic; wk = week; yr = year

All Comparisons: Network Meta-Analyses for Body Composition Outcomes

We conducted network meta-analyses for the outcomes of weight and body mass index (BMI). These outcomes represent two of the key outcomes that were reported by the most studies (weight, N = 71; BMI, N = 35). To make our results most clinically relevant and be able to include as much data as possible, data was combined regardless of followup duration and (for those with multiple timepoints) from each study's longest term followup; 14 studies for weight and 11 for BMI reported data for treatment durations 6 months or longer. As described in the methods chapter, network meta-analysis allows for simultaneous evaluation of a suite of comparisons (e.g., including placebo-controlled and head-to-head comparison) while still

preserving the within-study randomization. Results are presented in terms of a placebo referent, to rank the drugs based on a common comparator, but data from head-to-head comparisons were incorporated in the analysis. Tables 29 (weight) and 30 (BMI) contain the results for each antipsychotic reporting on these outcomes, in terms of the studies included, sample size of the applicable study arms, and each drug's relative effectiveness compared with placebo/no treatment (reference standard); the drugs are listed in order of their ranking in terms of having the most harm. It should be noted that the network approach accounts for direct and indirect comparisons such that other information contributes to the results. Figures 80 and 81 show plots of the findings. Appendix G contains the model, code, results of the diagnostic tests for consistency, and results for every possible comparison between the individual drugs. Key points for each analysis are presented, followed by a detailed analysis.

Key Points: Weight Gain Across Comparisons

- Not all SGAs appeared to contribute to more weight gain than FGAs.
- Results for olanzapine clearly separated this SGA as more harmful than most other SGAs. Results were most robust for the relative harm from olanzapine over aripiprazole, quetiapine, and risperidone.
- The magnitude of weight gain was generally applicable only to short-term treatment durations.

Key Points: Changes in BMI Across Comparisons

- Olanzapine and clozapine were more harmful than the other SGAs based on average effect, although the results for clozapine were considerably imprecise.

Detailed Analysis

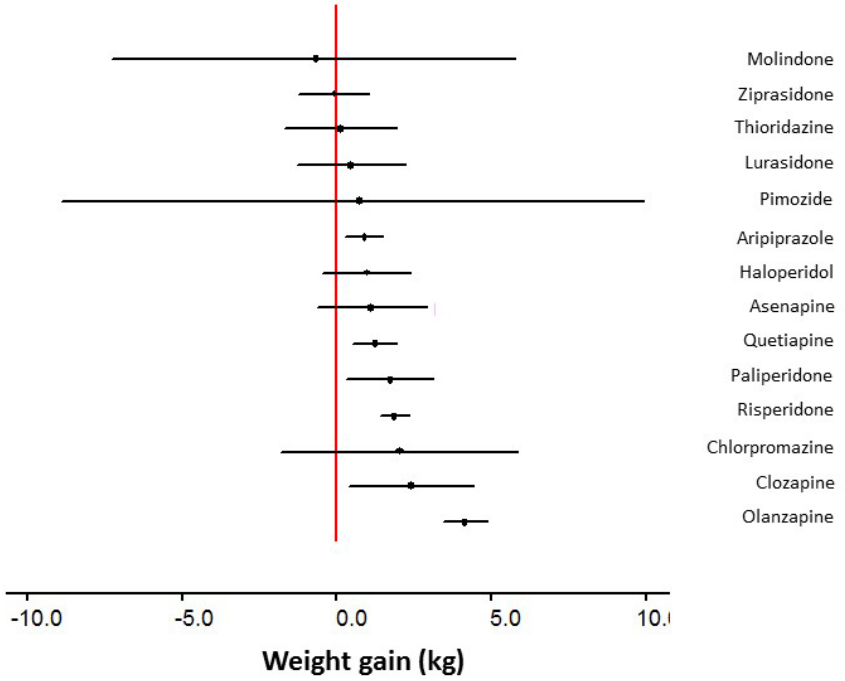
Findings from our analysis for weight gain indicate that patients taking most antipsychotics gain more weight than patients not receiving antipsychotics (Table 29 and Figure 80). Patients taking molindone and ziprasidone may gain less weight on average whereas those receiving olanzapine may gain as much as 5 kilograms during treatment durations of a relatively short timeframe (81% of studies for this analysis were short-term which was often 6-12 weeks duration). Not all SGAs appear to contribute to more weight gain than FGAs; ziprasidone, pimozide, and aripiprazole led to less average weight gain than did haloperidol.

Some of the antipsychotics, particularly for the FGAs, had few patients contributing data to the findings, which resulted in wide credible intervals; for instance, the results for pimozide, molindone, chlorpromazine, and lurasidone were considerably more imprecise than those for other antipsychotics. The relative harm from olanzapine is most robust compared with aripiprazole, quetiapine, and risperidone because of the precision in these estimates from larger sample sizes.

Table 29. Results from network meta-analysis for weight (kilogram) gain (reference standard placebo/no treatment)

Antipsychotic	Number of Studies, Citations	Total Sample Size	Mean Difference (kilogram) from Placebo	95% Credible Interval	Probability of being "worst"
Molindone	1[81]	20	-0.68	-7.29, 5.80	5.8%
Ziprasidone	3[71, 116, 167]	246	-0.10	-1.25, 1.05	0.0%
Placebo	44[71-73, 76, 86, 88, 90, 108-111, 114-121, 123, 125-129, 131, 132, 134, 135, 139, 147, 150-158, 167, 172, 178, 197]	1907	0	NA	0.0%
Thioridazine	1[150]	15	0.13	-1.71, 1.98	0.0%
Lurasidone	1[127]	149	0.45	-1.28, 2.19	0.0%
Pimozide	2[164, 166]	26	0.71	-8.87, 9.95	22.0%
Aripiprazole	11[73, 94, 110, 117, 121, 123, 131, 135, 172, 175, 183]	869	0.88	0.26, 1.50	0.0%
Haloperidol	6[77, 82, 99, 130, 133, 175]	72	0.97	-0.43, 2.38	0.0%
Asenapine	1[108]	302	1.12	-0.65, 2.90	0.1%
Quetiapine	12[67, 72, 109, 114, 115, 119, 155, 179, 180, 183, 184, 187]	655	1.25	0.51, 1.95	0.0%
Paliperidone	2[90, 94]	261	1.72	0.36, 3.12	0.1%
Risperidone	37[69, 79, 81, 82, 85, 88, 97, 99, 111, 113, 117, 125, 128, 129, 132-134, 139, 147, 151-154, 156-158, 164, 166, 178, 180, 181, 183, 184, 186, 187, 189, 199]	1535	1.85	1.40, 2.35	0.0%
Chlorpromazine	1[66]	36	2.04	-1.79, 5.85	10.5%
Clozapine	6[77, 78, 80, 97, 98, 186]	72	2.38	0.37, 4.40	2.6%
Olanzapine	22[66, 67, 69, 76, 78-82, 85, 86, 97-99, 113, 120, 126, 130, 179, 181, 182, 187]	611	4.12	3.43, 4.88	58.8%

Figure 80. Plot of network meta-analysis results for weight gain compared with reference standard (placebo/no treatment)



This plot shows the findings from a network meta-analysis combining placebo-controlled and head-to-head comparisons of first-generation and second-generation antipsychotics within one analysis. The effect shown represents the mean difference (kilograms [kg]) and credible intervals of each drug relative to placebo which was used as the reference standard.

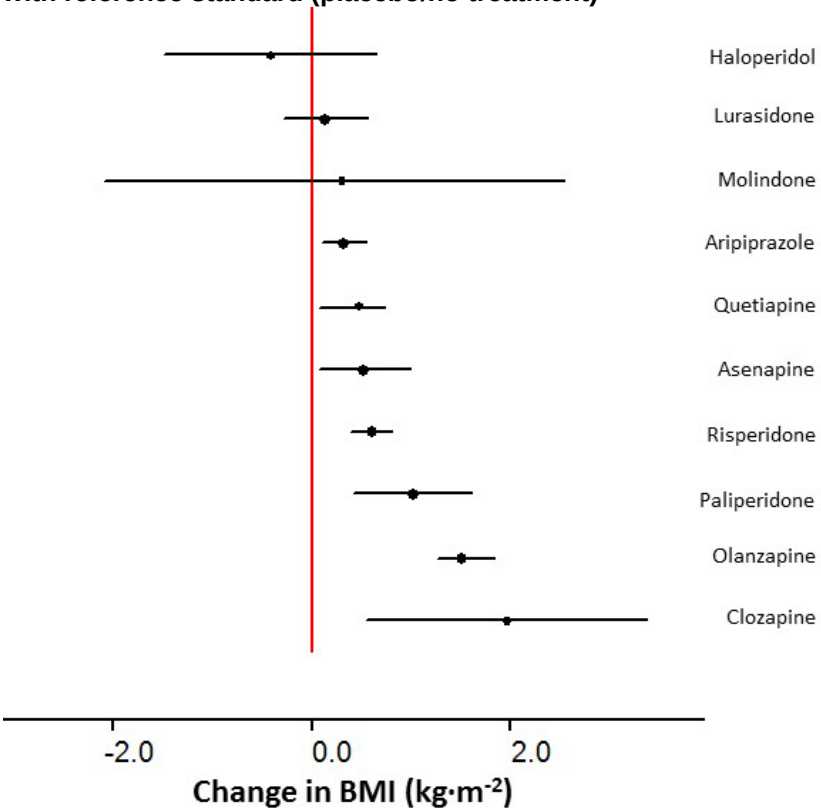
Results of the network meta-analysis for changes in BMI were similar to those for weight gain. The FGAs appear to be relatively less harmful for BMI than for weight (e.g., haloperidol moved from ninth to last place for being worst) but few studies and small samples contributed to the findings for FGAs. Olanzapine and clozapine were worst for average effect, although the results for clozapine are considerably imprecise. Seventy-one percent of studies had short-term treatment durations.

Table 30. Results from network meta-analysis for increase in body mass index (BMI) (reference standard placebo/no treatment)

Antipsychotic	Number of Studies, Citations	Total Sample Size	Difference from Placebo ($kg.m^{-2}$)	95% Credible Interval	Probability of being "worst"
Haloperidol	3[82, 96, 99]	33	-0.42	-1.46, 0.66	0.0%
Placebo	17[73, 76, 88, 108, 111, 114, 117, 118, 120, 127, 128, 131, 135, 153, 157, 158, 172, 199]	967	0	NA	0.0%
Lurasidone	1[127]	149	0.14	-0.29, 0.57	0.0%
Molindone	1[81]	20	0.30	-2.06, 2.54	7.8%
Aripiprazole	8[73, 94, 117, 131, 135, 144, 172, 183]	818	0.32	0.11, 0.55	0.0%
Quetiapine	6[66, 101, 114, 180, 181, 187]	143	0.48	0.08, 0.78	0.0%
Asenapine	1[108]	302	0.52	0.07, 0.98	0.0%
Risperidone	21[68, 80-82, 88, 99, 101, 111, 118, 128, 144, 153, 157, 158, 180, 181, 183, 186, 187, 197, 199]	1138	0.59	0.40, 0.81	0.0%
Paliperidone	1[94]	112	1.02	0.43, 1.62	1.5%

Antipsychotic	Number of Studies, Citations	Total Sample Size	Difference from Placebo ($kg.m^{-2}$)	95% Credible Interval	Probability of being "worst"
Olanzapine	16[66, 69, 76, 78, 80-82, 96, 99, 101, 120, 181, 183, 186, 187, 197]	470	1.51	1.28, 1.84	21.2%
Clozapine	2[78, 186]	28	1.96	0.55, 3.36	69.6%

Figure 81. Plot of network meta-analysis results for increase in body mass index (BMI) compared with reference standard (placebo/no treatment)



This plot shows the findings from a network meta-analysis combining placebo-controlled and head-to-head comparisons of first-generation and second-generation antipscyhotics within one analysis. The effect shown represents the mean difference in BMI (kilograms per meter^{-2}]) and credible intervals of each drug relative to placebo which was used as the reference standard.

The network analyses were reasonably consistent (Appendix G). A closed loop analysis showed that only 1 out of 15 triangular loops showed statistically significant inconsistency for the BMI analysis, while none of 18 loops showed significant inconsistency in the analysis of weight.

FGAs Versus SGAs

Findings for major and general AEs reported by studies comparing FGAs and SGAs are described below. Short- and long-term results are presented separately. Nine studies reported on major (4 long-term duration) and 16 reported on general AEs (2 long-term duration).

Key Points: Major AEs

- Few studies having small sample sizes reported on these rare outcomes.

- Based on this review with insufficient SOE for all major AE outcomes, the effects between FGAs and SGA for various major AEs are not known.

Key Points: General AEs

- FGAs probably cause lower gains in weight and BMI than SGAs.
- Compared with FGAs, SGAs may decrease the risk for experiencing any EPS symptom.
- The class of antipsychotic may make little or no difference for sedation.
- We could not make conclusions for other outcomes (e.g., akathisia, dystonia, hyperprolactinemia); SOE was insufficient because of ROB and imprecision due to small samples sizes for these rare events.

Detailed Analysis

Major AEs During Short-Term (< 6 Months) Treatment

Major AEs and major AEs limiting treatment. One RCT[81] (N = 116) reported on major AEs in comparisons between molindone, risperidone, and olanzapine in early-onset schizophrenia; two patients in the molindone and olanzapine groups, and four patients in the risperidone group experienced serious AEs. There was data from two RCTs[77, 82] (N = 71) on serious AEs limiting treatment in children with schizophrenia, from comparisons between haloperidol and clozapine (1 vs. 3 events, respectively),[77] olanzapine (2 vs. 0 events),[82] and risperidone (2 vs. 0 events).[82] One RCT[68] (N = 74) reported on major AEs limiting treatment in a comparison between chlorpromazine and olanzapine (3 vs. 2 events) in first episode psychotic bipolar mania.
Neuroleptic malignant syndrome. In an RCT[77] (N = 21) comparing haloperidol with clozapine in childhood-onset schizophrenia, one patient in the haloperidol group developed neuroleptic malignant syndrome.
Seizures. From data reported in one RCT[77] (N = 21) comparing haloperidol with clozapine, and an observational study[99] (N = 50) comparing haloperidol, olanzapine, and risperidone for treating schizophrenia, two patients in the clozapine group of one study experienced seizures while another three required prophylactic anticonvulsant treatment.
Cardiac arrhythmias. No patient with ASD experienced QT interval prolongation in a comparison (N =12) between haloperidol and olanzapine.[130]
Agranulocytosis and related effects. One RCT[77] (N = 21) comparing haloperidol with clozapine in childhood onset schizophrenia reported that five patients taking clozapine experienced neutropenia, two of whom did not have spontaneous normalization. Another RCT[66] (N = 74) comparing chlorpromazine with olanzapine in young adults with first episode psychotic mania had one patient in the olanzapine group who developed neutropenia.

Major AEs During Long-Term (≥ 6 Months) Treatment

Major AEs and major AEs limiting treatment. No patient experienced a major AE in one 6-month study[133] (N = 28) comparing haloperidol with risperidone in autism spectrum disorder (ASD).
Development of diabetes mellitus. A prospective cohort study[102] evaluated incidence of diabetes in early-onset schizophrenia for patients receiving haloperidol, clozapine, olanzapine, quetiapine, and risperidone during up to 5 year followup (N = 111). One patient receiving clozapine developed diabetes at 2 years.

Tardive dyskinesia. In a long-term extension (N = 54) comparing molindone, olanzapine, and risperidone in early-onset schizophrenia, no patient developed tardive dyskinesia.[81]
Cardiac arrhythmias. A dramatic QTc interval prolongation occurred after 6 months in one child taking pimozide in an NRCT[173] (N = 50) comparing this drug with aripiprazole in tic disorders. No patient in either group had echocardiographic (ECG) modification.

General AEs During Short- and Long-Term Treatment

Table 31 summarizes the findings from short-term studies for general AEs that provided at least low SOE; the footnotes for the table describe the SOE assessments. For the outcome of any AE limiting treatment, our meta-analysis found no significant difference between FGAs and SGAs over the short-term (6 studies, 343 patients; RR, 1.78; 95% CrI, 0.96 to 3.62)[66, 81, 82, 175] or at 12 months or longer duration (5 studies, 234 patients; RR, 0.42; 95% CrI, 0.11 to 1.19)[80, 101] Several other outcomes (e.g., hyperprolactinemia, hypertriglyceridemia) were reported by single studies or by two very small studies; findings for individual drug comparisons were all reported by few and small studies. The findings for all outcomes are presented in Appendix G

Table 31. Summary of findings for general adverse effects: Short-term durations of FGAs versus SGAs

Outcome	N Studies, N Patients	FGA Events	FGA N	SGA Events	SGA N	Relative Effects[a], Studies	Strength of Evidence; Conclusions
Any EPS	4, 110	16	37	13	73	RR, 2.59; 95% CrI, 1.00 to 7.00[99, 130, 172]	Low; SGAs may decrease risk[b]
Weight (kg)	14, 506	NA	190	NA	316	MD, -2.62; 95% CrI, -4.35 to -0.86 [66, 77, 81, 82, 99, 130, 133, 164, 166, 175, 194]	Moderate; FGAs probably better[c]
BMI ($kg \cdot m^{-2}$)	7, 236	NA	73	NA	163	MD, -1.57; 95% CrI, -2.49 to -0.53[81, 82, 96, 99]	Moderate; FGAs probably better[c]
Sedation	7, 345	70	160	79	185	RR, 1.04; 95% CrI, 0.86 to 1.37 [66, 81, 82, 99]	Low; may make little or no difference[d]

AE = adverse effect; BMI = body mass index; CrI = credible interval; FGA = first-generation antipsychotic; G = group; kg = kilogram; m = meter; MD = mean difference; N = number; RR = risk ratio; SGA = second-generation antipsychotic
[a]Risk ratios above 1.0 and positive MD favor SGAs.
[b]Downgraded for ROB and imprecision, based on small sample size.
[c]Downgraded for ROB.
[d]Downgraded for ROB and imprecision, because CrI includes possibility for clinically relevant benefit for SGAs.

FGAs Versus FGAs

Findings for major and general AEs in comparisons between two or more different FGAs, or different doses of an FGA, are presented below. Two short-term RCTs[148, 168] reported on major AEs. Two RCTs reported on a small number of general AEs; one short-term study compared haloperidol with pimozide,[168] and a 6-month study compared continuous versus discontinuous (i.e., 5 days per week) haloperidol.[136]

Key Points

- There was insufficient SOE for all major and general AEs in comparisons between different FGAs or different doses of the same FGA; the effects are unknown.

Detailed Analysis

Major AEs During Short-Term (< 6 Months) Treatment

Major AEs and major AEs limiting treatment. One RCT[168] (N = 44) reported on the number of patients with tic disorders who experienced major AEs in a comparison between haloperidol and pimozide (2 vs. 0 events, respectively).

Mortality. No child (6-12 years) died in a 9-12 week RCT[148] (N = 78) comparing four doses of molindone for treatment of serious conduct problems in ADHD.

General AEs During Short- or Long-Term Treatment

No findings for general AEs in comparisons of FGAs versus FGAs had low or greater SOE. Single studies reported data for a small number of outcomes within the short- and long-term duration categories. Any AE limiting treatment was reported in a comparison between haloperidol and pimozide; 9 of 22 patients on haloperidol and 3 of 22 on pimozide discontinued treatment because of AEs.[168] In a comparison of four different doses of molindone for treatment of ADHD, the incidence of AEs including changes to body composition seemed to increase with increasing dose although no statistical data was provided by the authors.[148] Data for outcomes with insufficient SOE are presented in Appendix G.

SGAs Versus SGAs: Comparison of Different Drugs

Findings by duration category for major and general AEs in comparisons between two or more SGAs are presented below. Sixteen (5 long-term) and 37 (13 long-term) studies reported on major and general AEs, respectively.

Key Points: Major AEs

- Aripiprazole (hazard ratio (HR) vs. no antipsychotic 7.72, 95% CI 3.70 to 16.12) may increase the risk for developing diabetes compared with risperidone (HR 2.20, 95% CI 1.14 to 4.26) (low SOE).
- Data for other rare AEs was mostly from single studies having small sample sizes and moderate or higher ROB, therefore SOE was deemed insufficient.

Key Points: General AEs

- ***Body composition***. Risperidone probably decreases slightly gains in weight (short-term) and BMI changes (short-and long-term) compared with olanzapine; similar findings were found for quetiapine versus olanzapine over the long- but not short-term where there may be little or no difference. There may be little or no difference between weight gains caused by olanzapine and clozapine over short-term treatment. Quetiapine and risperidone are probably of little or no difference for short-term changes in BMI and 7 percent or greater increase in weight, and may be of little or no difference for BMI changes or weight gain over the long-term. For 7 percent or greater gain in body weight, there may be little or no difference between olanzapine and quetiapine, or olanzapine and risperidone.
- ***Hyperprolactinemia***. Quetiapine may decrease the risk for hyperprolactinemia compared with risperidone.

- ***Sedation***. There may be little or no difference between olanzapine and risperidone for risk of sedation.

Detailed Analysis

Major AEs During Short-Term (< 6 Months) Treatment

Major AEs and major AEs limiting treatment. Two RCTs reported on short-term experience of major AEs in treatment of schizophrenia: one compared aripiprazole and paliperidone (N = 228) with each associated with seven major AEs,[94] and the other compared olanzapine and risperidone (N = 76) with two versus four patients having major AEs.[81] Three RCTs[78, 124, 165] reported on numbers of patients discontinuing SGA treatment because of major AEs. Four patients in each of groups receiving aripiprazole or risperidone in two RCTs of ASD and tic disorders (N = 116) had treatment-limiting major AEs.[124, 165] Four patients on clozapine versus one patient on olanzapine had treatment-limiting major AEs in the other study of childhood schizophrenia.[78]

Mortality. Mortality rates (n = 0) were reported in one RCT (N =228) of aripiprazole or paliperidone treatment in schizophrenia.[94]

Development of diabetes mellitus. In an RCT[78] (N = 39) comparing clozapine with olanzapine, one patient taking clozapine developed drug-induced diabetes at 12-weeks, and another patient on this drug was withdrawn for impaired glucose tolerance.

Seizures. Incidence of seizures was reported by four short-term studies.[80, 85, 99, 124] One patient with ASD treated with aripiprazole versus none on risperidone (N = 56) had one or more seizures.[124] No patients with schizophrenia on clozapine or olanzapine (N = 25) had seizures,[80] and one patient receiving risperidone versus none taking olanzapine had seizures in the two studies (N = 78) examining this comparison among patients with schizophrenia.[85, 99]

Tardive dyskinesia. Two studies[85, 186] reported on incidence of tardive dyskinesias over three drug comparisons. In the observational study (N = 51) of mixed conditions by Fleischhaker et al.,[186] there were no cases of tardive dyskinesia in groups taking clozapine, risperidone, and olanzapine. No patient with schizophrenia receiving risperidone or olanzapine developed tardive dyskinesia in another study (N = 44).[85]

Cardiac arrhythmias. Four studies reported on short-term outcomes related to cardiac arrhythmias over different drug comparisons in patients with bipolar disorder,[112] schizophrenia,[80] or mixed conditions.[186, 188] No patient receiving aripiprazole or risperidone (N = 60) had an abnormal ECG or pathological elongation in QTc values.[188] Anomalies on ECG were found for 2 of 12 and 1 of 13 patients on clozapine and olanzapine, respectively—none of which led to drug discontinuation.[80] None of the patients taking quetiapine or risperidone (N =22) had an abnormal ECG in one RCT.[112] Finally, one patient taking clozapine and olanzapine compared with none taking risperidone had an ECG alteration, without serious effects.[186]

Agranulocytosis and related effects. Two RCTs[78, 80] (N = 64) comparing clozapine with olanzapine for patients with schizophrenia reported on neutropenia for two patients taking each drug. One patient on clozapine developed neutropenia in a prospective observational study comparing clozapine, olanzapine, and risperidone for adverse effects (N = 51).[186]

Major AEs During Long-Term (≥ 6 Months) Treatment

Major AEs and major AEs limiting treatment. A 6-month RCT[67] (N = 50) comparing olanzapine with quetiapine in adolescents with a first psychotic episode reported that no patient experienced a major AE.

Development of diabetes mellitus. Three long-term observational studies examined development of diabetes in children taking various SGAs. Bobo et al.[193] conducted a retrospective cohort study of the Tennessee Medicaid program to investigate newly diagnosed type 2 diabetes in recent initiators of antipsychotics for conditions of which these drugs are not considered primary treatment (i.e., excluded patients with schizophrenia, ASD, tic disorders, and all patients taking clozapine). The absolute and relative risks for diabetes based on baseline antipsychotic exposure status are listed below; the difference between the hazard ratios (HR) for risperidone and aripiprazole was statistically significant ($p < 0.0001$).

- Risperidone (15,608 person-years): 16.7 cases per 10,000 person-years; HR 2.20, 95% CI 1.14 to 4.26
- Olanzapine (7,778 person-years): 20.6 cases per 10,000 person-years; HR 2.17, 95% CI 1.04 to 4.53
- Quetiapine (6,554 person-years): 30.5 cases per 10,000 person-years; HR 2.76, 95% CI 1.37 to 5.56
- Aripiprazole (2,470 person-years): 72.9 cases per 10,000 person-years; HR 7.72, 95% CI 3.70 to 16.12
- Ziprasidone (832 person-years): 48.1 cases per 10,000 person-years; HR 4.15, 95% CI 1.35 to 12.73

Censoring followup to whether switching of drugs occurred did not change the above findings (data not presented). Moreover, across all antipsychotics the risk remained elevated for up to one-year following discontinuation of the drug. Another study reporting on 5-year followup of 47 patients with early-onset psychosis taking various SGAs (risperidone, olanzapine, quetiapine, aripiprazole, clozapine), found that one patient taking clozapine was diagnosed with diabetes after 2 years of treatment.[102] A small study (N = 37) comparing risperidone and quetiapine found that no patient developed type 2 diabetes after a 12-month period.[180]

Seizures. One long-term prospective cohort study (N = 60) reported that no patient having a first episode of psychosis experienced seizures at 6 months in groups continuously receiving risperidone, quetiapine, or olanzapine.[101]

Tardive dyskinesia. A 12-month (N = 34) comparison between olanzapine and risperidone, in patients with schizophrenia responding to an 8-week trial, there were no incident cases of tardive dyskinesia.[81]

General AEs During Short- and Long-Term Treatment

Findings for any AE limiting treatment are contained in Table 32; only comparisons having more than two studies are included. Tables 33 and 34 present the findings for other general AEs having at least low SOE during short- and long-term treatment, respectively; the table footnotes provide rationale for the SOE assessments. All findings between clozapine and risperidone, and most between clozapine and olanzapine, were considered to have insufficient SOE mainly due to impression (all samples < 100 and wide 95% CIs), but also because of moderate ROB (weight) and inconsistency (BMI) for the risperidone comparisons. Likewise, the SOE was insufficient for findings in comparisons between aripiprazole and risperidone; apart from ROB, imprecision (akathisia, somnolence) and inconsistency (weight) were too great.

Table 32. Findings for adverse effects (AEs) limiting treatment in comparisons between different SGAs

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects[a], Studies
Aripiprazole vs. Risperidone	AE limiting treatment	2, 272	0 4	34 66	0 6	35 137	Not estimable[159] RR, 1.38; 95% CI, 0.40 to 4.74[179]
Aripiprazole vs. Ziprasidone	AE limiting treatment	2, 115	2 4	20 66	6 0	14 15	RR, 0.23; 95% CI, 0.05 to 0.99[192] RR, 2.15; 95% CI, 0.12 to 37.92[183]
Clozapine vs. Olanzapine	AE limiting treatment	2, 65	0 2	2 18	9 1	24 21	RR, 0.44; 95% CI, 0.03 to 5.78[191] RR, 2.33; 95% CI, 0.23 to 23.66[78]
	AE limiting treatment (12+ mo)	2, 65	1 4	12 28	0 4	13 12	RR, 3.23; 95% CI, 0.14 to 72.46[80] RR, 0.43; 95% CI, 0.13 to 1.44[102]
Olanzapine vs. Quetiapine	AE limiting treatment	2, 150	9 1	24 58	1 0	2 66	RR, 0.75; 95% CI, 0.17 to 3.29[191] RR, 3.41; 95% CI, 0.14 to 82.04[183]
	AE limiting treatment (6 to <12 mo)	2, 84	0 2	26 18	0 1	24 16	Not estimable[67] RR, 1.78; 95% CI, 0.18 to 17.80[101]
Olanzapine vs. Risperidone	AE limiting treatment	6, 436	16	164	30	272	RR, 0.87; 95% CrI, 0.21 to 2.18[79, 81, 82, 99, 183, 191]
	AE limiting treatment (12+ mo)	3, 148	12	43	23	105	RR, 1.23; 95% CrI, 0.36 to 4.09[81, 101, 102]
Olanzapine vs. Ziprasidone	AE limiting treatment	6, 436	16	164	30	272	RR, 0.87; 95% CrI, 0.21 to 2.18[79, 81, 82, 99, 183, 191]
	AE limiting treatment (12+ mo)	3, 148	12	43	23	105	RR, 1.23; 95% CrI, 0.36 to 4.09[81, 101, 102]
Quetiapine vs. Risperidone	AE limiting treatment	2, 250	1 0	2 66	13 6	45 137	RR, 1.73; 95% CI, 0.40 to 7.45[191] RR, 0.16; 95% CI, 0.01 to 2.77[183]

AE = adverse effect; CI = confidence interval; CrI = credible interval; G = group; N = number; mo = months; RR = risk ratio
[a]RRs above 1.0 favor group 2. We did not combine data from 1 or 2 studies so these results are always presented separately.

Table 33. Summary of findings for general adverse effects: Short-term findings of comparisons between different SGAs

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects[a], Studies	Strength of Evidence; Conclusions
Clozapine vs. Olanzapine	Weight (kg)	5 (136)	-	62	-	74	MD, -1.56; 95% CrI, -5.12 to 1.57[78, 80, 97, 98, 186]	Low; may make little or no difference [b]
Olanzapine vs. Quetiapine	Weight (kg)	3 (232)	-	116	-	116	MD, 4.00; 95% CrI, -1.67 to 10.79[181, 183, 187]	Low; may make little or no difference [c]
	BMI ($kg \cdot m^{-2}$)	3 (232)	-	116	-	116	MD, 1.36; 95% CrI, -0.29 to 3.40[181, 183, 187]	Low; may make little or no difference [c]
	≥ 7% increase in weight	3 (192)	72	99	47	93	RR: 1.41; 95% CI, 0.65 to 2.83[74, 177, 179]	Low; may make little or no difference [c]
Olanzapine vs. Risperidone	Weight (kg)	13 (936)	-	331	-	605	MD, 2.18; 95% CrI, 1.13 to 3.25[69, 79, 81, 82, 85, 97, 99, 113, 181, 183, 186, 187, 189]	Moderate; Risperidone probably slightly better[d]

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects[a], Studies	Strength of Evidence; Conclusions
	BMI (kg·m^{-2})	9 (737)	-	244	-	493	MD, 0.94; 95% CrI, 0.64 to 1.30[69, 81, 82, 99, 181, 183, 186, 187, 197]	Moderate; Risperidone probably slightly better[d]
	≥ 7% increase in weight	6 (504)	107	150	188	354	RR, 1.36; 95% CrI, 0.93 to 2.04[75, 85, 99, 181, 183, 186]	Low; may make little or no difference [c]
	Sedation	7 (321)	35	133	36	188	RR, 1.19; 95% CrI, 0.73 to 2.35[75, 81, 82, 99, 113, 191, 195]	Low; may make little or no difference [c]
Quetiapine vs. Risperidone	Weight (kg)	3 (463)	-	116	-	347	MD, 0.08; 95% CrI, -3.77 to 3.14[181, 183, 187]	Low; may make little or no difference [f]
	BMI (kg·m^{-2})	3 (463)	-	116	-	347	MD, 0.04; 95% CrI, -1.34 to 1.20[181, 183, 187]	Moderate; probably makes little or no difference [d]
	≥ 7% increase in weight	4 (417)	55	104	176	313	RR: 0.91; 95% CI, 0.56 to 1.44[75, 84, 181, 183]	Moderate; probably makes little or no difference [d]
	Hyper-prolactinemia	4 (118)	4	31	45	87	RR, 0.20; 95% CrI, 0.06 to 0.73[84, 112, 190, 191]	Low; Quetiapine may decrease risk[e]

BMI = body mass index; CrI = credible interval; kg = kilogram; m = meters; MD = mean difference; N = number; RR = risk ratio

[a] Positive MDs favor group 2; RR above 1.0 favor group 2

[b]Downgraded for ROB and imprecision, because CrI includes possibility for clinically relevant benefit for group 1.

cDowngraded for ROB and imprecision, because CrI includes possibility for clinically relevant benefit for group 2.

[d]Downgraded for ROB.

[e]Downgraded for ROB and imprecision, based on small sample size.

[f]Downgraded for ROB and inconsistency.

Table 34. Summary of findings for general adverse effects: Long-term findings of comparisons between different SGAs

Comparison	Outcome, Duration	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects[a], Studies	Strength of Evidence for Direction of Effect
Olanzapine vs. Quetiapine	Weight (kg), 6 to <12mo	3 (185)	-	90	-	95	MD, 7.91; 95% CrI, 3.65 to 12.29[67, 181, 187]	Moderate; Quetiapine probably better[b]
	BMI (kg·m^{-2}), 6 to <12mo	4 (203)	-	99	-	104	MD, 2.68; 95% CrI, 0.96 to 4.27[67, 101, 181, 187]	Moderate; Quetiapine probably better[b]
Olanzapine vs. Risperidone	Weight (kg), 6 to <12mo	4 (295)	-	85	-	210	MD, 4.40; 95% CrI, -0.54 to 9.86[81, 181, 186, 187]	Low; may make little or no difference [c]
	BMI (kg·m^{-2}), 6 to <12mo	5 (328)	-	94	-	234	MD, 1.66; 95% CrI, 0.19 to 3.42[81, 101, 181, 186, 187]	Moderate; Risperidone probably slightly better[b]
	≥ 7% increase in weight, 6 to <12 mo	3 (264)	28	64	64	200	RR: 1.44; 95% CI, 0.55 to 5.50}[102, 181, 186]	Low; may make little or no difference [c]

Comparison	Outcome, Duration	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects[a], Studies	Strength of Evidence for Direction of Effect
Quetiapine vs. Risperidone	Weight (kg), 6 to <12mo	3 (295)	-	93	-	202	MD, -1.48; 95% CrI, -4.16 to 1.18[180, 181, 187]	Low; may make little or no difference [d]
	BMI ($kg \cdot m^{-2}$), 6 to <12mo	4 (328)	-	102	-	226	MD, -0.32; 95% CrI, -1.56 to 1.12[101, 181, 187]	Low; may make little or no difference [d]

BMI = body mass index; CI = confidence interval; CrI = credible interval; kg = kilogram; m = meter; MD = mean difference; mo = months; N = number; RR = risk ratio

[a] Positive MDs and RRs above 1.0 favor group 2.

[b]Downgraded for ROB.

[c]Downgraded for ROB and imprecision, because CrI includes possibility for clinically relevant benefit for group 2.

[d]Downgraded for ROB and imprecision, because of small sample sizes.

SGAs Versus SGAs: Dose Comparisons

Findings for major and general AEs in comparisons between two or more doses of the same SGAs are presented below. Only one study[108] reported on long-term treatment, for a comparison between low- and high-dose aripiprazole for bipolar disorder.

Key Points: Major AEs

- The effects between different doses of SGAs in terms of major AEs during short-term treatment are mostly unknown (insufficient SOE).
- There may be no difference between 5 mg/day and 10 mg/day asenapine for risk of developing diabetes over 8 weeks of treatment (low SOE); both groups (n = 98, n = 102) had 7 percent incidence of possible new-onset diabetes (compared with 4 percent in placebo group).[92]

Key Points: General AEs

- ***Aripiprazole*** (three RCTs[73, 117, 131,] and a prospective cohort[185]): Different doses of aripiprazole are probably of little or no difference for short-term weight gain. There may be little or no difference between doses for any EPS symptoms, BMI, the proportion gaining 7 percent or more weight, and somnolence (all short-term); for these outcomes the 95% CIs included values favoring the low dose. There may be little or no difference for hypertriglyceridemia or increased total cholesterol.
- ***Asenapine*** (two RCTs[92,108]): There is probably little or no difference in the short-term between low and high doses of asenapine for weight gain, the proportion of patients gaining 7 percent or more weight, risk of somnolence, or risk for hyperprolactinemia.
- ***Quetiapine*** (two RCTs[72,119]): Low and high doses of quetiapine are probably of little or no difference for risk of gaining greater than 7 percent weight, somnolence, or sedation over the short-term.
- ***Risperidone*** (four RCTs[74, 88, 118, 128]): Risks for somnolence and EPS symptoms may be of little or no difference between low- and high-dose risperidone during short-term treatment; SOE was affected by ROB and inconsistency (somnolence) and imprecision (EPS symptoms).

Detailed Analysis

Major AEs During Short-Term (< 6 Months) Treatment

Aripiprazole

Three RCTs (schizophrenia,[73] bipolar disorder,[117] and ASD[131]) and a prospective cohort study[185] (mixed conditions) compared different doses of aripiprazole. One RCT[117] reported short- and long-term (30 week) results. The RCTs (N = 512) compared low-doses (5 and 10 mg/day,[131] or 10 mg/day[73, 117]) with high-doses (15 mg/day,[131] or 30 mg/day[73, 117]); our synthesis below focuses on the differences between these doses. The cohort study[185] (N = 21) investigated three high doses (20, 25, and 30 mg/day) for 3-4 weeks of treatment, and reported that no major AEs, deaths, or clinically relevant ECG changes occurred.

Major AEs and major AEs limiting treatment. Ten of 257 patients receiving a 10 mg/day dose of aripiprazole had a major AE, as did 6 of 255 assigned to the high-dose groups.[73, 117, 131] At 30-week followup, one (low dose, N = 75) and five (high dose, N = 71) patients had a major AE.[117]

Mortality. No patient receiving low- or high-dose aripiprazole died during short-term [73, 117, 131] or longer term treatment.[117]

Seizures. No patient on any dose in the study of Marcus et al.[131] experienced a seizure.

Tardive dyskinesia. Thirty-week treatment with aripiprazole did not result in any case of tardive dyskinesia.[117]

Cardiac arrhythmias. One RCT reported that four in the low dose (N = 98) and two in the high-dose (N = 99) groups had an abnormal QTcB value.[117]

Asenapine

Low-, medium-, and high-dose comparisons of asenapine were studied in two short-term RCTs for patients with schizophrenia (5 vs. 10 mg/day, 8 weeks, N = 204)[92] and bipolar disorder (5 vs. 10 vs. 20 mg/day, 3 weeks, N = 302).[108]

Major AEs and major AEs limiting treatment. Three patients in each of the low- and medium dose groups experienced a major AE in the longer study of schizophrenia,[92] and no patient in any group had a major AE in other RCT.[108]

Mortality. No patient in either study died.[92, 108]

Development of diabetes. Potential new-onset diabetes was identified in 7 patients (7%) in each of the low- and medium-dose asenapine groups in the 8-week RCT (compared with 4% of placebo-treated patients).[92] This study also found that 3 patients (1 receiving low dose and 2 receiving medium dose) developed metabolic syndrome.

Cardiac arrhythmias. Prolongation of the QTc interval was reported for one patient in each low-dose group of both asenapine studies,[92, 108] one patient in the medium-dose group in one study,[91, 107] and no patient receiving high-dose asenapine in the RCT including this dose.[108]

Lurasidone

Two RCTs studied different doses of lurasidone in patients with autism (20mg/day and 60mg/day, N = 100)[127] and schizophrenia, bipolar, autism, ADHD, or tourette's syndrome (20 vs. 40 vs. 80 vs. 120 vs. 160mg/day, N = 105).[179]

Major AEs and major AEs limiting treatment. Patients who discontinued due to major AEs were two in the 20 mg/day group, two in the 60 mg/day group[127], two in the 40 mg/day group, five in the 80mg/day group and one in the 120 mg/day group. [179]

Paliperidone

Two RCTs[89, 90] studied different doses of paliperidone in patients with schizophrenia and related disorders. In a dose escalation study of 6, 9, or 12 mg/day doses (N = 25), no patient had a serious AE (including death), but 1, 3, and 3 patients, respectively, had a prolonged value for the QTcB interval.[89] The other RCT[90] (N = 149) evaluated low (1.5 mg/day), medium (3 or 6 mg/day depending on weight), and high (6 or 12 mg/day) doses of paliperidone for 6 weeks; major AEs were rare (2, 1, and 1, respectively) and no patient died, developed tardive dyskinesia, experienced seizures, or had a prolonged QTcLD.

Quetiapine

Different doses of quetiapine were investigated in two RCTs—one compared 400 with 800 mg/day for 6 weeks in 147 patients with schizophrenia,[72] and the other compared 400 and 600 mg/day for 3 weeks in 193 patients with bipolar disorder.[119]

Major AEs and major AEs limiting treatment. Major AEs were experienced in four and five patients taking low and high doses in one study,[72] and five and four patients allocated to low and medium doses of quetiapine in another.[119]

Development of diabetes. Three patients taking low-dose and two patients taking medium dose quetiapine reported diabetes-related AEs (i.e., thirst, increased insulin and glycosolated hemoglobin).[119]

Cardiac arrhythmias. Multiple ECG variables were reported for patients taking low, medium, and high doses of quetiapine;[72, 119] no abnormal values were found for any patient.

Agranulocytosis and related effects. For both quetiapine studies,[72, 119] a shift to low neutrophil counts was found for five patients in the low-dose groups (N = 168), four patients taking a medium dose (N = 98), and one patient taking high dose (N = 74) of quetiapine.

Risperidone

Four short-term RCTs compared different doses of risperidone in schizophrenia,[74, 88] bipolar disorder,[118] and ASD.[128] Two studies included a low dose (0.125-0.6 mg/day; N = 162),[74, 128] three a medium dose (1.25-2.5 mg/day; N = 136),[88, 118, 128] one a high dose (1.5-6 mg/day; N = 125),[74] and two a higher dose (4-6 mg/day; N = 112).[88, 118] Study durations were 3,[118] 6,[88, 128] and 8 weeks.[74]

Four to six patients experienced a major AE in each of the four dose categories. No patient died in any group in the four RCTs. One study[74] reported that neither low nor high dose groups had a patient developing diabetes. Two studies reported that no patient developed tardive dyskinesia in up to a 4-6 mg/day dose,[88, 128] and none of the patients allocated to low or high-dose risperidone had a QTc prolongation.[74]

Ziprasidone

One RCT[65] compared the tolerability of 80 and 160 mg/day of ziprasidone in 63 patients with schizophrenia or bipolar disorder. Five of 23 taking low-dose and 8 of 40 taking high-dose ziprasidone experienced major AEs. No patient had a prolonged QTcF interval > 450 ms.

General AEs During Short- and Long-Term Treatment

Tables 35 and 36 include the findings, respectively, for any AE limiting treatment and for other outcomes where there was at least low SOE for an outcome of general AEs in studies comparing different doses of SGAs. The doses considered are identified for each drug.

One RCT[117] provided data for long-term placebo-controlled followup of a comparison of low (10 mg/day) and high (30 mg/day) doses of aripiprazole in patients with bipolar disorder responding to acute treatment. No significant differences were noted between doses for many AEs; Appendix G contains the findings for this study and the results from the other studies where SOE was insufficient, mainly due to risk of bias and imprecision from small samples in cases of rare events.

Table 35. Findings for any AE limiting treatment in short-term comparisons between different doses of SGAs

Comparison	High Dose Events	High Dose N	Low Dose Events	Low Dose N	Relative Effects[a], Studies
Aripiprazole High (15/30mg/day) vs. Low (10mg/day)	15	255	19	257	RR, 0.80; 95% CrI, 0.22 to 3.04[73, 117, 131]
Asenapine High (10mg/day) vs. Low (5mg/day)	8 3	106 99	6 7	98 104	RR, 1.23; 95%CI, 0.44 to 3.43[92] RR, 0.45; 95% CI, 0.12 to 1.69[108]
Lurasidone High (60/160mg/day) vs. Low (20mg/day)	0 2	16 49	0 2	20 51	Not estimable[179] RR, 1.04; 95% CI, 0.14 to 7.71[127]
Paliperidone High (6/12mg/day) vs. Low (3/6mg/day)	0 1	8 48	0 1	8 48	Not estimable[89] RR, 1.00; 95% CI, 0.06 to 15.53[90]
Quetiapine High (600/800 mg/day) vs. Low (400 mg/day)	7 7	74 98	5 15	73 95	RR, 1.38; 95% CI, 0.46 to 4.15[72] RR, 0.45; 95% CI, 0.19 to 1.06[119]
Risperidone High (3-6mg/day) vs. Low (0.5-3mg/day)	4 10	51 61	3 3	55 50	RR, 1.44; 95% CI, 0.34 to 6.12[88] RR, 2.73; 95% CI, 0.79 to 9.39[118]

CI = confidence interval; CrI = credible interval; N = number; RR = risk ratio.

[a]RR above 1.0 favor low dose groups. We did not combine data from 1 or 2 studies so these results are always presented separately.

Table 36. Summary of findings for general adverse effects: Short-term findings from comparisons between different doses of SGAs

Comparison	Outcome	High dose events	High dose N	Low dose events	Low dose N	Relative Effects[a], Studies	Strength of Evidence; Conclusions
Aripiprazole High (15/30mg/day) vs. Low (10mg/day)	Any EPS	39 12	99 54	23 13	98 59	RR, 1.68; 95% CI, 1.09 to 2.59[117] RR, 1.01; 95% CI, 0.50 to 2.02[131]	Low; may make little or no difference [b]
	Weight (kg)	-	229	-	234	MD, 0.22; 95% CrI, -0.64 to 1.09[73, 117, 131]	Moderate; probably makes little or no difference [c]
	BMI ($kg \cdot m^{-2}$)	-	223	-	233	MD, 0.14; 95% CrI, -0.47 to 5.86[73, 117, 131]	Low; may make little or no difference [b]
	≥ 7% weight increase	37	250	24	256	RR, 1.62; 95% CrI, 0.47 to 5.86[73, 117, 131]	Low; may make little or no difference [b]
	High cholesterol	28 0	65 54	27 0	64 59	RR, 1.02; 95% CI, 0.68 to 1.52[116] Not estimable[131]	Low; may make little or no difference [d]
	High triglycerides	22 2	65 54	22 6	65 59	RR, 1.00; 95% CI, 0.62 to 1.62[117] RR: 0.36; 95% CI, 0.08 to 1.73[129]	Low; may make little or no difference [d]
	Somnolence	62	255	47	257	RR, 1.31; 95% CrI, 0.46 to 3.80[73, 117, 131]	Low; may make little or no difference [b]
Asenapine High (10mg/day) vs. Low (5mg/day)	BMI ($kg \cdot m^{-2}$)	--	-	-	-	MD, 0.03; 95% CI, -0.04 to 0.10[92]	Low; may make little or no difference[e]
	≥ 7% weight increase	10 8	99 90	9 11	95 92	RR, 1.07; 95% CI, 0.45 to 2.51[92] RR, 0.74; 95% CI, 0.31 to 1.76[108]	Moderate; probably makes little or no difference [f]
	Somnolence	31 52	106 99	24 49	98 104	RR, 1.19; 95% CI, 0.76 to 1.89[92] RR, 1.11; 95% CI, 0.85 to 1.47[108]	Moderate; probably makes little or no difference [f]
	Hyperprolactinemia	20	106	23	98	RR, 1.24; 95% CI, 0.73 to 2.12[92]	Low; may make little or no difference[e]
Quetiapine High (600/800 mg/day) vs. Low (400 mg/day)	≥ 7% weight increase	14 10	74 98	17 14	73 95	RR, 0.81; 95% CI, 0.43 to 1.52[72] RR, 0.69; 95% CI, 0.32 to 1.48[119]	Moderate; probably makes little or no difference[c]
	Somnolence	22 31	74 98	20 27	73 95	RR, 1.09; 95% CI, 0.65 to 1.81[72] RR, 1.11; 95% CI, 0.72 to 1.71[119]	Moderate; probably makes little or no difference [c]
	Sedation	4 25	74 98	4 22	73 95	RR, 0.99; 95% CI, 0.26 to 3.80[72] RR, 1.10; 95% CI, 0.67 to 1.81[119]	Moderate; probably makes little or no difference [c]
Risperidone High (3-6mg/day) vs. Low (0.5-3mg/day)	Any EPS	20 15	51 61	18 4	55 50	RR, 1.20; 95% CI, 0.72 to 2.00[88] RR, 3.07; 95% CI, 1.09 to 8.68[118]	Low; may make little or no difference [b]
	Somnolence	6 34	51 61	13 21	55 50	RR, 0.50; 95% CI, 0.20 to 1.21[88] RR, 1.33; 95% CI, 0.89 to 1.97[118]	Low; may make little or no difference [g]

AE = adverse effect; BMI=body mass index; CI = confidence interval; CrI = credible interval; EPS = extrapyramidal symptoms; kg = kilogram; m = meter; mg = milligrams; MD = mean difference; N = number; RR = risk ratio

[a] Positive MDs and RRs above 1.0 favor the low dose group. We did not combine data from 1 or 2 studies so these results are always presented separately.

[b]Downgraded for ROB and imprecision, because CIs include possibility for clinically relevant benefit for the low dose group.

[c]Downgraded for ROB.

[d]Downgraded for ROB and imprecision due to small sample sizes.

[e]Downgraded for unknown consistency and imprecision from small smaples.

[f]Downgraded for imprecision, because CIs include possibility for clinically relevant benefit for the low dose group

[g]Downgraded for ROB and inconsistency between studies.

FGAs Versus Placebo

Findings for major and general AEs in comparisons between FGAs and placebo are presented below.

Key Points

- No findings for major or general AEs in comparisons between FGAs and placebo offered greater than insufficient SOE.

Detailed Analysis

Major AEs During Short-Term (< 6 Months) Treatment

Major AEs and major AEs limiting treatment. One RCT[168] (N = 44) reported than two patients with tic disorders receiving haloperidol and none receiving placebo experienced major AEs limiting treatment.

Seizures. Two patients with ADHD experienced seizures while receiving thoridazine and placebo (3 weeks each) in one cross-over RCT (N = 60).[150]

Major AEs During Long-Term (≥ 6 Months) Treatment

Tardive dyskinesia. No patient developed tardive dyskinesia in a small (N = 10) placebo-controlled maintenance RCT of pimozide versus placebo in tic disorders.[171]

General AEs During Short- or Long-Term (< 6 Months) Treatment

No findings for our key general AEs in comparisons between FGAs and placebo offered greater than insufficient SOE. Four small studies reported on general AEs to a varying extent with most outcomes having data for one study. A meta-analysis (N = 153) was conducted for the outcome of AEs limiting treatment in three comparisons between FGAs and placebo; no significant difference was found (RR, 2.43; 95% CrI, 0.47 to 23.08).[137, 168]

SGAs Versus Placebo

Findings for major and general AEs in comparisons between SGAs and placebo are presented below.

Key Points: Major AEs

- There is probably little or no difference in the short-term across all SGAs compared with placebo for mortality or for having a pathologically prolonged QT interval.
- Compared with no antipsychotic treatment, SGAs may increase the risk for developing diabetes (low SOE). A large retrospective cohort study compared incidence of type 2

diabetes in patients newly initiated on antipsychotics compared with matched patients not taking antipsychotics for at least 1 year; taking SGAs was associated with an increased risk (HR 2.89, 95% CI 1.64 to 5.10; 25.3 vs. 7.8 cases per 10,000 person-years followup).[193]

- Other outcomes were assessed as having insufficient SOE due to rare events occurring in samples too small to offer adequate power.

Key Points: General AEs

- ***All SGAs versus placebo***. SGAs are likely better than placebo for seven outcomes: any EPS symptoms, changes to body composition (weight, BMI, and ≥7% weight gain), increased triglycerides, sedation, and somnolence. The proportion of patients having high total cholesterol may be higher from taking SGAs. There may be little or no difference between SGAs and placebo for risk of akathisia. In the longer term, few studies provided insufficient SOE.
- ***Individual SGAs***.
  - Aripiprazole is likely slightly worse than placebo/no treatment for gains in weight and BMI, and may increase risk for any EPS, ≥7 percent weight gain, and somnolence.
  - Compared with placebo, olanzapine probably increases weight gain and BMI, and appears to increase risk for ≥7 percent weight gain and hyperprolactinemia.
  - Quetiapine likely increases slightly weight gain, and may make little or no difference in risk for sedation and somnolence.
  - Risperidone probably increases slightly weight gain and BMI, and likely increases risk for somnolence. It may increase risk for any EPS symptoms. In long-term studies, there appears to be little or no difference in changes in weight and BMI.
  - Ziprasidone probably makes little or no difference for weight gain, and may make little or no difference for somnolence.

Detailed Analysis

Major AEs During Short-Term (< 6 Months) Treatment

Table 37 includes all the findings on major AEs from studies comparing SGAs with placebo. Assessment of the SOE was not performed for the outcomes of any major AE, or for major AEs limiting treatment. Our SOE assessments were based on risk differences (absolute risks) for major AEs having very low event rates.

Table 37. Summary of findings for major adverse effects: Short-term findings for SGA versus placebo

Comparison	Outcome	N Studies, N Patients, Studies	SGA Events	SGA N	Placebo Events	Placebo N	Strength of Evidence; Conclusions
All SGAs vs Placebo/No treatment	Any MAE	26, 4282[71-73, 88, 90, 92, 106, 108, 109, 115-120, 123, 131, 132, 135, 139, 141, 147, 151, 154, 161, 167]	103	2739	45	1543	NA
	MAE limiting treatment	7, 950[71, 106, 108, 114, 128, 139, 167]	14	629	5	321	NA
	Mortality	13, 2447[73, 88, 90, 106, 108, 116-118, 120, 123, 128, 131, 135]	0	1635	0	812	Moderate; probably makes little or no difference [a]
	Diabetes mellitus	3, 703[92, 109, 119]	21	436	4	267	Insufficient
	NMS	2, 252[90, 125]	0	175	0	77	
	Seizures	2, 416[90, 131]	0	314	1	102	
	TD	5, 570[88, 118, 125, 139, 158]	0	336	2	234	
	Cardiac Arrhythmia	14, 2425[71, 72, 90, 92, 108, 109, 114, 117, 119, 135, 139, 151, 158, 172]	19	1490	9	935	Moderate; probably makes little or no difference [a]
	Agranulocytosis and related effects	5, 885[72, 109, 119, 120, 132]	14	514	7	371	Insufficient
Aripiprazole vs. Placebo	MAE	7, 1081[73, 106, 117, 123, 131, 135, 139]	17	701	8	380	NA
	MAE limiting treatment	1, 59[106]	2	30	1	29	NA
	Mortality	6, 1051[73, 106, 117, 123, 131, 135]	0	680	0	371	Low; may make little or no difference [b]
	Seizures	1, 216[131]	0	165	1	51	Insufficient
	Cardiac Arrhythmia	3, 453[117, 135, 172]	11	276	8	177	
	QTcF	1, 97[135]	0	47	0	50	
	QTcB	1, 97[135]	3	47	0	50	
Asenapine vs. Placebo	MAE	2, 709[92, 108]	10	506	6	203	NA
	MAE limiting treatment	1, 403[108]	1	302	2	101	
	Mortality	1, 403[108]	0	302	0	101	Insufficient
	Diabetes mellitus	1, 228[92]	14	151	4	77	
	Cardiac Arrhythmias	2, 631[92, 108]	3	453	0	178	
	QT Prolongation	1, 403[108]	0	302	0	101	
	Syncope	1, 403[108]	2	302	0	101	
Olanzapine vs. Placebo	MAE	1, 161[120]	3	107	0	54	NA
	Mortality	1, 161[120]	0	107	0	54	Insufficient
	Agranulocytosis and related effects	1, 161[120]	1	107	0	54	
Paliperidone vs. Placebo	MAE	1, 200[90]	4	149	1	51	NA
	Mortality	1, 200[90]	0	149	0	51	Insufficient
	NMS	1, 200[90]	0	149	0	51	
	Seizures	1, 200[90]	0	149	0	51	
	Cardiac Arrhythmias	1, 99[90]	0	48	0	51	
Quetiapine vs. Placebo	MAE	4, 727[72, 109, 115, 119]	19	447	11	280	NA
	MAE limiting treatment	1, 32[114]	1	17	0	15	

Comparison	Outcome	N Studies, N Patients, Studies	SGA Events	SGA N	Placebo Events	Placebo N	Strength of Evidence; Conclusions
	Diabetes mellitus	2, 475[109, 119]	7	285	0	190	Insufficient
	Cardiac Arrhythmias	4, 655[72, 109, 114, 119]	0	375	1	280	
	Agranulocytosis and related effects	3, 650[72, 109, 119]	12	358	7	265	
Risperidone vs. Placebo	MAE	8, 856[88, 118, 132, 139, 147, 151, 154, 161]	17	471	8	385	NA
	MAE limiting treatment	2, 145[128, 139]	2	71	1	74	
	Mortality	3, 395[88, 118, 128]	0	248	0	147	Insufficient
	NMS	1, 52[125]	0	26	0	26	
	TD	5, 570[88, 118, 125, 139, 158]	0	336	2	234	
	Cardiac Arrhythmias	3, 304[139, 151, 158]	1	145	0	159	
	Agranulocytosis and related effects	1, 101[132]	1	49	0	52	
Ziprasidone vs. Placebo	MAE	3, 548[72, 116, 167]	33	358	11	190	NA
	MAE limiting treatment	2, 311[72, 167]	8	209	1	102	
	Mortality	1, 237[116]	0	149	0	88	Insufficient
	Cardiac Arrhythmias	1, 283[72]	4	193	0	90	

MAE = major adverse effect; N = number; NA = not applicable; NMS = neuroleptic malignant syndrome; TD = tardive dyskinesia

[a] Downgraded for ROB.

[b] Downgraded for ROB and samples size inadequate (<2000).

Major AEs During Long-Term (≥ 6 Months) Treatment

Major AEs and major AEs limiting treatment. Two comparisons between aripiprazole and placebo reported on major AEs. Five versus one patient with bipolar disorder experienced a major AE after 30-weeks of treatment with 10- or 30 mg/day of aripiprazole (doses combined for this section) versus placebo, respectively (N = 210).[117] Fifty-two week placebo-controlled maintenance on aripiprazole 10-30 mg/day was associated with three major AEs in 98 (aripiprazole) and six events in 48 (placebo) patients with schizophrenia.[95] Luby et al.[129] compared low-dose risperidone with placebo in 23 preschool-aged children with ASD, none of whom experienced a major AE.

Mortality. Long-term studies reporting mortality rates did not have any deaths for comparisons between placebo and aripiprazole (2 RCTs of bipolar disorder, N = 270),[110, 117] and placebo with low-dose risperidone (N = 23).[129]

Development of diabetes mellitus. A previously described (SGAs vs. SGAs) retrospective cohort study of the Tennessee Medicaid program compared incidence of type 2 diabetes in patients newly initiated on antipsychotics compared with matched patients not taking antipsychotics for at least 1 year; taking SGAs was associated with an increased risk (HR 2.89; 95% CI 1.64 to 5.10; 25.3 vs. 7.8 cases per 10,000 person-years followup).[193]

Tardive dyskinesia. Rates of tardive dyskinesia were examined in children and adolescent psychiatric patients either receiving SGAs or naïve to antipsychotic treatment for ≥ 6 months; 5 out of 81 and 0 out of 80 patients in these two groups were affected.[201] A 6-month RCT[157] (N =

335) of placebo-controlled maintenance on risperidone for treating disruptive, impulse-control, or conduct disorders reported that no patient developed tardive dyskinesia.

Cardiac arrhythmias. One patient taking olanzapine as adjunctive treatment for an eating disorder had a prolonged QT interval during long-term treatment; only four patients had this variable monitored in this observational study with 43 patients taking olanzapine.[163] An RCT[157] of 6-month placebo-controlled maintenance treatment with risperidone for disruptive, impulse-control, or conduct disorders reported that one patient receiving risperidone had an abnormal ECG but that no patient had a clinically significant change in QT interval.

General AEs During Short- and Long-Term Treatment

Table 38 includes findings for any AE limiting treatment during all timepoints. Tables 39 and 40 contain a summary of the findings for other general AEs where there was at least low SOE in studies comparing SGAs with placebo over short and long durations, respectively. The major reason we deemed outcomes as having insufficient SOE was imprecision from small samples in situations of rare events. Despite a large sample (21 studies, 2009 patients), the short-term outcome of hyperprolactinemia was graded as having insufficient SOE across all SGAs because of inconsistency; for example, comparisons between olanzapine and placebo clearly favored placebo, while studies of aripiprazole found serum prolactin levels to reduce for treatment groups relative to placebo. Other outcomes graded as having insufficient SOE due to ROB and imprecision include akathisia for aripiprazole comparisons (7 studies, 1325 patients, 5% event rate in placebo group; RR, 0.86; 95% CrI, 0.31 to 2.149), and sedation for risperidone (4 studies, 408 patients; RR, 2.58; 95% CrI, 0.70 to 14.89) and ziprasidone (2 studies, 264 patients; not pooled but 95% CI limits between 0.73 and 13.98).

Table 38. Findings for adverse effects limiting treatment in short- and long-term comparisons between SGAs and placebo

Comparison	Duration	N Studies, N Patients	SGA Events	SGA N	Placebo Events	Placebo N	Relative Effects[a], Studies
All SGAs vs. placebo	<6 mo	24, 4043	183	2644	65	1399	RR, 1.47; 95% CrI, 1.05 to 2.13 [71, 72, 73, 88, 90, 92, 106, 108, 109, 114, 116-120, 127, 128, 131, 135, 151, 155, 156, 167, 170]
		5, 348	0	168	0	180	Not estimable[115, 123, 132, 153, 158]
	6-12 mo	3, 584	14	146	0	64	RR, 12.82; 95% CI, 0.78 to 211.72[117]
			2	172	1	163	RR, 1.90; 95% CI, 0.17 to 20.70[157]
			0	19	0	20	Not estimable[134]
	12+ mo	3, 266	0	30	0	30	Not estimable[110]
			1	98	1	48	RR, 0.49; 95% CI, 0.03 to 7.66[95]
			1	31	1	29	RR, 0.94; 95% CI, 0.06 to 14.27[86]
Aripiprazole vs. placebo	<6 mo	5, 969	46	680	12	371	RR, 1.91; 95% CrI, 0.82 to 4.65[73, 106, 117, 131, 135]
		1, 82					Not estimable[123]
	6-12 mo	1, 210	14	146	0	64	RR, 12.82; 95% CI, 0.78 to 211.72[117]
	12+ mo	2, 206	0	30	0	30	Not estimable[110]
			1	98	1	48	RR, 0.49; 95% CI, 0.03 to 7.66[95]
Asenapine vs. placebo	<6 mo	2, 709	17	302	4	101	RR, 1.42; 95% CI, 0.49 to 4.13 [108]
			14	204	3	102	RR, 2.33; 95% CI, 0.69 to 7.94[92]
Lurasidone vs placebo	<6 mo	1, 149	4	100	5	49	RR, 0.39; 95% CI, 0.11 to 1.40[127]
Olanzapine vs. placebo	<6 mo	1, 161	3	107	1	54	RR, 1.51; 95% CI, 0.16 to 14.21[120]
	12+ mo	1, 60	1	31	1	29	RR, 0.94; 95% CI, 0.06 to 14.27[86]
Paliperidone vs. placebo	<6 mo	1, 200	3	149	0	51	RR, 2.43; 95% CI, 0.13 to 46.19 [90]
Quetiapine vs. placebo	<6 mo	5, 748	38	458	19	290	RR, 1.21; 95% CrI, 0.30 to 4.73[155, 114, 109, 119, 72]
		1, 30					Not estimable[115]
Risperidone vs. placebo	<6 mo	6, 559	25	325	7	234	RR, 1.97; 95% CrI, 0.71 to 5.92[151, 156, 128, 118, 88, 170]
		3, 239					Not estimable[153, 158, 132]
	6-12 mo	2, 374	2	172	1	163	RR, 1.90; 95% CI, 0.17 to 20.70[157]
			0	19	0	20	Not estimable[134]
Ziprasidone vs. placebo	<6 mo	3, 548	33	358	14	190	RR, 1.36; 95% CrI, 0.37 to 6.34[116, 71, 167]

CI = confidence interval; CrI = credible interval; m =month; N = number; RR = risk ratio; SGA = second-generation antipsychotic

[a] RR above 1.0 indicate more harm from SGA. We did not combine data from 1 or 2 studies so these results are always presented separately.

Table 39. Summary of findings for general adverse effects: Short-term durations of comparisons between SGAs and placebo

Comparison	Outcome	N Studies, N Patients	SGA Events	SGA N	Placebo Events	Placebo N	Relative Effects[a], Studies	Strength of Evidence; Conclusions
All SGAs vs. placebo	Any EPS	15, 2730 2, 32	233 0	1757 17	40 0	973 15	RR, 2.94; 95% CI, 2.02 to 4.27[71-73, 88, 93, 117-119, 121, 123, 131, 139, 151 {Snyder, 2002 #117, 172 Not estimable[114, 170]	Moderate; SGAs probably increase risk[b]
	Akathisia	21, 3638	151	2433	56	1205	RR, 1.29; 95% CrI, 0.81 to 2.27[71, 73, 76, 88, 90, 92, 108, 116-118, 120, 121,127, 128, 131, 135, 142, 154, 155, 167, 172]	Low; may make little or no difference [c]
	Weight (kg)	37, 3919	-	2384	-	1535	MD, 1.48; 95% CI, 1.06 to 1.91[71-72, 76, 86, 90, 109, 111, 114-121, 123, 125-128, 131, 132, 135, 139, 147, 151-156, 158, 167, 172, 178, 192]	Moderate; SGAs probably increase slightly[b]
	BMI ($kg \cdot m^{-2}$)	16, 2462	-	1582	-	880	MD, 0.61; 95% CI, 0.38 to 0.85[73, 76, 108, 111, 114, 117, 118, 120, 127, 128, 131, 135, 153, 157, 158, 172]	Moderate; SGAs probably increase slightly[b]
	≥ 7% increase in weight	17, 3057	337	2023	42	1034	RR, 3.53; 95% CrI, 2.49 to 5.23[72, 73, 76, 86, 90, 92, 108, 109, 117-120, 123, 126, 131, 135, 178]	Moderate; SGAs probably increase risk[b]
	Increased total cholesterol	6, 643 1, 218	92 0	410 52	13 0	233 166	RR, 3.17; 95% CrI, 1.29 to 9.13[114, 117, 119, 120, 135, 192] Not estimable[87, 131]	Low; SGA may increase risk[d]
	Increased triglycerides	10, 1383	130	897	38	486	RR, 1.64; 95% CrI, 1.09 to 2.63[72, 76, 114, 117, 119, 120, 131, 135, 147, 192]	Moderate; SGAs probably increase risk[b]
	Sedation	21, 2710	288	1696	79	1014	RR, 2.19; 95% CrI, 1.50 to 3.41[72, 77, 93, 109, 114-119, 126,127, 128, 131, 135, 147, 155, 156, 162, 167, 172]	Moderate; SGA probably increase risk[b]
	Somnolence	26, 3942	560	2481	119	1461	RR, 2.91; 95% CrI, 2.27 to 3.86[71-73, 76, 86, 88, 90, 92, 109, 116-119, 121, 127, 128, 131, 132, 135, 139, 151, 153, 154, 158, 167, 172]	Moderate; SGAs probably increase risk[b]
Aripiprazole vs. placebo	Any EPS	6, 1000	117	655	17	345	RR, 3.10; 95% CrI, 1.26 to 7.01[73, 117, 121, 123, 131, 172]	Low; Aripiprazole may increase risk[e]
	Weight (kg)	7, 1042	-	647	-	395	MD, 0.98; 95% CrI, 0.54 to 1.48[73, 117, 121, 123, 1231, 135, 172]	Moderate; Aripiprazole probably increases slightly[b]
	BMI ($kg \cdot m^{-2}$)	5, 881	-	587	-	294	MD, 0.33; 95% CI, 0.07 to 0.67[73, 117, 131, 135, 172]	Moderate; Aripiprazole probably increases slightly[b]
	≥ 7% increase in weight	5, 991	93	647	15	344	RR, 3.01; 95% CrI, 1.33 to 7.10[73, 117, 123, 131, 135]	Low; Aripiprazole may increase[e]

Comparison	Outcome	N Studies, N Patients	SGA Events	SGA N	Placebo Events	Placebo N	Relative Effects[a], Studies	Strength of Evidence; Conclusions
	Somnolence	6, 1012	119	661	29	351	RR, 2.73; 95% CrI, 1.24 to 7.65[73, 117, 121, 131, 135, 172]	Low; Aripiprazole may increase risk[e]
Olanzapine vs. placebo	Weight (kg)	4, 337	-	215	-	122	MD, 3.96; 95% CI, 2.31 to 6.34[76, 86, 120, 127]	Moderate; Olanzapine probably increases[b]
	BMI (kg·m^{-2})	2, 267	- -	107 72	- -	54 34	MD, 1.16; 95% CI, 0.93 to 1.39[120] MD, 1.50; 95% CI, 1.06 to 1.94[76]	Moderate; Olanzapine probably increases[b]
	≥ 7% increase in weight	4, 337	99	215	8	122	RR, 6.08; 95% CrI, 1.84 to 27.06[76, 86, 120, 126]	Low; Olanzapine may increase risk[e]
	Hyper-prolactinemia	2, 268	50 58	107 72	1 6	54 35	RR, 25.53; 95% CI, 3.58 to 177.76[120] RR, 4.70; 95% CI, 2.25 to 9.82[76]	Low; Olanzapine may increase risk[e]
Quetiapine vs. placebo	Weight (kg)	6, 778	-	473	-	305	MD, 1.44; 95% CI, 0.60 to 2.31[72, 109, 114, 115, 119, 155]	Moderate; Quetiapine probably increases slightly[b]
	Sedation	6, 778	90	473	32	305	RR, 1.67; 95% CrI, 0.77 to 3.87[72, 109, 114, 115, 119, 155]	Low; may make little or no difference [c]
	Somnolence	3, 697	106	432	18	265	RR, 2.95; 95% CrI, 0.92 to 8.62[72, 109, 119]	Low; may make little or no difference [c]
Risperidone vs. placebo	Any EPS	5, 636	52	365	13	271	RR, 2.78; 95% CrI, 1.27 to 6.50[88, 118, 139, 151, 158]	Low; Risperidone may increase risk[e]
	Weight (kg)	14, 929	-	522	-	475	MD, 1.52; 95% CI, 0.78 to 2.29[111, 118, 125, 128, 132, 139, 147, 151-154, 156, 158, 178]	Moderate; Risperidone probably increases slightly[b]
	BMI (kg·m^{-2})	6, 730	-	397	-	333	MD, 0.68; 95% CI, 0.27 to 1.18[111, 118, 128, 153, 157, 158]	Moderate; Risperidone probably increases slightly[b]
	Somnolence	9, 862	163	473	43	389	RR, 3.25; 95% CrI, 1.96 to 5.94[128, 132, 151, 153, 154, 158, 88, 118, 139]	Moderate; Risperidone probably increases risk slightly[b]
Ziprasidone vs. placebo	Weight (kg)	3, 360	-	246	-	114	MD, -0.10; 95% CI, -1.34 to 1.13[71, 116, 167]	Moderate; probably makes little or no difference [b]
	Somnolence	3, 548	76	358	13	190	RR, 2.97; 95% CrI, 0.84 to 9.96[71, 116, 167]	Low; may make little or no difference [c]

AE = adverse effect; BMI = body mass index; CI = confidence interval; CrI = credible interval; kg = kilogram; m = meter; MD = mean difference; N = number; RR = risk ratio; SGA = second-generation antipsychotic
[a]Risk ratios above 1.0 and positive MD favor placebo.
[b]Downgraded for ROB.
[c]Downgraded for ROB and imprecision because point estimate and CrI includes clinically significant favor for placebo.
[d]Downgraded for ROB and inconsistency.
[e]Downgraded for ROB and imprecision, based on small sample size.

General AEs During Long-Term (≥ 6 Months) Treatment

Table 40. Summary of findings for general adverse effects: Long-term durations of SGAs versus placebo

Comparison	Outcome, Duration	N Studies, N Patients	Relative Effects[a], Studies	Strength of Evidence; Conclusions
Risperidone vs. placebo	Weight (kg), 6 to <12mo	4, 467	MD, 2.86; 95% CrI, -1.22 to 7.42[129, 134, 157, 199]	Low; may make little or no difference[b]
	BMI ($kg \cdot m^{-2}$), 6 to <12mo	2, 405	MD, 0.70; 95% CI, 0.49 to 0.91[157] MD, 1.80; 95% CI, -0.61 to 4.21[199]	Low; may make little or no difference[b]

BMI = body mass index; CI = confidence interval; CrI = credible interval; kg = kilogram; m = meter; MD = mean difference; N = number; RR = risk ratio; SGA = second-generation antipsychotic
[a] Positive MD favors placebo. We did not combine data from 1 or 2 studies so these results are always presented separately.
[b] Downgraded for ROB and imprecision because CrI includes clinically significant favor for placebo.

KQ 2a and b: Between- and Within-Study Subgroup Effects

This section presents findings from between-study and within-study analyses for subgroup effects. Table 41 includes the findings for between-study findings based on meta-regression analyses we conducted, and Table 42 includes the findings from a wide range of within study subgroup analyses. Figures 82 to 85 present plots of data used for the meta-regressions and for observations on whether harm key outcomes differed by condition of diagnosis. Key findings are followed by detailed analyses. Appendix G includes the model structure and code for the meta-regressions.

Key Points: Between-Study Subgroup Effects

- Meta-regressions were conducted for comparisons between SGAs and placebo/no treatment to determine if effects on four outcomes (weight change, proportion gaining 7% or more weight, somnolence, and EPS symptoms) were influenced by four subgroup variables (mean age, % male, % treatment naïve, and treatment duration). The only analysis with statistically significant findings was for treatment duration on weight change. Small increases of weight gain were seen for longer treatment duration (0.043 kg per week).
- Treatment duration was added as a study-level variable into the network meta-analyses for weight and BMI; although this variable was shown to statistically modify effects for BMI the results of either network meta-analysis were not changed to any meaningful extent.
- There did not appear to be any variable effects for the four harm outcomes (weight change, gaining 7% or more weight, somnolence, and EPS symptoms) across diagnostic conditions; harms appeared to occur to a similar magnitude in different conditions regardless of the typical dose used.

Key Points: Within-Study Subgroup Effects

- Twenty-six studies reported on subgroup analyses. Findings were often inconsistent on whether there are any moderating effects by various subgroup variables on harms.
- Body composition, fasting glucose, and prolactin elevations do not appear to differ in patients taking SGAs based on concurrent use of psychostimulants.
- Dose of SGAs—particularly when considering cumulative doses—was found in two large observational studies to increase the risk for metabolic effects including increased glucose levels and development of diabetes.
- Risperidone appears to increase serum prolactin more in females than males; few studies reported on other subgroup variables for this harm.
- Findings for effect moderation on risk for somnolence and neuromotor effects were mainly from single studies.

Detailed Analysis

Between-Study Subgroup Effects: Analyses for Key Subgroup Variables

We performed univariate meta-regression analyses on four key harm outcomes (weight, greater than 7% increase in weight, somnolence, and EPS symptoms) for the variables of age, sex, previous antipsychotic exposure, and treatment duration. Data from all followup durations for SGA versus placebo comparisons was used in order to maximize clinical relevance and include as many studies as possible; for studies with more than one followup timepoint we used data from the longest timepoint. For the outcome of EPS symptoms, we included data from findings on (in hierarchical order) akathisia, dystonia, and any EPS. The subgroup variables used were chosen because most studies reported on these variables and because of their relevance across conditions; other variables of interest included concomitant medication use, comorbidities, and phase of disorder, although these were considered either too complex to capture (e.g., in many cases of multiple comorbidities) or too condition specific (i.e., phase of disorder).

Table 41 presents the results (coefficient variable and 95% CrI) generated for each variable. The only finding that was statistically significant was for slightly greater weight changes over longer treatment durations (0.043 kg per week of additional treatment).

Table 41. Coefficient variables from univariate meta-regressions for the effects of subgroup variables on key harm outcomes in SGA versus placebo comparisons across conditions

Outcome	Subgroup Variable			
	Age (Mean Age in Years)	Sex (% Male)	Treatment Naïve (%)	Treatment Duration (Weeks)
Weight (kg)	0.012 (95% CrI, -0.13 to 0.16)	0.013 (95% CrI, -0.013 to 0.040)	-0.0009 (95% CrI, -0.019 to 0.017)	0.043 (95% CrI, 0.015 to 0.072)*
≥ 7% increase in weight	0.045 (-0.11 0.21)	0.0017 (-0.024, 0.026)	0.0089 (-0.006, 0.025)	0.0043 (-0.067, 0.067)
Somnolence	-0.010 (-0.01, 0.08)	0.032 (-0.02, 0.09)	0.002 (-0.005, 0.010)	-0.005 (-0.07, 0.06)
EPS Symptoms	0.029 (-0.09, 0.15)	-0.012 (-0.04, 0.01)	0.006 (-0.01, 0.02)	0.018 (-0.06, 0.10)

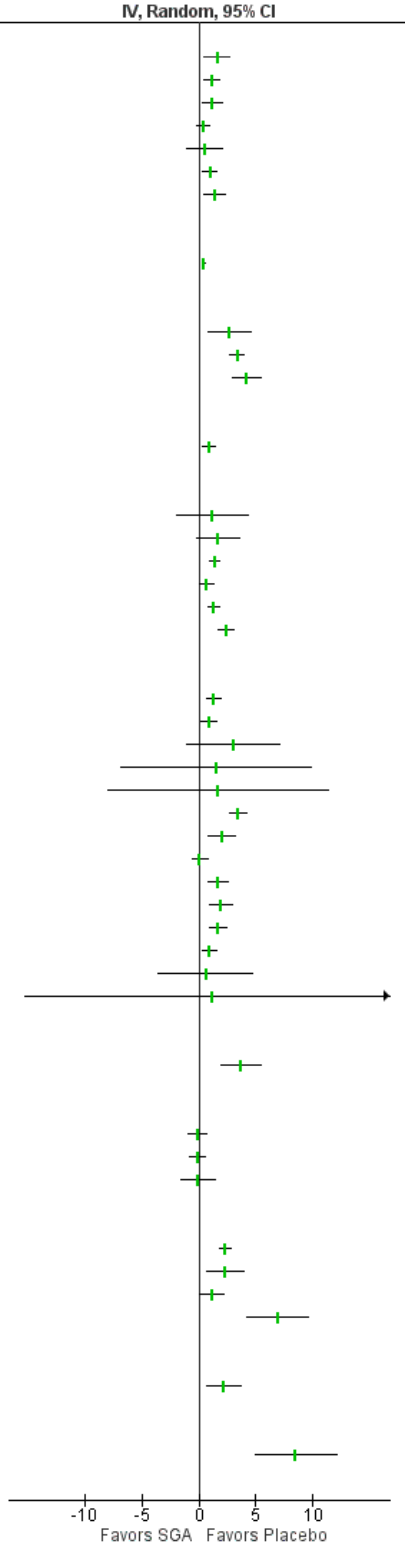
kg = kilograms
*Statistically significant

Because of the results showing treatment duration as a potential effect modifier for weight gain, this variable was added into the network meta-analyses for weight and BMI; although treatment duration was shown to statistically modify effects for BMI (i.e., regression coefficient β=0.55; 95% CrI, 0.09 to 1.91) the results of the network meta-analysis were not changed to any meaningful extent.

One of our subgroups for this KQ was in relation to treatment condition. Figures 82 to 85 present the data used for our meta-regressions, with each study identified by the condition it studied. Based on observations on these plots, we could not see any trends indicating the effects varied by condition. The results for conditions for which these drugs are typically used in lower doses (e.g., ADHD) than for other conditions (e.g., schizophrenia) appear to be very similar when looking across studies.

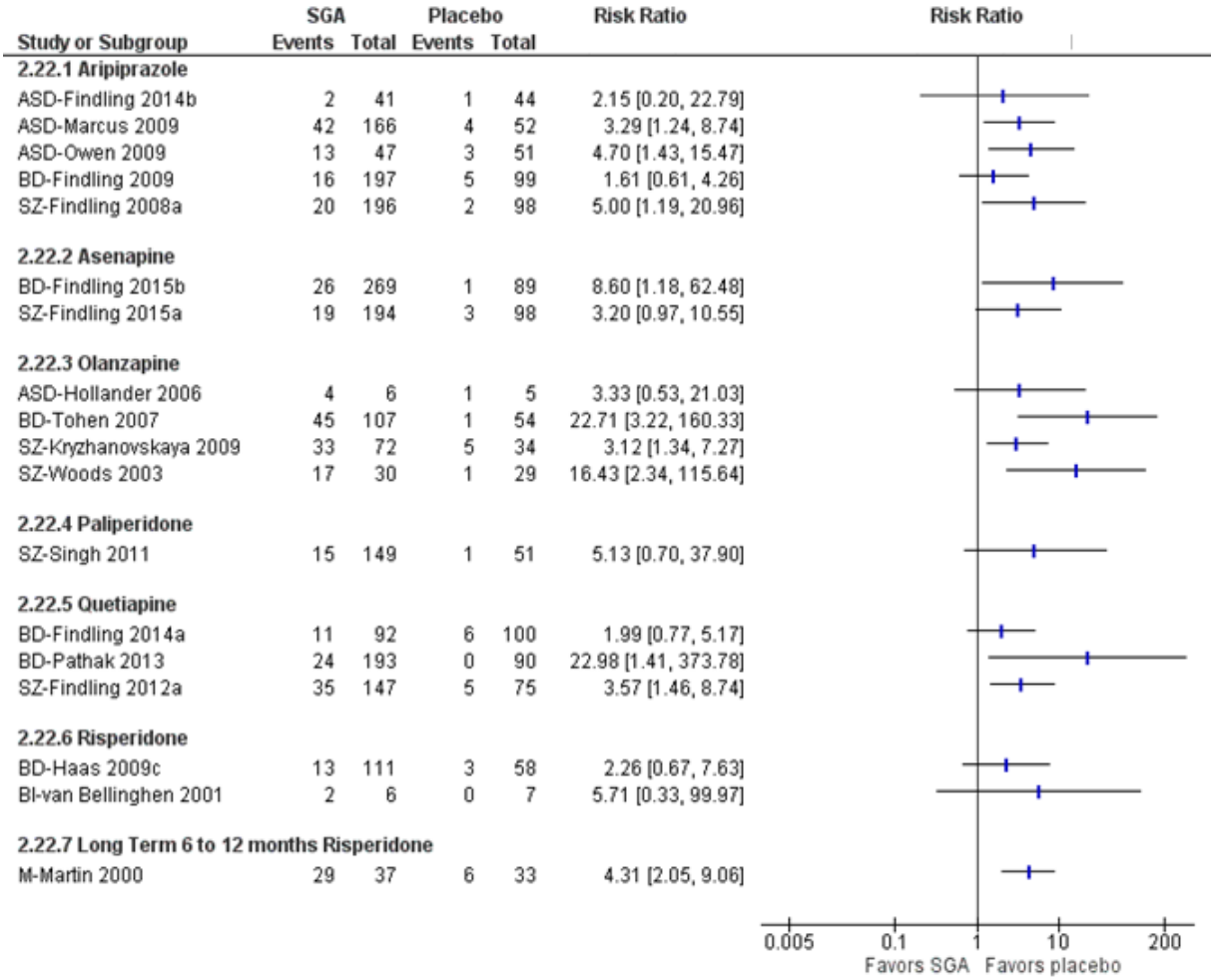
Figure 82. Plot of data for weight change (kilograms) at longest followup for comparisons between SGAs and placebo

Study or Subgroup	SGA Mean	SGA SD	SGA Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Random, 95% CI
2.14.1 Aripiprazole							
ASD-Findling 2014b	2.2	2.6	41	0.6	2.6	44	1.60 [0.49, 2.71]
ASD-Marcus 2009	1.4	2.1	165	0.3	2.1	51	1.10 [0.44, 1.76]
ASD-Owen 2009	2	2.112	47	0.8	2.112	51	1.20 [0.36, 2.04]
BD-Findling 2009	0.95	2.14	148	0.56	2.14	97	0.39 [-0.16, 0.94]
BD-Tramontina 2009	1.2	2.6	18	0.72	2.6	25	0.48 [-1.10, 2.06]
SZ-Findling 2008a	0.2	2.6	196	-0.8	2.6	98	1.00 [0.37, 1.63]
TD-Yoo 2013	1.6	2	32	0.2	1.7	29	1.40 [0.47, 2.33]
2.14.2 Lurasidone							
ASD - Loebel 2016	0.82	0.16	100	0.37	0.223	49	0.45 [0.38, 0.52]
2.14.3 Olanzapine							
ASD-Hollander 2006	3.4	2.18	6	0.68	0.68	5	2.72 [0.88, 4.56]
BD-Tohen 2007	3.66	2.18	107	0.3	1.67	54	3.36 [2.75, 3.97]
SZ-Kryzhanovskaya 2009	4.3	3.3	72	0.1	2.8	34	4.20 [2.99, 5.41]
2.14.4 Paliperidone							
SZ-Singh 2011	0.9	1.99	149	0	1.68	51	0.90 [0.34, 1.46]
2.14.5 Quetiapine							
ADHD/DICD-Connor 2008	2.3	3.53	9	1.1	3.53	10	1.20 [-1.98, 4.38]
BD-Delbello 2002	4.2	3.2	15	2.5	2.1	15	1.70 [-0.24, 3.64]
BD-Delbello 2009	2.3	0.6	17	0.9	0.6	15	1.40 [0.98, 1.82]
BD-Findling 2014a	1.3	2.14	92	0.6	2.39	100	0.70 [0.06, 1.34]
BD-Pathak 2013	1.7	2.16	193	0.4	1.72	90	1.30 [0.83, 1.77]
SZ-Findling 2012a	2	3.2	147	-0.4	2.1	75	2.40 [1.70, 3.10]
2.14.6 Risperidone							
ADHD/DICD-Aman 2002	2.2	1.8	55	0.9	1.5	63	1.30 [0.70, 1.90]
ADHD/DICD-Aman 2009	37.21	1	15	36.36	1	15	0.85 [0.13, 1.57]
ADHD/DICD-Aman 2014	1.8	14.97	84	-1.2	12.025	84	3.00 [-1.11, 7.11]
ADHD/DICD-Armenteros 2007	0.9	9.453	12	-0.6	11.905	13	1.50 [-6.90, 9.90]
ADHD/DICD-Buitelaar 2001	2.3	17.3	19	0.6	12.1	17	1.70 [-7.97, 11.37]
ADHD/DICD-Findling 2000	4.2	0.7	10	0.74	0.9	10	3.46 [2.75, 4.17]
ADHD/DICD-Snyder 2002	2.2	3.186	53	0.2	3.186	57	2.00 [0.81, 3.19]
ASD-Hellings 2006	44.22	1.1	19	44.13	1.1	19	0.09 [-0.61, 0.79]
ASD-Kent 2013	2.4	2.07	31	0.7	1.19	35	1.70 [0.87, 2.53]
ASD-McCracken 2002	2.7	2.9	49	0.8	2.2	52	1.90 [0.89, 2.91]
ASD-Shea 2004	2.7	2	40	1	1.6	38	1.70 [0.90, 2.50]
BD-Haas 2009c	1.63	1.94	111	0.7	1.9	58	0.93 [0.32, 1.54]
BD-Kowatch 2015	0.7	5.3	18	0.1	4.5	7	0.60 [-3.54, 4.74]
BI-van Bellinghen 2001	1.8	17.3	6	0.6	12.1	7	1.20 [-15.29, 17.69]
2.14.7 Variety SGA							
M-Ebert 2014	3.9	3.8	32	0.23	2.9	24	3.67 [1.92, 5.42]
2.14.8 Ziprasidone							
BD-Findling 2013b	0.7	2	96	0.8	2.5	50	-0.10 [-0.90, 0.70]
SZ-Findling 2013a	-0.1	2.4	134	0	2	52	-0.10 [-0.78, 0.58]
TD-Sallee 2000	0.7	1.5	16	0.8	2.3	12	-0.10 [-1.59, 1.39]
2.14.9 Long Term 6 to 12 months Risperidone							
ADHD/DICD-Reyes 2006	2.1	2.7	172	-0.2	2.2	163	2.30 [1.77, 2.83]
ASD-Luby 2006	2.96	2.53	11	0.61	1.1	12	2.35 [0.73, 3.97]
ASD-Nagaraj 2006	2.81	2.04	19	1.71	1.3	20	1.10 [0.02, 2.18]
M-Martin 2000	7	5.2	37	0.1	6.1	33	6.90 [4.23, 9.57]
2.14.10 Long Term 12+ months Aripiprazole							
BD-Findling 2012b	2.61	3.88	30	0.42	1.26	30	2.19 [0.73, 3.65]
2.14.11 Long Term 12+ months Olanzapine							
SZ-Woods 2003	8.79	9.05	30	0.3	4.24	29	8.49 [4.90, 12.08]



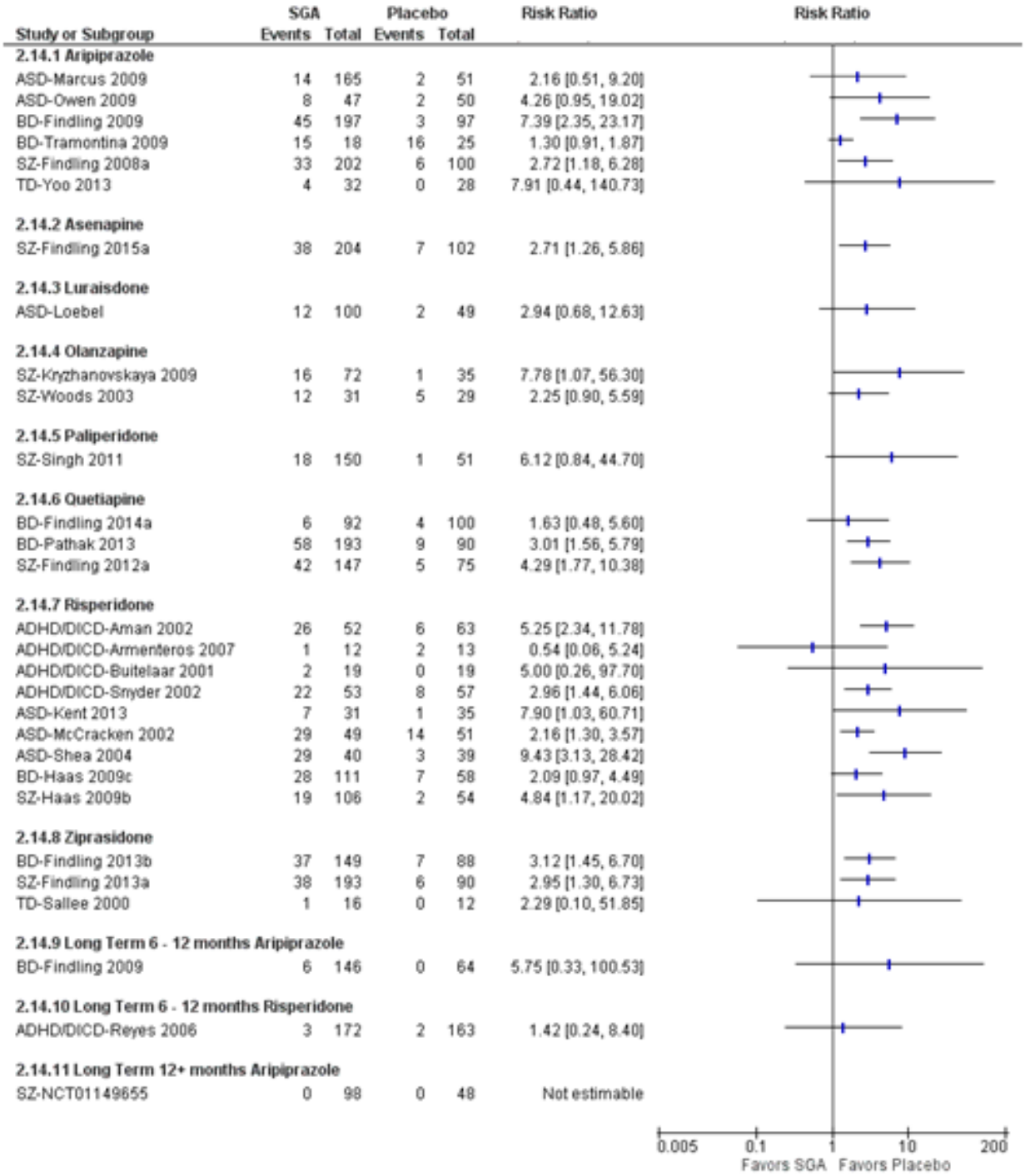
ADHD/DICD = attention deficit hyperactivity disorder, and disruptive, impulse-control, and conduct disorders; ASD = autism spectrum disorders; BI = behavioral issues outside of diagnosis; BD = bipolar disorder; M = mixed conditions; SZ = schizophrenia; TD = tic disorders

Figure 83. Plot of data for weight increase of 7 percent or greater at longest followup for comparisons between SGAs and placebo



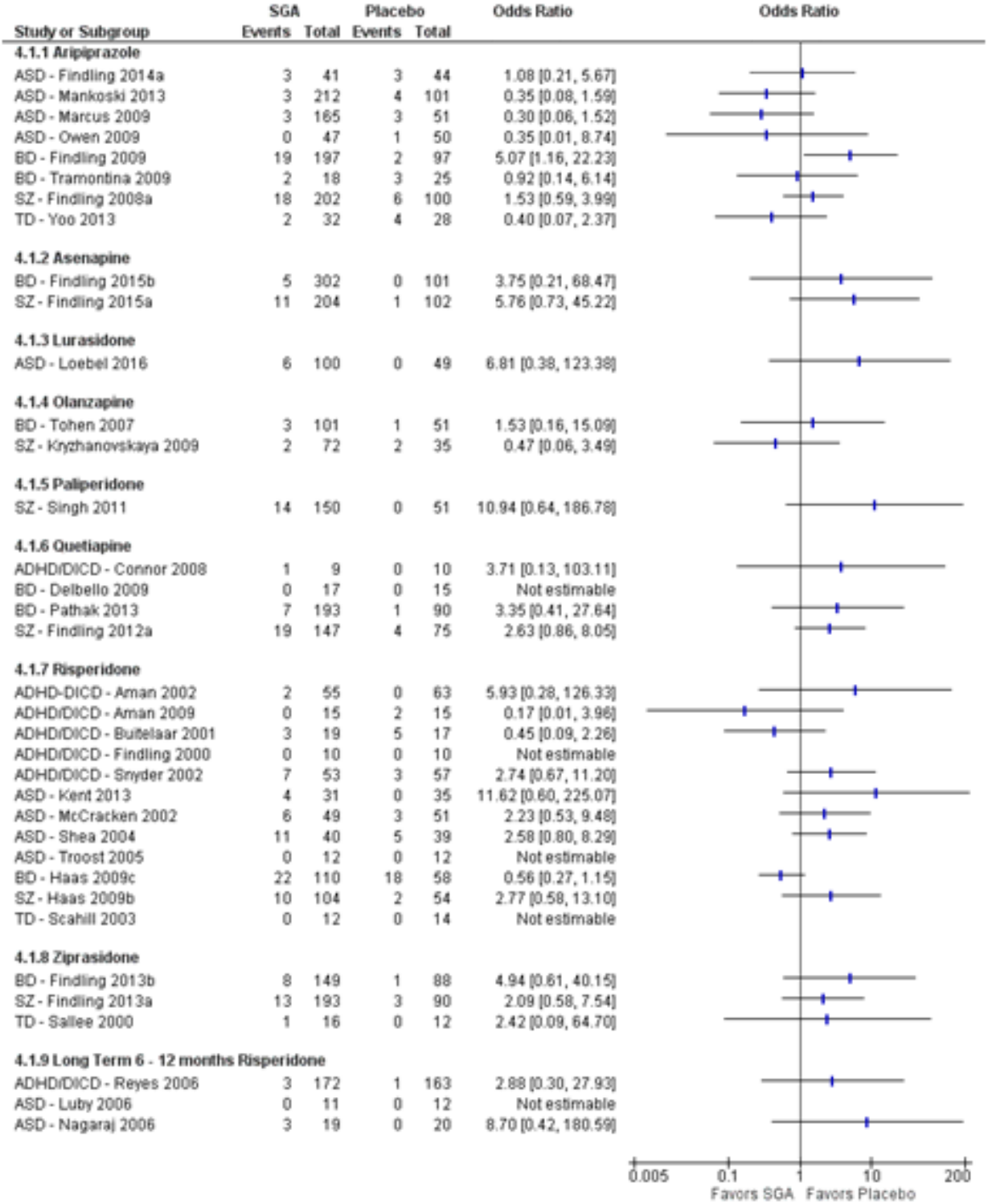
ASD = autism spectrum disorders; BI = behavioral issues outside of diagnosis; BD = bipolar disorder; M = mixed conditions; SZ = schizophrenia

Figure 84. Plot of data for proportion of patients reporting of somnolence at longest followup for comparisons between SGAs and placebo



ADHD/DICD = attention deficit hyperactivity disorder, and disruptive, impulse-control, and conduct disorders; ASD = autism spectrum disorders; BD = bipolar disorder; SZ = schizophrenia; TD = tic disorders

Figure 85. Plot of data for proportion of patients with EPS symptoms (akathisia, any EPS, and dystonia combined) at longest followup for comparisons between SGAs and placebo



ADHD/DICD = attention deficit hyperactivity disorder, and disruptive, impulse-control, and conduct disorders; ASD = autism spectrum disorders; BD = bipolar disorder; SZ = schizophrenia; TD = tic disorders

Between-Study Subgroup Effects: Analyses for Key Subgroup Variables

Twenty-six studies reported subgroup analysis for various variables of interest. A summary of the results by outcome is presented below; Table 42 provides details for the results by drug comparison and study.

Body composition. Thirteen studies examined how age (N = 6), gender (N = 6), ethnicity (N = 2), treatment history (N = 2), dose (N = 4), and/or concurrent medication use (N = 3) influenced weight gain during treatment with antipsychotics. No significant findings for age were found in trials of risperidone[131, 132, 157, 164] and aripiprazole,[121] or in a prospective cohort of children and adolescents taking risperidone, quetiapine, or olanzapine.[101] Obesity/excessive weight gain was significantly greater in children ages 13 and over versus younger than 13 when treated with haloperidol and various SGA ($p < 0.0001$).[196] Findings for sex were conflicting. Haloperidol, olanzapine, and risperidone appeared to cause weight gain of 7 percent or more body weight more often in males than females but findings were not significant;[99] quetiapine, risperidone and olanzapine significantly increased in BMI only for males in one study.[101] Two studies reported greater weight gain in females than males taking olanzapine and risperidone ($p > 0.5$),[69] or haloperidol and various SGAs ($p < 0.0001$).[101] Two cohort studies found no difference between sex and weight gain for children taking risperidone, olanzapine, or quetiapine[182] and risperidone.[199] Ethnicity was not associated with weight gain in patients on risperidone.[199] Weight gain was lower in African Americans taking haloperidol or various SGAs ($p = 0.01$).[196]

Three studies indicated that dose was generally not associated with weight gain; drugs included haloperidol, olanzapine and risperidone,[99] risperidone,[132] and risperidone, aripiprazole, olanzapine, and quetiapine.[183] Doses greater than >1.5 mg/day of risperidone were associated with greater increases in weight ($p < 0.0001$), waist ($p < 0.001$), fat mass ($p < 0.05$) and BMI z-score ($p < 0.05$).[183] Three studies reported no influence of stimulant use on weight gain for patients taking SGAs.[149, 151, 158, 183] Two studies reported that naïve versus previous users of antipsychotics (haloperidol, olanzapine, or risperidone,[99] and risperidone[158]) did not gain weight of a different magnitude. One study reported that patients who took multiple antipsychotic medications had a greater chance of obesity/excessive weight gain ($p < 0.0001$) compared to those taking one SGA.[196]

Fasting glucose and development of diabetes. Risperidone, olanzapine, and quetiapine were assocated with a significantly greater increase in serum glucose in children below the age of 12 compared with older children ($p < 0.0001$).[181] Olanzapine in doses of >10 mg/day led to significantly higher levels of glucose than did lower doses ($p < 0.05$).[183] Stimulant medication use did not significantly influence glucose levels in first-time users of SGAs.[183] A large retrospective cohort study found that patients ages 13 and over ($p < 0.00001$), females ($p < 0.00001$), and those taking more than one antipsychotic ($p < 0.001$) had a higher likelihood of developing type 2 diabetes when using SGAs.[196] Higher cumulative doses (< 5g vs. 5-99g vs. ≥100g) of risperidone and any SGA increased the risk for type 2 diabetes. (SGAs: HR, 2.89; 95% CI, 1.64 to 5.10, risperidone: HR, 2.20; 95% CI, 1.14 to 4.26).[193]

Prolactin. Ten studies examined whether age, sex, treatment history, and concurrent medication was associated with changes in AEs related to prolactin. Five studies of risperidone[66, 74, 88, 118, 157] and clozapine[100] found that prolactin levels (and prolactin-related effects[74]) were higher in females than males. One study reported opposite findings,[151] and another reported no difference between sexes.[158] Single studies found that aripiprazole decreased prolactin levels in males more than in females,[117] and quetiapine led to greater prolactin increases in males than females.[119] Two studies found no significant differences in prolactin elevations based on sex during

treatment with haloperidol and pimozide,[168] and haloperidol and olanzapine.[100] Prolactin levels were significantly lower for risperidone naïve patients compared to patients having previous exposure.[158] Prolactin levels did not significantly differ for patients taking SGAs with or without stimulants.[183]

Somnolence. Six studies examined whether demographic and clinical subgroup variables influenced reports of somnolence. Rates of somnolence were not affected by age or gender in a study of aripiprazole;[73] low-dose risperidone resulted in higher occurrence of somnolence in children under versus older than 12.[118] Somnolence was higher in females than males taking SGAs ($p < 0.004$).[196] Low and high doses of aripiprazole were associated with a higher risk for somnolence in Black patients.[73] Risperidone naïve subjects had higher rates of sedation than did previous users.[158] Patients taking risperidone experienced a dose-dependent increase in somnolence or fatigue.[118] Taking multiple versus single SGAs increased the likelihood of somnolence/sedation ($p < 0.004$).[196] Pooled analysis[149] of two RCTs[151, 158] found a numerical trend suggesting less somnolence in patients receiving combined risperidone/stimulant treatment versus treatment with risperidone alone. Patients taking high-dose quetiapine and stimulants had higher rates of sedation compared to other doses and non-stimulant users.[119]

Neuromotor effects. Three studies examined whether EPS symptoms were moderated by gender, polypharmacy, dose, and ethnicity. EPS were higher in females ($p < 0.004$) than in males, and in patients taking more than one SGA ($p < 0.00001$).[196] Pimozide in higher doses caused greater EPS, while haloperidol dose was not associated with incidence of EPS.[168] Rates of tardive dyskinesia were similar among patients taking SGAs with and without concurent stimulant, antidepressant, and mood-stabilizer use;[201] African American patients taking SGAs had more tardive dyskinesia than those of European-American descent.[201] One study found higher rates of dyskinesia, parkinsonism, and tardive dyskinesia, and no difference in akathisia in drug naïve patients compared with non-drug naïve patients taking various SGAs.

Table 42. Within-study analyses for subgroups of interest: Harms

First Author, Year, Comparison	Type of Analysis	Outcome	Authors' Conclusions
FGA vs FGA			
Sallee, 1997[168] *Haloperidol vs. pimozide vs. placebo*	Sex	Prolactin	No significant differences were found in prolactin levels by sex.
	Dose	EPS Symptoms	For pimozide, drug dose associated with EPS. Pimozide >2 mg/day exhibited EPS. 1-2 mg/day EPS in 10%; >2 mg/day EPS in 69%. For haloperidol, EPS not dose related.
FGA vs SGA			
Bruggeman, 2001[164] *Pimozide vs. risperidone*	Age	Weight	Patients <18 years had more weight gain than patients ≥18 years in the risperidone group, however this was not significant. Weight gain was comparable across age groups in the pimozide-treated patients.

First Author, Year, Comparison	Type of Analysis	Outcome	Authors' Conclusions
Ratzoni, 2002[99] *Haloperidol vs. olanzapine vs. risperidone*	Sex, treatment history, illness duration, dose, baseline weight, parental BMI, concern about weight gain, history of diet	Weight	Patients with lower baseline weight showed a significantly greater increase in weight. Paternal, but not maternal, BMI was significantly correlated with patient weight gain. Weight gain ≥7% occurred more frequently among males than females (nonsignificant). History of dieting, previous antipsychotic use, medication dose and duration of illness were not associated with weight gain. Drug-naïve patients did not gain more weight than those on previous antipsychotics.
		BMI	Among patients who showed concerned about weight gain, males showing an increase in BMI, but females did not.
Wudarsky, 1999[99] *Clozapine vs. haloperidol vs. olanzapine*	Sex	Prolactin	In patients receiving clozapine, females had significantly elevated prolactin levels than males. There was no significant sex difference in patients receiving haloperidol or olanzapine.
SGA vs SGA			
Arango, 2014[181] *Risperidone vs. Olanzapine vs. Quetiapine*	Age	Glucose	The younger group of patients (below the age of 12 years) showed a significant increase in glucose in comparison to the older group ($p < .0001$).
	Drug naive	Dyskinesia	Drug naïve patients had significant increases in dyskinesia than non-naïve patients. Drug naïve patients who were taking risperidone showed more dyskinesia than naïve patients on olanzapine or quetiapine.
	Age, drug naïve and dose	Parkinsonism	Patients on higher doses of risperidone, olanzapine and quetiapine ($p<0.001$) and older patients ($p <0.001$) had more parkinsonism than patients on lower doses and who were younger. Risperidone and olanzapine drug naïve patients had signficiantly higher parkinsonism than Quetiapine naïve patients.
	Age and antipsychotic exposure	TD	Older patients, patients with longer exposure to antipsychotics and drug naïve patients had a higher risk of developing TD.
	Drug naïve	Akathisia	There was no difference of akathisia between naïve and non-naïve patients.
Castro-Fornieles, 2008[101] *Quetiapine vs Risperidone vs Olanzapine*	Sex and age	BMI	Significant differences were found between sex and BMI increase, males presented a mean increase of 3.77 and females a mean increase of 1.34. Age was not significantly correlated with BMI increase.
Crocq, 2007[69] *Olanzapine vs. risperidone*	Sex	Weight and BMI	Weight and BMI increase was consistently but not statistically greater in girls than boys in all treatment groups.
Cuerda, 2011[184] *Risperidone vs. Olanzapine vs. Quetiapine*	Sex	Weight gain, waist circumference	Weight gain was not different in males and females ($p = 0.57$) , nor were there differences in the changes in waist circumference ($p = 0.93$) or body composition ($p = 0.07$) between genders.

First Author, Year, Comparison	Type of Analysis	Outcome	Authors' Conclusions
Findling, 2008a[73] *Low- vs. high-dose aripiprazole*	Ethnicity, age and gender	Somnolence	Black patients reported substantially higher rates (35% in the 10 mg arm and 55% in the 30 mg arm) than the overall population (12% in the 10 mg arm and 22% in the 30 mg arm) but this trend appeared to be only observed in the short-term study. No differences were noted in incidence stratified by age or gender.
Haas, 2009a[74] *Low- vs. high-dose risperidone*	Sex and age	Prolactin	The emergence of prolactin-related adverse events was higher in adolescent females than males.
Haas, 2009b[88] *Low- vs. high-dose risperidone*	Sex	Prolactin	Mean change in prolactin levels were higher in females than males.
Wink, 2014[144] *Risperidone vs. aripiprazole*	Analysis of covariance by intellectual disability (aripiprazole only)	BMI-z	Positive association between BMI-z score and persons with intellectual disability; slightly negative association in persons without intellectual disability.
SGA vs Placebo Aripiprazole			
Findling, 2009[117] *Low- vs. high-dose aripiprazole vs. placebo*	Sex	Prolactin	Decreases in prolactin levels were more pronounced for males than for females.
Tramontina, 2009[121] *Aripiprazole vs. placebo*	Age	Weight / BMI	There was no significant difference between patients ≤10 and >10 years of age for any primary outcome measure.
SGA vs Placebo Risperidone			
Aman, 2004[149] *Risperidone (with and without stimulants) vs placebo (with and without stimulants)*	Stimulant vs no stimulant	Weight	Children taking stimulants gained as much weight as those not receiving stimulants (p=0.42), interaction term), irrespective of combined use with risperidone or placebo.
		AE	There appeared to be a numerical trend for less somnolence (p=0.26), fewer headaches (p=0.29) and less vomitting (p=0.32) in patients with stimulant.
Aman, 2002[151] *Risperidone vs. placebo*	Sex	Prolactin	Males had a significantly greater increase in prolactin levels on risperidone than placebo, whereas increase in mean prolactin levels was not significant for females.

First Author, Year, Comparison	Type of Analysis	Outcome	Authors' Conclusions
Haas, 2009c[118] *Low- vs. high dose risperidone vs. placebo*	Age	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.
	Sex	Prolactin	A greater proportion of females had above pathological limits in prolactin levels at endpoint.
	Dose	Somnolence	There was a dose dependent increase in the percentage of riperidone-treated subjects who experienced somnolence or fatigue.
Martin, 2000[197] *Risperidone vs control*	Sex, ethnicity and age	Weight z scores and 7% weight gain	Baseline demographic and clinical characteristics (age, gender, pubertal status, ethnicity, baseline BMI, discharge diagnosis, concurrent medication use) were not associated with an increase likelihood to gain weight morbidly.
McCracken, 2002[132] *Risperidone vs. placebo*	Age, dose, sex, IQ, site, weight, initial leptin change	Weight	None of the variables or combinations of the variables listed were predictors of weight gain.
	Age, baseline BMI, caloric intake	BMI	There was no significant effect of age, baseline BMI or caloric intake on BMI z-score.
Reyes, 2006[157] *Risperidone vs placebo*	Sex, age, diagnosis, disease severity	Risk for symptom recurrance	Sex, age, diagnosis and baseline disruptive behavior severity did not affect risk for symptom recurrence.
	Age	Weight, AE	Weight gain was reported more frequently in children <12 years of age than those ≥12 years; however this trend was not significant. Other AEs were comparable between age groups.
	Sex	Prolactin	Females experienced greater increase in prolactin levels than males.
Snyder, 2002[158] *Risperidone vs. placebo*	Comorbidity, cotreatment, treatment history, condition, sex	Weight	Cotreatment with psychostimulant had no impact on weight. Mean weight increase was similar between patients who were risperidone-naïve and those previously treated.
		Prolactin	Risperidone-naïve patients had significantly lower prolactin levels than those previously treated with risperidone at extension study entry. Risperidone associated with significant increases in prolactin in both girls and boys
		Sedation	Sedation increased among risperidone-naïve patients, but not among previously treated patients.
SGA vs Placebo Quetiapine			
Pathak, 2013[119] *Low- vs. high dose quetiapine vs. placebo*	Age, sex and cotreatment	AE	Most common AEs (increased appetite and tachycardia) occurred more frequently in quetiapine-treated patients in the 10–12 year age group compared with older patients (aged 13 – 17 years). The incidence of individual common AEs (nausea, dizziness, sedation and increaded appetitie) was higher in concomitant psychostimulant users in the high-dose quetiapine group.

First Author, Year, Comparison	Type of Analysis	Outcome	Authors' Conclusions
		Prolactin	A greater proportion of males had changes in prolactin levels than females.
Multiple Comparisons			
Bobo, 2013[193] *SGA users vs. controls*	Dose	Diabetes	Risk for type 2 diabetes for SGA antipsychotics and risperidone increased with cumulative dose. SGA (HR=2.89 [95% CI=1.64-5.10]), risperidone [HR=2.20[95% CI=1.14-4.26]).
Correll, 2009[183] *SGA*	Dose	Body composition	Antipsychotic dose was not associated with body composition parameters changes in patients receiving aripiprazole, olanzapine, or quetiapine. With risperidone, does >1.5 mg/day were associated with greater increases in weight (p<0.0001), waist (p=0.001), fat mass (p<0.05), and BMI z-score (p<0.05).
		Metabolic effects	Metabolic effects did not differ by dose in groups taking aripiprazole or quetiapine. Significantly greater increases in several metabolic parameters were observed in patients treated with doses >10 mg/day of olanzapine (total cholesterol (p<0.01) and glucose (p<0.05)) and doses >1.5 mg/day of risperidone (total cholesterol (p<0.01) and triglycerides (p<0.01)).
	Stimulant vs no stimulant	Weight, metabolic effects, AEs	Body composition, glucose and lipid parameters, and prolactin were not significantly different among patients co-treated with or without stimulants (p values,0.13-0.99). Discontinuation rates for intolerability were similar between patients without versus with stimulant co-treatment. (7.4% vs 4.2%, p=0.50)
Jerrell, 2008[196] *Antipsychotics cohort*	Sex, age, race and multiple antipsychotic use.	Weight gain	The odds of being diagnosed with incident obesity/excessive weight gain being higher for females (p= <0.0001), adolescents 13 and over (p=0.0001), and those taking multiple antipsychotic medications (p=<0.0001), but lower for African Americans (p= 0.01).
		Diabetes and dyslipidemia	The odds of developing the metabolic conditions of Type II diabetes and dyslipidemia being higher for females (p=<0.00001), those taking multiple antipsychotic medications (p=0.001), and adolescents 13 and over (p= <0.00001).
		Cardiovascular , cerebrovascular and hypertension	The odds of developing cardiovascular conditions being higher for pediatric clients (p=0.99) and taking multiple antipsychotic medications (p=0.02).
		EPS, somnolence/ sedation, agitation, blurred vision	The odds of developing these problems (e.g., EPS, somnolence/sedation, agitation, blurred vision) were higher for females (p=0.004), and those taking multiple antipsychotics (p=<0.00001)..

First Author, Year, Comparison	Type of Analysis	Outcome	Authors' Conclusions
Wonodi, 2007[201] *Antipsychotic treatment ≥6 mo vs. Antipsychotic naive*	Ethnicity, psychostimulants, antidepressants and mood stabilizers	TD	Results were mostly driven by rates in African–American patients. 5 of 44 (11%) of this African–American subgroup (atypicals only) exhibited TD compared with 0 of 55 antipsychotic-naı¨ve subjects (p=0.015, Fisher's exact test). Rates of TD were much lower in the European American group and comparison group: 0 of 34 (0%) atypical agents, 0 of 23 (0%) comparison group. The rates of TD in this "non-psycho-stimulant" subgroup were similar to the 16% rate observed in the larger treated group: three of 20 (15%) atypicals-only exhibited TD. Among patients never treated with antidepressants, two of 16 (12%) atypicals-only exhibited TD. Similar rates were observed in the sample not treated with mood-stabilizers: two of 25 (8%) on only atypicals displayed TD.

AEs = adverse effects; BMI = body mass index; EPS = extrapyramidal symptoms; HR = hazard ratio; IQ = intelligence quotient; mg = milligrams; mo = months; SGA = second-generation antipsychotic; TD = tardive dyskinesia

Discussion

Key Findings for Intermediate and Effectiveness Outcomes Within Each Condition (Key Question 1)

The findings for key intermediate and effectiveness outcomes are summarized below. With the exception of studies examining schizophrenia, the evidence comparing FGAs with SGAs and antipsychotics within each class was limited. For most conditions, the majority of the findings focused on the comparison of SGAs versus placebo. Comparisons and outcomes for which the evidence was graded as insufficient (i.e., we had no confidence in the findings) are not discussed.

Schizophrenia and Related Psychosis. There appears to be little or no difference between FGAs and SGAs for negative symptoms, positive symptoms, response rates, and global impressions of illness severity. Between olanzapine and risperidone, there may be little or no difference for negative and positive symptoms, response rates, and global impressions of severity. Low (5 mg/day) and high (10 mg/day) doses of asenapine may not differ, or may differ little, in terms of response rates and illness severity. There is probably little or no difference between low- (400 mg/day) and high- (600/800 mg/day) dose quetiapine for clinician impressions of severity or global functioning, and may be little or no difference for negative symptom reduction or response rates. Compared with placebo, SGAs likely decrease negative and positive symptoms, increase response rates, and improve global impressions of improvement, severity, and functioning. The only outcome that seemed to result in a clinically meaningful benefit was response rates (RR, 1.52; 95% CrI, 1.15 to 2.02); the effect estimates for all other outcomes were of a small magnitude, which appears to be influenced by a substantial placebo effect in many cases. SGAs appear to make little or no difference for depression symptoms, suicide attempts, completed suicide, suicide ideations, or suicide behaviors in short-term studies. Studies of maintenance versus acute treatment, and of the prodrome phase of psychosis, did not contribute much heterogeneity to the results.

Bipolar Disorder. Most of the outcomes supported by low or higher SOE were for SGA versus placebo comparisons. One dose comparison offered low SOE to make some conclusions; a higher (10 mg/day) dose of asenapine may reduce manic symptoms slightly more than a lower (5 mg/day) dose, and the doses appear to offer little or no difference for global impressions of severity or for depression. SGAs probably reduced manic and depression symptoms, but the effect on mania was greater than for depression. SGAs likely increase response and remission rates for patients experiencing manic/mixed phases; clinical and statistical heterogeneity was introduced when including two RCTs examining quetiapine for patients with depressive episodes. SGAs probably improve slightly symptom severity and global functioning. For individual SGAs, the findings for aripiprazole were similar to those across all SGAs. Quetiapine likely reduces manic symptoms in patients experiencing manic/mixed episodes; however, it probably makes little or no difference for depression symptoms and appears to offer little or no difference response.

No different patterns from overall results for manic/mixed phases were found for patients with prodromal bipolar disorder or comorbid ADHD. Few studies examined subgroups of interest; however, concomitant use of psychostimulants does not seem to moderate effects for manic symptoms, and comorbid diagnosis of ADHD or a DICD may not affect results either for mania or depression.

For effectiveness outcomes, SGAs may make little or no difference for suicide ideations and attempts when compared with placebo.

Autism Spectrum Disorders. At least low SOE was only found for intermediate outcomes in comparisons between SGA and placebo. Insufficient SOE was found for all effectiveness outcomes and thus no conclusions could be drawn. SGAs likely improve: irritability, lethargy/social withdrawal, stereotypy, inappropriate speech, response rates, and global impressions of severity (all moderate SOE); they may increase global impressions of improvement. Only the results for irritability, response rates, and global symptom improvement reached a level that would likely be considered clinically meaningful. Maintenance treatment with an SGA appears to decrease remission rates.

Aripiprazole and risperidone showed similar effects for irritability and stereotypy (SOE reduced to low for risperidone), but conclusions were of little or no apparent difference for lethargy/social withdrawal and inappropriate speech, or unable to be drawn for other outcomes. The smaller sample sizes contributing to the evidence for each drug likely affected the ability to obtain a significant finding for most outcomes, with the exception of irritability which overall had the larger magnitude of effect.

ADHD and Disruptive, Impulse-Control, or Conduct Disorders (DICD). Most RCTs of ADHD and/or DICD examined acute phase treatment in patients either naïve to or not taking antipsychotics upon enrollment. RCTs varied in terms of whether concomitant stimulant use was permitted. All evidence graded as having at least low SOE was for outcomes between SGAs and placebo. SGAs, and risperidone alone, likely reduce conduct problems and aggression. Risperidone probably reduces hyperactivity, although our confidence in this finding is specific to studies of children having a primary diagnosis of DICD, or of patients with ADHD not responding to stimulants; a study[153] of children responding to stimulants found no benefit for risperidone on hyperactivity. SGAs (and risperidone) may improve clinical severity in treatment of children with a primary diagnosis of DICD; risperidone may make little or no difference for illness severity when it is used to augment treatment with parent training and/or stimulants. There appears to be little or no difference between SGAs and placebo for global impression of improvement. Risperidone may make little or no difference to response rates when treating patients with primarily ADHD and aggression.

From between-study observations, risperidone may preferentially reduce illness severity, and increase global improvement ratings, for DICD compared with ADHD particularly when used for ADHD as adjunctive treatment. Our meta-analysis favored SGAs for hyperactivity, but this may relate best to children with DICD, or with ADHD and not responding to stimulants. Sensitivity analyses removing the small study[152] enrolling children with a long-term history of response to risperidone did not affect the results. We did not find any evidence of a differential effect between studies having different inclusion criteria related to intellectual functioning.

Several studies examined outcomes from risperidone use in different subpopulations. Two RCTs found no difference based on age for the effects on aggression[156] or risk of symptom recurrence,[157] and another found no impact of comorbidities (including global developmental delay).[158] Cotreatment with psychostimulants did not impact effects on conduct problems or on hyperactivity in two RCTs.[149, 151, 158] Findings based on prior treatment history were conflicting.[154, 158]

Eating Disorders. No conclusions were able to be drawn for olanzapine or risperidone compared with placebo in terms of increased body weight (favorable for this condition) or reduced eating disorder symptomatology.

Tic Disorders. Tic severity may be reduced in patients receiving SGAs (aripiprazole, risperidone, and ziprasidone); SOE was low, however, the magnitude of the estimated effect reached clinical significance.[176]

Obsessive-Compulsive Disorder, Depression, and Behavioral Issues. Evidence was very limited and provided insufficient SOE on all outcomes in these conditions.

Key Findings for Harms Across All Conditions (Key Question 2)

All Comparisons: Network Meta-Analyses for Body Composition Outcomes. These analyses differed from the main analyses of pair-wise comparisons by incorporating data from comparisons of antipsychotics with placebo/no treatment and between two different antipsychotics; because of this more studies contributed to the findings, although our results should be considered exploratory in nature due to the use (i.e., modelling) of direct and indirect comparisons. Most antipsychotics resulted in more weight gain compared with placebo, and not all SGAs appear to contribute to more weight gain than FGAs. Results for olanzapine clearly separated this SGA as more harmful than most other SGAs. For BMI, olanzapine and clozapine showed the most harm. Most studies in these analyses had short-term treatment durations, and some of the antipsychotics—particularly molindone, pimozide, chlorpromazine, and lurasidone—had few patients contributing data to the findings which resulted in wide credible intervals. Nevertheless, findings are quite consistent with those from the pair-wise/direct comparisons described.

FGAs Versus SGAs, other FGAs, or Placebo. There was insufficient SOE for all major AE outcomes between FGAs and SGAs, but some conclusions could be drawn for general AEs. SGAs may have a lower risk for any EPS symptoms, and FGAs probably cause less weight gain and increase in BMI. The class of antipsychotic may make little or no difference for sedation. There was insufficient evidence to draw any conclusions for FGAs versus FGAs, or for FGAs versus placebo.

SGAs Versus SGAs: Comparison of Different Drugs or Different Doses of SGAs. Aripiprazole appears to reduce the risk for development of diabetes compared with risperidone. One large retrospective review of a Medicaid database found that patients newly initiating antipsychotics were at higher risk for developing diabetes if taking aripiprazole (HR 7.72, 95% CI 3.70 to 16.12) compared with risperidone (HR 2.20, 95% CI 1.14 to 4.26).[193] Another long-term study of various SGAs only had one incidence of diabetes in a patient taking clozapine.[102]

Risperidone probably causes slightly less weight gain (short-term) and BMI changes (short- and long-term) than olanzapine; similar findings were found for quetiapine versus olanzapine over the long-term, but not short-term where there may be little or no difference between the SGAs. Olanzapine and clozapine appear not to differ, or to differ little, for weight gain over short-term treatment. Probably little or no difference exists for changes in body composition between quetiapine and risperidone in the short-term (moderate SOE for BMI and ≥ 7% increase in weight), and there appears to be little or no difference for weight or BMI over the long-term. Quetiapine may reduce the risk for hyperprolactinemia compared with risperidone. There appears to be little or no difference between olanzapine and risperidone in risk for sedation.

Dose of asenapine probably makes little or no difference in risk for ≥7 percent weight gain or somnolence; and may make little or no difference for increase in BMI or risk for hyperprolactinemia (all short-term). High versus low doses of aripiprazole appears to make little or no difference for any EPS symptom, body composition, risk for high cholesterol or triglycerides, or for somnolence. There is probably little or no difference for ≥7 percent weight gain, somnolence, or sedation between high- and low-dose quetiapine. It may make little or no difference for risk of any EPS symptom or somnolence when treating with high or low doses of risperidone. All findings were for short-term treatment.

SGAs Versus Placebo. Moderate SOE showed that there is probably little or no difference in the short-term across all SGAs compared with placebo for mortality or prolonged QT interval. Patients newly initiated on SGAs may have a higher risk for developing type 2 diabetes than those not receiving this treatment over at least 1 year of treatment (HR 2.89, 95% CI 1.64 to 5.10).[193]

There is probably some degree of harm from SGAs for seven short-term general AEs: EPS symptoms, increase in body composition (weight, BMI, and ≥7% weight gain), and increased risk for hypertriglyceridemia, sedation, and somnolence. SGAs appear to increase risk for high total cholesterol, and make little to no difference in risk for akathisia. When looking at the effects from individual SGAs, rather than the class as a whole, aripiprazole, quetiapine, and risperidone likely increase weight gain slightly, olanzapine has a greater effect on weight gain, and ziprasidone may make little or no difference. Findings of little or no apparent difference between quetiapine and ziprasidone were shown for somnolence. The SOE was insufficient for all SGAs except aripiprazole (may increase risk) for any EPS symptoms.

Between- and Within Study Subgroup Effects. Bayesian univariate meta-regression analyses assessed the effect of mean age, percent male, proportion treatment naïve, and treatment duration on weight change, proportion gaining ≥ 7 percent weight, somnolence, and EPS symptoms. The only analysis with statistically significant findings was for treatment duration on weight change, with small increases in weight gain for longer treatment duration (0.043 kg per extra week). Observations based on diagnostic condition did not find any variability in effect; harms appeared to occur to a similar magnitude in different conditions regardless of the typical dose used.

Findings from 26 studies reporting subgroup analyses were often inconsistent on whether there are any moderating effects by various subgroup variables on harms. Body composition, fasting glucose, and prolactin elevations do not appear to differ in patients taking SGAs based on concurrent use of psychostimulants. Dose of SGAs—particularly when considering cumulative doses—appears to increase the risk for metabolic effects including increased glucose levels and development of diabetes. Risperidone appears to increase serum prolactin more in females than males; few studies reported on other subgroup variables.

Applicability of Findings

Study populations seem moderately applicable to general practice in terms of age, gender and existence of common comorbid diagnoses (e.g., ADHD comorbidity within primary diagnosis of bipolar or tic disorders) within each condition category. Findings will not be as applicable for patients with complex clinical diagnoses, less-than-moderate symptom severity, and (with the exception of studies of clozapine in schizophrenia) a history of poor response to antipsychotics.

The mean age for all condition categories was over 8 years, therefore the evidence is not highly applicable to young children. The majority of the studies excluded young adults; therefore, the results may have limited applicability to this population. Young adults were

included in approximately 25 percent of studies of schizophrenia, despite the natural history of schizophrenia which typically has its peak onset during these years. Although this population would be included in studies of adults, there are numerous unique issues associated with patients between the ages of 19 and 24, particularly because patients frequently lose access to services once they become legal adults at age 18. Many studies excluded patients with some comorbidities such as global developmental delay, psychosis, and substance abuse. Patients with a history of various adverse events, including tardive dyskinesia, suicide-related behaviors, neuroleptic malignant syndrome, or abnormal lab values, were often excluded. Additional restrictions that were commonly applied were use of adjunctive medications (e.g., mood stabilizers or antidepressants) and previous unresponsiveness to the study medication. Patients often needed to meet minimum criteria indicating at least moderate severity in symptomatology. In addition, several studies excluded patients who did not meet minimum response criteria or were nonadherent during the run-in period prior to the double-blind treatment phase. Because patients in clinical practice often have multiple diagnoses and undergo cotreatment with several drugs, these restrictions reduce the applicability of this body of evidence. Exclusion of patients with comorbidities, a history of various adverse events, and or less-than-moderate symptom severity may have overestimated estimates of efficacy and underestimated harms. Certainly the benefit-harm trade-offs in some patient populations would be different than those for the majority of patients in some studies.

Another factor restricting applicability is the short duration of followup. Adequate trials of antipsychotic treatment to assess response can be considered within 4 to 6 weeks,[16] which supports applicability from the evaluated studies for these outcomes at least over the short term; nevertheless, issues impacting longterm treatment success, such as treatment compliance and resistance, were not accounted for in many studies. Data on most effectiveness outcomes were deficient, and few studies allowed for conclusions on major adverse effects—especially those often arising with longterm treatment (e.g., tardive dyskinesias, diabetes). Adverse effects may have been underestimated due to the short followup periods; not all effects are likely to become evident in all patients within the 1-2 month treatment phase commonly investigated.

Applicability may also be limited due to monitoring practices within the trial settings to ensure treatment adherence as well as perform dose adjustments based on response and tolerability assessments. In typical practice settings, it is likely that patients will have lower rates of medication adherence—and therefore less symptom improvement—and may have higher rates of AEs because of poor monitoring. Although comprehensive and individualized monitoring for AEs has been recommended for several years,[14,202,203] there is evidence from Medicaid claims data[204-206] and clinician self-reports[207] that these practices remain inadequate. Guidelines for screening and monitoring have been developed, especially in the area of schizophrenia where antipsychotics are the primary treatment, although there has been some critique of their degree of rigor (e.g., use of systematic reviews of the evidence), stakeholder involvement, and efforts to make recommendations on organizational aspects.[208]

Findings in Relation to What Is Known

This section focuses on harms which were analyzed across all conditions. Our network meta-analysis revealed that olanzapine had the greatest potential to induce weight gain, followed by clozapine, risperidone, quetiapine, and aripiprazole. This finding is consistent with several published reviews,[11, 209-211] although there are inconsistencies in the rankings with some reports of clozapine being the worst.[13] Regarding change in BMI, our analysis suggested that clozapine

was worse than olanzapine although it is difficult to draw firm conclusions because of the small sample size that contributed to the findings for clozapine. Unclear findings on this rank order effect on BMI is consistent with other work.[13,210]

Several published studies have reported on the effects of antipsychotics on metabolic parameters based on serum levels of glucose, total cholesterol, lipids (HDL, LDL), and/or triglycerides. In a meta-analysis,[210] risperidone and olanzapine significantly increased glucose levels, while quetiapine and olanzapine significantly increased cholesterol and triglyceride levels when compared with placebo; analyses for the proportion of patients with clinically meaningful increases in these parameters were not conducted as these variables were poorly reported. In another meta-analysis,[209] a statistically significant increase in serum glucose and total cholesterol was reported for olanzapine, while some studies included in the analyses reported no change in these parameters when comparing risperidone and aripiprazole with placebo. One systematic review and meta-analysis of short term head-to-head comparisons, ranked SGAs (clozapine=olanzapine>risperidone) for impact on metabolic abnormalities.[13] From the short-term, placebo-controlled trials assessed, olanzapine caused elevation in triglycerides, total cholesterol, and LDL cholesterol; quetiapine and clozapine caused elevation in triglycerides only; aripiprazole did not cause any metabolic abnormalities, and data on the use of ziprasidone in children was reported as scarce. Authors of a descriptive review reported that a large proportion of data was not available.[11]

Our findings on metabolic effects are generally consistent with those of others. We chose to take advantage of the relatively large number of studies included in our review that reported on proportions of patients having *abnormal* levels of serum lipids, triglycerides, etcetera, to enhance the clinical relevance of the findings for decisionmakers. We also incorporated controlled observational studies which reported on several harm outcomes. Other studies did not quantify their confidence in the findings based on assessment of the quality of the body of work, and some of their conclusions were made based on what might be considered insufficient strength of evidence; we graded several of the outcomes as having insufficient SOE in comparisons between SGAs, and between individual SGAs and placebo.

Several studies have reported a decrease in prolactin levels with aripiprazole and statistically significant increases with other atypical antipsychotics when compared with placebo.[11, 13, 209, 210] This inconsistency between drug effects was one reason for our findings on hyperprolactinemia to have insufficient SOE when examining all SGAs versus placebo; we assessed the findings as insufficient for individual drugs compared with placebo but may have found different SOE had we compared serum prolactin rather than hyperprolactinemia.

In one meta-analysis[210] for combined sedation and somnolence in short-term studies, all SGAs significantly increased the risk of these outcomes compared with placebo. Clozapine was associated with the greatest risk, while quetiapine with the lowest. We conducted separate meta-analyses for sedation and somnolence and found similar findings for all SGAs versus placebo. For individual SGAs, we found no that there may be little or no difference between placebo and quetiapine or ziprasidone (low SOE).

All SGAs except quetiapine were reported from one review to significantly increase the risk of EPS when compared with placebo;[210] clozapine was not included in the analysis due to lack of data. We report similar findings from our meta-analysis for all SGAs versus placebo; however, except for aripiprazole (low SOE favoring placebo) there was insufficient SOE to make any conclusions for comparisons of individual drugs. Authors of a descriptive review of select studies[11] reported that SGAs were associated with less risk of akathisia and parkinsonism than

FGAs, and that treatment with risperidone was associated with higher dystonia rates that other SGAs. For these rare events large samples are required to make any firm conclusions, such that we found insufficient SOE for these harms in comparisons between or within classes of FGAs and SGAs.

Implications for Clinical and Policy Decisionmakers

There are some conclusions which can support clinician decisionmaking despite at best moderate SOE. SGAs showed benefit over placebo manic and mixed states in bipolar disorder, irritability and other symptoms in autism, and aggression and conduct problems in children with DICD with or without comorbid ADHD. It is not clear that antipsychotics improve clinical impressions of severity and hyperactivity in youth who have previously responded to psychostimulant medications. Moderate evidence for clinical benefit in these symptoms is present only for those for whom stimulant medications have not produced clinically significant reductions in ADHD symptoms, or for whom DICD is the primary diagnosis. Interestingly, comorbid ADHD did not impact the treatment effect across many conditions, and there was a significant placebo effect for treatment of positive and negative symptoms of schizophrenia. Limited evidence suggests that SGAs are effective for reduction in tic severity. It should also be noted that the effect on depressive symptoms may be small and possibly nonsignificant for bipolar disorder and schizophrenia. Reliance on findings from placebo-controlled studies for schizophrenia may not offer great help to those needing to choose between different antipsychotics for this condition which often relies on this treatment. Some of the findings for harms are quite considerable in light of the short-term duration of treatment of many of the studies contributing data. Nevertheless, some findings on harms—such as the low impact on weight suggested by studies of molindone—may provide some assistance when choosing between treatment alternatives. Continued guidance related to ongoing benefit-harm assessments for individual patients, regardless of which antipsychotic is prescribed, seems prudent.

Consistent with the role of systematic reviewers, we did not incorporate contextual considerations in our assessment of the SOE as may guideline developers.[61] For example, our assessment of precision in findings should be interpreted in view of our confidence in the direction and magnitude of the average effect and an estimated threshold rather than having a (possibly greater) threshold based on various benefit-harm considerations. Several of the findings for intermediate outcomes only support small effects, although the placebo effect in several studies (especially for schizophrenia) was substantial which makes some findings difficult to interpret in light of real-world practice. Likewise, we did not downgrade any evidence for lack of directness related to the comparability of study populations with those treated in clinical practice, for which there may be important differences.

Limitations of This CER

This review followed rigorous methodological standards, which were detailed a priori. Nevertheless, several limitations are inherent within systematic reviews in general.

First, there is a possibility of selective reporting bias (e.g., researchers only reporting positive outcomes) and publication bias, whereby large trials with unexpectedly strong results are selectively reported. In terms of selective outcome reporting, we were able to locate several trial registries and protocols to compare planned and published outcome reporting; most studies were judged as having low or medium bias in this respect. We also searched for, and located, regulatory documents containing data on harms that were not reported in the primary articles (see

Associated Publications in Appendix E). Our pre-specified tests for publication bias (small study effects) indicated potential bias for some harm outcomes (i.e., akathisia, dystonia, sedation, somnolence, 7% or greater weight gain); we believe this is not so much related to systemic publication/reporting bias but rather poor reporting practices for harms particularly in older studies where many of the harms were unanticipated. These outcomes were not usually the primary outcomes reported by studies, which would reduce their likelihood of leading to publication bias. We focused on studies published in English because we felt that these reports would be most applicable to the end-users of this review who create recommendations for antipsychotic use within the United States. Moreover, effect sizes in language restricted reviews have shown to not differ significantly (overestimating effect sizes by 2%) from those not having restrictions.[212] Non-English publications are thought most important to seek for reviews of certain interventions, such as complimentary or alternative medicine, or when the prevalence of the condition or use of the intervention is particularly high in foreign countries.[212-213] We based our assessments of methodological quality on study publications and did not contact authors to verify the methods used. Some studies may have been adequately conducted, but the methods were poorly reported.

Our findings from the sensitivity analyses and meta-regressions for subgroup variables are based on study-level data and because of this should be considered observational in nature. Some of our statistical analyses indicated heterogeneity between studies; we performed sensitivity analyses in several cases to explore and discuss possible reasons for heterogeneity. Combining data from trials and observational studies for harms outcomes may have added heterogeneity to the results, although close inspection of the data plots (e.g., Figures 82-85) indicated high variability within both types of study design and no indication of a systematic bias in any direction. Our reports of within-study subgroup analysis and our meta-regressions attempted to help explain some of this variability. The findings from our network meta-analyses should also be considered exploratory in nature. Apart from the assumptions made for all meta-analyses, the network approach assumes transitivity, where we assume that all treatment nodes not present in any trial are missing at random, and there is nothing systematically different about the populations or interventions in the various trials. Because of these limitations we did not use these results for making our assessments of the strength of the body of evidence. We note, however, that the consistency between direct and indirect evidence was acceptable, and that the adjusted analysis factoring in treatment duration (shown as significant treatment modifier from the pairwise meta-analysis) did not change the results.

This report was limited to direct comparisons of various antipsychotics and comparisons of antipsychotics with placebo. As such, evidence on the use of other drug classes (e.g., anticonvulsants, mood-stabilizers) that are frequently used in the treatment of these patient populations is not considered.

Systematic reviews may become outdated, at least in part, if new studies are published that change some or all of their conclusions. Although our comprehensive search was only undertaken to April 2016, we are quite confident there has been no evidence as of September 2016 which would change our findings in such a manner (e.g., to moderate or higher SOE for any outcome). A search update in Medline for April to September 8, 2016 identified three RCTs and one retrospective cohort study examining: (i) twice weekly versus daily aripiprazole in tic disorders (N=36, 6-18 year olds), without evidence of difference for tic severity at 8 weeks,[214] (ii) aripiprazole versus risperidone for ODD with ADHD (N=40, 3-6 year olds), showing no significant difference in clinical severity but higher serum prolactin from risperidone at 8

weeks,[215] (iii) aripiprazole versus risperidone for ASD comorbid with ADHD (N=44, 6-13 year olds), with no differences between these SGAs for illness severity or ADHD symptoms but higher prolactin from risperidone at 26 weeks,[216] and (iv) treatment of ASD with five SGAs for up to 5 years (N=202), with olanzapine showing greatest harm for weight gain, and quetiapine and ziprasidone showing insignificant increases in BMI z-scores.[217] There does, though, appear to be a trend for more comparative research between different SGAs, if not also between SGAs and FGAs as suggested from our findings.

Limitations of the Evidence Base

The evidence base was inadequate to fully answer the Key Questions, particularly with respect to some harms. Several effectiveness outcomes of importance to patients and policymakers, such as quality of life, school and occupational performance, and health care utilization, were reported by too few studies to confidently support conclusions of effect.

Many trials had methodological limitations introducing some risk of bias. Half of the trials had incomplete outcome data due to loss to followup and inadequate handling of missing data in the reporting and analyses, which may exaggerate treatment effects. Measures employed by 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 employed in trials and should be used routinely to avoid selection bias. The main reasons we downgraded the SOE was for risk of bias and imprecision from small samples or when the results included possibility of substantial benefit or harm when insignificant findings were found (i.e., limiting confidence in findings of no difference). It should be recognized that attaining high SOE from trials of antipsychotics in children with psychiatric conditions is likely very difficult and the overall evidence reviewed should not be interpreted as lacking in credibility.

Although some outcomes and scales were assessed fairly consistently for some conditions, there was great diversity in the scales used in studies for the other conditions. To capture as much data as possible and where feasible, we combined different scales for some outcomes (e.g., hyperactivity, aggression) using standardized mean differences; our findings based on these values may be difficult to interpret. Further, response and remission were based on different outcome measures and criteria across studies making comparisons across studies and interventions challenging. There were few outcomes (e.g., tic severity, psychotic symptoms) for which we found clear evidence supporting a particular clinically important magnitude of effect; for most outcomes we relied on clinicians to help determine values for use in our assessments (e.g., >1 point change on the Clinical Global Impressions [CGI] scales, approximately a 10% mean difference for most measurement scales [10 points for scale of 1 to 100], RR values <0.75 for harm or >1.25 for benefit); effect sizes below these thresholds but having low or higher SOE for a difference were considered slight or small.

The duration of followup was brief in many studies but especially in trials, therefore our findings need to be interpreted with this in mind. Although many of the trials included open-label extension phases to assess efficacy or harms, the majority failed to provide comparative data, precluding evaluation of effects between groups. In general, the small number of comparions between different antipsychotics is a limitation in the evidence base. Providing long-term comparative data for studies evaluating an active treatment versus placebo may not be feasible. As such, more high-quality observational studies are needed to provide data on patients using

different antipsychotics over the course of several years to determine the comparative benefits and risks associated with these drugs.

Research Gaps

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

- Studies examining long-term efficacy and, particularly, safety of antipsychotics (and differences between different antipsychotics) over the course of several years are needed. Future research should evaluate long-term developmental outcomes, such as growth, maturation, and cognitive and emotional development.
- Future studies should evaluate outcomes that are important to patients and parents, including health-related quality of life, school performance, and involvement with the legal system.
- Studies examining the impact of key patient subpopulations on important outcomes are needed to inform clinical practice. In particular, subgroup analyses examining young adults would be helpful in guiding clinical decisions due to the unique issues associated with this population.
- Consensus on outcomes and outcome measures is needed to ensure consistency and comparability across future studies. Moreover, consensus on minimal clinically important differences is needed to guide study design and interpretation of results.
- Large-scale effectiveness studies that are inclusive with respect to patient-selection criteria and closely match typical clinical practice are needed for greater applicability of results. Data on the real-world benefits and harms across groups defined by race/ethnicity, socioeconomic status, and geographical region would be informative.
- Studies incorporating therapeutic drug monitoring over long-term periods in naturalistic settings should be encouraged to help create quality standards and provide insight into operational considerations to inform recommendations for monitoring.
- Considering antipsychotics are recommended for use as adjunctive, or add-on, treatment for many conditions, more studies examining these approaches (e.g., behavioral/family interventions with and without antipsychotics for hyperactivity or irritability) may help practitioners create guidance on when to start a trial of antipsychotics.

Conclusions

The efficacy and safety of FGAs and SGAs have been studied in children, adolescents, and young adults (ages ≤ 24 years) for a wide array of psychiatric conditions. SGAs probably improve to some extent key intermediate outcomes for which they are usually prescribed, but they have a poorer harms profile than placebo or no antipsychotic treatment particularly for body composition and somnolence. Overall, data for head-to-head comparisons (FGAs vs. SGAs, FGAs vs. FGAs, and SGAs vs. SGAs) were generally of insufficient or low SOE; therefore, few conclusions regarding the relative benefits and harms of different antipsychotics could be drawn. For schizophrenia, there appears to be little or no difference between FGAs and SGAs for negative symptoms, positive symptoms, response rates, and global impressions of illness severity; deciding on which antipsychotic to use for this condition likely relies on close examination of the relative harms including considerations of their tolerance, management, and reversibility. The evidence examined suggests there may be little difference in effects between

different doses of antipsychotics, although longer-term data would help clarify these findings. Evidence was sparse for several patient- and family-important outcomes, such as health-related quality of life, involvement with the legal system, and school performance. Few studies reported long-term data.

Treatment benefit and risks were examined most frequently for schizophrenia. Fewer studies examined other conditions; only one study was eligible for each of depression and obsessive-compulsive disorder, and there were no eligible studies exclusively examining posttraumatic stress disorder, anxiety disorders, or substance use disorder. Young adults were rarely examined, particularly for conditions other than schizophrenia; young children were also not studied to any great extent. Additional research is needed to assess the treatment efficacy, and particularly the harms, of antipsychotics in these populations.

This review identified several areas where the evidence is sparse and which are priorities for future research. One of the greatest priorities is the systematic evaluation of harms. Studies incorporating therapeutic drug monitoring over long-term periods in naturalistic settings will hopefully help create a more accurate picture of the comparative harms between the large number of antipsychotics. They may also help define quality standards and provide insight into operational considerations to inform recommendations for monitoring. Comprehensive comparative effectiveness reviews such as this one, combined with active involvement of patients, families, and multidisciplinary practitioners may improve the applicability and usefulness of guidelines and help ensure uptake of their recommendations.

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Abbreviations and Acronyms

AACAP……	American Academy of Child and Adolescent Psychiatry
AD	anxiety disorders
ADHD	attention-deficit/hyperactivity disorder
ADHD/DICD	attention-deficit/hyperactivity disorder, or disruptive, impulse-control, or conduct disorders
AE	adverse effect
AHRQ	Agency of Healthcare Research and Quality
ASD	autism spectrum disorders
BD	bipolar disorder
BI	behavioral issues outside of diagnosis
Bid	'bis in die' or 'twice a day'
BMI	body mass index
CD	conduct disorder
CER	comparative effectiveness review
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CPT	continuous performance task
CrI	credible interval (reported when applying Bayesian meta-analyses)
CVLT	continuous verbal learning test
DBD	disruptive behavior disorder
DD	depressive disorders
DSM-IV	Diagnostics and Statistical Manual of Mental Disorders, 4th Edition
DSM-IV-TR	Diagnostics and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
DSM-V	Diagnostics and Statistical Manual of Mental Disorders, 5th Edition
EBSCO	Elton B. Stephens Co.
ECG	echocardiographic
ED	eating disorder
EMBASE	Excerpta Medica dataBASE
EPC	evidence-based practice center
EPS	extrapyramidal symptoms
ER	extended release
FDA	Food and Drug Administration
FGA	first-generation antipsychotic
G	group
GAD	general anxiety disorder
HDL	high-density lipoprotein
HR	hazard ratio
I^2	test for heterogeneity
IQ	intelligence quotient
IQR	interquartile range
kg	kilogram
$kg \cdot m^{-2}$	kilogram per meter square
KI	key informant
KQ	key question
LDL	low-density lipoprotein
m	meter
MAE	major adverse effect
MD	mean difference
MDD	major depressive disorder
MEDLINE	Medical Literature Analysis and Retrieval System Online
mg	milligram
mg/day	milligram per day
mg/kg/day	milligram per kilogram per day
mo	month
MR	mental retardation

N	number
NA	not applicable
NMS	neuroleptic malignant syndrome
NOS	not otherwise specified
NR	not reported
NRCT	nonrandomized controlled trial
OCD	obsessive-compulsive disorder
ODD	oppositional defiant disorder
PDD	pervasive developmental disorder
PDD-NOS	pervasive developmental disorder- not otherwise specified
PICOTS	populations, interventions, comparators, outcomes, timing, settings
PICOTS-D	populations, interventions, comparators, outcomes, timing, settings, digital data
PTSD	posttraumatic stress disorder
QTc	corrected QT interval
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
QTcLD	QT interval corrected for heart rate using the population specified linear derived method
RCT	randomized controlled trial
ROB	risk of bias
RR	risk ratio
SA	substance abuse
SD	standard deviation
SGA	second-generation antipsychotic
SMD	standardized mean difference
SOE	strength of evidence
SSRIs	selective serotonin reuptake inhibitors
Std.	standardized
SUD	substance use disorder
SZ	schizophrenia and related psychosis
TD	tic disorders
TEP	technical expert panel
TOXLINE	toxicology literature online
vs.	versus
wk	week
yr	year

Outcome measures (with ranges for scales used in assessment of strength of evidence):

ABC	Aberrant Behavior Checklist subscale score (subscales: irritability [range 0-45], lethargy/social withdrawal [range 0-48], stereotypic behavior [range 0-21], hyperactivity/noncompliance [range 0-48], inappropriate speech [range 0-12]).
ABC-I	Aberrant Behavior Checklist Irritability subscale
ADHD-SC4	ADHD Symptom Checklist-4
BPRS	Brief Psychiatric Rating Scale (range 24-168)
CARS	Childhood Autism Rating Scale
CASI-4R	Child and Adolescent Symptom Inventory-4R
CDRS-R	Children's Depression Rating Scale-Revised (17-113)
C-GAS	Global Assessment Scale for Children (range 1-100)
CGI-BP	Clinical Global Impressions for Bipolar Illness
CGI-I	Clinical Global Impression-Improvement score (7-point scale)
CGI-S	Clinical Global Impression-Severity score (7-points scale)
CHQ-PF50	Child Health Questionnaire
CPRS	Conners Parent Rating Scale (subscores: conduct problem, learning problem, psychosomatic, impulsive-hyperactive, anxiety, and hyperactivity index)
CY-BOCS	Children's Yale-Brown Obsessive Compulsive Scale (total 0-40; compulsions subscore 0-20)

GAF	Global Assessment of Functioning (range 1-100)
HAM-D	Hamilton Depression Rating Scale
IDS	Inventory of Depressive Symptomatology
MADRS	Montgomery-Åsberg Depression Rating Scale
NCBRF	Nisonger Child Behavior Rating Form (Problem Behaviors subscale score [conduct problem (range 0-16); insecure/anxious; hyperactive (range 0-9); self-injury/stereotypic; self-isolated/ritualistic; overly sensitive])
OAS	Overt Aggression Scale
PANSS	Positive and Negative Syndrome Scale (PANSS Total (range 30-210), PANSS Negative subscale (range 7-49), PANSS Positive subscale (range 7-49), PANSS General psychopathology; cluster for PANSS Anxiety/depression)
RAAPP	Rating of Aggression Against People and/or Property
SANS	Scale for the Assessment of Negative Symptoms (range 0-25)
SNAP-IV	Swanson, Nolan, and Pelham rating scale
TSGS	Tourette Syndrome Global Scale
YMRS	Young Mania Rating Scale (11-items; total range 0-60)
YGTSS	Yale Global Tic Severity Scale (Total 0-100; Total Tics 0-50)

Appendix A. Changes From Original Review

The Key Questions (KQs) from the original CER were reviewed by a stakeholder panel and underwent a public comment process via the AHRQ Effective Health Care Program website. There have been a few changes to the KQs. Rather than distinguishing between benefit outcomes primarily by type of outcome (symptom vs. other outcomes), they will be reported by timing and importance to patients; there is now only one KQ for benefits. Moreover, to enhance reporting on subgroups the previous KQ on subgroups has been integrated into the KQs on benefits and harms. The original CER used terminology specific to the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV), and the conditions for this update have been revised according to changes in the DSM-V (e.g., pervasive developmental disorders is currently classified as an autism spectrum disorder) published in 2013.[1] None of these changes were anticipated to impact the categorization or inclusion of previous studies for this update. Diagnosis of study participants based on DSM-V was not mandatory for study inclusion. Specific changes are described below in terms of the PICOTS (population, intervention, comparators, outcomes, timing, and setting).

Population

In terms of the study population, there has been the (1) addition of depressive disorders, anxiety disorders, and substance use disorders; (2) broadening of anorexia nervosa to include other eating disorders, and of Tourette's syndrome to include all tic disorders; and (3) specification that the category of behavioral issues includes treatment of symptoms outside the context of a disorder, as for example when antipsychotics are prescribed for sedation/sleep within certain environmental contexts (e.g., residential facilities). While these latter uses of antipsychotics are not endorsed by guidelines or indicated for antipsychotic use as per FDA approval, it was thought important by our stakeholders to review the evidence on all current uses of antipsychotics to provide information of benefit and harms for a broad range of stakeholders. The subgroups have been modified slightly to include phase and features of disorder (e.g., acute vs. maintenance treatment), medication dose, and use for cases of refractory treatment; these reflect some major components of the uncertainty currently faced by many clinicians. We have indicated the difference between patient- and intervention-level characteristics (i.e., dose and co-interventions).

Interventions and Comparators

One long-standing FDA-approved FGA (molindone) was discontinued at the time of the original CER, but a generic has recently received approval for marketing and therefore this FGA has been added as an eligible antipsychotic. The SGA lurasidone was approved by the FDA in 2010 (for schizophrenia and later for bipolar depression, both in adults) and was not reviewed in the original CER. Two other SGAs were approved in 2015: brexpiprazole in July for schizophrenia and adjunctive treatment of major depression in adults, and cariprazine in September for schizophrenia and bipolar disorder in adults. The comparators remain the same: placebo/no treatment, same antipsychotic of different dose, and another antipsychotic.

Outcomes

There have been changes to the terminology and classification of some outcomes, for example removal of the wording "patient- or family-reported outcomes" from a single outcome, because several of the outcomes are measured by patient/family report. Despite changes, all of the previous included outcomes will be captured in some manner. There has been the addition of an outcome for global impressions, which captures symptoms and overall clinical improvement, severity, and functioning. The outcomes related to harms have been modified slightly to have better consistency with the categories of major and general adverse effects. The outcomes that will be graded for strength of evidence have been modified to be more precise for symptoms that are treated with antipsychotics for each condition (e.g., "autistic symptoms" has been replaced with irritability) and to reflect any changes to terminology and classification.

Timing and Setting

The same criteria will be used for timing (1987 or later) and setting (all settings). Outcomes will be categorized in terms of short- (<6 months) and long- (≥ 6 months-<12 months; 12 months+) term followup.

Study Design

The original inclusion criteria for study design have been broadened slightly to include additional forms of observational studies beyond comparative cohort studies; we included controlled before-and-after studies as well as pooled analysis of individual patient data from trials.

Methods

There were a few methodological changes to align the methods with current guidance of AHRQ's EPC program, and to potentially enhance our ability to inform decisions in some areas. The original assessment of SOE was frequently downgraded due to high risk of bias for the relevant studies, which included consideration of industry funding. Refinement in EPC program methods guidance on risk of bias assessments of individual studies, in particular in relation to the role of industry funding, may not lead to similar assessments in the updated review.[2] For some outcomes (especially harms which were evaluated across disorders), the use of mixed-comparison meta-analytical techniques (i.e., combining placebo and head-to-head trials across a variety of drug comparison) may be possible and allow for more quantitative assessment of differences between antipsychotics in the absence of many head-to-head trials. Moreover, the assessment of findings for patient and clinical subgroups relied upon within-study analyses which were highly variable and did not encompass harms data; applying analytical techniques with study-level data—although exploratory in nature[3]—would allow for examining the related key questions (KQ1a, b; KQ2 a, b) to a greater extent. Lastly, differences in some harms outcomes (e.g., weight gain and metabolic risks) have been shown to vary by condition,[4, 5] such that only using aggregate data on harms across conditions may not capture some information important for patient-level decision making. We attempted to differentiate the impact on harms within as well as across conditions.

References

1. Association AP. Diagnostic and statistical manual of mental disorders, fifth edition. Washington, DC: American Psychiatric Association2013.
2. Viswanathan M, Ansari MT, Berkman ND, et al. Assessing the risk of bias of individual studies in systematic reviews of health care interventions methods guide for effectiveness and comparative effectiveness reviews. Rockville MD2008.
3. Higgins JPT, Green, S. Chapter 9: Analyzing data and undertaking meta-analysis Cochrane Handbook for Systematic Reviews of Interventions: The Cochrane Collaboration; 2009.
4. De Hert M, Dobbelaere M, Sheridan EM, et al. Metabolic and endocrine adverse effects of second-generation antipsychotics in children and adolescents: A systematic review of randomized, placebo controlled trials and guidelines for clinical practice. Eur Psychiatry. 2011 Apr;26(3):144-58. PMID: 21295450.
5. Maayan L, Correll CU. Weight gain and metabolic risks associated with antipsychotic medications in children and adolescents. J Child Adolesc Psychopharmacol. 2011 Dec;21(6):517-35. PMID: 22166172.

Appendix B. Literature Search Strategies

MEDLINE
CENTRAL
CINAHL
Ovid EMBASE
Ovid PsycINFO
Dissertations and Theses International
TOXLINE
ClinicalTrials.gov
WHO ICTRP

MEDLINE

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
Search Title: Antipsychotics_Child_Update
Search Date: 15 Oct 2015 (updated in April 2016)
Results: 6164

1. Adjustment Disorders/
2. Anorexia/
3. Anxiety/
4. exp Anxiety Disorders/
5. exp "Attention Deficit and Disruptive Behavior Disorders"/
6. exp Behavioral Symptoms/
7. Child Behavior Disorders/
8. exp Child Development Disorders, Pervasive/
9. exp Eating Disorders/
10. exp Hyperphagia/
11. exp Impulse Control Disorders/
12. exp Impulsive Behavior/
13. Irritable Mood/
14. Mental Disorders/
15. exp Mood Disorders/
16. Movement Disorders/
17. "Off-Label Use"/
18. Psychomotor Agitation/
19. Rett Syndrome/
20. exp "Schizophrenia and Disorders with Psychotic Features"/
21. Schizophrenia, Childhood/
22. exp Sleep Disorders/
23. exp Substance-Related Disorders/
24. exp Tic Disorders/
25. Violence/
26. (ADHD* or (attention deficit adj2 disorder*) or hyperkinetic syndrome).tw,kf.
27. ((adjustment or reactive) adj disorder*).tw,kf.
28. (affective adj2 (disorder* or disregulation or dysregulation)).tw,kf.
29. (aggressi* or agitat*).tw,kf.
30. agoraphobi*.tw,kf.
31. ((alcohol* or drug* or cannabi* or cocaine* or heroin or marijuana* or narcotic* or opiate* or opioid* or substance*) adj2 (abus* or addict* or depend* or disorder* or withdrawal*)).tw,kf.
32. ((addicti* or compulsi* or explosive or impuls*) adj2 (behavio* or disorder*)).tw,kf.
33. (((anankastic or compulsiv* or obsessive) adj (behavio* or disorder* or neuros* or personalit*)) or OCD).tw,kf.
34. anorexi*.tw,kf.
35. anxiety.tw,kf.
36. (autis* or asperger* or kanner* syndrome).tw,kf.

37. (behavio* adj2 (disorder* or disturb* or disrupt* or dyscontrol* or illness* or issue* or outburst* or problem*)).tw,kf.
38. (((behavio* or disorder* or episod*) adj (hypomanic or manic)) or mania*).tw,kf.
39. (binge adj (drink* or eat*)).tw,kf.
40. (bi polar or bipolar).tw,kf.
41. bulimi*.tw,kf.
42. (claustrophobi* or phobia* or phobic).tw,kf.
43. ((combat or war) adj (disorder* or neuros*)).tw,kf.
44. conduct disorder*.tw,kf.
45. cyclothymi*.tw,kf.
46. ((defiant or disrupt* or oppositional) adj (behavio* or disorder*)).tw,kf.
47. delusion*.tw,kf.
48. dementia praecox.tw,kf.
49. depress*.tw,kf.
50. ((dis integrative or disintegrative or dys integrative or dysintegrative) adj disorder*).tw,kf.
51. (dys somnia* or dyssomnia* or insomnia* or para somnia* or parasomnia*).tw,kf.
52. dysthymi*.tw,kf.
53. eating disorder*.tw,kf.
54. ((emotion* or mood) adj2 (disorder* or dis regulation or disregulation or dys regulation or dysregulation)).tw,kf.
55. (hoarder* or hoarding).tw,kf.
56. (hyper activ* or hyperactiv*).tw,kf.
57. hyperphagia*.tw,kf.
58. irritab*.tw,kf.
59. kleptomania*.tw,kf.
60. (minimal brain adj (dis function* or disfunction* or dys function* or dysfunction*)).tw,kf.
61. (mood adj2 (labil* or swing*)).tw,kf.
62. (off label* or offlabel* or unlabeled indication* or unlabeled use*).tw,kf.
63. (panic* adj (attack* or disorder*)).tw,kf.
64. (para suicid* or parasuicid*).tw,kf.
65. paranoi*.tw,kf.
66. pervasive development* disorder*.tw,kf.
67. ((post traumatic or posttraumatic) adj2 (disorder* or neuros*)).tw,kf.
68. ((psycho* or sociopath*) adj (disorder* or personalit*)).tw,kf.
69. psychos*.tw,kf.
70. PTSD*.tw,kf.
71. (rett* adj (syndrome* or disorder*)).tw,kf.
72. (self adj (destruct* or harm* or injur* or mutilat*)).tw,kf.
73. (schizo affect* or schizoaffect*).tw,kf.
74. schizophreni*.tw,kf.
75. shell shock*.tw,kf.
76. (sleep adj2 (disorder* or dysfunction*)).tw,kf.
77. stress disorder*.tw,kf.
78. tourette*.tw,kf.
79. tic disorder*.tw,kf.
80. unstable mood*.tw,kf.

81. violen*.tw,kf.
82. or/1-81
83. exp Antipsychotic Agents/
84. exp Butyrophenones/
85. exp Phenothiazines/
86. exp Thioxanthenes/
87. abilify.mp.
88. adasuve.mp.
89. aldazine.mp.
90. anatensol.mp.
91. anti naus.mp.
92. (anti psychotic* or antipsychotic*).mp.
93. aripiprazole.mp.
94. 82VFR53I78.rn.
95. arizole.mp.
96. asenapine.mp.
97. JKZ19V908O.rn.
98. atrolak.mp.
99. biquelle.mp.
100. brexpiprazole.mp.
101. 2J3YBM1K8C.rn.
102. buccastem.mp.
103. calmazine.mp.
104. cariprazine.mp.
105. chloractil.mp.
106. chlorpromanyl.mp.
107. chlorpromazine.mp.
108. U42B7VYA4P.rn.
109. clopine.mp.
110. clozapine.mp.
111. J60AR2IKIC.rn.
112. clozaril.mp.
113. compazine.mp.
114. compro.mp.
115. decazate.mp.
116. delucon.mp.
117. denzapine.mp.
118. dozic.mp.
119. droleptan.mp.
120. droperidol.mp.
121. O9U0F09D5X.rn.
122. ebesque.mp.
123. fanapt.mp.
124. fazaclo.mp.
125. fazalco.mp.
126. fentazin.mp.

127. fluphenazine.mp.
128. S79426A41Z.rn.
129. fortunan.mp.
130. geodon.mp.
131. haldol.mp.
132. halo peridol.mp.
133. haloperidol.mp.
134. J6292F8L3D.rn.
135. halperon.mp.
136. iloperidone.mp.
137. 133454-47-4.rn.
138. inapsine.mp.
139. invega.mp.
140. lanzek.mp.
141. largactil.mp.
142. latuda.mp.
143. loxapac.mp.
144. loxapine.mp.
145. LER583670J.rn.
146. loxitane.mp.
147. lurasidone.mp.
148. 22IC88528T.rn.
149. (major adj (tranquili?er* or tranquilli?er*)).mp.
150. mellaril*.mp.
151. melleril.mp.
152. mintreleq.mp.
153. moban.mp.
154. modecate.mp.
155. moditen.mp.
156. molindone.mp.
157. RT3Y3QMF8N.rn.
158. nausetil.mp.
159. navane.mp.
160. neuroleptic*.mp.
161. novo flurazine.mp.
162. novo peridol.mp.
163. novo ridazine.mp.
164. novo trifluzine.mp.
165. nu prochlor.mp.
166. olanzaccord.mp.
167. olanzapine.mp.
168. 132539-06-1.rn.
169. orap.mp.
170. ormazine.mp.
171. ozidal.mp.
172. ozin.mp.

173. paliperidone.mp.
174. 838F01T721.rn.
175. permitil.mp.
176. perphenazine.mp.
177. FTA7XXY4EZ.rn.
178. pimozide.mp.
179. 1HIZ4DL86F.rn.
180. procalm.mp.
181. prochlorazine.mp.
182. prochlorperazine.mp.
183. YHP6YLT61T.rn.
184. procomp.mp.
185. prolixin.mp.
186. promapar.mp.
187. prorazin.mp.
188. protran.mp.
189. proziere.mp.
190. prozine.mp.
191. quetiapine.mp.
192. BGL0JSY5SI.rn.
193. quetiaccord.mp.
194. quetin.mp.
195. resdone.mp.
196. rexulti.mp.
197. rideril.mp.
198. rispa.mp.
199. risperdal.mp.
200. risperidone.mp.
201. L6UH7ZF8HC.rn.
202. rispernia.mp.
203. rixadone.mp.
204. saphris.mp.
205. seotiapim.mp.
206. sequase.mp.
207. serenace.mp.
208. seronia.mp.
209. seroquel.mp.
210. solazine.mp.
211. sonazine.mp.
212. sondate.mp.
213. stelazine.mp.
214. stemetil.mp.
215. stemzine.mp.
216. sycrest.mp.
217. syquet.mp.
218. terfluzine.mp.

219. thioridazine.mp.
220. N3D6TG58NI.rn.
221. thiothixene.mp.
222. 7318FJ13YJ.rn.
223. thorazine.mp.
224. tiotixene.mp.
225. trifluoperazine.mp.
226. 214IZI85K3.rn.
227. trilafon.mp.
228. versacloz.mp.
229. vertigon.mp.
230. vraylar.mp.
231. xeplion.mp.
232. xomolix.mp.
233. xylac.mp.
234. zaluron.mp.
235. zaponex.mp.
236. zeldox.mp.
237. ziprasidone.mp.
238. 6UKA5VEJ6X.rn.
239. zylap.mp.
240. zypadhera.mp.
241. zypine.mp.
242. zyprexa.mp.
243. or/83-242
244. and/82,243
245. Adolescent/
246. Adolescent Medicine/
247. exp Child/
248. exp Minors/
249. exp Pediatrics/
250. exp Puberty/
251. Students/
252. Young Adult/
253. adolescen*.mp.
254. (boy* or girl* or teen*).mp.
255. (child* or grade school* or kid or kids or kindergar?en* or minors* or preschool* or pre school* or school age* or schoolchild* or toddler*).mp.
256. ((colleg* or high school* or highschool* or middle school* or universit*) adj2 (age* or student*)).mp.
257. (paediatric* or peadiatric* or pediatric*).mp.
258. (prepubescen* or pubescen* or pubert*).mp.
259. (young* adj (adult* or men or mens or people* or person* or women*)).mp.
260. (youth or youths).mp.
261. or/245-260
262. and/244,261

263. exp Epidemiologic Studies/
264. controlled clinical trial.pt.
265. randomized controlled trial.pt.
266. drug therapy.fs.
267. (case control or cohort* or follow up or followup or longitudinal or prospective* or retrospective).tw,kf.
268. ((compari* or epidemiologic* or experimental or observational) adj2 (analy* or study or studies)).tw,kf.
269. groups.ab.
270. placebo.ab.
271. random*.ab.
272. trial.ab.
273. or/263-272
274. exp animals/ not humans.sh.
275. 273 not 274
276. and/262,275
277. (case reports or comment or editorial or letter).pt.
278. 276 not 277
279. limit 278 to english
280. limit 279 to yr="1987-current"

CENTRAL

Database: CENTRAL via Cochrane Library
Search Title: Antipsychotics_Child_Update
Date Searched: 19 Oct 2015 (updated in April 2016)
Results: 1569

1. [mh ^"Adjustment Disorders"]
2. [mh ^Anorexia]
3. [mh ^Anxiety]
4. [mh "Anxiety Disorders"]
5. [mh "Attention Deficit and Disruptive Behavior Disorders"]
6. [mh "Behavioral Symptoms"]
7. [mh ^"Child Behavior Disorders"]
8. [mh "Child Development Disorders, Pervasive"]
9. [mh "Eating Disorders"]
10. [mh Hyperphagia]
11. [mh "Impulse Control Disorders"]
12. [mh "Impulsive Behavior"]
13. [mh ^"Irritable Mood"]
14. [mh ^"Mental Disorders"]
15. [mh "Mood Disorders"]
16. [mh ^"Movement Disorders"]
17. [mh ^"Off-Label Use"]
18. [mh ^"Psychomotor Agitation"]
19. [mh ^"Rett Syndrome"]

20. [mh "Schizophrenia and Disorders with Psychotic Features"]
21. [mh ^"Schizophrenia, Childhood"]
22. [mh "Sleep Disorders"]
23. [mh "Substance-Related Disorders"]
24. [mh "Tic Disorders"]
25. [mh ^Violence]
26. (ADHD* or ("attention deficit" n/2 disorder*) or "hyperkinetic syndrome"):ti,ab,kw
27. ((adjustment or reactive) next disorder*):ti,ab,kw
28. (affective n/2 (disorder* or disregulation or dysregulation)):ti,ab,kw
29. (aggressi* or agitat*):ti,ab,kw
30. agoraphobi*:ti,ab,kw
31. ((alcohol* or drug* or cannabi* or cocaine* or heroin or marijuana* or narcotic* or opiate* or opioid* or substance*) n/2 (abus* or addict* or depend* or disorder* or withdrawal*)):ti,ab,kw
32. ((addicti* or compulsi* or explosive or impuls*) n/2 (behavio* or disorder*)):ti,ab,kw
33. (((anankastic or compulsiv* or obsessive) next (behavio* or disorder* or neuros* or personalit*)) or OCD):ti,ab,kw
34. anorexi*:ti,ab,kw
35. anxiety:ti,ab,kw
36. (autis* or asperger* or (kanner* next syndrome)):ti,ab,kw
37. (behavio* n/2 (disorder* or disturb* or disrupt* or dyscontrol* or illness* or issue* or outburst* or problem*)):ti,ab,kw
38. (((behavio* or disorder* or episod*) next (hypomanic or manic)) or mania*):ti,ab,kw
39. (binge next (drink* or eat*)):ti,ab,kw
40. ("bi polar" or bipolar):ti,ab,kw
41. bulimi*:ti,ab,kw
42. (claustrophobi* or phobia* or phobic):ti,ab,kw
43. ((combat or war) next (disorder* or neuros*)):ti,ab,kw
44. (conduct next disorder*):ti,ab,kw
45. cyclothymi*:ti,ab,kw
46. ((defiant or disrupt* or oppositional) next (behavio* or disorder*)):ti,ab,kw
47. delusion*:ti,ab,kw
48. "dementia praecox":ti,ab,kw
49. depress*:ti,ab,kw
50. (("dis integrative" or disintegrative or "dys integrative" or dysintegrative) next disorder*):ti,ab,kw
51. ((dys next somnia*) or dyssomnia* or insomnia* or (para next somnia*) or parasomnia*):ti,ab,kw
52. dysthymi*:ti,ab,kw
53. (eating next disorder*):ti,ab,kw
54. ((emotion* or mood) n/2 (disorder* or "dis regulation" or disregulation or "dys regulation" or dysregulation)):ti,ab,kw
55. (hoarder* or hoarding):ti,ab,kw
56. ((hyper next activ*) or hyperactiv*):ti,ab,kw
57. (hyperphagia*):ti,ab,kw
58. (irritab*):ti,ab,kw

59. (kleptomania*):ti,ab,kw
60. ("minimal brain" next ((dis next function*) or disfunction* or (dys next function*) or dysfunction*)):ti,ab,kw
61. (mood n/2 (labil* or swing*)):ti,ab,kw
62. ((off next label*) or offlabel* or (unlabeled next indication*) or (unlabeled next use*)):ti,ab,kw
63. (panic* next (attack* or disorder*)):ti,ab,kw
64. ((para next suicid*) or parasuicid*):ti,ab,kw
65. (paranoi*):ti,ab,kw
66. (pervasive next development* next disorder*):ti,ab,kw
67. (("post traumatic" or posttraumatic) n/2 (disorder* or neuros*)):ti,ab,kw
68. ((psycho* or sociopath*) next (disorder* or personalit*)):ti,ab,kw
69. (psychos*):ti,ab,kw
70. (PTSD*):ti,ab,kw
71. (rett* next (syndrome* or disorder*)):ti,ab,kw
72. (self next (destruct* or harm* or injur* or mutilat*)):ti,ab,kw
73. ((schizo next affect*) or schizoaffect*):ti,ab,kw
74. (schizophreni*):ti,ab,kw
75. (shell next shock*):ti,ab,kw
76. (sleep n/2 (disorder* or dysfunction*)):ti,ab,kw
77. (stress next disorder*):ti,ab,kw
78. (tourette*):ti,ab,kw
79. (tic next disorder*):ti,ab,kw
80. (unstable next mood*):ti,ab,kw
81. violen*:ti,ab,kw
82. {or #1-#81}
83. [mh "Antipsychotic Agents"]
84. [mh Butyrophenones]
85. [mh Phenothiazines]
86. [mh Thioxanthenes]
87. (abilify or adasuve or aldazine or anatensol or "anti naus"):ti,ab,kw
88. ((anti next psychotic*) or antipsychotic*):ti,ab,kw
89. (aripiprazole or arizole or asenapine or atrolak or biquelle):ti,ab,kw
90. (brexpiprazole or buccastem or calmazine or cariprazine or chloractil):ti,ab,kw
91. (chlorpromanyl or chlorpromazine or clopine or clozapine or clozaril):ti,ab,kw
92. (compazine or compro or decazate or delucon or denzapine):ti,ab,kw
93. (dozic or droleptan or droperidol or ebesque or fanapt):ti,ab,kw
94. (fazaclo or fazalco or fentazin or fluphenazine or fortunan):ti,ab,kw
95. (geodon or haldol or "halo peridol" or haloperidol or halperon):ti,ab,kw
96. (iloperidone or inapsine or invega or lanzek or largactil):ti,ab,kw
97. (latuda or loxapac or loxapine or loxitane or lurasidone):ti,ab,kw
98. (major next (tranquili?er* or tranquilli?er*)):ti,ab,kw
99. (mellaril* or melleril or mintreleq or moban or modecate):ti,ab,kw
100. (moditen or molindone or nausetil or navane):ti,ab,kw
101. (neuroleptic*):ti,ab,kw

102. ("novo flurazine" or "novo peridol" or "novo ridazine" or "novo trifluzine" or "nu prochlor"):ti,ab,kw
103. (olanzaccord or olanzapine or orap or ormazine or ozidal):ti,ab,kw
104. (ozin or paliperidone or permitil or perphenazine or pimozide):ti,ab,kw
105. (procalm or prochlorazine or prochlorperazine or procomp or prolixin):ti,ab,kw
106. (promapar or prorazin or protran or proziere or prozine):ti,ab,kw
107. (quetiapine or quetiaccord or quetin or resdone or rexulti):ti,ab,kw
108. (rideril or rispa or risperdal or risperidone or rispernia):ti,ab,kw
109. (rixadone or saphris or seotiapim or sequase or serenace):ti,ab,kw
110. (seronia or seroquel or solazine or sonazine or sondate):ti,ab,kw
111. (stelazine or stemetil or stemzine or sycrest or syquet):ti,ab,kw
112. (terfluzine or thioridazine or thiothixene or thorazine or tiotixene):ti,ab,kw
113. (trifluoperazine or trilafon or versacloz or vertigon or vraylar):ti,ab,kw
114. (xeplion or xomolix or xylac or zaluron or zaponex):ti,ab,kw
115. (zeldox or ziprasidone or zylap or zypadhera or zypine or zyprexa):ti,ab,kw
116. {or #83-#115}
117. #82 and #116
118. [mh ^Adolescent]
119. [mh ^"Adolescent Medicine"]
120. [mh Child]
121. [mh Minors]
122. [mh Pediatrics]
123. [mh Puberty]
124. [mh ^Students]
125. [mh ^"Young Adult"]
126. (adolescen*):ti,ab,kw
127. (boy* or girl* or teen*):ti,ab,kw
128. (child* or (grade next school*) or kid or kids or kindergar?en* or minors* or preschool* or (pre next school*) or (school next age*) or schoolchild* or toddler*):ti,ab,kw
129. ((colleg* or (high next school*) or highschool* or (middle next school*) or universit*) n/2 (age* or student*)):ti,ab,kw
130. (paediatric* or peadiatric* or pediatric*):ti,ab,kw
131. (prepubescen* or pubescen* or pubert*):ti,ab,kw
132. (young* next (adult* or men or mens or people* or person* or women*)):ti,ab,kw
133. (youth or youths):ti,ab,kw
134. {or #118-#133}
135. #117 and #134 Publication Year from 1987 to 2015, in Trials

Note: Excluded 73 non-English language records in EndNote

CINAHL

Database: CINAHL Plus with Full Text via EbscoHOST
Search Title: Antipsychotics_Child_Update
Date Searched: 21 Oct 2015 (updated in April 2916)
Results: 1142

S1. MH "Adjustment Disorders+"
S2. MH "Affective Disorders+"
S3. MH "Affective Disorders, Psychotic+"
S4. MH "Affective Symptoms+"
S5. MH "Anxiety Disorders+"
S6. MH "Attention Deficit Hyperactivity Disorder"
S7. MH "Behavior, Addictive+"
S8. MH "Behavioral Symptoms"
S9. MH "Child Behavior Disorders"
S10. MH "Child Development Disorders, Pervasive+"
S11. MH "Compulsive Behavior"
S12. MH "Drugs, Off-Label"
S13. MH "Eating Disorders+"
S14. MH "Impulse Control Disorders+"
S15. MH "Mental Disorders"
S16. MH "Mental Disorders Diagnosed in Childhood"
S17. MH "Paranoid Disorders"
S18. MH "Psychomotor Agitation"
S19. MH "Psychomotor Disorders"
S20. MH "Psychotic Disorders+"
S21. MH "Rett Syndrome"
S22. MH "Schizoaffective Disorder"
S23. MH "Schizophrenia+"
S24. MH "Sleep Disorders+"
S25. MH "Substance Use Disorders+"
S26. MH "Suicide+"
S27. MH "Tourette Syndrome"
S28. MH "Violence"
S29. (ADHD* or ("attention deficit" N2 disorder*) or "hyperkinetic syndrome")
S30. ((adjustment or reactive) N1 disorder*)
S31. (affective N2 (disorder* or disregulation or dysregulation))
S32. (aggressi* or agitat*)
S33. agoraphobi*
S34. ((alcohol* or drug* or cannabi* or cocaine* or heroin or marijuana* or narcotic* or opiate* or opioid* or substance*) N2 (abus* or addict* or depend* or disorder* or withdrawal*))
S35. ((addicti* or compulsi* or explosive or impuls*) N2 (behavio* or disorder*))
S36. (((anankastic or compulsiv* or obsessive) N1 (behavio* or disorder* or neuros* or personalit*)) or OCD)
S37. anorexi*
S38. anxiety
S39. (autis* or asperger* or "kanner* syndrome")
S40. (behavio* N2 (disorder* or disturb* or disrupt* or dyscontrol* or illness* or issue* or outburst* or problem*))
S41. (((behavio* or disorder* or episod*) N1 (hypomanic or manic)) or mania*)
S42. (binge N1 (drink* or eat*))
S43. ("bi polar" or bipolar)

S44. bulimi*
S45. (claustrophobi* or phobia* or phobic)
S46. ((combat or war) N1 (disorder* or neuros*))
S47. "conduct disorder*"
S48. cyclothymi*
S49. ((defiant or disrupt* or oppositional) N1 (behavio* or disorder*))
S50. delusion*
S51. "dementia praecox"
S52. depress*
S53. (("dis integrative" or disintegrative or "dys integrative" or dysintegrative) N1 disorder*)
S54. ("dys somnia*" or dyssomnia* or insomnia* or "para somnia*" or parasomnia*)
S55. dysthymi*
S56. "eating disorder*"
S57. ((emotion* or mood) N2 (disorder* or "dis regulation" or disregulation or "dys regulation" or dysregulation))
S58. (hoarder* or hoarding)
S59. ("hyper activ*" or hyperactiv*)
S60. hyperphagia*
S61. irritab*
S62. kleptomania*
S63. ("minimal brain" N1 ("dis function*" or disfunction* or "dys function*" or dysfunction*))
S64. (mood N2 (labil* or swing*))
S65. ("off label*" or offlabel* or "unlabeled indication*" or "unlabeled use*")
S66. (panic* N1 (attack* or disorder*))
S67. ("para suicid*" or parasuicid*)
S68. paranoi*
S69. "pervasive development* disorder*"
S70. (("post traumatic" or posttraumatic) N2 (disorder* or neuros*))
S71. ((psycho* or sociopath*) N1 (disorder* or personalit*))
S72. psychos*
S73. PTSD*
S74. (rett* N1 (syndrome* or disorder*))
S75. (self N1 (destruct* or harm* or injur* or mutilat*))
S76. ("schizo affect*" or schizoaffect*)
S77. schizophreni*
S78. "shell shock*"
S79. (sleep N2 (disorder* or dysfunction*))
S80. "stress disorder*"
S81. tourette*
S82. "tic disorder*"
S83. "unstable mood*"
S84. violen*
S85. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR

S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84
S86. MH "Antipsychotic Agents+"
S87. (abilify or adasuve or aldazine or anatensol or "anti naus")
S88. ("anti psychotic*" or antipsychotic*)
S89. (aripiprazole or arizole or asenapine or atrolak or biquelle)
S90. (brexpiprazole or buccastem or calmazine or cariprazine or chloractil)
S91. (chlorpromanyl or chlorpromazine or clopine or clozapine or clozaril)
S92. (compazine or compro or decazate or delucon or denzapine)
S93. (dozic or droleptan or droperidol or ebesque or fanapt)
S94. (fazaclo or fazalco or fentazin or fluphenazine or fortunan)
S95. (geodon or haldol or "halo peridol" or haloperidol or halperon)
S96. (iloperidone or inapsine or invega or lanzek or largactil)
S97. (latuda or loxapac or loxapine or loxitane or lurasidone)
S98. (major N1 (tranquili?er* or tranquilli?er*))
S99. (mellaril* or melleril or mintreleq or moban or modecate)
S100. (moditen or molindone or nausetil or navane)
S101. neuroleptic*
S102. (novo N1 (flurazine or peridol or ridazine or trifluzine))
S103. ("nu prochlor" or olanzaccord or olanzapine or orap or ormazine)
S104. (ozidal or ozin or paliperidone or permitil or perphenazine)
S105. (pimozide or procalm or prochlorazine or prochlorperazine or procomp)
S106. (prolixin or promapar or prorazin or protran or proziere)
S107. (prozine or quetiapine or quetiaccord or quetin or resdone)
S108. (rexulti or rideril or rispa or risperdal or risperidone)
S109. (rispernia or rixadone or saphris or seotiapim or sequase)
S110. (serenace or seronia or seroquel or solazine or sonazine)
S111. (sondate or stelazine or stemetil or stemzine or sycrest)
S112. (syquet or terfluzine or thioridazine or thiothixene or thorazine)
S113. (tiotixene or trifluoperazine or trilafon or versacloz or vertigon)
S114. (vraylar or xeplion or xomolix or xylac or zaluron)
S115. (zaponex or zeldox or ziprasidone or zylap or zypadhera)
S116. (zypine or zyprexa)
S117. S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102 OR S103 OR S104 OR S105 OR S106 OR S107 OR S108 OR S109 OR S110 OR S111 OR S112 OR S113 OR S114 OR S115 OR S116
S118. S85 AND S117
S119. MH "Adolescence+"
S120. MH "Adolescent Medicine"
S121. MH "Child"
S122. MH "Child, Preschool"
S123. MH "Minors (Legal)"
S124. MH "Pediatrics"

S125. MH "Puberty"
S126. MH "Students, Elementary"
S127. MH "Students, High School"
S128. MH "Students, Middle School"
S129. MH "Students, Undergraduate"
S130. MH "Young Adult"
S131. adolescen*
S132. (boy* or girl* or teen*)
S133. (child* or "grade school*" or kid or kids or kindergar?en* or minors* or preschool* or "pre school*" or "school age*" or schoolchild* or toddler*)
S134. ((colleg* or "high school*" or highschool* or "middle school*" or universit*) N2 (age* or student*))
S135. (paediatric* or peadiatric* or pediatric*)
S136. (prepubescen* or pubescen* or pubert*)
S137. (young* N1 (adult* or men or mens or people* or person* or women*))
S138. (youth or youths)
S139. S119 OR S120 OR S121 OR S122 OR S123 OR S124 OR S125 OR S126 OR S127 OR S128 OR S129 OR S130 OR S131 OR S132 OR S133 OR S134 OR S135 OR S136 OR S137 OR S138
S140. S118 AND S139
S141. MH "Clinical Research+"
S142. MH "Comparative Studies"
S143. MH "Drug Therapy"
S144. MH "Experimental Studies+"
S145. MH "Nonexperimental Studies+"
S146. MH "Retrospective Design"
S147. Limiters - Publication Type: Clinical Trial, Randomized Controlled Trial
S148. ("case control" or cohort* or "follow up" or followup or longitudinal or prospective* or retrospective)
S149. ((compari* or epidemiologic* or experimental or observational) N2 (analy* or study or studies))
S150. AB groups
S151. AB placebo
S152. AB random*
S153. AB trial
S154. S141 OR S142 OR S143 OR S144 OR S145 OR S146 OR S147 OR S148 OR S149 OR S150 OR S151 OR S152 OR S153
S155. (MH "Animals+") not (MH "Humans")
S156. S154 NOT S155
S157. S140 AND S156
S158. PT (“case reports” or comment or editorial or letter)
S159. S157 NOT S158
S160. S159 Limiters – Language: English
S161. S160 Limiters – English Language; Published Date: 19870101-20151231

Ovid EMBASE

Database: Ovid Embase 1980 to 2015 Week 41
Search Title: Antipsychotics_Child_Update_1
Date Searched: 16 Oct 2015 (updated in April 2016)
Results: 7376

1. abnormal behavior/
2. exp addiction/
3. adjustment disorder/
4. aggression/
5. aggressiveness/
6. exp anger/
7. anorexia/
8. anxiety/
9. exp anxiety disorder/
10. attention deficit disorder/
11. exp autism/
12. automutilation/
13. behavior disorder/
14. disruptive behavior/
15. exp eating disorder/
16. exp impulse control disorder/
17. impulsiveness/
18. intermittent explosive disorder/
19. irritability/
20. kleptomania/
21. oppositional defiant disorder/
22. exp psychosis/
23. exp psychosocial disorder/
24. exp "substance use"/
25. exp suicidal behavior/
26. mental disease/
27. minimal brain dysfunction/
28. exp mood disorder/
29. motor dysfunction/
30. "off label drug use"/
31. restlessness/
32. exp sleep disorder/
33. exp tic/
34. exp violence/
35. (ADHD* or (attention deficit adj2 disorder*) or hyperkinetic syndrome).tw.
36. ((adjustment or reactive) adj disorder*).tw.
37. (affective adj2 (disorder* or disregulation or dysregulation)).tw.
38. (aggressi* or agitat*).tw.
39. agoraphobi*.tw.

40. ((alcohol* or drug* or cannabi* or cocaine* or heroin or marijuana* or narcotic* or opiate* or opioid* or substance*) adj2 (abus* or addict* or depend* or disorder* or withdrawal*)).tw.
41. ((addicti* or compulsi* or explosive or impuls*) adj2 (behavio* or disorder*)).tw.
42. (((anankastic or compulsiv* or obsessive) adj (behavio* or disorder* or neuros* or personalit*)) or OCD).tw.
43. anorexi*.tw.
44. anxiety.tw.
45. (autis* or asperger* or kanner* syndrome).tw.
46. (behavio* adj2 (disorder* or disturb* or disrupt* or dyscontrol* or illness* or issue* or outburst* or problem*)).tw.
47. (((behavio* or disorder* or episod*) adj (hypomanic or manic)) or mania*).tw.
48. (binge adj (drink* or eat*)).tw.
49. (bi polar or bipolar).tw.
50. bulimi*.tw.
51. (claustrophobi* or phobia* or phobic).tw.
52. ((combat or war) adj (disorder* or neuros*)).tw.
53. conduct disorder*.tw.
54. cyclothymi*.tw.
55. ((defiant or disrupt* or oppositional) adj (behavio* or disorder*)).tw.
56. delusion*.tw.
57. dementia praecox.tw.
58. depress*.tw.
59. ((dis integrative or disintegrative or dys integrative or dysintegrative) adj disorder*).tw.
60. (dys somnia* or dyssomnia* or insomnia* or para somnia* or parasomnia*).tw.
61. dysthymi*.tw.
62. eating disorder*.tw.
63. ((emotion* or mood) adj2 (disorder* or dis regulation or disregulation or dys regulation or dysregulation)).tw.
64. (hoarder* or hoarding).tw.
65. (hyper activ* or hyperactiv*).tw.
66. hyperphagia*.tw.
67. irritab*.tw.
68. kleptomania*.tw.
69. (minimal brain adj (dis function* or disfunction* or dys function* or dysfunction*)).tw.
70. (mood adj2 (labil* or swing*)).tw.
71. (off label* or offlabel* or unlabeled indication* or unlabeled use*).tw.
72. (panic* adj (attack* or disorder*)).tw.
73. (para suicid* or parasuicid*).tw.
74. paranoi*.tw.
75. pervasive development* disorder*.tw.
76. ((post traumatic or posttraumatic) adj2 (disorder* or neuros*)).tw.
77. ((psycho* or sociopath*) adj (disorder* or personalit*)).tw.
78. psychos*.tw.
79. PTSD*.tw.
80. (rett* adj (syndrome* or disorder*)).tw.
81. (self adj (destruct* or harm* or injur* or mutilat*)).tw.

82. (schizo affect* or schizoaffect*).tw.
83. schizophreni*.tw.
84. shell shock*.tw.
85. (sleep adj2 (disorder* or dysfunction*)).tw.
86. stress disorder*.tw.
87. tourette*.tw.
88. tic disorder*.tw.
89. unstable mood*.tw.
90. violen*.tw.
91. or/1-90
92. abilify.mp.
93. adasuve.mp.
94. aldazine.mp.
95. anatensol.mp.
96. anti naus.mp.
97. (anti psychotic* or antipsychotic*).tw.
98. aripiprazole.mp.
99. arizole.mp.
100. asenapine.mp.
101. atrolak.mp.
102. biquelle.mp.
103. brexpiprazole.mp.
104. buccastem.mp.
105. calmazine.mp.
106. cariprazine.mp.
107. chloractil.mp.
108. chlorpromanyl.mp.
109. chlorpromazine.mp.
110. clopine.mp.
111. clozapine.mp.
112. clozaril.mp.
113. compazine.mp.
114. compro.mp.
115. decazate.mp.
116. delucon.mp.
117. denzapine.mp.
118. dozic.mp.
119. droleptan.mp.
120. droperidol.mp.
121. ebesque.mp.
122. fanapt.mp.
123. fazaclo.mp.
124. fazalco.mp.
125. fentazin.mp.
126. fluphenazine.mp.
127. fortunan.mp.

128. geodon.mp.
129. haldol.mp.
130. halo peridol.mp.
131. haloperidol.mp.
132. halperon.mp.
133. iloperidone.mp.
134. inapsine.mp.
135. invega.mp.
136. lanzek.mp.
137. largactil.mp.
138. latuda.mp.
139. loxapac.mp.
140. loxapine.mp.
141. loxitane.mp.
142. lurasidone.mp.
143. (major adj (tranquili?er* or tranquilli?er*)).tw.
144. mellaril*.mp.
145. melleril.mp.
146. mintreleq.mp.
147. moban.mp.
148. modecate.mp.
149. moditen.mp.
150. molindone.mp.
151. nausetil.mp.
152. navane.mp.
153. neuroleptic*.tw.
154. novo flurazine.mp.
155. novo peridol.mp.
156. novo ridazine.mp.
157. novo trifluzine.mp.
158. nu prochlor.mp.
159. olanzaccord.mp.
160. olanzapine.mp.
161. orap.mp.
162. ormazine.mp.
163. ozidal.mp.
164. ozin.mp.
165. paliperidone.mp.
166. permitil.mp.
167. perphenazine.mp.
168. pimozide.mp.
169. procalm.mp.
170. prochlorazine.mp.
171. prochlorperazine.mp.
172. procomp.mp.
173. prolixin.mp.

174. promapar.mp.
175. prorazin.mp.
176. protran.mp.
177. proziere.mp.
178. prozine.mp.
179. quetiapine.mp.
180. quetiaccord.mp.
181. quetin.mp.
182. resdone.mp.
183. rexulti.mp.
184. rideril.mp.
185. rispa.mp.
186. risperdal.mp.
187. risperidone.mp.
188. rispernia.mp.
189. rixadone.mp.
190. saphris.mp.
191. seotiapim.mp.
192. sequase.mp.
193. serenace.mp.
194. seronia.mp.
195. seroquel.mp.
196. solazine.mp.
197. sonazine.mp.
198. sondate.mp.
199. stelazine.mp.
200. stemetil.mp.
201. stemzine.mp.
202. sycrest.mp.
203. syquet.mp.
204. terfluzine.mp.
205. thioridazine.mp.
206. thiothixene.mp.
207. thorazine.mp.
208. tiotixene.mp.
209. trifluoperazine.mp.
210. trilafon.mp.
211. versacloz.mp.
212. vertigon.mp.
213. vraylar.mp.
214. xeplion.mp.
215. xomolix.mp.
216. xylac.mp.
217. zaluron.mp.
218. zaponex.mp.
219. zeldox.mp.

220. ziprasidone.mp.
221. zylap.mp.
222. zypadhera.mp.
223. zypine.mp.
224. zyprexa.mp.
225. or/92-224
226. and/91,225
227. adolescen*.mp.
228. (boy* or girl* or teen*).mp.
229. (child* or grade school* or kid or kids or kindergar?en* or minors* or preschool* or pre school* or school age* or schoolchild* or toddler*).mp.
230. (paediatric* or peadiatric* or pediatric*).mp.
231. (prepubescen* or pubescen* or pubert*).mp.
232. (young* adj (adult* or men or mens or people* or person* or women*)).mp.
233. (youth or youths).mp.
234. or/227-233
235. and/226,234
236. exp comparative study/
237. exp controlled study/
238. experimental study/
239. observational study/
240. dt.fs.
241. (case control or cohort* or follow up or followup or longitudinal or prospective* or retrospective).tw.
242. ((compari* or epidemiologic* or experimental or observational) adj2 (analy* or study or studies)).tw.
243. groups.ab.
244. placebo.ab.
245. random*.ab.
246. trial.ab.
247. or/236-246
248. animals/ not (animals/ and humans/)
249. 247 not 248
250. and/235,249
251. (conference* or editorial or letter).pt.
252. 250 not 251
253. limit 252 to english
254. limit 253 to yr="1987-current"

Ovid PsycINFO

Database: Ovid PsycINFO 1987 to October Week 2 2015
Search Title: Antipsychotics_Child_Update_2
Date Searched: 20 Oct 2015 (updated in April 2016)
Results: 2296

1. Adjustment Disorders/

2. exp Affective Disorders/
3. Aggressive Behavior/
4. Agitation/
5. Anxiety/
6. exp Anxiety Disorders/
7. exp Attention Deficit Disorder/
8. exp Behavior Disorders/
9. exp Behavior Problems/
10. Conduct Disorder/
11. exp Drug Usage/
12. exp Eating Disorders/
13. exp Impulse Control Disorders/
14. Impulsiveness/
15. Irritability/
16. Kleptomania/
17. Mental Disorders/
18. Movement Disorders/
19. Oppositional Defiant Disorder/
20. exp Pervasive Developmental Disorders/
21. Psychiatric Patients/
22. Psychiatric Symptoms/
23. exp Psychosis/
24. Schizoaffective Disorder/
25. exp Sleep Disorders/
26. Tics/
27. Tourette Syndrome/
28. Violence/
29. (ADHD* or (attention deficit adj2 disorder*) or hyperkinetic syndrome).tw.
30. ((adjustment or reactive) adj disorder*).tw.
31. (affective adj2 (disorder* or disregulation or dysregulation)).tw.
32. (aggressi* or agitat*).tw.
33. agoraphobi*.tw.
34. ((alcohol* or drug* or cannabi* or cocaine* or heroin or marijuana* or narcotic* or opiate* or opioid* or substance*) adj2 (abus* or addict* or depend* or disorder* or withdrawal*)).tw.
35. ((addicti* or compulsi* or explosive or impuls*) adj2 (behavio* or disorder*)).tw.
36. (((anankastic or compulsiv* or obsessive) adj (behavio* or disorder* or neuros* or personalit*)) or OCD).tw.
37. anorexi*.tw.
38. anxiety.tw.
39. (autis* or asperger* or kanner* syndrome).tw.
40. (behavio* adj2 (disorder* or disturb* or disrupt* or dyscontrol* or illness* or issue* or outburst* or problem*)).tw.
41. (((behavio* or disorder* or episod*) adj (hypomanic or manic)) or mania*).tw.
42. (binge adj (drink* or eat*)).tw.
43. (bi polar or bipolar).tw.
44. bulimi*.tw.

45. (claustrophobi* or phobia* or phobic).tw.
46. ((combat or war) adj (disorder* or neuros*)).tw.
47. conduct disorder*.tw.
48. cyclothymi*.tw.
49. ((defiant or disrupt* or oppositional) adj (behavio* or disorder*)).tw.
50. delusion*.tw.
51. dementia praecox.tw.
52. depress*.tw.
53. ((dis integrative or disintegrative or dys integrative or dysintegrative) adj disorder*).tw.
54. (dys somnia* or dyssomnia* or insomnia* or para somnia* or parasomnia*).tw.
55. dysthymi*.tw.
56. eating disorder*.tw.
57. ((emotion* or mood) adj2 (disorder* or dis regulation or disregulation or dys regulation or dysregulation)).tw.
58. (hoarder* or hoarding).tw.
59. (hyper activ* or hyperactiv*).tw.
60. hyperphagia*.tw.
61. irritab*.tw.
62. kleptomania*.tw.
63. (minimal brain adj (dis function* or disfunction* or dys function* or dysfunction*)).tw.
64. (mood adj2 (labil* or swing*)).tw.
65. (off label* or offlabel* or unlabeled indication* or unlabeled use*).tw.
66. (panic* adj (attack* or disorder*)).tw.
67. (para suicid* or parasuicid*).tw.
68. paranoi*.tw.
69. pervasive development* disorder*.tw.
70. ((post traumatic or posttraumatic) adj2 (disorder* or neuros*)).tw.
71. ((psycho* or sociopath*) adj (disorder* or personalit*)).tw.
72. psychos*.tw.
73. PTSD*.tw.
74. (rett* adj (syndrome* or disorder*)).tw.
75. (self adj (destruct* or harm* or injur* or mutilat*)).tw.
76. (schizo affect* or schizoaffect*).tw.
77. schizophreni*.tw.
78. shell shock*.tw.
79. (sleep adj2 (disorder* or dysfunction*)).tw.
80. stress disorder*.tw.
81. tourette*.tw.
82. tic disorder*.tw.
83. unstable mood*.tw.
84. violen*.tw.
85. or/1-84
86. Neuroleptic Drugs/
87. Phenothiazine Derivatives/
88. (abilify or adasuve or aldazine or anatensol or anti naus).mp.
89. (anti psychotic* or antipsychotic*).mp.

90. (aripiprazole or arizole or asenapine or atrolak or biquelle).mp.
91. (brexpiprazole or buccastem or calmazine or cariprazine or chloractil).mp.
92. (chlorpromanyl or chlorpromazine or clopine or clozapine or clozaril).mp.
93. (compazine or compro or decazate or delucon or denzapine).mp.
94. (dozic or droleptan or droperidol or ebesque or fanapt).mp.
95. (fazaclo or fazalco or fentazin or fluphenazine or fortunan).mp.
96. (geodon or haldol or halo peridol or haloperidol or halperon).mp.
97. (iloperidone or inapsine or invega or lanzek or largactil).mp.
98. (latuda or loxapac or loxapine or loxitane or lurasidone).mp.
99. (major adj (tranquili?er* or tranquilli?er*)).mp.
100. (mellaril* or melleril or mintreleq or moban or modecate).mp.
101. (moditen or molindone or nausetil or navane).mp.
102. neuroleptic*.mp.
103. (novo adj (flurazine or peridol or ridazine or trifluzine)).mp.
104. (nu prochlor or olanzaccord or olanzapine or orap or ormazine).mp.
105. (ozidal or ozin or paliperidone or permitil or perphenazine).mp.
106. (pimozide or procalm or prochlorazine or prochlorperazine or procomp).mp.
107. (prolixin or promapar or prorazin or protran or proziere).mp.
108. (prozine or quetiapine or quetiaccord or quetin or resdone).mp.
109. (rexulti or rideril or rispa or risperdal or risperidone).mp.
110. (rispernia or rixadone or saphris or seotiapim or sequase).mp.
111. (serenace or seronia or seroquel or solazine or sonazine).mp.
112. (sondate or stelazine or stemetil or stemzine or sycrest).mp.
113. (syquet or terfluzine or thioridazine or thiothixene or thorazine).mp.
114. (tiotixene or trifluoperazine or trilafon or versacloz or vertigon).mp.
115. (vraylar or xeplion or xomolix or xylac or zaluron).mp.
116. (zaponex or zeldox or ziprasidone or zylap or zypadhera).mp.
117. (zypine or zyprexa).mp.
118. or/86-117
119. and/85,118
120. Adolescent Psychiatry/
121. Child Psychiatry/
122. exp Elementary School Students/
123. High School Students/
124. Junior High School Students/
125. Kindergarten Students/
126. Pediatrics/
127. adolescen*.mp.
128. (boy* or girl* or teen*).mp.
129. (child* or grade school* or kid or kids or kindergar?en* or minors* or preschool* or pre school* or school age* or schoolchild* or toddler*).mp.
130. ((colleg* or high school* or highschool* or middle school* or universit*) adj2 (age* or student*)).mp.
131. (paediatric* or peadiatric* or pediatric*).mp.
132. (prepubescen* or pubescen* or pubert*).mp.
133. (young* adj (adult* or men or mens or people* or person* or women*)).mp.

134. (youth or youths).mp.
135. or/120-134
136. and/119,135
137. Drug Therapy/
138. exp Experimental Design/
139. Observation Methods/
140. Treatment Effectiveness Evaluation/
141. (case control or cohort* or follow up or followup or longitudinal or prospective* or retrospective).tw.
142. ((compari* or epidemiologic* or experimental or observational) adj2 (analy* or study or studies)).tw.
143. groups.ab.
144. placebo.ab.
145. random*.ab.
146. trial.ab.
147. or/137-146
148. exp animals/ not humans.sh.
149. 147 not 148
150. and/136,149
151. limit 150 to English

Dissertations and Theses International

Database: ProQuest Dissertations & Theses Global
Search Title: Antipsychotics_Child_Update
Date Searched: 22 Oct 2015
Results: 51

((su.Exact("addictions" OR "addictive behaviors" OR "alcohol use" OR "alcoholism" OR "anorexia" OR "attention deficit disorder" OR "autism" OR "behavioral psychology" OR "bipolar disorder" OR "bulimia" OR "drug abuse" OR "drug addiction" OR "drug use" OR "eating disorders" OR "emotional disorders" OR "fear & phobias" OR "hyperactivity" OR "insomnia" OR "mental depression" OR "mental disorders" OR "panic attacks" OR "post traumatic stress disorder" OR "schizophrenia" OR "sleep disorders" OR "tourette syndrome" OR "violence") OR AB,TI(((addicti* OR compulsi* OR explosive OR impuls*) NEAR/2 (behavio* OR disorder*)) OR ADHD* OR aggressi* OR agitat* OR ((alcohol* OR drug* OR substance*) NEAR/2 (abus* OR addict* OR depend* OR disorder* OR withdrawal*)) OR (((compulsiv* OR obsessive) NEAR/1 (behavio* OR disorder* OR personalit*)) OR OCD) OR anorexi* OR anxiety OR asperger* OR "attention deficit" OR autis*) OR AB,TI((behavio* NEAR/2 (disorder* OR disturb* OR disrupt* OR illness* OR problem*)) OR "bi polar" OR (binge NEAR/1 (drink* OR eat*)) OR bipolar OR bulimi* OR ((combat OR war) NEAR/1 disorder*) OR "conduct disorder*" OR cyclothymi* OR depress*) OR AB,TI("eating disorder*" OR ((emotion* OR mood) NEAR/2 disorder) OR hyperactiv* OR hyperphagia* OR insomnia* OR irritab* OR mania* OR "off label*" OR offlabel* OR (panic* NEAR/1 (attack* OR disorder*)) OR paranoi* OR "pervasive development* disorder*" OR phobia* OR phobic OR (("post traumatic" OR posttraumatic) NEAR/2 (disorder* OR neuros*)) OR psychos* OR PTSD*) OR AB,TI("reactive disorder*" OR schizophreni* OR (self NEAR/1 (destruct* OR harm* OR injur*

OR mutilat*)) OR "sleep disorder*" OR "stress disorder*" OR tourette* OR "tic disorder*" OR "unlabeled indication*" OR "unlabeled use*" OR "unstable mood*" OR violen*)) AND AB,TI("anti psychotic*" OR antipsychotic* OR aripiprazole OR asenapine OR chlorpromazine OR clozapine OR droperidol OR fluphenazine OR haloperidol OR iloperidone OR loxapine OR lurasidone OR (major NEAR/1 (tranquili?er* OR tranquilli?er*)) OR molindone OR neuroleptic* OR olanzapine OR paliperidone OR perphenazine OR pimozide OR prochlorperazine OR quetiapine OR risperidone OR thiothixene OR thioridazine OR trifluoperazine OR ziprasidone) AND ALL(adolescen* OR boy* OR child* OR girl* OR kid OR kids OR minors OR paediatric* OR pediatric* OR peadiatric* OR prepubescen* OR pubert* OR pubescen* OR "school age*" OR schoolchild* OR teen* OR (young NEAR/1 (adult* OR men OR mens OR people* OR person* OR women*)) OR youth OR youths)) NOT ALL("animal model*" OR cadaver OR nonhuman OR primate* OR rat OR rats OR zebrafish)

Additional limits - Date: From January 01 1987 to December 31 2015; Language: English

TOXLINE

Database: TOXLINE (Toxicology Literature Online) - http://toxnet.nlm.nih.gov/cgi-bin/sis/search2
Search Title: N/A
Date Searched: 22 Oct 2015
Results: 183

Advanced Search
Search Term: exact words
Records with: all the words
Search Fields: all fields
Do not – add chemical synonyms and CAS numbers to search
Do not – include PubMed records
No maximum number of results specified
Year of publication: 1987 through 2015
Language: English

1. (adjustment disorders [mh] OR anorexia [mh] OR anxiety [mh] OR anxiety disorders [mh] OR "Attention Deficit and Disruptive Behavior Disorders" [mh] OR behavioral symptoms [mh] OR child behavior disorders [mh] OR child development disorders, pervasive [mh] OR eating disorders [mh] OR hyperphagia [mh] OR impulse control disorders [mh] OR impulsive behavior [mh] OR irritable mood [mh] OR mental disorders [mh] OR mood disorders [mh] OR "off-label use" [mh] OR psychomotor agitation [mh] OR rett syndrome [mh] OR "schizophrenia and disorders with psychotic features" [mh] OR schizophrenia, childhood [mh] OR sleep disorders [mh] OR substance-related disorders [mh] OR tic disorders [mh] OR violence [mh])

2. (ADHD* [ab] OR "attention deficit" [ab] OR "adjustment disorder*" [ab] OR "affective disorder*" [ab] OR aggressi* [ab] OR agitat* [ab] OR "alcohol abuse" [ab] OR "alcohol addiction*" [ab] OR anorexi* [ab] OR anxiety [ab] OR autis* [ab] OR asperger* [ab] OR "bi polar" [ab] OR bipolar [ab] OR bulimi* [ab] OR "compulsive behavior*" [ab] OR "compulsive

behaviour*" [ab] OR "compulsive disorder*" [ab] OR depress* [ab] OR "disintegrative disorder" OR "drug abuse" [ab] OR "drug addiction*" [ab] OR "eating disorder*" [ab])

3. (hyperactiv* [ab] OR insomnia [ab] OR irritab* [ab] OR "minimal brain dysfunction" [ab] OR "off label" [ab] OR offlabel [ab] OR "panic attack*" [ab] OR "pervasive development disorder" [ab] OR "post traumatic" [ab] OR posttraumatic [ab] OR psychos* [ab] OR PTSD* [ab] OR "schizo affect*" [ab] OR schizoaffect* [ab] OR schizophreni* [ab] OR"self harm" [ab] OR "self injury" [ab] OR "self mutilation" [ab] OR "sleep disorder*" [ab] OR "stress disorder*" [ab] OR "substance abuse" [ab] OR "substance addiction" [ab] OR tourette* [ab] OR "tic disorder*" [ab] OR "unlabeled indication*" [ab] OR "unlabeled use*" [ab] OR violen* [ab])

4. #1 OR #2 OR #3

5. (antipsychotic agents [mh] OR butyrophenones [mh] OR phenothiazines [mh] OR thioxanthenes [mh] OR antipsychotic* OR aripiprazole OR asenapine OR chlorpromazine OR clozapine OR droperidol OR fluphenazine OR haloperidol OR iloperidone OR loxapine OR lurasidone OR molindone OR neuroleptic* OR olanzapine OR paliperidone OR perphenazine OR pimozide OR prochlorperazine OR quetiapine OR risperidone OR thiothixene OR thioridazine OR trifluoperazine OR ziprasidone)

6. #4 AND #5

7. (adolescent [mh] OR child [mh] OR pediatrics [mh] OR young adult [mh] OR adolescen* [ab] OR child* [ab] OR paediatric* [ab] OR pediatric* [ab] OR teen* [ab] OR "young adult*" [ab])

8. #6 AND #7

9. (animals [mh] OR bovine [ti] OR mice [ti] OR mouse [ti] OR nonhuman [ti] OR pig [ti] OR pigs [ti] OR porcine [ti] OR rabbit* [ti] OR rat [ti] OR rats [ti] OR zebrafish [ti])

10. #8 NOT #9

ClinicalTrials.gov

Registry: ClinicalTrials.gov - https://clinicaltrials.gov/
Search Title: N/A
Date Searched: 26 Oct 2015
Results: 1498

Advanced Search

(1.) First Received: From 01/01/1987 to 12/31/2015
Targeted Search –

Conditions by category > Behaviors and Mental Disorders

"Adjustment Disorders" OR "Affective Disorders, Psychotic" OR "Affective Symptoms" OR Aggression OR Agoraphobia OR "Alcohol Drinking" OR "Alcohol-Related Disorders" OR Alcoholism OR "Anorexia Nervosa" OR "Anxiety Disorders" OR "Asperger Syndrome"

Interventions >
antipsychotics OR "anti psychotics" OR aripiprazole OR asenapine OR brexpiprazole OR cariprazine OR chlorpromazine OR clozapine OR droperidol OR fluphenazine OR haloperidol OR iloperidone OR loxapine OR lurasidone OR molindone OR olanzapine

Age Group: Child (birth -17)
Results: 104

(2.) First Received: From 01/01/1987 to 12/31/2015
Targeted Search –

Conditions by category > Behaviors and Mental Disorders
"Adjustment Disorders" OR "Affective Disorders, Psychotic" OR "Affective Symptoms" OR Aggression OR Agoraphobia OR "Alcohol Drinking" OR "Alcohol-Related Disorders" OR Alcoholism OR "Anorexia Nervosa" OR "Anxiety Disorders" OR "Asperger Syndrome"

Interventions>
paliperidone OR perphenazine OR pimozide OR prochlorperazine OR quetiapine OR risperidone OR thiothixene OR thioridazine OR trifluoperazine OR ziprasidone

Age Group: Child (birth -17)
Results: 51

(3.) First Received: From 01/01/1987 to 12/31/2015
Targeted Search –

Conditions by category > Behaviors and Mental Disorders
"Attention Deficit Disorder with Hyperactivity" OR "Attention Deficit and Disruptive Behavior Disorders" OR "Autistic Disorder" OR "Behavior, Addictive" OR " Behavioral Symptoms" OR "Binge Drinking" OR "Bipolar Disorder" OR " Bulimia Nervosa"

Interventions >
antipsychotics OR "anti psychotics" OR aripiprazole OR asenapine OR brexpiprazole OR cariprazine OR chlorpromazine OR clozapine OR droperidol OR fluphenazine OR haloperidol OR iloperidone OR loxapine OR lurasidone OR molindone OR olanzapine

Age Group: Child (birth -17)
Results: 144

(4.) First Received: From 01/01/1987 to 12/31/2015
Targeted Search –

Conditions by category > Behaviors and Mental Disorders
"Attention Deficit Disorder with Hyperactivity" OR "Attention Deficit and Disruptive Behavior Disorders" OR "Autistic Disorder" OR "Behavior, Addictive" OR " Behavioral Symptoms" OR "Binge Drinking" OR "Bipolar Disorder" OR " Bulimia Nervosa"

Interventions >
paliperidone OR perphenazine OR pimozide OR prochlorperazine OR quetiapine OR risperidone OR thiothixene OR thioridazine OR trifluoperazine OR ziprasidone

Age Group: Child (birth -17)
Results: 68

(5.) First Received: From 01/01/1987 to 12/31/2015
Targeted Search –

Conditions by category > Behaviors and Mental Disorders
"Child Behavior Disorders" OR " Child Development Disorders, Pervasive" OR " Cocaine-Related Disorders" OR " Combat Disorders" OR "Compulsive Behavior" OR "Conduct Disorder" OR "Cyclothymic Disorder" OR Depression OR "Depressive Disorder"

Interventions >
antipsychotics OR "anti psychotics" OR aripiprazole OR asenapine OR brexpiprazole OR cariprazine OR chlorpromazine OR clozapine OR droperidol OR fluphenazine OR haloperidol OR iloperidone OR loxapine OR lurasidone OR molindone OR olanzapine

Age Group: Child (birth -17)
Results: 66

(6.) First Received: From 01/01/1987 to 12/31/2015
Targeted Search –

Conditions by category > Behaviors and Mental Disorders
"Child Behavior Disorders" OR " Child Development Disorders, Pervasive" OR " Cocaine-Related Disorders" OR " Combat Disorders" OR "Compulsive Behavior" OR "Conduct Disorder" OR "Cyclothymic Disorder" OR Depression OR "Depressive Disorder"

Interventions >
paliperidone OR perphenazine OR pimozide OR prochlorperazine OR quetiapine OR risperidone OR thiothixene OR thioridazine OR trifluoperazine OR ziprasidone

Age Group: Child (birth -17)
Results: 31

(7.) First Received: From 01/01/1987 to 12/31/2015
Targeted Search –

Conditions by category > Behaviors and Mental Disorders
"Depressive Disorder, Major" OR " Depressive Disorder, Treatment-Resistant" OR "Dissociative Disorders" OR "Drinking Behavior" OR "Drug-Seeking Behavior" OR Dyssomnias OR "Dysthymic Disorder" OR "Eating Disorders"

Interventions >
antipsychotics OR "anti psychotics" OR aripiprazole OR asenapine OR brexpiprazole OR cariprazine OR chlorpromazine OR clozapine OR droperidol OR fluphenazine OR haloperidol OR iloperidone OR loxapine OR lurasidone OR molindone OR olanzapine

Age Group: Child (birth -17)
Results: 17

(8.) First Received: From 01/01/1987 to 12/31/2015
Targeted Search –

Conditions by category > Behaviors and Mental Disorders
"Depressive Disorder, Major" OR " Depressive Disorder, Treatment-Resistant" OR "Dissociative Disorders" OR "Drinking Behavior" OR "Drug-Seeking Behavior" OR Dyssomnias OR "Dysthymic Disorder" OR "Eating Disorders"

Interventions >
paliperidone OR perphenazine OR pimozide OR prochlorperazine OR quetiapine OR risperidone OR thiothixene OR thioridazine OR trifluoperazine OR ziprasidone

Age Group: Child (birth -17)
Results: 5

(9.) First Received: From 01/01/1987 to 12/31/2015
Targeted Search –

Conditions by category > Behaviors and Mental Disorders
"Feeding and Eating Disorders of Childhood" OR "Heroin Dependence" OR "Impulse Control Disorders" OR "Impulsive Behavior" OR "Marijuana Abuse" OR "Mental Disorders" OR "Mental Disorders Diagnosed in Childhood" OR "Mood Disorders"

Interventions >
antipsychotics OR "anti psychotics" OR aripiprazole OR asenapine OR brexpiprazole OR cariprazine OR chlorpromazine OR clozapine OR droperidol OR fluphenazine OR haloperidol OR iloperidone OR loxapine OR lurasidone OR molindone OR olanzapine

Age Group: Child (birth -17)
Results: 272

(10.) First Received: From 01/01/1987 to 12/31/2015

Targeted Search –

Conditions by category > Behaviors and Mental Disorders
"Feeding and Eating Disorders of Childhood" OR "Heroin Dependence" OR "Impulse Control Disorders" OR "Impulsive Behavior" OR "Marijuana Abuse" OR "Mental Disorders" OR "Mental Disorders Diagnosed in Childhood" OR "Mood Disorders"

Interventions >
paliperidone OR perphenazine OR pimozide OR prochlorperazine OR quetiapine OR risperidone OR thiothixene OR thioridazine OR trifluoperazine OR ziprasidone

Age Group: Child (birth -17)
Results: 130

(11.) First Received: From 01/01/1987 to 12/31/2015
Targeted Search –

Conditions by category > Behaviors and Mental Disorders
"Obsessive-Compulsive Disorder" OR "Opioid-Related Disorders" OR "Panic Disorder" OR Parasomnias OR "Phobic Disorders" OR "Psychomotor Agitation" OR "Psychotic Disorders" OR Schizophrenia OR "Schizophrenia and Disorders with Psychotic Features"

Interventions >
antipsychotics OR "anti psychotics" OR aripiprazole OR asenapine OR brexpiprazole OR cariprazine OR chlorpromazine OR clozapine OR droperidol OR fluphenazine OR haloperidol OR iloperidone OR loxapine OR lurasidone OR molindone OR olanzapine

Age Group: Child (birth -17)
Results: 279

(12.) First Received: From 01/01/1987 to 12/31/2015
Targeted Search –

Conditions by category > Behaviors and Mental Disorders
"Obsessive-Compulsive Disorder" OR "Opioid-Related Disorders" OR "Panic Disorder" OR Parasomnias OR "Phobic Disorders" OR "Psychomotor Agitation" OR "Psychotic Disorders" OR Schizophrenia OR "Schizophrenia and Disorders with Psychotic Features"

Interventions >
paliperidone OR perphenazine OR pimozide OR prochlorperazine OR quetiapine OR risperidone OR thiothixene OR thioridazine OR trifluoperazine OR ziprasidone

Age Group: Child (birth -17)
Results: 133

(13.) First Received: From 01/01/1987 to 12/31/2015

Targeted Search –

Conditions by category > Behaviors and Mental Disorders
"Schizophrenia and Disorders with Psychotic Features" OR "Schizophrenia, Childhood" OR "Schizophrenia, Disorganized" OR "Schizophrenia, Paranoid" OR "Schizotypal Personality Disorder" OR "Self Mutilation" OR "Self-Injurious Behavior"

Interventions >
antipsychotics OR "anti psychotics" OR aripiprazole OR asenapine OR brexpiprazole OR cariprazine OR chlorpromazine OR clozapine OR droperidol OR fluphenazine OR haloperidol OR iloperidone OR loxapine OR lurasidone OR molindone OR olanzapine

Age Group: Child (birth -17)
Results: 118

(14.) First Received: From 01/01/1987 to 12/31/2015
Targeted Search –

Conditions by category > Behaviors and Mental Disorders
"Schizophrenia and Disorders with Psychotic Features" OR "Schizophrenia, Childhood" OR "Schizophrenia, Disorganized" OR "Schizophrenia, Paranoid" OR "Schizotypal Personality Disorder" OR "Self Mutilation" OR "Self-Injurious Behavior"

Interventions >
paliperidone OR perphenazine OR pimozide OR prochlorperazine OR quetiapine OR risperidone OR thiothixene OR thioridazine OR trifluoperazine OR ziprasidone

Age Group: Child (birth -17)
Results: 53

(15.) First Received: From 01/01/1987 to 12/31/2015
Targeted Search –

Conditions by category > Behaviors and Mental Disorders
"Sleep Disorders" OR "Stress Disorders, Post-Traumatic" OR "Stress Disorders, Traumatic" OR "Stress Disorders, Traumatic, Acute" OR "Substance-Related Disorders" OR "Suicidal Ideation" OR "Tic Disorders" OR "Tourette Syndrome"

Interventions >
antipsychotics OR "anti psychotics" OR aripiprazole OR asenapine OR brexpiprazole OR cariprazine OR chlorpromazine OR clozapine OR droperidol OR fluphenazine OR haloperidol OR iloperidone OR loxapine OR lurasidone OR molindone OR olanzapine

Age Group: Child (birth -17)
Results: 22

(16.) First Received: From 01/01/1987 to 12/31/2015
Targeted Search –

Conditions by category > Behaviors and Mental Disorders
"Sleep Disorders" OR "Stress Disorders, Post-Traumatic" OR "Stress Disorders, Traumatic" OR "Stress Disorders, Traumatic, Acute" OR "Substance-Related Disorders" OR "Suicidal Ideation" OR "Tic Disorders" OR "Tourette Syndrome"

Interventions >
paliperidone OR perphenazine OR pimozide OR prochlorperazine OR quetiapine OR risperidone OR thiothixene OR thioridazine OR trifluoperazine OR ziprasidone

Age Group: Child (birth -17)
Results: 5

Total records downloaded: 1498
Total unique records: 295

WHO ICTRP

Registry: WHO International Clinical Trials Registry Platform
Search Title: N/A
Date Searched: 27 Oct 2015
Results: 317

Advanced Search
(1.)
Search for clinical trials in children (0-18)
Recruitment status is: ALL
Intervention >
antipsychotics OR aripiprazole OR asenapine OR brexpiprazole OR cariprazine OR chlorpromazine OR clozapine OR droperidol OR fluphenazine OR haloperidol OR iloperidone OR loxapine OR lurasidone OR molindone OR olanzapine
Results: 153

(2.)
Search for clinical trials in children (0-18)
Recruitment status is: ALL
Intervention >
paliperidone OR perphenazine OR pimozide OR prochlorperazine OR quetiapine OR risperidone OR thiothixene OR thioridazine OR trifluoperazine OR ziprasidone
Results: 164

Appendix C. Quality Assessment Ratings

References for Appendix C found at the end of Appendix D.

Table C1. Risk of bias assessments for trials

Author, Year	Sequence Generation	Allocation Concealment	Blinding-PP (Subjective)	Blinding-PP (Objective)	Blinding-OA (Subjective)	Blinding-OA (Objective)	Incomplete Outcome (Subjective)	Incomplete Outcome (Objective)	Other Sources of Bias	Overall (Subjective)	Overall (Objective)
Aman et al., 1991 [1]	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Unclear	Unclear
Aman et al., 2002 [2]	Yes	Unclear	Yes	Yes	N/A	Unclear	No	No	Yes	High	High
Aman et al., 2009 [3]	Yes	Unclear	Yes	Yes	N/A	N/A	Yes	Yes	Yes	Unclear	Unclear
Aman et al., 2014 [4]	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
Anderson et al., 1989 [5]	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes	Unclear	High	Unclear
Arango et al., 2009 [6]	Unclear	Unclear	No	No	No	No	No	No	Yes	High	High
Armenteros et al., 2007 [7]	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear
Berger et al., 2008 [8]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low
Biederman et al., 2005 [9]	Unclear	Unclear	No	No	Unclear	Unclear	No	No	Yes	High	High
Bruggeman et al., 2001 [10]	Yes	Unclear	NA	Yes	NA	Unclear	NA	Yes	Yes	NA	Unclear
Buchsbaum et al., 2007 [11]	Unclear	Unclear	Unclear	NA	Unclear	NA	Unclear	NA	Yes	Unclear	NA
Buitelaar et al., 2001 [12]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
Connor et al., 2008 [13]	Unclear	Yes	Yes	Yes	NA	Yes	No	No	Yes	High	High

Author, Year	Sequence Generation	Allocation Concealment	Blinding-PP (Subjective)	Blinding-PP (Objective)	Blinding-OA (Subjective)	Blinding-OA (Objective)	Incomplete Outcome (Subjective)	Incomplete Outcome (Objective)	Other Sources of Bias	Overall (Subjective)	Overall (Objective)
Conus et al., 2015 [14]	Yes	Unclear	No	No	Yes	Unclear	No	No	Yes	High	High
Crocq et al., 2007 [15]	No	No	NA	Yes	NA	Yes	NA	Unclear	Unclear	NA	High
de Haan et al., 2003 [16]	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	No	No	Yes	High	High
DelBello et al., 2002 [17]	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear
DelBello et al., 2008 [18]	Unclear	Unclear	No	Unclear	Unclear	Unclear	No	No	Yes	High	High
DelBello et al., 2009 [19]	Yes	Yes	Unclear	Unclear	Unclear	Unclear	No	No	Yes	High	High
Findling et al., 2000 [20]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	High	High
Findling et al., 2008a [21]	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear
Findling et al., 2009 [22]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
Findling et al., 2012a [23]	Yes	Unclear	Yes	Yes	Yes	Yes	No	No	No	High	High
Findling et al., 2012b [24]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No	No	No	High	High
Findling et al., 2013a [25]	Unclear	Unclear	Unclear	Yes	Unclear	Yes	No	No	Unclear	High	High
Findling et al., 2013b [26]	Unclear	Unclear	Unclear	Yes	Unclear	Yes	No	No	Unclear	High	High
Findling et al., 2014a [27]	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	No	No	Yes	High	High

Author, Year	Sequence Generation	Allocation Concealment	Blinding-PP (Subjective)	Blinding-PP (Objective)	Blinding-OA (Subjective)	Blinding-OA (Objective)	Incomplete Outcome (Subjective)	Incomplete Outcome (Objective)	Other Sources of Bias	Overall (Subjective)	Overall (Objective)
Findling et al., 2014b [28]	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	No	No	Yes	High	High
Findling et al., 2015a [29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low
Findling et al., 2015b [30]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low
Findling et al., 2015 [31]	Yes	Unclear	NA	No	NA	No	NA	Unclear	Yes	NA	High
Ghanizadeh et al., 2014a [32]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
Ghanizadeh et al., 2014b [33]	Yes	Unclear	Unclear	Yes	Yes	Yes	No	No	Unclear	High	High
Gilbert et al., 2004 [34]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	High	High
Gulisano et al., 2011 [35]	Unclear	Unclear	NA	Yes	NA	Yes	NA	Yes	Yes	NA	Unclear
Haas et al., 2009a [36]	Yes	Unclear	Unclear	Yes	Unclear	Yes	No	No	Yes	High	High
Haas et al., 2009b [37]	Yes	Unclear	Unclear	N/A	Unclear	Yes	No	No	Yes	High	High
Haas et al., 2009c [38]	Unclear	Unclear	Unclear	Yes	Unclear	Yes	No	No	Yes	High	High
Hagman et al., 2011 [39]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
Hellings et al., 2006 [40]	Unclear	Yes	Unclear	Yes	Unclear	Yes	No	No	No	High	High
Hollander et al., 2006 [41]	Unclear	Unclear	Unclear	Yes	Unclear	Yes	No	No	Yes	High	High

Author, Year	Sequence Generation	Allocation Concealment	Blinding-PP (Subjective)	Blinding-PP (Objective)	Blinding-OA (Subjective)	Blinding-OA (Objective)	Incomplete Outcome (Subjective)	Incomplete Outcome (Objective)	Other Sources of Bias	Overall (Subjective)	Overall (Objective)
Jensen et al., 2008 [42]	Yes	Unclear	No	Yes	No	Yes	No	No	Yes	High	High
Johnson & Johnson, 2011 [43]	Unclear	Unclear	No	No	No	No	Yes	Yes	Yes	High	High
Kafantaris et al., 2011 [44]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
Kent et al., 2013 [45]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
Kowatch et al., 2015 [46]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear
Kryzhanovskaya et al., 2009 [47]	Unclear	Unclear	Unclear	Yes	Unclear	Yes	No	No	Yes	High	High
Kumra et al., 1996 [48]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	High	High
Kumra et al., 2008 [49]	Yes	Yes	Unclear	Yes	Unclear	Yes	No	No	Yes	High	High
Loebel et al., 2016 [50]	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear
Luby et al., 2006 [51]	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Low
Malone et al., 2001 [52]	Yes	Unclear	No	Yes	No	Yes	Yes	Yes	Yes	High	Unclear
Marcus et al., 2009 [53]	Yes	Yes	Unclear	Yes	Unclear	Yes	No	No	Yes	High	High
Masi et al., 2013 [54]	Unclear	No	No	Yes	No	Yes	Yes	Yes	Yes	High	Unclear
Masi et al., 2015 [55]	Unclear	Unclear	No	No	No	No	Yes	Yes	Yes	High	High

Author, Year	Sequence Generation	Allocation Concealment	Blinding-PP (Subjective)	Blinding-PP (Objective)	Blinding-OA (Subjective)	Blinding-OA (Objective)	Incomplete Outcome (Subjective)	Incomplete Outcome (Objective)	Other Sources of Bias	Overall (Subjective)	Overall (Objective)
McCracken et al., 2002 [56]	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
McGorry et al., 2013 [57]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	High	High
Miral et al., 2008 [58]	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Unclear
Mozes et al., 2006 [59]	Unclear	Unclear	No	Yes	No	Yes	No	No	Yes	High	High
Nagaraj et al., 2006 [60]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low
NCT00194012, 2013 [61]	Unclear	Unclear	Yes	Yes	Yes	Yes	No	No	Yes	High	High
NCT01149655, 2014 [62]	Unclear	Unclear	Yes	Yes	Yes	Yes	No	No	No	High	High
Omranifard et al., 2013 [63]	Unclear	Unclear	No	NA	No	NA	Yes	NA	Yes	High	NA
Owen et al., 2009 [64]	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Low
Pathak et al., 2013 [65]	Yes	Yes	Yes	Yes	Unclear	Unclear	No	No	Yes	High	High
Perry et al., 1989 [66]	Unclear	Unclear	Yes	Yes	Yes	Yes	No	No	Yes	High	High
Remington et al., 2001 [67]	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No	High	High
Reyes et al., 2006 [68]	Unclear	Unclear	Yes	Yes	Yes	Yes	No	No	Yes	High	High
Rizzo et al., 2012 [69]	No	No	No	Yes	No	Yes	Yes	Yes	Yes	High	High

Author, Year	Sequence Generation	Allocation Concealment	Blinding-PP (Subjective)	Blinding-PP (Objective)	Blinding-OA (Subjective)	Blinding-OA (Objective)	Incomplete Outcome (Subjective)	Incomplete Outcome (Objective)	Other Sources of Bias	Overall (Subjective)	Overall (Objective)
RUPP et al., 2005 [70]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear
Sallee et al., 1994 [71]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Sallee et al., 1997 [72]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	High	High
Sallee et al., 2000 [73]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear
Savitz et al., 2015 [74]	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Unclear
Scahill et al., 2003 [75]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
Schneider et al., 2012 [76]	Unclear	Unclear	Unclear	Yes	Unclear	Yes	No	No	No	High	High
Sehgal et al., 1999 [77]	Unclear	Yes	Yes	NA	Yes	NA	Yes	NA	Yes	Unclear	NA
Shaw et al., 2006 [78]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear
Shea et al., 2004 [79]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear
Sikich et al., 2004 [80]	Yes	Unclear	Yes	NA	Yes	NA	No	No	Yes	High	High
Sikich et al., 2008 [81]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low
Singh et al., 2011 [82]	Unclear	Unclear	No	Yes	No	Yes	Yes	Yes	Yes	High	Unclear
Snyder et al., 2002 [83]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	High	High

Author, Year	Sequence Generation	Allocation Concealment	Blinding-PP (Subjective)	Blinding-PP (Objective)	Blinding-OA (Subjective)	Blinding-OA (Objective)	Incomplete Outcome (Subjective)	Incomplete Outcome (Objective)	Other Sources of Bias	Overall (Subjective)	Overall (Objective)
Spencer et al., 1994 [84]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear
Stocks et al., 2012 [85]	Unclear	Unclear	Unclear	Yes	Unclear	Yes	No	No	Yes	High	High
Swadi et al., 2010 [86]	Yes	Unclear	No	Yes	No	Yes	No	No	Yes	High	High
Tohen et al., 2007 [87]	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Unclear
Tramontina et al., 2009 [88]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low
Troost et al., 2005 [89]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low
Van Bellinghen et al., 2001 [90]	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Unclear
Van Bruggen et al., 2003 [91]	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	No	High	High
Woods et al., 2003 [92]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	High	High
Yen et al., 2004 [93]	Unclear	Unclear	Unclear	Yes	Unclear	Yes	No	No	Yes	High	High
Yoo et al., 2011 [94]	No	No	No	Yes	No	Yes	No	No	Yes	High	High
Yoo et al., 2013 [95]	Yes	Unclear	Yes	Yes	Yes	Yes	No	No	Yes	High	High

Blinding of OA = blinding of outcome assessors; Blinding of PP = blinding of participants and personnel; NA = not applicable

Table C2. Quality assessment ratings for observational studies using Newcastle-Ottawa Scale

Author, Year Study Design	Selection 1	Selection 2	Selection 3	Comparability	Outcome 1	Outcome 2	Outcome 3	Total Stars
Alacqua et al., 2008 [96] RCS	B	A	A	C	B	A	A	6
Aman et al., 2004 [97] PCS	A	A	B	A and B	A	A	C	7
Arango et al., 2014 [98] PCS	A	A	C	A and B	D	A	C	5
Bastiaens et al., 2009 [99] RCS	B	A	A	A and B	E	A	C	6
Bobo et al., 2013 [100] RCS	A	A	A	A and B	A	A	A	8
Calarge et al., 2014 [101] PCS	D	A	A	A	B	A	C	5
Castro-Fornieles et al., 2008 [102] PCS	A	A	B	A and B	D	A	C	6
Cianchetti et al., 2011 [103] PCS	A	A	B	C	D	A	B	5
Correll et al., 2009 [104] PCS	A	A	A	A and B	B	A	A	8
Cuerda et al., 2011 [105] PCS	A	A	D	A	B	A	C	6
Ebert et al., 2014 [106] RCS	A	A	A	C	D	A	A	5
Findling et al., 2008b [107] PCS	B	A	A	C	C	A	B	5
Fleischhaker et al., 2006 [108] PCS	D	C	B	C	E	A	A	3
Fraguas et al., 2008 [109] PCS	A	A	A	A and B	D	A	C	6

Author, Year Study Design	Selection 1	Selection 2	Selection 3	Comparability	Outcome 1	Outcome 2	Outcome 3	Total Stars
Friedlander et al., 2001 [110] RCS	C	A	A	C	E	A	A	4
Germano et al., 2014 [111] PCS	A	A	A	C	D	A	B	5
Gothelf et al., 2002 [112] PCS	C	C	A	C	B	A	D	3
Hrdlicka et al., 2009 [113] RCS	A	A	A	C	B	A	C	5
Jerrell et al., 2008 [114] RCS	A	A	A	C	B	A	A	6
Khan et al., 2009 [115] RCS	A	A	A	C	B	A	A	6
Khan et al., 2006 [116] RCS	D	C	A	C	B	A	A	4
Kumra et al., 1998 [117] PCS	B	A	B	C	E	A	A	5
Mankoski et al., 2013 [118] PCS	A	A	D	A and B	D	A	A	6
Martin et al., 2000 [119] PCS	A	A	A	C	B	A	A	6
Migliardi et al., 2009 [120] RCS	B	A	A	B	B	A	A	7
NCT00619190, 2013 [121] PCS	A	C	B	C	D	A	B	4
Norris et al., 2011 [122] RCS	A	A	A	A and B	B	A	A	7
Novaes et al., 2008 [123] RCS	A	A	A	A and B	B	A	A	8
O'Donoghue et al., 2014 [124] PCS	A	A	D	C	D	A	C	3

Author, Year Study Design	Selection 1	Selection 2	Selection 3	Comparability	Outcome 1	Outcome 2	Outcome 3	Total Stars
Oh et al., 2013 [125] PCS	A	A	A	B	B	A	C	6
Olfson et al., 2012 [126] RCS	A	A	A	A	B	A	A	7
Pandina et al., 2007 [127] PCS	A	A	D	A and B	D	A	A	6
Pogge et al., 2005 [128] RCS	A	A	A	C	A	A	A	6
Ratzoni et al., 2002 [129] PCS	D	C	B	C	E	A	A	3
Ronsley et al., 2015 [130] PCS	A	A	D	A	D	A	C	4
Saito et al., 2004 [131] PCS	B	A	A	B	D	A	A	6
Weisler et al., 2011 [132] RCS	A	A	A	A and B	D	A	B	6
Wink et al., 2014 [133] RCS	A	A	A	B	B	A	A	7
Wonodi et al., 2007 [134] RCS	A	A	A	A and B	A	A	A	8
Wudarsky et al., 1999 [135] PCS	A	A	A	A	A	A	A	7

PCS = prospective cohort study; RCS = retrospective cohort study

Appendix D. Study Characteristics

Table D1. Study characteristics

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Alacqua et al., 2008 [96] **Country:** Italy **Condition category:** Mixed conditions (ADHD, ASD, schizophrenia-related, tics) **Funding:** NR **Newcastle-Ottawa Scale:** 6/8 stars	**Recruitment dates:** Jan 2002 to Dec 2003 **Study design:** Retrospective cohort **Diagnostic criteria:** DSM-IV **Setting:** Outpatient/community **Inclusion criteria:** (1) ≤18 yr, (2) received an incident treatment with atypical antipsychotics or SSRIs during the study period **Exclusion criteria:** NR	**Enrolled:** 73 **Analyzed:** 73 **Completed:** 50 **GROUP 1** **N:** 2 **Age, mean±SD (range):** 15.5±0.7 **Males %:** 50 **Caucasian %:** NR **Diagnostic breakdown (n):** psychosis (1), schizophrenia (1) **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 2** **N:** 24 **Age, mean±SD (range):** 14.7±2.3 **Males %:** 42 **Caucasian %:** NR **Diagnostic breakdown (n):** affective disorder (2), anxiety disease (4), autism (1), CD (1), MR (3), personality disorder (2), psychosis (9), schizophrenia (2) **Treatment naïve (n):** all **Inpatients (n):** NR	**Treatment duration:** 3 mo **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Clozapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 150±70.1 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 7.1±4.4 **Concurrent treatments:** NR **GROUP 3** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 375±318.2 **Concurrent treatments:** NR **GROUP 4** **Drug name:** Risperidone **Dosing variability:** variable	**Benefits:** NR **Harms:** Behavioral issues, dyskinesia, dystonia, dermatologic AE, liver function, hepatic volume, prolactin, prolactin-related AE, sedation, sleepness, total AE, weight change	Adverse events occurred frequently during first 3 months of treatment with atypical antipsychotics.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		First episode psychosis (n): NR **Comorbidities:** NR **GROUP 3** **N:** 2 **Age, mean±SD (range):** 16.5±1.5 **Males %:** 100 **Caucasian %:** NR **Diagnostic breakdown (n):** psychosis (2) **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 4** **N:** 45 **Age, mean±SD (range):** 13±3.9 **Males %:** 80 **Caucasian %:** NR **Diagnostic breakdown (n):** ADHD (1), anxiety disease (2), autism (14), CD (7), conversion disorder (2), MR (8), psychosis (7), schizophrenia (2), tic disorder (2) **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR	**Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2±1.3 **Concurrent treatments:** NR		
Aman et al., 2014 [4] **Country:** USA	**Recruitment dates:** August 2008 – November 2012	**Enrolled:** 168 **Analyzed:** 168 **Completed:** 137	**Treatment duration:** 6 wk **Run-in phase:** Yes	**Benefits:** NCBRF, ABS, CGI-I, CGI-S, response	Risperidone provided moderate but variable improvement in

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Condition category: ADHD **Funding:** Non-industry **Risk of bias:** Medium (subjective), Medium (objective)	**Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-IV **Inclusion criteria:** 6-12 yr, DSM-IV diagnosis of DBD (CD or ODD) or ADHD, serious physical aggression (Overt Aggression Scale – M ≥3), evidence of seriously disruptive behavior (parent rating NCBRF D-Total ≥ 27, CGI-S ≥ 4 by blinded clinician **Exclusion criteria:** IQ < 71, pregnancy, history of seizure disorder or neurological or medical disorder, abnormal liver function, PDD, schizophrenia or other psychotic disorders, ED, hypomanic/biphasic score ≥ 36 on GBI (mood disorder), current or previous major depressive disorder or diagnosis of bipolar disorder, current use of psychotropic	**GROUP 1** **N:** 84 **Age, mean±SD (range):** 9.03±2.05 yr **Males %:** 77.4% **Caucasian %:** 57.1% **Diagnostic breakdown (n):** ADHD (84) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** CD (22), ODD (62) **GROUP 2** **N:** 84 **Age, mean±SD (range):** 8.75±1.98 yr **Males %:** 76.2% **Caucasian %:** 48.8% **Diagnostic breakdown (n):** ADHD (84) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** CD (22), ODD (62)	**Run-in phase duration:** 2 wk most drugs, 4 wk antipsychotics and fluoxetine **Permitted drugs:** methylphenidate **Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone **Dosing variability:** Variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.7±0.75 mg/day **Concurrent treatments:** Methylphenidate, parent training (PT) **GROUP 2** **Drug name:** Placebo **Dosing variability:** Variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.9±0.72 mg/day **Concurrent treatments:** Methylphenidate, parent training (PT)	**Harms:** metabolic effects, prolactin effects, sedation and sleep issues, GI, headache	aggressive and other seriously disruptive child behaviors when added to PT and optimized stimulant treatment.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	medications where discontinuation would be a significant risk, active substance use disorder, current child abuse or neglect, history of suicide attempt (past year) or current suicidal ideation, family history type 2 diabetes in ≥ 2 first-degree relatives				
Aman et al., 2009 [3] **Country:** USA **Condition category:** ADHD **Funding:** NR **Risk of bias:** Medium (subjective), Medium (objective)	**Recruitment dates:** NR **Study design:** RCT (crossover) **Diagnostic criteria:** DSM-IV, IQ test (Stanford-Binet, Weschsler Intelligence, Kaufman Brief) **Setting:** Inpatient and outpatient **Inclusion criteria:** (1) 4–14 yr, (2) IQ ≤84, (3) ODD or CD, (4) dx of austistic or PDD NOS, (5) availability of a reliable informant, (6) good physical health **Exclusion criteria:** (1) presence of psychosis, (2) history of NMS, (3) history of severe drug allergy/hypersensitivity,	**Enrolled:** 16 **Analyzed:** 15 **Completed:** NR **GROUP 1** **N:** 16 (crossover) **Age, mean±SD (range):** 8.56±2.6 yr **Males %:** 87.5% **Caucasian %:** 81.2% **Diagnostic breakdown (n):** ADHD (1), ADHD + CD (2), ADHD + ODD (6), CD (1), ODD (3), ASD (3) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** Borderline intellectual disability (10), mild intellectual disability (4), moderate intellectual disability (1) **GROUP 2** **N:** 16 (crossover)	**Treatment duration:** 4 wk **Run-in phase:** Yes **Run-in phase duration:** 1 wk **Permitted drugs: c**lonidine, lithium **Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.65±1.3 (0.4–5) **Concurrent treatments:** psychostimulants (5) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Benefits:** ABC, NCBRF Cognitive (MTS, STRM, CPT, GHT) **Harms:** Dyskinesia, SBP, DBP, pulse	Risperidone may have a beneficial effect on efficiency or responding, activity level, static tremor, and aspects of behavior.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	(4) medical disease, (5) pregnancy	**Age, mean±SD (range):** See group 1 **Males %:** See group 1 **Caucasian %:** See group 1 **Diagnostic breakdown (n):** See group 1 **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** See group 1			
Aman et al., 2004 [97] (see Aman 2002, Snyder 2002) **Country:** Canada, South Africa, USA **Condition category:** ADHD **Funding:** NR **Newcastle-Ottawa Scale:** 7/8 stars	**Study design:** Observational (pooled analysis)	**Enrolled:** NA **Analyzed:** 155 **Completed:** NA **GROUP 1** **N:** 43 **Age, mean±SD (range):** 8.6±2.1 yr **Males %:** 81.4% **Caucasian %:** 55.8% **Diagnostic breakdown (n):** CD, ODD, or DBD-NOS with ADHD (43) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** All have ADHD **GROUP 2** **N:** 35 **Age, mean±SD (range):** 9.0±1.7 yr **Males %:** 85.7% **Caucasian %:** 65.7%	**GROUP 1** **Drug name:** Risperidone (only) **Dosing variability:** Variable **Target dose (mg/day):** 0.06 mg/kg/day **Daily dose (mg/day), mean±SD (range):** 1.11 mg/day **Concurrent treatments:** See Aman 2002 and Snyder 2002 **GROUP 2** **Drug name:** Risperidone + stimulant **Dosing variability:** Variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.07 mg/day **Concurrent treatments:** See Aman 2002 and Snyder 2002 - psychostimulants **GROUP 3** **Drug name:** Placebo (only) **Dosing variability:** Variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR	**Benefits:** NCBRF, ABC **Harms:** metabolic effects, somnolence, headache, infections	Risperidone was a safe and effective treatment with or without stimulant added, for DBD and comorbid ADHD in children.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		Diagnostic breakdown (n): CD, ODD, or DBD-NOS with ADHD (35) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** All have ADHD **GROUP 3** **N:** 39 **Age, mean±SD (range):** 8.3±2.2 yr **Males %:** 74.4% **Caucasian %:** 56.4% **Diagnostic breakdown (n):** CD, ODD, or DBD-NOS with ADHD (39) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** All have ADHD **GROUP 4** **N:** 38 **Age, mean±SD (range):** 8.9±2.1 yr **Males %:** 92.1% **Caucasian %:** 73.7% **Diagnostic breakdown (n):** CD, ODD, or DBD-NOS with ADHD (38) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** All have ADHD	**Concurrent treatments:** See Aman 2002 and Snyder 2002 **GROUP 4** **Drug name:** Placebo + stimulant **Dosing variability:** Variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** See Aman 2002 and Snyder 2002 - psychostimulants		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Aman et al., 2002 [2] **Country:** USA **Condition category:** ADHD **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-IV, NCBRF **Inclusion criteria:** (1) total rating of ≥24 on the conduct problem subscale of the NCBRF, (2) dx of CD, ODD, or DBD NOS, (3) dx of subaverage IQ (≥36 and ≤84) and a VABS score ≤84, (4) patients with ADHD eligible if meeting all other criteria, (5) healthy, (6) 5–12 yr, (7) symptoms sufficiently severe for antipsychotic treatment, (8) a responsible person to accompany patient to study visits, provide reliable assessments, dispense study medication **Exclusion criteria:** (1) dx of PDD, schizophrenia, other psychotic disorders, (2) head injury as a cause	**Enrolled:** 119 **Analyzed:** 118 **Completed:** 118 **GROUP 1** **N:** NR **Age, mean±SD (range):** 8.7±2.1 yr **Males %:** 85 **Caucasian %:** 51 **Diagnostic breakdown (n):** CD (9), CD + ADHD (12), DBD (1) DBD + ADHD (4), ODD (12), ODD+ ADHD (17) **Treatment naïve (n):** 55 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (33), MR (borderline (32), mild (16), moderate (7)) **GROUP 2** **N:** NR **Age, mean±SD (range):** 8.1±2.3 yr **Males %:** 79 **Caucasian %:** 62 **Diagnostic breakdown (n):** CD (12), CD + ADHD (14), DBD (1) DBD + ADHD (2), ODD (13), ODD + ADHD (21) **Treatment naïve (n):** 63 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (37), MR (borderline	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** 1 wk **Permitted drugs:** antihistamines, chloral hydrate, medication for EPS, melatonin, psychostimulants (dose stable for ≥30 day before study) **Prohibited drugs:** anticonvulsants, antidepressants, antipsychotics, carbamazepine, cholinesterase inhibitors, lithium, medications for sleep/anxiety, valproic acid **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.2±0.6 **Concurrent treatments:** all groups: methylphenidate hydrochloride (35) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** see group 1	**Benefits:** ABC, BPI, CGI-I, NCBRF, VAS-MS Medication adherence, response (CGI) **Harms:** ECG changes, EPS, prolactin, prolactin-related AE, SAE, sedation, total AE, WAE, weight change	Risperidone was well tolerated and effective in children with disturbed behaviors and subaverage intelligence.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	of intellectual disability, (3) seizure disorder/ neuroleptics, (4) known hypersensitivity to risperidone or neuroleptics, (5) history of tardive dyskinesia or NMS, (6) serious or progressive illnesses, (7) presence of HIV, (8) use of an investigational drug within the previous 30 day, (9) previously received risperidone, (10) lab values outside of normal range unless not clinically relevant, (11) females of childbearing age, sexually active and not using birth control, (12) patients whose NCBRF conduct problem subscale score was reduced to <24 in response to a 1 wk placebo treatment before the study	(28), mild (22), moderate (13))			
Aman et al., 1991 [1] **Country:** New Zealand **Condition category:** ADHD **Funding:** Non-industry	**Recruitment dates:** NR **Study design:** RCT (crossover) **Setting:** Outpatient **Diagnostic criteria:** DISC-P, DSM-III	**Enrolled:** 30 **Analyzed:** 30 **Completed:** 30 **All participants** **N:** 30 **Age, mean±SD (range):** 10.1 (4.1-16.5) yr **Males %:** 83% **Caucasian %:** 70%	**Treatment duration:** 9 wk (3 wk per treatment) **Run-in phase:** Yes **Run-in phase duration:** NR **Permitted drugs:** epilepsy drugs (phenytoin, carbamazepine, phenobarbital, sodium valproate) **Prohibited drugs:** All psychotropics	**Benefits:** CTRS, RBPC, DCB, RLRS **Harms:** HR, BP, Weight, cognition	Clinical response to thioridazine was substantially less than the response to methylphenidate, with significant improvements confined to conduct and hyperactivity problems on teacher ratings.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Risk of bias: Medium (subjective), Medium (objective)	**Inclusion criteria:** Met criteria for ADD or CD, subnormal IQ (<76), attending special classes or special schools for mental retardation or adjustment classes for youngest children **Exclusion criteria:** NR	**Diagnostic breakdown (n):** ADHD (24), ADD (4), ADD Residual type (1), CD (3) **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities (n):** Significantly subnormal IQ (27), PDD (1) Subjects assigned to three orders of drugs: Thioridazine, methylphenidate, placebo	**GROUP 1** **Drug name:** Thioridazine **Dosing variability:** Fixed **Target dose (mg/day):** 1.75 mg/kg/day **Daily dose (mg/day), mean±SD (range):** 1.75 mg/kg/day in 2 daily doses **Concurrent treatments:** Phenytoin + carbamazepine (2), Phenobarbital + **GROUP 2** **Drug name:** Placebo **Dosing variability:** Fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2 identical placebo capsules per day **Concurrent treatments:** See group 1		
Anderson et al., 1989 [5] **Country:** USA **Condition category:** ASD **Funding:** Non-Industry **Risk of bias:** High (subjective), Medium (objective)	**Recruitment dates:** NR **Study design:** RCT (crossover) **Setting:** NR **Diagnostic criteria:** DSM-III **Inclusion criteria:** (1) Dx of infantile autism using DSM III, made independently by three child psychiatrists **Exclusion criteria:** (1) Patients with history of	**Enrolled:** 45 **Analyzed:** 42 **Completed:** 42 **GROUP 1** **N:** 14 **Age, mean±SD (range):** see below **Males %:** see below **Caucasian %:** NR **Diagnostic breakdown (n):** autistic disorder (all) **Treatment naïve (n):** NR **Inpatients (n):** 14 **First episode psychosis (n):** NR **Comorbidities:** see below	**Treatment duration:** 14 wk **Run–in phase:** Yes **Run–in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** RN **GROUP 1** **Drug name:** Haloperidol, Placebo, Placebo **Dosing variability:** variable **Target dose (mg/day):** 4.0 **Daily dose (mg/day), mean±SD (range):** 0.84±0.57 **Concurrent treatments:** NR **GROUP 2**	**Benefits:** CPRS, CGI-I, CGI-S, CGI-Efficacy, Conners PTQ, medication adherence **Harms:** sedation, acute dystonic reaction	Haloperidol did not have generalized facilitating effects on discrimination learning. However, it is important that haloperidol administration did not have an adverse effect on learning during the 4-wk period, and this itself is important information regarding a population where the majority is of subnormal intellectual

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	seizure disorder, gross neurological deficit, endocrine or systematic disease, or those with an identifiable cause for autism, (2) patients rated as hypoactive and anergic on baseline	**GROUP 2** **N:** 14 **Age, mean±SD (range):** see below **Males %:** see below **Caucasian %:** NR **Diagnostic breakdown (n):** autistic disorder (all) **Treatment naïve (n):** NR **Inpatients (n):** 14 **First episode psychosis (n):** NR **Comorbidities:** see below **GROUP 3** **N:** 14 **Age, mean±SD (range):** see below **Males %:** see below **Caucasian %:** NR **Diagnostic breakdown (n):** autistic disorder (all) **Treatment naïve (n):** NR **Inpatients (n):** 14 **First episode psychosis:**NR **Comorbidities:** NR **First episode psychosis (n):** NA **Comorbidities:** see below **Overall age, mean±SD (range):** 4.49±1.16 yr **Overall males %:** 77.8 **Overall comorbidities:** mild/low level retardation (42), of these, profoundly or severely retarded (29)	**Drug name:** Placebo, Haloperidol, Placebo **Dosing variability:** variable **Target dose (mg/day):** 4.0 **Daily dose (mg/day), mean±SD (range):** 0.84±0.57 **Concurrent treatments:** NR **GROUP 3** **Drug name:** Placebo, Placebo, Haloperidol **Dosing variability:** variable **Target dose (mg/day):** 4.0 **Daily dose (mg/day), mean±SD (range):** 0.84±0.57 **Concurrent treatments:** NR		functioning, having severe learning difficulties.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Arango et al., 2014 [98] **Country:** Spain **Condition category:** Mixed conditions **Funding:** Non-industry **Newcastle-Ottawa Scale:** 5/8 stars	**Recruitment dates:** May 2005 to Feb 2009 **Study design:** Prospective **Setting:** Inpatient/outpatient **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) 4-7 yr, (2) ≤30 days of lifetime exposure to SGAs, (3) met DSM-IV psychiatric diagnosis other than a primary eating disorder **Exclusion criteria:** NR	**Enrolled:** 303 **Analyzed:** 279 **Completed:** 165 (at 6mo) **GROUP 1** **N:** 157 **Age, mean±SD (range):** 14.0±3.3 yr **Males %:** 64.3 **Caucasian %:** 84.7 **Diagnostic breakdown (n):** Schizophrenia spectrum (48), mood spectrum disorders (34), behavioral disorders (42), other diagnosis (29) **Treatment naïve (n):** 80 **Inpatients (n):** see below **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 2** **N:** 44 **Age, mean±SD (range):** 15.4±1.8 yr **Males %:** 63.6 **Caucasian %:** 93.2 **Diagnostic breakdown (n):** Schizophrenia spectrum (15), mood spectrum disorders (17), behavioral disorders (5), other diagnosis (6) **Treatment naïve (n):** 14 **Inpatients (n):** see below **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 3**	**Treatment duration:** 6 mo **Run-in phase:** NR **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** Antidepressants (14), benzodiazepines (40), mood stabilizers (19), stimulants (1) **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** Antidepressants (14), benzodiazepines (18), mood stabilizers (7), stimulants (0) **GROUP 3** **Drug name:** Quetiapine **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** Antidepressants (11), benzodiazepines (12), mood stabilizers (7), stimulants (0)	**Benefits:** NA **Harms:** Weight (BMI, BMI-z), lipid values, fasting glucose, insulin, blood pressure (systolic/ diastolic)	Close screening and monitoring of cadio-metabolic side effects (CSE) is imperative, at least during the initial months of treatment, and suggest that there are differences in CSE risk and temporal pattern with olanzapine, risperidone, and quetiapine.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		N: 47 **Age, mean±SD (range):** 15.7±1.6 yr **Males %:** 53.2 **Caucasian %:** 89.4 **Diagnostic breakdown (n):** Schizophrenia spectrum (21), mood spectrum disorders (21), behavioral disorders (0), other diagnosis (3) **Treatment naïve (n):** 24 **Inpatients (n):** see below **First episode psychosis (n):** NR **Comorbidities:** NR **Overall inpatients (n):** 200			
Arango et al., 2009 [6] **Country:** Spain **Condition category:** Schizophrenia and related **Funding:** Industry, Academic **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient **Diagnostic criteria:** DSM-IV, K-SADS-PL **Inclusion criteria:** (1) adolescents admitted to the hospital with psychosis (schizophrenia or any other psychotic disorder (DSM-IV)) **Exclusion criteria:** (1) psychotic symptoms	**Enrolled:** 50 **Analyzed:** 49 **Completed:** 32 **GROUP 1** **N:** 26 **Age, mean±SD (range):** 15.7±1.4 **Males %:** 76 **Caucasian %:** 76 **Diagnostic breakdown (n):** bipolar disorder (5), other psychoses (12: major depressive episode with psychotic features (3), psychosis NOS (4), schizoaffective disorder (3), schizophreniform disorder (2)), schizophrenia (9) **Treatment naïve (n):** 10	**Treatment duration:** 6 mo **Run-in phase:** Yes **Run-in phase duration:** 3–5 day **Permitted drugs:** adjunctive medications **Prohibited drugs:** antipsychotics **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 9.7±6.6 **Concurrent treatments:** anticholinergics (8), antidepressants (10), antiepileptics (7), benzodiazepines (17), β-blockers (1), lithium (2)	**Benefits:** CGAS, CGI-S, PANSS, SDQ, YMRS, Cognitive function, medication adherence **Harms:** UKU, BAS, SAS, Akathisia, behavioral issues, BMI, constipation, hypokinesia, orthostatic dizziness prolactin-related AE, SAE, sedation, tachycardia, total AE, weight change	Psychotic symptoms in adolescents were reduced with both olanzapine and quetiapine, but cognitive measures were not improved. Significantly more weight gain was observed in patients treated with olanzapine.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	appearing to result from acute intoxication or withdrawal (if psychotic symptoms did not persist after 14 day of a negative urine drug screening), (2) DSM-IV criteria for any substance abuse, MR, or PDD, (3) organic CNS disorder, (4) history of TBI with loss of consciousness, (5) IQ <70 and a clinical criterion of impaired functioning prior to the onset of the disorder, (6) pregnant or breast feeding, (7) taking olanzapine or quetiapine before enrolment	**Inpatients (n):** all **First episode psychosis (n):** all **Comorbidities:** psychosis (all) **GROUP 2** **N:** 24 **Age, mean±SD (range):** 16.3±1.1 **Males %:** 79.2 **Caucasian %:** 87.5 **Diagnostic breakdown (n):** bipolar disorder (8), other psychoses (8; major depressive episode with psychotic features (2), psychosis NOS (2), schizoaffective disorder (2), schizophreniform disorder (2)), schizophrenia (8) **Treatment naïve (n):** 15 **Inpatients (n):** all **First episode psychosis (n):** all **Comorbidities:** psychosis (all)	**GROUP 2** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 532.8±459.6 **Concurrent treatments:** analgesics (2), anticholinergics (3), antidepressants (8), antiepileptics (7), benzodiazepines (14), β-blockers (2), cough medications (1), iron compouNRs (1), lithium (6), NSAIDs (1)		
Armenteros et al., 2007 [7] **Country:** USA **Condition category:** ADHD **Funding:** Industry **Risk of bias:** Medium (subjective),	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV, C-DISC 4	**Enrolled:** 25 **Analyzed:** 25 **Completed:** 23 **GROUP 1** **N:** 12 **Age, mean±SD (range):** 7.3±3.7 **Males %:** 83.3 **Caucasian %:** 50 **Diagnostic breakdown (n):** ADHD + aggressive behavior (12)	**Treatment duration:** 4 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** current psychostimulants **Prohibited drugs:** all medications other than current psychostimulants **GROUP 1** **Drug name:** Risperidone	**Benefits:** CGI-I, CGI-S Medication adherence, response (CAS-P, CAS-T, CGI-I) **Harms:** Behavioral issues, BMI, somnolence, total AE, WAE, weight change	Compared to placebo, risperidone was modestly effective in combination with psychostimulants for treatment-resistant agression in ADHD.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Medium (objective)	**Inclusion criteria:** (1) 7–12 yr, (2) constant dose of stimulant medication in the past 3 wk, (3) 3 acts of aggression in the past wk, 2 of which had to be acts of physical aggression against other people, objects, or self, (4) Aggression Questionnaire Predatory-Affective index score ≤0, (5) CGI-S ≥4, (6) Full Scale IQ ≥75, (7) normal results at screening from physical examination and laboratory tests **Exclusion criteria:** (1) substance use disorder, (2) unstable medical or neurological illness, (3) history of intolerance or failure to respond to an adequate trial of risperidone, (4) suicidal or homicidal	**Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (0), ODD (13), conduct disorder (6), GAD (1), separation anxiety disorder (3) **GROUP 2** **N:** 13 **Age, mean±SD (range):** 8.8±3.1 **Males %:** 92.3 **Caucasian %:** 46 **Diagnostic breakdown (n):** ADHD + aggressive behavior (13) **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see group1	**Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.1±0.6 mg/day **Concurrent treatments:** all groups: methylphenidate (15), mixed salts amphetamine (10) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1±0.5 mg/day **Concurrent treatments:** see group 1		
Bastiaens et al., 2009 [99] **Country:** USA **Condition category:** Mixed conditions (BP, Schizophrenia, MDD, ASD)	**Recruitment dates:** Dec 2004 to Sep 2005 **Study design:** Retrospective cohort **Setting:** Outpatient/community	**Enrolled:** 46 **Analyzed:** 34 **Completed:** 34 **GROUP 1** **N:** 24 **Age, mean±SD (range):** 11.7±2.4 **Males %:** 83 **Caucasian %:** NR	**Treatment duration:** 8.7 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** stable doses of concomitant medications **Prohibited drugs:** NR **GROUP 1**	**Benefits:** NA **Harms:** Behavioral issues, EPS, sedation, WAE, weight change	The two medications appeared to be tolerated well: the most common reported side effect was sedation. Excessive sedation was responsible for all documented disruptions in

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Funding: Internal funding **Newcastle-Ottawa Scale:** 6/8 stars	**Diagnostic criteria:** DSM-IV, Mini International Neuropsychiatric Interview for Children and Adolescents, Child/Adolescent Symptom Inventory **Inclusion criteria:** (1) 6–18 yr, (2) clinically significant aggressive behavior **Exclusion criteria:** NR	**Diagnostic breakdown (n):** bipolar disorder (6), CD (8), depressive disorder (0), mood disorder NOS (6), PDD (0), psychotic disorder (4) **Treatment naïve (n):** 18 **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 22 **Age, mean±SD (range):** 12.1±2.9 **Males %:** 91 **Caucasian %:** NR **Diagnostic breakdown (n):** bipolar disorder (6), CD (6), depressive disorder (6), mood disorder NOS (2), PDD (2), psychotic disorder (0) **Treatment naïve (n):** 16 **Inpatients (n):** NR **First episode psychosis (n):** NR	**Drug name:** Aripiprazole **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 4.5±2.3 **Concurrent treatments:** atomoxetine (8), stimulants (2) **GROUP 2** **Drug name:** Ziprasidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 42.9±18 **Concurrent treatments:** atomoxetine (6), stimulants (8)		treatment. Ziprasidone resulted in three times more frequent discontinuations, compared to Aripiprazole.
Berger et al., 2008 [8] **Country:** Australia **Condition category:** Schizophrenia and related **Funding:** Industry, Academic	**Recruitment dates:** July 2003 to Jan 2006 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, SCID-I/P **Inclusion criteria:** (1) 15–25 yr, (2) first	**Enrolled:** 141 **Analyzed:** 126 **Completed:** 126 **GROUP 1** **N:** 69 **Age, mean±SD (range):** 19.7±2.6 (15–24) **Males %:** 71 **Caucasian %:** NR **Treatment naïve (n):** 22 **Inpatients (n):** NR **First episode psychosis (n):** all	**Treatment duration:** 4 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** anticholinergics, benzodiazepines, sertraline (50–200 mg/day), zopiclone, zolpidem **Prohibited drugs:** antipsychotics **GROUP 1** **Drug name:** Quetiapine (low) **Dosing variability:** fixed **Target dose (mg/day):** 200	**Benefits:** BPRS, CGI-S, GAF, SANS, SOFAS, YMRS, health care system utilization, legal interaction, medication adherence, response, suicide **Harms:** UKU, Blood pressure, EPS, sedation, sexual dysfunction,	Quetiapine was safe and well-tolerated in acutely ill drug naïve first-episode psychosis patients.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Risk of bias: Low (subjective), Low (objective)	episode psychosis, (3) ≥1 of the following symptoms, present daily for ≥1 wk according to BPRS: somatic concerns, guilt, suspiciousness, hallucinations, unusual thought content, bizarre behavior, and/or conceptual disorganization **Exclusion criteria:** (1) previous treatment with antipsychotic medication (>1 wk), (2) presence of concurrent manic syndrome, MR (IQ<70), organic disorders presenting with a psychotic syndrome, epilepsy, (3) clinically significant physical illness, (4) history of brain surgery or brain infarct, (5) concomitant medications that prolong the QT interval, (6) 20% deviation from normal-range laboratory values at baseline, (7) participation in any other studies involving investigational or marketed products concomitantly or within 30 days (8) having donated blood or blood	**Comorbidities:** MR (0), psychosis (all), SA (28) **GROUP 2** **N:** 72 **Age, mean±SD (range):** 19±2.9 (15–24) **Males %:** 64.1 **Caucasian %:** NR **Treatment naïve (n):** 25 **Inpatients (n):** NR **First episode psychosis (n):** all **Comorbidities:** MR (0), psychosis (all), SA (30)	**Daily dose (mg/day), mean±SD (range):** 200 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Quetiapine (high) **Dosing variability:** fixed **Target dose (mg/day):** 400 **Daily dose (mg/day), mean±SD (range):** 400 **Concurrent treatments:** NR	somnolence, WAE, weight change	

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	products within the past 4 wk, (9) pregnant or lactating women, or women of childbearing potential not using an acceptable method of contraception				
Biederman et al., 2005 [9] **Country:** USA **Condition category:** Bipolar (manic, hypomanic, mixed) **Funding:** Government, Academic **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV, K-SADS **Inclusion criteria:** (1) 4–6 yr, (2) DSM-IV bipolar I or II disorder or bipolar disorder NOS with current manic, hypomanic , or mixed symptoms (with or without psychotic features), (3) YMRS score >15 **Exclusion criteria:** (1) any serious, unstable medical illness, (2) history of treatment with both study medications	**Enrolled:** 31 **Analyzed:** 31 **Completed:** 24 **GROUP 1** **N:** 15 **Age, mean±SD (range):** 5.0±0.8 **Males %:** 67 **Caucasian %:** 100 **Diagnostic breakdown (n):** major depression (11), mania (all) **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** ADHD (15), DBD (8) **GROUP 2** **N:** 16 **Age, mean±SD (range):** 5.3±0.8 **Males %:** 75 **Caucasian %:** 94 **Diagnostic breakdown (n):** major Depression (11), mania (all) **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR	**Treatment duration:** 8 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** benztropine mesylate (max 2 mg/day), lorazepam (≤2 mg/day) **Prohibited drugs:** antidepressants, antimanic or mood-stabilizing medications **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 6.3±2.3 (1.3–10) **Concurrent treatments:** all groups: benztropine (1), lorazepam (1) **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.4±0.5 (0.3–2.0) **Concurrent treatments:** see group 1	**Benefits:** BPRS, CDRS, YMRS, Response **Harms:** Behavioral issues, blood pressure, cardiovascular AE, dermatologic AE, glucose, lipid profile, neurologic AE, prolactin, pulse, sedation, weight change	Rispiradone and olanzapine showed reduction of symptoms of mania in preschool children with bipolar disorder.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		Comorbidities: ADHD (14), DBD (5)			
Bobo et al., 2013 [100] **Country:** USA **Condition category:** Mixed conditions **Funding:** Non-industry **Newcastle-Ottawa Scale:** 8/8 stars	**Recruitment dates:** Jan 1996 to Dec 2007 **Study design:** Retrospective **Setting:** NR **Diagnostic criteria:** NR **Inclusion criteria:** (1) adequate enrollment and health care utilization in the past year to ensure availability of data for study variables, (2) no evidence of life-threatening illness or institutional residence, (3) no evidence of diabetes, (4) no evidence of pregnancy (gestational diabetes might be misdiagnosed) or polycystic ovarian syndrome (treated with oral hypoglycemics), (5) cohort members could not have been in the hospital in the past month because changes in the medication regimen	**Enrolled:** NA **Analyzed:** 43287 **Completed:** 43287 **GROUP 1** **N:** 28858 **Age, mean±SD (range):** 14.5 yr **Males %:** 56.0 **Caucasian %:** 72.8 **Diagnostic breakdown (n):** BP (5281), depression (5569), other mood disorder (9609), ADHD (11225), CD (7301), anxiety (5944), alcohol use (894), other substance use (2568) **Treatment naïve (n):** 0 **Inpatients (n):** 4184 **First episode psychosis (n):** NR **Comorbidities:** Menstruation absent or infrequent (1096), menstruation disorder (1414), diagnosed obesity (1096), metabolic disorder (606), blood chemistry panel with glucose (6608), hypertension (750), other diagnosed cardiovascular disease (1298) **GROUP 2** **N:** 14429	**Treatment duration:** ≥1 yr **Run-in phase:** Yes **Run-in phase duration:** 365 d **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Antipsychotic users **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** [starting dose, median(IQ range)] 67(33-100)mg of chlorpromazine equivalents **Concurrent treatments:** Li (1212), valproate (2741), lamotrigine, carbamazepine, oxcarbazepine (2539), other mood stabilizer (519), SSRI (13563), heterocyclic antidepressant (4299), psychostimulant (9840), α-agonist (4213), benzodiazepine (3578) **GROUP 2** **Drug name:** Controls **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** Li (591), valproate (1341), lamotrigine, carbamazepine, oxcarbazepine (1298), other mood stabilizer (259), SSRI (6723), heterocyclic antidepressant (2063),	**Benefits:** NA **Harms:** Type 2 diabetes mellitus	In the study cohort (6 to24 yr), those recently initiating an antipsychotic medication had a 3-fold greater risk of newly diagnosed type 2 diabetes than did propensity score–matched controls. Risk was elevated during the first year of antipsychotic use, increased with increasing cumulative dose, and was present for children <18 yr.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	cannot be identified until up to 30 days following hospital discharge, (6) could have non-qualifying use of antipsychotics in the 90 days preceding the qualifying prescription but had to have a prior period of 365 days free of antipsychotic use, (7) cohort was restricted to recent users to include cases of diabetes that occurred early in therapy and to ensure that baseline covariateswere unaffected by chronic antipsychotic effects **Exclusion criteria:** (1) patientswithdiagnosed conditions for which antipsychotics generally are the only recommended treat-ment (eg. schizophrenia or related psychoses, or-ganic psychoses, autism, mental retardation, Tourette syndrome, or other tic disorders), (2) patients prescribed clozapine or long-acting injectable preparations, usually indicators of	**Age, mean±SD (range):** 14.5 yr **Males %:** 55.9 **Caucasian %:** 73.5 **Diagnostic breakdown (n):** BP (2654), depression (2813), other mood disorder (4689), ADHD (5526), CD (3592), anxiety (2871), alcohol use (476), other substance use (1341) **Treatment naïve (n):** NR **Inpatients (n):** 1991 **First episode psychosis (n):** NR **Comorbidities:** Menstruation absent or infrequent (533), menstruation disorder (72), diagnosed obesity (562), metabolic disorder (303), blood chemistry panel with glucose (3246), hypertension (360), other diagnosed cardiovascular disease (606)	psychostimulant (4862), α-agonist (2048), benzodiazepine (1818)		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	schizophrenia or related psychoses, as well as those with parenterally administered drugs, typically given for transient agitation.				
Bruggeman et al., 2001 [10] **Country:** Belgium, Netherlands, South Africa **Condition category:** Tic disorders **Funding:** Industry **Risk of bias:** NA (subjective), Medium (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-III-TR **Inclusion criteria:** (1) 10–65 yr, (2) primary dx of Tourette syndrome (DSM-III-R), (3) ≥3 on TSSS and CGI-S **Exclusion criteria:** NR	**Enrolled:** 50 **Analyzed:** 50 **Completed:** 41 **GROUP 1** **N:** 24 **Age, mean±SD (range):** NR (11–45) **Males %:** 87.5 **Caucasian %:** NR **Diagnostic breakdown (n):** Tourette syndrome (24) **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** ADHD (1), GAD (2), OCD (14) **GROUP 2** **N:** 26 **Age, mean±SD (range):** NR (11–50) **Males %:** 88.5 **Caucasian %:** NR **Diagnostic breakdown (n):** Tourette syndrome (26) **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR	**Treatment duration:** 2.8 mo **Run-in phase:** Yes **Run-in phase duration:** 2–5 wk **Permitted drugs:** antiparkinsonian medication and benzodiazepines (discontinued during washout period, limited during treatment) **Prohibited drugs:** antiparkinsonian medication and benzodiazepines (discontinued during washout period, limited during treatment), psychotropics (within 2 wk prior to and during study) **GROUP 1** **Drug name:** Pimozide **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2. 9 (1–6) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 3.8 (0.5–6) **Concurrent treatments:** NR	**Benefits:** NR **Harms:** Weight	Risperidone and pimozide were efficacious and well tolerated in patients with Tourette syndrome, but risperidone had a more favorable efficacy and tolerability profile.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		Comorbidities: ADHD (1), GAD (1), OCD (9)			
Buchsbaum et al., 2007 [11] **Country:** USA **Condition category:** Schizophrenia and related **Funding:** Industry, government **Risk of bias:** Medium (subjective), NA (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Outpatient **Diagnostic criteria:** DSM-IV using CASH (at least Psychosis NOS) **Inclusion criteria:** (1) 13-21 yr, (2) never previously medicated **Exclusion criteria:** NR	**Enrolled:** 30 **Analyzed:** 22 **Completed:** 22 **GROUP 1** **N:** 10 **Age, mean±SD (range):** both groups: 16.2±2.0 **Males %:** both groups: 52 **Caucasian %:** NR **Treatment naïve (n):** 10 **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 12 **Age, mean±SD (range):** see group 1 **Males %:** see group 1 **Caucasian %:** NR **Treatment naïve (n):** 12 **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 8-9 wks **Run-in phase:** NR **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** variable **Target dose (mg/day):** up to 20mg/day **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** up to 20mg/day **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Benefits:** BPRS **Harms:** NR	Both patients treated with olanzapine and haloperidol improved significantly from baseline to week 8 on the BPRS (positive, negative, and total symptom scores).
Buitelaar et al., 2001 [12] **Country:** Netherlands **Condition category:** ADHD **Funding:** Industry	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient **Diagnostic criteria:** DSM-IV	**Enrolled:** 38 **Analyzed:** 38 **Completed:** 35 **GROUP 1** **N:** 19 **Age, mean±SD (range):** 14.0±1.5 (11–18) **Males %:** 89.5 **Caucasian %:** NR	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** 2 wk **Permitted drugs:** biperidine, medication for somatic illness, oxazepam **Prohibited drugs:** psychotropics **GROUP 1** **Drug name:** Risperidone	**Benefits:** ABC, CGI-S, OAS-M Medication adherence **Harms:** Akathisia, dyskinesia, dystonia, ECG changes, fatigue, oculogyric crisis, parkinsonism, prolactin, prolactin-related AE, SAE,	Risperidone may be effective for severe aggression in adolescents with disruptive behavior disorders and subaverage intelligence.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Risk of bias: Medium (subjective), Medium (objective)	**Inclusion criteria:** (1) overt aggressive behavior persisted during hospitalization (modified OAS score ≥1), (2) failure to respond to behavioral treatment approaches, (3) clinical indication for drug treatment, (4) 12–18 yr, (5) principal dx of CD, ODD, or ADHD according to DSM-IV, (6) full-scale IQ 60–90 (WISC-R) **Exclusion criteria:** (1) neurologic, cardiac, pulmonary, or hepatic diseases, (2) primary mood disorders, schizophrenia or other active psychosis, or suicidality, (3) comorbid substance abuse disorder (DSM-IV), (4) pregnant or use of inadequate contraception, (5) major change in treatment strategy expected, (6) not feasible to discontinue current psychotropic medication	**Diagnostic breakdown (n):** CD (14), DBD NOS (1), ODD (4) **Treatment naïve (n):** 13 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (14), MR (6) **GROUP 2** **N:** 19 **Age, mean±SD (range):** 13.7±2 (11–18) **Males %:** 84.2 **Caucasian %:** NR **Diagnostic breakdown (n):** CD (16), DBD NOS (1), ODD (2) **Treatment naïve (n):** 13 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (12), anxiety disorder (3), MR (8)	**Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2.9 (1.5–4) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	somnolence, total AE, weight change, ESRS	
Calarge et al., 2014 [101] **Country:** USA	**Recruitment dates:** NR **Study design:** Prospective	**Enrolled:** 108 **Analyzed:** 101 **Completed:** 101 **GROUP 1** **N:** 74	**Treatment duration:** 6 mo, followed-up after 1.5 yr **Run-in phase:** NR **Run-in phase duration:** NR **Permitted drugs:** NR	**Benefits:** NA **Harms:** Weight (BMI-z), lipid values, glucose, insulin, blood pressure	Discontinuation of risperidone is associated with largely spontaneous resolution of the excessive weight

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Condition category: Mixed **Funding:** Non-industry **Newcastle-Ottawa Scale:** 5/8 stars	**Setting:** NR **Diagnostic criteria:** DSM-IV-TR, DISC-IV **Inclusion criteria:** (1) 7-7 yr, (2) treated with risperidone ≥6 mo, irrespective of primary diagnosis **Exclusion criteria:** (1) Participants with neurological or medical conditions that could confound the cardiometabolic assessments (e.g., seizure disorder, hypothyroidism, dyslipidemia, diabetes), (2) pregnant females, (3) those receiving hormonal contraception	**Age, mean±SD (range):** 13.3±2.7 yr **Males %:** 95 **Caucasian %:** 80 **Diagnostic breakdown (n):** DBD (68), ADHD (65), anxiety disorder (23), depressive disorder (3), ASD (12), tic disorder (17) **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 2** **N:** 9 **Age, mean±SD (range):** 12.3±2.6 yr **Males %:** 89 **Caucasian %:** 67 **Diagnostic breakdown (n):** DBD (7), ADHD (7), anxiety disorder (3), depressive disorder (0), ASD (2), tic disorder (3) **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 3** **N:** 18 **Age, mean±SD (range):** 13.1±2.3 yr **Males %:** 89 **Caucasian %:** 94 **Diagnostic breakdown (n):** DBD (14), ADHD	**Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone Continued **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** (mg/kg/d) 0.03±0.02 **Concurrent treatments:** Psychostimulants (59), α_2-agonists (25), antidepressants (43), mood stabilizers (6) **GROUP 2** **Drug name:** SGA Continued **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** Psychostimulants (5), α_2-agonists (6), antidepressants (8), mood stabilizers (0) **GROUP 3** **Drug name:** SGA Discontinued **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** Psychostimulants (11), α_2-agonists (5), antidepressants (20), mood stabilizers (2)	(systolic/ diastolic), prolactin	and a favorable change in cardiometabolic parameters.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		(17), anxiety disorder (5), depressive disorder (2), ASD (5), tic disorder (5) **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR			
Castro-Fornieles et al., 2008 [102] **Country:** Spain **Condition category:** Schizophrenia and related **Funding:** Government **Newcastle-Ottawa Scale:** 6/8 stars	**Recruitment dates:** NR **Study design:** Prospective cohort **Setting:** Inpatient (84% at recruitment) and outpatient **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) 7 to 17 yr, (2) psychotic episode less than 6 mo duration **Exclusion criteria:** (1) ASD, PTSD, SUD and other Axis I associated with psychosis, (2) MR and PDD	**Enrolled:** 110 **Analyzed:** 60 (only those remaining on same medication) **Completed:** 60 **All patients:** 15.5±1.8; Males 67%; White: 86%; 49% drug naive **GROUP 1** **N:** 31 **Age, mean±SD (range):** 15.1±2.1 **Males %:** 68 **Caucasian %: NR** **Treatment naïve (n):** NR **Inpatients (n): NR** **First episode psychosis (n):** 31 **GROUP 2** **N:** 15 **Age, mean±SD (range):** 16.4±1.1 **Males %:** 67 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** 15	**Treatment duration:** 24 mo **Run-in phase:** NR **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone **Dosing variability: variable** **Target dose (mg/day): NR** **Daily dose (mg/day), mean±SD (range):** 2.8±1.2mg/day **Concurrent treatments:** NR **GROUP 2** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 626.8±526 mg/day **Concurrent treatments:** NR **GROUP 3** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 11.7±7.0 mg/day **Concurrent treatments:** NR	**Benefits:** PANSS, CGI, GAF **Harms:** Weight, BMI, UKU, neurological AEs	Using the baseline score as covariate, there were no statistically significant differences between the three antipsychotics in the improvement achieved on any scale. Clinicians seem to prefer quetiapine or olanzapine to risperidone when there are marked affective symptoms.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		GROUP 3 **N:** 14 **Age, mean±SD (range):** 15.7±1.2 **Males %:** 71 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** 14			
Cianchetti et al., 2011 [103] **Country:** Italy **Condition category:** Schizophrenia and related **Funding:** NR **Newcastle-Ottawa Scale:** 5/8 stars	**Recruitment dates:** 1990 to 2005 **Study design:** Cohort study **Setting:** Inpatient (at recruitment) and outpatient **Diagnostic criteria:** DSM-IV **Inclusion criteria:** schizophrenia or schizoaffective disorder **Exclusion criteria:** (1) concomitant axis I disorder, (2) IQ less than 70, (3) neurological disorders and previous commotive head trauma	**Enrolled:** 58 **Analyzed:** 47 **Completed:** 47 **Whole cohort:** **Age:** 15.5 (range 10-17) **Males:** 45% **Caucasian**: 100%	**Treatment duration:** see below: 3 to 11 yrs **Run-in phase:** **Run-in phase duration:** **Permitted drugs:** mood stabilizers, anti-EPS (for haloperidol and high dose risperidone) **Prohibited drugs:** NR All patients treated per protocol, with analysis based on drugs used (haloperidol, risperidone, olanzapine, clozapine, quetiapine, aripiprazole; latter two had too few patients to compare) Haloperidol: (29) mean months treatment 9.4±14.3 Risperidone: (33) mean months of treatment 19.6±17.9 Olanzapine: (12) mean months of treatment 11.7±9.2 Clozapine: (28) mean months of treatment 31.5±916.3	**Benefits:** PANSS, CGI-I, CGI-EI, C-GAS, response **Harms:** EPS, weight, ECG, glucose, liver function tests, discontinuations, neutropenia, suicide	In the long-term, clozapine is more effective than haloperidol, risperidone and olanzapine. Despite a relevant incidence of adverse effects, clozapine seems to have unique effectiveness in treating children and adolescents with early-onset schizophrenic disorders.
Connor et al., 2008 [13] **Country:** USA	**Recruitment dates:** Nov 2003 to May 2005	**Enrolled:** 19 **Analyzed:** 19 **Completed:** 11	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** 1–4 wk	**Benefits:** CGI-I, CGI-S, Conner PRS, OAS	Quetiapine may be efficacious in the treatment of CD, but

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Condition category: ADHD **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** K-SADS-E **Inclusion criteria:** (1) 12–17 yr, (2) primary psychiatric dx of CD, (3) moderate to severe aggression (OAS score ≥25), (4) at least moderate severity of symptoms (CGI-S score ≥4) **Exclusion criteria:** (1) comorbid schizophrenia, schizoaffective disorder, psychotic disorder NOS, bipolar disorder, psychotic depression, or bipolar disorder NOS, (2) alcohol or substance abuse or dependence within 3 mo, (3) significantly subaverage IQ, (4) current or past history of leticular abnormality or juvenile cataracts, (5) seizure disorder, (6) concurrent administration of any psychoactive medication, (7) pregnant or lactating	**GROUP 1** **N:** 9 **Age, mean±SD (range):** 13.1±1.2 yr **Males %:** 78% **Caucasian %:** 78% **Diagnostic breakdown:** CD with moderate to severe aggression (9) **Treatment naïve (n):** 2 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (8), DBD (8), depression (1), dysthymia (2), GAD (3), MR (0), OCD (2), panic disorder (1), psychosis (0), PTSD (2), SA (1), separation anxiety (2), social phobia (2) **GROUP 2** **N:** 10 **Age, mean±SD (range):** 15±1.4 yr **Males %:** 70% **Caucasian %:** 70% **Diagnostic breakdown:** CD with moderate to severe aggression (10) **Treatment naïve (n):** 1 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (7), DBD (10), depression (3), dysthymia (3), GAD (0), MR (0), OCD (1), panic disorder (0), psychosis (0), PTSD (1)	**Permitted drugs:** benztropine **Prohibited drugs:** psychotropics, rescue medications for aggression **GROUP 1** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** 200 **Daily dose (mg/day), mean±SD (range):** 294±78 (200–600) **Concurrent treatments:** benztropine (0) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** 200 **Daily dose (mg/day), mean±SD (range):** 530±245 **Concurrent treatments:** benztropine (0)	Quality of life (Q-LES-Q), school attendance **Harms:** Akathisia, Behavioral issues, ECG changes, EPS, prolactin, pulse, SAE, sedation, severity of AE, WAE, weight change, AIMS	further research is required.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	females, (8) women of childbearing potential not using a medically accepted means of birth control, (9) unstable medical disease	SA (5), separation anxiety (1), social phobia (1)			
Conus et al., 2015 [14] **Country:** Australia **Condition category:** Bipolar **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** October 2001 and February 2006 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) participants (males and females aged 15 to 28) met DSM-IV criteria for a first manic or mixed episode with psychotic features within bipolar 1 or schizoaffective disorder, and had baseline Yound Mania Rating Scale (YMRS) score ≥ 20. **Exclusion criteria:** immediate risk of committing harm to self or others; use of neuroleptic medication or mood-stabilizers within two months of admission to the Early Psychosis Prevention	**Enrolled:** 98 **Analyzed:** 83 **Completed:** 74 **GROUP 1** **N:** 41 **Age, mean±SD (range):** 22.0±3.0 **Males %:** 63.9 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** 30 **First episode psychosis (n):** all **GROUP 2** **N:** 42 **Age, mean±SD (range):** 21.1±2.7 **Males %:** 71.1 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** 29 **First episode psychosis (n):** all	**Treatment duration:** 8 wks **Run-in phase:** Yes **Run-in phase duration:** 24 hours **Permitted drugs:** Benzodiazepines and anticholinergics **Prohibited drugs:** **GROUP 1** **Drug name:** Chlorpromazine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 185.9±126.7 **Concurrent treatments:** Lithium **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 12.2±7.8 **Concurrent treatments:** Lithium	**Benefits:** response, remission and symptomatic recovery **Harms:** weight, extrapyramidal side effects, neutropenia, sedation	Olanzapine and chlorpromazine have a similar safety profile in a uniquely representative cohort of patients with first episode psychotic mania.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	and Intervention Centre (EPPIC); organic mental disease; mental retardation; clinically signficant illness; clinically relevant biochemical or hematological abnormalities; pregnancy or lactation; history of epilespsy; drug allergy or hypersensitivity; or non-fluency in English.				
Correll et al., 2009 [104] **Country:** USA **Condition category:** Mixed conditions (bipolar, ADHD, ASD, schizophrenia-related) **Funding:** Government, Academic **Newcastle-Ottawa Scale:** 8/8 stars	**Recruitment dates:** Dec 2001 to Sep 2007 **Study design:** Prospective cohort **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, chart review, discussion with treating clinician, clinical interview **Inclusion criteria:** (1) 4–19 yr, (2) <1 wk lifetime antipsychotic treatment, (3) psychiatric illness prompting antipsychotic medication initiation, (4) consent, (5) baseline anthropometric and biochemical	**Enrolled:** 312 **Analyzed:** 257 **Completed:** 192 **GROUP 1** **N:** 47 **Age, mean±SD (range):** 13.4±3.1 (7–19.7) **Males %:** 56.1 **Caucasian %:** NR **Diagnostic breakdown (n):** disruptive or aggressive behavior spectrum disorder (9: ASD (4), ODD, CD, IED, ICD (5)), mood disorder spectrum (11: bipolar (3), MDD (10), NOS (5)), schizophrenia spectrum (14: psychosis NOS (11), schizophrenia/ schizoaffective disorder (3)) **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 2.8 mo **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** co-medications as necessary **Prohibited drugs:** co-medications as necessary **GROUP 1** **Drug name:** Aripriprazole **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** anticholinergics (2), antidepressants (13), anxiolytics or hypnotics (1), mood stabilizers (6), none (16), psychostimulants (5), psychotropics (4) **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR	**Benefits:** NR **Harms:** Fat mass, glucose, insulin resistance, lipid profile, metabolic syndrome, waist circumference, WAE, weight change	First-time SGA medication use was associated with significant weight gain and variable metabolic changes for each medication.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	assessments obtained within 7 day of antipsychotic medication initiation **Exclusion criteria:** (1) treatment with >1 antipsychotic agent, (2) active or past eating disorder, (3) biochemical evidence of thyroid dysfunction, (4) acute medical disorders, (5) pregnancy or breastfeeding, (6) wards of the state, (7) leaving the catchment area within 4 wk	**Comorbidities:** NR **GROUP 2** **N:** 52 **Age, mean±SD (range):** 14.7±3.2 (6.6–18.6) **Males %:** 64.4 **Caucasian %:** NR **Diagnostic breakdown (n):** disruptive or aggressive behavior spectrum disorder (9: ASD (2), ODD, CD, IED, ICD (7)), mood disorder spectrum (16: bipolar (9), MDD (8), NOS (4)), schizophrenia spectrum (14: psychosis NOS (5), schizophrenia/ schizoaffective disorder (9)) **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 3** **N:** 45 **Age, mean±SD (range):** 14±3.1 (6.1–19.4) **Males %:** 36.1 **Caucasian %:** NR **Diagnostic breakdown (n):** disruptive or aggressive behavior spectrum disorder (6: ASD (2), ODD, CD, IED, ICD (4)), mood disorder spectrum (9: bipolar (10), MDD (8), NOS (6)), schizophrenia spectrum	**Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** anticholinergics (0), antidepressants (10), anxiolytics or hypnotics (3), mood stabilizers (18), none (14), psychostimulants (4), psychotropics (1) **GROUP 3** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** anticholinergics (2), antidepressants (10), anxiolytics or hypnotics (1), mood stabilizers (15), none (8), psychostimulants (4), psychotropics (1) **GROUP 4** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** anticholinergics (18), antidepressants (43), anxiolytics or hypnotics (13), mood stabilizers (32), none (32), psychostimulants (26), psychotropics (9)		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		(6: psychosis NOS (4), schizophrenia/ schizoaffective disorder (2)) **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 4** **N:** 168 **Age, mean±SD (range):** 13.6±4 (4.3–19.9) **Males %:** 62.2 **Caucasian %:** NR **Diagnostic breakdown (n):** disruptive or aggressive behavior spectrum disorder (34: ASD (13), ODD, CD, IED, ICD (21)), mood disorder spectrum (55: bipolar (17), MDD (19), NOS (19)), schizophrenia spectrum (46: psychosis NOS (33), schizophrenia/ schizoaffective disorder (13)) **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR			
Crocq et al., 2007 [15] **Country:** France **Condition category:**	**Recruitment dates:** NR **Study design:** NRCT (parallel) **Setting:** Inpatient	**Enrolled:** NR **Analyzed:** 52 **Completed:** NR **GROUP 1** **N:** NR	**Treatment duration:** 2.8 mo **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR	**Benefits:** NR **Harms:** BMI, weight	Significantly greater increases in weight and BMI were found for olanzapine SOT compared to olanzapine ODT, as well as for

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Schizophrenia and related **Funding:** NR **Risk of bias:** NA (subjective), High (objective)	**Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) hospitalized adolescents with schizophreniform disorder **Exclusion criteria:** NR	**Age, mean±SD (range):** 16.5±1.7 **Males %:** 31.3 **Caucasian %:** all **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR **GROUP 2** **N:** NR **Age, mean±SD (range):** 17±1.3 **Males %:** 60 **Caucasian %:** all **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR **GROUP 3** **N:** NR **Age, mean±SD (range):** 15.2±1.4 **Males %:** 57.7 **Caucasian %:** all **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR	**GROUP 1** **Drug name:** Olanzapine (oral disintegrating tablet) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 16.6±4.4 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Olanzapine (standard oral tablet) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 18±4.2 **Concurrent treatments:** NR **GROUP 3** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2. 8±1.2 **Concurrent treatments:** NR		olanzapine ODT compared to risperidone.
Cuerda et al., 2011 [105] **Country:** Spain **Condition category:** Mixed conditions **Funding:** Non-industry	**Recruitment dates:** Feb 2005-Sept 2007 **Study design:** Prospective **Setting:** NR **Diagnostic criteria:** DSM-IV	**Enrolled:** 61 **Analyzed:** 46 **Completed:** 16 **GROUP 1** **N:** 18 **Age, mean±SD (range):** 16.1±1.9 yr **Males %:** 83.3 **Caucasian %:** 72.2	**Treatment duration:** 1 yr **Run-in phase:** NR **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone **Dosing variability:** NR	**Benefits:** NR **Harms:** Weight, BMI, lipid values, glucose, insulin, prolactin	Hypometabolism may explain weight gain in patients taking SGAs. Lifestyle recommendations involving reduced calorie intake and increased physical activity should be prescribed in all

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Newcastle-Ottawa Scale: 6/8 stars	**Inclusion criteria:** (1) 11-18 yr, (2) mental disorder requiring treatment with antipsychotics, (3) antipsychotic naïve patients or quasi-naïve (<72hr of exposure to antipsychotics), (4) written informed consent signed by parents or legal representatives and patients after the syudy was explained **Exclusion criteria:** (1) Concomitant use of medications that can influence body weight (corticosterioids, valproic acid or lithium), (2) presence of diabetes mellitus and severe dyslipidemia, (3) if a second antipsychotic was prescribed, (4) if treatment was changed or withdrawn during follow up, (5) if adherence was poor	**Diagnostic breakdown (n):** BP (1), brief psychosis/schizophria disorder (4), conduct disorder (3), depression with psychotic symptoms (2), OCD (0), psychosis NOS (6), schizophrenia (2), scholar phobia (0), depression (0), intellectual disability (0), personality disorder (0) **Treatment naïve (n):** 10 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 2** **N:** 12 **Age, mean±SD (range):** 16.1±1.3 yr **Males %:** 66.7 **Caucasian %:** 91.7 **Diagnostic breakdown (n):** BP (4), brief psychosis/schizophria disorder (2), conduct disorder (1), depression with psychotic symptoms (0), OCD (1), psychosis NOS (2), schizophrenia (1), scholar phobia (1), depression (0), intellectual disability (0), personality disorder (0) **Treatment naïve (n):** 5 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR	**Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 3** **Drug name:** Quetiapine **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR		patients starting these treatments.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		GROUP 3 **N:** 16 **Age, mean±SD (range):** 16.6±0.7 yr **Males %:** 62.5 **Caucasian %:** 81.3 **Diagnostic breakdown (n):** BP (2), brief psychosis/schizophria disorder (4), conduct disorder (0), depression with psychotic symptoms (1), OCD (2), psychosis NOS (3), schizophrenia (1), scholar phobia (0), depression (1), intellectual disability (1), personality disorder (1) **Treatment naïve (n):** 5 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR			
de Haan et al., 2003 [16] **Country:** Netherlands **Condition category:** Schizophrenia and related **Funding:** Government	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) 17–28 yr, (2) DSM-IV criteria for schizophrenia, (3)	**Enrolled:** 24 **Analyzed:** 19 **Completed:** 20 **GROUP 1** **N:** 12 **Age, mean±SD (range):** 21.0±2.8 (17–26) **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** 9 **Comorbidities:** MR (0)	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** 1 wk **Permitted drugs:** oxazepam **Prohibited drugs:** antidepressants, antipsychotics, mood stabilizers **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2.5	**Benefits:** CGI-I, PANSS, health related quality of life (Subjective Well-Being Under Neuroleptics scale), medication adherence **Harms:** BAS, SAS, akathisia, parkinsonism	Olanzapine showed no superior subjective response over haloperidol in patients with recent-onset schizophrenia.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Risk of bias: High (subjective), High (objective)	admitted to the Adolescent Clinic **Exclusion criteria:** (1) neurological or endocrine disease, (2) MR, (3) use of adjunctive medications such as mood stabilizers or antidepressants, (4) history of treatment with clozapine, (5) history of unresponsiveness to haloperidol or olanzapine, (6) intramuscular antipsychotic treatment within the last yr	**GROUP 2** **N:** 12 **Age, mean±SD (range):** 21±2.3 (17–25) **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** 11 **Comorbidities:** MR (0)	**Concurrent treatments:** oxazepam (6) **GROUP 2** **Drug name:** Olanzapine **Dosing variability: f**ixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 7.5 **Concurrent treatments:** oxazepam (5)		
DelBello et al., 2009 [19] **Country:** USA **Condition category:** Bipolar (depressive) **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Mar 2006 to June 2007 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV-TR, WASH-U-KSADS **Inclusion criteria:** (1) 12–18 yr, (2) dx of bipolar I disorder, depressive episode, (3) screening and baseline CDRS-R score ≥40	**Enrolled:** 32 **Analyzed:** 32 **Completed:** 20 **GROUP 1** **N:** 17 **Age, mean±SD (range):** 16.0±2 **Males %:** 29 **Caucasian %:** 82 **Treatment naïve (n):** 12 **Inpatients (n):** 7 **First episode psychosis (n):** NR **Comorbidities:** ADHD (2), anxiety disorder (5), DBD (6), psychosis (2) **GROUP 2** **N:** 15	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** NR **Permitted drugs:** lorazepam (max 4 mg/day days 1–7, 2 mg/day days 8–14) **Prohibited drugs:** antidepressants (<3 day), anticonvulsants (<3 day), antipsychotics or atomoxetine (<3 day), fluoxetine (<4 wk), psychostimulant (<48 hr) **GROUP 1** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** 600 **Daily dose (mg/day), mean±SD (range):** 403±133 (300–600)	**Benefits:** CDRS, CGI-BP, HAM-A, YMRS, response (response, remission, suicide attempt) **Harms:** Blood pressure, BMI, diabetes, EPS, glucose, LFT, lipid profile, mania, prolactin, pulse, SAE, sedation, tachycardia, WAE, weight change, EPS	Quetiapine monotherapy was no more effective in treating depression in adolescents with bipolar disorder than treatment with placebo.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	Exclusion criteria: (1) substance use disorder (other than nicotine) within the previous 3 mo, (2) unstable medical or neurological illness, (3) history of intolerance or nonresponse to quetiapine monotherapy, (4) treatment with an antidepressant (other than fluoxetine), an anticonvulsant (other than valproate or carbamazepine), antipsychotic or atomoxetine within 3 day, fluoxetine within 4 wk, or a psychostimulant within 48 hr of baseline, (5) risk of suicide	**Age, mean±SD (range):** 15±2 **Males %:** 33 **Caucasian %:** 80 **Treatment naïve (n):** 11 **Inpatients (n):** 8 **First episode psychosis (n):** NR **Comorbidities:** ADHD (2), anxiety disorder (3), DBD (2), psychosis (1)	**Concurrent treatments:** lorazepam (0) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** 600 **Daily dose (mg/day), mean±SD (range):** 413±151 (300–600) **Concurrent treatments:** lorazepam (0)		
DelBello et al., 2008 [18] **Country:** USA **Condition category:** Bipolar & schizophrenia-related **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV-TR **Inclusion criteria:** (1) 10–17 yr, (2) bipolar I disorder (YMRS score ≥17), (3) schizophrenia-related	**Enrolled:** 63 **Analyzed:** 63 **Completed:** 38 **GROUP 1** **N:** 23 **Age, mean±SD (range):** 13.2 (bipolar), 14.4 (schiz) **Males %:** 52 **Caucasian %:** NR **Diagnostic breakdown (n):** bipolar I (15), schizophrenia or schizoaffective disorder (8) **Treatment naïve (n):** NR	**Treatment duration:** 3 wk **Run-in phase:** Yes **Run-in phase duration:** 24 hr **Permitted drugs:** benztropine and/or propranolol, lorazepam or similar benzodiazepine **Prohibited drugs:** antidepressants, mood stabilizers, stimulants **GROUP 1** **Drug name:** Ziprasidone (low) **Dosing variability:** fixed **Target dose (mg/day):** 80	**Benefits:** YMRS, BPRS, CGI-S **Harms:** Akathisia, behavioral issues, dystonia, ECG changes, EPS (AIMS, SAS, BAS), fatigue, glucose, lipid profile, prolactin, SAE, sedation, somnolence, WAE, weight change	Neither low- nor high- dose ziprasidone was associated with unexpected tolerability findings, and a starting dose of 20 mg/d, titrated to 80–160 mg/d over 1–2 wk was optimal.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	disorder (BPRS-A score ≥35, with a score of ≥4 on at least one of: unusual thought content, hallucinations, suspiciousness, or conceptual disorganization), (4) BMI between 5th and 95th percentile **Exclusion criteria:** (1) currently on stable well-tolerated treatment, (2) substance-induced psychotic disorder, (3) treatment with clozapine within 12 wk, (4) depot antipsychotic within 4 wk, (5) MAO-I within 2 wk, (6) imminent risk of suicide or homicide, (7) MR, (8) autism or other PDD, (8) pregnancy, breastfeeding, or unwillingness to use birth control, (9) serious unstable medical or neurologic illness, (10) any screening laboratory value that deviated significantly from reference range, (11) clinically significant hypokalemia or hypomagnesemia, (12) history of cardiac arryhthmias,	**Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (0), SA (0) **GROUP 2** **N:** 40 **Age, mean±SD (range):** 13.8 (bipolar), 14.7 (schiz) **Males %:** 75 **Caucasian %:** NR **Diagnostic breakdown (n):** biploar I (31), schizophrenia or schizoaffective disorder (9) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (0), SA (0)	**Daily dose (mg/day), mean±SD (range):** (20–80) **Concurrent treatments:** benztropine (3) **GROUP 2** **Drug name:** Ziprasidone (high) **Dosing variability:** fixed **Target dose (mg/day):** 160 **Daily dose (mg/day), mean±SD (range):** (40–160) **Concurrent treatments:** benztropine (4)		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	conduction abnormalities, QTc prolongation, or genetic risk for prolonged QT syndrome, (13) psychoactive substance or alcohol abuse or dependence (other than nicotine or caffeine) within 1 mo (DSM-IV-TR)				
DelBello et al., 2002 [17] **Country:** USA **Condition category:** Bipolar (manic, mixed) **Funding:** Industry **Risk of bias:** Medium (subjective), Medium (objective)	**Recruitment dates:** May 2000 to May 2001 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, WASH-U-KSADS **Inclusion criteria:** (1) 12–18 yr, (2) DSM-IV criteria for bipolar I disorder, currently mixed or manic, (3) YMRS score ≥20 **Exclusion criteria:** (1) pregnant, (2) manic symptoms secondary to substance intoxication or withdrawal, (3) substance use disorder within the past 3 mo, (4) MR, (5)	**Enrolled:** 30 **Analyzed:** 30 **Completed:** 22 **GROUP 1** **N:** 15 **Age, mean±SD (range):** 14.1±2 **Males %:** 53 **Caucasian %:** 80 **Diagnostic breakdown (n):** mixed episode (10) **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR **Comorbidities:** ADHD (10), psychosis (7) **GROUP 2** **N:** 15 **Age, mean±SD (range):** 14.5±2 **Males %:** 53 **Caucasian %:** 87 **Diagnostic breakdown (n):** mixed episode (13) **Treatment naïve (n):** NR **Inpatients (n):** all	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** NR **Permitted drugs:** lorazepam (≤2 mg/day for first 14 day) **Prohibited drugs:** NR **GROUP 1** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** 450 **Daily dose (mg/day), mean±SD (range):** 432 **Concurrent treatments:** lorazepam (2) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** lorazepam (3)	**Benefits:** YMRS, Medication adherence, response **Harms:** Blood cells, blood pressure, ECG changes, prolactin, SAE, sedation, thyroid function, WAE, weight change, EPS (AIMS, BAS, SAS)	Quetiapine in combination with divalproate is more effective for the treatment of adolescent bipolar mania than divalproate with placebo.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	unstable medical or neurological disorder, cataracts, or clinically significant baseline laboratory abnormalities, (6) history of hypersensitivity, intolerance, or nonresponse to quetiapine or valproate, (7) treated with a depot neuroleptic within 3 mo, an antidepressant or antipsychotic within 1 wk (fluoxetine within 1 mo), a benzodiazepine or psychostimulant within 72 hr, or other antiepileptic agents within 72 hr	**First episode psychosis (n):** NR **Comorbidities:** ADHD (8), psychosis (7)			
Ebert et al., 2014 [106] **Country:** Israel **Condition category:** Mixed conditions **Funding:** NR **Newcastle-Ottawa Scale:** 5/8 stars	**Recruitment dates:** 2011-2012 **Study design:** Retrospective **Setting:** Inpatient **Diagnostic criteria:** NR **Inclusion criteria:** NR **Exclusion criteria:** NR	**Enrolled:** 72 **Analyzed:** 56 **Completed:** 56 **GROUP 1** **N:** 32 **Age, mean±SD (range):** 9.6±1.6 yr **Males %:** 91.7 **Caucasian %:** NR **Diagnostic breakdown (n):** See below **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** Anemia (1), ichthyosis (1)	**Treatment duration:** mean 10-17 wk for groups **Run-in phase:** NR **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Atypical antipsychotic treatment **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Benefits:** NR **Harms:** Weight, BMI, lipid values, fasting glucose, transaminases (ALT, AST)	Weight and metabolic monitoring is essential as supposedly weight neutral antipsychotics (aripiprazole, ziprasidone, and amisulpride) may not be weight neutral in youth, especially in antipsychotic-naïve youth.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		GROUP 2 **N:** 24 **Age, mean±SD (range):** 9.3±1.8 yr **Males %:** 87.5 **Caucasian %:** NR **Diagnostic breakdown (n):** See below **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** Epilepsy (1), central precocious puberty (1) **Overall diagnostic breakdown (n):** Psychotic spectrum disorder (15), BP (4), DBD (29), ADHD (26), anxiety spectrum disorder (8), depression disorder (13), PDD (5), MR (3), OCD (1), adjustment disorder (2), ED (1), tic disorder (2)	**GROUP 2** **Drug name:** Control **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR		
Findling et al., 2015b [30] **Country:** USA **Condition category:** Bipolar I (manic, mixed) **Funding:** Industry	**Recruitment dates:** Jul 2011 to Sept 2013 **Study design:** RCT (parallel) **Setting:** Outpatient **Diagnostic criteria:** DSM-IV-TR, K-SADS-PL	**Enrolled:** 404 **Analyzed:** 403 **Completed:** 350 **GROUP 1** **N:** 104 **Age, mean±SD (range):** 13.7±2.1 yr **Males %:** 50 **Caucasian %:** 72.1	**Treatment duration:** 3 wk **Run-in phase:** Yes **Run-in phase duration:** 2-14 d **Permitted drugs:** Chronic use medication such as hormonal birth control, common over-the-counter medications (i.e., nutritional supplements, pain relievers, antacids); short-acting benzodiazepines (e.g., lorazepam and equivalents) as needed or	**Benefits:** YMRS, CGI-BP-S, CGAS, CDRS-R, response, suicidal ideation, attempted suicide, psychiatric disorders, worsening of mania, medication adherence **Harms:** Mortality, somnolence, EPS	All asenapine doses versus placebo were superior based on change in YMRS at day 21. Asenapin was generally well tolerated in patients aged 10 to 17years with bipolar I disorder in manic or mixed states.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Risk of bias: Low (subjective), Low (objective)	**Inclusion criteria:** (1) Dx of bipolar I disorder acute manic or mixed episode with DSM-IV-TR and K-SADS-PL, (2) YMRS score ≥20, (3) CGI-BP overall ≥4, (4) guardian living with the child who was able to ensure adherence with treatment, outpatient visits, and study protocol **Exclusion criteria:** (1) Pervasive development disorder, schizophrenia, schizoaffective disorder, posttraumatic stress disorder, obsessive-compulsive disorder, psychosis due to a medical condition, (2) prohibited concomitant medication, (3) uncontrolled, unstable, clinically significant medical condition	**Diagnostic breakdown (n):** Manic (40), mixed (64) **Treatment naïve (n):** 38 **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** ADHD (62) **GROUP 2** **N:** 99 **Age, mean±SD (range):** 13.8±2.0 yr **Males %:** 43.4 **Caucasian %:** 67.7 **Diagnostic breakdown (n):** Manic (43), mixed (56) **Treatment naïve (n):** 24 **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** ADHD (45) **GROUP 3** **N:** 99 **Age, mean±SD (range):** 13.9±2.1 yr **Males %:** 58.6 **Caucasian %:** 65.7 **Diagnostic breakdown (n):** Manic (44), mixed (55) **Treatment naïve (n):** 32 **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** ADHD (61)	diazepam; use of psychostimulants and other ADHD medications, medications to treat extrapyramidal symptoms (EPS; e.g., anticholinergics, short-acting benzodiazepines). . **Prohibited drugs:** Antipsychotics, depot neuroleptics, benzodiazepines [except for lorazepam, up to 4 mg daily, or otherwise the equivalent dose of short-acting benzodiazepines that were clinically indicated], antidepressants, mood stabilizers, miscellaneous psychotropics, and herbal drugs/dietary supplements for depression, anxiety, or insomnia) **GROUP 1** **Drug name:** Asenapine (2.5 mg) **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** Stimulant (29) **GROUP 2** **Drug name:** Asenapine (5 mg) **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** Stimulant (22) **GROUP 3** **Drug name:** Asenapine (10 mg)	(ESRS), akathisia, dystonia, weight gain, BMI, ECG, lipid values, fasting insulin, glucose, prolactin, nausea, orthostatic hypotension related adverse events	Increases in weight and fasting insulin were associated with asenapine.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		GROUP 4 **N:** 101 **Age, mean±SD (range):** 13.7±2.0 yr **Males %:** 37.6 **Caucasian %:** 67.3 **Diagnostic breakdown (n):** Manic (44), mixed (57) **Treatment naïve (n):** 43 **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** ADHD (52)	**Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** Stimulant (25) **GROUP 4** **Drug name:** Placebo **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** Stimulant (20)		
Findling et al., 2015a [29] **Country:** USA (19 centers), international (60 centers) **Condition category:** Schizophrenia and related **Funding:** Industry **Risk of bias:** Low (subjective), Low (objective)	**Recruitment dates:** April 2011 to April 2013 **Study design:** RCT (parallel) **Setting:** in and outpatient (mostly outpatient) **Diagnostic criteria:** DSM-IV-TR, K-SADS-PL **Inclusion criteria:** (1) 12-17 yrs, (2) schizophrenia, (3) PANSS total ≥80, CGI-S ≥4, and ≥4 on 2+ items on PANSS positive subscale	**Enrolled:** 306 **Analyzed:** **Completed:** **GROUP 1** **N:** 106 **Age, mean±SD (range):** 15.4±1.5 **Males %: 63** **Caucasian %: 52** **Treatment naïve (n):** 33 **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 98 **Age, mean±SD (range):** 15.2±1.5 **Males %:** 63 **Caucasian %: 55** **Treatment naïve (n):** 28 **Inpatients (n):** NR	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** 3-10 day **Permitted drugs:** short-acting benzodiazepines (lorazepam 4mg or equivalent; or diazepam £ 40 mg/day in countries with no approved short-acting benzodiazepines) for relief of transient symptoms of agitation, anxiety, insomnia, restlessness, or akathisia, and anticholinergics or short-acting benzodiazepines to treat EPS symptoms **Prohibited drugs:** antipsychotics; depot neuroleptics; antidepressants; benzodiazepines; mood stabilizers; stimulants and other ADHD medications; miscellaneous psychotropics; and	**Benefits:** PANSS, CGI-S, response **Harms:** EPS, somnolence, weight, BMI, lipids, glucose, insulin, prolactin, metabolic syndrome, mortality, suicide, any AE, serious AEs,	Although improvements in PANSS total score at day 56 of the acute phase were numerically greater for both asenapine 2.5 and 5mg b.i.d. than for placebo and were maintained in the OLE, the primary end-point did not achieve statistical significance in the acute phase.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	Exclusion criteria: (1) treatment with clozapine, (2) comorbid Axis I condition responsible for current symptoms, (3) uncontrolled or unstable clinically significant general medical condition (eg, renal, endocrine, hepatic, respiratory, cardiovascular, hematologic, immunologic, or cerebrovascular disease, or malignancy) or an abnormal laboratory, vital sign, physical examination, or ECG findings), (4) uncontrolled diabetes or significant abnormal blood glucose, (5) suicide ideation over past 2 mo or behavior over past 6 mo, (6) beginning psychotherapy after trial initiation, (7) MR or SUD	**First episode psychosis (n):** NR **GROUP 3** **N:** 102 **Age, mean±SD (range):** 15.4±1.4 **Males %:** 61 **Caucasian %:** 56 **Treatment naïve (n):** 36 **Inpatients (n):** NR **First episode psychosis (n):** NR	herbal drugs/dietary supplements for depression, anxiety, and insomnia **GROUP 1** **Drug name:** Asenapine **Dosing variability:** fixed **Target dose (mg/day):** 5mg bid (2.5mg bid days 1-4; 5mg bid onwards) **Daily dose (mg/day), mean±SD (range):** **Concurrent treatments:** anti-EPS (12) **GROUP 2** **Drug name:** Asenapine **Dosing variability:** fixed **Target dose (mg/day):** 2.5mg bid **Daily dose (mg/day), mean±SD (range):** **Concurrent treatments:** anti-EPS (2) **GROUP 3** **Drug name:** Placebo **Dosing variability:** fixed **Target dose (mg/day):** NA **Daily dose (mg/day), mean±SD (range):** NA **Concurrent treatments:** anti-EPS (3)		
Findling et al., 2014b [28] **Country:** USA **Condition category:** ASD	**Recruitment dates:** Mar 2011 to Jun 2012 **Study design:** RCT (parallel) **Setting:** NR	**Enrolled:** 85 **Analyzed:** 82 **Completed:** 41 **GROUP 1** **N:** 41 **Age, mean±SD (range):** 10.1±2.8 yr	**Treatment duration:** 16 wk **Run–in phase:** No **Run–in phase duration:** NA **Permitted drugs:** Diphenhydramine for sleep or serious behaviour problems, nonbenzodiazepine sleep aids (eg,	**Benefits:** ABC-I, CGI-I, CGI-S, PedsQL, CGSQ, relapse, medication adherence **Harms:** Constipation, EPS (AIMS, BAS,	The safety and efficacy of aripiprazole and risperidone were comparable. The choice between these two medications should

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Funding: Industry **Risk of bias:** High (subjective), High (objective)	**Diagnostic criteria:** DSM-IV-TR, ADI-R **Inclusion criteria:** (1) Male of female, (2) 6-17 yr, (3) meets DSM-IV-TR criteria for autistic disorder, confirmed by ADI-R and also had serious behavioural problems (ie, tantrums, aggression, self-injurious behaviour, or a combination of these), (4) ABC-I score ≥18, CGI-S score ≥4 at screening and baseline **Exclusion criteria:** (1) Treatment resistant to antipsychotic medication (lack of therapeutic response to 2 different antipsychotics with treatment of ≥3 wks each) or previously treated with an adequate dose of aripiprazole for ≥3 wks without a clinically meaningful response, (2) lifetime dx of bipolar disorder, psychosis, or shizophrenia or a current dx of major depressive disorder, pervasive developmental	**Males %:** 73.2 **Caucasian %:** 75.6 **Diagnostic breakdown (n):** ASD (all) **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 2** **N:** 44 **Age, mean±SD (range):** 10.8±2.8 yr **Males %:** 86.4 **Caucasian %:** 63.6 **Diagnostic breakdown (n):** ASD (all) **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR	zolpidem, zaleplon, zopiclone, eszopiclone) for insomnia, and melatonin for insomnia (not permitted to start or make changes to their sleep aid treatment durng phase 2) **Prohibited drugs:** Antipsychotics other than aripiprazole, antidepressants, benzodiazepines, stimulants, α-agonists, mood stabilizers, and atomoxetine **GROUP 1** **Drug name:** Aripiprazole **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 9.0±4.5 [initial of phase 2], 9.7±4.9 [end dose at wk 16] **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 9.5±4.2 [initial of phase 2], 10.0±4.2 [end dose at wk 16] **Concurrent treatments:** NR	SAS), akathisia, mortality, lipid profile, glucose, prolactin, sexual maturation	be on the basis of clinical equipoise considering the patient's preference and clinical profile.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	disorder-NOS, Asperger syndrome, Rett syndrome, childhood disintegrativedisorder, or fragile X syndrome, (3) hisory of neoroleptic malignant syndrome, history of seizures within the past year or of severe head trauma or stroke, a history or current unstable medical conditions, a history of low white blood cell count, or abnormal laboratory test results that were medically significant				
Findling et al., 2014a [27] **Country:** USA **Condition category:** Bipolar I,II (depressed) **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Jan 2009 to Nov 2010 **Study design:** RCT (parallel) **Setting:** Outpatient **Diagnostic criteria:** DSM-IV-TR, K-SADS-PL **Inclusion criteria:** (1) Boys and girls, (2) 10–17 yr, (3) dx of bipolar I or bipolar II disorder, current or most recent episode depressed; duration ≥4 wk (DSM-IV-TR, confirmed by K-SADS-PL), (4) CDRS-	**Enrolled:** 193 **Analyzed:** 192 **Completed:** 144 **GROUP 1** **N:** 92 **Age, mean±SD (range):** 13.9±2.2 yr **Males %:** 48.9 **Caucasian %:** 70.7 **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** ADHD (38) **GROUP 2** **N:** 100	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** 7-28 d **Permitted drugs:** Psychostimulants (centrally acting sympathomimetics, including amphetamine, dexamphetamine, methylphenidate) in patients with ADHD if prescribed dose stable ≥30 d prior to baseline. No dose adjustment allowed during study. Nonpsychoactive medications considered necessary for patient's well being **Prohibited drugs:** Adjunctive medications for EPS **GROUP 1** **Drug name:** Quetiapine	**Benefits:** CDRS-R, CGI-BP-S, CGI-BP-C, response, remission, suicidal ideation, aggression, medication adherence, health care system utilization, exacerbation of bipolar I and depressive symptoms, mania (YMRS) **Harms:** somnolence, fatigue, nausea, agitation, EPS (AIMS, BAS, SAS), ECG, transaminase, fasting glucose,	QuetiapineXR(150 to 300 mg/day) did not demonstrate efficacy relative to placebo in this large, 8 week, randomized study of youth with bipolar I or II depression. These observations contrast with the efficacy of quetiapine XR demonstrated in adults with bipolar de-pression or MDD. Consistent with studies in adults, quetiapine XR

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	R total score ≥45 (5) YMRS score ≤16 at screening and baseline, (6) Patients with rapid cycling, defined as ≥4 episodes/yr, and a secondary diagnosis of comorbid ADHD, were permitted **Exclusion criteria:** (1) current DSM-IV-TR Axis I disorder other than bipolar I or bipolar II depression or ADHD, (2) YMRS total score >16 at screening or baseline, (3) criteria for bipolar disorder, most recent episode mania/ hypomania/ mixed, as determined by the K-SADS-PL, (4) history of nonresponse to adequate treatment with more than two antidepressants during the current episode or of treatment noncompliance, (5) use of valproate within 3 days, an antipsychotic, other mood stabilizer, antidepressant, an-xiolytic, hypnotic, or other psychoactive drug within 7 days, or fluoxetine within 28 days before baseline,	**Age, mean±SD (range):** 14.0±2.1 yr **Males %:** 52.0 **Caucasian %:** 60.0 **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** ADHD (46)	**Dosing variability:** variable **Target dose (mg/day):** 300 **Daily dose (mg/day), mean±SD (range):** mean modal dose, 204.9mg/day **Concurrent treatments: Total** psychostimulants (20), other (35) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** psychostimulants (27), other (37)	dyslipidemia, TSH, throxine, prolactin, weight gain, blood pressure, pulse	at the dose range investigated was generally safe and well tolerated in these pediatric patients.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	(6) a requirement for psychotherapy during the study period, unless initiated at least 3 mo before, (7) being a current serious suicidal or homicidal risk, CDRS-R intem 13 score ≥3 at enrollment or randomization, (8) clinically significant deviations from normal reference ranges of clinical laboratory parameters				
Findling, 2013a [25] **Country:** Canada, Columbia, Costa Rica, Germany, India, Malaysia, Mexico, Peru, Russia, Singapore, Sweden, Ukraine, USA **Condition category:** Schizophrenia and related **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Apr 2006 to Mar 2009 (terminated prematurely) **Study design:** RCT (parallel) **Setting:** In- and outpatient **Diagnostic criteria:** DSM-IV, KID-SCID **Inclusion criteria:** (1) 13–17 yr, (2) schizophrenia (DSM-IV, confirmed by KID-SCID), (3) current symptoms present for ≥7 days prior to screening, (4) first episode psychosis allowed, (5) BPRS Anchored score ≥35	**Enrolled:** 284 **Analyzed:** 283 **Completed:** NR **GROUP 1** **N:** 193 **Age, mean±SD (range):** 15.3 **Males %:** 56 **Caucasian %:** 60 **Diagnostic breakdown (n):** paranoid type (127) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 90 **Age, mean±SD (range):** 15.4 **Males %:** 69 **Caucasian %:** 67 **Diagnostic breakdown (n):** paranoid type (57)	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** 14 days **Permitted drugs:** lorazepam or diazepam, diphenhydramine, zolpidem, benzotropine, anticholinergics, propranolol **Prohibited drugs:** antipsychotic, mood stabilizers, stimulants, antidepressants, anti-emetics, several antihypertensives **GROUP 1** **Drug name:** Ziprasidone **Dosing variability:** variable **Target dose (mg/day):** 40–80 (<45 kg), 120–160 (≥45 kg) **Daily dose (mg/day), mean±SD (range):** 67.8 (<45kg), 129.3 (≥45kg) **Concurrent treatments:** 51% **GROUP 2**	**Benefits:** BPRS-A, PANSS, CGI-S, CGI-I, CGAS, health related quality of life (Child Health Questionnaire), suicide, depression **Harms:** Serious AE, SARS, BARS, AIMS, akathisia, behavioral issues, dermatologic AE, ECG changes, QTcF, fatigue, EPS, liver function, mortality, SAE, somnolence, total AE, WAE, weight change, blood pressure, pulse rate, lipids	Oral ziprasidone failed to demonstrate superiority over placebo in adolescents with schizophrenia.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	and a score ≥4 on ≥1 of the following items: unusual thought content, hallucinations, suspiciousness, or conceptual disorganization at screening and baseline visits, (6) BMI Z-score 1.65–2.00, inclusive **Exclusion criteria:** substance-induced psychotic disorder, a DSM-IV–defined psychoactive substance or alcohol abuse/ dependence in the preceding month, a rating of 7 on the single suicidal ideation item on the Child Depression Rating Scale-Revised (CDRS-R), significant MR, or ASD, or if they were judged by investigator to be at imminent risk of suicide or homicide. Other general criteria for exclusion included serious/ unstable medical conditions, history of significant cardiovascular disease, cardiac arrhythmias, conduction abnormalities, QT prolongation, clinically significant ECG	**Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR	**Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** 60–80 (<45 kg), 120–160 (≥45 kg) **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** 39%		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	abnormalities, and Fridericia's corrected QT (QTcF) interval ‡460ms at screening or baseline.				
Findling et al., 2013b [26] **Country:** USA **Condition category:** Bipolar I (manic, mixed) **Funding:** Industry, non-industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Jan 2006 to Jul 2007 **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-IV, K-SADS **Inclusion criteria:** (1) 10–17 yr, (2) primary dx of bipolar I disorder (DSM-IV, confirmed by K-SADS), (3) current symptoms present for ≥7 day prior to screening, (4) YMRS score >17 at screening and baseline visits, (5) BMI Z-score 1.65–2.00, inclusive **Exclusion criteria:** (1) current or prior treatment with ziprasidone, (2) known allergy to ziprasidone, (3) serious suicidal risk, (4) a Fridericia-corrected QT interval (QTcF) ≥460 ms, (5) DSM-IV substance abuse/dependence	**Enrolled:** 238 **Analyzed:** 229 **Completed:** 148 **GROUP 1** **N:** 149 **Age, mean±SD (range):** 13.2±2.4 yr (males), 14.1±2.0 yr (females) **Males %:** 56.4 **Caucasian %:** 81.2 **Diagnostic breakdown (n):** Single manic (14), manic (45), mixed (90) **Treatment naïve (n):** 149 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (66) **GROUP 2** **N:** 88 **Age, mean±SD (range):** 13.5±2.0 yr (males), 14.0±1.9 yr (females) **Males %:** 53.4 **Caucasian %:** 81.8 **Diagnostic breakdown (n):** Single manic (8), manic (23), mixed (57) **Treatment naïve (n):** 88 **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 4 wk **Run-in phase:** Yes **Run-in phase duration:** 1–10 day **Permitted drugs:** Lorazepam or a comparable benzodiazepine as required ≤2mg/day. Not to be administered ≤6 hours prior to clinical assessments. **Prohibited drugs:** Other antipsychotics, lithium and anticonvulsants, stimulants, antidepressants, antiemetics (dopamine antagonists such as prochlorperazine and metoclopramide), treatment with clozapine ≤12 weeks, treatment with a depot antipsychotic ≤4 weeks, treatment with a monoamine oxidase inhibitor ≤2 weeks, or treatment with an investigational agent ≤4 weeks of baseline. **GROUP 1** **Drug name:** Ziprasidone **Dosing variability:** variable **Target dose (mg/day):** 60–80 (<45 kg), 120–160 (≥45 kg) **Daily dose (mg/day), mean±SD (range):** 69.2(<45 kg), 118.8 (≥45 kg) **Concurrent treatments:** NR **GROUP 2**	**Benefits:** YMRS, CGI-S, CGI-I, CGAS, CDRS-R, suicidal ideation, aggression **Harms:** dystonia, akathisia, dyskinesia, EPS (AIMS, BAS, SARS), somnolence, weight change, nausea, prolonged QTc interval, increased hepatic enzymes, extrapyramidal disorder, self-injurious behavior, prolactin, lipid profile, fatigue	Ziprasidone at doses of 40–160 mg/day is an effective and generally well-tolerated treatment for children and adolescents 10–17 years of age with a manic or mixed episode associated with bipolar I disorder.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	(except nicotine or caffeine) in the preceding month, and (5) numerous other standard medical and psychiatric exclusion criteria	**Comorbidities:** ADHD (36)	**Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** 60–80 (<45 kg), 120–160 (>45 kg) **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR		
Findling et al., 2012b [24] **Country:** USA **Condition category:** Bipolar I,II, NOS, cyclothymia **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** May 2004 to Nov 2008 **Study design:** RCT (parallel) **Setting:** Outpatient **Diagnostic criteria:** DSM-IV, K-SADS-PL **Inclusion criteria:** (1) 4-9 yr, (2) met DSM-IV criteria for bipolar I, II, NOS or cyclothymia, (3) screened by highly trained raters completing K-SADS-PL, (4) patients must have adhered to study-related procedures during phase 1, (5) tolerated a minimum daily aripiprazole dose of 0.05 mg/kg/day for at least 6 wk, (6) met a priori response criteria **Exclusion criteria:** (1) evidence of pervasive developmental disorder, Rett's syndrome, mental	**Enrolled:** 60 **Analyzed:** 60 **Completed:** 6 **GROUP 1** **N:** 30 **Age, mean±SD (range):** 7.1±1.5 yr **Males %:** 63 **Caucasian %:** NR **Diagnostic breakdown (n):** bipolar disorder NOS (17), bipolar I disorder (10), cyclothymia (3) **Treatment naïve (n):** 0 **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** DBD (6), ADHD (27), any anxiety disorder (0) **GROUP 2** **N:** 30 **Age, mean±SD (range):** 6.7±1.7 yr **Males %:** 77 **Caucasian %:** NR **Diagnostic breakdown (n):** bipolar disorder NOS (16), bipolar I disorder (11), cyclothymia (3) **Treatment naïve (n):** 0	**Treatment duration:** 72 wk (after 16 wk of open label study: phase I) **Run-in phase:** NR **Run-in phase duration:** NR **Permitted drugs:** Continued coadministration of stable dose of psychostimulants from phase 1 **Prohibited drugs:** Other psychotropic medications **GROUP 1** **Drug name:** Aripiprazole **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 0.23±0.07 [at randomization], 0.26±0.11 [end of study] **Concurrent treatments:** Stimulants (12) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 0.22±0.07 [at randomization], 0.22±0.07 [end of study] **Concurrent treatments:** Stimulants (13)	**Benefits:** YMRS, CDRS-R, CGAS, CGI-S, time to discontinuation of medication **Harms:** weight, EPS (AIMS, BAS, SAS), lipid values, prolactin, fasting glucose, blood pressure, pulse, mortality	Even though aripiprazole maintenance was statistically superior to placebo maintenance, alone it was not sufficient to keep most youth stable for extended periods of time.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	retardation, (2) a general medical or neurologic condition for which treatment with aripiprazole would be contraindicated	**Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** DBD (5), ADHD (27), any anxiety disorder (2)			
Findling et al., 2012a [23] **Country:** Asia, Central and Eastern Europe, South Africa, United States **Condition category:** Schizophrenia and related **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Oct 2004 to June 2007 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, K-SADS-PL **Inclusion criteria:** (1) inpatients and outpatients, (2) 13–17 yr, (3) schizophrenia (DSM-IV, confirmed by K-SADS-PL), (4) PANSS total score ≥60 and a score ≥4 on delusions, conceptual disorganization, or hallucinations **Exclusion criteria:** DSM-IV Axis I diagnosis of BD, schizophreniform disorder, schizoaffective disorder, psychotic disorder NOS, or acute PTSD, psychosis	**Enrolled:** 222 **Analyzed:** 220 **Completed:** 220 **GROUP 1** **N:** 73 **Age, mean±SD (range):** 15.5±1.3 (13–17) **Males %:** 58.9 **Caucasian %:** 61.6 **Diagnostic breakdown (n):** disorganized (6), paranoid (53), residual (0), undifferentiated (14) **Treatment naïve (n):** NR **Inpatients (n):** 31 **First episode psychosis (n):** NR **GROUP 2** **N:** 74 **Age, mean±SD (range):** 15.5±1.3 (13–17) **Males %:** 59.5 **Caucasian %:** 59.5 **Diagnostic breakdown (n):** disorganized (5), paranoid (50), residual (1), undifferentiated (18) **Treatment naïve (n):** NR **Inpatients (n):** 28 **First episode psychosis (n):** NR	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** 1 day–4 wk **Permitted drugs:** antidepressants, lorazepam **Prohibited drugs:** antipsychotics, psychostimulants, CYP3A4 inhibitors/inducres, monoamine oxidase inhibitors, atomoxetine, prophylactic benztropine **GROUP 1** **Drug name:** Quetiapine (low) **Dosing variability:** fixed **Target dose (mg/day):** 400 **Daily dose (mg/day), mean±SD (range):** 400 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Quetiapine (high) **Dosing variability:** fixed **Target dose (mg/day):** 800 **Daily dose (mg/day), mean±SD (range):** 800 **Concurrent treatments:** NR **GROUP 3** **Drug name:** Placebo **Dosing variability: fixed** **Target dose (mg/day):** NA	**Benefits:** BSPSd, CGAS, CGI-I, CGI-S, PANSS, Caregiver Strain Questionnaire, response, agitation, aggression, medication adherence **Harms:** Withdrawals from AEs, serious AEs, SAS, BARS, AIMS-7, behavioral issues, ECG changes, EPS, fatigue, lipid profile, glucose concentration, mortality, prolactin, pulse, SAE, sedation, somnolence, tachycardia, thyroid, liver and renal function, total AE, WAE, weight change	Quetiapine at a dose of 400 mg/day and 800 mg/day provided significant improvements in symptoms associated with schizophrenia in adolescent patients, including the primary efficacy measure of PANSS total score change. Quetiapine was generally well tolerated with a profile broadly similar to that reported previously in adult and adolescent populations.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	judged to be a direct consequence of a medical condition or its treatment, history of suicide attempts or homicidal risk or behavior within the past 3 months, DSM-IV-defined SUD, laboratory test results outside the normal reference range, hospital admission for diabetes or diabetes-related illness in the past 3 months, renal, cardiovascular, hepatic, hematologic, endocrinologic, ophthalmologic, or other medical conditions that were unstable or may have affected or been affected by the study medication, pregnancy and lactation.	**GROUP 3** **N:** 73 **Age, mean±SD (range):** 15.3±1.4 (13–17) **Males %:** 57.5 **Caucasian %:** 63 **Diagnostic breakdown (n):** disorganized (5), paranoid (52), residual (0), undifferentiated (16) **Treatment naïve (n):** NR **Inpatients (n):** 36 **First episode psychosis (n):** NR	**Daily dose (mg/day), mean±SD (range):** NA **Concurrent treatments:** NR		
Findling et al., 2009 [22] **Country:** USA **Condition category:** Bipolar (manic, mixed) **Funding:** Industry **Risk of bias:** Medium	**Recruitment dates:** Mar 2005 to Feb 2007 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, K-SADS-PL **Inclusion criteria:** (1) 10–17 yr, (2) bipolar I	**Enrolled:** 296 **Analyzed:** 294 **Completed:** 237 **GROUP 1** **N:** 98 **Age, mean±SD (range):** 13.7±2.2 **Males %:** 53.1 **Caucasian %:** 66.3 **Diagnostic breakdown (n):** manic (41), mixed (43), unknown (14) **Treatment naïve (n):** 41	**Treatment duration:** 4 wk **Run-in phase:** Yes **Run-in phase duration:** 3 day **Permitted drugs:** anticholinergics, benzodiazepines **Prohibited drugs:** Mood stabilizers, other psychotropics **GROUP 1** **Drug name:** Aripiprazole (low) **Dosing variability:** variable **Target dose (mg/day):** 10	**Benefits:** CDRS, CGAS, CGI-BP, YMRS, health related quality of life (P-QLES-Q), response, suicide **Harms:** Akathisia, BMI, dyskinesia, dystonia, ECG changes, EPS (AIMS, BAS, SAS), fatigue, glucose, lipid profile, mortality,	Aripiprazole in daily doses of 10 mg or 30 mg was effective and generally well-tolerated for acute treatment of pediatric subjects with bipolar I mania or mixed episodes.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
(subjective), Medium (objective)	disorder with current manic or mixed episodes, with or without psychotic features (DSM-IV), (3) YMRS score ≥20 **Exclusion criteria:** (1) bipolar II disorder, bipolar disorder NOS, PDD, schizophrenia, schizoaffective disorder, psychosis due to other medical condition or concomitant medication, (2) MR, (3) DSM-IV substance or alcohol use disorder, (4) positive drug screen for cocaine or other substances of abuse during screening, (5) sexual activity without contraceptive use, pregnancy, lactation, (6) other medical reason determined by investigator, (7) noncompliance with medication washout, (8) inability to swallow tablets whole, (9) history of antipsychotic treatment resistance or NMS, (10) suicide attempt in the past 6 mo, score >3 on the Suicidal Ideation item of the CDRS-R, or	**Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (48), DBD (28) **GROUP 2** **N:** 99 **Age, mean±SD (range):** 13.3±2.3 **Males %:** 51.5 **Caucasian %:** 68.7 **Diagnostic breakdown (n):** manic (40), mixed (39), unknown (20) **Treatment naïve (n):** 49 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (50), DBD (34) **GROUP 3** **N:** 99 **Age, mean±SD (range):** 13.3±2.1 **Males %:** 56.6 **Caucasian %:** 60.6 **Diagnostic breakdown (n):** manic (38), mixed (43), unknown (18) **Treatment naïve (n):** 36 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (55), DBD (31)	**Daily dose (mg/day), mean±SD (range):** (2–10) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Aripiprazole (high) **Dosing variability:** variable **Target dose (mg/day):** 30 **Daily dose (mg/day), mean±SD (range):** (2–30) **Concurrent treatments:** NR **GROUP 3** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	parkinsonism, prolactin, SAE, somnolence, total AE, WAE, weight change	

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	determined by the investigator to be at risk of suicide, (11) clinically important laboratory test results, vital signs, or ECG, and unstable medical conditions, diabetes melitus, epilepsy, (12) prior participation in an aripiprazole study, allergy or hypersensitivity to aripiprazole, or participation in an investigational drug trial in the past month				
Findling et al., 2008a [21] **Country:** Asia, Caribbean, Europe, South Africa, South America, USA **Condition category:** Schizophrenia and related **Funding:** Industry **Risk of bias:** Medium (subjective), Medium (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, K-SADS-PL **Inclusion criteria:** (1) 13–17 yr, (2) primary dx of schizophrenia (DSM-IV Axis I, confirmation with K-SADS-PL), (3) baseline PANSS ≥ 70 **Exclusion criteria:** (1) current psychiatric comorbidity requiring pharmacology, (2)	**Enrolled:** 302 **Analyzed:** 294 **Completed:** 258 **GROUP 1** **N:** 100 **Age, mean±SD (range):** 15.6±1.3 **Males %:** 45 **Caucasian %:** 54 **Diagnostic breakdown (n):** For all: schizophrenia (1), BP (12), Tourette syndrome (5), ADHD/CD (1), OCD (1), PDD (1) **Treatment naïve (n):** 25 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 2** **N:** 102	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** ≥3 day **Permitted drugs:** anticholinergics, benzodiazepines **Prohibited drugs:** antidepressants, atomoxetine, mood stabilizers, other psychotropics, stimulants **GROUP 1** **Drug name:** Aripiprazole (low) **Dosing variability:** variable **Target dose (mg/day):** 10 **Daily dose (mg/day), mean±SD (range):** 9.8 (2–10) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Aripiprazole (high) **Dosing variability:** variable **Target dose (mg/day):** 30	**Benefits:** CGAS, CGI-I, CGI-S, PANSS Health related quality of life (P-QLES-Q), response, suicide **Harms:** Akathisia, behavioral issues, BMI, dyskinesia, dystonia, ECG changes, EPS, EPS (SAS), glucose, lipid profile, mortality, prolactin, parkinsonism, SAE, somnolence, WAE, weight change	Aripiprazole (10 or 30 mg/d) was well tolerated and was more effective than placebo in improving symptoms of schizophrenia.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	evidence of suicide risk, (3) history, or current dx of schizoaffective disorder, MR, major depressive episodes, NMS, any neurologic disorder other than Tourette syndrome, severe head trauma, unstable medical condition, (4) resistant to antipsychotics according to trials of two different antipsychotics of adequate dose and duration, (5) pregnancy, breast-feeding, sexually active patients who refused abstinence or birth control, (6) positive screens for illegal drugs within 3 mo of baseline or during study, (7) hospitalized for acute schizophrenia within 4 wk of baseline	**Age, mean±SD (range):** 15.4±1.4 **Males %:** 63.7 **Caucasian %:** 60.8 **Diagnostic breakdown (n):** See group 1 **Treatment naïve (n):** 27 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 3** **N:** 100 **Age, mean±SD (range):** 15.4±1.4 **Males %:** 61 **Caucasian %:** 64 **Diagnostic breakdown (n):** See group 1 **Treatment naïve (n):** 27 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR	**Daily dose (mg/day), mean±SD (range):** 28.9 (2–30) **Concurrent treatments:** NR **GROUP 3** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR		
Findling et al., 2008b [107] **Country:** USA **Condition category:** Mixed conditions **Funding:** Industry	**Recruitment dates:** NR **Study design:** OLE **Setting:** NR **Diagnostic criteria:** **Inclusion criteria:** (1) 13-17 yr; (2) dx of	**Enrolled:** 24 **Analyzed:** 21 (safety); 20 (efficacy) **Completed:** 17 **All** **N:** 21 **Age, mean±SD (range):** 12.2±2.1 **Males %:** 66.7 **Caucasian %:** 76.1	**Treatment duration:** 26 d **Run-in phase:** NR **Run-in phase duration:** NR **Concurrent treatments:** Analgesics (paracetamol; Vicks formula 44M) (5); anesthetics (lidocaine) (4); antiasthmatics (budesonide; salbutamol; other) (2); antiparkinsonism drugs (benztropine; benztropine	**Benefits:** CGI-I/S **Harms:** AEs, physical examination, vital signs, ECGs, clinical laboratory parameters, and EPS (SAS, AIMS, BARS)	Aripiprazole at doses of 20, 25, and 30 mg/d seemed generally safe and well tolerated in children and adolescents with psychiatric disorders. All 3 planned aripiprazole dose levels were

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Newcastle-Ottawa Scale: 5/8 stars	schizophrenia or bipolar **Exclusion criteria:** (1) sexually active pt not practicing double-barrier birth control; (2) pregnancy/lactation; (3) current/hx of drug or alcohol abuse; (4) mental retardation; (5) neurologic disorders (except PDD, ADHD, or TS); (6) use of antipsychotic or psychotropic medication, CYP2D6 and CYP3A4 inhibitors, or CYP3A4 inducers <14 d; (7) participation in another clinical study <1 mo (or 6 mo if the study involved psychotropic medication); (8) major surgery or blood transfusion/donation <30 d; (9) abnormal physical, ECG, or clinical laboratory examinations; (10) significant risk of suicide or homicide	**Diagnostic breakdown (n):** schizophrenia (1); bipolar disorder (12); TS (5); ADHD and CD (1); OCD (1); PDD (1) **Treatment naïve (n):** **Inpatients (n):** **First episode psychosis (n):** **Comorbidities:** GROUP **1** **N:** 8 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 2** **N:** 7 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 3** **N:** 6	mesylate) (2); anti-inflammatories or antirheumatics (naproxen sodium; ibuprofen) (2); antipruritics including antihistamines (diphenhydramine hydrochloride) (1); antacids (dihydroxyaluminum sodium carbonate) (1); antibacterials (minocycline) (1); sex hormones (progestogens and estrogens) (1); antidiabetics (insulin lispro; insulin and analog) (1); nasal preparations (Dimetapp) (1) **GROUP 1** **Drug name:** Aripiprazole **Dosing variability:** 2 mg/d (starting dose), then increased to target dose every 2 d for 8 d **Target dose (mg/day):** 20 mg/d **Daily dose (mg/day), mean±SD (range):** NR **GROUP 2** **Drug name:** Aripiprazole **Dosing variability:** 2 mg/d (starting dose), then increased to target dose every 2 d for 10 d **Target dose (mg/day):** 25 mg/d **Daily dose (mg/day), mean±SD (range):** NR **GROUP 3** **Drug name:** Aripiprazole **Dosing variability:** 2 mg/d (starting dose), then increased to target dose every 2 d for 12 d **Target dose (mg/day):** 30 mg/d **Daily dose (mg/day), mean±SD (range):** NR		judged to be tolerated.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		Age, mean±SD (range): NR **Males %:** NR **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR			
Findling et al., 2000 [20] **Country:** USA **Condition category:** ADHD **Funding:** Industry, Foundation **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV, K-SADS, clinical interview **Inclusion criteria:** (1) outpatients with primary dx of CD, (2) 5–15 yr, (3) at least moderate degree of overall symptom severity (CGI), (4) Aggression subscale T-score ≥2 SD above the mean for age- and gender-matched peers (CBCL) **Exclusion criteria:** (1) moderate/severe ADHD, (2) significant psychiatric comorbidity	**Enrolled:** 20 **Analyzed:** 20 **Completed:** 9 **GROUP 1** **N:** 10 **Age, mean±SD (range):** 10.7±3.4 yr **Males %:** NR **Caucasian %:** NR **Diagnostic breakdown:** CD with aggression (10) **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 2** **N:** 10 **Age, mean±SD (range):** 8.2±1.9 yr **Males %:** NR **Caucasian %:** NR **Diagnostic breakdown:** CD with aggression (10) **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR	**Treatment duration:** 10 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** benztropine **Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 0±0.004 (0.8–1.5) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** (0.3–3) **Concurrent treatments:** NR	**Benefts:** CBCL, CGI-I, CGI-S, Conner PRS, RAAPP Medication adherence **Harms:** Dermatologic AE, EPS, liver function, sedation, total AE, WAE, AIMS, SAS	Low doses of risperidone may be effective in the treatment of youths with CD and are not associated with extrapyramidal symptoms.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	(including mood disorder), (3) treatment with a psychotropic medication within 1 wk of initiating double-blind therapy, (4) positive toxicology screen, (5) suicide attempt within the past mo, (6) organic mental syndromes, (7) pregnant or nursing females and females of childbearing potential who were not using an acceptable method of birth control, (8) a standard score equivalent to <70 on the Peabody Picture Vocabulary Test-Revised	**Comorbidities:** NR			
Findling et al., 2015 [31] **Country:** USA **Condition category:** Mixed conditions **Funding:** Industry **Risk of bias:** NA (subjective), High (objective)	**Recruitment dates:** June 2012 to May 2013 **Study design:** Prospective cohort **Setting:** Outpatient **Diagnostic criteria:** NR **Inclusion criteria:** male or female outpatients between the ages of 6 and 17 years with a diagnosis of schizophrenia spectrum disorder,	**Enrolled:** 105 **Analyzed:** 102 **Completed:** 90 **GROUP 1** **N:** 20 **Age, mean±SD (range):** see below **Males %:** see below **Caucasian %:** see below **Diagnostic breakdown (n):** see below **Treatment naïve (n):** NR **Inpatients (n):** see below **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 2**	**Treatment duration:** 3 wk **Run-in phase:** Yes **Run-in phase duration:** 2 days **Permitted drugs:** NR . **Prohibited drugs:** Inhibitors or inducers of CYP3A4 or any medication that could have significantly prolonged the QT/QTc interval **GROUP 1** **Drug name:** Lurasidone **Dosing variability:** fixed **Target dose (mg/day):** 20 **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Benefits:** NR **Harms:** AE, laboratory tests, weight	Adverse events were qualitiatively similar to those reported in adults. Discontinuation due to adverse events were dose related with lurasidone doses <120 mg/d being better tolerated than higher doses, especially in younger children. The PK and tolerability results suggest that the dose range of 20 to 80 mg/d provides adequate serum

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	bipolar spectrum disorder, autism spectrum disorder, attention deficit/hyperactivity disorder with aggressive behavior (ie comorbid conduct disorder or other disruptive behavior), or Tourette's syndrome. **Exclusion criteria:** clinically significant alcohol or drug abuse/dependence within the previous 6 months or a positive breath alcohol test or urine screen for drugs of abuse at screening; severe cognitive impairment; clinical instability or an imminent risk for suicide or injury to self, others, or property; a clinically significant major medical condition or abnormal laboratory value or vital sign measurement; and/or pregnant, breastfeeding, or sexual activity without the use of medically approved birth control.	**N:** 25 **Age, mean±SD (range):** see below **Males %:** see below **Caucasian %:** see below **Diagnostic breakdown (n):** see below **Treatment naïve (n):** NR **Inpatients (n):** see below **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 3** **N:** 19 **Age, mean±SD (range):** see below **Males %:** see below **Caucasian %:** see below **Diagnostic breakdown (n):** see below **Treatment naïve (n):** NR **Inpatients (n):** see below **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 4** **N:** 25 **Age, mean±SD (range):** see below **Males %:** see below **Caucasian %:** see below **Diagnostic breakdown (n):** See below **Treatment naïve (n):** NR **Inpatients (n):** see below **First episode psychosis (n):** NR **Comorbidities:** NR	**GROUP 2** **Drug name:** Lurasidone **Dosing variability:** fixed **Target dose (mg/day):** 40 **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 3** **Drug name:** Lurasidone **Dosing variability:** fixed **Target dose (mg/day):** 80 **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 4** **Drug name:** Lurasidone **Dosing variability:** fixed **Target dose (mg/day):** 120 **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 5** **Drug name:** Lurasidone **Dosing variability:** fixed **Target dose (mg/day):** 160 **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR		concentrations, but with improved tolerability compared with higher doses.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		GROUP 5 **N:** 16 **Age, mean±SD (range):** see below **Males %:** see below **Caucasian %:** see below **Diagnostic breakdown (n):** see below **Treatment naïve (n):** NR **Inpatients (n):** see below **First episode psychosis (n):** NR **Comorbidities:** NR **All Groups** **N:** 102 **Age, mean±SD (range):** 12.7 **Males %:** 65 **Caucasian %:** 78 **Diagnostic breakdown (n):** ADHD (78), BP (19), Schizophrenia (5), Tourette's (2), ASD (1). **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** NR			
Fleischhaker et al., 2006 [108] **Country:** Germany **Condition category:** Mixed conditions **Funding:** NR	**Recruitment dates:** NR **Study design:** Prospective cohort **Setting:** Inpatient **Diagnostic criteria:** ICD-10	**Enrolled:** 51 **Analyzed:** 51 **Completed:** 51 **GROUP 1** **N:** 16 **Age, mean±SD (range):** 17.2±1.8 (14.4–21.3) **Males %:** 68.9 **Caucasian %:** NR **Treatment naïve (n):** NR	**Treatment duration:** 7.4 wk (mean) **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Clozapine	**Benefits:** NR **Harms:** Akathisia, behavioral issues, bradycardia, blood cells, blood pressure, BMI, constipation, dystonia, dermatologic AE, ECG changes, liver function tachycardia,	Olanzapine caused significant weight gain in children and adolescents, potentially influencing medication compliance and health risk. Clozapine and risperidone were

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Newcastle-Ottawa Scale: 3/8 stars	**Inclusion criteria:** NR **Exclusion criteria:** NR	**Diagnostic breakdown (n):** Schizophrenia (31), PDD (5), AN (1), Cannabis-related disorders (4), AD (3), DBD (3), OCD (2), TD (1) for all groups **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** NR **GROUP 2** **N:** 16 **Age, mean±SD (range):** 15.8±1.4 (12.8–17.8) **Males %:** 56.3 **Caucasian %:** NR **Treatment naïve (n):** NR **Diagnostic breakdown (n):** See group 1 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** NR **GROUP 3** **N:** 19 **Age, mean±SD (range):** 15.6±2.6 (9.7–19) **Males %:** 68.4 **Caucasian %:** NR **Treatment naïve (n):** NR **Diagnostic breakdown (n):** See group 1 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** NR	**Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 321.9±156.5 (125–600) **Concurrent treatments:** all groups: amisulpride, biperiden, chlorprotixene, fluboxamine, fluoxetine, haloperidol, imipramine, lactulose, levomepromazine, lorazepam, metixene, metoclopramid, metoprolol, paroxetine, perazine, pimozide, pipamperone, pirenzepine, promethazine **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 16.6±7.1 (7.5–30) **Concurrent treatments:** see group 1 **GROUP 3** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 3.9±1.7 (1–6) **Concurrent treatments:** see group 1	tardive dyskinesia, weight change	associated with less marked changes in weight, but gains were still more pronounced than those seen in adults.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Fraguas et al., 2008 [109] **Country:** Spain **Condition category:** Mixed conditions **Funding:** Government, Foundation, Other NR **Newcastle-Ottawa Scale:** 6/8 stars	**Recruitment dates:** Mar 2005 to Oct 2006 **Study design:** Prospective cohort **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) new prescription of olanzapine, risperidone of quetiapine within 30 days, (2) no history of prior lifetime antipsychotic treatment **Exclusion criteria:** (1) receiving >1 antipsychotic or needed another antipychotic during followup	**Enrolled:** 92 **Analyzed:** 66 **Completed:** 66 **GROUP 1** **N:** 25 **Age, mean±SD (range):** 15.9±1.5 (12–17) **Males %:** 65 **Caucasian %:** 90 **Diagnostic breakdown (n):** bipolar (2), depression (1), eating disorders (3), PDD (1), psychosis NOS (5), schizophrenia (3), schizophreniform (5) **Treatment naïve (n):** 9 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** psychosis (14), SA (12) **GROUP 2** **N:** 29 **Age, mean±SD (range):** 16.3±1.3 (13–18) **Males %:** 58.3 **Caucasian %:** 95.8 **Diagnostic breakdown (n):** ADHD (0), bipolar (5), CD (1), depression (2), eating disorders (2), OCD (2), PDD (0), psychosis NOS (4), schizophrenia (4), schizophreniform (4) **Treatment naïve (n):** 8 **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 6 mo **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** anticholinergics, antidepressants, benzodiazepines **Prohibited drugs:** antipsychotics **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 9.8±5.6 **Concurrent treatments:** antidepressants (3), benzodiazepines (14), biperiden (4) **GROUP 2** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 390.8±321.2 **Concurrent treatments:** antidepressants (9), benzodiazepines (12), biperiden (4) **GROUP 3** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 3.5±3.1 **Concurrent treatments:** antidepressants (9), benzodiazepines (11), biperiden (6)	**Benefits:** NR **Harms:** Blood pressure, BMI, glucose, lipid profile, thyroid function, weight change	Metabolic and hormonal adverse events should be carefully monitored when prescribing SGAs.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		Comorbidities: psychosis (14), SA (18) **GROUP 3** **N:** 38 **Age, mean±SD (range):** 13.4±4 (4–17) **Males %:** 77.3 **Caucasian %:** 81.8 **Diagnostic breakdown (n):** ADHD (4), bipolar (1), CD (7), depression (1), eating disorders (1), OCD (2), PDD (1), psychosis NOS (3), schizophrenia (2), schizophreniform (0) **Treatment naïve (n):** 8 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** psychosis (6), SA (13)			
Friedlander et al., 2001 [110] **Country:** Canada **Condition category:** Mixed conditions **Funding:** NR **Newcastle-Ottawa Scale:** 4/8 stars	**Recruitment dates:** NR **Study design:** Retrospective cohort **Setting:** NR **Diagnostic criteria:** DSM-IV, author consensus on chart review **Inclusion criteria:** (1) 13–24 yr, (2) developmental disabilities and complex psychiatric	**Enrolled:** 44 **Analyzed:** 44 **Completed:** NR **GROUP 1** **N:** 14 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Diagnostic breakdown (n):** Developmental disabilities (all), Schizophrenia/other psychotic (15), PDD (16), mood disorders (11), ADHD/DBD (6), Tic-	**Treatment duration:** 6 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** all groups: anticholinergics (5), anticonvulsants (12), anxiolytics (9), clonidine (1), mood stabilizers	**Benefits:** NR **Harms:** Akathisia, dyskinesia, dystonia, EPS, prolactin-related AE, sedation, total AE, WAE, weight change	Adolescents and young adults with developmental disabilities treated with SGAs for multiple conditions were particularly sensitive to neuroleptic induced movement disorders.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	problems, (3) active files with the mental health sites in the Greater Vancouver area **Exclusion criteria:** NR	related disorders (3), AD (2), Impulse control disorder (1) for all patients **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** Addison's disease (1), hypothyroidism (4), MR (borderline (1), mild (17), moderate (15), severe (9)), Neurodevelopmental syndrome (15), Seizure disorder (9) **GROUP 2** **N:** 40 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Diagnostic breakdown (n):** see group 1 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see group 1	(21), non-SSRI antidepressants (8), SSRIs (9), stimulants (2), tetrabenazine (2) **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** see group 1		
Germano et al., 2014 [111] **Country:** Italy **Condition category:** Mixed **Funding:** NR	**Recruitment dates:** Jan 2009-Dec 2012 **Study design:** Prospective **Setting:** NR **Diagnostic criteria:** NR	**Enrolled:** 65 **Analyzed:** 60 **Completed:** 60 **GROUP 1** **N:** 29 **Age, mean±SD (range):** See below **Males %:** See below **Caucasian %:** NR	**Treatment duration:** 2 mo **Run-in phase:** Yes **Run-in phase duration:** 2 wk **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Aripiprazole **Dosing variability:** NR	**Benefits:** NR **Harms:** ECG parameters	Treatment with risperidone and aripiprazole in children and adolescents with psychiatric disorders is not associated with clinically relevant modifications of the QT interval on ECG.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Newcastle-Ottawa Scale: 5/8 stars	**Inclusion criteria:** (1) child and adolescent pateints, (2) ≤17 yr **Exclusion criteria:** NR	**Diagnostic breakdown (n):** See below **Treatment naïve (n):** See below **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 2** **N:** 31 **Age, mean±SD (range):** See below **Males %:** See below **Caucasian %:** NR **Diagnostic breakdown (n):** See below **Treatment naïve (n):** See below **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR **Overall age, mean±SD (range):** 10.2±2.6 yr **Overall Males %:** 91.6 **Overall diagnostic breakdown (n):** PDD (22), ODD (12), ADHD (21), MR with psychotic disorder (11), Tourette syndrome and other tic disorders (9) **Overall treatment naïve (n):** 22	**Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 7.4±3.1 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Risperidone **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.5±1.0 **Concurrent treatments:** NR		Aripiprazole use can be associated to a slight increase of QTd value only, along with risperidone use that can be associated to an increase of both QTc and QTd values. Therefore, monitoring of both QTc and QTd parameters during AP treatment in pediatric Population should be considered.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Ghanizadeh et al., 2014a [32] **Country:** Iran **Condition category:** ASD **Funding:** Industry/ non-industry **Risk of bias:** Medium (subjective), Medium (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Outpatient **Diagnostic criteria:** DSM-IV-TR, ADI-R **Inclusion criteria:** (1) Meets DSM-IV-TR and ADI-R criteria,(2) has a clinicain rating of at least moderate severity of autistic symptoms (CGI severity score of C4) **Exclusion criteria:** (1) Children with a history of medically significant or uncontrolled medical conditions such as hypothyroidism, diabetes or cancer, (2) history of drug or alcohol abuse, (3) could not have received risperidone or aripiprazole during at least 2 wk before entering this trial, (4) could not have received additional behavioural interventions above the regular educational programming during this trial	**Enrolled:** 59 **Analyzed:** 59 **Completed:** 50 **GROUP 1** **N:** 29 **Age, mean±SD (range):** 9.6±3.3 yr **Males %:** 86.2 **Caucasian %:** NR **Diagnostic breakdown (n):** see below **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 2** **N:** 30 **Age, mean±SD (range):** 9.5±4.6 yr **Males %:** 76.7 **Caucasian %:** NR **Diagnostic breakdown (n):** see below **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** NR **Overall diagnostic breakdown (n):** Autism (38), Asperger disorder (8), PDD-NOS (9), childhood disruptive behavior disorder (1)	**Treatment duration:** 2 mo **Run–in phase:** NR **Run–in phase duration:** NR **Permitted drugs:** Any (with no marked change in dose allowed during the trial and during 2 wk before the trial onset) **Prohibited drugs:** Antipsychotics **GROUP 1** **Drug name:** Aripiprazole **Dosing variability:** variable **Target dose (mg/day):** 10 (<40 kg), 15 (>40kg) **Daily dose (mg/day), mean±SD (range):** 5.5 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** 2 (<40 kg), 3 (>40kg) **Daily dose (mg/day), mean±SD (range):** 1.12 **Concurrent treatments:** NR	**Benefits:** ABC, CGI-S, CGI-I, discontinuation due to lack of efficacy **Harms:** Fatigue, constipation, dystonia, dyskinesia, nausea, seizure, agitation, weight	The safety and efficacy of aripiprazole and risperidone were comparable. The choice between these two medications should be on the basis of clinical equipoise considering the patient's preference and clinical profile.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Ghanizadeh et al., 2014b [33] **Country:** Iran **Condition category:** Tic disorders **Funding:** Non-industry **Risk of Bias:** High (subjective), High (objective)	**Recruitment Dates:** NR **Study design:** RCT (parallel) **Diagnostic criteria:** DSM-IV-TR **Setting:** outpatient **Inclusion criteria:** 6-18 yr, primary diagnosis of tic disorder **Exclusion criteria:** Current mood disorders, psychotic symptoms, PDD, substance-related disorder, severe uncontrolled medical conditions such as neurological problems, diabetes, epilepsy, Huntington's chorea, reported cardiac problems, or clinically estimated mental retardation	**Enrolled:** 60 **Analyzed:** 60 **Completed:** 35 **GROUP 1:** **N:**31 **Age, mean±SD (range):**11.12±3.3 yr **Males %:** 82.8 **Caucasian %:**NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** NR **GROUP 2:** **N:** 29 **Age, mean±SD (range):** 10.22±2.3 yr **Males %:** 86.2 **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** NR	**Treatment duration:** 8 weeks **Run-in phase:** Unclear **Run-in phase duration:** 2 weeks **Permitted drugs:** Nortriptyline, Biperiden, Citalopram, Clonidine, Fluvoxamine, Propanolol, Methylphenidate **Prohibited drugs:** NR **GROUP 1** **Drug name:** Aripiprazole **Dosing variability:** Variable **Target dose (mg/day):** 15mg/day **Daily dose (mg/day), mean±SD (range):** 4.0±2.4 mg/day **Concurrent treatments:** Nortripyline (1), Citalopram (1), Clonidine + fluvoxamine + propranolol (1), Methylphenidate (2) **GROUP 2:** **Drug name:** Risperidone **Dosing variability:** Variable **Target dose (mg/day):** 3mg/day **Daily dose (mg/day), mean±SD (range):** 0.6±0.2 mg/day **Concurrent treatments:** Nortriptyline (1), Biperiden (1), Clonidine (1), Methylphenidate (2)	**Benefits:** YGTSS, PedsQL, ADHD RS-IV **Harms:** Neuromotor effects, metabolic effects, somnolence, exercise intollerance	Aripiprazole decreased tic scores as much as risperidone in children and adolescents with tic disorder. However this should not be interpreted as arapiprazole and risperidone being equivalent. Efficacsy and safety of other doses of these medications are recommended. Long term use of the medications needs further studies.
Gilbert et al., 2004 [34] **Country:** USA **Condition category:** Tic disorders	**Recruitment dates:** NR **Study design:** RCT (crossover) **Setting:** NR	**Enrolled:** 19 **Analyzed:** NR **Completed:** 13 **GROUP 1** **N:** 19 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** 2 wk **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Pimozide	**Benefits:** CGI-I, TSSR, YGTSS **Harms:** EPS (ESRS), ECG changes, weight changes	Risperidone was superior to pimozide for tic suppression but it induced weight gain.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Funding: Industry, Government **Risk of bias:** High (subjective), High (objective)	**Diagnostic criteria:** DSM-IV-TR, clinical assessment **Inclusion criteria:** (1) 7–17 yr, (2) Tourette syndrome or chronic motor tic disorder, (3) CGI tic severity score >4 after 2 wk with no medication **Exclusion criteria:** (1) transient tic disorder, anorexia nervosa, PDD, substance/alcohol abuse or dependence within the past yr, or any psychotic disorder, (2) serious or unstable medical illness or abnormal ECG or laboratory findings, (3) sexually active females of childbearing potential not using contraceptives	**Diagnostic breakdown (n):** Tourette syndrome (16), Chronic tic disorder (3) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (7), **c**onduct disorder (1), learning disorder (3), OCD (2), oppositional defiant disorder (2) **GROUP 2** **N:** 19 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Diagnostic breakdown (n):** See group 1 **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see group 1	**Dosing variability:** variable **Target dose (mg/day):** 4 **Daily dose (mg/day), mean±SD (range):** 2.4 (1–4) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** 4 **Daily dose (mg/day), mean±SD (range):** 2.5 (1–4) **Concurrent treatments:** NR		
Gothelf et al., 2002 [112] **Country:** Israel **Condition category:** Schizophrenia and related **Funding:** Government	**Recruitment dates:** NR **Study design:** Prospective cohort (NR) **Setting:** Inpatient **Diagnostic criteria:** DSM-IV, K-SADS **Inclusion criteria:** NR	**Enrolled:** 20 **Analyzed:** NR **Completed:** NR **GROUP 1** **N:** 10 **Age, mean±SD (range):** 17.0±1.6 **Males %:** 100 **Caucasian %:** NR **Treatment naïve (n):** ND **Inpatients (n):** all	**Treatment duration:** 4 wk **Run-in phase:** Yes **Run-in phase duration:** 17.6 day (mean) **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** variable **Target dose (mg/day):** NR	**Benefits:** NR **Harms:** Abdominal circumference, BMI, weight	Body mass index significantly increased in adolescent male inpatients treated with olanzapine but not in those given haloperidol.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Newcastle-Ottawa Scale: 3/8 stars	**Exclusion criteria:** (1) taking medications that affect weight	**First episode psychosis (n):** NR **GROUP 2** **N:** 10 **Age, mean±SD (range):** 17±1.6 **Males %:** 100 **Caucasian %:** NR **Treatment naïve (n):** 1 **Inpatients (n):** all **First episode psychosis (n):** NR	**Daily dose (mg/day), mean±SD (range):** 6.5±3.4 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 14±4.1 **Concurrent treatments:** NR		
Gulisano et al., 2011 [35] **Country:** Italy **Condition category:** Tic disorders **Funding:** Non-industry **Risk of Bias:** NA (subjective), Medium (objective)	**Recruitment Dates:** NR **Study design:** NRCT (parallel) **Diagnostic criteria:** DSM-IV-TR **Setting:** NR **Inclusion criteria:** With TS, 6-18 yr, normal IQ **Exclusion criteria:** Patient or family history of cardiovascular symptoms	**Enrolled:** 50 **Analyzed:** 50 **Completed:** 50 **GROUP 1:** **N:**25 **Age, mean±SD (range):** 13.1±2.3 yr **Males %:** 84 **Caucasian %:** NR **Diagnostic breakdown (n):** Tourette syndrome (25) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** ADHD (15), OCD (11) **GROUP 2:** **N:**25 **Age, mean±SD (range):** 9.1±2.9 yr **Males %:** 88 **Caucasian %:** NR	**Treatment duration:** 24 mo **Run-in phase:** Yes **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Arapiprazole **Dosing variability:** Variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 5.3±2.4 **Concurrent treatments:** NR **GROUP 2:** **Drug name:** Pimozide **Dosing variability:** Variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 4.4±1.5 **Concurrent treatments:** NR	**Benefits:** NR **Harms:** HR, BP, QTc	At equivalent doses, arapiprazole is characterized by a safer cardiovascular profile than pimozide, being associated with a lower frequency of QTc prolongation.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		Diagnostic breakdown (n): Tourette syndrome (25) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** ADHD (13), OCD (13)			
Haas et al., 2009b [37] **Country:** India, Russia, Ukraine, USA **Condition category:** Schizophrenia and related **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Aug 2004 to Dec 2005 **Study design:** RCT (parallel) **Setting:** Inpatient/outpatient **Diagnostic criteria:** DSM-IV, K-SADS-PL **Inclusion criteria:** (1) male and females, (2) aged 13 to 17 years, (3) DSM-IV diagnosis of schizophrenia, (4) inpatients or outpatients, experiencing an acute episode with a total PANSS score of 60 to 120 (inclusive), (5) no serious illnesses or neurological conditions, (6) females were required to a have negative pregnancy test and to be using an acceptable form of contraception.	**Enrolled:** 160 **Analyzed:** 158 **Completed:** 125 **GROUP 1** **N:** 55 **Age, mean±SD (range):** 15.7±1.3 **Males %:** 55 **Caucasian %:** 60 **Diagnostic breakdown (n):** Paranoid (38), Undifferentiated (8), Disorganized (8), Catatonic (1), Residual (0) **Treatment naïve (n):** NR **Inpatients (n):** 30 **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 2** **N:** 51 **Age, mean±SD (range):** 15.7±1.3 **Males %:** 73 **Caucasian %:** 47 **Diagnostic breakdown (n):** Paranoid (34), Undifferentiated (13),	**Treatment duration:** 6 wk **Run–in phase:** Yes **Run–in phase duration:** ≤5 day **Permitted drugs:** Propanolol was allowed for treatment-emergent akathisia. Antiparkinsonian medications could be initiated for treatment-emergent EPS. Use of all rescue medications was kept to a minimum, and the permitted doses of certain medications progressively decreased over the course of the study. Subjects could receive limited supportive psychotherapy or psychoeducation. **Prohibited drugs:** antidepressants, mood stabilizers, anticonvulsants, psychostimulants, direct dopamine agonists, cholinesterase inhibitors, herbal or over-the-counter medications with psychotripic properties, or antipsychotic other than the study medication. Drugs with sedative, hypnotic, or anxiolytic properties were not allowed, with some exceptions. Subjects were not permitted to receive insight-	**Benefits:** CGAS, CGI-I, CGI-S, PANSS, response, suicide **Harms:** SAS, BAS, AIMS, Behavioral issues, BMI, EPS, glucose-related AE, mortality, prolactin, prolactin-related AE, SAE, somnolence, tachycardia, tardive dyskinesia, total AE, WAE, weight change	Risperidone treatment for 6-weeks was safe and effective at daily doses of 1–3 and 4–6 mg in adolescents experiencing acute exacerbations of schizophrenia

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	Exclusion criteria: (1) DSM-IV criteria for dissociative disorder, bipolar disorder, MDD, schizoaffective disorder, schizophreniform disorder, autistic disorder, or primary substance-induced psychotic disorder at screening, (2) MR (IQ<70), (3) substance dependence diagnosed by DSM-IV criteria in 3 months preceding screening, (4) significant risk of suicide or violent behavior, (5) failed to respond to adequate treatment with >2 antipsychotic drugs during the current psychotic episode, (6) hypersensitivity or intolerance to risperidone, (7) history of neuroleptic malignant syndrome or any severe drug allergy,	Disorganized (4), Catatonic (0), Residual (0) **Treatment naïve (n):** NR **Inpatients (n):** 25 **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 3** **N:** 54 **Age, mean±SD (range):** 15.5±1.4 **Males %:** 65 **Caucasian %: 50** **Diagnostic breakdown (n):** Paranoid (38), Undifferentiated (12), Disorganized (3), Catatonic (0), Residual (1) **Treatment naïve (n):** NR **Inpatients (n):** 23 **First episode psychosis (n):** NR **Comorbidities:** NR	oriented or cognitive-behavioral psychotherapy. **GROUP 1** **Drug name:** Risperidone (low) **Dosing variability:** fixed **Target dose (mg/day):** 1–3 **Daily dose (mg/day), mean±SD (range):** NR (1–3) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Risperidone (high) **Dosing variability:** fixed **Target dose (mg/day):** 4–6 **Daily dose (mg/day), mean±SD (range):** NR (4–6) **Concurrent treatments:** NR **GROUP 3** **Drug name:** Placebo **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR		
Haas et al., 2009c [38] **Country:** USA **Condition category:** Bipolar (manic, mixed)	**Recruitment dates:** Dec 2003 to Dec 2005 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient	**Enrolled:** 170 **Analyzed:** 169 **Completed:** 137 **GROUP 1** **N:** 50 **Age, mean±SD (range):** NR (10–17)	**Treatment duration:** 3 wk **Run-in phase:** Yes **Run-in phase duration:** ≤5 day **Permitted drugs:** medication for EPS; sedatives/hypnotics (run-in and wk 1 only)	**Benefits:** BPRS, CGI-BP, YMRS, Medication adherence, response, suicide **Harms:** Behavioral issues, BMI,	A significant reduction in manic symptoms was seen in youth when treated with risperidone (0.5–2.5 mg/d or 3–6 mg/d)

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Funding: Industry **Risk of bias:** High (subjective), High (objective)	**Diagnostic criteria:** DSM-IV, K-SADS-PL **Inclusion criteria:** (1) 10–17 yr, (2) medically stable, (3) acute manic/mixed episode (K-SADS-PL), (4) total score ≥20 at screening and baseline on YMRS, (5) responsible caregiver **Exclusion criteria:** (1) known intellectual impairment	**Males %:** 56 **Caucasian %:** 70 **Diagnostic breakdown (n):** manic episode (20), mixed episode (30) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (25), DBD (27) **GROUP 2** **N:** 61 **Age, mean±SD (range):** NR (10–17) **Males %:** 43 **Caucasian %:** 82 **Diagnostic breakdown (n):** manic episode (21), mixed episode (40) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (33), DBD (40) **GROUP 3** **N:** 58 **Age, mean±SD (range):** NR (10–17) **Males %:** 48 **Caucasian %:** 78 **Diagnostic breakdown (n):** manic episode (19), mixed episode (39) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR	**Prohibited drugs:** anticonvulsants, antidepressants, antimanic medications, other antipsychotics (including herbal substances); methylphenidate/other medication for ADHD **GROUP 1** **Drug name:** Risperidone (low) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** (0.5–2.5) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Risperidone (high) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 3 (26%), 4 (19%), 5 (15%), 6 (41%) (3–6) **Concurrent treatments:** NR **GROUP 3** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	dermatologic AE, EPS (AIMS, BAS, SAS), fatigue, glucose, lipid profile, mortality, prolactin, prolactin-related AE, SAE, sedation, somnolence, tardive dyskinesia, total AE, WAE, weight change	compared to placebo.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		Comorbidities: ADHD (27), DBD (34)			
Haas et al., 2009a [36] **Country:** Belgium, Bulgaria, Czech Republic, Estonia, Germany, Poland, Romania, USA **Condition category:** Schizophrenia and related **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Apr 2001 to Mar 2006 **Study design:** RCT (parallel) **Setting:** Inpatient **Diagnostic criteria:** DSM-IV, K-SADS-PL **Inclusion criteria:** (1) 13–17 yr, (2) schizophrenia, (3) currently hospitalized for an acute episode (PANSS total score 60–120) **Exclusion criteria:** (1) significant risk for suicidal or violent behavior, (2) history of NMS, tardative dyskinesia, or a known or suspected seizure disorder, (3) BMI <5th percentile or >95th percentile, (4) schizophreniform disorder	**Enrolled:** 257 **Analyzed:** 255 **Completed:** 172 **GROUP 1** **N:** 132 **Age, mean±SD (range):** 15.6±1.32 (13–17) **Males %:** 61 **Caucasian %:** 85 **Diagnostic breakdown (n):** catatonic (3), disorganized (6), paranoid (92), residual (7), undifferentiated (24) **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR **GROUP 2** **N:** 125 **Age, mean±SD (range):** 15.6±1.25 (13–17) **Males %:** 52 **Caucasian %:** 85 **Diagnostic breakdown (n):** catatonic (4), disorganized (13), paranoid (83), residual (0), undifferentiated (25) **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** ≥7 day **Permitted drugs:** antiparkinsonian medications (first 3 wk), propranolol, rescue medications (diazepam, hydroxyzine, lorazepam, zolpidem, zopiclone) **Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone (low) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 0.4 (0.2–0.6) **Concurrent treatments:** all groups: rescue medication (133) **GROUP 2** **Drug name:** Risperidone (high) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 4 (1.5–6) **Concurrent treatments:** see group 1	**Benefits:** CGI-I, CGI-S, PANSS, medication adherence, response, suicide **Harms:** SAS, BAS, AIMS, Akathisia, behavioral issues, dyskinesia, dystonia, ECG changes, EPS, glucose, mortality, prolactin, prolactin-related AE, SAE, somnolence, tachycardia, total AE, WAE, weight change	A greater improvement in total PANSS score was found with high dose risperidone than with low dose risperidone.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Hagman et al., 2011 [39] **Country:** USA **Condition category:** Eating disorders **Funding:** Non-industry **ROB:** Medium (subjective), Medium (objective)	**Recruitment dates:** Aug 2004 to Sept 2008 **Study design:** RCT (parallel) **Setting:** Inpatient/outpatient **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) primary diagnosis of AN, (2) female gender, (3) 12-21 yr, (4) active in a level of care in the eating disorders program **Exclusion criteria:** (1) previous enrollment in study, (2) allergic reaction to risperidone or another atypical neuroleptic drug, (3) a positive pregnancy test result, (4) taking a psychotropic medication other than an antidepressant, (5) active hepatic or renal disease, (6) male gender, (7) wards of court	**Enrolled:** 41 **Analyzed:** 40 **Completed:** 40 **GROUP 1** **N:** 18 **Age, mean±SD (range):** 16.2±(2.5) yr **Males %:** 0 **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** depression (NR), obsessive-compulsive disorder (NR), anxiety disorder (NR), bulimia nervosa (NR) **GROUP 2** **N:** 22 **Age, mean±SD (range):** 15.8±(2.3) yr **Males %:** 0 **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see group 1	**Treatment duration:** 9 wk **Run-in phase:** NR **Run-in phase duration:** NR **Permitted drugs:** antidepressants (if on stable dose for >1 wk before entering the study, no dose adjustments during study), multivitamin, zinc, medications for other medical conditions (constipation, asthma, gastritis) **Prohibited drugs:** new psychotropic medications **GROUP 1** **Drug name:** Risperidone **Dosing variability:** flexible **Target dose (mg/day):** 4.0 **Daily dose (mg/day), mean±SD (range):** 2.5±1.2 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** flexible **Target dose (mg/day):** 4.0 **Daily dose (mg/day), mean±SD (range):** 3.0±1.0 **Concurrent treatments:** NR	**Benefits:** EDI-2 DT, EDI-2 BD, ADJ-current, ADJ-desired, CAPT, MASC, suicidal ideation, anxiety, depression **Harms:** EPS (AIMS, SAS), glucose, lipid profile, prolactin, fatigue, blood pressure	This exploratory pilot study does not demonstrate a clear benefit from the addition of risperidone in the course of active treatment and weight restoration in adolescents with AN.
Hellings et al., 2006 [40] **Country:** USA	**Recruitment dates:** NR	**Enrolled:** 26 **Analyzed:** 26 **Completed:** NR	**Treatment duration:** 5.1 mo (6 wk at each dose) **Run-in phase:** Yes	**Benefits:** ABC, CGI-I, PAC, VAS	Compared to placebo, risperidone was more effective in treating

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Condition category: ASD **Funding:** Industry, Government **Risk of bias:** High (subjective), High (objective)	**Study design:** RCT (crossover) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) 6–65 yr, (2) MR (IQ <70), (3) at least 6 mo history of aggression, property destruction, or self-injury, (4) above normal baseline Irritability score for age, gender and setting (ABC-C) **Exclusion criteria:** (1) previous risperidone hypersensitivity, (2) history of NMS, (3) seizures within the past yr, (4) degenerative brain disease, (5) problematic living situation	**GROUP 1** **N:** 26 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** Autistic Disorder (ND), MR (Mild (8), moderate (6), severe (8), profound (4)), PDD-NOS (ND) **GROUP 2** **N:** 26 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see group 1 **GROUP 3** **N:** 26 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see group 1	**Run-in phase duration:** 5–7 wk **Permitted drugs:** divalproex, gabapentin (if epilepsy was in remission ≥1 yr) **Prohibited drugs:** psychotropics, including stimulants **GROUP 1** **Drug name:** Risperidone (low) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** all groups: divalproex (5), gabapentin (1) **GROUP 2** **Drug name:** Risperidone (high) **Dosing variability:** variable **Target dose (mg/day):** 0.05 mg/kg/day **Daily dose (mg/day), mean±SD (range):** 2 (1.2–2.9) **Concurrent treatments:** see group 1 **GROUP 3** **Drug name:** Placebo II **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** see group 1	**Harms:** NMS, tardive dyskinesia, weight change	problematic behaviors in children and adolescents with MR. Low doses were better tolerated and were equally effective compared to high doses.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Hollander et al., 2006 [41] **Country:** USA **Condition category:** ASD **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-IV, ADI-R, ADOS **Inclusion criteria:** (1) 6–17 yr, (2) meets DSM-IV and ADI-R criteria with a rating of at least moderate (≥4) on the CGI **Exclusion criteria:** (1) response to prior pharmacological treatment, (2) psychotic disorders and a history of any clinically significant medical illness (with the exception of a stable seizure disorder)	**Enrolled:** 11 **Analyzed:** 11 **Completed:** 8 **GROUP 1** **N:** 6 **Age, mean±SD (range):** 9.3±2.9 (6–14.8) **Males %:** 100 **Caucasian %:** 50 **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (normal (2), mild (2), severe (2)) **GROUP 2** **N:** 5 **Age, mean±SD (range):** 8.9±2.1 (6.1–11) **Males %:** 60 **Caucasian %:** 80 **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (normal (2), mild (3))	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** 4 wk **Permitted drugs:** anticonvulsants (stable dose ≥3 mo), clonidine, chloral hydrate **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 10±2 (7.5–12.5) **Concurrent treatments:** none **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 10±2 (7.5–12.5) **Concurrent treatments:** none	**Benefits:** CGI-I, response (CGI-I, CPRS) **Harms:** Constipation, EPS (AIMS, BAS, SAS), sedation, weight change	Olazapine improved global functioning in children and adolescents with PDD, but was associated with a significant risk of weight gain.
Hrdlicka et al., 2009 [113] **Country:** Czech Republic **Condition category:** Schizophrenia and related	**Recruitment dates:** 1997 to 2007 **Study design:** Retrospective cohort **Setting:** Inpatient **Diagnostic criteria:** ICD-10	**Enrolled:** 109 **Analyzed:** NR **Completed:** 52 **GROUP 1** **N:** 24 **Age, mean±SD (range):** 15.8±1.6yr (all) **Males %:** 48% (all) **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR	**Treatment duration:** 6 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Typical (Haloperidol, Perphenazine, Sulpiride) **Dosing variability:** variable	**Benefits:** NR **Harms:** Weight changes	Weight gain did not differ between the groups on typical and atypical antipsychotics.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Funding: Government, Academic **Newcastle-Ottawa Scale:** 5/8 stars	**Inclusion criteria:** (1) schizophrenia dx (F20-29), (2) medical record quality sufficient to evaluate the patient, (3) the first treatment used following admission was considered (with the exception of clozapine), (4) only antipsychotic treatments initiated after admission to the Department of Child Psychiatry were analyzed **Exclusion criteria:** NR	**First episode psychosis (n):** NR **GROUP 2** **N:** 85 **Age, mean±SD (range):** see above **Males %:** see above **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR	**Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** Haloperidol 6.8±1.1, Perphenazine 12±6.9, Sulpiride 450±409.3 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Atypical (Clozapine, Olanzapine, Risperidone, Ziprasidone) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** Clozapine 247.5±118, Olanzapine 15±6.1, Risperidone 2.7±1.3, Ziprasidone 80±0 **Concurrent treatments:** NR		
Jensen et al., 2008 [42] **Country:** USA **Condition category:** Schizophrenia and related **Funding:** NR **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** May 2003 to June 2006 **Study design:** RCT (parallel) **Setting:** Inpatient (most) **Diagnostic criteria:** DSM-IV, K-SADS **Inclusion criteria:** (1) 10–18 yr, (2) schizophrenia/ schizoaffective disorder, schizophreniform, or psychotic disorder NOS, (3) ≥1 positive or	**Enrolled:** 30 **Analyzed:** 29 **Completed:** 21 **GROUP 1** **N:** 10 **Age, mean±SD (range):** 15.3±1.5 **Males %:** 50 **Caucasian %:** 50 **Diagnostic breakdown (n):** psychotic disorder NOS (6), schizophrenia, schizoaffective, schizophreniform disorder (4) **Treatment naïve (n):** NR **Inpatients (n):** 9 **First episode psychosis (n):** NR	**Treatment duration:** 2.8 mo **Run-in phase:** Yes **Run-in phase duration:** 2 wk **Permitted drugs:** diphenhydramine (≤100 mg/day), lorazepam (0.5–2 mg/day) **Prohibited drugs:** antidepressants, mood stabilizers, and stimulants (discontinued prior to or within first 2 wk of trial) **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** 20 **Daily dose (mg/day), mean±SD (range):** 14±4.6 (5–20)	**Benefits:** PANSS, CGAS, CGI-S, medication adherence, response **Harms:** AIMS, SAS, akathisia, behavioral issues, dyskinesia, EPS, mastitis, sedation, WAE, weight change	There was no statistically significant difference between groups in the reduction of PANSS scores; however a larger RCT may be warranted to test the clinical significance of differences between treatment with quetiapine and risperidone.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	negative symptom associated with schizophrenia present throughout the past 2 wk (PANSS) **Exclusion criteria:** (1) MR or affective disorder with psychotic features, (2) current alcohol or drug dependence or abuse, (3) history of serious adverse reactions or nonresponse to an adequate trial of any of the proposed treatments, (4) pregnant or refusal to practice contraception, (5) serious and unstable medical condition	**Comorbidities:** MR (0), psychosis (all) **GROUP 2** **N:** 10 **Age, mean±SD (range):** 14.8±2.3 **Males %:** 70 **Caucasian %:** 60 **Diagnostic breakdown (n):** psychotic disorder NOS (3), schizophrenia, schizoaffective, schizophreniform disorder (7) **Treatment naïve (n):** NR **Inpatients (n):** 9 **First episode psychosis (n):** NR **Comorbidities:** MR (0), psychosis (all) **GROUP 3** **N:** 10 **Age, mean±SD (range):** 15.6±2.5 **Males %:** 80 **Caucasian %:** 70 **Diagnostic breakdown (n):** psychotic disorder NOS (0), schizophrenia, schizoaffective, schizophreniform disorder (10) **Treatment naïve (n):** NR **Inpatients (n):** 9 **First episode psychosis (n):** NR **Comorbidities:** MR (0), psychosis (all)	**Concurrent treatments:** anticholinergics (0), dietary counselling, psychoeducation **GROUP 2** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** 800 **Daily dose (mg/day), mean±SD (range):** 611±253.4 (100–800) **Concurrent treatments:** anticholinergics (0), dietary counselling, psychoeducation **GROUP 3** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** 6 **Daily dose (mg/day), mean±SD (range):** 3.4±1.5 (1–6) **Concurrent treatments:** anticholinergics (0), dietary counselling, psychoeducation,		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Jerrell et al., 2008 [114] **Country:** USA **Condition category:** Mixed **Questions:** KQ2, KQ3 **Funding:** Non-industry **Newcastle-Ottawa Scale:** 6/8 stars	**Recruitment dates:** Jan 1996 to Dec 2005 **Study design:** Retrospective **Setting:** Inpatient/ outpatient **Diagnostic criteria:** ICD-9-CM **Inclusion criteria:** (1) Child and adolescent pateints, (2) ≤17 yr, (3) enrolled in and eligible for Medicaid for ≥ 9 mo in each calendar year, (4) who had a service encounter, (5) who were prescribed 1 of 5 atypical (aripiprazole, ziprasidone, quetiapine, risperidone, olanzapine) or 2 conventional antipsychotics (haloperidol or fluphenazine) **Exclusion criteria:** NR	**Enrolled:** NA **Analyzed:** 4140 **Completed:** 4140 **GROUP 1** **N:** 4140 **Age, mean±SD (range):** NR **Males %:** 68 **Caucasian %:** 42 **Diagnostic breakdown (n):** Schizophrenia or other psychotic disorders (1507), major affective disorders (2261), ADHD (3258) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** Epilepsy (954), CNS disorders (919), organic brain syndrome or severe MR (704), congenital heart defects (146), endocrine disorder (168), preexisting obesity (680), preexisting type II diabetes mellitus or dyslipidemia (404), preexisting cardiovascular disorder (246)	**Treatment duration:** ≥9 mo **Run-in phase:** NR **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Antipsychotics cohort **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 7.4±3.1 **Concurrent treatments:** SSRI (2367), , weight-inducing antidepressants (3292), psychostimulants (3170), multiple antipsychotics (1756), mood stabilizers (1898)	**Benefits:** NR **Harms:** Weight gain, type 2 diabetes mellitus, dyslipidemia, hypertension, cardiovascular/ cerebrovascular events, orthostatic hypotension/ syncope, EPS, seizures, sedation/ somnolence, sexual/ reproductive	When evaluating the overall benefit-risk ratio of all psychotropics prescribed in children and adolescents, the practitioner needs to give careful consideration to possible toxicities that have been previously demonstrated in this and other studies, especially in individuals receiving concomitant psychotropic medications, and to children with preexisting/comorbid medical conditions or diet/family risk factors that might increase their potential for experiencing adverse reactions.
Johnson & Johnson, 2011 [43] **Country:** NR	**Recruitment dates:** Mar to Aug 2006 **Study design:** RCT (parallel)	**Enrolled:** 25 **Analyzed:** 25 **Completed:** 24 **GROUP 1** **N:** 8	**Treatment duration:** 7 days **Run–in phase:** Yes **Run–in phase duration:** 21 days maximum **Permitted drugs:** NR	**Benefits:** NR **Harms:** total AE, serious AEs, mortality, prolactin, prolactin-related AE,	Pediatric subjects tolerated doses from 4 to 12 mg paliperidone ER (corresponding to weight-adjusted

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Condition category: Schizophrenia and related **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Setting:** NR **Diagnostic criteria:** DSM-IV-TR **Inclusion criteria:** (1) male or female, (2) aged 10 to 17 years, (3) height and weight within the 5th to 95th percentile for age and sex, (4) DSM-IV-TR diagnosis of schizophrenia of any subtype, schizoaffective or schizophreniform (3) otherwise healthy, (4) CGI-S score of =< 3 **Exclusion criteria:** NR	**Age, mean±SD (range):** all groups: 14.6±2.2 (10–17) **Males %:** all groups: 72 **Caucasian %:** all groups: 56 **Diagnostic breakdown (n):** all groups: schizophreniform disorder (8), schizoaffective disorder (7), paranoid (6), undifferentiated (3), disorganized (1) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 9 **Age, mean±SD (range):** see group 1 **Males %:** see group 1 **Caucasian %:** see group 1 **Diagnostic breakdown (n):** see group 1 **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 3** **N:** 8 **Age, mean±SD (range):** see group 1 **Males %:** see group 1 **Caucasian %:** see group 1	**Prohibited drugs:** NR **GROUP 1** **Drug name:** Paliperidone ER **Dosing variability:** fixed **Target dose (mg/day):** 0.086 mg/kg/day **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 2** **Drug name:** Paliperidone ER **Dosing variability:** fixed **Target dose (mg/day):** 0.129 mg/kg/day **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 3** **Drug name:** Paliperidone ER **Dosing variability:** fixed **Target dose (mg/day):** 0.171 mg/kg/day **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	orthostatic hypotension, ECG changes, EPS scales	doses ranging from 0.086 and 0.171 mg/kg).

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		Diagnostic breakdown (n): see group 1 **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR			
Kafantaris et al., 2011 [44] **Country:** USA **Condition category:** Eating disorders **Funding:** Industry **ROB:** Medium (subjective), Medium (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient/outpatient **Diagnostic criteria:** EDE (Eating Disorder Examination) **Inclusion criteria:** (1) females who received treatment for AN at the Eating Disorder Treatment Program over a 4 yr period, (2) between 12-21 yr, (3) primary diagnosis of ANR **Exclusion criteria:** (1) past or current binge/purge type, (2) serious suicidal risk, (3) prior treatment with olanzapine, (4) not on a sable medication regimen for 8 wk prior to study entry	**Enrolled:** 20 **Analyzed:** 20 **Completed:** 15 **GROUP 1** **N:** 10 **Age, mean±SD (range):** 16.4±2.2 yr **Males %:** 0 **Caucasian %:** see below **Diagnostic breakdown (n):** NR **Treatment naïve (n):** 10 **Inpatients (n):** see below **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 2** **N:** 10 **Age, mean±SD (range):** 18.1±2.0 yr **Males %:** 0 **Caucasian %:** see below **Diagnostic breakdown (n):** NR **Treatment naïve (n):** 10 **Inpatients (n):** see below **First episode psychosis (n):** NR **Comorbidities:** NR **Overall Caucasian %:** 80 **Overall inpatients (n):** 9	**Treatment duration:** 10 wk **Run-in phase:** NR **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** flexible **Target dose (mg/day):** 10 **Daily dose (mg/day), mean±SD (range):** NR (started with 2.5mg single oral dose; increased by 2.5mg each wk to reach target dose) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** flexible **Target dose (mg/day):** 10 **Daily dose (mg/day), mean±SD (range):** NR (started with 2.5mg single oral dose; increased by 2.5mg each wk to reach target dose) **Concurrent treatments:** NR	**Benefits:** HDRS, Brief Psychiatric Rating Scale, EDE, YBC-EDS, medication adherence **Harms:** dystonia, akathisia, dyskinesia, weight gain (BMI), glucose, insulin, cardiac function	The lack of support for olanzapine's efficacy relative to placebo in the context of our comprehensive treatment setting, coupled with concerns regarding increases in insulin and glucose, dissuaded us from pursuing a larger placebo-controlled study of adjunctive olanzapine for adolescents with AN-R at our setting.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Kent et al., 2013 [45] **Country:** USA **Condition category:** ASD **Funding:** Industry **Risk of bias:** Medium (subjective), Medium (objective)	**Recruitment dates:** Dec 2007 to Mar 2010 **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-IV-TR, ADI-R **Inclusion criteria:** (1) Male or female 5–17 years old, (2) Body weight of ≥20 kg (3) DSM-IV diagnosis of Autistic Disorder (299.00), corroborated by standard cut-off scores on the ADI-R, ABC-I Subscale score of 18 or more, CGI-S of ≥4, (4) mental age >18 months, (5) patients with history of seizures required to be seixure free for at least 6 consecutive months or on stable dosage of antiepileptic frugs ≥ 4 weeks before screening, (6) normal fasting glucose and creatinine, and liver funcion tests levels <1.5 times normal upper limit **Exclusion criteria:** (1) Previous or current	**Enrolled:** 96 **Analyzed:** 96 **Completed:** 77 **GROUP 1** **N:** 30 **Age, mean±SD (range):** NR **Males %:** 83 **Caucasian %:** 70 **Diagnostic breakdown (n):** autistic disorder (all) **Treatment naïve (n):** 26 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 2** **N:** 31 **Age, mean±SD (range):** NR **Males %:** 90 **Caucasian %:** 81 **Diagnostic breakdown (n):** autistic disorder (all) **Treatment naïve (n):** 29 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 3** **N:** 35 **Age, mean±SD (range):** NR **Males %:** 89 **Caucasian %:** 60 **Diagnostic breakdown (n):** autistic disorder (all)	**Treatment duration:** 6 wk **Run–in phase:** Yes **Run–in phase duration:** 3 wk **Permitted drugs:** Anticholinergics, antihistamine, hypnotic, sedative (lorazepam, diphenhydramine) **Prohibited drugs:** Psychotropic medications for atleast 1 week (4 weeks for fluoxetine, 8 weeks for depot medications) **GROUP 1** **Drug name:** Risperidone **Dosing variability:** fixed **Target dose (mg/day):** 0.125 (20<45 kg), 0.175 (≥45kg) **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** methylphenidate (1) **GROUP 2** **Drug name:** Risperidone **Dosing variability:** fixed **Target dose (mg/day):** 1.25 (20<45 kg), 1.75 (≥45kg) **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** methylphenidate (1) **GROUP 3** **Drug name:** Placebo **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR	**Benefits:** ABC-I, ABC (other sub scales), CGI-S, CYBOCS, CGI-I, response, aggression **Harms:** EPS (AIMS, BAS, SAS) Somnolence, weight increase (BMI), mortality, akathisia, tardive dyskinesia, prolactin, prolactin-related AE (oligomenorrhea), glucose metabolism related AE, elevated insulin levels, lipid profile, nausea, ECG, constipation, agitation	Data from this study demonstrate that risperidone at higher doses of 1.25 and 1.75 mg/day were efficacious; however, risperidone at doses <0.25 mg did not demonstrate significant efficacy in the treatment of irritability and related behaviors associated with autistic disorder in children and adolescents, consistent with current labeling.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	DSM-IV diagnosis of psychotic disorder or PDD other than autism, (2) neurologic disorders, (3) moderate/severe extrapyramidal symptoms or tardive dyskinesia, (4) lack of response to risperidone treatment in the past, (5) pregnant/breast feeding girls	**Treatment naïve (n):** 32 **Inpatients (n):** NR **First episode psychosis:**NR **Comorbidities:** NR	**Concurrent treatments:** methylphen- idate (1), alprazolam (1), melatonin (2)		
Khan et al., 2009 [115] **Country:** USA **Condition category:** Mixed conditions **Funding:** NR **Newcastle-Ottawa Scale:** 6/8 stars	**Recruitment dates:** Sept 2003 to Aug 2005 **Study design:** Retrospective **Setting:** Inpatient **Diagnostic criteria:** Medical record **Inclusion criteria:** (1) <18 yr, (2) treated with olanzapine or risperidone between Sept 2003 to Aug 2005 at the child and adolescent psychiatric unit of the Austin State Hospital **Exclusion criteria:** (1) ≥18 yr, (2) who received antipsychotic polypharmacy or >2 wk of cross titration between	**Enrolled:** NA **Analyzed:** 49 **Completed:** 49 **GROUP 1** **N:** 25 **Age, mean±SD (range):** 13.0±3.5 yr **Males %:** 64 **Caucasian %:** 72 **Diagnostic breakdown (n):** See below **Treatment naïve (n):** NR **Inpatients (n):** 25 **First episode psychosis (n):** NR **Comorbidities:** See below **GROUP 2** **N:** 24 **Age, mean±SD (range):** 13.0±3.5 yr **Males %:** 83 **Caucasian %:** 58 **Diagnostic breakdown (n):** See below	**Treatment duration:** Olanzapine 27±12 d, risperidone 26±13 d **Run-in phase:** Yes **Run-in phase duration:** 2-4 wk **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 12.5 (range 5-25 mg) **Concurrent treatments:** Stimulants (5) **GROUP 2** **Drug name:** Risperidone **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2.6 (range 1-7 mg) **Concurrent treatments:** Stimulants (6)	**Benefits:** NA **Harms:** BMI, systolic/ diastolic blood pressure, lipid profile, fasting glucose	Treatment with both olanzapine and risperidone results in a significant increase in BMI. Also, olanzapine significantly increases risk factors for diabetes mellitus and overall risk factors for metabolic syndrome. Clinicians should consider potential metabolic effects while selecting antipsychotics and educate patients on these effects.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	antipsychotics, (3) who received one of the study medications within 4 wk prior to their inpatient admission or who received the study medication <2 wk during inpatient hospital stay, (4) subjects who did not have either a lipid profile or a glucose level drawn during admission	**Treatment naïve (n):** NR **Inpatients (n):** 24 **First episode psychosis (n):** NR **Comorbidities:** See below **Overall diagnostic breakdown (n):** BP (NR), mood disorder NOS (NR), major depressive disorder (NR), schizoaffective disorder, schizophrenia, and schizophreniform disorder (7) **Overall comorbidities:** SUD (14), ADHD (8)			
Khan et al., 2006 [116] **Country:** USA **Condition category:** Mixed conditions **Funding:** NR **Newcastle-Ottawa Scale:** 4/8 stars	**Recruitment dates:** Jan 2003 to Jan 2005 **Study design:** Retrospective cohort **Setting:** Inpatient **Diagnostic criteria:** NR **Inclusion criteria:** (1) <18 yr, (2) hospitalized with any mental illness, (3) treatment with IM ziprasidone or olanzapine for acute agitation/agression, (4) hospitalized during study period	**Enrolled:** NA **Analyzed:** 100 **Completed:** 100 **GROUP 1** **N:** 50 **Age, mean±SD (range):** 13.7±2.4 **Males %:** 68 **Caucasian %:** 60 **Diagnostic breakdown (n):** any Axis I dx with psychosis (18) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** PTSD (18), SA (27) **GROUP 2** **N:** 50	**Treatment duration:** Olanzapine 3.7 (2.4) wk, Ziprasidone 4.9 (3.4) wk (mean(SD)) **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** total 8.2±2.4, children 6±2.2, adolescents 9.20±1.8 **Concurrent treatments:** antipsychotic other than ziprasidone (41); aripiprazole, quetiapine most commonly prescribed	**Benefits:** NA **Harms:** Dermatologic AE, pseudoparkinsonism, sedation	IM ziprasidone and IM olanzapine may be equally effective for the treatment of children and adolescents with agitation and aggression.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	Exclusion criteria: (1) >18 yr, (2) moderate, severe or profound MR, (3) patients who did not receive IM ziprasidone/ olanzapine for agitation or agression during their inpatient stay, (4) patients receiving both IM ziprasidone and olanzapine	**Age, mean±SD (range):** 14.6±2.1 **Males %:** 32 **Caucasian %:** 68 **Diagnostic breakdown (n):** any Axis I dx with psychosis (16) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see group 1	**GROUP 2** **Drug name:** Ziprasidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** total 19.1±2.7, children 15.7±4.4, adolescents 19.5±2.1 **Concurrent treatments:** antipsychotics (48) (olanzapine (13), clozapine (4)); aripiprazole, quetiapine the most commonly prescribed		
Kowatch et al., 2015 [46] **Country:** USA **Condition category:** Bipolar disorder **Funding:** Non-industry **Risk of bias:** Medium (subjective), Medium (objective)	**Recruitment dates:** Sept 2005 to Sept 2010 **Study design:** RCT (parallel) **Setting:** Outpatient **Diagnostic criteria:** DSM-IV-TR, K-SADS, PAPA **Inclusion criteria:** (1) Male and female, (2) aged 3-7yr 11 mo, (3) bipolar I disorder , mixed or manic, psychotic or nonpsychotic (according to DSM-IV-TR, K-SADS [for 6-7 yr] and PAPA [for3-5 yr]), (4)) permitted to have comorbid ADHD **Exclusion criteria:** (1) Clinically significant or	**Enrolled:** 25 **Analyzed:** 25 **Completed:** 23 **GROUP 1** **N:** 18 **Age, mean±SD (range):** 5.31±1.3 yr **Males %:** 61 **Caucasian %:** 61 **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** ADHD (37%), ODD (4.3%), GAD (8.7%) **GROUP 2** **N:** 7 **Age, mean±SD (range):** 5.19±1.0 yr **Males %:** 71 **Caucasian %:** 71	**Treatment duration:** 6 wk **Run–in phase:** Yes **Run–in phase duration:** 4 wk (aripiprazole/fluoxetine), 2 wk (other psychotropic) **Permitted drugs:** Oral chlorpromazine in low doses for sleep disturbance and agitation during the first 2 wk of trial **Prohibited drugs:** Antipsychotic, antidepressant, mood stabilizer/ anticonvulsant other than study drug **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 0.5(0.5-0.75)mg/day **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable	**Benefits:** YMRS, CGI-I, CDRS, response, irritability **Harms:** EPS (AIMS, BAS, SAS), ECG, lipid profile, liver function tests, prolactin, insulin, weight (BMI), hematologic values	In this small sample of preschool children with BD, risperidone demonstrated clear efficacy versus placebo. Treatment with risperidone over 6 weeks led to increased prolactin levels, liver functions, metabolic measures, and weight/BMI.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	unstable hepatic, renal, gastroenterological, respiratory, cardiovascular, endocrine, immunological, hematological, or other systemic medical conditions, (2) neurological disorders including epilepsy, stroke, or severe head trauma, (3) clinically significant laboratory abnormalities on complete blood count (CBC) with differential, electrolytes, blood urea nitrogen (BUN), creatinine, hepatic transaminases, urinalysis, thyroid indices (T3, total T4, tree T4, thyroid-stimulating hormone [TSH]) and electrocardiogram (ECG), (4) mania caused by a general medical condition or substance-induced mania, (5) mental retardation (intelligence quotient [IQ] < 70); evidence of fetal alcohol syndrome or an alcohol-related neurodevelopmental disorder, (6) or schizophrenia or other	**Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** ADHD (15.2%), ODD (0%), GAD (6.5%)	**Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	psychotic disorders (including schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder caused by a general medical condition, substance-induced psychotic disorder, psychotic disorder not otherwise specified) as defined in the DSM-IV				
Kryzhanovskaya et al., 2009 [47] **Country:** Russia, USA **Condition category:** Schizophrenia and related **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Nov 2002 to Apr 2005 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV-TR, K-SADS **Inclusion criteria:** (1) 13–17 yr, (2) schizophrenia (paranoid, disorganized, catatonic, undifferentiated, and residual types), (3) able to perform all protocol–required examinations, (4) total	**Enrolled:** 107 **Analyzed:** 107 **Completed:** 64 **GROUP 1** **N:** 72 **Age, mean±SD (range):** 16.1±1.3 (13–18) **Males %:** 70.8 **Caucasian %:** 72.2 **Treatment naïve (n):** 21 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (0), SA (0) **GROUP 2** **N:** 35 **Age, mean±SD (range):** 16.3±1.6 (13.1–18) **Males %:** 68.6 **Caucasian %:** 71.4	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** 2–14 day **Permitted drugs:** anticholinergics (2–6mg/day), benzodiazepines (2 mg/day lorazepam equivalents for ≤3 consecutive days) **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 11.1 (2.5–20) **Concurrent treatments:** anticholinergics (3), benzodiazepines (21) **GROUP 2** **Drug name:** Placebo	**Benefits:** BPRS-C, PANSS, CGI-I, CGI-S, OAS, medication adherence, response, suicide **Harm:** AIMS, BAS, SAS, BMI, ECG changes, glucose, hepatic enzyme, lipid profile, mortality, prolactin, sedation, schizophrenia, somnolence, WAE, weight change	Adolescents with schizophrenia experienced significant symptom improvement when treated with olanzapine compared to placebo.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	score ≥35 on the anchored version of the BPRS-C16 and a score ≥3 on at least one of the following BPRS-C items at enrolment and randomization: hallucinations, delusions, or peculiar fantasies, (5) previously treated with clozapine and other atypical antipsychotics **Exclusion criteria:** (1) previous participation in a clinical trial of oral olanzapine, (2) treatment within 30 day of the trial with a drug without regulatory approval for any indication, (3) documented olanzapine allergic reaction, (4) previous nonresponse to an adequate dose/duration of olanzapine treatment, (5) potential safety concerns, (6) pregnancy, nursing, or refusal to practice acceptable contraception, (7) acute/ unstable medical conditions, (8) current/expected use of any concomitant	**Treatment naïve (n):** 5 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (0), SA (0)	**Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** anticholinergics (2), benzodiazepines (18)		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	psychotropic medications (except for permitted drugs), (9) baseline prolactin ≥200 ng/mL, (10) clinically significant laboratory abnormalities, (11) DSM-IV-TR substance dependence within 30 day (except nicotine and caffeine) (12) current DSM-IV-TR dx of a comorbid psychiatric or developmental disorder				
Kumra et al., 2008 [49] **Country:** USA **Condition category:** Schizophrenia and related **Funding:** NR **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Sep 2001 to Mar 2006 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, K-SADS-PL, structured interview **Inclusion criteria:** (1) 10–18 yr, (2) schizophrenia or schizoaffective disorder, (3) treatment refractoriness (documented treatment failure of ≥2 prior adequate antipsychotic trials and a baseline BRPS total score ≥35 and at least moderate	**Enrolled:** 40 **Analyzed:** 39 **Completed:** 28 **GROUP 1** **N:** 19 **Age, mean±SD (range):** 15.8±2.2 **Males %:** 44.4 **Caucasian %:** 11.1 **Diagnostic breakdown (n):** schizoaffective disorder (7), schizophrenia (11) **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** 0 **Comorbidities:** MR (0) **GROUP 2** **N:** 21 **Age, mean±SD (range):** 15.5±2.1 **Males %:** 61.9	**Treatment duration:** 2.8 mo **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** current medications tapered as tolerated (first 4 wk of trial) **Prohibited drugs:** NR **GROUP 1** **Drug name:** Clozapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 403.1±201.8 (50–700) **Concurrent treatments:** all groups: antidepressants (4), depakoate (3), lithium (7), mood stabilizer (6), naltrexone (1), stimulant (1); group 1: n=6 **GROUP 2** **Drug name:** Olanzapine (high dose)	**Benefits:** BPRS, CGAS, CGI-I, CGI-S, SANS, response **Harms:** Blood cells, BMI, constipation, diabetes, EPS, glucose, lipid profile, prolactin, SAE, WAE, weight change	A greater number of children diagnosed with schizophrenia/ schizoaffective disorder and treated with clozapine met drug response criteria than children treated with olanzapine. Clinicians should be aware of potential metabolic adverse events of long-term clozapine treatment.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	on one or more psychotic items on the BRPS) **Exclusion criteria:** (1) premorbid dx of MR, (2) history of serious adverse reactions to the proposed treatments, (3) pregnant, (4) serious and unstable medical condition, (5) failed an adequate trial of clozapine (≥12 wk) at adequate doses (≥300mg/day) and/or failed an adequate trial of olanzapine (≥8wk) at high doses (≥20mg/day)	**Caucasian %:** 28.6 **Diagnostic breakdown (n):** schizoaffective disorder (7), schizophrenia (14) **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** 0 **Comorbidities:** MR (0)	**Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 26.2±6.5 (10–30) **Concurrent treatments:** see group 1; group 2: n=11		
Kumra et al., 1998 [117] **Country:** USA **Condition category:** Schizophrenia and related **Funding:** Industry **Newcastle-Ottawa Scale:** 5/8 stars	**Recruitment dates:** NR **Study design:** Prospective cohort **Setting:** Inpatient **Diagnostic criteria:** DSM-III-TR, K-SADS-E **Inclusion criteria:** (1) schizophrenia with psychotic symptoms documented by 12 yr (DSM-III-R), (2) failure of two prior neuroleptic treatments, (3) communication capability, (4)	**Enrolled:** 23 **Analyzed:** 23 **Completed:** 21 **GROUP 1** **N:** 15 **Age, mean±SD (range):** 13.6±1.5 **Males %:** 53.3 **Caucasian %:** NR **Diagnostic breakdown (n):** disorganized (8), paranoid (2), undifferentiated (5) **Treatment naïve (n):** 0 **Inpatients (n):** all **First episode psychosis (n):** 0 **GROUP 2**	**Treatment duration:** Clozapine 6 wk, Olanzapine 8 wk **Run-in phase:** Yes **Run-in phase duration:** 17.5 day (mean) **Permitted drugs:** benzodiazepines (<8 mg/day) **Prohibited drugs:** NR **GROUP 1** **Drug name:** Clozapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 317±147 (100–600) **Concurrent treatments:** NR **GROUP 2**	**Benefits:** BPRS, SANS, SAPS, response **Harms:** Behavioral issues, blood cells, constipation, EPS, liver function, seizure, somnolence, tachycardia, weight change	Preliminary data suggested clozapine and olanzapine were efficacious in children and adolescents with treatment-refractory schizophrenia.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	premorbid Full Scale IQ >70 **Exclusion criteria:** (1) any significant unstable neurological or medical disorder, (2) current serious suicidal risk, (3) active alcohol or drug abuse	**N:** 8 **Age, mean±SD (range):** 15.3±2.3 **Males %:** 50 **Caucasian %:** NR **Diagnostic breakdown (n):** disorganized (3), paranoid (1), undifferentiated (4) **Treatment naïve (n):** 0 **Inpatients (n):** all **First episode psychosis (n):** 0	**Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 17.5±2.3 (12.5–20) **Concurrent treatments:** benzodiazepines (7), lithium (1)		
Kumra et al., 1996 [48] **Country:** USA **Condition category:** Schizophrenia and related **Funding:** NR **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient **Diagnostic criteria:** DSM-III-TR, K-SADS, DICA-R **Inclusion criteria:** (1) schizophrenia with documented psychotic symptoms by 12 yr (DSM-III-TR), (2) intolerance, nonresponse, or both to ≥2 different neuroleptic drugs, (3) full-scale IQ ≥70 **Exclusion criteria:** (1) neurologic or medical disease	**Enrolled:** 21 **Analyzed:** 21 **Completed:** 17 **GROUP 1** **N:** 11 **Age, mean±SD (range):** 13.7±1.6 **Males %:** 54.6 **Caucasian %:** NR **Diagnostic breakdown (n):** disorganized (5), paranoid (1), undifferentiated (5) **Treatment naïve (n):** NR **Inpatients (n):** 11 **First episode psychosis (n):** 0 **GROUP 2** **N:** 10 **Age, mean±SD (range):** 14.4±2.9 **Males %:** 50 **Caucasian %:** NR **Diagnostic breakdown (n):** disorganized (5), undifferentiated (5)	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** 6 wk **Permitted drugs:** group 1: benztropine mesylate (≤6 mg/day); group 2: identical placebo; all: atenolol, antibiotics, anticonvulsants **Prohibited drugs:** NR **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 16±8 (7–27) **Concurrent treatments:** benzotropine **GROUP 2** **Drug name:** Clozapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 176±149 (25–525)	**Benefits:** BPRS-C, CGAS, CGI-I, SANS, SAPS, **Harms:** Blood cells, blood pressure, EPS (SAS, AIMS), drowsiness, hepatic enzyme, NMS, seizure, tachycardia, weight	Clozapine was more effective in controlling positive and negative symptoms in treatment-refractory childhood onset schizophrenia than haloperidol.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		Treatment naïve (n): NR **Inpatients (n):** 10 **First episode psychosis (n):** 0	**Concurrent treatments:** amoxicillin (1), penicillin (1)		
Loebel et al., 2016 [50] **Country:** USA **Condition category:** ASD **Funding:** Industry **Risk of Bias:** Medium (subjective, Medium (objective)	**Recruitment dates:** Sept 2013 to Nov 2014 **Study design:** RCT **Setting:** Outpatient **Diagnostic criteria:** DSM-IV-TR **Inclusion criteria:** (1) ≥18 on the Irritability subscale of the Aberrant behavior checklist, (2) ≥4 on the Clinical Global Impression severity **Exclusion criteria:** current diagnosis of bipolar disorder, schizophrenia, major depressive disorder, Fragile-X syndrome, or childhood disintegrative disorder or a confirmed genetic disorder associated with cognitive and/or behavioral disturbance or profound intellectual disability. History of seizures, unless they were seizure-free and off antiepileptic drugs for at least 6 months.	**Enrolled:** 150 **Analyzed:** 149 **Completed:** 128 **GROUP 1** **N:** 48 **Age, mean±SD (range):** 10.5±3 **Males %:** 79.2 **Caucasian %:** 71 **Treatment naïve (n):** 64.6 **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 2** **N:** 51 **Age, mean±SD (range):** 10.5±3 **Males %:** 84.3 **Caucasian %:** 74.5 **Treatment naïve (n):** 67.6 **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 3** **N:** 49 **Age, mean±SD (range):** 11±3 **Males %:** 81.6 **Caucasian %:** 86	**Treatment duration:** 6 weeks **Run-in phase:** NR **Run-in phase duration:** NR **Permitted drugs:** diphenhydramine, melatonin, benztropine, diphenhydramine or propranolol **Prohibited drugs:** psychotropic medications **GROUP 1** **Drug name:** Lurasidone **Dosing variability:** fixed **Target dose (mg/day):** 20 mg/d **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 2** **Drug name:** Lurasidone **Dosing variability:** fixed **Target dose (mg/day):** 60 mg/d **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 3** **Drug name:** Placebo **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Benefits:** ABC irritability, hyperactivity, stereotypic behavior, inappropriate speech, lethargy/withdrawal, CGI-I, CGI-S, CY-BOCS, CGSQ global strain **Harms:** TEAE, weight, BMI, fasting laboratory parameters	Modest changes were observed in weight and selected metabolic parameters. Doses of 20 and 60mg/day of lurasidone were not demonstrated to be efficacious compared to placebo for the short-term treatment of children and adolescents with moderate-to-severe irritability associated with autistic disorder.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		Diagnostic breakdown (n): Treatment naïve (n): 61.2 **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** NR			
Luby et al., 2006 [51] **Country:** USA **Condition category:** ASD **Funding:** Industry **Risk of bias:** Medium (subjective), Low (objective)	**Recruitment dates:** Nov 1999 to Nov 2002 **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) 2.5–6 yr, (2) autism or PDD-NOS (DSM-IV), (3) absence of other known significant CNS disorders, (4) absence of significant medical problems or other psychiatric disorders requiring pharmacotherapy **Exclusion criteria:** NR	**Enrolled:** 24 **Analyzed:** 23 **Completed:** NR **GROUP 1** **N:** 12 **Age, mean±SD (range):** 4.1±0.9 **Males %:** 75 **Caucasian %:** 91 **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 12 **Age, mean±SD (range):** 4±1.1 **Males %:** 66.7 **Caucasian %:** 92 **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 6 mo **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.1±0.3 (0.5–1.5) **Concurrent treatments:** applied behavior analysis (mean 21.2 hr/wk) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.4±0.6 (0.5–1.5) **Concurrent treatments:** applied behavior analysis (mean 11.3 hr/wk)	**Benefits:** CARS **Harms:** Constipation, EPS, mortality, prolactin, SAE, sedation, WAE, weight change	Risperidone was well tolerated in preschoolers, but only minimal improvement in target symptoms was evident.
Malone et al., 2001 [52] **Country:** USA	**Recruitment dates:** NR **Study design:** RCT (parallel)	**Enrolled:** 12 **Analyzed:** 12 **Completed:** 12 **GROUP 1**	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** 1 wk **Permitted drugs:** NR	**Benefits:** CGI-S, CPRS, response (CGI-I)	The use of olanzapine is promising in children with autistic disorder, although

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Condition category: ASD **Funding:** Industry **Risk of bias:** High (subjective), Medium (objective)	**Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) primary dx of PDD, (2) 5–17 yr, (3) at least moderate impairment on ≥2 of the first 28 items on the CPRS **Exclusion criteria:** (1) major medical problems, (2) seizure disorder or gross neurological deficit, (3) treatment with concomitant psychotropic medication, (4) history of previous treatment with haloperidol or olanzapine	**N:** 6 **Age, mean±SD (range):** 7.3±1.9 (5–10.1) **Males %:** 66.7 **Caucasian %:** 66.7 **Diagnostic breakdown (n):** autistic disorder (5), PDD NOS (1) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (mild (1), moderate (2), severe (3)) **GROUP 2** **N:** 6 **Age, mean±SD (range):** 8.5±2.4 (4.9–11.8) **Males %:** 66.7 **Caucasian %:** 50 **Diagnostic breakdown (n):** autistic disorder (all) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (mild (0), moderate (3), severe (2))	**Prohibited drugs:** NR **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.4±0.7 (0.5–2.5) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 7.9±2.5 (5–10) **Concurrent treatments:** NR	**Harms:** Dermatologic AE, EPS (AIMS, SAS), EPS, fatigue, tachycardia, weight changes	placebo-controlled and long-term studies are needed.
Mankoski et al., 2013 [118] (see Marcus 2009 & Owen 2009) **Country:** USA **Condition category:** ASD	**Study design:** Retrospective (pooled analysis), evaluate impact of prior antipsychotic exposure (PAE) on safety and tolerability outcomes in pediatric subjects receiving aripiprazole treatment	**Enrolled:** NA **Analyzed:** 313 **Completed:** NA **GROUP 1** **N:** 176 **Age, mean±SD (range):** see below **Males %:** see below **Caucasian %:** NR	**GROUP 1** **Drug name:** Aripiprazole (antipsychotic naïve) **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 2**	**Benefits:** ABC-I, CGI-S **Harms:** NA	Antipsychotic naïve subjects receiving aripiprazole for the treatment of irritability associated with ASD showed greater risk for weight gain and somnolence-related AEs than subjects

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Funding: Industry **Newcastle-Ottawa Scale:** 6/8 stars		**Diagnostic breakdown (n):** NR **Treatment naïve (n):** 176 **Inpatients (n):** NR **First episode psychosis (n):** NA **Comorbidities:** NR **GROUP 2** **N:** 80 **Age, mean±SD (range):** see below **Males %:** see below **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** 80 **Inpatients (n):** NR **First episode psychosis (n):** NA **Comorbidities:** NR **GROUP 3** **N:** 36 **Age, mean±SD (range):** see below **Males %:** see below **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** NA **Comorbidities:** NR **GROUP 4** **N:** 21 **Age, mean±SD (range):** see below	**Drug name:** Placebo (antipsychotic naïve) **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 3** **Drug name:** Aripiprazole (PAE) **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 4** **Drug name:** Placebo (PAE) **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR		receiving placebo. Changes in metabolic parameters in antipsychotic naïve subjects receiving aripiprazole treatment were small and similar to those in subjects receiving placebo.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		Males %: see below **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** NA **Comorbidities:** NR **Overall Age, mean±SD (range):** mean(9.4-10) yr **Overall Males %:** 87.3-96.5%			
Marcus et al., 2009 [53] **Country:** USA **Condition category:** ASD **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** June 2006 to Jun 2008 **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV-TR, ADI-R, CGI-S, ABC-I **Inclusion criteria:** (1) 6–17 yr, (2) DSM-IV-TR criteria for autistic disorder and behaviors such as tantrums, aggression, self–injury, or a combination, with a dx corroborated by ADI-R certified trainer, (3) CGI-S score ≥4 and ABC Irritability subscale score ≥18 at screening and baseline, (4) ≥15 kg,	**Enrolled:** 218 **Analyzed:** 213 **Completed:** 178 **GROUP 1** **N:** 53 **Age, mean±SD (range):** 9.0±2.8 **Males %:** 88.7 **Caucasian %:** 69.8 **Treatment naïve (n):** 43 **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 59 **Age, mean±SD (range):** 10±3.2 **Males %:** 84.7 **Caucasian %:** 69.5 **Treatment naïve (n):** 45 **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 3**	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** ≤6 wk **Permitted drugs:** anxiolytics, benztropine or propranolol, diphenhydramine (≤50 mg/day), psychotropic medication, sleep aids **Prohibited drugs:** antidepressants, antipsychotics, anxiolytics, mood stabilizers, neuroleptics, psychostimulants (washout ≥4 day) **GROUP 1** **Drug name:** Aripiprazole (low) **Dosing variability:** fixed **Target dose (mg/day):** 5 **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** analgesics and antipyretics (12), anxiolytics (2), benztropine (2), hypnotics and sedatives (2), propranolol (2)	**Benefits:** ABC, CYBOCS, CGI-I, CGI-S, PedsQL, CGSQ, medication adherence, response (ABC-I, CGI-I), suicide **Harms:** Akathisia, BMI, dermatologic AE, ECG changes, EPS, EPS (AIMS, BAS, SAS), fatigue, glucose, lipid profile, mortality, prolactin, SAE, sedation, seizure/convulsion, somnolence, total AE, WAE, weight change, constipation	Aripiprazole was efficacious, safe, and well tolerated in children and adolescents with irritability assocated with autistic disorder.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	(5) stable nonpharmacologic therapy **Exclusion criteria:** (1) bipolar disorder, psychosis, schizophrenia, major depression, fragile X syndrome, or another ASD, (2) history of NMS, (3) significant risk of committing suicide, (4) seizure in the past yr, (5) history of severe head trauma or stroke, (6) history or current evidence of any unstable medical condition or or an abnormal laboratory test result considered clinically significant, (7) antipsychotic treatment resistant, (8) known allergy or hypersensitivity to aripiprazole	**N:** 54 **Age, mean±SD (range):** 9.5±3.1 **Males %:** 92.6 **Caucasian %:** 77.8 **Treatment naïve (n):** 44 **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 4** **N:** 52 **Age, mean±SD (range):** 10.2±3.1 **Males %:** 92.3 **Caucasian %:** 67.3 **Treatment naïve (n):** 40 **Inpatients (n):** NR **First episode psychosis (n):** NR	**GROUP 2** **Drug name:** Aripiprazole (medium) **Dosing variability:** fixed **Target dose (mg/day):** 10 **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** analgesics and antipyretics (12), anxiolytics (1), benztropine (1), hypnotics and sedatives (1) **GROUP 3** **Drug name:** Aripiprazole (high) **Dosing variability:** fixed **Target dose (mg/day):** 15 **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** analgesics and antipyretics (12), anxiolytics (1), benzotropine (5), hypnotics and sedatives (1) **GROUP 4** **Drug name:** Placebo **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** analgesics and antipyretics (9), anxiolytics (3), hypnotics and sedatives (2), propranolol (1)		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Martin et al., 2000 [119] **Country:** USA **Condition category:** Mixed conditions **Funding:** Non--industry **Newcastle-Ottawa Scale:** 6/8 stars	**Recruitment dates:** 1998 **Study design:** Retrospective **Setting:** Inpatient **Diagnostic criteria:** NR **Inclusion criteria:** All children and adolescents admitted to Riverview Hospital in 1998, (2) started on risperidone during their hospital stay, (3) no previous neuroleptic exposure, (4) no change in other psychotropic drugs used for 4 wk prior to risperidone introduction, (5) maintained on risperidone for ≥6 consecutive mo **Exclusion criteria:** NR	**Enrolled:** NA **Analyzed:** 70 **Completed:** 70 **GROUP 1** **N:** 37 **Age, mean±SD (range):** 12.5±2.4 yr **Males %:** 76 **Caucasian %:** 64 **Diagnostic breakdown (n):** Psychotic (9), affective (11), anxiety (12), disruptive (30), PDD/MR (10), polysubstance (0), ED (0) **Treatment naïve (n):** NR **Inpatients (n):** 37 **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 2** **N:** 33 **Age, mean±SD (range):** 13.5±2.9 yr **Males %:** 49 **Caucasian %:** 61 **Diagnostic breakdown (n):** Psychotic (2), affective (19), anxiety (11), disruptive (27), PDD/MR (8), polysubstance (2), ED (2) **Treatment naïve (n):** NR **Inpatients (n):** 33 **First episode psychosis (n):** NR **Comorbidities:** NR	**Treatment duration:** ≥6 mo **Run-in phase:** Yes **Run-in phase duration:** 4 wk **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2.8±1.9 **Concurrent treatments:** Valproate (12), SSRI (8), stimulant (8), α_2 agonist (8), traditional neuroleptic (0) **GROUP 2** **Drug name:** Control **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** Valproate (10), SSRI (9), stimulant (6), α_2 agonist (6), traditional neuroleptic (9)	**Benefits:** NR **Harms:** Weight (BMI, BMI z-score)	Studies of children and adolescents are needed to prospectively monitor weight change (as well as serum glucose, liver enzyme, and triglyceride levels) during chronic exposure to risperidone and other atypical neuroleptics. Long-term effects, as well as changes following drug discontinuation are likewise needed. Until those empirical data become available, it seems prudent to recommend careful monitoring of height, weight, and BMI of all children treated with atypical antipsychotics, as well as to consider glucose, liver enzyme, and lipid levels as part of their routine safety monitoring.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Masi et al., 2015 [55] **Country:** Italy **Condition category:** Bipolar II (hypomanic) **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Jan 2013 to Jan 2014 **Study design:** RCT (parallel) **Setting:** Inpatient/outpatient **Diagnostic criteria:** DSM-IV-TR, K-SADS-PL **Inclusion criteria:** (1) diagnosis of Bipolar II hypomanic episode as confirmed by DSM-IV-TR, K-SADS-PL and YMRS total score of ≥17 at baseline, (2) CGI-S≥4, (3) CGAS≤50 **Exclusion criteria:** NR	**Enrolled:** 24 **Analyzed:** 22 **Completed:** 22 **GROUP 1** **N:** 12 **Age, mean±SD (range):** 14.9±1.1 **Males %:** 41.7 **Caucasian %:** 100 **Diagnostic breakdown (n):** hypomanic (all) **Treatment naïve (n):** 12 **Inpatients (n):** 3 **First episode psychosis (n):** NR **Comorbidities:** CD (all) ADHD (2), anxiety disorders (3), substance use disorder (1), eating disorder NOS (1) **GROUP 2** **N:** 10 **Age, mean±SD (range):** 15.1±1.8 **Males %:** 70 **Caucasian %:** 100 **Diagnostic breakdown (n):** hypomanic (all) **Treatment naïve (n):** 12 **Inpatients (n):** 3 **First episode psychosis (n):** NR **Comorbidities:** CD (all), ADHD (3), anxiety disorders (2), substance use disorder (2), eating disorder NOS (1)	**Treatment duration:** 12 wk **Run–in phase:** NR **Run–in phase duration:** NR (all treatment naïve) **Permitted drugs:** Methyphenidate at stable dose in 1 patient in risperidone group **Prohibited drugs:** Psychotropics≤6mo **GROUP 1** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 163.30±55.20 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.90±0.60 **Concurrent treatments:** NR	**Benefits:** YMRS, CGI-S, CGAS, HDRS, HAM-A, MOAS, response **Harms:** BMI, prolactin, somnolence, fatigue, EPS, ECG	Risperidone and quetiapine did not differ in BMI increase according to the main analysis, although the post hoc analysis suggests a possible BMI increase with risperidone but not with quetiapine. Data on higher prolactin increase during risperidone treatment, compared with quetiapine, are in line with previous studies. However, our findings about safety, namely, the modest BMI increase and the absence ofQTc prolongation, should be cautiously considered in the context of the limited time of the study.
Masi et al., 2013 [54]	**Recruitment Dates:** NR	**Enrolled:** 69 **Analyzed:** 69 **Completed:** 69	**Treatment duration:** ≥ 12 wk **Run-in phase:** NR **Run-in phase duration:** NR	**Benefits:** C-GAS, CGI-S, CGI-I, response	In tic-related pediatric OCD, augmentation of

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Country: Italy **Condition category:** OCD **Funding:** No funding provided **Risk of Bias:** High (subjective), Medium (objective)	**Study design:** NRCT (parallel) **Diagnostic criteria:** DSM-IV, K-SADS-PL (OCD), DSM-IV-TR (Tic) **Setting:** Outpatient **Inclusion criteria:** Diagnosis of OCD, CGI score ≥ 4 and C-GAS score ≤ 60. Comorbid tic disorder, ≥ 40 on YGTSS, non-responder to SSRI **Exclusion criteria:** Diagnosis of mental retardation, PDD, schizophrenia	**GROUP 1:** **N:** 35 **Age, mean±SD (range):** 13.3±2.2 yr **Males %:** 94.3% **Caucasian %:** NR **Diagnostic breakdown (n):** OCD with comorbid tic disorder (35) **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** GAD (7), separation AD (4), panic disorder (2), social phobia (13), simple phobia (4), depression (8), BP (6), ADHD (6), ODD (9) **GROUP 2:** **N:** 34 **Age, mean±SD (range):** 13.9±2.5 yr **Males %:** 85.3% **Caucasian %:** NR **Diagnostic breakdown (n):** OCD with comorbid tic disorder (34) **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** GAD (1), separation AD (1), panic disorder (1), social phobia (6), depression (4), BP (2), ADHD (14), ODD (7)	**Permitted drugs:** SSRI **Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone **Dosing variability:** Variable **Target dose (mg/day):** 3 mg/day **Daily dose (mg/day), mean±SD (range):** 1.7±0.8 (0.5-3) mg/day **Concurrent treatments:** SSRI (35), mood stabilizers (3), stimulants (1), psychotherapy (20) **GROUP 2:** **Drug name:** Aripiprazole **Dosing variability:** Variable **Target dose (mg/day):** 12.5 mg/day **Daily dose (mg/day), mean±SD (range):** 8.9±3.1 (2.5-12.5) mg/day **Concurrent treatments:** SSRI (34), mood stabilizers (1), stimulants (1), psychotherapy (14)	**Harms:** Weight, sedation, tremors	SSRIs with risperidone or aripiprazole was tolerated and effective in about half of the patients who did not respond to SSRIs alone.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
McCracken et al., 2002 [56] **Country:** USA **Condition category:** ASD **Funding:** Industry, Government, Foundation **Risk of bias:** Medium (subjective), Medium (objective)	**Recruitment dates:** Jun 1999 to Apr 2001 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, ADI-R **Inclusion criteria:** (1) ASD (DSM-IV), (2) 5–17 yr, (3) weight ≥15 kg, (4) score ≥18 on the Irritability subscale of the ABC at baseline, (5) free of serious medical disorders and of other psychiatric disorders requiring medication, (6) medication free for at least 2 wk for all psychotropic medications (4 wk for fluoxetine or depot neuroleptics), (7) anticonvulsants used for the treatment of a seizure disorder were permitted if the dosage had been stable for 4 wk and the patient had been seizure free for ≥6 mo, (8) CGI-S score ≥ 4 at baseline, (9) mental age ≥18 mo as measured by the age-appropriate form of the	**Enrolled:** 101 **Analyzed:** 101 **Completed:** 80 **GROUP 1** **N:** 49 **Age, mean±SD (range):** NR **Males %:** 80 **Caucasian %:** NR **Treatment naïve (n):** 45 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (average/above average IQ (3), borderline IQ (8), mild/ moderate retardation (20), severe retardation (15)) **GROUP 2** **N:** 52 **Age, mean±SD (range):** NR **Males %:** 83 **Caucasian %:** NR **Treatment naïve (n):** 51 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (average/above average IQ (2), borderline IQ (4), mild/ moderate retardation (23), severe retardation (16))	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** 1–4 wk **Permitted drugs:** anticonvulsants (constant dose ≥4 wk and seizure-free for ≥6 mo), benztropine **Prohibited drugs:** antihistamines, ceterazine, erythromycin, metoclopromide, pseudoephedrine, and any drug that may impact risperidone concentrations or lead to drug interactions; psychotropics **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.8±0.7 (0.5–3.5) **Concurrent treatments:** anticonvulsants (2) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2.4±0.6 (0.5–3.5) **Concurrent treatments:** anticonvulsants (2)	**Benefits:** ABC, CYBOCS, CGI-I, CGI-S, RFRLRS, VAS, AIMS, Cognitive, medication adherence, patient, parent/care provider reported outcomes (diet/intake, sleep), response **Harms:** Behavioral issues, blood cells, BMI, constipation, dyskinesia, dermatologic AE, ECG changes, EPS (AIMS, SAS), fatigue, liver function, prolactin, prolactin-related AE, SAE, seizure, tachycardia, WAE, weight change	Risperidone was effective and well tolerated for the treatment of tantrums, aggression, or self-injurious behavior in children with autistic disorder. Discontinuation, after 6 month of treatment, was associated with rapid return of disruptive and aggressive behavior in most subjects.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	IQ test, (10) inpatients or outpatients **Exclusion criteria:** (1) receiving a psychotropic drug that was deemed effective for the treatment of aggression, tantrums, or self-injurious behavior, (2) positive β-HCG pregnancy test, (3) evidence of a prior adequate trial with risperidone, (4) evidence of hypersensitivity to risperidone, (5) past history of NMS, (6) DSM-IV dx of schizophrenia, another psychotic disorder, or substance abuse, (7) significant medical condition, (8) weight <15 kg				
McGorry et al., 2013 [57] **Country:** Australia **Condition category:** Schizophrenia and related **Funding:** Industry	**Recruitment dates:** August 2000 to May 2006 **Study design:** RCT (parallel) **Setting:** Outpatient **Diagnostic criteria:** Ultra-high risk: (1) the presence of attenuated (subthreshold) psychotic symptoms	**Enrolled:** 87 **Analyzed:** NR **Completed:** 56 **GROUP 1** **N:** 43 **Age, mean±SD (range):** 17.6±3.0 **Males %:** 35 **Caucasian %:** NR **Treatment naïve (n):** 100 **Inpatients (n):** 0 **First episode psychosis (n):** UHR	**Treatment duration:** 52 wk **Run-in phase:** NA **Run-in phase duration:** NA **Permitted drugs:** NR **Prohibited drugs:** mood-stabilizing medications **GROUP 1** **Drug name:** Cognitive therapy + risperidone **Dosing variability:** variable **Target dose (mg/day):** up to 2mg/day	**Benefits:** BPRS, SANS, GAF, HDRS, quality of life, transition rates **Harms:** UKU	The equivalent transition rates fail to provide support for the first-line use of antipsychotic medications in patients at ultra-high risk of psychosis, and an initial approach with supportive therapy is likely to be effective and carries fewer risks.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Risk of bias: High (subjective), High (objective)	within the previous 12 months; (2) a history of brief self-limited psychotic symptoms, which spontaneously resolve, within the previous 12 months; and (3) a presumed genetic vulnerability to psychotic disorder plus persistent low functioning for at least 1 month within the previous 12 months **Inclusion criteria:** 14-30 yrs; see above criteria **Exclusion criteria:** (1) known history of a previous psychotic or manic episode, (2) history of a medical condition that may account for symptoms leading to initial referral (eg, epilepsy), (3) clinically relevant neurologic, biochemical, or hematologic abnormalities, (4) serious coexisting illnesses, (5) lifetime antipsychotic dose of 15mg of haloperidol (or equivalent) or greater, (6) any previous or current use of mood-	**GROUP 2** **N:** 44 **Age, mean±SD (range):** 18.0±2.7 **Males %:** 39 **Caucasian %:** NR **Treatment naïve (n):** 100 **Inpatients (n): 0** **First episode psychosis (n):** UHR	**Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 2** **Drug name:** Cogntive therapy + placebo **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 0 **Concurrent treatments:** NR		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	stabilizing medication, (7) history of severe drug allergy, (8) intellectual disability (IQ < 70), (9) pregnancy or lactation, (10) insufficient English language				
Migliardi et al., 2009 [120] **Country:** Italy **Condition category:** Mixed conditiopns **Funding:** NR **Risk of bias:** 7/8 stars	**Recruitment dates:** NR **Study design:** Retrospective cohort **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) children and adolescents seen at the Division of Child and Neurology at the University of Messina, Italy, (2) not previously treated with antipsychotics for various psychiatric disorders, (3) completed at least 12 months of treatment on only one antipsychotic and no co-medication **Exclusion criteria:** NR	**Enrolled:** 42 **Analyzed:** 41 **Completed:** 42 **GROUP 1** **N:** 13 **Age, mean±SD (range):** 14.1 **Males %:** 53.8 **Caucasian %:** NR **Treatment naïve (n):** all **Diagnostic breakdown (n):** DBD (4), early-onset schizophrenia (3), BD (2), autism/PDD (2), OCD (1) **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 2** **N:** 29 **Age, mean±SD (range):** 10.7 **Males %:** 78.6 **Caucasian %:** NR **Treatment naïve (n):** all **Diagnostic breakdown (n):** Autism/PDD (13), DBD (9), early-onset schizophrenia (2), OCD (2), Tic disorder (2) **Inpatients (n):** 0	**Treatment duration:** 12 mo **Run–in phase:** No **Run–in phase duration:** NA **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 8.1 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.8 **Concurrent treatments:** NR	**Benefits:** NA **Harms:** prolactin-related AE, prolactin	After adjusting for dose and greater potency of risperidone, the increase in prolactin levels during risperidone treatment was 10.3 times higher than during olanzapine treatment.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		First episode psychosis (n): NR **Comorbidities:** NR			
Miral et al., 2008 [58] **Country:** Turkey **Condition category:** ASD **Funding:** Industry **Risk of bias:** Medium (subjective), Medium (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) 8–18 yr, (2) parental informed consent, (3) agree to followup **Exclusion criteria:** (1) epilepsy, (2) concomitant neuropsychiatric illness, (3) psychotic disorder or symptoms, (4) other PDDs	**Enrolled:** 30 **Analyzed:** 28 **Completed:** 28 **GROUP 1** **N:** 15 **Age, mean±SD (range):** 10.9±2.9 (7–17) **Males %:** 86.7 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (0), psychosis (0) **GROUP 2** **N:** 15 **Age, mean±SD (range):** 10±2.7 (7–17) **Males %:** 73.3 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (0), psychosis (0)	**Treatment duration:** 24 wk **Run-in phase:** Yes **Run-in phase duration:** 1–2 wk **Permitted drugs:** antianalgesics, antibiotics, anticholinergics, antipyretics, decongestants **Prohibited drugs:** benzodiazepines/other sedatives **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** variable **Target dose (mg/day):** 0.08 mg/kg/day **Daily dose (mg/day), mean±SD (range):** 2.6±1.3 (1–5.7) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** 0.08 mg/kg/day **Daily dose (mg/day), mean±SD (range):** 2.6±0.8 (1.2–4.0) **Concurrent treatments:** NR	**Benefits:** ABC, CGI, RFRLRS **Harms:** Blood pressure, constipation, EPS (ESRS, UKU), height, parkinsonism/ dystonia/ dyskinesia (ESRS), prolactin-related AE, SAE, weight	Risperidone was more effective than haloperidol, showing improvements in behavioral symptoms and social skills.
Mozes et al., 2006 [59] **Country:** Israel **Condition category:** Schizophrenia and related	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient	**Enrolled:** 25 **Analyzed:** 25 **Completed:** 20 **GROUP 1** **N:** 12 **Age, mean±SD (range):** 11.5±1.6 (8.5–14) **Males %:** 41.7	**Treatment duration:** 2.8 mo **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** biperiden, prior nonantipsychotics (continued for 2–12 wk) **Prohibited drugs:** NR	**Benefits:** BPRS, CGAS, PANSS, response **Harms:** BAS, SAS akathisia, prolactin, WAE, weight change	Risperidone and olanzapine were efficacious and well tolerated in pediatric inpatients with child-onset schizophrenia.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Funding: No funding **Risk of bias:** High (subjective), High (objective)	**Diagnostic criteria:** DSM-IV, K-SADS **Inclusion criteria:** (1) hospitalized childhood-onset schizophrenic children **Exclusion criteria:** (1) MR	**Caucasian %:** NR **Diagnostic breakdown (n):** disorganized schizophrenia (3), paranoid schizophrenia (2), schizophreniform disorder (6), unspecified schizoprehenia (1) **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR **Comorbidities:** ADHD (2), familial mediterranean fever (1), MR (0), tic disorder (1) **GROUP 2** **N:** 13 **Age, mean±SD (range):** 10.7±1.4 (8.8–13.3) **Males %:** 38.5 **Caucasian %:** NR **Diagnostic breakdown (n):** disorganized schizophrenia (4), paranoid schizophrenia (4), schizophreniform disorder (4), unspecified schizoprehenia (1) **Treatment naïve (n):** NR **Inpatients (n):** all **First episode psychosis (n):** NR **Comorbidities:** ADHD (1), epilepsy (2), MR (0), neurofibromatosis (1), OCD (3)	**GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 8.2±4.4 (2.5–20) **Concurrent treatments:** biperiden (2), carbamazepine (2), citalopram (1), colchicine (1), methylphenidate (2), promethizine (2), valproic acid (1) **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.6±1 (0.3–4.5) **Concurrent treatments:** biperiden (4), citalopram (2), fluoxetine (1), phenytoin (1), promethizine (1), valproic acid (1)		
Nagaraj et al., 2006 [60]	**Recruitment dates:** Jan 2002 to Dec 2003	**Enrolled:** 40 **Analyzed:** 39 **Completed:** 39	**Treatment duration:** 6 mo **Run-in phase:** Yes **Run-in phase duration:** ≥1 mo	**Benefits:** CARS, CGAS, response (CARS, CGAS,	Risperidone improved global functioning and

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Country: India **Condition category:** ASD **Funding:** Industry, Academic **Risk of bias:** Low (subjective), Low (objective)	**Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) ≤12 yr, (2) autism (DSM-IV) **Exclusion criteria:** (1) severe MR, (2) any significant coexisting disease or illness, (3) severe malnutrition	**GROUP 1** **N:** 19 **Age, mean±SD (range):** 4.8±1.7 **Males %:** 84.2 **Caucasian %:** NR **Treatment naïve (n):** 15 **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** aggression (9), irritability (17), seizures (5), self-injurious behavior (7) **GROUP 2** **N:** 21 **Age, mean±SD (range):** 5.3±1.7 **Males %:** 90 **Caucasian %:** NR **Treatment naïve (n):** 16 **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** aggression (11), irritability (19), seizures (3), self-injurious behavior (5)	**Permitted drugs:** antiepileptics **Prohibited drugs:** no other drugs permitted **GROUP 1** **Drug name:** Risperidone **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1 (0.5–1) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1 (0.5–1) **Concurrent treatments:** NR	Global Impression of Parents) **Harms:** Dyskinesia, sedation, weight change	social responsiveness, reduced hyperactivity and aggression, and was well tolerated in children with autism.
NCT00194012, 2013 [61] **Country:** USA **Condition category:** Bipolar **Funding:**	**Recruitment dates:** August 2004-May 2012 **Study design:** RCT **Setting:** Outpatient	**Enrolled:** 59 **Analyzed:** NR **Completed:** 21 (15 Group 1; 6 Group 2) **GROUP 1** **N:** 30 **Age, mean±SD (range):** <18 yr (all) **Males %:** 66.7	**Treatment duration:** 12 wk, plus 6 wk open label extension **Run-in phase:** NR **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** psychotropic agents taken <1 wk of baseline (2	**Benefits:** YMRS **Harms:** AEs (major and minor)	NR

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Industry, Institution (hospital) **Risk of bias:** High (subjective). High (objective)	**Diagnostic criteria:** (1) DSM-IV criteria for either cyclothymia, or BP NOS based on K-SADS-PL and WASH-U K-SADS, (2) a clinical interview with a child and adolescent psychiatrist **Inclusion criteria:** (1) outpatient, (2) 5-17 yr, (3) symptoms of mania, depression, or both <2 wk, (4) offspring of a parent with BP spectrum disorder, (5) another 1st or 2nd degree relative with a mood disorder, (6) participated in ≥4 sessions of psychotherapy and continues to have clinically significant symptomatology **Exclusion criteria:** intolerance to APZ at doses of 0.1mg/kg/day, (2) manic episode with APZ monotherapy at a dose of 0.2 mg/kg/day, (3) contraindications for which tx with APZ, (4) ASD, Asperger's disorder, Rett's syndrome or other	**Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** None **First episode psychosis (n):** NR **GROUP 2** **N:** 29 **Age, mean±SD (range):** <18 yr (all) **Males %:** 51.7 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** None **First episode psychosis (n):** None	wk for fluoxetine; 3 days for psychostimulants) **GROUP 1** **Drug name:** Abilify (aripiprazole) **Dosing variability:** 2-15 mg **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	PDD, (5) mental retardation, (6) allergic or hypersensitive to APZ, (7) unable to swallow pills/capsules, (8) hospitalization during the study, (9) started a new psychotherapeutic intervention <4 wk prior to randomization, (10) general medical or neurological condition that: i) may be the etiology of the pts mood disorder, ii) contraindicate tx with an AAP, iii) may interfere with the interpretation of clinical response to APZ; (11) other psychotropic agents <1 wk of baseline (2 wk for fluoxetine; 3 days for psychostimulants); (12) <6 mo prior to randomization: i) a suicide attempt requiring medical/ psychiatric, ii) met DSM-IV criteria for SA, (13) pt who are pregnant or lactating, (14) sexually active				

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	females, not using an adequate birth control				
NCT00619190, 2013 [121] **Country:** USA **Condition category:** ASD **Funding:** Institution (University) **Newcastle-Ottawa Scale:** 4/8	**Recruitment dates:** NR **Study design:** Controlled before-after study **Setting:** NR **Diagnostic criteria:** NR **Inclusion criteria:** NR **Exclusion criteria:** NR	**Enrolled:** 30 **Analyzed:** **Completed:** 29 **GROUP 1** **N:** 21 **Age, mean±SD (range):** 8.3±3.75 **Males %:** 90.5 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 9 **Age, mean±SD (range):** 11.1±4.5 **Males %:** 88.9 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 12 wk **Run-in phase:** NR **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Apriprazole **Dosing variability:** 1-30 mg **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 2** **Drug name:** No medication **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Benefits:** ABC-I, CGI-S, ABC-Lethargy/Social Withdrawal **Harms:** AEs (major and minor)	
NCT01149655, 2014 [62] **Country:** Multiple countries **Condition category:** Schizophrenia and related **Funding:** Industry (pharmaceutical)	**Recruitment dates:** July 2011-Dec 2013 **Study design:** RCT **Setting:** Outpatient **Diagnostic criteria:** DSM-IV-TR diagnosis of schizophrenia **Inclusion Criteria:**	**Enrolled:** 146 **Analyzed:** **Completed:** 21 (15 (group 1), 6 (groupd 2)) **GROUP 1** **N:** 98 **Age, mean±SD (range):** 15.3±1.3 (male); 15.4±1.1 (female) **Males %:** 63.3 **Caucasian %:** NR **Treatment naïve (n):** 0	**Treatment duration:** 52 wk **Run-in phase:** Yes (stabilized on 10-30 mg/day of aripiprazole prior to randomization) **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Apriprazole **Dosing variability:** 10-30 mg/day	**Benefits:** Relapse Rate (CGI-I/S, PANSS, hospitalization, suicide ideation, violent/aggressive behavior), % exacerbation or relapse/impending relapse, % responders, % achieved remission,	

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Risk of bias: High (subjective). High (objective)	(1) schizophrenia, (2) hx of illness ≥6 mo prior to screening, (3) shown previous response to antipsychotic tx (other than clozapine), (4) currently being treated with oral or depot antipsychotics other than clozapine, (5) hx of relapse and/or exacerbation of symptoms when off antipsychotic tx. **Exclusion criteria:** (1) dx other than schizophrenia, (2) delirium, dementia, amnesia or other cognitive disorders, (3) psychotic symptoms better accounted for by another medical condition(s) or direct effect of a substance, (4)comorbid dx of ADD or ADHD, (5) tx with stimulants at any time over the last 1 yr prior to screening, (6) any neurodevelopmental disorder, except Tourette's syndrome, (7) acute depressive symptoms ≤30 days prior to screening, (8) DSM-IV-TR criteria for substance dependence ≤180	**Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 48 **Age, mean±SD (range):** 15.6±1.1 (males), 15.3±1.0 (females) **Males %:** 70.8 **Caucasian %:** NR **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** NR	**Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	% discontinued, CGAS **Harms:** AEs (minor and serious)	

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	days prior to screening, (9) Hx of: epilepsy, seizures, severe head trauma, stroke, or other unstable medical conditions, subclinical hypothyroidism (TSH ≥ 4.0 mIU/L), known hypothyroidism or hyperthyroidism (unless stabilized with medication for ≥ 90 days prior to entry into Phase 1 or Phase 2), uncontrolled diabetes, labile or unstable diabetes (brittle diabetes), newly diagnosed diabetes, or clinically significant abnormal blood glucose levels				
Norris et al., 2011 [122] **Country:** Canada **Condition category:** Eating disorders (Anorexia nervosa) **Funding:** Non-industry **Newcastle-Ottawa Scale:** 7/8 stars	**Recruitment dates:** Jan 2000 to Dec 2006 **Study design:** Retrospective **Setting:** inpatient and outpatient **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) 10-17 yr, (2) female, (3) diagnosed with AN or EDNOS according to DSM-IV	**Enrolled:** 86 **Analyzed:** 86 **Completed:** 86 **GROUP 1** **N:** 43 **Age, mean±SD (range):** 14.4±1.9 yr **Males %:** 0 **Caucasian %:** NR **Diagnostic breakdown (n):** ANR (29), ANBP (2), EDNOS-R (12) **Treatment naïve (n):** NR **Inpatients (n):** 35 **First episode psychosis (n):** NR	**Treatment duration:** 2 wk for weight outcomes **Run-in phase:** NR **Run-in phase duration:** NR **Permitted drugs:** SSRI/SNRI (17), benzodiazepine (3) (at the time of olanzapine initiation) **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** flexible **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** [median (IQR)] 5.0 (3.75-7.5)	**Benefits:** CDI, MASC, EDI-2DT, EDI-2BD **Harms:** change in body composition (weight, BMI), dyslipidemia, liver function test, sedation, rebound weight loss and increased psychological stress after initial discontinuation of olanzapine	Patients treated with olanzapine presented with greater acuity and more complex psychopathology than those patients not treated with olanzapine, which made comparisons regarding efficacy of the drug impossible. The observed side-effect profile noted in patients treated with olanzapine indicates the need for close monitoring

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	Exclusion criteria: (1) males, (2) concurrent diagnosis of psychosis, or a concurrent illness with psychotic features, or whose primary treatment was not under the direction of the eating disorder team	**Comorbidities:** Anxiety (29), depression (26), obsessive compulsive disorder (3) **GROUP 2** **N:** 43 **Age, mean±SD (range):** 14.8±1.6 yr **Males %:** 0 **Caucasian %:** NR **Diagnostic breakdown (n):** ANR (29), ANBP (2), EDNOS-R (12) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities: :** Anxiety (13), depression (15), obsessive compulsive disorder (1)	**Concurrent treatments:** SSRI/SNRI (17), benzodiazepine (3) **GROUP 2** **Drug name:** Not olanzapine **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR		during the entire course of treatment, regardless of the patient's absolute weight.
Novaes et al., 2008 [123] **Country:** Brazil **Condition category:** ASD **Funding:** Foundation **Newcastle-Ottawa Scale:** 8/8 stars	**Recruitment dates:** Jan 2001 to June 2006 **Study design:** Retrospective cohort **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) ASD, (2) behavioral disturbances (psychomotor agression or agitation)	**Enrolled:** NA **Analyzed:** 26 **Completed:** 26 **GROUP 1** **N:** 1 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** Aggression/Agitation (26), MR (20)	**Treatment duration:** 17 mo (mean) **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Typical antipsychotic **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Benefits:** Response (CGI-I) **Harms:** NR	SGAs appeared to reduce agitation and aggression in patients with ASD.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	Exclusion criteria: NR	**GROUP 2** **N:** 13 and 5 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** see group 1 **GROUP 3** **N:** 4 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see group 1 **GROUP 4** **N:** 3 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see group 1	**GROUP 2** **Drug name:** Risperidone/Risperidone + Typical antipsychotic **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 3** **Drug name:** Atypical antipsychotic (not risperidone) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 4** **Drug name:** Typical + atypical antipsychotic **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** one treatment (12), ≥2 treatments (7)		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
O'Donoghue et al., 2014 [124] **Country:** Austria **Condition category:** Schizophrenia and related **Funding:** NR **Newcastle-Ottawa Scale:** 3/8 stars	**Recruitment dates:** January 2001 to August 2005 **Study design:** Prospective cohort **Setting:** NR **Diagnostic criteria:** DSM-III **Inclusion criteria:** (1) 13-17 yr, (2) schizophrenia spectrum disorder, (3) no previous antipsychotic medications **Exclusion criteria:** (1) IQ <70	**Enrolled:** 44 **Analyzed:** 36 **Completed:** 36 **GROUP 1** **N:** 16 **Age, mean±SD (range):** 15.9±1.2 (all groups) **Males %:** 58 **Caucasian %:** NR **Treatment naïve (n):** 16 **Inpatients (n):** NR **First episode psychosis (n):** 16 **GROUP 2** **N:** 20 **Age, mean±SD (range):** 15.9±1.2 (all groups) **Males %:** 58 **Caucasian %:** NR **Treatment naïve (n):** 20 **Inpatients (n):** NR **First episode psychosis (n):** 20	**Treatment duration:** mean 31 wk **Run-in phase:** No **Run-in phase duration:** NA **Permitted drugs:** SSRI **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine & quetiapine **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** SSRI (31% all groups) **GROUP 2** **Drug name:** Risperidone **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** SSRI (31% all groups)	**Benefits:** NR **Harms:** triglycerides, BMI, cholesterol	One-third of children and adolescents had abnormal serum triglycerides and cholesterol; however, a dose–response was not demonstrated. Olanzapine and quetiapine had a greater increase in serum triglycerides.
Oh et al., 2013 [125] **Country:** South Korea **Condition category:** Bipolar I, II, NOS **Funding:** NR **Newcastle-Ottawa Scale:** 6/8 stars	**Recruitment dates:** Jan 2010 to Oct 2011 **Study design:** Retrospective **Setting:** Outpatient **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) Male and female outpatients, (2) aged 4 to 18 years, (3) DSM-	**Enrolled:** 183 **Analyzed:** 127 **Completed:** 32 **GROUP 1** **N:** 62 **Age, mean±SD (range):** 13.16±2.80 yr **Males %:** 66.1 **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** 0	**Treatment duration:** 7-8 mo **Run–in phase:** NR **Run–in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Aripiprazole **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 9.58±5.38	**Benefits:** ADHD RS-IV, CGI-S, CGI-I **Harms:** Akathisia, sedation, nausea	The early treatment effects and long-term tolerability of aripiprazole were found to be excellent compared with those of other atypical antipsychotics. The superior treatment effects of aripiprazole, which was also associated with comparatively mild side effects,

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	IV diagnosis of bipolar I disorder, bipolar II disorder, bipolar disorder, and bipolar affective disorder **Exclusion criteria:** (1) Another diagnosis as main reason for treatment (eg: tic disorder, ADHD), (2) who visited the clinic only once or did not take medication	**First episode psychosis (n):** NR **Comorbidities:** See below **GROUP 2** **N:** 65 **Age, mean±SD (range):** 11.46±3.95 yr **Males %:** 76.9 **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** See below **Overall comorbidities:** ADHD (50), tic related disorders (17), conduct disorders and ODD (5), autism spectrum disorder (12)	**Concurrent treatments:** See below **GROUP 2** **Drug name:** Others **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** Risperidone (1.46±1.08), quetiapine (207.46±200.53), paliperidone (4.50±2.12) **Concurrent treatments:** See below **Overall concurrent treatments:** mood stabilizers (20), methyphenidate (34), atomoxetine (12), antidepressants (27)		may enhance the treatment compliance of pediatric patients and their guardians. However, these results must be confirmed in the future through multi-center, double-blind, placebo-control studies.
Olfson et al., 2012 [126] **Country:** USA **Condition category:** Schizophrenia and related **Funding:** Government	**Recruitment dates:** Medicaid claims file 2001-2005 **Study design:** Retrospective cohort **Setting:** Inpatients (<10%) and outpatients **Diagnostic criteria:** ICD-9-CM	**Enrolled:** 1745 **Analyzed:** 1745 **Completed:** NA **GROUP 1** **N:** 805 **Age, mean±SD (range):** NR **Males %:** 62 **Caucasian %: 38** **Treatment naïve (n):** 805 **Inpatients (n):**	**Treatment duration:** **Run-in phase:** **Run-in phase duration:** **Permitted drugs:** None **Prohibited drugs:** None **GROUP 1** **Drug name:** Risperidone **Dosing variability:** **Target dose (mg/day):**	**Benefits:** Medication adherence (all-cause discontinuation), psychiatric hospital admission **Harms:** NR	The results suggest that rapid antipsychotic medication discontinuation and psychiatric hospital admission are common in the community treatment of early-onset schizophrenia.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Newcastle-Ottawa Scale: 7/8 stars	**Inclusion criteria:** (1) 6-17 yr, (2) eligible for Medicaid (fee-for-service plans) for ≥180 days after antipsychotic Initiation, (3) schizophrenia and related disorders **Exclusion criteria:** (1) not enrolled in Medicare, (2) free of any antipsychotic prescriptions for at least 180 continuous days before filling a risperidone, olanzapine, aripiprazole, quetiapine, or ziprasidone prescription of ≤30 days supply	**First episode psychosis (n):** NR **GROUP 2** **N:** 382 **Age, mean±SD (range):** NR **Males %:** 69 **Caucasian %:** 38 **Treatment naïve (n):** 382 **Inpatients (n):** **First episode psychosis (n):** NR **GROUP 3** **N:** 260 **Age, mean±SD (range):** NR **Males %:** 52 **Caucasian %: 48** **Treatment naïve (n):** 260 **Inpatients (n):** **First episode psychosis (n):** NR **GROUP 4** **N:** 173 **Age, mean±SD (range):** NR **Males %:** 55 **Caucasian %: 42** **Treatment naïve (n):** 173 **Inpatients (n):** **First episode psychosis (n):** NR **GROUP 5** **N:** 125	**Daily dose (mg/day), mean±SD (range):** **Concurrent treatments:** **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** **Target dose (mg/day):** **Daily dose (mg/day), mean±SD (range):** **Concurrent treatments:** **GROUP 3** **Drug name:** Quetiapine **Dosing variability:** **Target dose (mg/day):** **Daily dose (mg/day), mean±SD (range): Concurrent treatments:** **GROUP 4** **Drug name:** Aripiprazole **Dosing variability:** **Target dose (mg/day):** **Daily dose (mg/day), mean±SD (range): Concurrent treatments:** **GROUP 5** **Drug name:** Ziprasidone **Dosing variability:** **Target dose (mg/day): Daily dose (mg/day), mean±SD (range):** **Concurrent treatments:**		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		Age, mean±SD (range): NR **Males %:** 57 **Caucasian %:** 44 **Treatment naïve (n):** 125 **Inpatients (n):** **First episode psychosis (n):** NR			
Omranifard et al, 2013 [63] **Country:** Iran **Condition category:** Behavioral issues **Funding:** Institution (University) **Risk of bias:** High (subjective), NA (objective)	**Recruitment dates:** 2009 **Study design:** RCT **Setting:** Outpatient **Diagnostic criteria:** NR **Inclusion criteria:** (1) informed consent; (2) boys and girls 3-7 yr; (3) dx masturbation problem by a psychiatrist; (4) masturbates as a daily habit **Exclusion criteria:** (1) any condition that would interfere with the safe study participation; (2) any current neurological or axis I psychiatric disorders that needs chronic drug treatment; (3) treated for masturbation in the last month; (4) infection of genitalia.	**Enrolled:** 90 **Analyzed:** 87 **Completed:** 87 **GROUP 1** **N:** 42 **Age, mean±SD (range):** 5.3±1.1 **Males %:** 52.3 **Caucasian %:** NR **Diagnostic breakdown (n):** **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 45 **Age, mean±SD (range):** 49.9±1.1 **Males %:** 57.7 **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR	**GROUP 1** **Drug name:** risperidone **Dosing variability:** 0.25-1 mg/d **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 2** **Drug name:** placebo **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Benefits:** Efficacy (frequency of masturbation) **Harms:** None	In contrast to the behavioral treatment which was only effective in younger ages in the control group, the addition of risperidone to the behavioral treatment was effective in all ages.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Owen et al., 2009 [64] **Country:** USA **Condition category:** ASD **Funding:** Industry **Risk of bias:** Medium (subjective), Low (objective)	**Recruitment dates:** June 2006 to April 2008 **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-IV-TR, ADI-R, CGI-S, ABC-I **Inclusion criteria:** (1) 6–17 yr, (2) DSM-IV-TR criteria for autistic disorder and behaviors such as tantrums, aggression, self–injury, or a combination, with a dx corroborated by ADI-R certified trainer, (3) CGI-S score ≥4 and ABC Irritability subscale score ≥18 at screening and baseline, (4) ≥15 kg, (5) stable nonpharmacologic therapy **Exclusion criteria:** (1) bipolar disorder, psychosis, schizophrenia, major depression, fragile X syndrome, or another ASD, (2) history of NMS, (3) significant risk of committing suicide, (4) seizure in the past yr, (5) history	**Enrolled:** 164 **Analyzed:** 98 **Completed:** 75 **GROUP 1** **N:** 47 **Age, mean±SD (range):** 9.7±3.2 **Males %:** 89.4 **Caucasian %:** 68.1 **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NA **GROUP 2** **N:** 51 **Age, mean±SD (range):** 8.8±2.6 **Males %:** 86.3 **Caucasian %:** 80.4 **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NA	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** ≤6 wk **Permitted drugs:** anxiolytics, benztropine or propranolol, diphenhydramine (≤50 mg/day), psychotropic medication, sleep aids **Prohibited drugs:** antidepressants, antipsychotics, anxiolytics, mood stabilizers, neuroleptics, psychostimulants (washout ≥4 day), fluoxetine, olanzapine/fluoxetine (washout ≥4 wk before screen visit) **GROUP 1** **Drug name:** Aripiprazole **Dosing variability:** flexible **Target dose (mg/day):** 5, 10, 15 **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** analgesics and antipyretics hypnotics and sedatives **GROUP 2** **Drug name:** Placebo **Dosing variability:** flexible **Target dose (mg/day):** 5, 10, 15 **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** analgesics and antipyretics, hypnotics and sedatives	**Benefits:** ABC, CYBOCS, CGI-I, CGI-S, PedsQL, CGSQ, response (ABC-I, CGI-I), suicide **Harms:** EPS (AIMS, BAS, SAS), fatigue, glucose, lipid profile, prolactin, LDL, total cholesterol, HDL, somnolence, aggression, total AE, weight change	During an 8-week period, aripiprazole was efficacious and generally well tolerated in the treatment of irritability associated with autistic disorder in children and adolescents who may be experiencing tantrums, aggression, self-injurious behavious, or a combination ofthese symptoms.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	of severe head trauma or stroke, (6) history or current evidence of any unstable medical condition or or an abnormal laboratory test result considered clinically significant, (7) antipsychotic treatment resistant, (8) known allergy or hypersensitivity to aripiprazole				
Pandina et al., 2007 [127] (see Aman 2002, Snyder 2002) **Country:** Canada, South Africa, USA **Condition category:** ADHD **Funding:** NR **Newcastle-Ottawa Scale:** 6/8 stars	**Study design:** Observational (pooled analysis)	**Enrolled:** NA **Analyzed:** 228 **Completed:** NA **GROUP 1** **N:** 108 **Age, mean±SD (range):** 8.6 yr **Males %:** 81 **Caucasian %:** 64 **Diagnostic breakdown (n):** CD (40), ODD (29), Axis 1 (34), BD NOS (5) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (78) **GROUP 2** **N:** 88 **Age, mean±SD (range):** 8.4 yr **Males %:** 77 **Caucasian %:** 68	**GROUP 1** **Drug name:** Risperidone **Dosing variability:** Variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.3±0.7 mg/day **Concurrent treatments:** See Aman 2002 and Snyder 2002 **GROUP 2** **Drug name:** Placebo **Dosing variability:** Variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** See Aman 2002 and Snyder 2002	**Benefits:** continuous performance task (CPT), VLT-C **Harms:** NA	Cognitive function was not altered by risperidone in short term studies.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		Diagnostic breakdown (n): CD (48), ODD (30), Axis 1 (37), BD NOS (5) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (77)			
Pathak et al., 2013 [65] **Country:** USA **Condition category:** Bipolar I (manic) **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Aug 2004 to Jul 2006 **Study design:** RCT (parallel) **Setting:** Inpatient/outpatient **Diagnostic criteria:** DSM-IV, KID-SCAD-PL **Inclusion criteria:** (1) Male and female inpatients and outpatients, (2) aged 10 to 17 years, (3) DSM-IV diagnosis of Bipolar I mania as confirmed by K-SADS-PL, (4) YMRS total score of ≥20 at both screening and randomization, (5) permitted to have secondary diagnosis of ADHD **Exclusion criteria:** (1) Current DSM-IV-diagnosed Axis I disorder other than	**Enrolled:** 284 **Analyzed:** 277 **Completed:** 222 **GROUP 1** **N:** 93 **Age, mean±SD (range):** 13.1±2.2 **Males %:** 50.5 **Caucasian %:** 78.5 **Diagnostic breakdown (n):** manic (92), mixed (1) **Treatment naïve (n):** 68 **Inpatients (n):** NR **First episode psychosis (n):** 6 **Comorbidities:** ADHD (49) **GROUP 2** **N:** 95 **Age, mean±SD (range):** 13.2±2.2 **Males %:** 57.9 **Caucasian %:** 76.8 **Diagnostic breakdown (n):** manic (91), mixed (4) **Treatment naïve (n):** 79 **Inpatients (n):** NR **First episode psychosis (n):** 6	**Treatment duration:** 3 wk **Run–in phase:** Yes **Run–in phase duration:** 1–28 day **Permitted drugs:** Psychostimulants, diphenhydramine, hydroxyzine, lorazepam, benztropine **Prohibited drugs:** Prophylactic use of benztropine **GROUP 1** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** 400 **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 2** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** 600 **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 3** **Drug name:** Placebo **Dosing variability:** NR **Target dose (mg/day):** NR	**Benefits:** CGAS, CGI-BP-S, CGI-BP-I, YMRS,CDRS-R, OAS-M, CGSQ, response, remission, suicidal ideation, aggression, bipolar disorder exacerbation **Harms:** EPS (AIMS, BAS, SAS), akathisia, mortality, weight gain, somnolence, fatigue, glucose measures, lipid values, liver function, thyroid function, prolactin, tachycardia, pulse, heart rate, ECG changes, hematology values,	Quetiapine at 400 mg/d and 600 mg/d was significantly more effective than placebo for treating acute manic symptoms in youth with bipolar I disorder. Quetiapine at these doses was generally well tolerated and AE were consistent with the profile of quetiapine in adults with bipolar disorder.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	bipolar I disorder or ADHD, (2) history of serious suicide attempts, (3) current risk for suicide or homicide in the judgment of investigators	**Comorbidities:** ADHD (40) **GROUP 3** **N:** 89 **Age, mean±SD (range):** 13.3±2.1 **Males %:** 60.7 **Caucasian %:** 74.2 **Diagnostic breakdown (n):** manic (all) **Treatment naïve (n):** 74 **Inpatients (n):** NR **First episode psychosis (n):** 7 **Comorbidities:** ADHD (35)	**Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR		
Perry et al., 1989 [66] **Country:** USA **Condition category:** ASD **Funding:** Industry, Government, Foundation **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-III-TR **Inclusion criteria:** (1) dx of infantile autism, full syndrome present, (2) only children with good response to haloperidol and requiring further drug treatment were accepted into the study **Exclusion criteria:** (1) identifiable cause for	**Enrolled:** 70 **Analyzed:** 60 **Completed:** 52 **GROUP 1** **N:** 34 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 36 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR	**Treatment duration:** 6 mo **Run-in phase:** Yes **Run-in phase duration:** 2 wk **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Haloperidol (continuous) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.2 (0.5–4) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Haloperidol (discontinuous) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1 (0.5–4.0)	**Benefits:** CGI-I, Response (CGI-I, CGI-S) **Harms:** Dyskinesia, parkinsonism, sedation	Haloperidol, administered on a long-term basis, effectively reduced maladaptive symptoms in austic children. Drug efficacy was not deminished by discontinuous drug administration.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	autism, (2) seizure disorder, (3) preexisting movement disorder	**First episode psychosis (n):** NR	**Concurrent treatments:** NR		
Pogge et al., 2005 [128] **Country:** USA **Condition category:** Mixed conditions **Funding:** NR **Newcastle-Ottawa Scale:** 6/8 stars	**Recruitment dates:** NR **Study design:** Prospective **Setting:** Inpatient **Diagnostic criteria:** NR **Inclusion criteria:** All adolescent inpatients discharged from a private psychiatric hospital during a 2 yr period who received 1 of the medications (olanzapine, risperidone) as an inpatient and a follow up prescription **Exclusion criteria:** NR	**Enrolled:** 86 **Analyzed:** 86 **Completed:** 86 **GROUP 1** **N:** 43 **Age, mean±SD (range):** See below **Males %:** See below **Caucasian %:** See below **Diagnostic breakdown (n):** Depressive disorder (11), mood disorder NOS (10), SUD (8), DBD (7), psychotic disorder (9), anxiety disorder (7), BP (8), ADHD (4), ED (1) **Treatment naïve (n):** 0 **Inpatients (n):** 43 **First episode psychosis (n):** NR **Comorbidities:** NR **GROUP 2** **N:** 43 **Age, mean±SD (range):** See below **Males %:** See below **Caucasian %:** See below **Diagnostic breakdown (n):** Depressive disorder (26), mood disorder NOS (7), SUD (7), DBD (8), psychotic disorder (3),	**Treatment duration:** 12 wk -18 mo follow up **Run-in phase:** NA **Run-in phase duration:** NA **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 2** **Drug name:** Risperidone **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Benefits:** NA **Harms:** Weight	The general lack of significant relationships between symptoms or diagnosis, other than substance abuse, and non adherence is not surprising, given heterogeneity of the sample and the general tendencies toward non adherence on the part of adolescents with both medical and psychiatric conditions.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		anxiety disorder (5), BP (2), ADHD (3), ED (1) **Treatment naïve (n):** 0 **Inpatients (n):** 43 **First episode psychosis (n):** NR **Comorbidities:** NR **Overall age, mean±SD (range):** 14.9±1.3 yr **Overall males %:** 41.9 **Overall Caucasian %:** 65.1			
Ratzoni et al., 2002 [129] **Country:** Israel **Condition category:** Schizophrenia and related **Funding:** Government, Foundation **Newcastle-Ottawa Scale:** 3/8 stars	**Recruitment dates:** Jan 2000 to Aug 2000 **Study design:** Prospective cohort **Setting:** Inpatient **Diagnostic criteria:** DSM-IV, K-SADS-PL (Hebrew version), consensus of 2 child psychiatrists **Inclusion criteria:** (1) adolescent patients who started treatment with olanzapine, risperidone, or haloperidol from Jan to Aug 2000 **Exclusion criteria:** (1) receiving other medications that cause weight gain/loss, (2) alcohol/substance	**Enrolled:** 50 **Analyzed:** 50 **Completed:** 36 **GROUP 1** **N:** 8 **Age, mean±SD (range):** 17.3±1.3 (15–19) **Males %:** 62.5 **Caucasian %:** NR **Treatment naïve (n):** 1 **Inpatients (n):** all **First episode psychosis (n):** NR **GROUP 2** **N:** 21 **Age, mean±SD (range):** 17±1.6 (14–19) **Males %:** 66.7 **Caucasian %:** NR **Treatment naïve (n):** 2 **Inpatients (n):** all **First episode psychosis (n):** NR **GROUP 3**	**Treatment duration:** 2.8 mo **Run-in phase:** Yes **Run-in phase duration:** 5.2 day (mean) **Permitted drugs:** anticholinergics, lorazepam **Prohibited drugs:** antipsychotics, heterocyclic antidepressants, lithium, medications that can cause weight gain/loss, SSRIs, valproic acid **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 7.6±4 (3–15) **Concurrent treatments:** biperiden (6), lorazepam (5), trihexyphenidyl (2) **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable	**Benefits:** PANSS, medication adherence **Harms:** Akathisia, behavioral issues, BMI, constipation, dermatologic AE, dystonia, any EPS, fatigue, hypokinesia-akinesia, sedation, seizure, sexual desire, tachycardia, WAE, weight	Adolsecents experienced greater weight gain when taking olanzapine or risperidone compared to effects reported in adults.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	abuse, (3) medical illnesses affecting body weight	**N:** 21 **Age, mean±SD (range):** 17.1±2.1 (13–20.5) **Males %:** 57.1 **Caucasian %:** NR **Treatment naïve (n):** 3 **Inpatients (n):** all **First episode psychosis (n):** NR	**Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 12.7±3.1 (7.5–20) **Concurrent treatments:** biperiden (6), lorazepam (5), trihexyphenidyl (2) **GROUP 3** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 3.2±1.1 (1–5) **Concurrent treatments:** biperiden (6), lorazepam (5), trihexyphenidyl (2)		
Remington et al., 2001 [67] **Country:** Canada **Condition category:** ASD **Funding:** Non-industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (crossover) **Setting:** NR **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) DSM-IV diagnosis of autism confirmed independently bt two investigators, (2) evidence that haloperidol or clomipramine had not been used previously, or, if so, that an adequate therapeutic trial was not completed	**Enrolled:** 37 **Analyzed:** 33 **Completed:** 23/33 (H), 12/32 C, 21/32 (P) **GROUP 1** **N:** 33 **Age, mean±SD (range):** 16.3 (10–36) yr **Males %:** 83.3 **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR	**Treatment duration:** 7 wk **Run-in phase:** Yes **Run-in phase duration:** 1 wk before and between each arm of the treatment regimen **Permitted drugs:** benztropine **Prohibited drugs:** no other antipsychotic medications **GROUP 1** **Drug name:** Chlomipramine-Placebo-Haloperidol (CPH), PHC, HCP **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1-1.5 **Concurrent treatments:** NR	**Benefits:** ABC, CARS **Harms:** fatigue, ESRS, dystonia, depression, ECG, arrythmias	Results favor haloperidol over clomipramine in the treatment of autistic disorder. The two agents demonstrated comparable improvement when compared with baseline if there was a full therapeutic trial; however, significantly fewer individuals treated with clomipramine were able to do this, for reasons related both to side effects and efficacy.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	Exclusion criteria: NR				
Reyes et al., 2006 [68] **Country:** Belgium, Germany, Great Britain, Israel, Netherlands, Poland, South Africa, Spain **Condition category:** ADHD **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Aug 2001 to Sep 2003 **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-IV, K-SADS-PL **Inclusion criteria:** (1) 5–17 yr, (2) no moderate or severe intellectual impairment (IQ ≥55), (3) CD serious enough to warrant clinical treatment, (4) score ≥24 on the conduct problem subscale of the NCBRF, (5) responsible caregiver **Exclusion criteria:** (1) schizophrenia and bipolar disorder	**Enrolled:** 335 **Analyzed:** 335 **Completed:** 162 **GROUP 1** **N:** 172 **Age, mean±SD (range):** 10.9±2.9 **Males %:** 82 **Caucasian %:** NR **Diagnostic breakdown (n):** CD (62), DBD NOS (3), ODD (107) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (117) **GROUP 2** **N:** 163 **Age, mean±SD (range):** 10.8±2.9 **Males %:** 91 **Caucasian %:** NR **Diagnostic breakdown (n):** CD (61), DBD NOS (5), ODD (97) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (110)	**Treatment duration:** 7.4 mo **Run-in phase:** Yes **Run-in phase duration:** 6 wk **Permitted drugs:** medication for EPS (only after dose reduction attempted), psychostimulants **Prohibited drugs:** anticonvulsants, antidepressants, antipsychotics, lithium **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 0.8±0.3 (<50 kg), 1.2±0.4 (≥50 kg) **Concurrent treatments:** analgesics (26), psychostimulants (36) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** analgesics (20), psychostimulants (36)	**Benefits:** CGAS, CGI-I, CGI-S, NCBRF, VAS-MS Cognitive (MVLT, CPT), growth (tannar stages), response (relapse, symptom recurrence) **Harms:** Akathisia, BMI, dystonia, EPS, fatigue, parkinsonism, prolactin, prolactin-related AE, SAE, somnolence, tardive dyskinesia, total AE, WAE, weight change	Patients who responded to initial treatment with risperidone benefited from continued, long-term treatment. Risperidone was safe and well tolerated during a 1-year extension.
Rizzo et al., 2012 [69] **Country:** Italy	**Recruitment Dates:** NR	**Enrolled:** 75 **Analyzed:** 75 **Completed:** 75	**Treatment duration:** 24 mo **Run-in phase:** Yes **Run-in phase duration:** 4 wk	**Benefits:** NR **Harms:** BMI, glycemia,	Pimozide and aripiprazole have slightly different contraindications for

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Condition category: Tic disorders **Funding:** Non-industry **Risk of Bias:** High (subjective), High (objective)	**Study design:** NRCT (parallel) **Diagnostic criteria:** DSM-IV-TR **Setting:** Outpatients **Inclusion criteria:** TS according to DSM-IV-TR, from Neurology Unit of Catania University **Exclusion criteria:** NR	**GROUP 1:** **N:** 25 **Age, mean±SD (range):** 11.6 ±2.2 yr **Males %:** 88% **Caucasian %:** NR **Diagnostic breakdown (n):** Tourette syndrome (25) **Treatment naïve (n):** (1) **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** OCD (11), ADHD (3) **GROUP 2:** **N:** 25 **Age, mean±SD (range):** 11.2±3.1 yr **Males %:** 92% **Caucasian %:** NR **Diagnostic breakdown (n):** Tourette syndrome (25) **Treatment naïve (n):** (22) **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** OCD (9), ADHD (5) **GROUP 3:** **N:** 25 **Age, mean±SD (range):** 10.2±2.8 yr **Males %:** 88% **Caucasian %:** NR **Diagnostic breakdown (n):** Tourette syndrome (25)	**Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Aripiprazole **Dosing variability:** Variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.25-15 mg/day **Concurrent treatments:** Fluoxetine (10), Biperiden cloridrate (7) **GROUP 2:** **Drug name:** Pimozide **Dosing variability:** Variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1-4 mg/day **Concurrent treatments:** Fluoxetine (7), Biperiden cloridrate (12) **GROUP 3:** **Drug name:** No medication **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	triglyceridemia, cholesterolemia	use in children with Tourette syndrome. Pimozide may be less well-suited to diabetic patients. Patients with predisposition to cholesterol problems may require closer monitoring when taking aripiprazole.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		Treatment naïve (n): (25) **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** OCD (0), ADHD (2)			
Ronsley et al., 2015 [130] **Country:** Canada **Condition category:** Mixed conditions **Funding:** Industry **Newcastle-Ottawa Scale:** 4/8 stars	**Recruitment dates:** Feb 2009 to Mar 2012 **Study design:** Prospective Cohort **Setting:** Outpatient **Diagnostic criteria:** DSM-IV-TR **Inclusion criteria:** (1) 2-18 years of age (2) having a mental health condition diagnosed based on the DSM-IV-TR, (3) SGA treatment with either risperidone or quetiapine independently initiated by a psychiatrist less than 7 days before study consent; and never previously exposed to an SGA. **Exclusion criteria:** pre-existing DM (types 1 or 2), diagnosis of an eating disorder, treatment with more than 1 antipsychotic, ortreatment with other	**Enrolled:** 130 **Analyzed:** 37 **Completed:** 37 **GROUP 1** **N:** 20 **Age, mean±SD (range):** 14 **Males %:** 50 **Caucasian %:** 40 **Diagnostic breakdown (n):** Psychotic disorders (5), mood disorder (1), depressive disorder (3), bipolar disorder(3), ADHD(4), ODD(4), Anxiety disorder(6), adjustment disorder(1), mental retardation or personality disorder(2) **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 17 **Age, mean±SD (range):** 14.1 **Males %:** 47.1 **Caucasian %:** 52.9 **Diagnostic breakdown (n):** Psychotic disorders (4), mood disorder (3),	**Treatment duration:** 12 months **Run-in phase:** NR **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR **GROUP 2** **Drug name:** Quetiapine **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Benefits:** NR **Harms:** weight, BMI, waist circumference, blood pressure, laboratory parameters	Children treated with risperidone or quetiapine are at a significant risk for developing obesity, elevated waist circumference, and dyslipidemia during 12 months of treatment. These data emphasize the importance for early idenification and treatment of metabolic side effects.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	medications known to affect meatbolism.	depressive disorder (5), bipolar disorder(3), ADHD(4), PDD(1), Anxiety disorder(7), reactive attachment disorder(2), mental retardation or personality disorder(5) **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR			
RUPP et al., 2005 [70] **Country:** USA **Condition category:** ASD **Funding:** Industry/ Non-industry **Risk of bias:** Medium (subjective), Medium (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) responders at the end of 4 mo extension study. For initial inclusion criteria refer to McCracken 2002 **Exclusion criteria:** NR. For initial exclusion criteria refer to McCracken 2002	**Enrolled:** 38 **Analyzed:** NR **Completed:** 32 **GROUP 1** **N:** 16 **Age, mean±SD (range):** see below **Males %:** see below **Caucasian %:** see below **Diagnostic breakdown (n):** NR **Treatment naïve (n):** see below **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see below **GROUP 2** **N:** 16 **Age, mean±SD (range):** see below **Males %:** see below **Caucasian %:** see below **Diagnostic breakdown (n):** NR	**Treatment duration:** 8 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** anticonvulasant treatment if child had been taking stable dose for 4 wk and had been free of seizures for 6 mo **Prohibited drugs:** other psychotropic medication **GROUP 1** **Drug name:** Risperidone **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 3.5 (15-45 kg), 4.5 (>45 kg) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 25% dosage reduction/wk **Concurrent treatments:** NR	**Benefits:** Relapse, ABC **Harms:** NR	Risperidone showed persistent efficacy and good tolerability for intermediate-length treatment of children with autism characterized by tantrums, aggression, and/or self-injurious behavior. Discontinuation after 6 months was associated with a rapid return of disruptive and aggressive behavior in most subjects.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		Treatment naïve (n): see below **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see below **Overall age, mean±SD (range):** 9.0±2.5 yr **Overall males %:** 86.8 **Caucasian %:** 60.5 **Overall treatment naïve (n):** 7 **Overall comorbidities:** IQ average (2), IQ borderline (5), MR (27)			
Saito et al., 2004 [131] **Country:** USA **Condition category:** Mixed conditions **Funding:** Government **Newcastle-Ottawa Scale:** 6/8 stars	**Recruitment dates:** Sept 2001 to Mar 2003 **Study design:** Prospective cohort **Setting:** Inpatient/outpatient **Diagnostic criteria:** NR **Inclusion criteria:** (1) male and females, (2) aged 5 to 18 years, (3) treatment naïve or at least a 1-month interval since their last treatment with antipsychotic agents, (4) inpatients or outpatients at a suburban children's hospital	**Enrolled:** 40 **Analyzed:** 40 **Completed:** 40 **GROUP 1** **N:** 13 **Age, mean±SD (range):** all groups: 13.4±3.4 (5–18) **Males %:** all groups: 55 **Caucasian %:** NR **Diagnostic breakdown (n):** all groups: schizophrenia or other psychosis (14), mood disorders (14), DBD (9), intermittent explosive disorder (1), PDD NOS (1), eating disorder NOS (1) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 11.2 wk **Run–in phase:** Yes **Run–in phase duration:** 1 mo. **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 7.8±4.2 **Concurrent treatments:** all groups: divalproex sodium (7), lithium (5), SSRI (11), stimulants (9), benzodiazepines (3), alpha-adrenergic agonists (3) **GROUP 2** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** NR	**Benefits:** NA **Harms:** prolactin, prolactin-related AEs	Prolactin levels were significantly increased in children and adolescents treated with risperidone, compared to those treated with olanzapine or quetiapine.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	Exclusion criteria: (1) females receiving hormonal contraception	**Comorbidities (n):** NR **GROUP 2** **N:** 6 **Age, mean±SD (range):** see group 1 **Males %:** see group 1 **Caucasian %:** NR **Diagnostic breakdown (n):** see group 1 **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** NR **GROUP 3** **N:** 21 **Age, mean±SD (range):** see group 1 **Males %:** NR **Caucasian %:** NR **Diagnostic breakdown (n):** see group 1 **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** NR	**Daily dose (mg/day), mean±SD (range):** 283.3±222.9 **Concurrent treatments:** see group 1 **GROUP 3** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2.2±2 **Concurrent treatments:** see group 1		
Sallee et al., 2000 [73] **Country:** USA **Condition category:** Tic disorders **Funding:** Industry	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV	**Enrolled:** 28 **Analyzed:** 27 **Completed:** 24 **GROUP 1** **N:** 16 **Age, mean±SD (range):** 11.3 (7–14) **Males %:** 87.5 **Caucasian %:** NR	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** 4–8 wk **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Ziprasidone **Dosing variability:** variable	**Benefits:** CGI-TS, CYBOCS, YGTSS **Harms:** Akathisia, prolactin, prolactin-related AESAE, sedation, somnolence, total AE, WAE, weight change	Ziprasidone was well tolerated in children and adolscents with Tourette syndrome, and may also be an effective anti-tic medication.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Risk of bias: Medium (subjective), Medium (objective)	**Inclusion criteria:** (1) 7–17 yr, (2) DSM-IV dx of Tourette syndrome or chronic tic disorder, with symptoms severe enough to warrant medication, (3) not pregnant or breast feeding **Exclusion criteria:** (1) secondary tic disorder, (2) DSM-IV criteria for major depression, PDD, autism, MR, anorexia nervosa/bulimia, substance abuse, or any psychotic disorder	**Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (9), DBD (4), OCD (10; all groups), learning disability (2; all groups) **GROUP 2** **N:** 12 **Age, mean±SD (range):** 11.8 (8–16) **Males %:** 66.7 **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (6), DBD (1), OCD (10; all groups), learning disability (2; all groups)	**Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 28.2±9.6 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR		
Sallee et al., 1997 [72] **Country:** USA **Condition category:** Tic disorders **Funding:** Industry, Government	**Recruitment dates:** NR **Study design:** RCT (crossover) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-III-TR, K-SADS-P **Inclusion criteria:** (1) principal DSM-III-R dx	**Enrolled:** 22 **Analyzed:** 22 **Completed:** 22 **GROUP 1** **N:** 22 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** >2 wk **Permitted drugs:** diphenhydramine hydrochloride **Prohibited drugs:** adjunctive treatment, anticholinergics, concomitant medications **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** variable	**Benefits:** CGAS, CGI-S Medication adherence, response **Harms:** Akathisia, akinesia, behavioral issues, electrocardiovascular, EPS (AIMS, ESRS), prolactin, treatment limiting AE, WAE, weight change	Pimozide is superior to haloperidol for controlling symptoms of Tourette syndrome in children and adolescents.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Risk of bias: High (subjective), High (objective)	of Tourette syndrome; may have multiple Axis I and II dx, (2) 7–16 yr, 11 mo, (3) TSGS score >20, (4) previous exposure to neuroleptics permitted, but treatment must have been withdrawn ≥2 wk before baseline **Exclusion criteria:** (1) chronic motor tic disorder or transient tic disorder, (2) serious medical illness, (3) abnormal ECG, (4) inability to perform required measurements, (5) use of concurrent medication that may alter or interact with haloperidol or pimozide, (6) history of drug or alcohol abuse, (7) autism or childhood schizophrenia	**First episode psychosis (n):** NR **Comorbidities:** ADHD (13), OCD (5) **GROUP 2** **N:** 22 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see G1 **GROUP 3** **N:** 22 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** see G1	**Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 3.5±2.2 (1–8) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Pimozide **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 3.4±1.6 (1–6) **Concurrent treatments:** NR **GROUP 3** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR		
Sallee et al., 1994 [71] **Country:** USA **Condition category:** Tic disorders	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Outpatient/community	**Enrolled:** 41 **Analyzed:** 41 **Completed:** NR **GROUP 1** **N:** 17 **Age, mean±SD (range):** 10.4 **Males %:** NR	**Treatment duration:** 6 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1**	**Benefits:** CBCL-TRF, cognitive (CPT, MST) **Harms:** NR	The effect of pimozide treatment on cognition was superior to haloperidol in children with Tourette syndrome with comorbid ADHD.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Funding: Foundation **Risk of bias:** Medium (subjective), Medium (objective)	**Diagnostic criteria:** DSM-III-TR, TSGS **Inclusion criteria:** (1) consecutive outpatient children who met DSM-III-R criteria for Tourette syndrome and severity criteria using the TSGS **Exclusion criteria:** NR	**Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (6) **GROUP 2** **N:** 24 **Age, mean±SD (range):** 10.8 **Males %:** NR **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (7)	**Drug name:** Haloperidol **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.5±0.6 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Pimozide **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 3.7±1.4 **Concurrent treatments:** NR		
Savitz et al., 2015 [74] **Country:** India, Romania, Russia, Slovakia, Spain, Ukraine, and the United States **Condition category:** Schizophrenia and related **Funding:** Industry	**Recruitment dates:** November 2009 to June 2012 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) 12-17 yr, (2) body weight ≥ 29kg, (3) diagnosis of	**Enrolled:** 228 **Analyzed:** 226 **Completed:** 174 **GROUP 1** **N:** 112 **Age, mean±SD (range):** 15.2±1.5 **Males %:** 65 **Caucasian %:** 75 **Treatment naïve (n):** 13 **Inpatients (n):** 70 (at screening) **First episode psychosis (n):** 0 **GROUP 2**	**Treatment duration:** 8wk acute, 18 wk maintenance **Run-in phase:** Yes **Run-in phase duration:** ≤3 wks **Permitted drugs:** antidepressants, certain benzodiazepines, and non-benzodiazepine hypnotics; anticholinergics, topical antifungal agents, antihistamines, anti-inflammatory drugs except systemic corticosteroids, histamine-2 (H2) blockers, and rescue medications for the treatment of restlessness, agitation, insomnia, or extrapyra-midal symptoms	**Benefits:** PANSS, maintenance of stability, CGI-S, response **Harms:** AIMS, BAS, SAS, any AE, C-SSRS, prolactin, weight, ECG, glucose, insulin, lipids	Palirperidone ER did not demonstrate superiority to aripiprazole in treating adolescent schizophrenia.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Risk of bias: Medium (subjective), Medium (objective)	schizophrenia ≥1yr, (4) Positive and Negative Symptom Score (PANSS) total score of 60 to 120 (inclusive) at screening, (5) ≥1 prior adequate treatment with antipsychotic medication, (6) clinician belief that suboptimnal current treatment **Exclusion criteria:** (1) diagnosis of BD, MDD, schizoaffective disorder, schizophreniform disorder, ASD, MR, primary substance-induced psychotic disorder, dissociative disorder or SUD in 3 months before screening, (2) history of seizure disorder, neuroleptic malignant syndrome, encephalopathic syndrome, tardive dyskinesia, or insulin-dependent diabetes mellitus, (3) receiving clozapine (2 months before screening), (4) depot antipsychotic therapy within 2 treatment cycles before screening, or electroconvulsive	**N:** 114 **Age, mean±SD (range):** 15.4±1.5 **Males %:** 67 **Caucasian %:** 77 **Treatment naïve (n):** 11 **Inpatients (n):** 68 (at screening) **First episode psychosis (n):** 0	**Prohibited drugs:** antipsychotics, psychostimulants or other dopamine agonists, certain sedatives (including barbiturates), hypnotics, or anxiolytics, mood stabilizers or anticonvulsants, electroconvulsive therapy, inhibitors or inducers of CYP3A4 or CYP2D6 **GROUP 1** **Drug name:** Paliperidone ER **Dosing variability:** variable **Target dose (mg/day):** 6 mg per day [days 1–7], flexibly dosed 3, 6, or 9mg per day from day 8 to end of study [EOS] **Daily dose (mg/day), mean±SD (range):** 6.75±1.8 **Concurrent treatments:** anti-EPS medications or antihistamines (26%) **GROUP 2** **Drug name:** Aripiprazole **Dosing variability:** variable **Target dose (mg/day):** 2 mg per day ([days 1 and 2], 5 mg per day [days 3 and 4], 10 mg per day [days 5–7], flexibly dosed 5, 10, or 15 mg per day from day 8 to EOS **Daily dose (mg/day), mean±SD (range):** 11.6±3.0 **Concurrent treatments:** anti-EPS medications or antihistamines (25%)		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	therapy (3 months before baseline visit), (5) sexually nonabstinent girls who were pregnant, nursing, or of childbearing capacity.				
Scahill et al., 2003 [75] **Country:** USA **Condition category:** Tic disorders **Funding:** Industry, Government **Risk of bias:** Medium (subjective), Medium (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV, joint parent and child interview **Inclusion criteria:** (1) 7–65 yr, (2) Tourette syndrome (DSM-IV), (3) Total Tic score ≥22 on the YGTSS **Exclusion criteria:** (1) evidence of current major depression, GAD, separation anxiety disorder, or psychotic symptoms (clinical evaluation or DSM-IV), (2) WISC age-appropriate IQ <70, (3) prior adequate trial of risperidone (dose ≥1.0 mg/day for ≥2 wk), (4) psychotropic medication within 2 wk,	**Enrolled:** 26 **Analyzed:** 26 **Completed:** NR **GROUP 1** **N:** 12 **Age, mean±SD (range):** 11.1 (2.20) yrs (whole pediatric sample) **Males %:** 96% (whole pediatric sample) **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (11), MR (0), OCD (4) **GROUP 2** **N:** 14 **Age, mean±SD (range):** See group 1 **Males %:** see group 1 **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** 1–2 wk **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** 3 **Daily dose (mg/day), mean±SD (range):** 2.5±0.9 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** 3 **Daily dose (mg/day), mean±SD (range):** 3.3±0.9 **Concurrent treatments:** NR	**Benefits:** CGI-I, YGTSS Response **Harms:** Weight, EPS, social phobia	For short-term treatment of tics in children, risperidone appeared to be safe and effective.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	(5) significant medical problem, (6) moderate or greater obsessive-compulsive symptoms (YBOCS>15)	**Comorbidities:** see group 1			
Schneider et al., 2012 [76] **Country:** USA **Condition category:** Bipolar I (manic, mixed) **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-IV-TR, K-SADS-PL **Inclusion criteria:** (1) 10-17 yr, (2) DSM-IV-TR bipolar I disorder confirmed with K-SADS-PL, (3) YMRS score ≥16 at both screening and baseline **Exclusion criteria:** (1) dx of substance abuse or dependence in the previous month for any substance other than nicotine or caffeine, (2) being clinically stable on a well-tolerated treatment regimen, (3) prior treatment with ziprasidone, a known allergy to ziprasidone, or a serious suicidal risk, (4) any history of head injury resulting in loss of consciousness	**Enrolled:** 23 **Analyzed:** 17 **Completed:** 11 **GROUP 1** **N:** 14 **Age, mean±SD (range):** 14.7±2.3 yr **Males %:** 64 **Caucasian %:** 86 **Diagnostic breakdown (n):** mixed (9) **Treatment naïve (n):** see below **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (3) **GROUP 2** **N:** 9 **Age, mean±SD (range):** 14.5±2.2 yr **Males %:** 22 **Caucasian %:** 89 **Diagnostic breakdown (n):** mixed (9) **Treatment naïve (n):** see below **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (7)	**Treatment duration:** 4 wk **Run-in phase:** Yes **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Ziprasidone **Dosing variability:** variable **Target dose (mg/day):** ≥45kg: 120-160, <45kg: 60-80 **Daily dose (mg/day), mean±SD (range):** 20 [initial dose] **Concurrent treatments:** all groups: benztropine (1), lorazepam (1) **GROUP 2** **Drug name:** Placebo **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Benefits:** YMRS, response, medication adherence **Harms:** NR	Further research is needed to determine whether treatment related increases in ventral prefrontal activation are associated with improvements in sustained attention and other executive function domains, if there are differences in patterns of change patients experiencing manic versus mixed episodes, as well as to investigate whether functional alterations in specific regions of ventral prefrontal cortex may be useful as specific biomarkers of ziprasidone response in patients with mania.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	for > 10 minutes, or any unstable medical or neurological disorder.	**Overall Treatment naïve (n):** 7			
Sehgal et al., 1999 [77] **Country:** USA **Condition category:** Tic disorders **Funding:** Industry, Government, Foundation **Risk of bias:** Medium (subjective), NA (objective)	**Recruitment dates:** Oct 1993 to Nov 1995 **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-III-TR **Inclusion criteria:** (1) DSM-III-R diagnostic criteria for Tourette syndrome at participating medical centers **Exclusion criteria:** NR	**Enrolled:** 10 **Analyzed:** 10 **Completed:** 8 **GROUP 1** **N:** 4 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** NR **GROUP 2** **N:** 6 **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** NR	**Treatment duration:** 8 mo **Run-in phase:** Yes **Run-in phase duration:** 4 mo **Permitted drugs:** NR **Prohibited drugs:** antidepressants, benzodiazepines, clonidine, stimulants (washout ≥2 wk prior to enrolment) **GROUP 1** **Drug name:** Pimozide (short-term) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 3. 8 (2–6) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Pimozide (long-term) **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 3.5 (1–7) **Concurrent treatments:** NR	**Benefits:** Response **Harms:** Tardive dyskinesia, sedation	In children with Tourette syndrome, longer term treatment with pimozide appears to be more effective on the course of tics than a short-term course of the drug used to suppress an acute exacerbation of tics.
Shaw et al., 2006 [78] **Country:** USA	**Recruitment dates:** Jan 1998 to June 2005 **Study design:** RCT (parallel)	**Enrolled:** 25 **Analyzed:** 25 **Completed:** 24 **GROUP 1** **N:** 12	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** 3 wk **Permitted drugs:** NR	**Benefits:** BPRS-24, CGI-S, SANS, SAPS, response **Harms:** Behavioral issues, blood cells,	Clozapine had a more favorable profile of clinical response and adverse events than olanzapine.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Condition category: Schizophrenia and related **Funding:** NR **Risk of bias:** Medium (subjective), Medium (objective)	**Setting:** Inpatient **Diagnostic criteria:** DSM-IV, K-SADS, medical and school record review, interview with child and parents **Inclusion criteria:** (1) schizophrenia with definite onset of symptoms ≤13 yr , (2) IQ >70, (3) no history of progressive neurological or medical disorders, (4) failure to respond to 2 antipsychotic medications (typical or atypical) used at adequate doses (>100 mg chlorpromazine equivalents) and for adequate duration (>4 wk unless terminated owing to intolerable adverse effects) **Exclusion criteria:** (1) nonresponse to an adequate trial of olanzapine or clozapine (8 wk of olanzapine at 20 mg/d or of clozapine at 200 mg/d)	**Age, mean±SD (range):** 11.7±2.3 **Males %:** 66.7 **Caucasian %:** 58.3 **Treatment naïve (n):** 0 **Inpatients (n):** all **First episode psychosis (n):** 0 **Comorbidities:** ADHD (4), anxiety disorders (6), MR (0) **GROUP 2** **N:** 13 **Age, mean±SD (range):** 12.8±2.4 **Males %:** 53.8 **Caucasian %:** 53.8 **Treatment naïve (n):** 0 **Inpatients (n):** all **First episode psychosis (n):** 0 **Comorbidities:** ADHD (3), anxiety disorders (1), MR (0)	**Prohibited drugs:** NR **GROUP 1** **Drug name:** Clozapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 327±113 (150–500) **Concurrent treatments:** diphenhydramine hydrochloride (4), guanfacine hydrochloride (1), lorazepam (2), sedatives (4), ≤4 hr specialized education, recreational and occupational therapy **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 18.1±4.3 **Concurrent treatments:** clomipramine hydrochloride (1), diphenhydramine hydrochloride (6), lorazepam (3), sedatives (3), valproate sodium (2), ≤4 hr specialized education, recreational and occupational therapy	blood pressure, constipation, dermatologic AE, ECG changes, STESS, AIMS, SAS, lipid profile, seizure, sleepiness, somnolence, tachycardia, weight change, BMI change	
Shea et al., 2004 [79] **Country:** Canada	**Recruitment dates:** NR	**Enrolled:** 80 **Analyzed:** 79 **Completed:** 72	**Treatment duration:** 8 wk **Run-in phase:** No **Run-in phase duration:** NR	**Benefits:** ABC, NCBRF, VAS-MS Response (ABC-I, CGI-C)	In children with ASD, risperidone was well tolerated and efficacious in

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Condition category: ASD **Funding:** Industry **Risk of bias:** Medium (subjective), Medium (objective)	**Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) physically healthy outpatients, (2) 5–12 yr, (3) DSM-IV Axis I dx of PDD, (4) a total score >30 on the CARS with or without MR **Exclusion criteria:** (1) patients with schizophrenia, other psychotic disorders, clinically relevant nonneurologic disease, clinically significant laboratory abnormalities, or a seizure disorder for which they were receiving >1 anticonvulsant or if they had had a seizure in the last 3 mo, (2) history of hypersensitivity to neuroleptics, tardive dyskinesia, NMS, drug or alcohol abuse, or HIV infection, (3) used risperidone in the last 3 mo or previously	**GROUP 1** **N:** 41 **Age, mean±SD (range):** 7.6±0 (5–12) **Males %:** 72.5 **Caucasian %:** NR **Diagnostic breakdown (n):** Asperger's disorder (5), autistic disorder (27), childhood disintegrative disorder (1), PDD NOS (7), Rett disorder (0) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (15) **GROUP 2** **N:** 39 **Age, mean±SD (range):** 7.3±0 (5–12) **Males %:** 82.1 **Caucasian %:** NR **Diagnostic breakdown (n):** Asperger's disorder (7), autistic disorder (28), childhood disintegrative disorder (0), PDD NOS (4), Rett disorder (0) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (12)	**Permitted drugs:** anticholinergics, anticonvulsants and/or medications for sleep or anxiety (constant dose ≥30 days before enrolment), medications for preexisting organic disorders **Prohibited drugs:** α-2 antagonists, antidepressants, antipsychotics, cholinesterase inhibitors, clonidine, guanfacine, lithium, naltrexone, psychostimulants **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.2 **Concurrent treatments:** analgesics (15), anti-asthmatics (6), antibiotics (5), anticholinergics (3), cough and cold preparations (10), sedatives/hypnotics (11) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** analgesics (7), anti-asthmatics (4), antibiotics (5), anticholinergics (1), cough and cold preparations (4), sedatives/hypnotics (9)	**Harms:** Anorexia, behavioral issues, blood pressure, constipation, EPS (ESRS), fatigue, hyperkinesias, pulse, SAE, somnolence, tachycardia, tardive dyskinesia, total AE, WAE, weight change	the treatment of autism associated behavioral symptoms.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	unresponsive or intolerant to risperidone, (4) using a prohibited medication				
Sikich et al., 2008 [81] **Country:** USA **Condition category:** Schizophrenia and related **Funding:** Government **Risk of bias:** Low (subjective), Low (objective)	**Recruitment dates:** Feb 2002 to May 2006 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, KID-SCID **Inclusion criteria:** (1) 8–19 yr (30% or fewer 16 or older), (2) DSM-IV dx of schizophrenia, schizoaffective disorder, or schizophreniform disorder with current positive psychotic symptoms of at least moderate intensity, (PANSS or BRRS-C), (3) good physical health, (4) able to provide informed consent and guardian's written informed consent **Exclusion criteria:** (1) premorbid dx of MR, (2) current major depressive episode, active substance abuse, (3) history of	**Enrolled:**116 **Analyzed:** NR **Completed:** 70 **GROUP 1** **N:** 41 **Age, mean±SD (range):** NR **Males %:** 57.5 **Caucasian %:** 70 **Diagnostic breakdown (n):** schizoaffective disorder (14), schizophrenia (26) **Treatment naïve (n):** 16 **Inpatients (n):** 4 **First episode psychosis (n):** 35 **Comorbidities:** ADHD (12), affective disorder (9), anxiety disorder (6), ASD (2), DBD (4), learning disability (7), MR (0), none (14), psychosis (7), SA (4) **GROUP 2** **N:** 36 **Age, mean±SD (range):** NR **Males %:** 71.4 **Caucasian %:** 60 **Diagnostic breakdown (n):** schizoaffective disorder (13), schizophrenia (22) **Treatment naïve (n):** 13	**Treatment duration:** 8 wk (10.1 mo extension) **Run-in phase:** Yes **Run-in phase duration:** 2 wk **Permitted drugs:** antidepressants or non-antipsychotic mood stabilizers (≥4 wk prior to study entry); anticholinergics, benzodiazepines, propranolol (concomitant); thymoleptics (maintenance phase) **Prohibited drugs:** NR **GROUP 1** **Drug name:** Molindone **Dosing variability:** variable **Target dose (mg/day):** 140 **Daily dose (mg/day), mean±SD (range):** 59.9±33.5 (10–140) **Concurrent treatments:** antidepressants (4), benzodiazepines (39%), mood stabilizers (3), propranolol (13%), benzotropine (45%) **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** 20 **Daily dose (mg/day), mean±SD (range):** 11.4±5 (2.5–20) **Concurrent treatments:** antidepressants (4), benzodiazepines (20%),	**Benefits:** BPRS-C, CGI-I, CGI-S, CAFAS, PANSS, medication adherence, response, suicide **Harms:** Akathisia, behavioral issues, blood pressure, BMI, constipation, dystonia, ECG changes, SAS, BAS, AIMS, EPS, glucose, homeostasis, insulin, lipid profile, liver function, prolactin, prolactin-related AE, pulse, SAE, sedation, tardive dyskinesia, total AE, WAE, weight change	Rispiridone and olanzapine failed to show superior efficacy over molindone in the treatment of early-onset schizophrenia and schizoaffective disorder.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	intolerance or nonresponse to any of the study treatments during a prior episode, (4) history of successful use of the study treatments during the current episode (≥8 wk of treatment, including ≥2 wk at the maximal dose allowed in the current study), (5) imminent risk of harming themselves or others, (6) bipolar disorder, primary PTSD, primary personality disorder, or psychosis NOS (dx by clinician, confirmed by KID-SCID), (7) endocrinological or neurological conditions that confound the dx or are a contraindication to treatment, (8) pregnancy or refusal to practice contraception during the study, (9) use of a depot antipsychotic within the past 6 mo	**Inpatients (n):** 2 **First episode psychosis (n):** 33 **Comorbidities:** ADHD (13), affective disorder (7), anxiety disorder (9), ASD (2), DBD (6), learning disability (1), MR (0), none (17), psychosis (4), SA (2) **GROUP 3** **N:** 42 **Age, mean±SD (range):** NR **Males %:** 65.9 **Caucasian %:** 61 **Diagnostic breakdown (n):** schizoaffective disorder (13), schizophrenia (28) **Treatment naïve (n):** 9 **Inpatients (n):** 6 **First episode psychosis (n):** 40 **Comorbidities:** ADHD (9), affective disorder (12), anxiety disorder (12), ASD (3), DBD (10), learning disability (2), MR (0), none (15), psychosis (6), SA (2)	benztropine (14%), mood stabilizers (2), propranolol (11%) **GROUP 3** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** 6 **Daily dose (mg/day), mean±SD (range):** 2.8±1.4 (0.5–6) **Concurrent treatments:** antidepressants (5), benzodiazepines (41%), benztropine (34%), mood stabilizers (4), propranolol (7%)		
Sikich et al., 2004 [80] **Country:** USA **Condition category:**	**Recruitment dates:** Nov 1997 to May 2001 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient	**Enrolled:** 50 **Analyzed:** 50 **Completed:** 32 **GROUP 1** **N:** 15 **Age, mean±SD (range):** 15.4±2.2	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** 1–2 wk **Permitted drugs:** amantadine (200 mg/day), antidepressants and mood stabilizers (if taken ≥4 wk preceding study entry or if clinically	**Benefits:** BPRS-C, CPRS, CGI-I, CGI-S, response, medication adherence **Harms:** Withdrawal due to AEs, akathisia, BMI, constipation,	Risperidone and olanzapine were effective in acutely reducing symptoms in psychotic youth.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Schizophrenia and related **Funding:** Industry, Government, Foundation **Risk of bias:** High (subjective), High (objective)	**Diagnostic criteria:** DSM-IV, K-SADS-P **Inclusion criteria:** (1) ≥1 positive psychotic symptom of moderate or greater severity on the BPRS-C, present throughout the past 2 wk, (2) full scale IQ >69, (3) patients with current or recent dx of ADHD, Tourette syndrome, OCD, or a history of substance abuse or dependence were allowed to participate only if their psychotic symptoms were not better accounted for by the comorbid disorder **Exclusion criteria:** (1) psychotic symptoms resulting from acute substance intoxication or withdrawal, (2) history of serious adverse reactions or nonresponse to an adequate trial of any of the study medications during this psychotic episode, (3) prior dx of PDD or a serious medical or neurological disorder, (4) pregnancy or refusal to practice contraception, (5) imminent risk in current	**Males %:** 53 **Caucasian %:** 73 **Diagnostic breakdown (n):** affective disorders (7), schizophrenia spectrum (8) **Treatment naïve (n):** 3 **Inpatients (n):** 10 **First episode psychosis (n):** 12 **GROUP 2** **N:** 16 **Age, mean±SD (range):** 14.6±3.1 **Males %:** 56 **Caucasian %:** 63 **Diagnostic breakdown (n):** affective disorders (11), schizophrenia spectrum (5) **Treatment naïve (n):** 8 **Inpatients (n):** 12 **First episode psychosis (n):** 12 **GROUP 3** **N:** 19 **Age, mean±SD (range):** 14.6±2.9 **Males %:** 68 **Caucasian %:** 47 **Diagnostic breakdown (n):** affective disorders (6), schizophrenia spectrum (13) **Treatment naïve (n):** 2 **Inpatients (n):** 15 **First episode psychosis (n):** 15	significant affective symptoms persisted after 4 wk of study treatment), benztropine (1–3 mg/day), lorazepam (0.5–3 mg/day), propranolol (20–60 mg/day), trihexyphenidyl (4–6 mg/day) **Prohibited drugs:** NR **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** variable **Target dose (mg/day):** 1–5 **Daily dose (mg/day), mean±SD (range):** 5±2 (1–5) **Concurrent treatments:** amantadine (1), benztropine/trihexyphenidyl (7), buproprion (4), citalopram (1), gabapentin (1), lithium (1), lorazepam (3), paroxetine (1), sertraline (3), valproate (2), venlaflaxine (1), inpatient or residential treatment (9) **GROUP 2** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** 2.5–12.5 **Daily dose (mg/day), mean±SD (range):** 12.3±3.5 (2.5–12.5) **Concurrent treatments:** benztropine/trihexyphenidyl (5), buproprion (2), carbamazepine (1), fluoxetine (2), fluvoxamine (1), lithium (1), lorazepam (1), paroxetine (1), propranolol (2), sertraline (1), valproate (1), inpatient or residential treatment (10)	dermatolodic AE, dystonia, ECG changes, EPS, SAS, AIMS, tardive dyskinesias, glucose, lipid profile, prolactin, prolactin-related AE, sedation, WAE, weight changes, white blood cells	

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	setting to harm self or others		**GROUP 3** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** 0.5–3 **Daily dose (mg/day), mean±SD (range):** 4±1.2 (0.5–3) **Concurrent treatments:** amantadine(2), benztropine/ trihexyphenidyl (4), citalopram (1), clomipramine (1), gabapentin with lamotrigine (1), lorazepam(2), propranolol (1), sertraline (2), trazadone (1), valproate (3), inpatient or residential treatment (11)		
Singh, 2011 [82] **Country:** Russia, India, Ukraine, United States, Romania **Condition category:** Schizophrenia and related **Funding:** Industry **Risk of bias:** High (subjective), Medium (objective)	**Recruitment dates:** Jul 2007 to Mar 2009 **Study design:** RCT (parallel) **Setting:** Hospitalization permitted for first 3 wks **Diagnostic criteria:** DSM-IV, K-SADS-PL **Inclusion criteria:** (1) 12–17 yr, (2) body weight ≥29 kg, (3) DSM-IV criteria for schizophrenia ≥1 yr before screening and history of at least 1 antipsychotic, (4) PANSS total score 60–120 (acute symptomatic), (5) physically healthy	**Enrolled:** 201 **Analyzed:** 200 **Completed:** 139 **GROUP 1** **N:** 54 **Age, mean±SD (range):** 15.1±1.5 **Males %:** 56 **Caucasian %:** 65 **Treatment naïve (n):** 7 **Inpatients (n):** NR **First episode psychosis (n):** 0 **GROUP 2** **N:** 48 **Age, mean±SD (range):** 15.3±1.6 **Males %:** 65 **Caucasian %:** 71 **Treatment naïve (n):** 4 **Inpatients (n):** NR **First episode psychosis (n):** 0	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** ≤3 wk **Permitted drugs:** propranolol (for akathisia), antiparkinsonians (benzotropine, biperiden), lorazepam (rescue) **Prohibited drugs:** alcohol, antipsychotics, antidepressants, drugs of abuse, lithium, psychostimulants, anticonvulsants, sedatives, cholinesterase inhiitors **GROUP 1** **Drug name:** Paliperidone ER (low) **Dosing variability:** fixed **Target dose (mg/day):** 1.5 (all weights) **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** anti-EPS (2), benzodiazepines (13), propranolol (1)	**Benefits:** CGAS, CGI-S, PANSS, VAS-sleep, response rate, suicide, medication adherence **Harms:** Blood pressure, ECG changes, QTcLD, orthostatic hypotension, NMS, tachycardia, glucose, insulin resistance, prolactin levels, mortality, NMS, serious AEs, seizure, total AE, WAE, weight change, glucose homeostasis, AIMS, SAS	The medium dose paliperidone ER group was statistically superior to the placebo group according to the primary efficacy analysis by weight-based, fixed-dose treatment group. When analyzed by actual dose group, all three doses of paliperidone showed improvement relative to placebo.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	based on medical history, physical examination, ECG, and laboratory test results **Exclusion criteria:** (1) dissociative disorder, BD, MDD, schizoaffective disorder, schizophreniform disorder, ASD, or primary substance induced psychotic disorder (DSM-IV), (2) mild, moderate, or severe MR, (3) pregnant, (4) known or suspected history of seizure disorder, NMS, encephalopathic syndrome, tardive dyskinesia, or insulin dependent diabetes mellitus, (5) presence of any significant or unstable systemic disease, (6) clozapine in 2 months before treatment	**GROUP 3** **N:** 48 **Age, mean±SD (range):** 15.5±1.6 **Males %:** 70 **Caucasian %:** 68 **Treatment naïve (n):** 7 **Inpatients (n):** NR **First episode psychosis (n):** 0 **GROUP 4** **N:** 51 **Age, mean±SD (range):** 15.7±1.4 **Males %:** 55 **Caucasian %:** 69 **Treatment naïve (n):** 3 **Inpatients (n):** NR **First episode psychosis (n):** 0	**GROUP 2** **Drug name:** Paliperidone ER (medium) **Dosing variability:** fixed **Target dose (mg/day):** 3 (<51 kg), 6 (≥51 kg) **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** anti-EPS (7), benzodiazepines (16), propranolol (1) **GROUP 3** **Drug name:** Paliperidone ER (high) **Dosing variability:** fixed **Target dose (mg/day):** 6 (<51 kg), 12 (≥51 kg **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** anti-EPS (14), benzodiazepines (15), propranolol (1) **GROUP 4** **Drug name:** Placebo **Dosing variability:** fixed **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** anti-EPS (0), benzodiazepines (19), propranolol (0)		
Snyder et al., 2002 [83] **Country:** Canada, South Africa, USA	**Recruitment dates:** NR **Study design:** RCT (parallel)	**Enrolled:** 110 **Analyzed:** 110 **Completed:** 85 **GROUP 1** **N:** 53	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** 1 wk **Permitted drugs:** stable doses (≥30 days prior to study) of anticholinergics, antihistamines,	**Benefits:** ABC, BPI, CGI-I, CGI-S, NCBRF, VAS Medication adherence	Risperidone was adequately tolerated and was effective in treating children with subaverage IQs and severe disruptive behaviors.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Condition category: ADHD **Funding:** Foundation **Risk of bias:** High (subjective), High (objective)	**Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV, VABS **Inclusion criteria:** (1) CD, ODD, or DBD-NOS (DSM-IV), (2) parent/ caregiver rating ≥24 on the Conduct Problem subscale of the NCBRF, (3) IQ 36–84 inclusive, (4) VABS score ≤84, (5) healthy on the basis of a pretrial physical examination, medical history, and ECG, (6) consent by parent/ caregiver, (7) 5–12 yr **Exclusion criteria:** (1) PDD, schizophrenia, or other psychotic disorders, (2) head injury as a cause of impaired IQ, (3) seizure condition requiring medication, (4) females who were sexually active without a reliable form of birth control, (5) serious or progressive illness or clinically abnormal laboratory values, (6) history of tardive dyskinesia, NMS, or hypersensitivity to any antipsychotic drug, (7)	**Age, mean±SD (range):** 8.6±0.3 (5–12) **Males %:** 77.4% **Caucasian %:** 78.8% **Diagnostic breakdown (n):** CD (3), CD/ADHD (16), Combined/No ADHD (9), ODD/ DBD (6), ODD/DBD/ADHD (28) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (44) **GROUP 2** **N:** 57 **Age, mean±SD (range):** 8.8±0.3 (5–12) **Males %:** 73.7% **Caucasian %:** 73.7% **Diagnostic breakdown (n):** CD (7), CD/ADHD (15), Combined/No ADHD (17), ODD/ DBD (10), ODD/DBD/ADHD (25) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (40)	chloral hydrate, medication for preexisting medical conditions, melatonin, psychostimulants (comorbid ADHD) **Prohibited drugs:** no other medication permitted **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1±0.1 SE (0.4–3.8) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Harms:** Anorexia, behavioral issues, Bucco-linguo-masticatory score, BMI, ECG changes, EPS, fatigue, parkinsonism, prolactin, prolactin-related AE, pulse, SAE, somnolence, tardive dyskinesia, total AE, WAE, weight change	

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	known presence of HIV, (8) previous treatment with risperidone				
Spencer et al., 1994 [84] **Country:** USA **Condition category:** Schizophrenia and related **Funding:** Industry, Government **Risk of bias:** Medium (subjective), Medium (objective)	**Recruitment dates:** Sep 1989 to May 1991 **Study design:** RCT (crossover) **Setting:** Inpatient **Diagnostic criteria:** DSM-III-TR, DICA-R **Inclusion criteria:** (1) actively psychotic prepubertal patients, (2) 5–11 yr, (3) admitted to the Bellevue Hospital Children's Inpatient Psychiatric Unit, (4) schizophrenia **Exclusion criteria:** (1) intercurrent systemic illness, (2) seizure disorder, (3) MR below borderline, (4) tardive dyskinesia, (5) infantile autism, (6) receipt of psychoactive medication within 4 wk of double-blind treatment	**Enrolled:** 16 **Analyzed:** 16 **Completed:** 16 **GROUP 1** **N:** 16 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 16 (crossover) **Age, mean±SD (range):** NR **Males %:** NR **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** 2 wk **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2 (0.5–3.5) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2.5±0.5 (0.5–3.5) **Concurrent treatments:** NR	**Benefits:** BPRS-C, CGI-I, CGI-S, CPRS **Harms:** Drowsiness, dystonia	Haloperidol improved the target psychotic symptoms in children with schizophrenia.
Stocks et al., 2012 [85] **Country:** USA	**Recruitment dates:** October 2008 – September 2009	**Enrolled:** 78 **Analyzed:** 78 **Completed:** 55 **GROUP 1**	**Treatment duration:** 8-11 wk (2-5 wk titration, 6 wk maintenance) **Run-in phase:** Yes **Run-in phase duration:** 2 wk	**Benefits:** NCBRF-TIQ, CGI-I, CGI-S, SNAP-IV	Molindone showed clinical benefit with an acceptable side-effect profile in this study. Preliminary

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Condition category: ADHD **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Study design:** RCT (parallel) **Setting:** outpatient **Diagnostic criteria:** K-SADS-PL, DSM-IV-TR **Inclusion criteria:** 6-12 yr, ADHD with persistent serious conduct problems (≥27 on DBD, ≥2 on Conduct problem subscale of NCBRF-TIQ for: knowingly destroys property, gets in physical fights, physically attacks people. Weigh ≥ 16kg, IQ ≥ 71, free of antipsychotics for at least 2 weeks pre-baseline, receiving stable dose of an FDA approved psychostimulant for at least 30 days pre-baseline, otherwise in good physical health **Exclusion criteria:** Current or lifetime diagnosis of BP, PTSD, personality disorder, psychotic disorder, currently meeting diagnostic criteria for major depressive disorder,	**N:** 20 **Age, mean±SD (range):** 8.5±1.88 yr **Males %:** 95% **Caucasian %:** 55% **Diagnostic breakdown (n):** ADHD (20) **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** 0 **Comorbidities (n):** Asthma (5), CD (2), Enuresis (4), Insomnia (1), ODD (6), Seasonal allergies (2) **GROUP 2** **N:** 19 **Age, mean±SD (range):** 9.4±1.98 yr **Males %:** 84.2% **Caucasian %:** 57.9% **Diagnostic breakdown (n):** ADHD (19) **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** 0 **Comorbidities (n):** Asthma (3), CD (2), Eczema (3), Enuresis (3), Environmental allergies (1), Insomnia (2), ODD (7), Seasonal allergies (1) **GROUP 3** **N:** 19 **Age, mean±SD (range):** 8.8±2.12 yr	**Permitted drugs:** methylphenidate, amphetamine, benzotropine **Prohibited drugs:** other antipsychotics, antidepressants, hypnotics, anticonvulsants, antihypertensives, antihistamines **GROUP 1** **Drug name:** Molindone hydrochloride **Dosing variability:** Fixed **Target dose (mg/day):** <30 kg: 5 mg/day; ≥ 30 kg: 10 mg/day **Daily dose (mg/day), mean±SD (range):** <30 kg: 5 mg/day; ≥ 30 kg: 10 mg/day **Concurrent treatments:** Stable dose of FDA approved psychostimulant (methylphenidate or amphetamine) **GROUP 2** **Drug name:** Molindone hydrochloride **Dosing variability:** Fixed **Target dose (mg/day):** <30 kg: 10 mg/day; ≥ 30 kg: 20 mg/day **Daily dose (mg/day), mean±SD (range):** <30 kg: 10 mg/day; ≥ 30 kg: 20 mg/day **Concurrent treatments:** Stable dose of FDA approved psychostimulant (methylphenidate or amphetamine) **GROUP 3** **Drug name:** Molindone hydrochloride **Dosing variability:** Fixed	**Harms:** Somnolence, metabolic effects, neuromotor effects, infection, prolactin related events	efficacy results suggest that molindone produces dose-related behavioral improvements over 9-12 weeks.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	OCD, PDD or other AD as primary disorder	**Males %:** 68.4% **Caucasian %:** 42.1% **Diagnostic breakdown (n):** ADHD (19) **Treatment naïve (n):** **Inpatients (n):** **First episode psychosis (n):** 0 **Comorbidities (n):** Asthma (4), CD (3), Eczema (2), Enuresis (2), Environmental allergies (1), ODD (6) **GROUP 4** **N:** 20 **Age, mean±SD (range):** 8.8±2.00 yr **Males %:** 95% **Caucasian %:** 65% **Diagnostic breakdown (n):** ADHD (20) **Treatment naïve (n):** NR **Inpatients (n):** 0 **First episode psychosis (n):** 0 **Comorbidities (n):** Asthma (1), CD (1), Eczema (1), Enuresis (3), Environmental allergies (2), Insomnia (2), ODD (7), Seasonal allergies (2)	**Target dose (mg/day):** <30 kg: 15 mg/day; ≥ 30 kg: 30 mg/day **Daily dose (mg/day), mean±SD (range):** <30 kg: 15 mg/day; ≥ 30 kg: 30 mg/day **Concurrent treatments:** Stable dose of FDA approved psychostimulant (methylphenidate or amphetamine) **GROUP 4** **Drug name:** Molindone hydrochloride **Dosing variability:** Fixed **Target dose (mg/day):** <30 kg: 20 mg/day; ≥ 30 kg: 40 mg/day **Daily dose (mg/day), mean±SD (range):** <30 kg: 20 mg/day; ≥ 30 kg: 40 mg/day **Concurrent treatments:** Stable dose of FDA approved psychostimulant (methylphenidate or amphetamine)		
Swadi et al., 2010 [86] **Country:** New Zealand **Condition category:**	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient	**Enrolled:** 22 **Analyzed:** 22 **Completed:** 22 **GROUP 1** **N:** 11 **Age, mean±SD (range):** NR	**Treatment duration:** 6 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR	**Benefits:** BPRS, PANSS, response (BPRS, CGI-S, HAM-D, PANSS, YMRS) **Harms:** Blood pressure, SAS, BAS, AIMS, glucose, lipid	Risperidone may be more beneficial than quetiapine for adolescent patients with bipolar disorder.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Schizophrenia and related **Funding:** Industry **Risk of bias:** High (subjective), High (objective)	**Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) <19 yr, (2) first obset psychotic disorder or a mood disorder with psychotic features **Exclusion criteria:** (1) alcohol or substance dependence not in full remission, (2) prior treatment with atypical antipsychotic drugs	**Males %:** 54.5 **Caucasian %:** NR **Treatment naïve (n):** 11 **Inpatients (n):** all **First episode psychosis (n):** 11 **Comorbidties**: SUD (0) **GROUP 2** **N:** 11 **Age, mean±SD (range):** NR **Males %:** 63.6 **Caucasian %:** NR **Treatment naïve (n):** 11 **Inpatients (n):** all **First episode psychosis (n):** 11 **Comorbidties**: SUD (0)	**GROUP 1** **Drug name:** Quetiapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 607 (100–800) **Concurrent treatments:** anticholinergics (1), cognitive behavioral therapy, family work, activity-based interventions allowed **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 2.9 (1.5–5) **Concurrent treatments:** anticholinergics (5), cognitive behavioral therapy, family work, activity-based interventions allowed	profile, liver function, prolactin, sedation, weight change	
Tohen et al., 2007 [87] **Country:** Puerto Rico, USA **Condition category:** Bipolar disorder **Funding:** Industry **Risk of bias:** Medium (subjective), Medium (objective)	**Recruitment dates:** Nov 2002 to May 2005 **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV-TR, K-SADS-PL **Inclusion criteria:** (1) 12–17 yr, (2) manic or mixed bipolar episodes (with or without psychotic features), (3) inpatient or outpatient, (4) total score ≥20 on	**Enrolled:** 161 **Analyzed:** 161 **Completed:** 120 **GROUP 1** **N:** 107 **Age, mean±SD (range):** 15.1±1.3 **Males %:** 57 **Caucasian %:** 66.4 **Diagnostic breakdown (n):** mixed (61), psychotic features (22), rapid cycling (25) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (45), DBD (37)	**Treatment duration:** 3 wk **Run-in phase:** Yes **Run-in phase duration:** 2–14 day **Permitted drugs:** anticholinergics (2–6mg/day), benzodiazepines/hypnotics (≤2 mg/day lorazepam equivalents for ≤3 consecutive days), psychostimulants (constant dose ≥30 day prior to randomization and through study) **Prohibited drugs:** anticholinergics **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR	**Benefits:** CDRS, CGI-BP (overall, mania, depression subscales), ADHS IV, OAS, YMRS (total+item analysis), HRQoL(subscales); Olsen 2012, response, suicide **Harms:** Bipolar exacerbation, blood cells, blood pressure, BMI, ECG changes, EPS (AIMS, BAS, SAS), glucose, hepatic enzyme, lipid profile, mortality, prolactin, prolactin-	Olanzapine was more effective in treating adolescents with bipolar mania and placebo; however, it resulted in significantly greater weight gain.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	the Adolescent Structured YMRS **Exclusion criteria:** (1) prior nonreponse to olanzapine, (2) treatment within the previous 30 day with an experimental medication not available for clinical use, (3) suicide risk, (4) clinically significant abnormal laboratory values at baseline, (5) DSM-IV-TR substance dependence (excluding nicotine and caffeine) within the last 30 days, (6) treatment with long-lasting neuroleptic within 14 day prior to randomization	**GROUP 2** **N:** 54 **Age, mean±SD (range):** 15.4±1.2 **Males %:** 44.4 **Caucasian %:** 75.9 **Diagnostic breakdown (n):** mixed (25), psychotic features (7), rapid cycling (5) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** ADHD (13), DBD (12)	**Daily dose (mg/day), mean±SD (range):** 8.9 (2.5–20) **Concurrent treatments:** anticholinergics (4.7%), benzodiazepines (12.1%) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** anticholinergic medication (0), benzodiazepines (7.4%)	related AE, pulse, SAE, weight change	
Tramontina et al., 2009 [88] **Country:** Brazil **Condition category:** Bipolar disorder **Funding:** Industry, Government, Hospital **Risk of bias:** Low (subjective), Low (objective)	**Recruitment dates:** Jan 2005 to Nov 2007 **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV, K-SADS-E **Inclusion criteria:** (1) 8–17 yr, (2) DSM IV bipolar I or II disorder comorbid with ADHD, (3) clear reports of	**Enrolled:** 43 **Analyzed:** 43 **Completed:** 41 **GROUP 1** **N:** 18 **Age, mean±SD (range):** 11.7±2.7 **Males %:** 33 **Caucasian %:** 83 **Treatment naïve (n):** ND **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** ADHD (all), anxiety disorders	**Treatment duration:** 6 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Aripiprazole **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 13.6±5.4 (5–20) **Concurrent treatments:** none **GROUP 2**	**Benefits:** CDRS, CGI-S, CMRS-P, YMRS, medication adherence, response, suicide **Harms:** Akathisia, behavioral issues, dermatologic AE, dyskinesia, EPS, fatigue, seizure, somnolence, weight change	Aripiprazole was effective in decreasing mania symptoms and improving global functioning without resulting in severe advserse events or weight gain.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	ADHD symptom onset preceding any mood symptomology, (4) acutely manic or mixed states (YMRS score ≥20 at baseline visit) **Exclusion criteria:** (1) estimated IQ < 70 (WISC-III), (2) use of any medication 4 wk prior to entering the study, (3) dx of PDD, schizophrenia, or substance abuse or dependence, (4) severe suicide/homicide risk, (5) previous use of aripiprazole, (6) other acute or chronic diseases, (7) pregnancy	(8), DBD (15), psychosis (8), SA (0) **GROUP 2** **N:** 25 **Age, mean±SD (range):** 12.2±2.8 **Males %:** 56 **Caucasian %:** 96 **Treatment naïve (n):** ND **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities:** ADHD (all), anxiety disorders (13), DBD (20), psychosis (8), SA (0)	**Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 15±3.2 (10–20) **Concurrent treatments:** none		
Troost et al., 2005 [89] **Country:** Netherlands **Condition category:** ASD **Funding:** Industry, Foundation **Risk of bias:** Low (subjective), Low (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient and outpatient **Diagnostic criteria:** DSM-IV-TR, ADI-R **Inclusion criteria:** (1) DSM-IV-TR criteria for PDD, (2) demonstrated clinically significant tantrums, aggression, self-injurious behavior,	**Enrolled:** 24 **Analyzed:** 24 **Completed:** NR **GROUP 1** **N:** 12 **Age, mean±SD (range):** 9.4±3.4 **Males %:** 91.6 **Caucasian %:** 100 **Diagnostic breakdown (n):** Asperger's disorder (1), autistic disorder (3), PDD NOS (8) **Treatment naïve (n):** 11 **Inpatients (n):** NR **First episode psychosis (n):** NR	**Treatment duration:** 6 mo **Run-in phase:** Yes **Run-in phase duration:** 1–4 wk **Permitted drugs:** anticonvulsants (stable dose for ≥4 wk and patient seizure-free for ≥6 mo), stimulants (comorbid ADHD) **Prohibited drugs:** psychotropics **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.9±0.7	**Benefits:** ABC (sub scores), CGI, VAB, cognitive (focused and divided attention task), response (relapse) **Harms:** Dyskinesia (SAS, AIMS)	Risperidone was effective in reducing disruptive behavior in about half of children with ASD.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	or a combination of these, (3) 5–17 yr, (4) weight ≥15 kg, (5) mental age ≥18 mo **Exclusion criteria:** (1) children on effective psychotropic drug treatment for disruptive behavior	**Comorbidities:** MR (2) **GROUP 2** **N:** 12 **Age, mean±SD (range):** 8.7±1.2 **Males %:** 91.6 **Caucasian %:** 83 **Diagnostic breakdown (n):** Asperger's disorder (1), autistic disorder (3), PDD NOS (8) **Treatment naïve (n):** all **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** MR (0)	**Concurrent treatments:** stimulants (1), stimulant and anticonvulsant (1) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.7±0.5 **Concurrent treatments:** stimulants (2)		
Van Bellinghen et al., 2001 [90] **Country:** Belgium **Condition category:** Behavioral issues **Funding:** Industry **Risk of bias:** Medium (subjective), Medium (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient **Diagnostic criteria:** clinical assessment and parent interview **Inclusion criteria:** (1) 6–18 yr, (2) IQ 45–85, (3) demonstrating persistent behavioral disturbances **Exclusion criteria:** (1) presence of a clinically relevant non-neurologic disease, (2) abnormal laboratory tests, (3) epileptic	**Enrolled:** 13 **Analyzed:** 13 **Completed:** 13 **GROUP 1** **N:** 6 **Age, mean±SD (range):** NR (6–14) **Males %:** 33.3 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** anxiety (0), depression (0), mania (0), MR (all) **GROUP 2** **N:** 7 **Age, mean±SD (range):** NR (7–14) **Males %:** 42.9 **Caucasian %:** NR	**Treatment duration:** 4 wk **Run-in phase:** No **Run-in phase duration:** NR **Permitted drugs:** antiepileptics **Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 1.2 **Concurrent treatments:** valproate (1) **GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** NR	**Benefits:** ABC, CGI-I, PAC, VAS **Harms:** Parkinsonism, pulse, somnolence, total AE, weight change, EP disorder (ESRS)	Risperidone was well tolerated, and there was no difference between risperidone- and placebo-treated groups with respect to the occurrence of extrapyramidal side effects.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	crisis in the previous 3 mo, (4) participation in a drug trial in the previous 4 wk, (5) remoxipride treatment in the previous 4 wk, (6) oral neuroleptics and other psychotropics in the previous wk, (6) previous treatment with remoxipride combined with abnormal hematologic values, (7) a depot neuroleptic injection within one treatment cycle of the time of selection, (8) female patients of reproductive age if their contraceptive use was considered inadequate, (9) pregnant or lactating	**Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** anxiety (0), depression (0), mania (0), MR (all)			
Van Bruggen et al., 2003 [91] **Country:** Netherlands **Condition category:** Schizophrenia and related **Funding:** Industry, Government	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** Inpatient **Diagnostic criteria:** DSM-IV **Inclusion criteria:** (1) 16–28 yr, (2) first or second psychotic episode according to DSM-IV criteria of schizophrenia,	**Enrolled:** 44 **Analyzed:** 42 **Completed:** NR **GROUP 1** **N:** 18 **Age, mean±SD (range):** 21.0±2.8 **Males %:** 72 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** 16 **GROUP 2** **N:** 26	**Treatment duration:** Olanzapine 9.8 wk, Risperidone 6.7 wk **Run-in phase:** No **Run-in phase duration:** NA **Permitted drugs:** NR **Prohibited drugs:** antipsychotics **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 15.6±4 (5–30) **Concurrent treatments:** anticholinergics (2),	**Benefits:** PANSS, medication adherence, response **Harms:** BAS, SAS, AIMS, akathisia, parkinsonism, prolactin, prolactin-related AE, sedation, seizure, sexual dysfunction, somnolence, tachycardia, tardive dyskinesia, weight change	Symptom response was similar in the olanzapine and risperidone groups.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Risk of bias: High (subjective), High (objective)	schizofreniform or schizoaffective disorder, (3) actively symptomatic at study entry (PANSS score of moderate or higher on items for delusions, conceptual disorganization, or hallucinations) **Exclusion criteria:** (1) epilepsy, (2) toxic psychosis or infectious disorder, (3) a primary dx of substance abuse (drugs or alcohol), (4) MR, (5) pregnant or lactating female patients, (6) concomitant use of other antipsychotic agents, (7) treatment with an injectable depot neuroleptic less than one dosing interval before study entry, (8) narrow-angle glaucoma and known hypersensitivity to olanzapine or risperidone, (9) insufficient knowledge of the Dutch language	**Age, mean±SD (range):** 20.6±3.0 **Males %:** 85 **Caucasian %:** NR **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** 22	antidepressants (0), benzodiazepines (7), mood stabilizers (0) **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 4.4±1.5 (1–8) **Concurrent treatments:** anticholinergics (7), antidepressants (4), benzodiazepines (8), mood stabilizers (0)		
Weisler et al., 2011 [132] **Country:** USA	**Recruitment Dates:** NR **Study design:** Observational (pooled analysis of 2 trials)	**Enrolled:** 35 **Analyzed:** 35 **Completed:** 35 **GROUP 1:** **N:** 16 **Age, mean±SD (range):**	**Treatment duration:** 6 wk **Run-in phase:** No **Run-in phase duration:** NA **Permitted drugs:** Escitalopram, fluoxetine, paroxetine CR, sertraline, venlafaxine XR	**Benefits:** suicide-related events and ideation **Harms:** NR	Adjunctive aripiprazole treatment represents a generally safe and relatively well-tolerated and efficacious treatment

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Condition category: Depression **Funding:** Industry **Newcastle-Ottawa Scale:** 6/8 stars	**Diagnostic criteria:** DSM-IV-TR **Setting:** outpatients **Inclusion criteria:** Outpatients 18-65 yr (only looking at subgroup ≤ 25 yr here), major depressive episode ≥ 8 wk, inadequate response to ≥ 1 historical antidepressant **Exclusion criteria:** Significant risk of committing suicide during course of trial	≤ 25 yr **Males %:** NR **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** 0 **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities (n):** NR **GROUP 2:** **N:** 19 **Age, mean±SD (range):** ≤ 25 yr **Males %:** NR **Caucasian %:** NR **Diagnostic breakdown (n):** NR **Treatment naïve (n):** 0 **Inpatients (n):** 0 **First episode psychosis (n):** NR **Comorbidities (n):** NR	**Prohibited drugs:** NR **GROUP 1** **Drug name:** Aripiprazole **Dosing variability:** Variable **Target dose (mg/day):** 15 mg/day (paroxetine or fluoxetine) or 20 mg/day (all other patients) **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** Escitalopram, fluoxetine, paroxetine CR, sertraline, venlafaxine XR **GROUP 2:** **Drug name:** Placebo **Dosing variability:** Variable **Target dose (mg/day):** NA **Daily dose (mg/day), mean±SD (range):** NA **Concurrent treatments:** Escitalopram, fluoxetine, paroxetine CR, sertraline, venlafaxine XR		option for patients with MDD who had had an inadequate response to standard antidepressant medication.
Wink et al., 2014 [133] **Country:** USA **Condition category:** ASD **Funding:** Industry/ non-industry **Newcastle-Ottawa Scale:** 7/8 stars	**Recruitment dates:** July 2004 to Apr 2012 **Study design:** Retrospective **Setting:** NR **Diagnostic criteria:** DSM-IV-TR **Inclusion criteria:** (1) 2-20 yr,(2) meets DSM-IV-TR criteria for ASD diagnosis, (3)	**Enrolled:** 142 **Analyzed:** 142 **Completed:** NR **GROUP 1** **N:** 72 **Age, mean±SD (range):** 8.41±3.59yr **Males %:** 83.3 **Caucasian %:** 77.8 **Diagnostic breakdown (n):** Autistic disorder (40), PDD-NOS (29), Asperger's disorder (3) **Treatment naïve (n):** NR	**Treatment duration:** Risperidone (2.37±2.55 yr), Aripiprazole (1.47±1.21 yr) **Run–in phase:** NR **Run–in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR	**Benefits:** CGI-I **Harms:** Weight change (BMI, BMI-z)	Our results warrant further investigation using a prospective random assignment study design. Greater control of baseline characteristics, tracking detailed historical and lifestyle factors, use of methodical dosing guidelines, and limiting treatment duration may impact

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	subjects treated at the Christian Sarkine Autism Treatment Center (CSATC) **Exclusion criteria:** (1) Risperidone or aripiprazole use initiated prior to evaluation at CSATC, (2) individual received multiple antipsychotics at any time during treatment, (3) if <2 BMI data points were available	**Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** intellectual disability (34) **GROUP 2** **N:** 70 **Age, mean±SD (range):** 9.74±3.46yr **Males %:** 80 **Caucasian %:** 75.7 **Diagnostic breakdown (n):** Autistic disorder (44), PDD-NOS (19), Asperger's disorder (7) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** intellectual disability (30)	**Daily dose (mg/day), mean±SD (range):** 2.23±1.30 **Concurrent treatments:** SSRI (20), antiepileptic (5), stimulant (15), metformin (4), α 2-agonist (27), other (26) **GROUP 2** **Drug name:** Aripiprazole **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 11.85±7.23 **Concurrent treatments:** SSRI (21), antiepileptic (4), stimulant (10), metformin (2), α 2-agonist (22), benzodiazepine (2), other (24)		the results of such a study.
Wonodi et al., 2007 [134] **Country:** USA **Condition category:** Mixed conditions **Funding:** Non-industry **Newcastle-Ottawa Scale:** 8/8 stars	**Recruitment dates:** NR **Study design:** Retrospective **Setting:** Inpatient/ outpatient **Diagnostic criteria:** NR **Inclusion criteria:** All children (5-18 yr) already receiving or likely to be prescribed antipsychotic	**Enrolled:** 424 **Analyzed:** 198 **Completed:** 198 **GROUP 1** **N:** 118 **Age, mean±SD (range):** 11.9±2.8 yr **Males %:** 77.1 **Caucasian %:** 44.1 **Diagnostic breakdown (n):** Mood disorder NOS (103), ADHD (75) **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR	**Treatment duration:** ≥6mo **Run-in phase:** NR **Run-in phase duration:** NR **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Antipsychotic treatment ≥ 6mo **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** Anti-depressants (88), mood stabilizers (88), psychostimulants (80)	**Benefits:** NR **Harms:** Tardive dyskinesia	Identifying the risk profiles of antipsychotic treatment in children would improve treatment outcomes in this vulnerable clinical population. Side-effect profile of the atypical antipsychotic drugs in children may be much different than in adults, underscoring the importance of risk-benefit discussions with patient families

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	medications at the referring facilities **Exclusion criteria:** NR	**GROUP 2** **N:** 80 **Age, mean±SD (range):** 10.7±3.9 yr **Males %:** 72.5 **Caucasian %:** 28.8 **Diagnostic breakdown (n):** Mood disorder NOS (67), ADHD (48) **Treatment naïve (n):** 80 **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities:** NR	**GROUP 2** **Drug name:** Antipsychotic naïve **Dosing variability:** NR **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** NR **Concurrent treatments:** Anti-depressants (38), mood stabilizers (22), psychostimulants (37)		before treatment initiation, and ongoing monitoring for motor and other (e.g., metabolic) adverse events.
Woods et al., 2003 [92] **Country:** Canada, USA **Condition category:** Schizophrenia and related **Funding:** Industry, Government **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** Jan 1998 to July 2001 **Study design:** RCT (parallel) **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV, COPS, Presence of Psychosis Scale **Inclusion criteria:** (1) help-seeking persons responding to advertisements or refered by clinicians, (2) 12–45 yr, (3) prodromal syndromes criteria using the Structured Interview for Prodromal Syndromes, (4) ability to understand and	**Enrolled:** 60 **Analyzed:** 59 **Completed:** 41 **GROUP 1** **N:** 31 **Age, mean±SD (range):** 18.2±5.5 **Males %:** 67.7 **Caucasian %:** 74.2 **Treatment naïve (n):** 28 **Inpatients (n):** NR **First episode psychosis (n):** all **Comorbidities:** SA (18) **GROUP 2** **N:** 29 **Age, mean±SD (range):** 17.2±4 **Males %:** 62.1 **Caucasian %:** 58.6 **Treatment naïve (n):** 26 **Inpatients (n):** NR **First episode psychosis (n):** all	**Treatment duration:** 1 yr **Run-in phase:** Yes **Run-in phase duration:** 3–14 day **Permitted drugs:** antidepressants, benztropine mesylate or biperiden (≤6 mg/day), chloral hydrate (max 1000 mg/day), diazepam (max 40 mg/day), lorazepam (max 8 mg/day), nizatidine (300–600 mg/day), propranalol hydrochloride **Prohibited drugs:** psychoactive medications **GROUP 1** **Drug name:** Olanzapine **Dosing variability:** variable fixed at 5-15 mg/d **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 8±3.1 (5–15) **Concurrent treatments:** anticholinergics (1), benzodiazepines (7), nizatidine (1)	**Benefits:** SOPS, CGI-S, GAF, PANSS, MARDS, YMRS, cognitive (neurocognitive measures), medication adherence, response/conversion to psychosis **Harms:** Behavioral issues, blood pressure, EPS (AIMS, Barnes, ASA), glucose, fatigue, lipid profile, pulse, somnolence, WAE, weight change	The conversion-to-psychosis rate was not significantly different between treatment groups; however, olanzapine might reduce the conversion rate and delay onset of psychosis. Compared to placebo, olanzapine was efficacious for positive prodromal symptoms but induced weight gain.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	communicate with investigator, (5) informed consent/assent **Exclusion criteria:** (1) past or current DSM-IV psychotic disorder, (2) treatable psychiatric disorder that could account for prodromal symptoms, (3) suicidal or homicidal, (4) prodromal symptoms primarily sequelae of alcohol or drug use, (5) IQ <80, (6) seizure disorder without a clear or resolved etiology, (7) pregant or lactating, (8) took nonprotocol psychotropic medications	**Comorbidities:** SA (9)	**GROUP 2** **Drug name:** Placebo **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 9.3±2.8 (5–15) **Concurrent treatments:** anticholinergics (2), benzodiazepines (2)		
Wudarsky et al., 1999 [135] **Country:** USA **Condition category:** Schizophrenia and related **Funding:** NR **Newcastle-Ottawa Scale:** 7/8 stars	**Recruitment dates:** NR **Study design:** Prospective cohort **Setting:** Outpatient/community **Diagnostic criteria:** DSM-IV, DSM-III-TR, structured interviews **Inclusion criteria:** (1) DSM dx of schizophrenia, (2) resistant to treatment with two different FGAs	**Enrolled:** 47 **Analyzed:** 47 **Completed:** NR **GROUP 1** **N:** 15 **Age, mean±SD (range):** 13.7±1.5 **Males %:** 60 **Caucasian %:** NR **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** 0 **GROUP 2** **N:** 22	**Treatment duration:** 6 wk **Run-in phase:** Yes **Run-in phase duration:** 3 wk **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 15.3±8.2 **Concurrent treatments:** NR **GROUP 2** **Drug name:** Clozapine	**Benefits:** NR **Harms:** Prolactin	Mean prolactin levels were significantly elevated after 6 weeks of treatment with haloperidol, clozapine, and olanzapine in patients with childhood-onset schizophrenia.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	Exclusion criteria: (1) onset of symptoms at ≥13 yr, (2) neurological or medical disease, (3) premorbid IQ <70	**Age, mean±SD (range):** 14.7±2.3 **Males %:** 72.7 **Caucasian %:** NR **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** 0 **GROUP 3** **N:** 10 **Age, mean±SD (range):** 14.2±2.9 **Males %:** 70 **Caucasian %:** NR **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** 0	**Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 325.4±211 **Concurrent treatments:** NR **GROUP 3** **Drug name:** Olanzapine **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 17±3.5 **Concurrent treatments:** NR		
Yen et al., 2004 [93] **Country:** Taiwan **Condition category:** Schizophrenia and related **Funding:** Hospital **Risk of bias:** High (subjective), High (objective)	**Recruitment dates:** NR **Study design:** RCT (parallel) **Setting:** NR **Diagnostic criteria:** DSM-III-TR **Inclusion criteria:** (1) 18–65 yr, (2) total score >60 on PANSS **Exclusion criteria:** (1) psychoses other than schizophrenia, (2) early childhood brain damage, (3) unable to comply with the medication, (4) severe	**Enrolled:** 8 **Analyzed:** 8 **Completed:** 8 **GROUP 1** **N:** 2 (≤24 yr) **Age, mean±SD (range):** 24.0 (24) **Males %:** 0 **Caucasian %:** NR **Treatment naïve (n):** 0 **Inpatients (n):** NR **First episode psychosis (n):** NR **GROUP 2** **N:** 6 (≤24 yr) **Age, mean±SD (range):** 20.7 (20–22) **Males %:** 66.7 **Caucasian %:** NR **Treatment naïve (n):** 0	**Treatment duration:** 2.8 mo **Run-in phase:** Yes **Run-in phase duration:** 1–4 wk **Permitted drugs:** biperiden or trihexylphenidyl; lorazepam, oxazepam or temazepam **Prohibited drugs:** NR **GROUP 1** **Drug name:** Haloperidol **Dosing variability:** variable **Target dose (mg/day):** NR **Daily dose (mg/day), mean±SD (range):** 11.2±6.9 (2–25) **Concurrent treatments:** NR **GROUP 2** **Drug name:** Risperidone **Dosing variability:** variable **Target dose (mg/day):** NR	**Benefits:** PANSS **Harms:** NR	Risperidone was superior to haloperidol in improving negative symptoms and better tolerated during the treatment of schizophrenia.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	illness, (5) pregnant or lactating women	**Inpatients (n):** NR **First episode psychosis (n):** NR	**Daily dose (mg/day), mean±SD (range):** 4.4±2.6 (1–8) **Concurrent treatments:** NR		
Yoo et al., 2013 [95] **Country:** South Korea **Condition category:** Tic disorders **Funding:** Industry **Risk of Bias:** High (subjective), High (objective)	**Recruitment Dates:** August 2008 – April 2010 **Study design:** RCT (parallel) **Diagnostic criteria:** DSM-IV **Setting:** Outpatient clinics **Inclusion criteria:** 6-18 yr, DSM-IV diagnosis of Tourette syndrome or chronic motor or vocal tic disorder. Baseline total tic score ≥22 on YGTSS **Exclusion criteria:** Current mood disorders, schizophrenia and other psychotic disorders, or other psychiatric comorbidity requiring medication during study period, history of psychotropic substance or alcohol use disorders during 3 months pre-screening. IQ ≤ 70, seizure disorders, history of neuroleptic malignant	**Enrolled:** 61 **Analyzed:** 61 **Completed:** 54 **GROUP 1:** **N:** 32 **Age, mean±SD (range):** 11±2.5 yr **Males %:** 93.8% **Caucasian %:** NR **Diagnostic breakdown (n):** Tourette syndrome (32) **Treatment naïve (n):** NR **Inpatients (n):** (0) **First episode psychosis (n):** NR **Comorbidities (n):** ADHD (5), ODD (3), AD (0) **GROUP 2:** **N:** 29 **Age, mean±SD (range):** 10.9±3.0 yr **Males %:** 79.3% **Caucasian %:** NR **Diagnostic breakdown (n):** Tourette syndrome (29) **Treatment naïve (n):** NR **Inpatients (n):** (0) **First episode psychosis (n):** NR **Comorbidities (n):** ADHD (1), ODD (0), AD (1)	**Treatment duration:** 10 wk **Run-in phase:** Yes **Run-in phase duration:** Free of antipsychotic or antiparkinson drugs 1 wk before randomization, free of fluoxetine 4 wk before **Permitted drugs:** Aripiprazole (for group 1) **Prohibited drugs:** All other drugs **GROUP 1** **Drug name:** Aripiprazole **Dosing variability:** Fixed **Target dose (mg/day):** 20 mg/day **Daily dose (mg/day), mean±SD (range):** 11.0±6.1 mg/day **Concurrent treatments:** NR **GROUP 2:** **Drug name:** Placebo **Dosing variability:** Fixed **Target dose (mg/day):** NA **Daily dose (mg/day), mean±SD (range):** NA **Concurrent treatments:** NR	**Benefits:** YGTSS, CGI-TS, response **Harms:** Neuromotor effects, GI disorders, metabolic effects, QT	Aripiprazole is efficacious and tolerated in children and adolescents with Tourette syndrome.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	syndrome, serious brain injury, stroke, or other neurologic disorders. Secondary tic symptoms accompanied by tardive tics, Huntington disease, neuroacanthocytosis, autism. Significant medical problems. History of allergy or hypersensitivity reactions to aripiprazole, nonresponsive to antipsychotic treatment, participating in another clinical study within 1 month before screening, pregnant or lactating, female adolescents who did not consent to contraception during study and up to 8 weeks after. Requiring cognitive behavioral therapy during study period.				
Yoo et al., 2011 [94] **Country:** South Korea **Condition category:** Tic disorders **Funding:** NR	**Recruitment Dates:** August 2005 – March 2007 **Study design:** NRCT (parallel) **Diagnostic criteria:** DSM-IV, Total tic scores ≥22 on Korean version of YGTSS	**Enrolled:** 48 **Analyzed:** 48 **Completed:** 37 **GROUP 1:** **N:** 31 **Age, mean±SD (range):** 11.2±3.5 (6-18) yr **Males %:** 71% **Caucasian %:** NR	**Treatment duration:** 8 wk **Run-in phase:** Yes **Run-in phase duration:** Drug free for 2 wk before study entry **Permitted drugs:** NR **Prohibited drugs:** NR **GROUP 1** **Drug name:** Aripiprazole	**Benefits:** YGTSS, CGI-I, CGI-S **Harms:** ESRS, AE checklist	Aripiprazole may be effective and tolerable in the treatment of children and adolescents with tic disorders. Additional controlled studies are needed to determine efficacy and tolerability of aripiprazole in

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Risk of Bias: High (subjective), High (objective)	**Setting:** outpatient **Inclusion criteria:** Tic disorders, drug free ≥ 2 weeks before study entry, no significant medical problems **Exclusion criteria:** Current mood disorders, psychotic symptoms, AD (OCD allowed), IQ ≤ 70, previous or current seizure episodes, EEG abnormalities, previously used aripiprazole	**Diagnostic breakdown (n):** Tourette syndrome (19), Chronic motor and vocal tic disorder (7), Transient tic disorder (5) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** ADHD (9), ODD (2), OCD (3) **GROUP 2:** **N:** 17 **Age, mean±SD (range):** 8.6±2.9 (6-16) yr **Males %:** 64.7% **Caucasian %:** NR **Diagnostic breakdown (n):** Tourette syndrome (7), Chronic motor and vocal tic disorder (4), Transient tic disorder (6) **Treatment naïve (n):** NR **Inpatients (n):** NR **First episode psychosis (n):** NR **Comorbidities (n):** ADHD (6)	**Dosing variability:** Variable **Target dose (mg/day):** 20 mg/day **Daily dose (mg/day), mean±SD (range):** 10.6±5.2 (2.5-20) mg/day **Concurrent treatments:** NR **GROUP 2:** **Drug name:** Haloperidol **Dosing variability:** Variable **Target dose (mg/day):** 4.5 mg/day **Daily dose (mg/day), mean±SD (range):** 1.9±1.1 (0.75-4.5) mg/day **Concurrent treatments:** NR		patients with tic disorders.

ABC = Aberrant Behavior Checklist; ABC-C = Aberrant Behavior Checklist-Community; ADI-R = Autism Diagnostic Interview-Revised; ADOS = Autism Diagnostic Observation Schedule; AE = Adverse Event; ASD = autism spectrum disorder; β-HCG = beta human chorionic gonadotropin; BMI = body mass index; BPRS = Brief Psychiatric Rating Scale; BPRS-A = Brief Psychiatric Rating Scale-Anchored; C-DISC 4 = Computerized Diagnostic Interview Schedule for Children, version four; CARS = Childhood Autism Rating Scale; CAS-P = Children's Aggression Scale-Parent; CAS-T = Children's Aggression Scale-Teacher; CBCL = Child Behavior Checklist; CD = conduct disorder; CDRS-R = Children's Depression Rating Scale, Revised; CGI-C = Clinical Global Impression-Change; CGI-I = Clinical Global Impressions-Improvement; CGI-S = Clinical Global Impressions-Severity; CNS = central nervous system; COPS = Criteria of Prodromal Syndromes; CPRS = Children's Psychiatric Rating Scale; day = day(s); CPT = Continuous performance task ; DBD = disruptive behavior disorder; DICA-R = Diagnostic Interview for Children and Adolescents-Revised; DSM = Diagnostic and Statistical Manual of Mental Disorders; ECG = electrocardiogram; FGA = first-generation antipsychotics; GAD = generalized anxiety disorder; HALFS = Health And Life Functioning Scale ; HIV = human immunodeficiency virus; hr = hour(s); IED = intermittent explosive disorder; IM = intramuscular; IQ = intelligence quotient; KID-SCID = childhood disorders form of the Structured Clinical Interview for DSM-IV Disorders; K-SADS = Kiddie-Schedule for Affective Disorders and Schizophrenia; K-SADS-E = Kiddie-Schedule for Affective Disorders and Schizophrenia (Epidemiological Version); K-SADS-P = Kiddie-Schedule for Affective Disorders and Schizophrenia (Present Episode Version); K-SADS-PL = Kiddie-Schedule for Affective Disorders and Schizophrenia (Present and

Lifetime Version); KQ = key question; LT = long term; MAO-I = monoamine oxidase inhibitor; MDD = major depressive disorder; mo = month(s); MVLT = Modified Version of the California Verbal Learning Test; N = number; NCBRF = Nisonger Child Behavior Rating Form; NMS = neuroleptic malignant syndrome; NOS = not otherwise specified; NR = not reported; NRCT = non-randomized controlled trial; NSAID = non-steroidal anti-inflammatory drug; OAS = Overt Aggression Scale; ODD = oppositional defiant disorder; P-LES-Q = Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire; PANSS = Positive and Negative Syndrome Scale; PDD = pervasive developmental disorder; PTSD = post-traumatic stress disorder; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; RCT = randomized controlled trial; SA = substance abuse; SCID-I/P = Clinical Interview for DSM-IV-TR Axis I Disorders-Patient Edition; SGA = second-generation antipsychotic; SSRI = selective serotonin reuptake inhibitor; ST = short term; TBI = traumatic brain injury; TSGS = Tourette Syndrome Global Scale; TSSS = Tourette Symptom Severity Scale; VABS = Vineland Adaptive Behavior Scale; WASH-U-KSADS = Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia; WISC = Wechsler Intelligence Scale for Children; YBOCS = Yale-Brown Obsessive Compulsive Scale; YGTSS = Yale Global Tic Severity Scale; YMRS = Young Mania Rating Scale; yr = year(s)

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Appendix E. Associated Publications

Main Publication	Associated Publications
Aman MG, Marks RE, Turbott SH, et al. Clinical effects of methylphenidate and thioridazine in intellectually subaverage children. Journal of the American Academy of Child & Adolescent Psychiatry. 1991 Mar;30(2):246-56. PMID: 2016229.	Aman MG, Marks RE, Turbott SH et al. Methylphenidate and thioridazine in the treatment of intellectually subaverage children: effects on cognitive-motor performance. Journal of the American Academy of Child & Adolescent Psychiatry, 1991;30(5), 816-824.
Aman MG, De Smedt G, Derivan, A, et al. Double-blind, placebo-controlled study of risperidone for the treatment of disruptive behaviors in children with subaverage intelligence. Am J Psychiatry 2002;159(8):1337-46.	Aman M, Findling A, Derivan U. Risperidone versus placebo for severe conduct disorder in children with mental retardation. Int J Neuropsychopharmacol 2000:S144.
	Aman MG, Findling RL, Derivan AT, et al. Effects of risperidone on the behavior of children with subaverage IQ's and conduct disorder or oppositional defiant disorder. Annual Meeting of the American Psychiatric Association; 2001.
	Aman MG, Findling RL. Effects of risperidone on the behavior of children with subaverage IQ's and conduct disorder or oppositional defiant disorder. 155th Annual Meeting of the American Psychiatric Association; 2002.
	Biederman J, Mick E, Faraone SV, et al. Risperidone for the treatment of affective symptoms in children with disruptive behavior disorder: a post hoc analysis of data from a 6-week, multicenter, randomized, double-blind, parallel-arm study. Clin Ther 2006;28(5):794-800.
	Findling RL, Aman MG, Eerdekens M, et al. Long-term, open-label study of risperidone in children with severe disruptive behaviors and below-average IQ. Am J Psychiatry 2004;161(4):677-84.
	Turgay A. Risperidone in children with disruptive behavior disorder and ADHD. 154th Annual Meeting of the American Psychiatric Association; 2001.
Aman MG, Bukstein OG, Gadow KD, et al. What does risperidone add to parent training and stimulant for severe aggression in child attention-deficit/hyperactivity disorder? Journal of the American Academy of Child & Adolescent Psychiatry. 2014 Jan;53(1):47-60.e1. PMID: 24342385.	Arnold LE, Gadow KD, Farmer CA, et al. Comorbid anxiety and social avoidance in treatment of severe childhood aggression: response to adding risperidone to stimulant and parent training; mediation of disruptive symptom response. Journal of Child & Adolescent Psychopharmacology, 2015;25(3), 203-212.
	Gadow KD, Arnold, LE, Molina, BS, et al. Risperidone added to parent training and stimulant medication: effects on attention-deficit/hyperactivity disorder, oppositional defiant disorder, conduct disorder, and peer aggression. Journal of the American Academy of Child & Adolescent Psychiatry. 2014;53(9), 948-959.e941.
Arango C, Robles O, Parellada M, et al. Olanzapine compared to quetiapine in adolescents with a first psychotic episode. Eur Child Adolesc Psychiatry 2009;18(7):418-28.	Robles O, Zabala A, Bombin I, et al. Cognitive Efficacy of Quetiapine and Olanzapine in Early-Onset First-Episode Psychosis. Schizophr Bull 2009:1-11.
Arango C, Giraldez M, Merchan-Naranjo J, et al. Second-generation antipsychotic use in children and adolescents: A six-month prospective cohort study in drug-naive patients. Journal of the American Academy of Child & Adolescent Psychiatry. 2014 Nov;53(11):1179-90,90.e1-4. PMID: 25440308.	Merchan-Naranjo J, Tapia C, Bailon C, et al. Secondary effects of antipsychotic treatment in naive or quasi-naive children and adolescents: design of a follow-up protocol and baseline results. Revista de Psiquiatria y Salud Mental. 2012;5(4), 217-228.
	Garcia-Amador, M, Merchn-Naranjo, J, Tapia, C, et al. Neurological Adverse Effects of Antipsychotics in Children and Adolescents. Jounral of Clinical Psychopharmacology. 2015:35(6), 686-693.

Main Publication	Associated Publications
Buitelaar JK, van der Gaag RJ, Cohen-Kettenis P, et al. A randomized controlled trial of risperidone in the treatment of aggression in hospitalized adolescents with subaverage cognitive abilities. J Clin Psychiatry 2001;62(4):239-48.	Buitelaar JK, van der Gaag RJ, Melman CT. Risperidone in the treatment of aggressive behaviour disorders in adolescents with mild mental retardation: a prospective, randomised, double-blind, placebo-controlled trial. Paris: 11th European College of Neuropsychopharmacology Congress; 1998.
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Correll CU, Manu P, Olshanskiy V, et al. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. JAMA - Journal of the American Medical Association302(16)()(pp 1765-1773), 2009Date of Publication: 2009. 2009(16):1765-73.	Carbon M, Kapoor S, Sheridan E, et al. Neuromotor Adverse Effects in 342 Youth During 12 Weeks of Naturalistic Treatment With 5 Second-Generation Antipsychotics. Journal of the American Academy of Child & Adolescent Psychiatry. 2015; 54(9), 718-727.e713.
	Penzner JB, Dudas M, Saito E, et al.Lack of effect of stimulant combination with second-generation antipsychotics on weight gain, metabolic changes, prolactin levels, and sedation in youth with clinically relevant aggression or oppositionality. Journal of Child & Adolescent Psychopharmacology. 2009; 19(5), 563-573.
Findling RL, McNamara NK, Branicky LA, et al. A double-blind pilot study of risperidone in the treatment of conduct disorder. J Am Acad Child Adolesc Psychiatry 2000;39(4):509-16.	Findling RL, McNamara NK, Branicky LA. Conduct disorder in children treated with risperidone. 37th Annual Meeting of the American College of Neuropsychopharmacology; 1998 Dec 14-18; Las Croabas; 1998.
	Findling RL, Branicky LA, Branicky LA, et al. Conduct disorder in children treated with risperidone. 152nd Annual Meeting of the American Psychiatric Association; 1999.
	Findling RL, McNamara NK, Branicky LA, et al. Risperidone in children with conduct disorder conference abstract. Schizophrenia Research. Abstracts of The VIIth International Congress on Schizophrenia Research; Santa Fe, NM; 1999:17-21.
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Findling RL, Robb A, Nyilas M, et al. A multiple-center, randomized, double-blind, placebo-controlled study of oral aripiprazole for treatment of adolescents with schizophrenia. Am J Psychiatry 2008;165(11):1432-41.	Loze JY, Mathew SJ, McQuade RD, et al. Somnolence and sedation in adolescents with schizophrenia treated with aripiprazole (acute and long term follow-up). European Neuropsychopharmacology. 2009;S690-s691.
	Robb AS, Carson WH, Nyilas M, et al. Changes in positive and negative syndrome scale-derived hostility factor in adolescents with schizophrenia treated with aripiprazole: post hoc analysis of randomized clinical trial data. J Child Adolesc Psychopharmacol 2010;20(1):33-8.
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Findling RL, Nyilas M, Forbes RA, et al. Acute treatment of pediatric bipolar i disorder, manic or mixed episode, with aripiprazole: A randomized, double-blind, placebo-controlled study. Journal of Clinical Psychiatry. 2009;70(10):1441-51.	Findling RL, Youngstrom EA, Zhao J, et al. Respondent and item level patterns of response of aripiprazole in the acute treatment of pediatric bipolar I disorder. Journal of Affective Disorders. 2012;143(1-3), 231-235.
	Findling RL, Correll CU, Nyilas M, et al. Aripiprazole for the treatment of pediatric bipolar I disorder: a 30-week, randomized, placebo-controlled study. Bipolar Disorders. 2013 15(2), 138-149.

Main Publication	Associated Publications
	Mankoski R, Zhao J, Carson WH, et al. Young mania rating scale line item analysis in pediatric subjects with bipolar I disorder treated with aripiprazole in a short-term, double-blind, randomized study. Journal of Child & Adolescent Psychopharmacology. 2011;21(4), 359-364.
	Youngstrom E, Zhao J, Mankoski R, et al. Clinical significance of treatment effects with aripiprazole versus placebo in a study of manic or mixed episodes associated with pediatric bipolar I disorder. Journal of Child & Adolescent Psychopharmacology. 2013; 23(2), 72-79.
Fleischhaker C, Heiser P, Hennighausen K, et al. Clinical drug monitoring in child and adolescent psychiatry: side effects of atypical neuroleptics. J Child Adolesc Psychopharmacol 2006;16(3):308-16.	Fleischhaker C, Heiser P, Hennighausen K, et al. Weight gain associated with clozapine, olanzapine and risperidone in children and adolescents. J Neural Transm 2007;114(2):273-80.
	Fleischhaker C, Heiser P, Hennighausen K, et al. Weight gain in children and adolescents during 45 weeks treatment with clozapine, olanzapine and risperidone. J Neural Transm 2008;115(11):1599-608.
Haas M, Delbello MP, Pandina G, et al. Risperidone for the treatment of acute mania in children and adolescents with bipolar disorder: a randomized, double-blind, placebo-controlled study. Bipolar Disord 2009;11(7):687–700.	Delbello M. Research on the effectiveness of risperidone in bipolar disorder in adolescents and children (REACH): a double-blind, randomized, placebo-controlled study of the efficacy and safety of risperidone for the treatment of acute mania in bipolar I disorder. Johnson & Johnson Pharmaceutical Research; 2010.
Hellings JA, Zarcone JR, Reese RM, et al. A crossover study of risperidone in children, adolescents and adults with mental retardation. J Autism Dev Disord 2006;36(3):401–11.	Hellings JA, Zarcone JR, Crandall K, et al. Weight gain in a controlled study of risperidone in children, adolescents and adults with mental retardation and autism J Child Adolesc Psychopharmacol 2001;11(3):229–38.
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	Jerrell JM. Adverse events associated with psychotropic treatment in African American children and adolescents. Journal of the National Medical Association. 2010;102(5), 375-383.
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Kumra S, Kranzler H, Gerbino-Rosen G, et al. Clozapine and "high-dose" olanzapine in refractory early-onset schizophrenia: a 12-week randomized and double-blind comparison. Biol Psychiatry 2008;63(5):524–9.	Kumra S, Kranzler H, Gerbino-Rosen G, et al. Clozapine versus "high-dose" olanzapine in refractory early-onset schizophrenia: an open-label extension study. J Child Adolesc Psychopharmacol 2008;18(4):307–16.
Marcus RN, Owen R, Kamen L, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. J Am	Robb AS, Andersson C, Bellocchio EE, et al. Safety and tolerability of aripiprazole in the treatment of irritability associated with autistic disorder in pediatric subjects (6-17 years old):results from a pooled analysis of 2 studies. The Primary Care Companion to CNS Disorders. 2011; 13(1).

Main Publication	Associated Publications
Acad Child Adolesc Psychiatry 2009;48(11):1110–9.	Varni JW, Handen BL, Corey-Lisle PK, et al. Effect of aripiprazole 2 to 15 mg/d on health-related quality of life in the treatment of irritability associated with autistic disorder in children: a post hoc analysis of two controlled trials. Clinical Therapeutics. 2012; 34(4), 980-992.
McCracken JT, McGough J, Shah B, et al. Risperidone in children with autism and serious behavioral problems. N Engl J Med 2002;347(5):314–21.	Aman MG, Arnold LE, McDougle CJ, et al. Acute and long-term safety and tolerability of risperidone in children with autism. J Child Adolesc Psychopharmacol 2005;15(6):869–84.
	Aman MG, Hollway JA, McDougle CJ, et al. Cognitive effects of risperidone in children with autism and irritable behavior. J Child Adolesc Psychopharmacol 2008;18(3):227–36.
	Anderson GM, Scahill L, McCracken JT, et al. Effects of short- and long-term risperidone treatment on prolactin levels in children with autism. Biol Psychiatry 2007;61(4):545–50.
	Arnold LE, Vitiello B, McDougle C, et al. Parent-defined target symptoms respond to risperidone in RUPP autism study: customer approach to clinical trials. J Am Acad Child Adolesc Psychiatry 2003;42(12):1443–50.
	Arnold LE, Farmer C, Kraemer HC, et al. Moderators, mediators, and other predictors of risperidone response in children with autistic disorder and irritability. Journal of Child & Adolescent Psychopharmacology. 2010; 20(2), 83-93.
	Lindsay RL, Eugene AL, Aman MG, et al. Dietary status and impact of risperidone on nutritional balance in children with autism: a pilot study. J Intellect Dev Disabil 2006;31(4):204–9.
	Martin A, Scahill L, Anderson GM, et al. Weight and leptin changes among risperidone-treated youths with autism: 6-month prospective data. Am J Psychiatry 2004;161(6):1125–7.
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	Scahill L, McCracken J, McDougle CJ, et al. Methodological issues in designing a multisite trial of risperidone in children and adolescents with autism. J Child Adolesc Psychopharmacol 2001;11(4):377–88.
Mcgorry PD, Nelson B, Phillips LJ, et al. Randomized controlled trial of interventions for young people at ultra-high risk of psychosis: Twelve-month outcome. Journal of Clinical Psychiatry. 2013 Apr;74(4):349-56. PMID: 23218022.	Phillips LJ, Nelson B, Yuen HP, et al. Randomized controlled trial of interventions for young people at ultra-high risk of psychosis: study design and baseline characteristics. Australian & New Zealand Journal of Psychiatry. 2009; 43(9), 818-829.
	Yung AR, Phillips LJ, Nelson B, et al. Randomized controlled trial of interventions for young people at ultra high risk for psychosis: 6-month analysis. Journal of Clinical Psychiatry. 2011; 72(4), 430-440.
Miral S, Gencer O, Inal-Emiroglu FN, et al. Risperidone versus haloperidol in children and adolescents with AD : a randomized, controlled, double-blind trial. Eur Child Adolesc Psychiatry 2008;17(1):1–8.	Gencer O, Inal-Emiroglu FN, Miral S, et al. Comparison of long-term efficacy and safety of risperidone and haloperidol in children and adolescents with autistic disorder. An open label maintenance study. Eur Child Adolesc Psychiatry 2008;17(4):217–25.
Owen R, Sikich L, Marcus RN, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. Pediatrics. 2009;124(6):1533-40. PMID: 19948625.	Robb AS, Andersson C, Bellocchio EE, et al. Safety and tolerability of aripiprazole in the treatment of irritability associated with autistic disorder in pediatric subjects (6-17 years old):results from a pooled analysis of 2 studies. The Primary Care Companion to CNS Disorders. 2011; 13(1).
	Varni JW, Handen BL, Corey-Lisle PK, et al. Effect of aripiprazole 2 to 15 mg/d on health-related quality of life in the treatment of irritability associated with autistic disorder in children: a post hoc analysis of two controlled trials. Clinical Therapeutics. 2012; 34(4), 980-992.

Main Publication	Associated Publications
Ratzoni G, Gothelf D, Brand-Gothelf A, et al. Weight gain associated with olanzapine and risperidone in adolescent patients: a comparative prospective study. Journal of the J Am Acad Child Adolesc Psychiatry 2002;41(3):337–43.	Gothelf D, Apter A, Reidman J, et al. Olanzapine, risperidone and haloperidol in the treatment of adolescent patients with schizophrenia. J Neural Transm 2003;110(5):545–60.
Research Units on Pediatric Psychopharmacology Autism Network. Risperidone treatment of autistic disorder: longer-term benefits and blinded discontinuation after 6 months. Am J Psychiatry 2005;162(7):1361–9.	Aman MG, Arnold LE, McDougle CJ, et al. Acute and long-term safety and tolerability of risperidone in children with autism. J Child Adolesc Psychopharmacol 2005;15(6):869–84.
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Main Publication	Associated Publications
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Appendix G. Analytical Models and Code, and Additional Results for Key Question 2 From Network Meta-Analysis and for General Adverse Effects

1. **Mathematical models and WinBUGS code for (i) pairwise meta-analyses, (ii) meta-regressions, and (iii) network meta-analyses**
2. **Figures of star plots and inconsistency factor plotting for network meta-analyses**
3. **Tables with findings for all pairwise comparisons from network meta-analyses**
4. **Findings tables for general adverse effects**

1. Mathematical models and WinBUGS code for (i) pairwise meta-analyses, (ii) meta-regressions, and (iii) network meta-analyses

(i) Pairwise Meta-analysis Model and Code

All pairwise meta-analyses were conducted using a Bayesian random effects model. The following model was used:

$$Y_i \sim N(\delta_i, V_i) \quad i = 1, \ldots, Nstud$$

$$\delta_i \sim N(d, \tau^2)$$

$$d \sim N(0, 10000)$$

$$\tau \sim Uniform(0, m)$$

Where Y_i is the observed effect in study in i with variance V_i, δ_i is the true (unknown) study specific effect, and Nstud is the number of studies in the meta-analysis. The δ_i's are allowed to be different from each other and are assumed to come from a normal distribution with mean d and variance τ^2. The d parameter is the main parameter of interest that is estimated from the model with 95% credible interval, while τ^2 is the between study variance nuisance parameter. The d parameter is given a non-informative prior distribution with mean 0 and variance of 10000, while the between study standard deviation (the square root of the variance) was given a uniform prior with 0 as the lower bound and varying upper bounds (here classified as *m*) that varied depending on the units of the analysis.

For continuous analyses, δ_i represents the mean difference as the parameter of interest. For dichotomous analyses, it represents the log of the risk ratio. In the former case the variance estimates were either computed, imputed, or taken directly from the individual studies. For the latter case the variance of the log risk ratio estimates was computed as $V = 1/a + 1/c - 1/n_1 - 1/n_2$ where a and c are the number of events and n_1 and n_2 are the total sample sizes respectively in the two groups. In dichotomous outcomes, studies with 0 events in both groups (i.e. a = c = 0) were excluded from the analysis. For studies with 0 events in exactly 1 arm, we added 0.5 to a and c, while adding 1 to n_1 and n_2 in order to be able to compute a risk ratio.

Code

```
model
{
  for (i in 1:21)
     {
       V[i] <- sd[i]*sd[i]
       P[i] <- 1/V[i]
              u[i] ~ dnorm(delta[i], P[i])
              delta[i] ~ dnorm(d, prec)
            }
            d ~ dnorm(0, 1.0E-5)
            rr <- exp(d)


            tau~dunif(0,2)
```

```
        tau.sq<-tau*tau
        prec<-1/(tau.sq)
}
```

Data

u[]	sd[]
-1.02914783	0.754132191
-1.174119841	0.800623643
-1.037987667	1.620563325
-0.076961041	0.858939915
1.594092343	0.731173426
0.395514777	0.455271048
-0.826678573	0.826459748
1.309135281	1.472655401
1.704748092	1.037402144
0.415317405	1.141851348
-0.721318058	0.978539566
2.301259712	1.429374769
1.193922468	1.573454027
-0.622051259	0.649521535
2.315007613	1.470780216
-0.43936666	0.273272415
0.95403106	0.756218287
1.55283205	1.052105011
0.70345655	0.627665478
0.830348302	1.590886564
1.861851846	1.457376123

END

Initial Values

```
list(d=0, delta=c(0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0 ), tau=1)
```

(ii) Meta-regression Model and Code

The Bayesian random effects meta-regressions analysis done in this review used the same model as listed above in the pairwise analysis, with the exception that a covariate term was added:

$$Y_i \sim N(\delta_i + \beta x_i, V_i) \quad i = 1, \ldots, Nstud$$

Where β is the regression coefficient and x_i is the value of the covariate of the ith study. The β parameter is of primary interest in this analysis and is given a non-informative uniform prior:

$$\beta \sim N(0,10000)$$

With this exception all other parametrizations are identical to those stated in the pairwise analysis.

Code:

```
model
{
  for (i in 1:22)
    {
      V[i] <- sd[i]*sd[i]
      P[i] <- 1/V[i]
              mu[i] <- delta[i]+beta*(cv[i]-mean(cv[]))
              u[i] ~ dnorm(mu[i], P[i])
              delta[i] ~ dnorm(d, prec)
```

```
        }
        d ~ dnorm(0, 1.0E-5)
        rr <- exp(d)
        beta ~ dnorm(0,1.0E-5)


        tau~dunif(0,2)
        tau.sq<-tau*tau
        prec<-1/(tau.sq)
}
```

Data

u[]	sd[]	cv[]
0.070617567	0.787114445	0
-1.02914783	0.754132191	82
-1.174119841	0.800623643	79
-1.037987667	1.620563325	76.5
1.542799048	0.732970776	43
0.395514777	0.455271048	26
1.309135281	1.472655401	34
1.704748092	1.037402144	32
-0.721318058	0.978539566	24
2.301259712	1.429374769	10
1.193922468	1.573454027	15.8
-0.117783036	1.97026507	72
1.18302963	1.061397515	79.8
1.742969305	1.538349069	100
-1.609437912	1.508310313	0
-0.622051259	0.649521535	68
2.315007613	1.470780216	91
1.861851846	1.457376123	64.5
0.733152515	0.678221198	95
1.994700313	1.479221159	77.5
-0.43936666	0.273272415	0
1.55283205	1.052105011	100

END

Initial Values

list(d=0, delta=c(0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0), tau=1,beta=0)

(iii) Network Meta-analysis Model and Code

The network meta-analyses were conducted using a Bayesian random effects model. The following model was used:

$$\delta_{(j,b,k)} \sim N(d_{(b,k)}, \sigma^2) \sim N(d_{(P,k)} - d_{(P,b)}); \quad j=1,..,Nstud; \quad b,k=1,\ldots,Ntreat \quad b<k$$

$$d_{(P,k)} \sim N(0,10000); k=2,\ldots,Ntreat$$

$$\sigma \sim Unif(0,m)$$

In this model δ_(j,b,k) represents the study level differences between treatments b and k. Similar to the pairwise model, these are allowed to differ by study. Since this is a consistency model, all treatments are compared to the reference standard (placebo—coded P), so the actual quantity being estimated is the equivalent parameter of "difference between treatment k and placebo minus difference between treatment b and placebo" (d_(P,k)-d_(P,b)) . This parametrization helps facilitate the running of the model in WinBUGS. Each difference between a treatment intervention and the placebo is given a prior distribution with mean 0 and variance 10000. The between study variance is represented is represented here by σ^2 and similar to the pairwise analysis, it was given a uniform distribution with a varying upper bound depending upon the unit being measured.

Model convergence was verified using autocorrelation, paying particular attention to prior distributions on between study variance parameters. Goodness of fit was evaluated by monitoring deviance parameters in each analysis.

Code:

```
#Random effects model for multi-arm trials (any number of arms)
model{
for(i in 1:NS){
      w[i,1] <-0
            delta[i,1]<-0
            mu[i] ~ dnorm(0,.0001)                                  # vague priors for trial baselines
            for (k in 1:na[i])  {
                pr[i,k]<-1/(o[i,k]*o[i,k])
                    u[i,k]~dnorm(mean[i,t[i,k]],pr[i,k])          # normal likelihood
                    mean[i,t[i,k]]<-mu[i] + delta[i,k] }          # model
                     for (k in 2:na[i]) {
          delta[i,k] ~ dnorm(md[i,k],taud[i,k])          # trial-specific mean distributions
          md[i,k] <-  d[t[i,k]] - d[t[i,1]]  + sw[i,k]          # mean of distributions
           taud[i,k] <- tau *2*(k-1)/k                          #precision of distributions
           w[i,k] <- (delta[i,k]  - d[t[i,k]] + d[t[i,1]])      #adjustment, multi-arm RCTs
           sw[i,k] <-sum(w[i,1:k-1])/(k-1) }            # cumulative adjustment for multi-arm trials
 }

d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) }                 #  vague priors for basic parameters

sd~dunif(0,10)                                  #  vague prior for random effects standard
deviation
tau<-1/pow(sd,2)

# ranking
for (k in 1:NT) { rk[k]<-rank(d[],k)
                  worst[k]<-equals(rk[k],NT)}

# pairwise values
for (c in 1:(NT-1))
      {  for (k in (c+1):NT)
          {  diff[c,k] <- d[k] - d[c]               # Use this for differences
                                                        log(rr[c,k]) <- diff[c,k]          # Use this for risk ratios
                      }
       }
}
```

NT=no. treatments, NS=no. studies;
NB : set up M vectors each r[,]. n[,] and t[,], where M is the Maximum number of treatments
per trial in the dataset. In this dataset M is 3.

list(NT=15,NS=71)

u[,1]	o[,1]	u[,2]	o[,2]	u[,3]	o[,3]	u[,4]	o[,4]	t[,1]	t[,2]	t[,3]	t[,4]	na[]
0.6	0.391964748		2.2	0.406051781		NA	NA	NA	NA	1	2	NA
	NA	2										
0.3	0.294058818		1.4	0.163484778		NA	NA	NA	NA	1	2	NA
	NA	2										
0.8	0.295739154		2	0.308066862		NA	NA	NA	NA	1	2	NA
	NA	2										
0.72	0.52	1.2	0.612825877		NA	NA	NA	NA	1	2	NA	NA
2												
-0.8	0.262639662		0.2	0.185714286		NA	NA	NA	NA	1	2	NA
	NA	2										
0.2	0.315682075		1.6	0.353553391		NA	NA	NA	NA	1	2	NA
	NA	2										
0.68	0.304105245		3.4	0.889981273		NA	NA	NA	NA	1	3	NA
	NA	2										
0.3	0.227258215		3.66	0.210748555		NA	NA	NA	NA	1	3	NA
	NA	2										
0.1	0.480196038		4.3	0.38890873		NA	NA	NA	NA	1	3	NA
	NA	2										
0	0.235247054		0.9	0.163027152		NA	NA	NA	NA	1	4	NA
	NA	2										
1.1	1.116284014		2.3	1.176666667		NA	NA	NA	NA	1	5	NA
	NA	2										
2.5	0.542217668		4.2	0.826236447		NA	NA	NA	NA	1	5	NA
	NA	2										
0.9	0.154919334		2.3	0.145521375		NA	NA	NA	NA	1	5	NA
	NA	2										
0.6	0.239	1.3	0.223110423		NA	NA	NA	NA	1	5	NA	NA
2												
0.4	0.181303919		1.7	0.155480202		NA	NA	NA	NA	1	5	NA
	NA	2										
-0.4	0.242487113		2	0.263931552		NA	NA	NA	NA	1	5	NA
	NA	2										
0.9	0.188982237		2.2	0.24271195		NA	NA	NA	NA	1	6	NA
	NA	2										
-1.2	1.312035065		1.8	1.633360908		NA	NA	NA	NA	1	6	NA
	NA	2										
-0.6	3.301852918		0.9	2.728846047		NA	NA	NA	NA	1	6	NA
	NA	2										
0.74	0.284604989		4.2	0.221359436		NA	NA	NA	NA	1	6	NA
	NA	2										
0.2	0.421996009		2.2	0.437630757		NA	NA	NA	NA	1	6	NA
	NA	2										
0.7	0.201146713		2.4	0.371782975		NA	NA	NA	NA	1	6	NA
	NA	2										
0.8	0.305085108		2.7	0.414285714		NA	NA	NA	NA	1	6	NA
	NA	2										
1	0.259554274		2.7	0.316227766		NA	NA	NA	NA	1	6	NA
	NA	2										
0.7	0.249482222		1.63	0.184136651		NA	NA	NA	NA	1	6	NA
	NA	2										
0.1	1.700840129		1.8	1.24922198		NA	NA	NA	NA	1	6	NA
	NA	2										
0.6	4.573370123		1.8	7.062695425		NA	NA	NA	NA	1	6	NA
	NA	2										
0.8	0.353553391		0.7	0.204124145		NA	NA	NA	NA	1	7	NA
	NA	2										
0	0.277350098		-0.1	0.207328422		NA	NA	NA	NA	1	7	NA
	NA	2										
0.8	0.66395281		0.7	0.375	NA	NA	NA	NA	1	7	NA	NA
2												
4.09	0.649114782		1.45	0.926723619		NA	NA	NA	NA	3	8	NA
	NA	2										

7.2	1.374772708	3.9	1.047445873	1.1	1.166726189	NA	NA	3	6	NA	NA	3
7.2	6.5375	4.9	5.322445026	3.6	6.30005291	NA	NA	3	6	8	NA	3
4.3	2.444885287	4.6	4.634670071	NA	NA	NA	NA	6	8	NA	NA	2
4.5	4.315693262	2.7	6.784462291	NA	NA	NA	NA	6	9	NA	NA	2
1.9	4.118012423	1	4.118012423	NA	NA	NA	NA	6	9	NA	NA	2
1.28	0.246777685	1.68	0.333243949	NA	NA	NA	NA	2	8	NA	NA	2
0.94	0.871367786	0.9	2.045993646	NA	NA	NA	NA	8	10	NA	NA	2
4.4	0.559016994	3.6	0.360555128	2.1	1.511857892	NA	NA	3	6	NA	10	3
3.4	1.449568901	5	1.549193338	NA	NA	NA	NA	3	10	NA	NA	2
87	3.983368201	76.3	3.633286285	NA	NA	NA	NA	3	10	NA	NA	2
3.6	1.109400392	3.8	1.732050808	NA	NA	NA	NA	3	10	NA	NA	2
4.48	0.377790328	8.6	0.59491596	6.11	0.594794082	5.38	0.272345413	2	3	5	6	4
3.2	1.309068371	2.2	0.96	NA	NA	NA	NA	3	6	NA	NA	2
2.24	0.654368062	1.96	0.599319381	NA	NA	NA	NA	3	6	NA	NA	2
5.27	0.889582789	1	0.353009043	NA	NA	NA	NA	3	6	NA	NA	2
5.78	0.937700282	4.45	0.956666667	NA	NA	NA	NA	3	6	NA	NA	2
3.6	0.981155781	4.5	1.3	NA	NA	NA	NA	3	6	NA	NA	2
11.52	1.370369061	6.27	1.428018267	7.08	0.742220803	NA	NA	3	5	6	NA	3
16.2	3.111269837	7.2	1.67600716	9.5	2.685268453	NA	NA	3	6	10	NA	3
11.1	1.744133022	2.5	1.388044188	5	1.023363439	NA	NA	3	5	6	NA	3
11.1	1.553160549	11	1.287485552	7.6	3.06740933	NA	NA	3	6	11	NA	3
15.5	1.529705854	5.4	1.388044188	NA	NA	NA	NA	3	5	NA	NA	2
-0.2	0.172317299	2.1	0.20587307	NA	NA	NA	NA	1	6	NA	NA	2
0.61	0.317542648	2.96	0.762823702	NA	NA	NA	NA	1	6	NA	NA	2
1.71	0.290688837	2.81	0.468008097	NA	NA	NA	NA	1	6	NA	NA	2
0.1	1.061873701	7	0.854874734	NA	NA	NA	NA	1	6	NA	NA	2
0.42	0.230043474	2.61	0.708387841	NA	NA	NA	NA	1	2	NA	NA	2
0.3	0.787348234	8.79	1.652296382	NA	NA	NA	NA	1	3	NA	NA	2
0.4	0.404605071	2.3	0.360011161	NA	NA	NA	NA	2	4	NA	NA	2
36.36	0.312420657	37.21	0.312420657	NA	NA	NA	NA	1	6	NA	NA	2
33.61	0.229797012	33.74	0.229797012	NA	NA	NA	NA	1	13	NA	NA	2
0.6	2.934681063	2.3	3.968892196	NA	NA	NA	NA	1	6	NA	NA	2
44.13	0.252357307	44.22	0.252357307	NA	NA	NA	NA	1	6	NA	NA	2
0.56	0.265434332	0.95	0.163576992	NA	NA	NA	NA	1	2	NA	NA	2
0.48	0.156220839	1.6	0.117388809	NA	NA	NA	NA	1	12	NA	NA	2

12	2.6708814456	NA	14	3.644790803	10	2.101438283	NA	NA	3	5	
0.12	0.40824829	NA	1.396	0.294174203	NA	NA	NA	NA	1	6	NA
9.7	1.607533401	NA	10.8	1.48045234	NA	NA	NA	NA	5	6	NA
-0.9	0.9428571432		1.769	0.603	NA	NA	NA	NA	1	14	NA	NA
7.7	1.2004385162		5.6	1.2	NA	NA	NA	NA	3	15	NA	NA

END

```
list(
d=c(NA,0,0,0,0,0,0,0,0,0,0,0,0,0),
sd=5,
mu=c(0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0,
0,0,0,0,0, 0,0,0,0,0, 0)
)
```

2. Figures of star plots and inconsistency factor plotting for network meta-analyses

Figure G1. Weight network analysis star plot

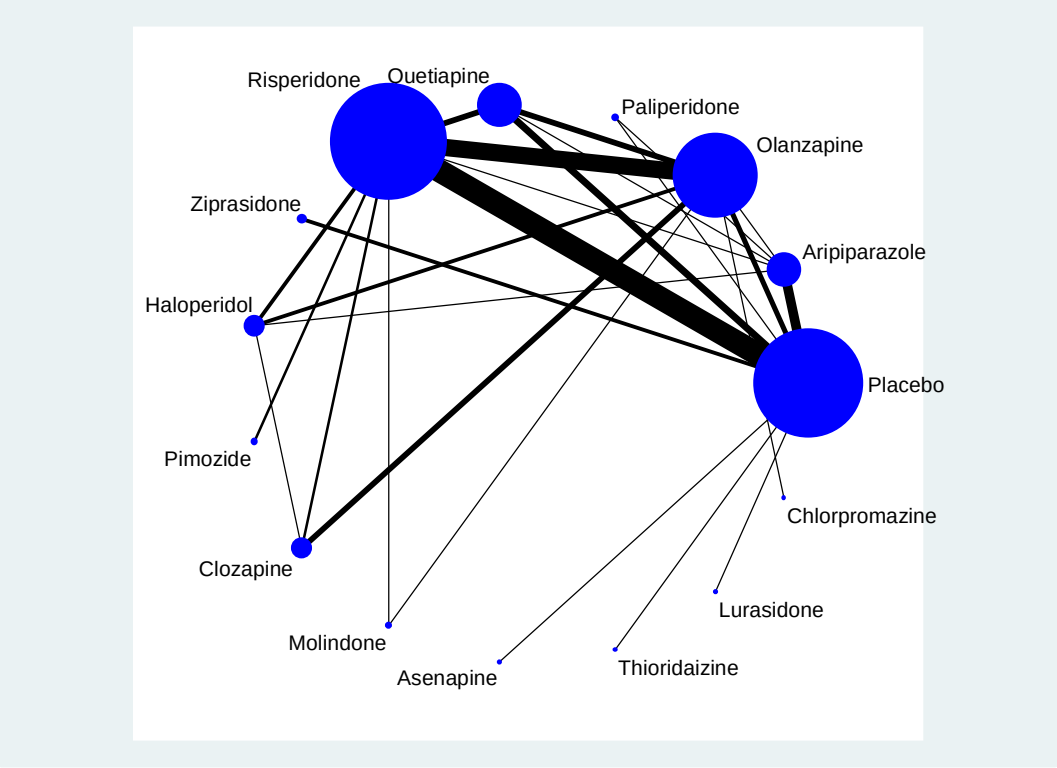
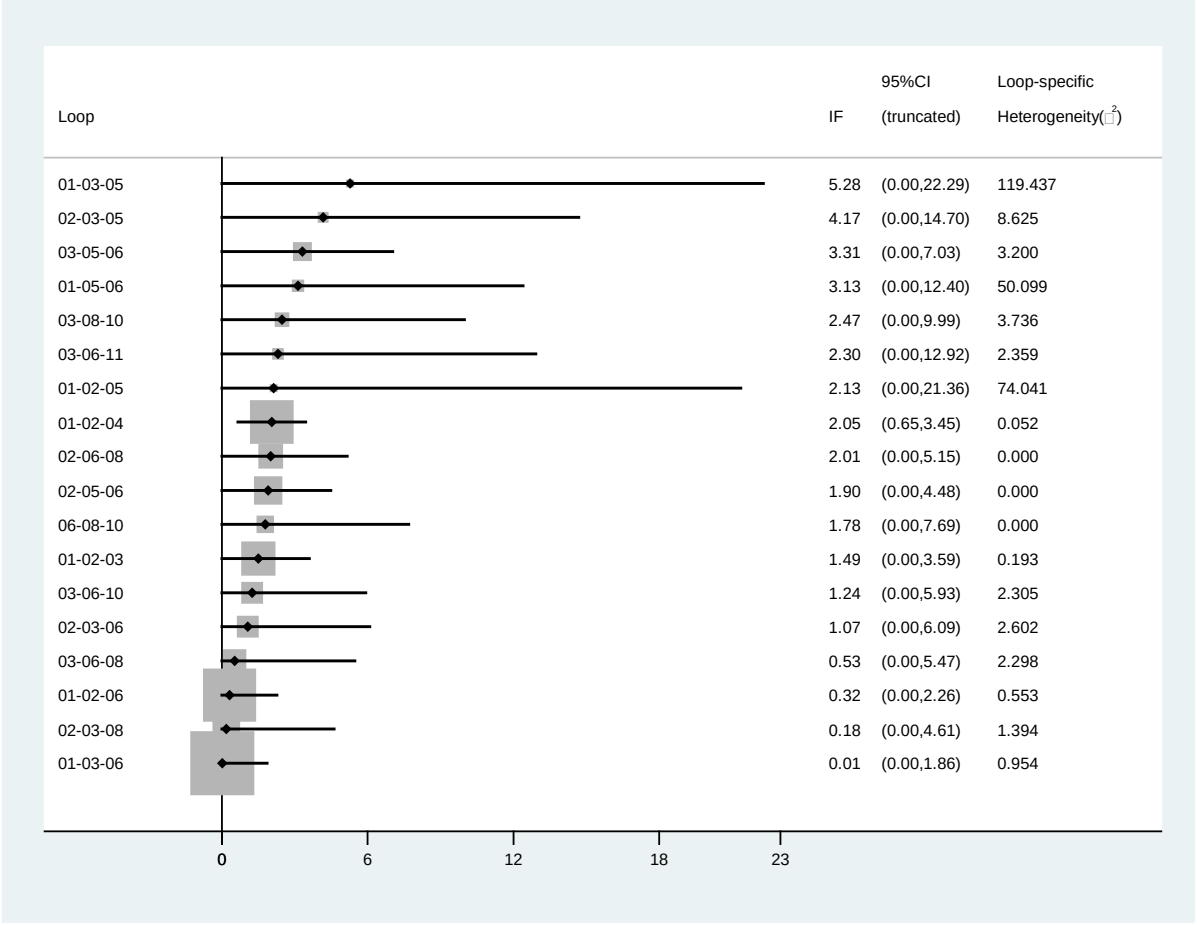


Figure G2. Weight inconsistency factor plot



1 Placebo
2 Aripiprazole
3 Olanzapine
4 Paliperidone
5 Quetiapine
6 Risperidone
7 Ziprasidone
8 Haloperidol
9 Pimozide
10 Clozapine
11 Molindone
12 Asenapine
13 Thioridazine
14 Lurasidone
15 Chlorpromazine

Figure G3. BMI network analysis star plot

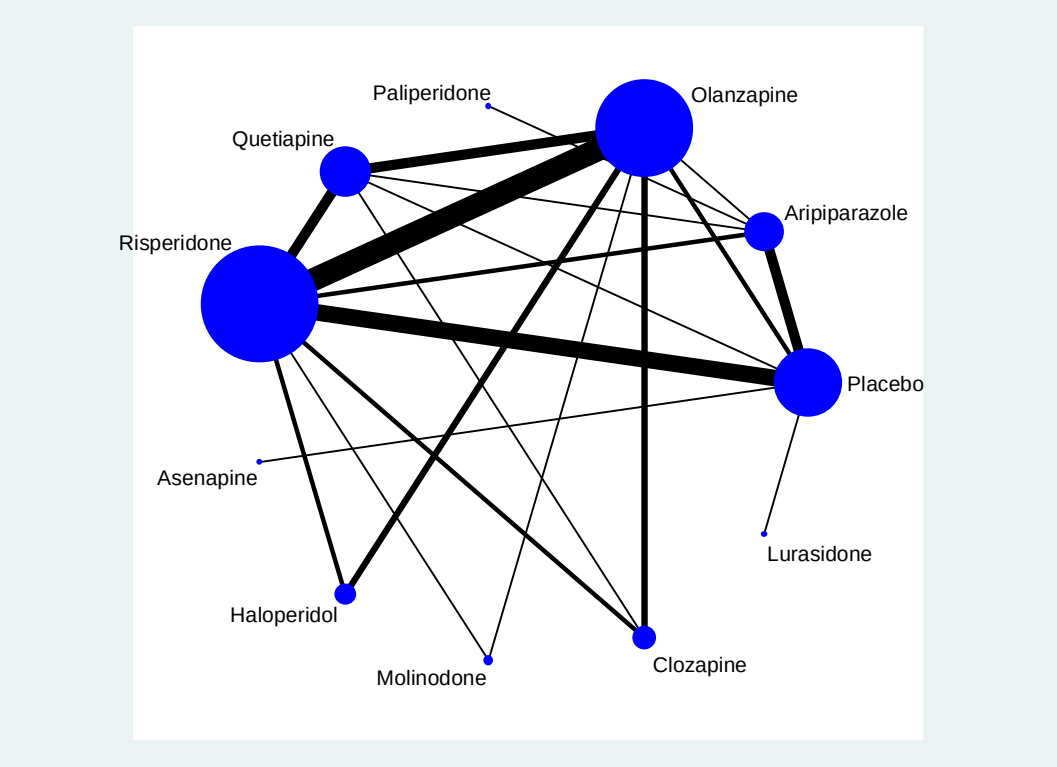
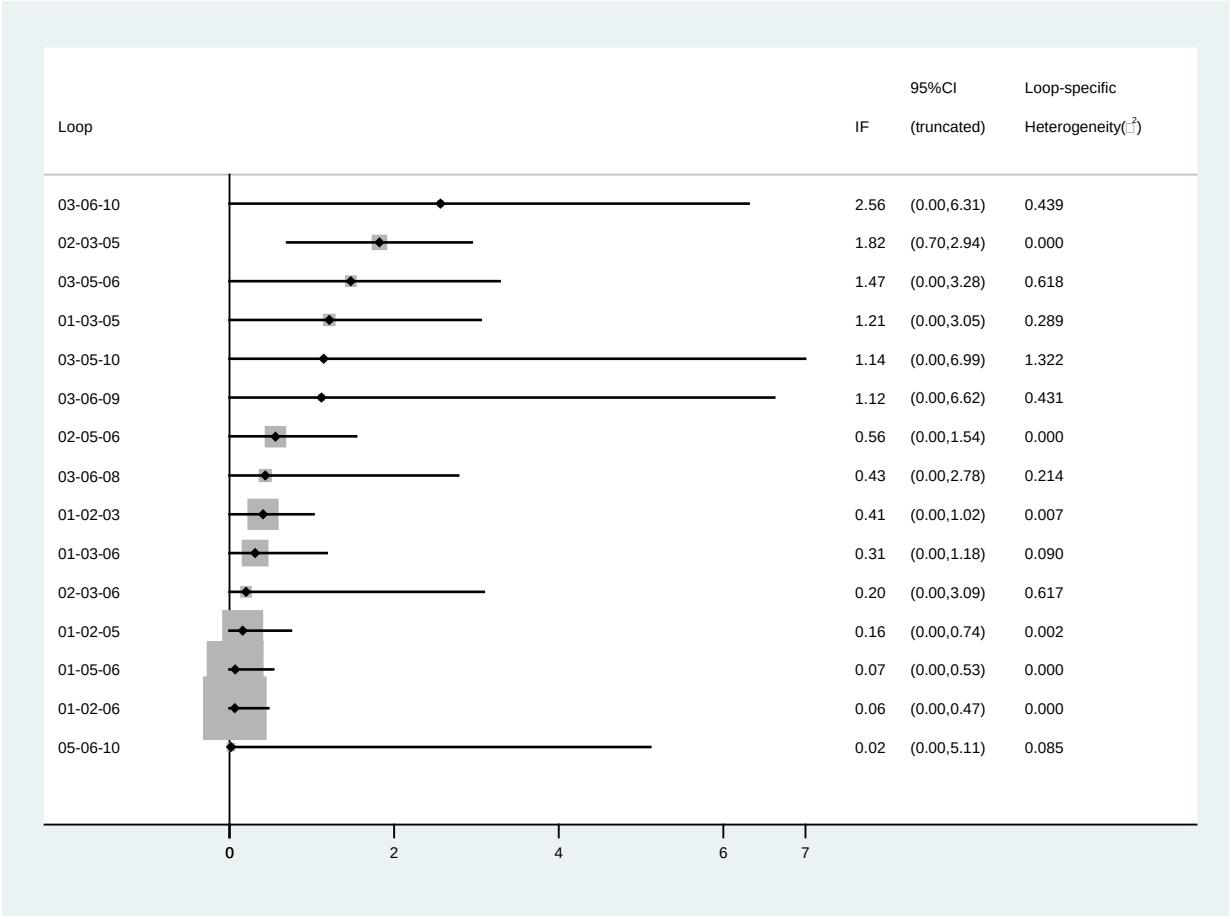


Figure G4. BMI inconsistency factor plot



1. Placebo
2. Aripiprazole
3. Olanzapine
4. Paliperidone
5. Quetiapine
6. Risperidone
7. Asenapine
8. Haloperidol
9. Molindone
10. Clozapine
11. Lurasidone

3. Pairwise comparisons from network meta-analyses

Table G1. Pairwise comparsions from network meta-analysis for weight gain

	Placebo	Aripiprazole	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone	Haloperidol	Pimozide	Clozapine	Molindone	Asenapine	Thioridazine	Lurasidone
Aripiprazole	0.88 (0.26, 1.50)													
Olanzapine	4.12 (3.43, 4.88)	3.24 (2.38, 4.17)												
Paliperidone	1.72 (0.36, 3.12)	0.84 (-0.53, 2.26)	-2.40 (-3.96, -0.89)											
Quetiapine	1.25 (0.51, 1.95)	0.37 (-0.58, 1.27)	-2.87 (-3.89,-1.95)	-0.47 (-2.07, 1.03)										
Risperidone	1.85 (1.40, 2.35)	0.98 (0.25, 1.75)	-2.27 (-2.97,-1.58)	0.13 (-1.30, 1.59)	0.60 (-0.17, 1.47)									
Ziprasidone	-0.10 (-1.25, 1.05)	-0.98 (-2.28, 0.32)	-4.22 (-5.62,-2.90)	-1.82 (-3.63,-0.04)	-1.35 (-2.68, 0.04)	-1.95 (-3.22,-0.74)								
Haloperidol	0.97 (-0.43, 2.38)	0.10 (-1.30, 1.49)	-3.15 (-4.62,-1.74)	-0.74 (-2.69, 1.16)	-0.28 (-1.81, 1.30)	-0.88 (-2.32, 0.53)	1.07 (-0.74, 2.89)							
Pimozide	0.71 (-8.87, 9.95)	-0.18, (-9.77, 9.10)	-3.42 (-13.02, 5.83)	-1.03 (-10.67, 8.34)	-0.54 (-10.12, 8.76)	-1.16 (-10.72, 8.10)	0.81 (-8.85, 10.12)	-0.27 (-9.93, 9.05)						
Clozapine	2.38 (0.37, 4.40)	1.50 (-0.55, 3.58)	-1.74 (-3.71, 0.21)	0.66 (-1.75, 3.09)	1.13 (-0.97, 3.27)	0.52 (-1.47, 2.52)	2.48 (0.17, 4.80)	1.41 (-0.81, 3.66)	1.70 (-7.78, 11.46)					
Molindone	-0.68 (-7.29, 5.80)	-1.56 (-8.19, 4.95)	-4.81 (-11.39, 1.69)	-2.41 (-9.12, 4.23)	-1.92 (-8.55, 4.59)	-2.54 (-9.13, -3.92)	-0.58 (-7.29, 6.00)	-1.66 (-8.37, 4.94)	-1.33 (-12.92, 10.06)	-3.07 (-9.95, 3.73)				
Asenapine	1.12 (-0.65, 2.90)	0.24 (-1.65, 2.12)	-3.00 (-4.97,-1.13)	-0.60 (-2.87, 1.64)	-0.14 (-2.02, 1.81)	-0.73 (-2.60, 1.07)	1.22 (-0.90, 3.34)	0.15 (-2.12, 2.40)	0.41 (-9.03, 10.14)	-1.26 (-3.95, 1.40)	1.81 (-4.92, 8.61)			
Thioridazine	0.13 (-1.71, 1.98)	-0.74 (-2.69, 1.19)	-3.98 (-6.00,-2.06)	-1.59 (-3.90, 0.69)	-1.12 (-3.06, 0.89)	-1.72 (-3.65, 0.16)	0.23 (-1.93, 2.40)	-0.84 (-3.15, 1.47)	-0.57 (-10.02, 9.20)	-2.25 (-4.98, 0.45)	0.82 (-5.93, 7.66)	-0.99 (-3.54, 1.58)		
Lurasidone	0.45 (-1.28, 2.19)	-0.43 (-2.27, 1.41)	-3.66 (-5.59, -1.85)	-1.27 (-3.50, 0.93)	-0.80 (-2.64, 1.10)	-1.40 (-3.23, 0.37)	0.55 (-1.54, 2.63)	-0.52 (-2.75, 1.71)	-0.25 (-9.69, 9.45)	-1.93 (-4.59, 0.69)	1.14 (-5.57, 7.95)	-0.67 (-3.16, 1.82)	0.32 (-2.22, 2.83)	
Chlorpromazine	2.04 (-1.79, 5.85)	1.16 (-2.72, 5.01)	-2.09 (-5.86, 1.64)	0.32 (-3.76, 4.36)	0.80 (-3.09, 4.67)	0.18 (-3.67, 3.99)	2.14 (-1.85, 6.12)	1.06 (-2.95, 5.09)	1.31 (-8.64, 11.58)	-0.35 (-4.58, 3.88)	2.73 (-4.79, 10.27)	0.92 (-3.29, 5.14)	1.90 (-2.34, 6.15)	1.59 (-2.61, 5.79)

All results are row minus column. Positive values indicate that row drug had higher weight; negative values indicate that column value had higher weight.

Table G2. Pairwise comparisons from network meta-analysis for BMI

	Placebo	Aripiprazole	Olanzapine	Paliperidone	Quetiapine	Risperidone	Asenapine	Haloperidol	Molindone	Clozapine
Aripiprazole	0.32 (0.11, 0.55)									
Olanzapine	1.51 (1.28, 1.84)	1.19 (0.90, 1.56)								
Paliperidone	1.02 (0.43, 1.62)	0.70 (0.14, 1.26)	-0.49 (-1.18, 0.11)							
Quetiapine	0.47 (0.08, 0.76)	0.16 (-0.30, 0.49)	-1.04 (-1.55, -0.66)	-0.54 (-1.29, 0.08)						
Risperidone	0.59 (0.40, 0.81)	0.27 (0.01, 0.56)	-0.92 (-1.21, -0.68)	-0.43 (-1.04, 0.20)	0.12 (-0.21, 0.55)					
Asenapine	0.52 (0.07, 0.98)	0.21 (-0.31, 0.70)	-0.97 (-1.58, -0.52)	-0.49 (-1.25, 0.24)	0.04 (-0.45, 0.68)	-0.06 (-0.59, 0.41)				
Haloperidol	-0.42 (-1.46, 0.66)	-0.73 (-1.80, 0.35)	-1.93 (-2.98, -0.86)	-1.43 (-2.63, -0.21)	-0.88 (-1.96, 0.25)	-1.01 (-2.05, 0.05)	-0.94 (-2.07, 0.23)			
Molindone	0.30 (-2.06, 2.54)	-0.01 (-2.39, 2.22)	-1.22 (-3.59, 1.01)	-0.71 (-3.17, 1.58)	-0.16 (-2.53, 2.10)	-0.29 (-2.66, 1.93)	-0.22 (-2.63, 2.06)	0.70 (-1.89, 3.14)		
Clozapine	1.96 (0.55, 3.36)	1.65 (0.21, 3.05)	0.45 (-0.98, 1.84)	0.94 (-0.58, 2.45)	1.50 (0.05, 2.93)	1.37 (-0.04, 2.75)	1.45 (-0.04, 2.90)	2.38 (0.65, 4.09)	1.67 (-1.02, 4.41)	
Lurasidone	0.14 (-0.29, 0.57)	-0.17 (-0.67, 0.29)	-1.35 (-1.95, 0.94)	-0.88 (-1.62, -0.16)	-0.34 (-0.81, 0.27)	-0.45 (-0.95, 0.00)	-0.38 (-1.01, 0.24)	0.56 (-0.60, 1.67)	-0.16 (-2.43, 2.24)	-1.82 (-3.28, -0.35)

All results are row minus column. Positive values indicate that row drug had higher weight; negative values indicate that column value had higher weight.

4. Findings tables for general adverse effects

Table G3. Findings for GAE: FGA versus SGA

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
FGA vs. SGA	Any AE	3, 204	89	97	86	107	RR, 1.16; 95% CrI, 0.71 to 1.92[1, 2]
	Any AE (6to<12)	2, 74	17 17	20 20	15 13	21 13	RR, 1.19; 95% CI, 0.56 to 1.65[1] RR, 0.86; 95% CI, 0.70 to 1.07[1]
	AE limiting treatment	6, 343 2, 50	39	163	23	180	RR, 1.82; 95% CrI, 0.90 to 4.42[1-3, 68] Not estimable[4]
	AE limiting treatment (12+)	5, 234	13	127	27	107	RR, 0.42; 95% CrI, 0.11 to 1.19[1, 5]
	Any EPS	4, 110	16	37	13	73	RR, 2.59; 95% CrI, 1.00 to 7.00[4, 6, 7]
	Akathisia	4, 115	10	44	3	71	RR, 4.30; 95% CrI, 0.93 to 22.71[3, 4]
	Dystonia	4, 115	8	44	1	71	RR, 6.53; 95% CrI, 1.29 to 34.18[3, 4]
	Weight (kg)	14, 506	NA	190	NA	316	MD, -2.67; 95% CrI, -4.61 to -0.70[1-4, 6, 8-12, 68]
	Weight (kg) (6to<12)	2, 54	NA NA	10 10	NA NA	13 21	MD, -3.50; 95% CI, -10.24 to 3.24[1] MD, -3.40; 95% CI, -9.92 to 3.12[1]
	BMI ($kg \cdot m^{-2}$)	7, 236	NA	73	NA	163	MD, -1.57; 95% CrI, -2.49 to -0.53[1, 3, 4, 13]
	BMI ($kg \cdot m^{-2}$) (6to<12)	2, 54	NA NA	10 10	NA NA	13 21	MD, -0.70; 95% CI, -3.08 to 1.68[1] MD, -0.80; 95% CI, -3.15 to 1.55[1]
	≥7% increase in weight, see haloperidol vs. olanzapine	2, 41					
	Increased total cholesterol, see various FGA's vs. various SGA's	1, 48					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides, see various FGA's vs. various SGA's	1, 48					
	Increased fasting glucose, see various FGA's vs. various SGA's	1, 48					

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	Sedation	7, 345	70	160	79	185	RR, 1.05; 95% CrI, 0.75 to 1.89[1, 3, 4, 68]
	Sedation (6to<12)	2, 74	5 5	20 20	2 3	21 13	RR, 2.63; 95% CI, 0.57 to 12.02[1] RR, 1.08; 95% CI, 0.31 to 3.78[1]
	Sedation (12+)	3, 160	18	87	5	73	RR, 2.84; 95% CrI, 0.34 to 92.81[5]
	Somnolence	3, 83	15	41	26	42	RR, 0.53; 95% CrI, 0.14 to 1.75[6, 9, 12]
	Hyperprolactinemia	2, 45	9 9	10 10	0 7	15 10	RR, 27.64; 95% CI, 1.79 to 427.25[14] RR, 1.29; 95% CI, 0.82 to 2.03[14]
	Hyperprolactinemia (12+)	3, 160	0 0 0	29 29 29	0 2 6	28 12 33	Not estimable[5] RR, 0.09; 95% CI, 0.00 to 1.68[5] RR, 0.09; 95% CI, 0.01 to 1.48[5]
	Prolactin-related events	3, 106	14	50	13	56	RR, 1.20; 95% CrI, 0.39 to 3.85[3, 15]
	Prolactin-related events (12+)	3, 160	0 0 0	29 29 29	0 0 1	28 12 33	Not estimable[5] Not estimable[5] RR, 0.38; 95% CI, 0.02 to 8.93[5]
Chlorpromazine vs Olanzapine	Any AE	0					
	AE limiting treatment	1, 74	3	36	2	38	RR, 1.58; 95% CI, 0.28 to 8.93[68]
	Any EPS	0					
	Akathisia	0					
	Dystonia	0					
	Weight (kg)	1, 74	-	36	-	38	MD, -2.62; 95% CrI, -4.35 to -0.86[68]
	BMI ($kg \cdot m^{-2}$)	0					
	≥7% increase in weight	0					
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	1, 74	32	36	33	38	RR, 1.04; 95% CI, 0.86 to 1.37[68]
	Somnolence	0					
	Hyperprolactinemia	0					
	Prolactin-related events	0					
	Any AE	1, 48	17	17	25	31	RR, 1.22; 95% CI, 1.01 to 1.48[2]
	AE limiting treatment	1, 48	6	17	5	31	RR, 2.19; 95% CI, 0.78 to 6.12[2]

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
Haloperidol vs. aripiprazole	Any EPS	1, 48	7	17	6	31	RR, 2.13; 95% CI, 0.85 to 5.32[2]
	Akathisia	0					
	Dystonia	0					
	Weight (kg)	1, 48	NA	17	NA	31	MD, 0.40; 95% CI, -0.41 to 1.21[2]
	BMI ($kg \cdot m^{-2}$)	0					
	≥7% increase in weight	0					
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	0					
	Somnolence	0					
	Hyperprolactinemia	0					
	Prolactin-related events	0					
Haloperidol vs. clozapine	Any AE	0					
	AE limiting treatment	0					
	AE limiting treatment (12+)	1, 57	1	29	4	28	RR, 0.24; 95% CI, 0.03 to 2.03[5]
	Any EPS	0					
	Akathisia	0					
	Dystonia	0					
	Weight (kg)	1, 21	NA	11	NA	10	MD, 0.04; 95% CI, -4.32 to 4.40[12]
	BMI ($kg \cdot m^{-2}$)	0					
	≥7% increase in weight	0					
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	Sedation	0					
	Sedation (12+)	1, 57	6	29	4	28	RR, 1.45; 95% CI, 0.46 to 4.59[5]
	Somnolence	1, 21	3	11	9	10	RR, 0.30; 95% CI, 0.11 to 0.81[12]
	Hyperprolactinemia	1, 25	9	10	0	15	RR, 27.64; 95% CI, 1.79 to 427.25[14]
	Hyperprolactinemia (12+)	1, 57	0	29	0	28	Not estimable[5]
	Prolactin-related events	0					
	Prolactin-related events (12+)	1, 57	0	29	0	28	Not estimable[5]
Haloperidol vs. olanzapine	Any AE	0					
	AE limiting treatment	2, 57	0 7	7 15	0 0	19 16	Not estimable[4] RR, 15.94; 95% CI, 0.99 to 256.93[3]
	AE limiting treatment (12+)	1, 41	1	29	4	12	RR, 0.10; 95% CI, 0.01 to 0.83[5]
	Any EPS	2, 38	1 4	6 7	0 3	6 19	RR, 3.00; 95% CI, 0.15 to 61.74[6] RR, 3.62; 95% CI, 1.07 to 12.27[4]
	Akathisia	2, 57	3 2	7 15	0 2	19 16	RR, 17.50; 95% CI, 1.01 to 301.78[4] RR, 1.07; 95% CI, 0.17 to 6.64[3]
	Dystonia	2, 57	2 2	7 15	0 0	19 16	RR, 12.50; 95% CI, 0.67 to 232.59[4] RR, 5.31; 95% CI, 0.28 to 102.38[3]
	Weight (kg)	3, 61	NA	18	NA	43	MD, -3.87; 95% CrI, -11.3 to 2.80[3, 4, 6]
	BMI ($kg \cdot m^{-2}$)	3, 69	NA	22	NA	47	MD, -1.87; 95% CrI, -4.36 to 0.93[3, 4, 13]
	≥7% increase in weight	2, 41	2 1	6 8	6 19	6 21	RR, 0.38; 95% CI, 0.14 to 1.06[6] RR, 0.14; 95% CI, 0.02 to 0.87[4]
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	2, 57	3 14	7 15	9 15	19 16	RR, 0.90; 95% CI, 0.34 to 2.41[4] RR, 1.00; 95% CI, 0.83 to 1.20[3]
	Sedation (12+)	1, 41	6	29	0	12	RR, 5.63; 95% CI 0.34 to 92.81[5]
	Somnolence	1, 12	2	6	5	6	RR, 0.40; 95% CI, 0.12 to 1.31[6]
	Hyperprolactinemia	1, 20	9	10	7	10	RR, 1.29; 95% CI, 0.82 to 2.03[14]

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	Hyperprolactinemia (12+)	1, 41	0	29	2	12	RR, 0.09; 95% CI, 0.00 to 1.68[5]
	Prolactin-related events	1, 31	4	15	3	16	RR, 1.42; 95% CI, 0.38 to 5.33[3]
	Prolactin-related events (12+)	1, 41	0	29	0	12	Not estimable[5]
Haloperidol vs. risperidone	Any AE	0					
	AE limiting treatment	2, 58	0 7	7 15	0 5	17 19	Not estimable[4] RR, 1.77; 95% CI, 0.70 to 4.48[3]
	AE limiting treatment (12+)	1, 62	1	29	9	33	RR, 0.13; 95% CI, 0.02 to 0.94[5]
	Any EPS	1, 24	4	7	4	17	RR, 2.43; 95% CI, 0.83 to 7.08[4]
	Akathisia	2, 58	3 2	7 15	1 0	17 19	RR, 7.29; 95% CI, 0.91 to 58.61[4] RR, 6.25; 95% CI, 0.32 to 121.14[3]
	Dystonia	2, 58	2 2	7 15	1 0	17 19	RR, 4.86; 95% CI, 0.52 to 45.32[4] RR, 6.25; 95% CI, 0.32 to 121.14[3]
	Weight (kg)	3, 81	NA	26	NA	55	MD, -2.02; 95% CrI, -9.40 to 6.30[3, 4, 8]
	BMI ($kg \cdot m^{-2}$)	2, 51	NA NA	4 7	NA NA	21 19	MD, -1.00; 95% CI, -2.47 to 0.47[4] MD, -0.40; 95% CI, -8.03 to 7.23[3]
	≥7% increase in weight	0					
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	2, 58	3 14	7 15	3 17	17 19	RR, 2.43; 95% CI, 0.64 to 9.24[4] RR, 1.04; 95% CI, 0.85 to 1.28[3]
	Sedation (12+)	1, 62	6	29	1	33	RR, 6.83; 95% CI, 0.87 to 53.43[5]
	Somnolence	0					
	Hyperprolactinemia	0					
	Hyperprolactinemia (12+)	1, 62	0	29	6	33	RR, 0.09; 95% CI, 0.01 to 1.48[5]
	Prolactin-related events	2, 75	4 6	15 20	4 6	19 21	RR, 1.27; 95% CI, 0.38 to 4.24[3] RR, 1.05; 95% CI, 0.41 to 2.72[15]

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	Prolactin-related events (12+)	1, 62	0	29	1	33	RR, 0.38; 95% CI, 0.02 to 8.93[5]
Molindone vs. olanzapine	Any AE	1, 75	36	40	26	35	RR, 1.21; 95% CI, 0.97 to 1.51[1]
	Any AE (6to<12)	1, 33	17	20	13	13	RR, 0.86; 95% CI, 0.70 to 1.07[1]
	AE limiting treatment	1, 75	8	40	6	35	RR, 1.17; 95% CI 0.45 to 3.04[1]
	AE limiting treatment (12+)	1, 33	5	20	3	13	RR, 1.08; 95% CI, 0.31 to 3.78[1]
	Any EPS	0					
	Akathisia	0					
	Dystonia	0					
	Weight (kg)	1, 55	NA	20	NA	35	MD, -5.80; 95% CI, -7.54 to -4.06[1]
	Weight (kg) (6to<12)	1, 23	NA	10	NA	13	MD, -3.50; 95% CI, -10.24 to 3.24[1]
	BMI ($kg \cdot m^{-2}$)	1, 55	NA	20	NA	35	MD, -2.05; 95% CI, -2.73 to -1.37[1]
	BMI ($kg \cdot m^{-2}$) (6to< 12)	1, 23	NA	10	NA	13	MD, -0.70; 95% CI, -3.08 to 1.68[1]
	≥7% increase in weight	0					
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	1, 75	2	40	1	35	RR, 1.75; 95% CI, 0.17 to 18.48[1]
	Sedation (6to<12)	1, 33	5	20	3	13	RR, 1.08; 95% CI, 0.31 to 3.78[1]
	Somnolence	0					
	Hyperprolactinemia	0					
	Prolactin-related events	0					
Molindone vs. risperidone	Any AE	1, 81	36	40	35	41	RR, 1.05; 95% CI, 0.90 to 1.24[1]
	Any AE (6to<12)	1, 41	17	20	15	21	RR, 1.19; 95% CI, 0.86 to 1.65[1]
	AE limiting treatment	1, 81	8	40	5	41	RR, 1.64; 95% CI, 0.59 to 4.59[1]
	AE limiting treatment (12+)	1, 41	5	20	7	21	RR, 0.75; 95% CI, 0.28 to 1.98[1]
	Any EPS	0					
	Akathisia	0					
	Dystonia	0					
	Weight (kg)	1, 61	NA	20	NA	41	MD, -3.30; 95% CI, -5.06 to -1.54[1]

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	Weight (kg) (6to<12)	1, 31	NA	10	NA	21	MD, -3.40; 95% CI, -9.92 to 3.12[1]
	BMI ($kg \cdot m^{-2}$)	1, 61	NA	20	NA	41	MD, -1.15; 95% CI, -1.87 to -0.43[1]
	BMI ($kg \cdot m^{-2}$) (6to<12)	1, 31	NA	10	NA	21	MD, -0.80; 95% CI, -3.15 to 1.55[1]
	≥7% increase in weight	0					
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	1, 81	2	40	1	41	RR, 2.05; 95% CI, 0.19 to 21.72[1]
	Sedation (6to<12)	1, 41	5	20	2	21	RR, 2.63; 95% CI, 0.57 to 12.02[1]
	Somnolence	0					
	Hyperprolactinemia	0					
	Prolactin-related events	0					
Pimozide vs. risperidone	Any AE	0					
	AE limiting treatment	0					
	Any EPS	0					
	Akathisia	0					
	Dystonia	0					
	Weight (kg)	2, 57	NA NA	7 19	NA NA	12 19	MD, -1.80; 95% CI, -18.53 to 14.93[9] MD, -0.90; 95% CI, -12.31 to 10.51[10]
	BMI ($kg \cdot m^{-2}$)	0					
	≥7% increase in weight	0					
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	0					
	Somnolence	1, 50	10	24	12	26	RR, 0.90; 95% CI, 0.48 to 1.69[9]

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	Hyperprolactinemia	0					
	Prolactin-related events	0					
Various FGA's vs various SGA's	Any AE	0					
	AE limiting treatment	0					
	Any EPS	0					
	Akathisia	0					
	Dystonia	0					
	Weight (kg)	1, 48	NA	16	NA	32	MD, -2.80; 95% CI, -5.33 to -0.27[11]
	BMI ($kg \cdot m^{-2}$)	0					
	≥7% increase in weight	0					
	Increased total cholesterol	1, 48	1	16	3	32	RR, 0.67; 95% CI, 0.08 to 5.91[11]
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	1, 48	3	16	1	32	RR, 6.00; 95% CI, 0.68 to 53.19[11]
	Increased fasting glucose	1, 48	0	16	0	32	Not estimable[11]
	Sedation	0					
	Somnolence	0					
	Hyperprolactinemia	0					
	Prolactin-related events	0					

AE = adverse event; BMI = body mass index; CI = confidence interval; EPS = extrapyramidal symptoms;FGA = first generation antipsychotic; G1 = group 1; G2 = group 2; HDL = high density lipoprotein; LDL = low density lipoprotein; MD = mean difference; N = number; NA = not applicable; RR = risk ratio; SGA = second generation antipsychotic

Table G4. Findings for GAE: FGA versus FGA

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
FGA vs. FGA	Any AE	0					
	AE limiting treatment, see haloperidol vs. pimozide	1, 44					
	Any EPS	0					
	Akathisia	0					

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	Dystonia	0					
	Weight (kg)	0					
	BMI ($kg \cdot m^{-2}$)	0					
	≥7% increase in weight	0					
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation (6to<12), see haloperidol continuous vs. haloperidol discontinuous	1, 120					
	Somnolence	0					
	Hyperprolactinemia	0					
	Prolactin-related events	0					
Haloperidol continuous vs. haloperidol discontinuous	Any AE	0					
	AE limiting treatment	0					
	Any EPS	0					
	Akathisia	0					
	Dystonia	0					
	Weight (kg)	0					
	BMI ($kg \cdot m^{-2}$)	0					
	≥7% increase in weight	0					
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	Sedation (6to<12)	1, 120	0	60	0	60	Not estimable[16]
	Somnolence	0					
	Hyperprolactinemia	0					
	Prolactin-related events	0					
Haloperidol vs. pimozide	Any AE	0					
	AE limiting treatment	1, 44	9	22	3	22	RR, 3.00; 95% CI, 0.94 to 9.62[17]
	Any EPS	0					
	Akathisia	0					
	Dystonia	0					
	Weight (kg)	0					
	BMI ($kg \cdot m^{-2}$)	0					
	≥7% increase in weight	0					
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	0					
	Somnolence	0					
	Hyperprolactinemia	0					
	Prolactin-related events	0					

AE = adverse event; BMI = body mass index; CI = confidence interval; EPS = extrapyramidal symptoms; FGA = first generation antipsychotic; G1 = group 1; G2 = group 2; HDL = high density lipoprotein; LDL = low density lipoprotein; MD = mean difference; N = number; NA = not applicable; RR = risk ratio

Table G5. Findings for GAE: SGA versus SGA

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
Aripiprazole vs. Olanzapine	Any AE	0					
	AE limiting treatment	1, 124	4	66	1	58	RR, 3.52; 95% CI, 0.40 to 30.56[18]
	Any EPS	0					
	Akathisia	1, 124	5	66	3	58	RR, 1.46; 95% CI, 0.37 to 5.86[18]
	Dystonia	0					
	Weight (kg)	1, 99	NA	47	NA	52	MD, -4.12; 95% CI, -5.50 to -2.74[18]
	BMI ($kg \cdot m^{-2}$)	1, 99	NA	47	NA	52	MD, -1.34; 95% CI, -1.85 to -0.83[18]
	≥7% increase in weight	1, 86	24	41	38	45	RR, 0.69; 95% CI, 0.52 to 0.92[18]
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	0					
	Somnolence	0					
	Hyperprolactinemia	0					
	Prolactin-related events	0					
Aripiprazole vs. Paliperidone	Any AE	1, 227	76	114	87	113	RR, 0.87; 95% CI, 0.73 to 1.02[19]
	AE limiting treatment	1, 228	0	115	5	113	RR, 0.09; 95% CI, 0.00 to 1.60[19]
	Any EPS	0					
	Akathisia	0					
	Akathesia (6to<12)	1, 226	6	114	7	112	RR, 0.84; 95% CI, 0.29 to 2.43[19]
	Dystonia	0					
	Weight (kg)	1, 226	NA	114	NA	112	MD, -1.28; 95% CI, -1.95 to -0.61[19]
	Weight (kg) (6to<12)	1, 226	NA	114	NA	112	MD, -1.90; 95% CI, -2.96 to -0.84[19]
	BMI ($kg \cdot m^{-2}$)	1, 226	NA	114	NA	112	MD, -0.50; 95% CI, -0.74 to -0.26[19]
	BMI ($kg \cdot m^{-2}$) (6to<12)	1, 226	NA	114	NA	112	MD, -0.70; 95% CI, -1.07 to -0.33[19]
	≥7% increase in weight	0					
	≥7% increase in weight (6to<12)	1, 226	20	114	29	112	RR, 0.68; 95% CI, 0.41 to 1.12[19]
	Increased total cholesterol	0					

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	1, 227	3	114	6	113	RR, 0.50; 95% CI, 0.13 to 1.93[19]
	Somnolence	1, 227	12	114	12	113	RR, 0.99; 95% CI, 0.47 to 2.11[19]
	Hyperprolactinemia	0					
	Hyperprolactinemia (6to<12)	1, 227	5	114	59	113	RR, 0.04; 95% CI, 0.02 to 0.11[19]
	Prolactin-related events	0					
Aripiprazole vs. Quetiapine	Any AE	0					
	Any AE (6to<12)	1, 73	25	62	10	11	RR, 0.44; 95% CI, 0.31 to 0.63[20]
	AE limiting treatment	1, 132	4	66	0	66	RR, 9.00; 95% CI,0.49 to 163.90[18]
	Any EPS	0					
	Akathisia	1, 132	5	66	1	66	RR, 5.00; 95% CI, 0.60 to 41.65[18]
	Akathesia (6to<12)	1, 73	5	62	1	11	RR, 0.89; 95% CI, 0.11 to 6.88[20]
	Dystonia	0					
	Weight (kg)	1, 92	NA	47	NA	45	MD, -1.63; 95% CI, -3.01 to -0.25[18]
	BMI ($kg \cdot m^{-2}$)	1, 92	NA	47	NA	45	MD, -0.45; 95% CI, -0.96 to 0.06[18]
	≥7% increase in weight	1, 77	24	41	20	36	RR, 1.05; 95% CI, 0.71 to 1.56[18]
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	0					
	Sedation (6to<12)	1, 73	1	62	1	11	RR, 0.18; 95% CI, 0.01 to 2.63[20]
	Somnolence	0					
	Hyperprolactinemia	0					
	Prolactin-related events	0					
	Any AE	1, 69	8	34	12	35	RR, 0.69; 95% CI, 0.32 to 1.47[21]

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
Aripiprazole vs. Risperidone	Any AE (6to<12)	1, 114	25	62	39	52	RR, 0.54; 95% CI, 0.38 to 0.76[20]
	AE limiting treatment	2, 272	0 4	34 66	0 6	35 137	Not estimable[21] RR, 1.38; 95% CI, 0.40 to 4.74[18]
	Any EPS	0					
	Akathisia	2, 263	5 0	66 31	7 0	137 29	RR, 1.48; 95% CI, 0.49 to 4.50[18] Not estimable[22]
	Akathesia (6to<12)	1, 114	5	62	3	52	RR, 1.40; 95% CI, 0.35 to 5.57[20]
	Dystonia	1, 59	3	29	1	30	RR, 3.10; 95% CI, 0.34 to 28.15[23]
	Weight (kg)	1, 215	NA	47	NA	168	MD, -0.90; 95% CI, -1.81 to 0.01[18]
	BMI ($kg \cdot m^{-2}$)	1, 215	NA	47	NA	168	MD, -0.25; 95% CI, -0.62 to 0.12[18]
	BMI ($kg \cdot m^{-2}$) (12+)	1, 142	NA	70	NA	72	MD, -0.31; 95% CI, -1.78 to 1.16[24]
	≥7% increase in weight	2, 245	24 0	41 34	87 7	135 35	RR, 0.91; 95% CI, 0.68 to 1.21[18] RR, 0.07; 95% CI, 0.58 to 1.04[21]
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	1, 56	1	27	0	29	RR, 3.21; 95% CI, 0.14 to 75.68[23]
	Sedation (6to<12)	1, 114	1	62	2	52	RR, 0.42; 95% CI, 0.04 to 4.49[20]
	Somnolence	2, 116	6 8	27 31	5 5	29 29	RR, 1.29; 95% CI, 0.44 to 3.74[23] RR, 1.50; 95% CI, 0.55 to 4.05[22]
	Hyperprolactinemia	0					
	Prolactin-related events	0					
Aripiprazole vs. Ziprasidone	Any AE	0					
	AE limiting treatment	2, 115	2 4	20 66	6 0	14 15	RR, 0.23; 95% CI, 0.05 to 0.99[25] RR, 2.15; 95% CI, 0.12 to 37.92[18]
	Any EPS	1, 34	2	40	0	14	RR, 3.57; 95% CI, 0.18 to 69.14[25]
	Akathisia	1, 81	5	66	0	15	RR, 2.63; 95% CI, 0.15 to 45.11[18]
	Dystonia	0					
	Weight (kg)	0					
	BMI ($kg \cdot m^{-2}$)	0					
	≥7% increase in weight	0					

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	0					
	Somnolence	0					
	Hyperprolactinemia	0					
	Prolactin-related events	0					
Clozapine vs. Olanzapine	Any AE	2, 109	1 12	2 55	15 13	24 28	RR, 0.80; 95% CI, 0.19 to 3.31[26] RR, 0.47; 95% CI, 0.25 to 0.89[27]
	AE limiting treatment	2, 65	0 2	2 18	9 1	24 21	RR, 0.44; 95% CI, 0.03 to 5.78[26] RR, 2.33; 95% CI, 0.23 to 23.66[28]
	AE limiting treatment (12+)	2, 65	1 4	12 28	0 4	13 12	RR, 3.23; 95% CI, 0.14 to 72.46[27] RR, 0.43; 95% CI, 0.13 to 1.44[5]
	Any EPS	0					
	Akathisia	1, 32	1	16	1	16	RR, 1.00; 95% CI, 0.07 to 14.64[29]
	Dystonia	2, 58	0 1	2 16	1 1	24 16	RR, 2.78; 95% CI, 0.14 to 54.04[26] RR, 1.00; 95% CI, 0.07 to 14.64[29]
	Weight (kg)	5, 136	NA	62	NA	74	MD, -1.56; 95% CrI, -5.12 to 1.57[27-31]
	Weight (kg) (6to<12)	1, 23	NA	15	NA	8	MD, -6.70; 95% CI, -14.76 to 1.36[29]
	BMI ($kg \cdot m^{-2}$)	3, 87	NA	40	NA	47	MD, -0.66; 95% CrI, -2.59 to 1.23[27-29]
	BMI ($kg \cdot m^{-2}$) (6to<12)	2, 40	NA NA	15 8	NA NA	8 9	MD, -2.30; 95% CI, -5.42 to 0.82[29] MD, 1.00; 95% CI, -2.67 to 4.67[32]
	≥7% increase in weight	2, 69	5 3	15 18	9 2	15 21	RR, 0.56; 95% CI, 0.24 to 1.27[29] RR, 1.75; 95% CI, 0.33 to 9.34[28]
	≥7% increase in weight (6to<12)	2, 63	9 1	15 28	7 3	8 12	RR, 0.69; 95% CI, 0.42 to 1.12[29] RR, 0.14; 95% CI, 0.02 to 1.24[32]
	Increased total cholesterol	2, 55	2 1	13 12	4 0	17 13	RR, 0.65; 95% CI, 0.14 to 3.04[28] RR, 3.23; 95% CI, 0.23 to 3.55[27]
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	2, 57	10 1	14 12	8 0	18 13	RR, 1.61; 95% CI, 0.87 to 2.97[28] RR, 3.23; 95% CI, 0.14 to 72.46[27]

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	Increased fasting glucose	0					
	Sedation	1, 26	0	2	0	24	Not estimable[26]
	Sedation (12+)	1, 40	4	28	0	12	RR, 4.03; 95% CI, 0.23 to 69.58[5]
	Somnolence	3, 96	20	46	21	50	RR, 1.09; 95% CrI, 0.41 to 2.75[27-29]
	Hyperprolactinemia	2, 51	0 0	2 15	2 7	24 10	RR, 1.67; 95% CI, 0.10 to 27.14[26] RR, 0.05; 95% CI, 0.00 to 0.72[14]
	Hyperprolactinemia (12+)	1, 40	0	28	2	12	RR, 0.09; 95% CI, 0.00 to 1.74[5]
	Prolactin-related events	1, 25	1	12	0	13	RR, 3.23; 95% CI, 0.14 to 72.46[27]
	Prolactin-related events (12+)	1, 40	0	28	0	12	Not estimable[5]
Clozapine vs. Quetiapine	Any AE	1, 4	1	2	1	2	RR, 1.00; 95% CI, 0.14 to 7.10[26]
	AE limiting treatment	1, 4	0	2	1	2	RR, 0.33; 95% CI, 0.02 to 5.33[26]
	Any EPS	0					
	Akathisia	0					
	Dystonia	1, 4	0	2	0	2	Not estimable[26]
	Weight (kg)	0					
	BMI ($kg \cdot m^{-2}$)	0					
	≥7% increase in weight	0					
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	1, 4	0	2	0	2	Not estimable[26]
	Somnolence	0					
	Hyperprolactinemia	0					
	Prolactin-related events	0					
Clozapine vs. Risperidone	Any AE	1, 47	1	2	33	45	RR, 0.68; 95% CI, 0.17 to 2.76[26]
	AE limiting treatment	1, 31	0	2	13	29	RR, 0.37; 95% CI, 0.03 to 4.80[26]
	AE limiting treatment (12+)	1, 61	4	28	9	33	RR, 0.52; 95% CI, 0.18 to 1.52[5]

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	Any EPS	0					
	Akathisia	1, 35	1	16	0	19	RR, 3.53; 95% CI, 0.15 to 81.11[18]
	Dystonia	2, 82	0 1	2 16	1 2	45 19	RR, 5.11; 95% CI, 0.26 to 100.62[26] RR, 0.59; 95% CI, 0.06 to 5.96[29]
	Weight (kg)	2, 89	NA NA	15 7	NA NA	15 52	MD, -0.30; 95% CI, -1.91 to 1.31[29] MD,-1.50: 95% CI, -4.55 to 1.55[30]
	Weight (kg) (6to<12)	1, 25	NA	15	NA	10	MD, 2.30; 95% CI, -3.90 to 8.50[29]
	BMI ($kg \cdot m^{-2}$)	1, 30	NA	15	NA	15	MD, -0.20; 95% CI, -0.77 to 0.37[29]
	BMI ($kg \cdot m^{-2}$) (6to<12)	2, 57	NA NA	15 8	NA NA	10 24	MD, 1.00; 95% CI, -0.95 to 2.85[29] MD, 3.80; 95% CI, 1.37 to 6.23[32]
	≥7% increase in weight	1, 30	5	15	4	15	RR, 1.25; 95% CI, 0.41 to 3.77[29]
	≥7% increase in weight (6to<12)	2, 86	9 1	15 28	6 2	10 33	RR, 1.00; 95% CI, 0.52 to 1.92[29] RR, 0.59; 95% CI, 0.06 to 6.16[32]
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	1, 47	0	2	3	45	RR, 2.19; 95% CI, 0.14 to 33.36[26]
	Sedation (12+)	1, 61	4	28	1	33	RR, 4.71; 95% CI, 0.56 to 39.78[5]
	Somnolence	1, 35	9	16	6	19	RR, 1.78; 95% CI, 0.81 to 3.93[29]
	Hyperprolactinemia	1, 47	0	2	11	45	RR, 0.67; 95% CI, 0.05 to 8.79[26]
	Hyperprolactinemia (12+)	1, 61	0	28	6	33	RR, 0.09; 95% CI, 0.01 to 1.53[5]
	Prolactin-related events	1, 47	0	2	5	45	RR, 1.39; 95% CI, 0.10 to 19.71[26]
	Prolactin-related events (12+)	1, 61	0	28	1	33	RR, 0.39; 95% CI, 0.02 to 9.23[5]
Olanzapine vs. Quetiapine	Any AE	1, 26	15	24	1	2	RR, 1.25; 95% CI, 0.30 to 5.17[26]
	AE limiting treatment	2, 150	9 1	24 58	1 0	2 66	RR, 0.75; 95% CI, 0.17 to 3.29[26] RR, 3.41; 95% CI, 0.14 to 82.04[18]
	AE limiting treatment (6to<12)	2, 84	0 2	26 18	0 1	24 16	Not estimable[33] RR, 1.78; 95% CI, 0.18 to 17.80[32]
	AE limiting treatment (12+)	1, 34	5	18	1	16	RR, 4.44; 95% CI, 0.58 to 34.14[32]

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	Any EPS						
	Akathisia	3, 194	13	94	8	100	RR, 1.65; 95% CrI, 0.42 to 8.06[18, 33, 34]
	Akathisia (6to<12)	2, 79	8 0	26 14	6 0	24 15	RR, 1.26; 95% CI, 0.50 to 3.03[33] Not estimable[32]
	Dystonia	1, 26	1	24	0	2	RR, 0.36; 95% CI, 0.02 to 7.00[26]
	Dystonia (6to<12)	1, 29	0	14	0	15	Not estimable[32]
	Weight (kg)	3, 232	NA	116	NA	116	MD, 4.00; 95% CrI, -1.67 to 10.79[18, 35, 36]
	Weight (kg) (6to<12)	3, 185	NA	90	NA	95	MD, 7.91; 95% CrI, 3.65 to 12.29[33, 35, 36]
	BMI ($kg \cdot m^{-2}$)	3, 232	NA	116	NA	116	MD, 1.36; 95% CrI, -0.29 to 3.40[18, 35, 36]
	BMI ($kg \cdot m^{-2}$) (6to<12)	4, 203	NA	99	NA	104	MD, 2.68; 95% CrI, 0.96 to 4.27[32, 33, 35, 36]
	≥7% increase in weight	3, 192	72	99	47	93	RR, 1.41; 95% CrI, 0.65 to 2.83[18, 34, 35]
	≥7% increase in weight (6to<12)	1, 91	18	44	22	47	RR, 0.87; 95% CI, 0.55 to 1.40[35]
	Increased total cholesterol	1, 33	0	13	1	20	RR, 0.5 ; 95% CI, 0.02 to 11.42[37]
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	1, 33	1	13	1	20	RR, 1.54: 95% CI, 0.11 to 22.49[37]
	Increased fasting glucose	0					
	Sedation	2, 46	0 3	24 10	0 1	2 10	Not estimable[26] RR, 3.00; 95% CI, 0.37 to 24.17[34]
	Sedation (6to<12)	1, 50	12	26	11	24	RR, 1.01; 95% CI, 0.55 to 1.84[33]
	Somnolence	0					
	Hyperprolactinemia	2, 45	2 5	24 13	0 1	2 6	RR, 0.60; 95% CI, 0.04 to 9.77[26] RR, 2.31; 95% CI, 0.34 to 15.69[38]
	Hyperprolactinemia (12+)	1, 28	3	12	2	16	RR, 2.00; 95% CI, 0.39 to 10.16[37]
	Prolactin-related events	1, 19	3	13	2	6	RR, 0.69; 95% CI, 0.15 to 3.12[38]
	Prolactin-related events (6to<12)	1, 50	0	26	0	24	Not estimable[33]
	Any AE	3, 199	50	73	97	126	RR, 0.87; 95% CrI, 0.49 to 1.55[1, 26, 39]
	Any AE (6to<12)	1, 34	13	13	15	21	RR, 1.37; 95% CI, 1.03 to 1.83[1]

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
Olanzapine vs. Risperidone	AE limiting treatment	6, 436 (1 Study n=36 no events)	16	164	30	272	RR, 0.87; 95% CrI, 0.21 to 2.18[1, 3, 4, 18, 26, 40]
	AE limiting treatment (6to<12)	1, 69	2	18	5	51	RR, 1.13; 95% CI, 0.24 to 5.34[32]
	AE limiting treatment (12+)	3, 148	12	43	23	105	RR, 1.23; 95% CrI, 0.36 to 4.09[1, 5, 32]
	Any EPS	3, 115	13	45	19	70	RR, 0.94; 95% CrI, 0.30 to 2.82[4, 39, 40]
	Akathisia	9, 507	20	192	24	315	RR, 1.17; 95% CrI, 0.59 to 2.40[1, 3, 4, 18, 29, 34, 39-41]
	Akathisia (6to<12)	1, 45	0	14	4	31	RR, 0.24; 95%CI, 0.01 to 4.13[32]
	Dystonia	5, 270	10	108	13	162	RR, 1.65; 95% CrI, 0.44 to 6.07[1, 3, 4, 26, 29, 39]
	Dystonia (6to<12)	1, 45	0	14	1	31	RR, 0.71; 95% CI, 0.03 to 16.45[32]
	Weight (kg)	13, 936	NA	331	NA	605	MD, 2.18; 95% CrI, 1.13 to 3.25[1, 3, 4, 18, 29, 30, 35, 36, 40-44]
	Weight (kg) (6to<12)	4, 295	NA	85	NA	210	MD, 4.40; 95% CrI, -0.54 to 9.86[1, 33, 35, 36]
	BMI ($kg \cdot m^{-2}$)	9, 737	NA	244	NA	493	MD, 0.94; 95% CrI, 0.64 to 1.30[1, 3, 4, 18, 29, 35, 36, 44, 45]
	BMI ($kg \cdot m^{-2}$) (6to<12)	5, 328	NA	94	NA	234	MD, 1.66; 95% CrI, 0.19 to 3.42[1, 32, 33, 35, 36]
	≥7% increase in weight	6, 504	107	150	188	354	RR, 1.36; 95% CrI, 0.93 to 2.04[4, 18, 29, 34, 35, 41]
	≥7% increase in weight (6to<12)	3, 264	28	64	64	200	RR, 1.44; 95% CrI, 0.55 to 5.50}[5, 29, 35]
	Increased total cholesterol	1, 34	0	13	1	21	RR, 0.52; 95% CI, 0.02 to 11.98[37]
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	1, 34	1	13	5	21	RR, 0.32; 95% CI, 0.04 to 2.47[37]
	Increased fasting glucose	1, 49	0	25	0	24	Not estimable[45]
	Sedation	7, 321	35	133	36	188	RR, 1.19; 95% CrI, 0.68 to 2.35[1, 3, 4, 26, 34, 39, 42]
	Sedation (6to<12)	1, 34	3	13	2	21	RR, 2.42; 95% CI, 0.47 to 12.62[1]
	Sedation (12+)	1, 45	0	12	1	33	RR, 0.87; 95% CI, 0.04 to 20.06[5]
	Somnolence	2, 66	9 3	16 12	6 13	19 19	RR, 1.78; 95% CI, 0.81 to 3.93[29] RR, 0.37; 95% CI, 0.13 to 1.02[41]
	Hyperprolactinemia	3, 128	7	49	27	79	RR, 0.46; 95% CrI, 0.11 to 1.70[26, 38, 40]

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	Hyperprolactinemia (12+)	2, 75	3 2	12 12	9 6	18 33	RR, 0.50; 95% CI, 0.17 to 1.48[37] RR, 0.92; 95% CI, 0.21 to 3.94[5]
	Prolactin-related events	5, 221	7	84	16	137	RR, 0.78; 95% CrI, 0.24 to 2.35[3, 26, 38, 41, 46]
	Prolactin-related events (6to<12)	1, 34	3	13	2	21	RR, 2.42; 95% CI, 0.47 to 12.62[1]
	Prolactin-related events (12+)	1, 45	0	12	1	33	RR, 0.87; 95% CI, 0.04 to 20.06[5]
Olanzapine vs. Ziprasidone	Any AE	0					
	AE limiting treatment	1, 73	1	58	0	15	RR, 0.81; 95% CI, 0.03 to 19.03[18]
	Any EPS						
	Akathisia	1, 73	3	58	0	15	RR, 1.90; 95% CI, 0.10 to 34.89)[18]
	Dystonia	0					
	Weight (kg)	0					
	BMI ($kg \cdot m^{-2}$)	0					
	≥7% increase in weight	0					
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	0					
	Somnolence	0					
	Hyperprolactinemia	0					
	Prolactin-related events	0					
Quetiapine vs. Risperidone	Any AE	1, 47	1	2	33	45	RR, 0.68; 95% CI, 0.17 to 2.76[26]
	Any AE (6to<12)	1, 63	10	11	39	52	RR, 1.21; 95% CI, 0.95 to 1.55[20]
	AE limiting treatment	2, 250	1 0	2 66	13 6	45 137	RR, 1.73; 95% CI, 0.40 to 7.45[26] RR, 0.16; 95% CI, 0.01 to 2.77[18]
	AE limiting treatment (6to<12)	1, 67	1	16	5	51	RR, 0.64; 95% CI, 0.08 to 5.06[32]
	AE limiting treatment (12+)	1, 67	1	16	7	51	RR, 0.46; 95% CI, 0.06 to 3.43[32]
	Any EPS	1, 22	0	12	0	10	Not estimable[47]

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	Akathisia	2, 223	1 1	66 10	7 4	137 10	RR, 0.30; 95% CI, 0.04 to 2.36[18] RR, 0.25; 95% CI, 0.03 to 1.86[34]
	Akathisia (6to<12)	2, 109	1 0	11 15	3 4	52 31	RR, 1.58; 95% CI, 0.18 to 13.77[20] RR, 0.22; 95% CI, 0.01 to 3.88[32]
	Dystonia	1, 47	0	2	1	45	RR, 5.11; 95% CI, 0.26 to 100.62[26]
	Dystonia (6to<12)	1, 46	0	15	1	31	RR, 0.67; 95% CI, 0.03 to 15.46[32]
	Weight (kg)	3, 463	NA	116	NA	347	MD, 0.08; 95% CrI, -3.77 to 3.14[18, 35, 36]
	Weight (kg) (6to<12)	3, 295	NA	93	NA	202	MD, -1.48; 95% CI, -4.16 to 1.18[35, 36, 71]
	BMI ($kg \cdot m^{-2}$)	3, 463	NA	116	NA	347	MD, 0.04; 95% CrI, -1.34 to 1.20[18, 35, 36]
	BMI ($kg \cdot m^{-2}$) (6to<12)	4, 328	NA	102	NA	226	MD, -0.32; 95% CrI, -1.56 to 1.12[32, 35, 36, 71]
	≥7% increase in weight	4, 417	55	104	176	313	RR, 0.91; 95% CrI, 0.56 to 1.44[18, 34, 35, 48]
	≥7% increase in weight (6to<12)	1, 204	22	47	56	157	RR, 1.31; 95% CI, 0.91 to 1.90[35]
	Increased total cholesterol	1, 41	1	20	1	21	RR, 1.05; 95% CI, 0.07 to 15.68[37]
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	1, 41	1	20	5	21	RR, 0.21; 95% CI, 0.03 to 1.64[37]
	Increased fasting glucose	0					
	Sedation	3, 89	8	23	12	66	RR, 0.98; 95% CrI, 0.22 to 4.28[26, 34, 48]
	Sedation (6to<12)	1, 63	1	11	2	52	RR, 2.36; 95% CI, 0.23 to 23.83[20]
	Somnolence	1, 22	3	12	1	10	RR, 2.50; 95% CI, 0.31 to 20.45[47]
	Hyperprolactinemia	4, 118	4	31	45	87	RR, 0.20; 95% CrI, 0.06 to 0.73[26, 38, 47, 48]
	Hyperprolactinemia (12+)	1, 34	2	16	9	18	RR, 0.25; 95% CI, 0.06 to 0.99[37]
	Prolactin-related events	2, 74	0 2	2 6	5 5	45 21	RR, 1.39; 95% CI, 0.10 to 19.71[26] RR, 1.40; 95% CI, 0.36 to 5.49[38]
Quetiapine vs. Ziprasidone	Any AE	0					
	AE limiting treatment	1, 81	0	66	0	15	Not estimable[18]
	Any EPS	0					
	Akathisia	1, 81	1	66	0	15	RR, 0.72; 95% CI, 0.03 to 16.78[18]
	Dystonia	0					
	Weight (kg)	0					
	BMI ($kg \cdot m^{-2}$)	0					

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	≥7% increase in weight	0					
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	0					
	Somnolence	0					
	Hyperprolactinemia	0					
	Prolactin-related events	0					
Risperidone vs. Ziprasidone	Any AE	0					
	AE limiting treatment	1, 152	6	137	0	15	RR, 1.51; 95% CI, 0.09 to 25.53[18]
	Any EPS						
	Akathisia	1, 152	7	137	0	15	RR, 1.74; 95% CI, 0.10 to 29.05[18]
	Dystonia	0					
	Weight (kg)	0					
	BMI ($kg \cdot m^{-2}$)	0					
	≥7% increase in weight	0					
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	0					
	Somnolence	0					
	Hyperprolactinemia	0					
	Prolactin-related events	0					

AE = adverse event; BMI = body mass index; CI = confidence interval; EPS = extrapyramidal symptoms; G1 = group 1; G2 = group 2; HDL = high density lipoprotein; LDL = low density lipoprotein; MD = mean difference; N = number; NA = not applicable; RR = risk ratio; SGA = second generation antipsychotic

Table G6. Findings for GAE: Dose comparisons - aripiprazole

Outcome	Author, Year	Low Dose		Medium Dose		High dose (1)		High dose (2)		High dose (3)		High dose (4)	
	Findling 2008a(1)[49] Findling 2008b(2)[50] Findling 2009(3)[51] Marcus 2009(4)[52]	5 mg/day		10 mg/day 10 mg/day 10 mg/day		15 mg/day		20 mg/day		25 mg/day		30mg/day 30mg/day 30 mg/day	
		Count	N	Count	N	Count	N	Count	N	Count	N	Count	N
Any AE	2 3 4	- - 45	- - 52	- 72 53	- 98 59	- - 45	- - 54	8 - -	8 - -	7 - -	7 - -	6 75 -	6 99 -
AE limiting treatment	1 2 3 3 (6to<12) 4	- - - - 5	- - - - 52	7 - 4 3 8	100 - 98 75 59	- - - - 4	- - - - 54	- 0 - - -	- 8 - - -	- 1 - - -	- 7 - - -	4 0 7 11 -	102 6 99 71 -
≥7% increase in weight	1 3 4	- - 17	- - 52	11 4 9	99 98 59	- - 16	- - 54	- - -	- - -	- - -	- - -	9 12 -	97 99 -
High cholesterol	3 3 (6to<12) 4	- - 0	- - 52	27 30 0	64 73 59	- - 0	- - 54	- - -	- - -	- - -	- - -	28 34 -	65 68 -
High LDL	4	0	52	0	59	0	54	-	-	-	-	-	-
Low HDL	3 3 (6to<12) 4	- - 1	- - 52	10 13 0	65 73 59	- - 2	- - 54	- - -	- - -	- - -	- - -	9 6 -	65 67 -
High triglycerides	3 3 (6to<12) 4	- - 6	- - 52	22 21 6	65 73 59	- - 2	- - 54	- - -	- - -	- - -	- - -	22 28 -	65 67 -
High fasting glucose	1 3 3 (6to<12) 4	- - - 6	- - - 52	2 1 0 6	86 65 73 59	- - - 1	- - - 54	- - - -	- - - -	- - - -	- - - -	0 2 2 -	79 64 67 -
Prolactin-related events	3 (6to<12)	-	-	3	75	-	-	-	-	-	-	0	71
Any EPS	3 3 (6to<12) 4	- - 12	- - 52	23 3 13	98 75 59	- - 12	- - 54	- - -	- - -	- - -	- - -	39 2 -	99 71 -

Outcome	Author, Year	Low Dose		Medium Dose		High dose (1)		High dose (2)		High dose (3)		High dose (4)	
Akathisia	1 3 3 (6to<12) 4	- - - 1	- - - 52	5 8 1 2	100 98 75 59	- - - 0	- - - 54	- - - -	- - - -	- - - -	- - - -	12 11 2 -	102 99 71 -
Dystonia	1 2 3 3 (6to<12)	- - - -	- - - -	4 - 0 2	100 - 98 75	- - - -	- - - -	- 1 - -	- 8 - -	- 1 - -	- 7 - -	2 0 5 1	102 6 99 71
Somnolence	1 2 3 3 (6to<12) 4	- - - - 4	- - - - 52	11 - 19 5 5	100 - 98 75 59	- 1 - - 5	- 8 - - 54	- 0 - - -	- 7 - - -	- 1 - - -	- 6 - - -	22 - 27 1 -	102 - 99 71 -
Sedation	2 3 4	- - 9	- - 52	- 2 17	- 98 59	- - 13	- - 54	0 - -	8 - -	0 - -	7 - -	1 0 -	6 99 -
		Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N
BMI ($kg \cdot m^{-2}$)	1 3 4	- - 0.6 (0.2)	- - 52	0.0(0.8) 0.2(0.8) 0.6(0.2)	99 75 59	- - 0.8 (0.2)	- - 59	- - -	- - -	- - -	- - -	0.0(0.8 0.3(1.1) -	97 72 -
Weight (kg)	1 2 3 3 (6to<12) 4	- - - - 1.3 (2.2)	- - - - 53	0.0(2.1) - 0.8(1.7) 6.5(NR) 1.3	100 - 75 75 59	- - - - 1.5(2.2)	- - - - 54	- -0.2(2.5) - - -	- 8 - - -	- 0.9(2.3) - - -	- 7 - - -	0.2(2.3) 0.4(1.8) 1.1(2.3) 6.6(NR) -	102 6 73 71 -

AE = adverse event; BMI = body mass index; EPS = extrapyramidal symptoms; HDL = high density lipoprotein; LDL = low density lipoprotein; N = number

Table G7. Findings for GAE: Dose comparisons - asenapine

Outcome	Author, Year	Low Dose		Medium Dose		High dose	
	Findling 2015a(1)[53] Findling 2015b(2)[54]	5 mg/day 5 mg/day		10 mg/day 10 mg/day		 20 mg/day	
		Count	N	Count	N	Count	N
Any AE	1 2	61 78	98 104	71 72	106 99	- 85	- 99
AE limiting treatment	1 2	6 7	98 104	8 3	106 99	- 5	- 99
≥7% increase in weight	1 2	9 11	95 92	10 8	99 90	- 7	- 87
Hyperprolactinemia	1	23	98	20	106	-	-
Any EPS	1 2	5 4	98 104	11 4	106 99	- 5	- 99
Akathisia	1 2	4 2	98 104	7 2	106 99	- 1	- 99
Somnolence	1 2	24 49	98 104	31 52	106 99	- 48	- 99
Metabolic syndrome	1	1	98	2	106	-	-
		Mean (SD)	N	Mean (SD)	N	Mean (SD)	N
BMI ($kg \cdot m^{-2}$)	2	0.60(0.79)	104	0.57(0.89)	99	0.49(0.81)	99
Weight (kg)	1	0.09(0.21)	95	0.06(0.20)	99	-	-

AE = adverse event; BMI = body mass index; EPS = extrapyramidal symptoms; N = number

Table G8. Findings for GAE: Dose comparisons lurasidone

Outcome	Author, Year	Low Dose		Medium Dose		High dose (1)		High dose (2)		High dose (3)		High dose (4)	
	Findling 2015(1) [69] Loebel 2016(2) [70]	20 mg 20 mg		40 mg		60mg		80 mg		120 mg		160 mg	
		Count	N	Count	N	Count	N	Count	N	Count	N	Count	N
Any AE	1 2	4 35	20 49	17	25	- 38	- 51	17	19	24	25	16	16
AE limiting treatment	1 2	0 2	20 49	3	25	- 2	- 51	5	19	1	25	0	16
Akathisia	2	3	49			3	51						
Dystonia	1	0	20	0	25	-	-	0	19	4	25	2	16
Sedation	1 2	0 3	20 49	3	25	- 1	- 51	5	19	7	25	4	16
Somnolence	1 2	0 3	20 49	11	25	- 9	- 51	7	19	16	25	10	16
		Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)					
BMI	2	0.3(6.5)	49			3.3(9.5)	51						
Weight (kg)	2	0.8 (5.4)	49			2.7(6.5)	51						

Table G9. Findings for GAE: Dose comparisons - paliperidone

Outcome	Author, Year	Low Dose		Medium Dose		High dose (1)		High dose (2)	
	Johnson 2011(1)[56] Singh 2011(2)[57]	1.5 mg/day		6 mg/day 3/6 mg/day		9 mg/day		12 mg/day 6/12 mg/day	
		Count	N	Count	N	Count	N	Count	N
Any AE	1 2	27	54	3 32	8 48	6	9	6 36	8 48
AE limiting treatment	1 2	1	54	0 1	8 48	0	9	0 1	8 48
≥7% increase in weight	2	3	54	6	48	-	-	6	47
Hyperprolactinemia	1	-	-	4	8	6	9	3	8
Prolactin-related events	1 2	0	54	0 2	8 48	0	9	0 0	8 48
Akathisia	2	2	54	4	48	-	-	7	47
Dystonia	2	1	54	1	48	-	-	4	47
Somnolence	2	3	54	7	48	-	-	10	48
		Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N
Weight (kg)	2	0.3(1.52)	54	1.1(2.13)	48	-	-	1.4(2.16)	48

AE = adverse event; N = number

Table G10. Findings for GAE: Dose comparisons - quetiapine

Outcome	Author, Year	Low Dose		Medium Dose		High dose (1)		High dose (2)	
	Berger 2008(1)[58] Findling 2012a(2)[59] Pathak 2013(3)[60]	200 mg/day		400 mg/day 400 mg/day 400 mg/day		600 mg/day		800 mg/day	
		Count	N	Count	N	Count	N	Count	N
Any AE	1 2	1 -	46 -	3 58	45 73	- -	- -	- 55	- 74
AE limiting treatment	2 3	- -	- -	5 15	73 95	- 7	- 98	7 -	74 -
≥7% increase in weight	2 3	- -	- -	17 14	73 95	- 10	- 98	14 -	74 -
High cholesterol	3	- -	- -	15 -	55 -	15 -	54 -	- -	- -
High LDL	3	-	-	0	90	1	85	-	-
Low HDL	3	-	-	2	77	13	77	-	-
High Triglycerides	3	-	-	14	76	15	73	-	-
High fasting glucose	3	-	-	1	86	1	81	-	-
Hyperprolactinemia	2 3	- -	- -	1 12	40 76	- 10	- 81	3 -	36 -
Any EPS	2 3	9 4	73 95	- 3	- 98	10 -	74 -		
Somnolence	2 3	- -	- -	20 27	73 95	- 31	- 98	22 -	74 -
Sedation	2 3	- -	- -	4 22	73 95	- 25	- 98	4 -	74 -
		Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N
Weight (kg)	1 2	- -	- -	2.2(2.6) 1.7(1.98)	73 95	- 1.7(2.34)	- 98	1.8(2.8) -	74 -

AE = adverse event; EPS = extrapyramidal symptoms; HDL = high density lipoprotein; LDL = low density lipoprotein; N = number

Table G11. Findings for GAE: Dose comparisons - risperidone

Outcome	Author, Year	Low Dose		Medium Dose		High dose (1)		High dose (2)	
	Haas 2009a(1)[61] Haas 2009b(2)[62] Haas 2009c(3)[63] Kent 2013(4)[64]	0.15-0.6 mg/day 0.125/0.175 mg/day		 1-3 mg/day 0.5-2.5 mg/day 1.25/1.75 mg/day		1.5-6 mg/day		 4-6 mg/day 3-6 mg/day	
		Count	N	Count	N	Count	N	Count	N
Any AE	1 2 3 4	86 - - 18	132 - - 30	- 41 45 27	- 55 50 31	93 - - -	125 - - -	- 39 58 -	- 51 61 -
AE limiting treatment	1 2 3 4	6 - - 0	132 - - 30	- 3 3 1	- 55 50 31	5 - - -	125 - - -	- 4 10 -	- 51 61 -
≥7% increase in weight	3	-	-	7	50	-	-	6	61
Hyperprolactinemia	1	55	132	-	-	70	125	-	-
Prolactin-related events	1 2 3 4	2 - - 0	132 - - 30	- 0 2 1	- 55 50 31	7 - - -	125 - - -	- 0 3 -	- 51 61 -
Any EPS	1 2 3	13 - -	132 -	- 18 4	- 55 50	41 - -	125 - -	- 20 15	- 51 61
Akathisia	1	2	132	-	-	11	125	-	-
Dystonia	1	8	132	-	-	23	125	-	-
Somnolence	2 3 4	- - 0	- - 30	13 21 7	55 50 31	- - -	- - -	6 34 -	51 61 -
Sedation	3 4	- 1	- 30	10 8	50 31	- -	- -	13 -	61 -
		Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N
BMI ($kg \cdot m^{-2}$)	2 3 4	- - 0.4(0.7)	- - 30	0.36(NR) 0.7(0.9) 1.1(1.35)	55 50 31	- - -	- - -	0.48(NR) 0.5(0.9) -	51 61 -
Weight (kg)	1 2 3 4	1.7 - - 1.2	132 - - 30	- 1.3(NR) 1.9(1.7) 2.4(2.07)	- 55 50 31	3.2(3.49) - - -	125 - - -	- 1.5(NR) 1.4(2.4) -	- 51 61 -

AE = adverse event; BMI = body mass index; EPS = extrapyramidal symptoms; N = number

Table G12. Findings for GAE: Dose comparisons - ziprasidone

Outcome	Author, Year	Low Dose		High Dose	
	Delbello 2008(1)[65]	80 mg/day		160 mg/day	
		Count	N	Count	N
Any AE	1	21	23	38	40
AE limiting treatment	1	3	23	16	40
≥7% increase in weight	1	3	23	1	40
High fasting glucose	1	0	23	0	40
Akathisia	1	1	23	3	40
Dystonia	1	1	23	3	40
Somnolence	1	5	23	15	40
Sedation	1	5	23	15	40

AE = adverse event; N = number

Table G13. Findings for GAE: FGA versus placebo

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
FGA vs. placebo	Any AE	0					
	AE limiting treatment	3, 153	22	77	11	76	RR, 2.43; 95% CrI, 0.47 to 23.08[17, 66]
	Any EPS	0					
	Akathisia	0					
	Dystonia, see haloperidol	1, 66					
	Dystonia (12+), see haloperidol	1, 66					
	Weight (kg), see various FGA's	2, 40					
	BMI ($kg \cdot m^{-2}$)	0					
	≥7% increase in weight	0					
	Increased total cholesterol, see various FGA's	1, 40					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides, see various FGA's	1, 40					
	Increased fasting glucose, see various FGA's	1, 40					
	Sedation	0					
	Somnolence, see haloperidol	1, 72					
	Hyperprolactinemia	0					
	Prolactin-related events	0					
Haloperidol vs. placebo	Any AE	0					
	AE limiting treatment	2, 109	10 9	33 22	11 0	32 22	RR, 0.88; 95% CI, 0.44 to 1.78[66] RR, 19.00; 95% CI, 1.17 to 307.63[17]
	Any EPS	0					
	Akathisia	0					
	Dystonia	1, 66	1	33	0	33	RR, 3.00; 95% CI, 0.13 to 71.07[66]
	Dystonia (12+)	1, 66	9	33	0	33	RR, 19.00; 95% CI, 1.15 to 313.64[67]
	Weight (kg)	0					

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	BMI ($kg \cdot m^{-2}$)	0					
	≥7% increase in weight	0					
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	0					
	Somnolence	1, 72	5	36	0	36	RR, 11.00; 95% CI, 0.63 to 191.88[66]
	Hyperprolactinemia	0					
	Prolactin-related events	0					
Pimozide vs. placebo	Any AE	0					
	AE limiting treatment	1, 44	3	22	0	22	RR, 7.00; 95% CI, 0.38 to 128.02[17]
	Any EPS	0					
	Akathisia	0					
	Dystonia	0					
	Weight (kg)	0					
	BMI ($kg \cdot m^{-2}$)	0					
	≥7% increase in weight	0					
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	0					
	Somnolence	0					
	Hyperprolactinemia	0					
	Prolactin-related events	0					
	Any AE	0					

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
Various FGA's vs. placebo	AE limiting treatment	0					
	Any EPS	0					
	Akathisia	0					
	Dystonia	0					
	Weight (kg)	1, 40	NA	16	NA	24	MD, 0.87; 95% CI, -1.58 to 3.32[11]
	BMI ($kg \cdot m^{-2}$)	0					
	≥7% increase in weight	0					
	Increased total cholesterol	1, 40	1	16	0	24	RR, 4.41; 95% CI, 0.19 to 102.00[11]
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	1, 40	3	16	1	24	RR, 4.50; 95% CI, 0.51 to 39.53[11]
	Increased fasting glucose	1, 40	0	16	0	24	Not estimable[11]
	Sedation	0					
	Somnolence	0					
	Hyperprolactinemia	0					
	Prolactin-related events	0					

AE = adverse event; BMI = body mass index; CI = confidence interval; EPS = extrapyramidal symptoms;FGA = first generation antipsychotic; G1 = group 1; G2 = group 2; HDL = high density lipoprotein; LDL = low density lipoprotein; MD = mean difference; N = number; NA = not applicable; RR = risk ratio

Table G14. Findings for GAE: SGA versus placebo

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
SGA vs. placebo	Any AE	27, 3667	1448	2332	707	1335	RR, 1.25; 95% CrI, 1.16 to 1.35[1-26, 70]
	Any AE (6to<12) see risperidone	1, 335					
	Any AE (12+)	2, 233	10 41	43 98	13 25	44 48	RR, 0.79; 95% CI, 0.39 to 1.60[27] RR, 0.80; 95% CI, 0.56 to 1.15[28]
	AE limiting treatment	24, 4043 5, 348	183	2644	65	1399	RR, 1.47; 95% CrI, 1.05 to 2.13 [2, 4-6, 8, 9, 11, 14, 17, 19, 21, 23-26, 29-31, 70] Not estimable[1, 15, 18, 32, 33]
	AE limiting treatment (6to<12)	3, 584	14 2 0	146 172 19	0 1 0	64 163 20	RR, 12.82; 95% CI, 0.78 to 211.72[5] RR, 1.90; 95% CI, 0.17 to 20.70[34] Not estimable[35]
	AE limiting treatment (12+)	3, 266	0 1 1	30 98 31	0 1 1	30 48 29	Not estimable[36] RR, 0.49; 95% CI, 0.03 to 7.66[28] RR, 0.94; 95% CI, 0.06 to 14.27[37]
	Any EPS	15, 2730 2, 32	233	1757	40	973	RR, 2.94; 95% CI, 2.02 to 4.27[1, 2, 5, 7, 9, 13, 14 {Snyder, 2002 #116, 20, 21, 23, 25, 29, 38, 39] Not estimable[31, 40]
	Any EPS (6to<12)	2, 629	62 3	197 172	7 1	97 163	RR, 4.36; 95% CI, 2.08 to 9.17[5] RR, 2.84; 95% CI, 0.30 to 27.06[34]
	Akathisia	21, 3638	151	2433	56	1205	RR, 1.29; 95% CrI, 0.81 to 2.27[2, 4, 5, 7-9, 11, 16, 19, 21, 23-26, 29, 30, 38, 41-43, 70]
	Akathisia (6to<12)	2, 629	20 0	197 172	2 0	97 163	RR, 4.92; 95% CI, 1.17 to 20.64[5] Not estimable[34]
	Dystonia	6, 1497 4, 194	21	1032	4	465	RR, 1.65; 95% CrI, 0.44 to 6.07[5, 7, 8, 11, 24, 29] Not estimable[14, 16, 17, 44]
	Dystonia (6to<12)	3, 652	7 2 0	197 172 11	2 1 0	97 163 12	RR, 1.72; 95% CI, 0.36 to 8.14[5] RR, 1.90; 95% CI, 0.17 to 20.70[34] Not estimable[44]
	Weight (kg)	37, 3919	NA	2384	NA	1535	MD, 1.53; 95% CI, 1.11 to 1.98[1, 2, 4, 5, 7, 10-22, 24-26, 29, 30, 32, 33, 37-40, 42, 43, 45-49, 70]
	Weight (kg) (6to<12), see risperidone	4, 467					
	Weight (kg) (12+)	2, 119	NA NA	30 30	NA NA	30 29	MD, 2.19; 95% CI, 0.73 to 3.65[36] MD, 8.49; 95% CI, 4.90 to 12.08[37]
	BMI ($kg \cdot m^{-2}$)	16, 2462	NA	1582	NA	880	MD, 0.66; 95% CI, 0.44 to 0.91[2, 4, 5, 7, 8, 15, 18, 19, 21, 29, 30, 34, 40, 42, 48, 70]
	BMI ($kg \cdot m^{-2}$) (6to<12), see risperidone	2, 405					
	≥7% increase in weight	17, 3057	337	2023	42	1034	RR, 3.53; 95% CrI, 2.49 to 5.23[1, 2, 4, 5, 8-13, 21, 22, 29, 30, 37, 39, 42]

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	≥7% increase in weight (6to<12), see risperidone	1, 70					
	Increased total cholesterol	6, 643 2, 218	92	410	13	233	RR, 3.17; 95% CI, 1.29 to 9.13[4, 5, 30, 39, 40, 49] Not estimable[2, 37]
	Increased total cholesterol (6to<12), see aripiprazole	1, 198					
	Increased LDL	3, 384 2, 294	4	239	0	145	RR, 2.71; 95% CrI, 0.32 to 23.42[4, 39, 40] Not estimable[2, 30]
	Decreased HDL	6, 839	46	564	24	275	RR, 0.95; 95% CrI, 0.48 to 2.04[2, 4, 5, 30, 39, 40]
	Decreased HDL (6to<12), see aripiprazole	1, 197					
	Increased triglycerides	10, 1383	130	897	38	486	RR, 1.64; 95% CrI, 1.09 to 2.63[2, 4, 5, 13, 30, 39, 40, 42, 46, 49]
	Increased triglycerides (6to<12), see aripiprazole	1, 197					
	Increased fasting glucose	7, 1204 2, 154	10	797	5	407	RR, 0.85; 95% CrI, 0.26 to 2.76[2, 5, 29, 30, 39, 40, 46] Not estimable[4, 49]
	Increased fasting glucose (6to<12), see aripiprazole	1, 197					
	Sedation	21, 2710	288	1696	79	1014	RR, 2.19; 95% CrI, 1.50 to 3.41[2, 4, 5, 7, 9, 10, 12, 13, 17, 19, 21, 24, 26, 32, 39, 40, 42, 43, 46, 50, 70]
	Sedation (6to<12) see risperidone	1, 23					
	Sedation (12+), see aripiprazole	1, 60					
	Somnolence	26, 3942	560	2481	119	1461	RR, 2.91; 95% CrI, 2.27 to 3.86[2, 4, 5, 7, 9, 11-16, 18-21, 23-26, 29, 33, 37-39, 42, 70]
	Somnolence (6to<12)	2, 545	3 6	172 146	2 0	163 64	RR, 1.42; 95% CI, 0.24 to 8.40[34] RR, 5.75; 95% CI, 0.33 to 100.53[5]
	Somnolence (12+), see aripiprazole	1, 146					
	Hyperprolactinemia	12, 2009	231	1261	98	748	RR, 2.04; 95% CrI, 0.82 to 5.44[4, 9, 13, 18, 24, 26, 29, 30, 32, 39, 42, 46]
	Prolactin-related events	6, 783 5, 457	11	506	3	277	RR, 1.47; 95% CrI, 0.41 to 5.37[5, 11, 18, 19, 21, 26] Not estimable[14, 16, 23, 33, 47]

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	Prolactin-related events (6to<12)	2, 545	3 5	146 172	2 0	64 163	RR, 0.66; 95% CI, 0.11 to 3.84[5] RR, 10.43; 95% CI, 0.58 to 187.10[34]
Aripiprazole vs. placebo	Any AE	7, 840	266	531	123	309	RR, 1.26; 95% CrI, 0.88 to 2.06[1-7]
	Any AE (12+)	1, 146	41	98	25	48	RR, 0.80; 95% CI, 0.56 to 1.15[28]
	AE limiting treatment	5, 969 1, 82	46	641	12	328	RR, 1.91; 95% CrI, 0.82 to 4.65[2, 4-6, 29] Not estimable[1]
	AE limiting treatment (6to<12)	1, 210	14	146	0	64	RR, 12.82; 95% CI, 0.78 to 211.72[5]
	AE limiting treatment (12+)	2, 206	0 1	30 98	0 1	30 48	Not estimable[36] RR, 0.49; 95% CI, 0.03 to 7.66[28]
	Any EPS	6, 1000	117	655	17	345	RR, 3.10; 95% CrI, 1.26 to 7.01[1, 2, 5, 7, 29, 38]
	Any EPS (6to<12)	1, 294	62	197	7	97	RR, 4.36; 95% CI, 2.08 to 9.17[5]
	Akathisia	7, 1325	48	873	23	452	RR, 0.86; 95% CrI, 0.31 to 2.14[2, 4, 5, 7, 29, 38, 41]
	Akathisia (6to<12)	1, 294	20	197	2	97	RR, 4.92; 95% CI, 1.17 to 20.64[5]
	Dystonia	3, 656	13	431	4	225	RR, 1.42; 95% CrI, 0.21 to 8.90 [5, 7, 29]
	Dystonia (6to<12)	1, 294	7	197	2	97	RR, 1.72; 95% CI, 0.36 to 8.14[5]
	Weight (kg)	7, 1042	NA	647	NA	395	MD, 0.98; 95% CrI, 0.54 to 1.48[1, 2, 4, 5, 7, 29, 38]
	Weight (kg) (12+)	1, 60	NA	30	NA	30	MD, 2.19; 95% CI, 0.73 to 3.65[36]
	BMI ($kg \cdot m^{-2}$)	5, 881	NA	587	NA	294	MD, 0.33; 95% CI, 0.07 to 0.67[2, 4, 5, 7, 29]
	≥7% increase in weight	5, 991	93	647	15	344	RR, 3.01; 95% CrI, 1.33 to 7.10[1, 2, 4, 5, 29]
	Increased total cholesterol	3, 511	0 1 55	52 47 130	0 0 11	166 51 65	Not estimable[2] RR, 3.25; 95% CI, 0.14 to 77.88 [4] RR, 2.50; 95% CI, 1.41 to 4.44[5]
	Increased total cholesterol (6to<12)	1, 198	64	141	15	57	RR, 1.72; 95% CI, 1.08 to 2.76[5]
	Increased LDL	2, 316	0 1	52 47	0 0	166 51	Not estimable[2] RR, 3.25; 95% CI, 0.14 to 77.88[4]
	Decreased HDL	3, 509	22	342	13	167	RR, 0.82; 95% CrI, 0.17 to 4.20[2, 4, 5]
	Decreased HDL (6to<12)	1, 197	19	140	13	57	RR, 0.60; 95% CI, 0.32 to 1.12[5]
	Increased triglycerides	3, 509	64	342	22	167	RR, 1.51; 95% CrI, 0.53 to 4.65[2, 4, 5]
	Increased triglycerides (6to<12)	1, 197	49	140	21	57	RR, 0.95; 95% CI, 0.63 to 1.43[5]
	Increased fasting glucose	3, 651 1, 98	7	459	3	192	RR, 0.90; 95% CrI, 0.16 to 5.44[2, 5, 29] Not estimable[4]
	Increased fasting glucose (6to<12)	1, 197	2	140	1	57	RR, 0.81; 95% CI, 0.08 to 8.80[5]
	Sedation	4, 667	50	441	7	226	RR, 2.71; 95% CrI, 0.77 to 9.78[2, 4, 5, 7]
	Sedation (12+)	1, 60	3	30	2	30	RR, 1.50; 95% CI, 0.27 to 8.34[36]

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	Somnolence	6, 1012	119	661	29	351	RR, 2.73; 95% CrI, 1.24 to 7.65[2, 4, 5, 7, 29, 38]
	Somnolence (6to<12)	1, 210	6	146	0	64	RR, 5.75; 95% CI, 0.33 to 100.53[5]
	Somnolence (12+)	1, 146	0	98	0	48	Not estimable[28]
	Hyperprolactinemia	1, 98	1	47	3	51	RR, 0.36; 95% CI, 0.04 to 3.36[4]
	Prolactin-related events	1, 210	1	146	0	64	RR, 1.33; 95% CI, 0.05 to 32.13[5]
	Prolactin-related events (6to<12)	1, 210	3	146	2	64	RR, 0.66; 95% CI, 0.11 to 3.84[5]
Asenapine vs. placebo	Any AE	2, 709	17 132	302 204	4 48	101 102	RR, 1.42; 95% CI, 0.49 to 4.13[8] RR, 1.38; 95% CI, 1.09 to 1.73[9]
	AE limiting treatment	2, 709	17 14	302 204	4 3	101 102	RR, 1.42; 95% CI, 0.49 to 4.13 [8] RR, 2.33; 95% CI, 0.69 to 7.94[9]
	Any EPS	1, 306	16	204	4	102	RR, 2.00; 95% CI, 0.69 to 5.83[9]
	Akathisia	2, 709	5 11	302 204	0 1	101 102	RR, 3.70; 95% CI, 0.21 to 66.39[8] RR, 5.50; 95% CI, 0.72 to 42.01[9]
	Dystonia	1, 403	1	302	0	101	RR, 1.01; 95% CI, 0.04 to 24.60[8]
	Weight (kg)	0					
	BMI ($kg \cdot m^{-2}$)	1, 403	NA	302	NA	101	MD, 0.52; 95% CI, 0.36 to 0.69[8]
	≥7% increase in weight	2, 650	26 19	269 194	1 3	89 98	RR, 8.60; 95% CI, 1.18 to 62.48[8] RR, 3.20; 95% CI, 0.97 to 10.55[9]
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	1, 306	16	204	2	102	RR, 4.00; 95% CI, 0.94 to 17.06[9]
	Somnolence	1, 306	38	204	7	102	RR, 2.71; 95% CI, 1.26 to 5.86[9]
	Hyperprolactinemia	1, 306	42	204	13	102	RR, 1.62; 95% CI, 0.91 to 2.87[9]
	Prolactin-related events	0					
Lurasidone va placebo	Any AE	1, 149	73	100	28	49	RR, 1.25; 95% CI, 1.16 to 1.35[70]
	AE limiting treatment	1, 149	4	100	5	49	RR, 1.47; 95% CI, 1.05 to 2.13[70]
	Any EPS	0					
	Akathisia	1, 149	6	100	0	49	RR, 1.29; 95% CI, 0.81 to 2.27[70]
	Dystonia	0					
	Weight (kg)	1, 149	NA	100	NA	49	MD, 1.53; 95% CrI, 1.11 to 1.98[70]
	BMI ($kg \cdot m^{-2}$)	1, 149	NA	100	NA	49	MD, 0.66; 95% CrI, 0.44 to 2.27[70]

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	≥7% increase in weight	0					
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	1, 149	4	100	1	49	RR, 2.19; 95% CI, 1.50 to 3.41[70]
	Somnolence	1, 149	12	100	2	49	RR, 2.91; 95% CI, 2.27 to 3.86[70]
	Hyperprolactinemia	0					
	Prolactin-related events	0					
Olanzapine vs. placebo	Any AE	1, 11	6	6	5	5	RR, 1.00; 95% CI, 0.73 to 1.37[10]
	AE limiting treatment	1, 161	3	107	1	54	RR, 1.51; 95% CI, 0.16 to 14.21[30]
	AE limiting treatment (12+)	1, 60	1	31	1	29	RR, 0.94; 95% CI, 0.06 to 14.27[37]
	Any EPS	0					
	Akathisia	2, 259	3 2	101 72	1 2	51 35	RR, 1.51; 95% CI, 0.16 to 14.20[30] RR, 0.49; 95% CI, 0.07 to 3.31[42]
	Dystonia	0					
	Weight (kg)	4, 337	NA	215	NA	122	MD, 3.96; 95% CI, 2.31 to 6.34[10, 30, 37, 42]
	Weight (kg) (12+)	1, 59	NA	30	NA	29	MD, 8.49; 95% CI, 4.90 to 12.08[37]
	BMI ($kg \cdot m^{-2}$)	2, 267	NA NA	107 72	NA NA	54 34	MD, 1.16; 95% CI, 0.93 to 1.39[30] MD, 1.50; 95% CI, 1.06 to 1.94[42]
	≥7% increase in weight	4, 337	99	215	8	122	RR, 6.08; 95% CrI, 1.84 to 27.06[10, 30, 37, 42]
	Increased total cholesterol	1, 109	1	75	0	34	RR, 1.38; 95% CI, 0.06 to 33.07[30]
	Increased LDL	1, 76	0	50	0	26	Not estimable[30]
	Decreased HDL	1, 83	6	51	5	32	RR, 0.75; 95% CI, 0.25 to 2.27[30]
	Increased triglycerides	2, 202	5 20	65 72	0 6	30 35	RR, 5.17; 95% CI, 0.29 to 90.53[30] RR, 1.62; 95% CI, 0.72 to 3.67[42]
	Increased fasting glucose	1, 120	1	81	0	39	RR, 1.46; 95% CI, 0.06 to 35.13[30]
	Sedation	3, 138	16	88	3	50	RR, 2.93; 95% CrI, 0.62 to 14.41[10, 42, 50]

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	Somnolence	2, 167	16 12	72 31	1 5	35 29	RR, 7.78; 95% CI, 1.07 to 56.30[42] RR, 2.25; 95% CI, 0.90 to 5.59[37]
	Hyperprolactinemia	2, 268	50 58	107 72	1 6	54 35	RR, 25.53; 95% CI, 3.58 to 177.76[30] RR, 4.70; 95% CI, 2.25 to 9.82[42]
	Prolactin-related events	0					
Paliperidone vs. placebo	Any AE	1, 200	90	149	30	51	RR, 1.03; 95% CI, 0.79 to 1.34[11]
	AE limiting treatment	1, 200	3	149	0	51	RR, 2.43; 95% CI, 0.13 to 46.19 [11]
	Any EPS	0					
	Akathisia	1, 201	14	150	0	51	RR, 9.99; 95% CI, 0.61 to 164.48[11]
	Dystonia	1, 201	6	150	0	51	RR, 4.48; 95% CI, 0.26 to 78.10[11]
	Weight (kg)	1, 200	NA	149	NA	51	MD, 0.90; 95% CI, 0.34 to 1.46[11]
	BMI ($kg \cdot m^{-2}$)	0					
	≥7% increase in weight	1, 200	15	149	1	51	RR, 5.13; 95% CI, 0.70 to 37.90[11]
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	0					
	Somnolence	1, 201	18	150	1	51	RR, 6.12; 95% CI, 0.84 to 44.70[11]
	Hyperprolactinemia	0					
	Prolactin-related events	1, 200	3	149	0	51	RR, 2.43; 95% CI, 0.13 to 46.19[11]
Quetiapine vs. placebo	Any AE	2, 414	68 112	92 147	66 45	100 75	RR, 1.12; 95% CI, 0.93 to 1.35[12] RR, 1.27; 95% CI, 1.03 to 1.56[13]
	AE limiting treatment	5, 748 1, 30	38	458	19	290	RR, 1.21; 95% CrI, 0.30 to 4.73[12, 13, 39, 40, 43] Not estimable[32]
	Any EPS	3, 537	0 7 19	17 193 147	0 1 4	15 90 75	Not estimable[40] RR, 3.26; 95% CI, 0.41 to 26.14 [39] RR, 2.42; 95% CI, 0.86 to 6.87[13]
	Akathisia	1, 19	1	9	0	10	RR, 3.30; 95% CI, 0.15 to 72.08[43]
	Dystonia	0					
	Weight (kg)	6, 778	NA	473	NA	305	MD, 1.44; 95% CI, 0.60 to 2.31[12, 13, 32, 39, 40, 43]
	BMI ($kg \cdot m^{-2}$)	1, 32	NA	17	NA	15	MD, 0.60; 95% CI, 0.39 to 0.81[40]

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	≥7% increase in weight	3, 697	70	432	11	265	RR, 3.41; 95% CrI, 0.95 to 18.37[12, 13, 39]
	Increased total cholesterol	2, 185	2 30	17 109	0 2	15 44	RR, 4.44; 95% CI, 0.23 to 85.83[40] RR, 6.06; 95% CI, 1.51 to 24.26[39]
	Increased LDL	2, 286	2 1	17 175	0 0	15 79	RR, 4.44; 95% CI, 0.23 to 85.83[40] RR, 1.36; 95% CI, 0.06 to 33.11[39]
	Decreased HDL	2, 247	3 15	17 154	2 4	15 61	RR, 1.32; 95% CI, 0.25 to 6.88[40] RR, 1.49; 95% CI, 0.51 to 4.30[39]
	Increased triglycerides	3, 463	39	313	9	150	RR, 2.11; 95% CrI, 0.55 to 12.79[13, 39, 40]
	Increased fasting glucose	2, 280	0 2	17 167	1 0	15 81	RR, 0.30; 95% CI, 0.01 to 6.77[40] RR, 2.44; 95% CI, 0.12 to 50.25[39]
	Sedation	6, 778	90	473	32	305	RR, 1.67; 95% CrI, 0.77 to 3.87[12, 13, 32, 39, 40, 43]
	Somnolence	3, 697	106	432	18	265	RR, 2.95; 95% CrI, 0.92 to 8.62[12, 13, 39]
	Hyperprolactinemia	3, 535	33	355	12	180	Value[13, 32, 39]
	Prolactin-related events	0					
Risperidone vs. placebo	Any AE	10, 796	384	443	244	353	RR, 1.25; 95% CrI, 1.13 to 1.40[14-23]
	Any AE (6to<12)	1, 335	82	172	59	163	RR, 1.32; 95% CI, 1.02 to 1.70[34]
	Any AE (12+)	1, 87	10	43	13	44	RR, 0.79; 95% CI, 0.39 to 1.60[27]
	AE limiting treatment	6, 559 3, 239	25	325	7	234	RR, 1.97; 95% CrI, 0.71 to 5.92[14, 17, 19, 21, 23, 31] Not estimable[15, 18, 33]
	AE limiting treatment (6to<12)	2, 374	2 0	172 19	1 0	163 20	RR, 1.90; 95% CI, 0.17 to 20.70[34] Not estimable[35]
	Any EPS	5, 636	52	365	13	271	RR, 2.78; 95% CrI, 1.27 to 6.50[14, 18, 20, 21, 23]
	Any EPS (6to<12)	1, 335	3	172	1	163	RR, 2.84; 95% CI, 0.30 to 27.06[34]
	Akathisia	4, 428	39	264	25	164	RR, 1.03; 95% CrI, 0.35 to 4.98[16, 19, 21, 23]
	Akathisia (6to<12)	1, 335	0	172	0	163	Not estimable[34]
	Dystonia	4, 194	0 0 0 0	52 19 10 11	0 0 0 0	63 17 10 12	Not estimable[14] Not estimable[16] Not estimable[17] Not estimable[44]
	Dystonia (6to<12)	2, 358	2 0	172 11	1 0	163 12	RR, 1.90; 95% CI, 0.17 to 20.70[34] Not estimable[44]
	Weight (kg)	14, 929	NA	522	NA	475	MD, 1.52; 95% CI, 0.78 to 2.29[14-22, 33, 45-48]
	Weight (kg) (6to<12)	4, 467	NA	239	NA	228	MD, 2.86; 95% CrI, -1.22 to 7.42[34, 35, 44, 51]
	BMI ($kg \cdot m^{-2}$)	6, 730	NA	397	NA	333	MD, 0.68; 95% CI, 0.27 to 1.18[15, 18, 19, 21, 34, 48]
	BMI ($kg \cdot m^{-2}$) (6to<12)	2, 405	NA NA	172 37	NA NA	163 33	MD, 0.70; 95% CI, 0.49 to 0.91[34] MD, 1.80; 95% CI, -0.61 to 4.21[51]

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	≥7% increase in weight	2, 182	13 2	111 6	3 0	58 7	RR, 2.26; 95% CI, 0.67 to 7.63[21] RR, 5.71; 95% CI, 0.33 to 99.97[22]
	≥7% increase in weight (6to<12)	1, 62	29	37	6	33	RR, 4.31; 95% CI, 2.05 to 9.06[51]
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	1, 153	1	73	0	80	RR, 3.28; 95% CI, 0.14 to 79.36[46]
	Increased fasting glucose	1, 153	0	73	1	80	RR, 0.36; 95% CI, 0.02 to 8.82[46]
	Sedation	4, 408	52	225	24	183	RR, 2.58; 95% CrI, 0.70 to 14.89[17, 19, 21, 46]
	Sedation (6to<12)	1, 23	5	11	4	12	RR, 1.36; 95% CI, 0.49 to 3.82[44]
	Somnolence	9, 862	163	473	43	389	RR, 3.25; 95% CrI, 1.96 to 5.94[14-16, 18, 19, 33 20, 21, 23]
	Somnolence (6to<12)	1, 335	3	172	2	163	RR, 1.42; 95% CI, 0.24 to 8.40[34]
	Hyperprolactinemia	2, 251	4 6	68 53	4 0	73 57	RR, 1.07; 95% CI, 0.28 to 4.12[46] RR, 13.96; 95% CI, 0.81 to 241.98[18]
	Prolactin-related events	3, 345 5, 457	6	195	3	150	RR, 1.21; 95% CrI, 0.19 to 7.69[18, 19, 21] Not estimable[14, 16, 23, 33, 47]
	Prolactin-related events (6to<12)	1, 335	5	172	0	163	RR, 10.43; 95% CI, 0.58 to 187.10[34]
Various SGA's vs. placebo	Any AE	0					
	AE limiting treatment	0					
	Any EPS	0					
	Akathisia	0					
	Dystonia	0					
	Weight (kg)	1, 56	NA	32	NA	24	MD, 3.67; 95% CI, 1.92 to 5.42[49]
	BMI ($kg \cdot m^{-2}$)	0					
	≥7% increase in weight	0					
	Increased total cholesterol	1, 56	3	32	0	24	RR, 5.30; 95% CI, 0.29 to 98.06[49]
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	1, 56	1	32	1	24	RR, 0.75; 95% CI, 0.05 to 11.39[49]
	Increased fasting glucose	1, 56	0	32	0	24	Not estimable[49]
	Sedation	0					

Comparison (G1 vs. G2)	Outcome	N Studies, N Patients	G1 Events	G1 N	G2 Events	G2 N	Relative Effects
	Somnolence	0					
	Hyperprolactinemia	0					
	Prolactin-related events	0					
Ziprasidone vs. placebo	Any AE	3, 548	300	358	114	190	RR, 1.43; 95% CrI, 0.85 to 2.59[24-26]
	AE limiting treatment	3, 548	33	358	14	190	RR, 1.36; 95% CrI, 0.37 to 6.34[24-26]
	Any EPS	1, 283	22	193	1	90	RR, 10.26; 95% CI, 1.40 to 74.93[25]
	Akathisia	3, 548	22	358	4	190	RR, 2.63; 95% CrI, 0.55 to 13.39[24-26]
	Dystonia	1, 237	1	149	0	88	RR, 1.78; 95% CI, 0.07 to 43.23[24]
	Weight (kg)	3, 360	NA	246	NA	114	MD, -0.10; 95% CI, -1.34 to 1.13[24-26]
	BMI ($kg \cdot m^{-2}$)	0					
	≥7% increase in weight	0					
	Increased total cholesterol	0					
	Increased LDL	0					
	Decreased HDL	0					
	Increased triglycerides	0					
	Increased fasting glucose	0					
	Sedation	2, 264	49 11	149 16	5 5	88 11	RR, 5.79; 95% CI, 2.40 to 13.98[24] RR, 1.51; 95% CI, 0.73 to 3.13[26]
	Somnolence	3, 548	76	358	13	190	RR, 2.97; 95% CrI, 0.84 to 9.96[24-26]
	Hyperprolactinemia	2, 265	17 5	149 16	2 0	88 12	RR, 5.02; 95% CI, 1.19 to 21.22[24] RR, 8.41; 95% CI, 0.51 to 138.82[26]
	Prolactin-related events	1, 28	1	16	0	12	RR, 2.29; 95% CI, 0.10 to 51.85[26]

AE = adverse event; BMI = body mass index; CI = confidence interval; EPS = extrapyramidal symptoms; G1 = group 1; G2 = group 2; HDL = high density lipoprotein; LDL = low density lipoprotein; MD = mean difference; N = number; NA = not applicable; RR = risk ratio; SGA = second generation antipsychotic

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