

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



Comparative Effectiveness Review

Number 184

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

Prepared for:

Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. 290-2015-00001-I

Prepared by:

University of Alberta Evidence-based Practice Center
Edmonton, AB, Canada

Investigators:

Jennifer Pillay, B.Sc.
Khrista Boylan, M.D., Ph.D., FRCPC
Normand Carrey, M.D., FRCPC
Amanda Newton, R.N., Ph.D.
Ben Vandermeer, M.Sc.
Megan Nuspl, B.Sc.
Tara MacGregor, B.A.
Syed Hamza Ahmed Jafri, B.D.S., M.P.H.
Robin Featherstone, M.L.I.S.
Lisa Hartling, Ph.D.

AHRQ Publication No. 17-EHC001-EF

March 2017

Errata January 2018

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 is made available to the public under the terms of a licensing agreement between the author and the Agency for Healthcare Research and Quality. This report may be used and reprinted without permission except those copyrighted materials that are clearly noted in the report. Further reproduction of those copyrighted materials is prohibited without the express permission of copyright holders.

AHRQ or U.S. Department of Health and Human Services endorsement of any derivative products that may be developed from this report, such as clinical practice guidelines, other quality enhancement tools, or reimbursement or coverage policies, may not be stated or implied.

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.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact EffectiveHealthCare@ahrq.hhs.gov

Suggested citation: Pillay J, Boylan K, Carrey N, Newton A, Vandermeer B, Nuspl M, MacGregor T, Ahmed Jafri SH, Featherstone R, Hartling L. First- and Second-Generation Antipsychotics in Children and Young Adults: Systematic Review Update. Comparative Effectiveness Review No. 184. (Prepared by the University of Alberta Evidence-based Practice Center under Contract No. 290-2015-00001-I.) AHRQ Publication No. 17-EHC001-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2017. Errata January 2018. www.effectivehealthcare.ahrq.gov/reports/final/cfm. doi: <https://doi.org/10.23970/AHRQEPCCER184>.

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 $\text{kg}\cdot\text{m}^{-2}$, 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 $0.15\text{ kg}\cdot\text{m}^{-2}$ rather than $2.92\text{ kg}\cdot\text{m}^{-2}$.

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.

Sharon B. Arnold, Ph.D.
Acting Director
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Arlene S. Bierman, M.D., M.S.
Director
Center for Evidence and Practice
Improvement
Agency for Healthcare Research and Quality

Laura Pincock, Pharm.D., M.P.H.
Task Order Officer
Center for Evidence and Practice
Improvement
Agency for Healthcare Research and Quality

Christine Chang, M.D., M.P.H.
Center for Evidence and Practice
Improvement
Agency for Healthcare Research and Quality

Acknowledgments

We acknowledge with appreciation the staff at AHRQ, Laura Pincock and Christine Chang, for their efforts in helping us engage with Key Informants and the Technical Expert Panel for this review; they also provided constructive comments on our draft report. Additionally, we greatly value the time spent and excellent comments on our report by EPC Associate Editor Marian McDonagh.

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.

The list of Key Informants who provided input to this report follows:

Oscar G. Bukstein, M.D., M.P.H.
Vice-Chair, Department of Psychiatry
Boston Children's Hospital
Boston, MA

Christoph U. Correll, M.D.
Medical Director, Recognition and Prevention Program (RAP), Zucker Hillside Hospital
Professor, Psychiatry and Molecular Medicine, Hofstra North Shore-LIJ School of Medicine
Investigator, Feinstein Institute for Medical Research
Glen Oaks, NY

Jana Davidson, M.D., FRCPC
Psychiatrist-in-Chief, B.C. Children's Hospital, PHSA
Clinical Professor, Psychiatry
Head, Division of Child & Adolescent Psychiatry at University of British Columbia
Vancouver, BC, Canada

Gregory Gale, M.D.
Medical Director, Behavioral Health
LifeSynch-HUMANA
Irving, TX

Michael Naylor, M.D.
Director, Behavioral Health and Welfare Program
Director, Comprehensive Assessment and Response Training System

Director, Clinical Services in Psychopharmacology, Institute for Juvenile Research
Associate Professor of Psychiatry, Clinical Teaching Track, University of Illinois at Chicago,
Department of Psychiatry
Chicago, IL

Theresa Nguyen, L.S.W.
Director of Policy and Programming
Mental Health America
Alexandria, VA

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.

The list of Technical Experts who provided input to this report follows:

Oscar G. Bukstein, M.D., M.P.H.*
Vice-Chair, Department of Psychiatry
Boston Children's Hospital
Boston, MA

Jana Davidson, M.D., FRCPC*
Psychiatrist-in-Chief, B.C. Children's Hospital, PHSA
Clinical Professor, Psychiatry
Head, Division of Child & Adolescent Psychiatry at University of British Columbia
Vancouver, BC, Canada

Tiffany Farchione, M.D.*
Deputy Director, Division of Psychiatry Products
Food and Drug Administration/CDER
Silver Spring, MD

Christopher Fannesbeck, Ph.D.*
Assistant Professor of Biostatistics, Vanderbilt University
Vanderbilt Evidence-based Practice Center
Nashville, TN

Charissa Fotinos, M.D., M.Sc.*
Deputy Chief Medical Officer, Washington State Healthcare Authority
Seattle, WA

Michael Naylor, M.D.
Director, Behavioral Health and Welfare Program
Director, Comprehensive Assessment and Response Training System
Director, Clinical Services in Psychopharmacology, Institute for Juvenile Research
Associate Professor of Psychiatry, Clinical Teaching Track, Department of Psychiatry,
University of Illinois at Chicago
Chicago, IL

Benedetto Vitiello, M.D.*
Chief, Treatment and Prevention Intervention Branch
Division of Services and Intervention Research
National Institute of Mental Health
Bethesda, MD

*Provided input on draft report.

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.

The list of Peer Reviewers follows:

Nathan Blum, M.D.
Chief, Division of Developmental and Behavioral Pediatrics
The Children's Hospital of Philadelphia
Professor of Pediatrics, Perelman School of Medicine at the University of Pennsylvania
Philadelphia, PA

Rongwei (Rochelle) Fu, Ph.D.
Professor of Biostatistics
School of Public Health
Oregon Health & Science University
Portland, OR

Renee Hilliard, Pharm.D., C.G.P.
Pharmacist, Policy, Quality and Clinical Pharm.D.
Centers for Medicare & Medicaid Services
Baltimore, MD

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 hyperactivity 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

Executive Summary	1
Introduction	1
Background	1
Use of Antipsychotics	2
Objectives	5
Scope of Review and Key Questions	6
Conditions of Interest.....	6
Key Questions	6
Analytic Framework	7
Organization of This Report	7
Methods	10
Topic Refinement and Review Protocol	10
Inclusion/Exclusion Criteria	10
Outcomes	11
Literature Search Strategy.....	14
Study Selection	14
Data Abstraction and Data Management	15
Assessment of Methodological Quality of Individual Studies	16
Data Synthesis.....	16
Pairwise and Network Meta-Analyses.....	17
Analysis of Subgroups	18
Grading the Strength of the Body of Evidence.....	19
Interpretations Throughout Report	20
Applicability	20
Peer Review and Public Commentary	20
Results	21
Literature Search and Screening	21
Description of Included Studies.....	23
Methodological Quality of Included Studies	24
Key Question 1: Intermediate and Effectiveness Outcomes.....	26
Schizophrenia and Related Psychoses: Overview	26
Schizophrenia and Related Psychoses: Intermediate Outcomes.....	35
Schizophrenia and Related Psychoses: Effectiveness Outcomes	58
Schizophrenia and Related Psychoses: Within-Study Subgroup Effects	65
Bipolar Disorder: Overview.....	66
Bipolar Disorder: Intermediate Outcomes	70
Bipolar Disorder: Effectiveness Outcomes.....	81
Bipolar Disorder: Within-Study Subgroup Effects.....	84
Autism Spectrum Disorders: Overview	86
Autism Spectrum Disorders: Intermediate Outcomes	90
Autism Spectrum Disorders: Effectiveness Outcomes	101
Autism Spectrum Disorders: Within-Study Subgroup Effects	102
ADHD and Disruptive, Impulse-Control, or Conduct Disorders: Overview.....	103
ADHD and Disruptive, Impulse-Control, or Conduct Disorders: Intermediate Outcomes	107

ADHD and Disruptive, Impulse-Control, or Conduct Disorders: Effectiveness Outcomes	116
ADHD and Disruptive, Impulse-Control, or Conduct Disorders: Within-Study Subgroup Effects	118
Obsessive-Compulsive Disorder: Overview	119
Obsessive-Compulsive Disorder: Intermediate Outcomes	120
Depression: Overview	120
Depression: Effectiveness Outcomes	120
Eating Disorders: Overview	121
Eating Disorders: Intermediate Outcomes	122
Tic Disorders: Overview	123
Tic Disorders: Intermediate Outcomes	126
Tic Disorders: Effectiveness Outcomes	130
Tic Disorders: Within-Study Subgroup Effects	131
Behavioral Issues: Overview	131
Behavioral Issues: Intermediate Outcomes	131
Key Question 2: Harms	132
Mixed Condition Studies: Overview	132
All Comparisons: Network Meta-Analyses for Body Composition Outcomes	138
FGAs Versus SGAs	142
FGAs Versus FGAs	144
SGAs Versus SGAs: Comparison of Different Drugs	145
SGAs Versus SGAs: Dose Comparisons	150
FGAs Versus Placebo	155
SGAs Versus Placebo	155
KQ 2a and b: Between- and Within-Study Subgroup Effects	163
Discussion	178
Key Findings for Intermediate and Effectiveness Outcomes Within Each Condition (Key Question 1)	178
Key Findings for Harms Across All Conditions (Key Question 2)	180
Applicability of Findings	181
Findings in Relation to What Is Known	182
Implications for Clinical and Policy Decisionmakers	184
Limitations of This CER	184
Limitations of the Evidence Base	186
Research Gaps	187
Conclusions	187
References	189
Abbreviations and Acronyms	194

Tables

Table A. PICOTS (population, interventions, comparators, outcomes, timing, setting)	ES-5
Table B. Summary of findings for schizophrenia and related psychosis: Key intermediate and effectiveness outcomes having at least low strength of evidence	ES-12
Table C. Summary of findings for bipolar disorder: Key intermediate and effectiveness outcomes having at least low strength of evidence	ES-14

Table D. Summary of findings for autism spectrum disorders: Key intermediate outcomes having at least low strength of evidence.....	ES-16
Table E. Summary of findings for ADHD and disruptive, impulse-control, or conduct disorders: Key intermediate outcomes having at least low strength of evidence.....	ES-18
Table F. Summary of findings for tic disorders: Key intermediate outcomes having at least low strength of evidence.....	ES-20
Table G. Summary of findings for general adverse effects: Short-term durations of FGAs versus SGAs.....	ES-23
Table H. Summary of findings for general adverse effects: Short- and long-term findings of comparisons between different SGAs.....	ES-24
Table I. Summary of findings for general adverse effects: Short-term findings from comparisons between different doses of SGAs.....	ES-26
Table J. Summary of findings for general adverse effects: Short- and long-term durations of comparisons between SGAs and placebo.....	ES-28
Table K. Summary of findings for general adverse effects: Long-term durations of SGAs versus placebo.....	ES-30
Table 1. PICOTS (population, interventions, comparators, outcomes, timing, setting).....	11
Table 2. Head-to-head comparisons examined in the review	24
Table 3. Characteristics of trials examining schizophrenia and related psychosis	27
Table 4. Characteristics of observational studies examining schizophrenia and related psychosis	33
Table 5. Strength of evidence for schizophrenia and related psychosis: Key intermediate outcomes having at least low strength of evidence.....	37
Table 6. Strength of evidence for schizophrenia and related psychosis: Key effectiveness outcomes having at least low strength of evidence.....	59
Table 7. Within-study analyses for subgroups of interest for schizophrenia and related psychoses	66
Table 8. Characteristics of trials examining bipolar disorder	67
Table 9. Characteristics of observational studies examining bipolar disorder	70
Table 10. Strength of evidence for bipolar disorder: Key intermediate outcomes having at least low strength of evidence	72
Table 11. Strength of evidence for bipolar disorder: Key effectiveness outcomes having at least low strength of evidence	82
Table 12. Within-study analyses for subgroups of interest in bipolar disorder	85
Table 13. Characteristics of trials examining autism spectrum disorders	87
Table 14. Characteristics of observational studies examining autism spectrum disorders.....	90
Table 15. Strength of evidence for autism spectrum disorders: Key intermediate outcomes having at least low strength of evidence	91
Table 16. Within-study analysis for subgroup effects	103
Table 17. Characteristics of trials examining ADHD and disruptive, impulse-control, or conduct disorders.....	104
Table 18. Characteristics of observational studies examining ADHD and disruptive, impulse-control, or conduct disorders.....	106
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	108

Table 20. Within-study analyses for subgroups of interest in ADHD and disruptive, impulse-control, or conduct disorders.....	119
Table 21. Characteristics of studies examining obsessive-compulsive disorder	120
Table 22. Study characteristics of trials examining eating disorders.....	122
Table 23. Characteristics of observational studies examining eating disorders	122
Table 24. Characteristics of trials examining tic disorders.....	124
Table 25. Strength of evidence for tic disorders: Key intermediate outcomes having at least low strength of evidence	126
Table 26. Within-study analysis for subgroup effects in tic disorders	131
Table 27. Characteristics of trials examining behavioral issues	131
Table 28. Characteristics of studies reporting on harms for mixed conditions	133
Table 29. Results from network meta-analysis for weight (kilogram) gain (reference standard placebo/no treatment).....	140
Table 30. Results from network meta-analysis for increase in body mass index (BMI) (reference standard placebo/no treatment).....	141
Table 31. Summary of findings for general adverse effects: Short-term durations of FGAs versus SGAs.....	144
Table 32. Findings for adverse effects (AEs) limiting treatment in comparisons between different SGAs.....	148
Table 33. Summary of findings for general adverse effects: Short-term findings of comparisons between different SGAs.....	148
Table 34. Summary of findings for general adverse effects: Long-term findings of comparisons between different SGAs.....	149
Table 35. Findings for any AE limiting treatment in short-term comparisons between different doses of SGAs.....	153
Table 36. Summary of findings for general adverse effects: Short-term findings from comparisons between different doses of SGAs	154
Table 37. Summary of findings for major adverse effects: Short-term findings for SGA versus placebo	157
Table 38. Findings for adverse effects limiting treatment in short- and long-term comparisons between SGAs and placebo	160
Table 39. Summary of findings for general adverse effects: Short-term durations of comparisons between SGAs and placebo	161
Table 40. Summary of findings for general adverse effects: Long-term durations of SGAs versus placebo	163
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	164
Table 42. Within-study analyses for subgroups of interest: Harms.....	172

Figures

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.....	ES-4
Figure B. Flow of literature through study search and selection process.....	ES-10
Figure C. Plot of network meta-analysis results for weight gain compared with reference standard (placebo/no treatment).....	ES-22

Figure D. Plot of network meta-analysis results for increase in body mass index (BMI) compared with reference standard (placebo/no treatment).....	ES-22
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.....	9
Figure 2. Flow of literature through study search and selection process.....	22
Figure 3. Risk of bias summary for trials of first- and second-generation antipsychotics in children and young adults.....	25
Figure 4. Summary of ratings of methodological quality for observational studies of first- and second-generation antipsychotics in children and young adults.....	25
Figure 5. FGAs versus SGAs on negative symptoms in schizophrenia and related psychosis ...	39
Figure 6. FGAs versus SGAs on positive symptoms in schizophrenia and related psychosis	39
Figure 7. FGAs versus SGAs for psychiatric symptoms on BPRS in schizophrenia and related psychosis.....	40
Figure 8. FGAs versus SGAs for schizophrenia symptoms using PANSS total score in schizophrenia and related psychosis.....	41
Figure 9. FGAs versus SGAs for response rates in schizophrenia and related psychosis.....	41
Figure 10. FGAs versus SGAs for discontinuation due to lack of efficacy in schizophrenia and related psychosis.....	42
Figure 11. FGAs versus SGAs for global impressions of improvement using CGI-I in schizophrenia and related psychosis.....	42
Figure 12. FGAs versus SGAs for global impressions of severity using CGI-S in schizophrenia and related psychosis.....	43
Figure 13. FGAs versus SGAs on depression symptoms in schizophrenia and related psychosis.....	43
Figure 14. FGAs versus SGAs for psychiatric symptoms using CPRS total score in schizophrenia and related psychosis.....	43
Figure 15. Clozapine versus olanzapine for negative symptoms on SANS in schizophrenia and related psychosis.....	45
Figure 16. Clozapine versus olanzapine on overall psychiatric symptoms using the BPRS in schizophrenia and related psychosis.....	45
Figure 17. Clozapine versus olanzapine for response rates in schizophrenia and related psychosis.....	45
Figure 18. Clozapine versus olanzapine on global impressions of severity (CGI-S) in schizophrenia and related psychosis.....	46
Figure 19. Olanzapine versus risperidone for negative symptoms in schizophrenia and related psychosis.....	47
Figure 20. Olanzapine versus risperidone for positive symptoms in schizophrenia and related psychosis.....	47
Figure 21. Olanzapine versus risperidone for psychiatric symptoms on BPRS in schizophrenia and related psychosis.....	47
Figure 22. Olanzapine versus risperidone for schizophrenia symptoms on PANSS total score in schizophrenia and related psychosis.....	48
Figure 23. Olanzapine versus risperidone for response rates in schizophrenia and related psychosis.....	48
Figure 24. Olanzapine versus risperidone for discontinuation for lack of efficacy in schizophrenia and related psychosis.....	48

Figure 25. Olanzapine versus risperidone for global severity using CGI-S in schizophrenia and related psychosis	49
Figure 26. Quetiapine versus risperidone on response rates in schizophrenia and related psychosis	49
Figure 27. Quetiapine versus risperidone on discontinuation due to lack of efficacy in schizophrenia and related psychosis	50
Figure 28. SGAs versus placebo for negative symptoms on PANSS in schizophrenia and related psychosis	52
Figure 29. SGAs versus placebo for positive symptoms on PANSS in schizophrenia and related psychosis	52
Figure 30. SGAs versus placebo for depressive symptoms on PANSS in schizophrenia and related psychosis	53
Figure 31. SGAs versus placebo for overall schizophrenia symptoms using PANSS Total score in schizophrenia and related psychosis	53
Figure 32. SGAs versus placebo for overall psychiatric symptoms on BPRS in schizophrenia and related psychosis	54
Figure 33. SGAs versus placebo for response rates in schizophrenia and related psychosis	54
Figure 34. SGAs versus placebo for discontinuation due to lack of efficacy in schizophrenia and related psychosis	55
Figure 35. SGAs versus placebo for symptom improvement using the CGI-I in schizophrenia and related psychosis	55
Figure 36. SGAs versus placebo for symptom severity using the CGI-S in schizophrenia and related psychosis	56
Figure 37. SGAs versus placebo for global functioning using the C-GAS in schizophrenia and related psychosis	57
Figure 38. SGAs versus placebo on poor medication adherence in schizophrenia and related psychosis	57
Figure 39. SGAs versus placebo for increased appetite in schizophrenia and related disorders..	58
Figure 40. SGAs versus placebo for negative symptoms at 12 months in schizophrenia and related psychosis	63
Figure 41. SGAs versus placebo for depression symptoms at 12 months in schizophrenia and related psychosis	63
Figure 42. SGAs versus placebo for transition to psychosis at 12 months in schizophrenia and related psychosis	64
Figure 43. SGAs versus placebo for 12-month global impressions of functioning in schizophrenia and related psychosis	64
Figure 44. SGAs versus placebo for manic symptoms using YMRS in bipolar disorder	75
Figure 45. SGAs versus placebo for depression using CDRS-R in bipolar disorder	76
Figure 46. SGAs versus placebo for response rates in bipolar disorder	77
Figure 47. SGAs versus placebo for rates of remission in bipolar disorder	77
Figure 48. SGAs versus placebo for discontinuation due to lack of efficacy in bipolar disorder	78
Figure 49. SGAs versus placebo for global impression of severity using CGI-S/CGI-BP in bipolar disorder	79
Figure 50. SGAs versus placebo for global impression of functioning using C-GAS in bipolar disorder	79
Figure 51. SGAs versus placebo for poor medication compliance in bipolar disorder	80

Figure 52. SGAs versus placebo for increases in appetite in bipolar disorder	80
Figure 53. SGAs versus placebo for suicide attempts in bipolar disorder.....	83
Figure 54. SGAs versus placebo for suicide ideation in bipolar disorder	84
Figure 55. SGAs versus placebo for irritability using ABC in autism spectrum disorders.....	94
Figure 56. SGAs versus placebo for lethargy/social withdrawal using ABC in autism spectrum disorders.....	95
Figure 57. SGAs versus placebo for stereotypy using ABC in autism spectrum disorders.....	95
Figure 58. SGAs versus placebo for inappropriate speech using ABC in autism spectrum disorders.....	96
Figure 59. SGAs versus placebo for compulsions using CY-BOCS in autism spectrum disorders	97
Figure 60. SGAs versus placebo for response rates in autism spectrum disorders.....	98
Figure 61. SGAs versus placebo for relapse rates in autism spectrum disorders	98
Figure 62. SGAs versus placebo for discontinuation due to lack of efficacy in autism spectrum disorders.....	99
Figure 63. SGAs versus placebo for global impressions of improvement in autism spectrum disorders.....	99
Figure 64. SGAs versus placebo for global impressions of severity in autism spectrum disorders	100
Figure 65. SGAs versus placebo for increases in appetite in autism spectrum disorders.....	100
Figure 66. SGAs versus placebo for conduct problems in ADHD and/or disruptive, impulse-control, or conduct disorders.....	110
Figure 67. SGAs versus placebo for aggression in ADHD and/or disruptive, impulse-control, or conduct disorders	110
Figure 68. SGAs versus placebo for hyperactivity in ADHD and/or disruptive, impulse-control, or conduct disorders.....	111
Figure 69. SGAs versus placebo for aberrant behaviors using ABC total score in ADHD and/or disruptive, impulse-control, or conduct disorders.....	112
Figure 70. SGAs versus placebo for hyperactivity/noncompliance using ABC subscale in ADHD and/or disruptive, impulse-control, or conduct disorders	112
Figure 71. SGAs versus placebo for rates of discontinuation due to lack of efficacy in ADHD and/or disruptive, impulse-control, or conduct disorders	112
Figure 72. SGAs versus placebo for global impression of improvement in ADHD and/or disruptive, impulse-control, or conduct disorders.....	113
Figure 73. SGAs versus placebo for global impressions of severity in ADHD and/or disruptive, impulse-control, or conduct disorders.....	114
Figure 74. SGAs versus placebo for medication adherence in ADHD and/or disruptive, impulse-control, or conduct disorders.....	114
Figure 75. SGAs versus placebo for increased appetite in ADHD and/or disruptive, impulse-control, or conduct disorders.....	115
Figure 76. FGAs versus SGAs for tic severity using YGTSS Total Tic score in tic disorders ..	127
Figure 77. SGAs versus placebo for tic severity using YGTSS Total Tic score in tic disorders	129
Figure 78. SGAs versus placebo for response rates in tic disorders.....	129
Figure 79. SGAs versus placebo for global impressions of severity using Tourette’s Syndrome CGI-S in tic disorders	129

Figure 80. Plot of network meta-analysis results for weight gain compared with reference standard (placebo/no treatment).....	141
Figure 81. Plot of network meta-analysis results for increase in body mass index (BMI) compared with reference standard (placebo/no treatment).....	142
Figure 82. Plot of data for weight change (kilograms) at longest followup for comparisons between SGAs and placebo	166
Figure 83. Plot of data for weight increase of 7 percent or greater at longest followup for comparisons between SGAs and placebo	168
Figure 84. Plot of data for proportion of patients reporting of somnolence at longest followup for comparisons between SGAs and placebo	169
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	170

Appendixes

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

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 insurance² and living in foster homes⁴ 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)?

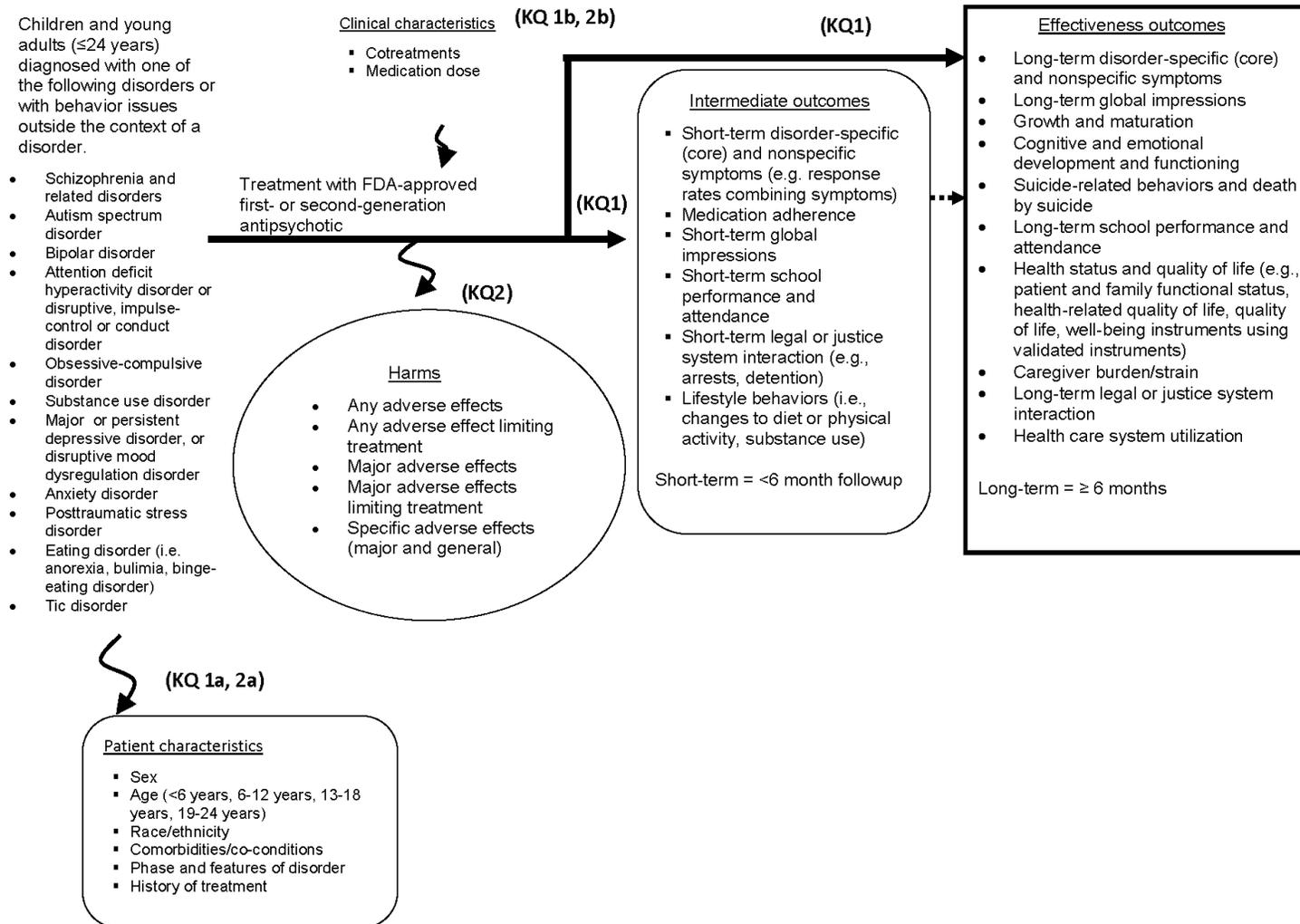
a. Do the harms vary with respect to patient characteristics, such as age, sex, race/ethnicity, diagnosis, medical comorbidities, phase of disorder, and prior exposure to antipsychotics?

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 guidance²⁵ 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 ($\leq 5\%$ 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

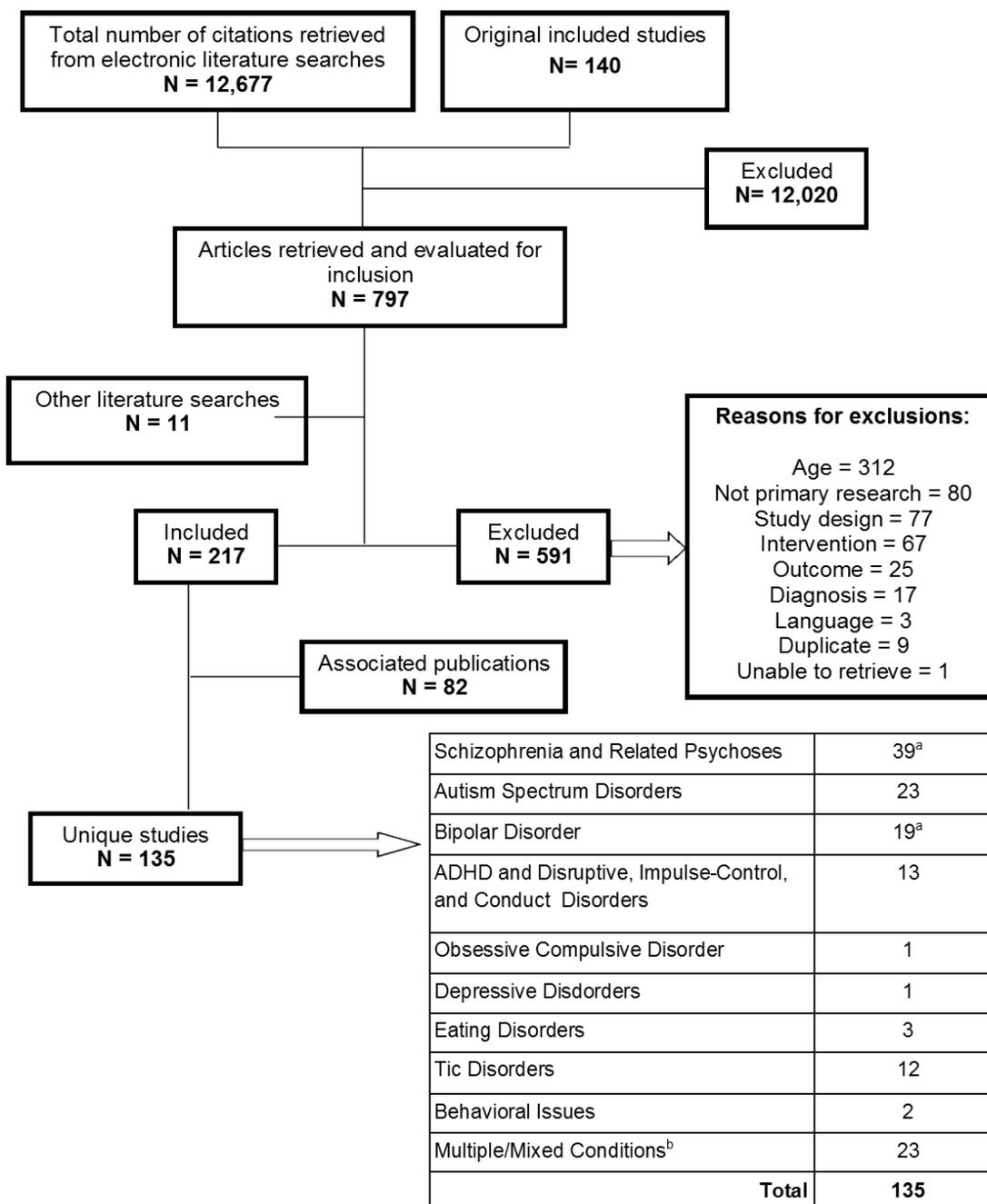
We chose to use standard wording to describe our interpretations of the SOE and of the magnitude of the effects.²⁷ For findings supported by high, moderate, low, and insufficient SOE (for which we have similar confidence in the results) we use “will”, “probably/likely”, “may/appears to”, and “not known”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



ADHD = attention deficit hyperactivity disorder

^a One study provided separate data for both bipolar disorder and schizophrenia; ^bStudies 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 inconsistency 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	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	Manic symptoms (3, 387)	MD, -7.08; 95% CrI, -10.96 to -3.24 (YMRS; range 0-60)	Moderate; Aripiprazole probably decreases ^c	
	Intermediate Outcomes	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	Manic symptoms (3, 339)	MD, -5.34; 95% CrI, -9.92 to -0.44 (YMRS; range 0-60)	Moderate; Quetiapine probably decreases ^c	
	Intermediate Outcomes	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; Quetiapine 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 Downgraded 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 (D/CD). 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 D/CD. 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 D/CD 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 D/CD 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 DCD 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 DCD)	MD, -1.98; 95% CrI, -3.18 to -0.93	Low; SGAs may reduce in DCD ^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 DCD 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 DCD 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)

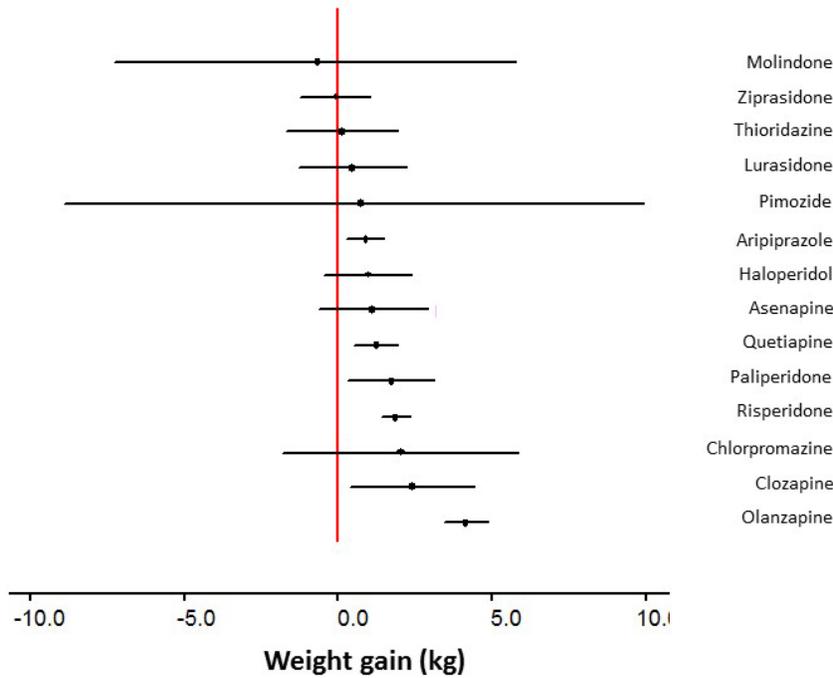
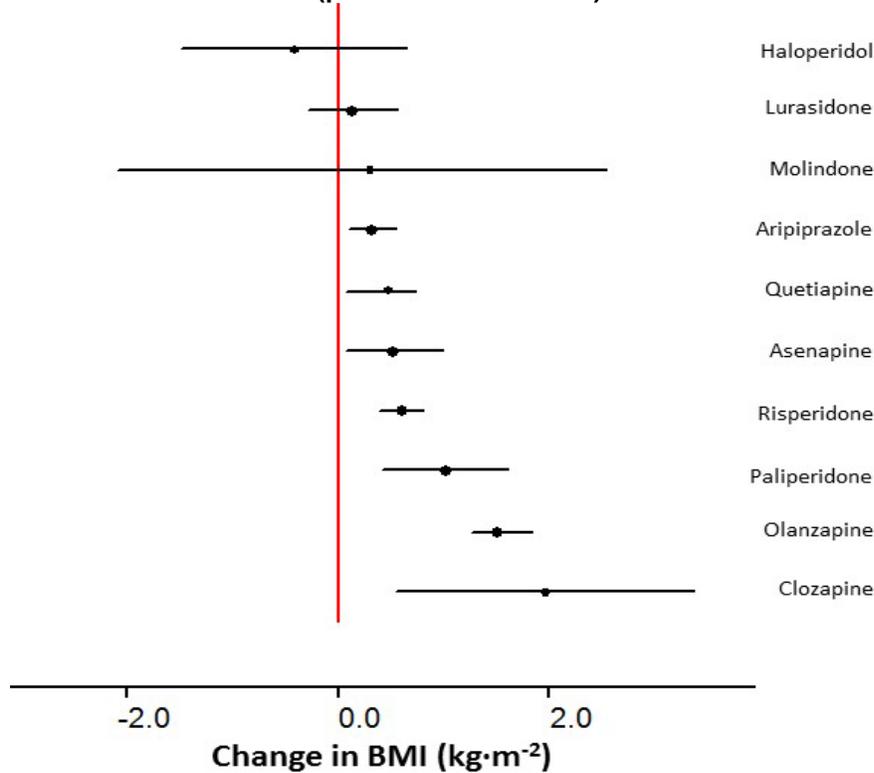


Figure D. Plot of network meta-analysis results for increase in body mass index (BMI) compared with reference standard (placebo/no treatment)



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·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

^aRisk ratios above 1.0 and positive MD favor SGAs.

^bDowngraded for ROB and imprecision, based on small sample size.

^cDowngraded for ROB.

^dDowngraded 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		G2		Relative Effects ^a	Strength of Evidence, Conclusions
			Events	N	Events	N		
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·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·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·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	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
Long-term	BMI (kg·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	Weight (kg)	3 (463)	-	116	-	347	MD, 0.08; 95% CrI, -3.77 to 3.14	Low; may make little or no difference ^f
Short-term	BMI (kg·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
	Hyperprolactinemia	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	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
Long-term	BMI (kg·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

^bDowngraded 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.

^dDowngraded for ROB.

^eDowngraded for ROB and imprecision, based on small sample size.

^fDowngraded 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		Low Dose		Relative Effects ^a	Strength of Evidence; Conclusions
		Events	N	Events	N		
Aripiprazole High (15/30mg/day) vs. Low (10mg/day)	Any EPS	39	99	23	98	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·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	65	27	64	RR, 1.02; 95% CI, 0.68 to 1.52	Low; may make little or no difference ^d
		0	54	0	59	Not estimable	
	High triglycerides	22	65	22	65	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
	2	54	6	59			
	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·m ⁻²)	--	-	-	-	MD, 0.03; 95% CI, -0.04 to 0.10	Low; may make little or no difference ^e
	≥ 7% weight increase	10	99	9	95	RR, 1.07; 95% CI, 0.45 to 2.51	Moderate; probably makes little or no difference ^e
		8	90	11	92	RR, 0.74; 95% CI, 0.31 to 1.76	
	Somnolence	31	106	24	98	RR, 1.19; 95% CI, 0.76 to 1.89	Moderate; probably makes
		52	99	49	104		

						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 make 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 ($\leq 5\%$ 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 $\geq 7\%$ 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 Not estimable	Moderate; SGAs probably increase risk ^b
	Akathisia	2, 32	0	17	0	15		
	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·m ⁻²)	16, 2462	-	1582	-	880	MD, 0.61; 95% CI, 0.38 to 0.85	Moderate; SGAs probably increase slightly ^b
	$\geq 7\%$ 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·m ⁻²)	5, 881	-	587	-	294	MD, 0.33; 95% CrI, 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% CrI, 2.31 to 6.34	Moderate; Olanzapine probably increases ^b
	BMI (kg·m ⁻²)	2, 267	-	107 72	-	54 34	MD, 1.16; 95% CrI, 0.93 to 1.39 MD, 1.50; 95% CrI, 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
	Hyperprolactinemia	2, 268	50 58	107 72	1 6	54 35	RR, 25.53; 95% CrI, 3.58 to 177.76 RR, 4.70; 95% CrI, 2.25 to 9.82	Low; Olanzapine may increase risk ^e
Quetiapine vs. placebo	Weight (kg)	6, 778	-	473	-	305	MD, 1.44; 95% CrI, 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% CrI, 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·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

^aRisk ratios above 1.0 and positive MD favor placebo.

^bDowngraded for ROB.

^cDowngraded for ROB and imprecision because point estimate and CrI includes clinically significant favor for placebo.

^dDowngraded for ROB and inconsistency.

^eDowngraded 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·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

^aPositive MD favors placebo.

^bDowngraded 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; although 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 data³⁰⁻³² and clinician self-reports³³ 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 DCD 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 DCD 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 comparisons 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 RCTs³⁵⁻³⁷ 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.

References

1. Olfson M, Crystal S, Huang C, et al. Trends in antipsychotic drug use by very young, privately insured children. *J Am Acad Child Adolesc Psychiatry*. 2010 Jan;49(1):13-23. PMID: 20215922.
2. Pathak P, West D, Martin BC, et al. Evidence-based use of second-generation antipsychotics in a state Medicaid pediatric population, 2001-2005. *Psychiatr Serv*. 2010 Feb;61(2):123-9. doi: 10.1176/appi.ps.61.2.123. PMID: 20123816.
3. Zito JM, Safer DJ, de Jong-van den Berg LT, et al. A three-country comparison of psychotropic medication prevalence in youth. *Child Adolesc Psychiatry Ment Health*. 2008;2(1):26. doi: 10.1186/1753-2000-2-26. PMID: 18817536.
4. Zito JM, Safer DJ, Sai D, et al. Psychotropic medication patterns among youth in foster care. *Pediatrics*. 2008 Jan;121(1):e157-63. doi: 10.1542/peds.2007-0212. PMID: 18166534.
5. Olfson M, King M, Schoenbaum M. Treatment of young people with antipsychotic medications in the United States. *JAMA Psychiatry*. 2015 Sep;72(9):867-74. doi: 10.1001/jamapsychiatry.2015.0500. PMID: 26132724.
6. Zito JM, Derivan AT, Kratochvil CJ, et al. Off-label psychopharmacologic prescribing for children: history supports close clinical monitoring. *Child Adolesc Psychiatry Ment Health*. 2008;2(1):24. doi: 10.1186/1753-2000-2-24. PMID: 18793403.

7. Patten SB, Waheed W, Bresee L. A review of pharmacoepidemiologic studies of antipsychotic use in children and adolescents. *Can J Psychiatry*. 2012 Dec;57(12):717-21. PMID: 23228229.
8. Fraguas D, Correll CU, Merchan-Naranjo J, et al. Efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders: comprehensive review of prospective head-to-head and placebo-controlled comparisons. *Eur Neuropsychopharmacol*. 2011 Aug;21(8):621-45. doi: 10.1016/j.euroneuro.2010.07.002. PMID: 20702068.
9. Panagiotopoulos C, Ronsley R, Elbe D, et al. First do no harm: promoting an evidence-based approach to atypical antipsychotic use in children and adolescents. *J Can Acad Child Adolesc Psychiatry*. 2010 May;19(2):124-37. PMID: 20467549.
10. Pringsheim T, Lam D, Ching H, et al. Metabolic and neurological complications of second-generation antipsychotic use in children: a systematic review and meta-analysis of randomized controlled trials. *Drug Saf*. 2011 Aug 1;34(8):651-68. doi: 10.2165/11592020-000000000-00000. PMID: 21751826.
11. Correll CU, Penzner JB, Parikh UH, et al. Recognizing and monitoring adverse events of second-generation antipsychotics in children and adolescents. *Child Adolesc Psychiatr Clin N Am*. 2006 Jan;15(1):177-206. doi: 10.1016/j.chc.2005.08.007. PMID: 16321730.
12. Rettew DC, Greenblatt J, Kamon J, et al. Antipsychotic medication prescribing in children enrolled in Medicaid. *Pediatrics*. 2015 Apr;135(4):658-65. doi: 10.1542/peds.2014-2260. PMID: 25733747.
13. Birnbaum ML, Saito E, Gerhard T, et al. Pharmacoepidemiology of antipsychotic use in youth with ADHD: trends and clinical implications. *Curr Psychiatry Rep*. 2013 Aug;15(8):382. doi: 10.1007/s11920-013-0382-3. PMID: 23881713.
14. Crystal S, Olfson M, Huang C, et al. Broadened use of atypical antipsychotics: safety, effectiveness, and policy challenges. *Health Aff (Millwood)*. 2009 Sep-Oct;28(5):w770-81. doi: 10.1377/hlthaff.28.5.w770. PMID: 19622537.
15. Schmid I, Burcu M, Zito JM. Medicaid prior authorization policies for pediatric use of antipsychotic medications. *JAMA*. 2015 Mar 3;313(9):966-8. doi: 10.1001/jama.2015.0763. PMID: 25734740.
16. Findling RL, Drury SS, Jensen PS; American Academy of Child and Adolescent Psychiatry. Practice Parameter for the use of Atypical Antipsychotic Medications in Children and Adolescents. 2012. Available at www.aacap.org
17. Seida JC, Schouten JR, Mousavi SS, et al. First- and Second-Generation Antipsychotics for Children and Young Adults. Comparative Effectiveness Review No. 39. AHRQ Publication No. 11(12)-EHC077-EF. Rockville MD: Agency for Healthcare Research and Quality; 2012. Available at www.effectivehealthcare.ahrq.gov
18. Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: AHRQ; 2014. Available at www.effectivehealthcare.ahrq.gov
19. First and Second Generation Antipsychotics for Children and Young Adults-Comparative Effectiveness Review Update Protocol Agency of Healthcare Research and Quality. 2015. <https://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2149>
20. Higgins JP, Green, S. Section 8. Assessing the risk of bias of included studies. In: *Cochrane Handbook for Systematic Reviews of Interventions: The Cochrane Collaboration*; 2011. Available at www.handbook.cochrane.org
21. Wells G, Shea B, O'Connell N, et al. The Newcastle-Ottawa Scale for Assessing the Quality of Nonrandomized Studies in Meta-analyses. Ottawa, ON: Department of Epidemiology and Community Medicine, University of Ottawa 2009.
22. Cornell JE, Mulrow CD, Localio R, et al. Random-effects meta-analysis of inconsistent effects: a time for change. *Ann Intern Med*. 2014 Feb 18;160(4). doi: 10.7326/m13-2886. PMID: 24727843.
23. Sutton AJ, Abrams KR. Bayesian methods in meta-analysis and evidence synthesis. *Stat Methods Med Res*. 2001 Aug;10(4):277-303. doi: 10.1177/096228010101000404. PMID: 11491414.

24. Golder S, Loke YK, Bland M. Meta-analysis of adverse effects data derived from randomised controlled trials as compared to observational studies: methodological overview. *PLoS Med*. 2011;8(5):e1001026. doi: 10.1371/journal.pmed.1001026. PMID: 21559325.
25. Berkman ND, Lohr KN, Ansari M, et al. Grading the strength of a body of evidence when assessing health care interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: an update. In: *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: AHRQ January 2014. Chapters available at www.effectivehealthcare.ahrq.gov.
26. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol*. 2011 Dec;64(12):1283-93. doi: 10.1016/j.jclinepi.2011.01.012. PMID: 21839614.
27. Glenton C, Santesso N, Rosenbaum S, et al. Presenting the results of Cochrane systematic reviews to a consumer audience: a qualitative study. *Med Decis Making*. 2010; 30:566-577. doi: 10.1177/0272989X10375853. PMID: 20643912
28. Storch EA, De Nadai AS, Lewin AB, et al. Defining treatment response in pediatric tic disorders: A signal detection analysis of the Yale Global Tic Severity Scale. *J Child Adolesc Psychopharmacol*. 2011 01 Dec;21(6):621-7. doi: <http://dx.doi.org/10.1089/cap.2010.0149>. PMID: 2012000755.
29. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *J Clin Psychiatry*. 2004 Feb;65(2):267-72. PMID: 15003083.
30. Edelsohn GA, Parthasarathy M, Terhorst L, et al. Measurement of metabolic monitoring in youth and adult Medicaid recipients prescribed antipsychotics. *J Manag Care Spec Pharm*. 2015 Sep;21(9):769-77, 77a-77cc. doi: 10.18553/jmcp.2015.21.9.769. PMID: 26308224.
31. Morrato EH, Druss BG, Hartung DM, et al. Small area variation and geographic and patient-specific determinants of metabolic testing in antipsychotic users. *Pharmacoepidemiol Drug Saf*. 2011 Jan;20(1):66-75. doi: 10.1002/pds.2062. PMID: 21182154.
32. Morrato EH, Druss B, Hartung DM, et al. Metabolic testing rates in 3 state Medicaid programs after FDA warnings and ADA/APA recommendations for second-generation antipsychotic drugs. *Arch Gen Psychiatry*. 2010 Jan;67(1):17-24. doi: 10.1001/archgenpsychiatry.2009.179. PMID: 20048219.

33. Rodday AM, Parsons SK, Mankiw C, et al. Child and adolescent psychiatrists' reported monitoring behaviors for second-generation antipsychotics. *J Child Adolesc Psychopharmacol*. 2015 May;25(4):351-61. doi: 10.1089/cap.2014.0156. PMID: 25918843.
34. De Hert M, Vancampfort D, Correll CU, et al. Guidelines for screening and monitoring of cardiometabolic risk in schizophrenia: systematic evaluation. *Br J Psychiatry*. 2011 Aug;199(2):99-105. doi: 10.1192/bjp.bp.110.084665. PMID: 21804146
35. Ghanizadeh A. Twice-weekly aripiprazole for treating children and adolescents with tic disorder, a randomized controlled clinical trial. *Ann Gen Psychiatry*. 2016;15:21. PMID: 27579050.
36. Safavi P, Hasanpour-Dehkordi A, AmirAhmadi M. Comparison of risperidone and aripiprazole in the treatment of preschool children with disruptive behavior disorder and attention deficit-hyperactivity disorder: A randomized clinical trial. *J Adv Pharm Technol Res*. 2016;7:43-7. PMID: 27144151.
37. Lamberti M, Siracusano R, Italiano D, et al. Head-to-head comparison of aripiprazole and risperidone in the treatment of ADHD symptoms in children with autistic spectrum disorder and ADHD: a pilot, open-label, randomized controlled study. *Pediatr Drugs*. 2016;18: 319-328. PMID: 27278054.
38. Yoon Y, Wink LK, Pedapati EV, et al. Weight gain effects of second-generation antipsychotic treatment in autism spectrum disorder. *J Child Adolesc Psychopharmacol*. 2016 DOI: 10.1089/cap.2016.0049. PMID: 27389348.

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 insurance² and living in foster homes⁴ 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 unspecified 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 Program⁴⁴ 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

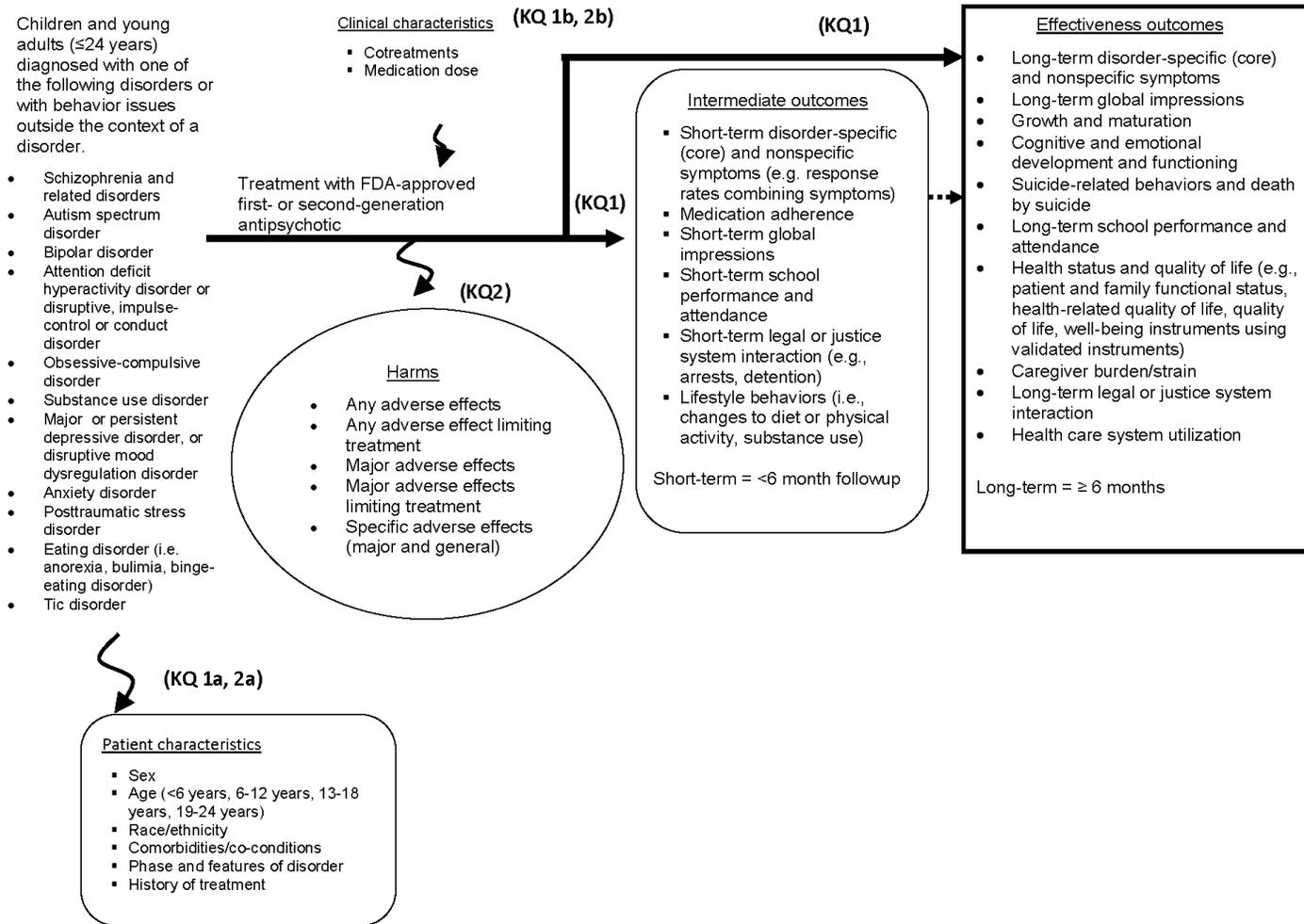
Appendix D: Study Characteristics

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 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 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 $\geq 7\%$ 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 ascertainment) and methodological (i.e., study design, conduct and quality) similarities. We often started with combining 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 guidance⁵⁰ 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 findings 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

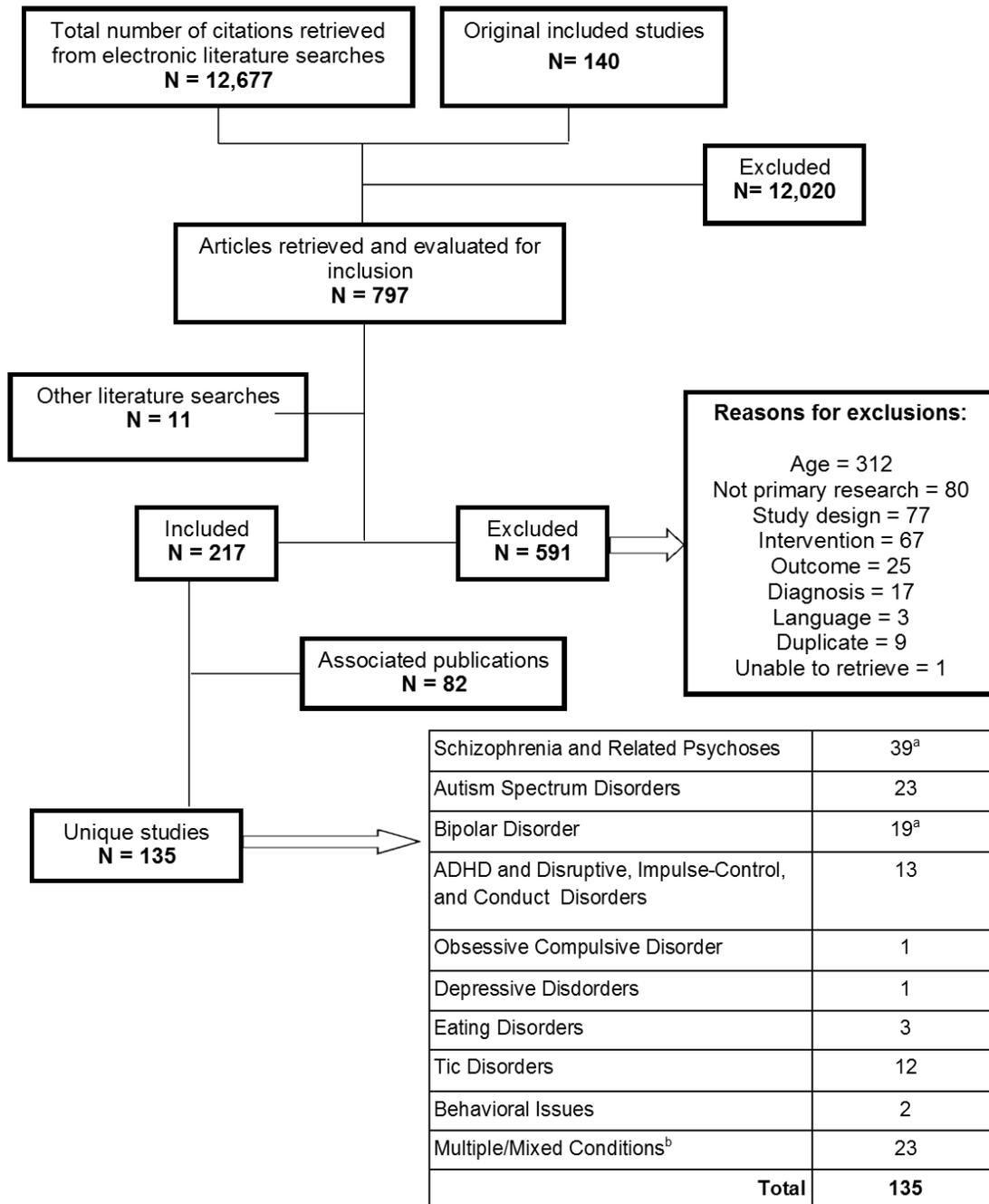
This chapter begins with a summary of our literature search and selection. A description of the characteristics and methodological quality of the studies follows. We then present the findings for intermediate and effectiveness outcomes (Key Question [KQ] 1) using separate sections for each condition 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



ADHD = attention deficit hyperactivity disorder

^a One study provided separate data for both bipolar disorder and schizophrenia; ^bStudies 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
<i>Haloperidol vs. pimozide</i>	2	<i>Aripiprazole vs. olanzapine</i>	3
		<i>Aripiprazole vs. paliperidone</i>	1
FGAs vs. SGAs	27	<i>Aripiprazole vs. quetiapine</i>	3
<i>Chlorpromazine vs olanzapine</i>	1	<i>Aripiprazole vs. risperidone</i>	8
<i>Haloperidol vs. aripiprazole</i>	1	<i>Aripiprazole vs. various SGAs</i>	1
<i>Haloperidol vs. clozapine</i>	3	<i>Aripiprazole vs. ziprasidone</i>	3
<i>Haloperidol vs. olanzapine</i>	8	<i>Clozapine vs. olanzapine</i>	7
<i>Haloperidol vs. risperidone</i>	5	<i>Clozapine vs. quetiapine</i>	1
<i>Molindone vs. olanzapine</i>	1	<i>Clozapine vs. risperidone</i>	3
<i>Molindone vs. risperidone</i>	1	<i>Olanzapine vs. quetiapine</i>	11
<i>Pimozide vs. aripiprazole</i>	2	<i>Olanzapine vs. risperidone</i>	22
<i>Pimozide vs. risperidone</i>	2	<i>Olanzapine vs. ziprasidone</i>	3
<i>Various FGAs vs. various SGAs</i>	3	<i>Quetiapine vs. risperidone</i>	13
		<i>Quetiapine vs. ziprasidone</i>	2
		<i>Risperidone vs various SGAs</i>	2
		<i>Risperidone vs. ziprasidone</i>	1

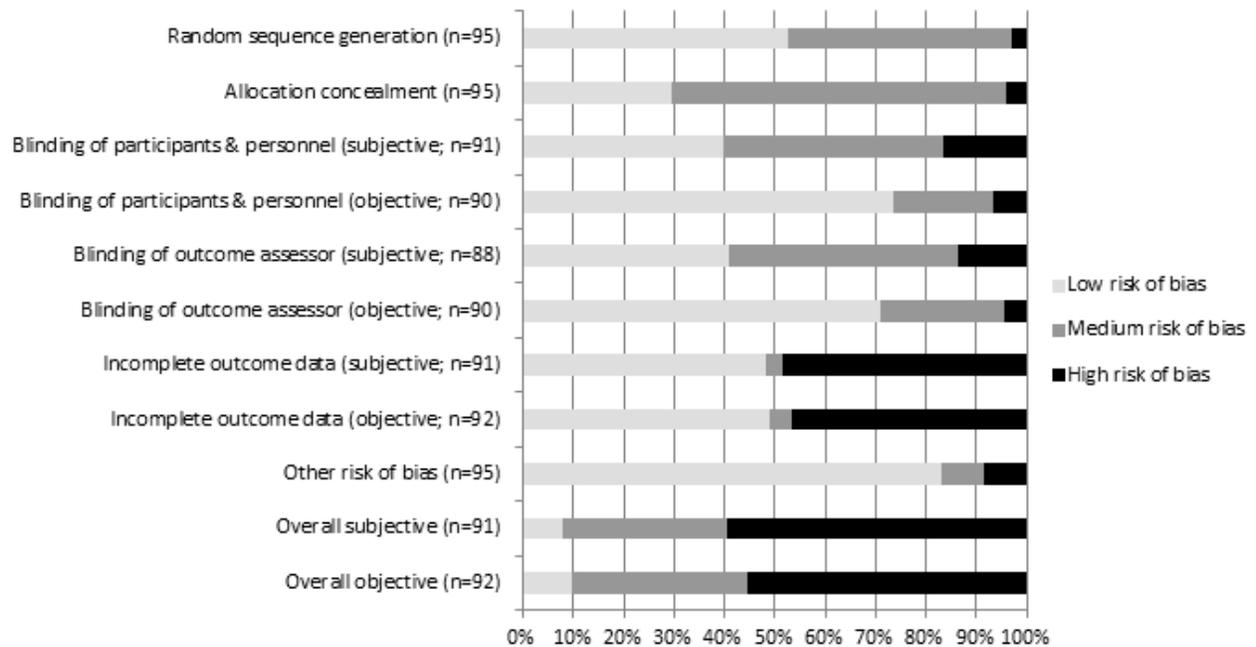
FGA = first-generation antipsychotic; SGA = second-generation antipsychotic

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.

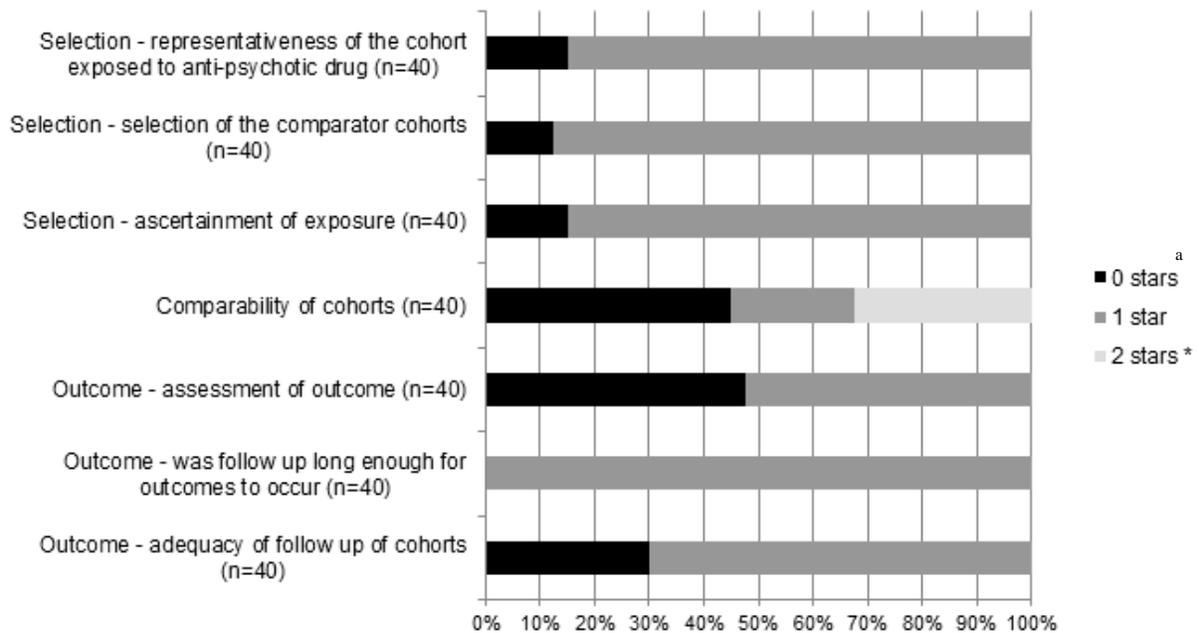
For subjective outcomes in trials, the overall ROB was rated as high for 60 percent; only eight were assessed as low ROB. The ROB reduced to a small extent for objective outcomes. The main contributor to ROB was incomplete outcome data, which has rated as high ROB when drop-out/incompletion rates were ≥ 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., $\geq 30\%$ 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 \pm SD	Age, Mean \pm 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 \pm 8 mg/day G2: Clozapine (10), 176 \pm 149 mg/day	G1: 13.7 \pm 1.6 yr / Male: 55% / White: NR G2: 14.4 \pm 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 \pm 2.8 yr / Male: NR / White: NR G2: 21 \pm 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: Olanzapine (12), up to 20 mg/day	G1: 16.2 \pm 2.0 yr / 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 \pm 2 mg/day G2: Olanzapine (16), 12.3 \pm 3.5 mg/day G3: Risperidone (19), 4 \pm 1.2 mg/day	G1: 15.4 \pm 2.2 yr / Male: 53% / White: 73% G2: 14.6 \pm 3.1 yr / Male: 56% / White: 63% G3: 14.6 \pm 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 schizophrenia (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

^aAll 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 naïve 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 study⁹⁹): 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 cohort⁹⁹): 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 paliperidone⁹⁴, clozapine and olanzapine^{78, 80, 98}, olanzapine and quetiapine⁷⁴, 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 ziprasidone⁶⁵): 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 RCT⁸³): 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 ziprasidone⁷¹): 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 1.97 ^{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

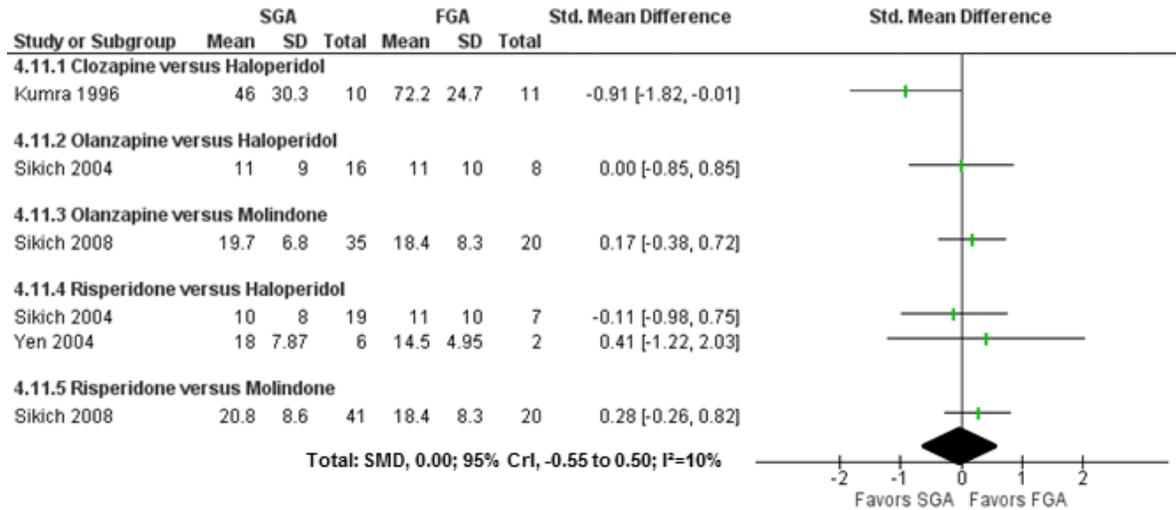
Seven studies provided data on intermediate outcomes for the following FGA versus SGA comparisons: haloperidol versus clozapine,⁷⁷ haloperidol versus olanzapine,^{70, 82, 91, 99} haloperidol versus risperidone,^{82, 87, 99} molindone versus olanzapine,⁸¹ and molindone versus risperidone.⁸¹ The comparisons between SGAs and molindone from one study⁸¹ 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]).

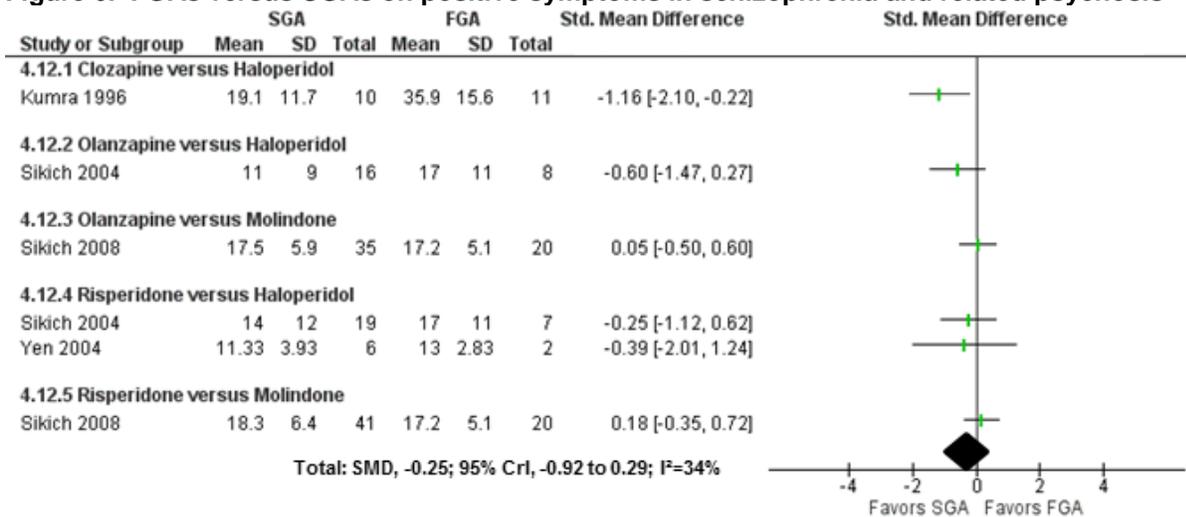
Short-term core symptoms. Two meta-analyses of four studies found no significant differences between SGAs and FGAs on the negative (SMD, 0.0; 95% CrI, -0.55 to 0.50) or positive (SMD, -0.25; 95% CrI, -0.92 to 0.29) symptom scores of the PANSS, CPRS, and Scale for the Assessment of Negative Symptoms (SANS) (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

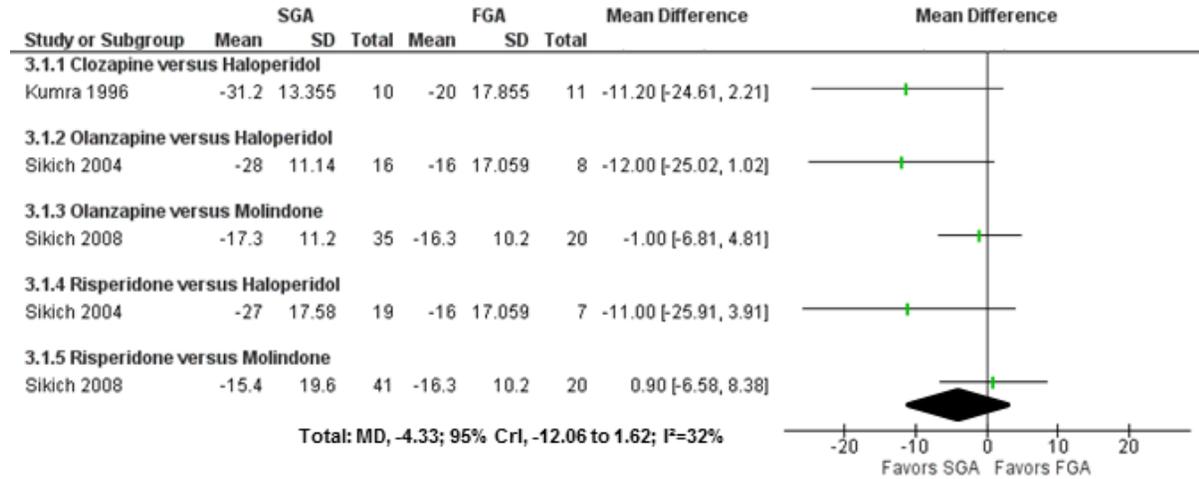
Figure 6. FGAs versus SGAs on positive symptoms in schizophrenia and related psychosis



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.

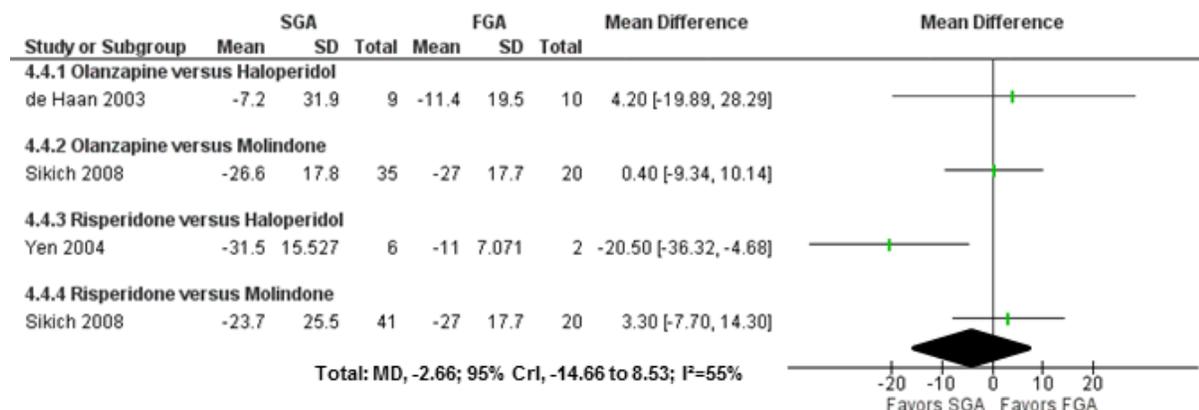
Figure 7. FGAs versus SGAs for psychiatric symptoms on BPRS in schizophrenia and related psychosis



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

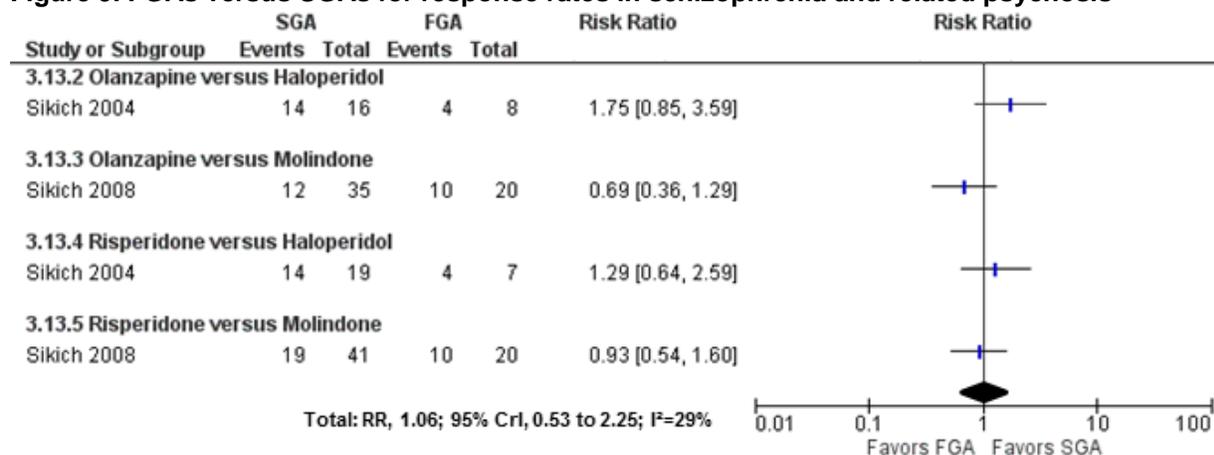
Figure 8. FGAs versus SGAs for schizophrenia symptoms using PANSS total score in schizophrenia and related psychosis



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

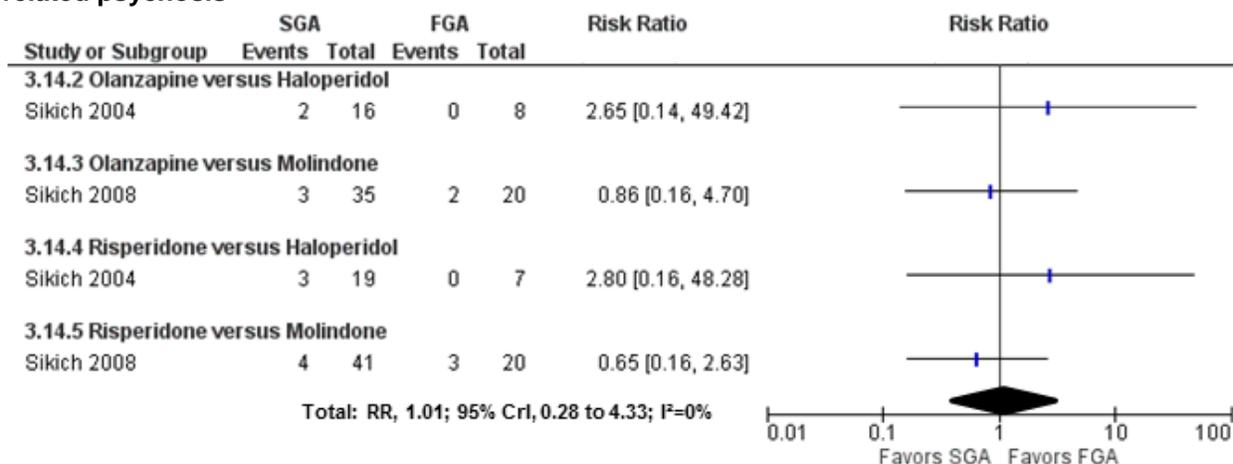
A meta-analysis was performed using data from four comparisons in two trials comparing response rates for SGAs and FGAs (Figure 9).^{81, 82} No difference was found (RR, 1.10; 95% CrI, 0.53 to 2.27). Another meta-analysis pooled data on discontinuations due to lack of efficacy from the same two trials,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

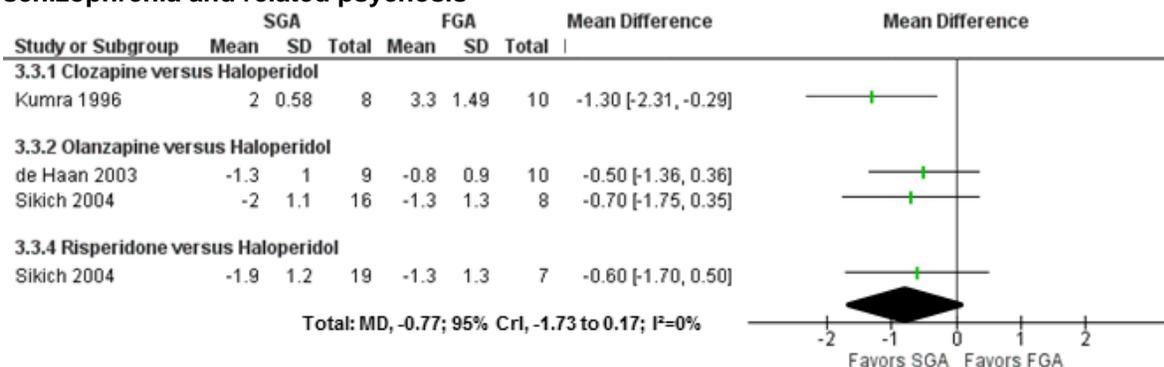
Figure 10. FGAs versus SGAs for discontinuation due to lack of efficacy in schizophrenia and related psychosis



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

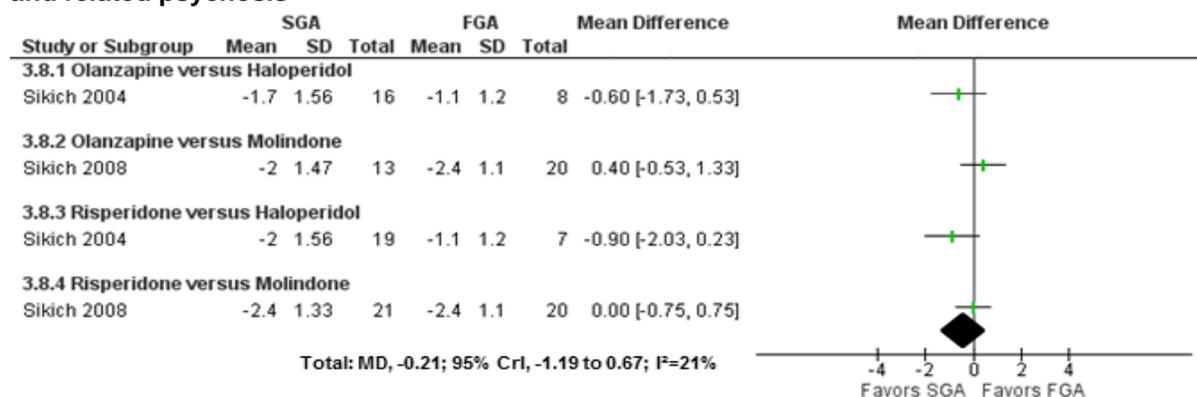
Short-term global impressions. Three RCTs provided data for a meta-analysis on the efficacy of FGAs versus SGAs on global impressions of improvement using the CGI-I (Figure 11).^{70, 77, 82} The pooled estimate was not significant for any difference (MD, -0.77; 95% CrI, -1.73 to 0.17). Two RCTs with 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

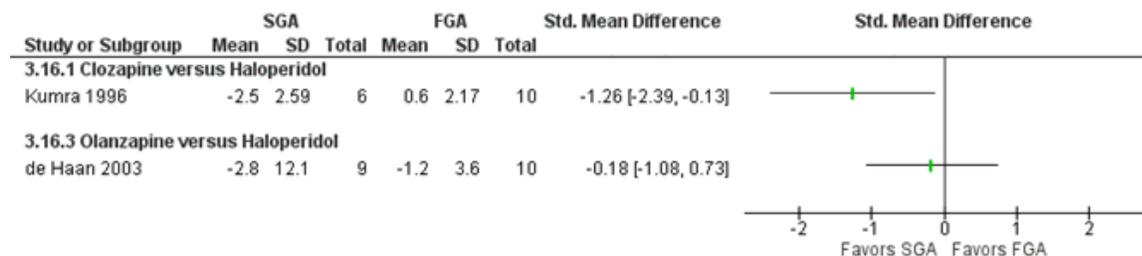


CGI-S = Clinical Global Impressions–Severity; CrI = credible interval; FGA = first-generation antipsychotic; MD = mean difference; SD = standard deviation; SGA = second-generation antipsychotic

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-Åsberg Depression Rating Scale⁷⁰ and the BPRS⁷⁷ (Figure 13). Clozapine had a favorable effect over haloperidol in the study of treatment-resistance conducted by Kumra et al.⁷⁷

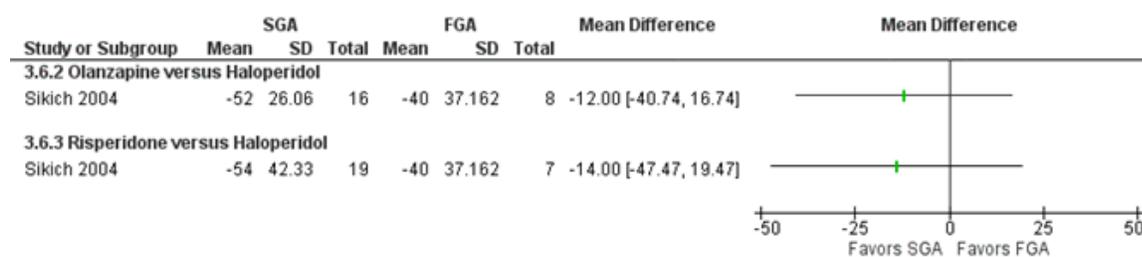
Figure 13. FGAs versus SGAs on depression symptoms in schizophrenia and related psychosis



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 clozapine⁷⁷ 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 haloperidol⁸² 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.

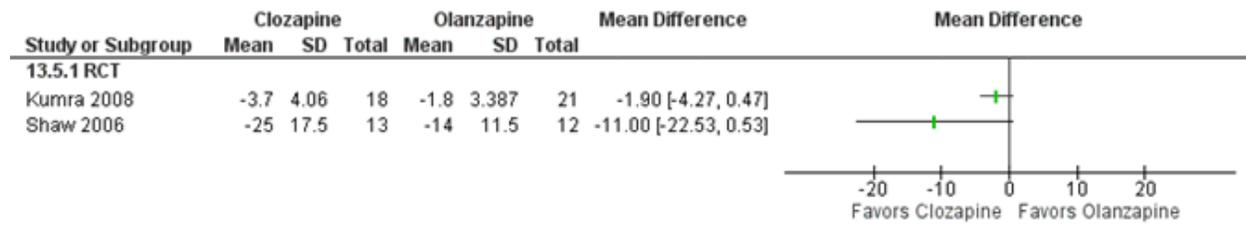
Aripiprazole Versus Paliperidone

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 12⁷⁸ 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

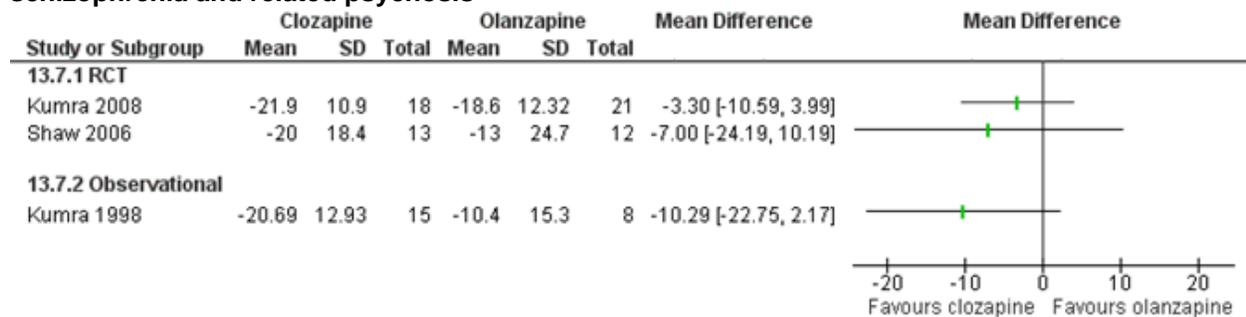
Figure 15. Clozapine versus olanzapine for negative symptoms on SANS in schizophrenia and related psychosis



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

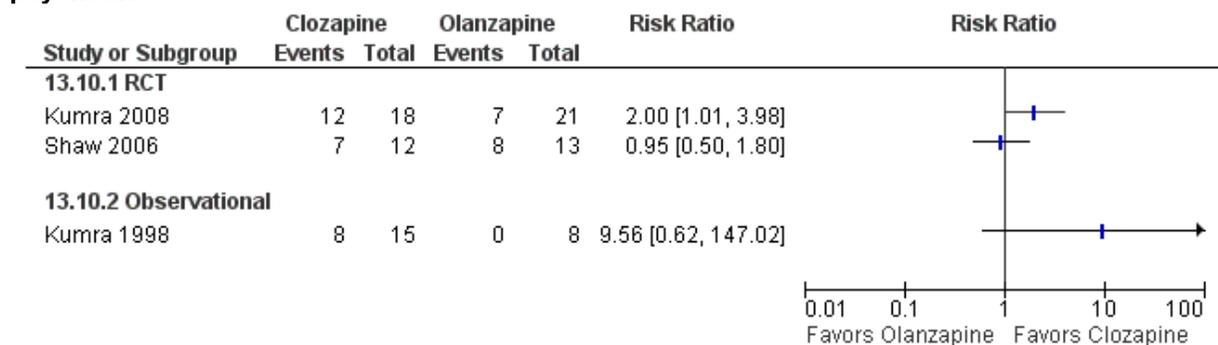
Short-term nonspecific symptoms. All three studies comparing clozapine with olanzapine reported on nonspecific symptom reduction for overall psychiatric symptoms (BPRS) and for response rates (Figures 16 and 17).^{78, 80, 98} No significant differences between the drugs were found when using the BPRS ($p = 0.38$,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

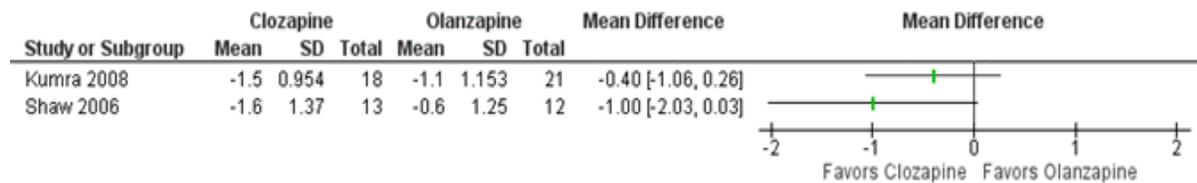


RCT = randomized controlled trial

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 ($p = 0.24$).

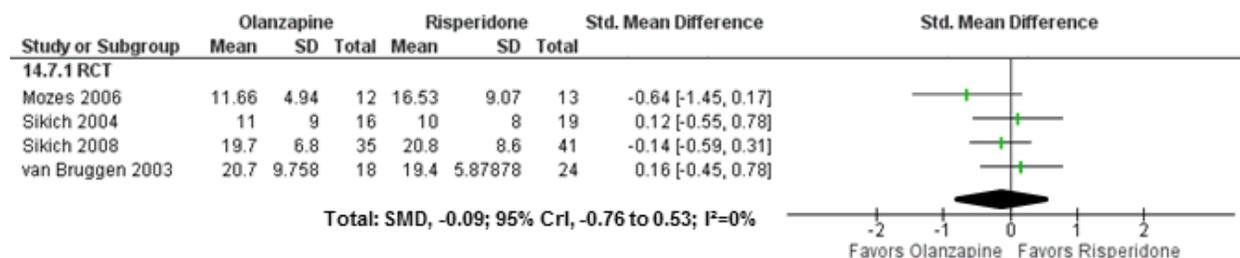
Olanzapine Versus Risperidone

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.

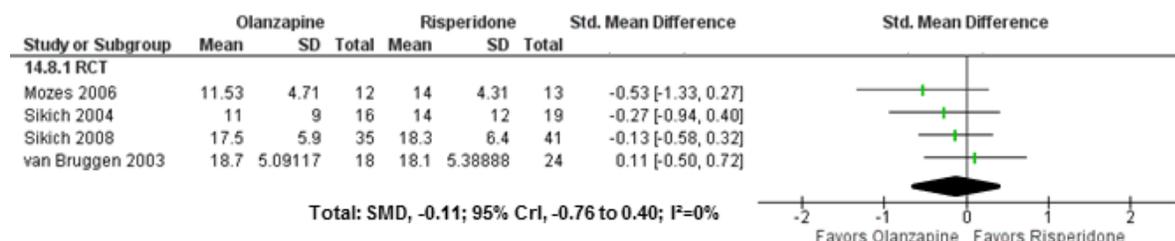
Short-term core symptoms. Two meta-analyses were conducted for negative and positive symptoms; SMDs were generated for these outcomes using data from PANSS and CPRS measures (Figures 19 and 20).^{79, 81, 82, 85} Results found no difference between olanzapine and risperidone for these outcomes (negative 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

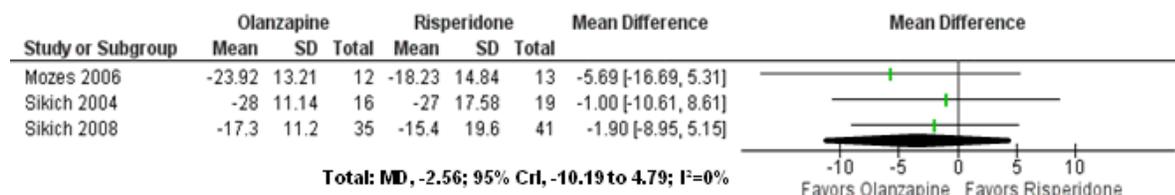
Figure 20. Olanzapine versus risperidone for positive symptoms in schizophrenia and related psychosis



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).

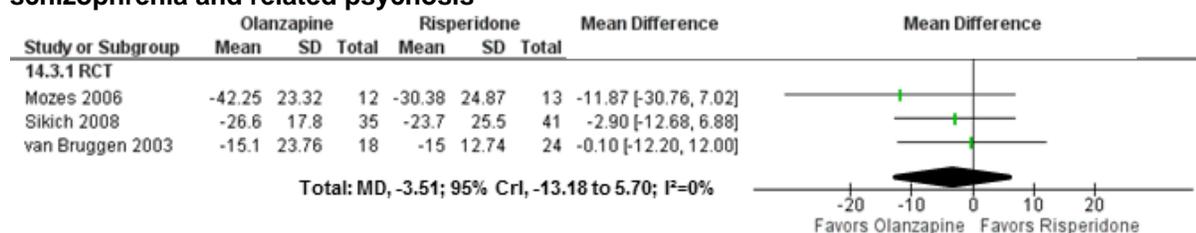
Figure 21. Olanzapine versus risperidone for psychiatric symptoms on BPRS in schizophrenia and related psychosis



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

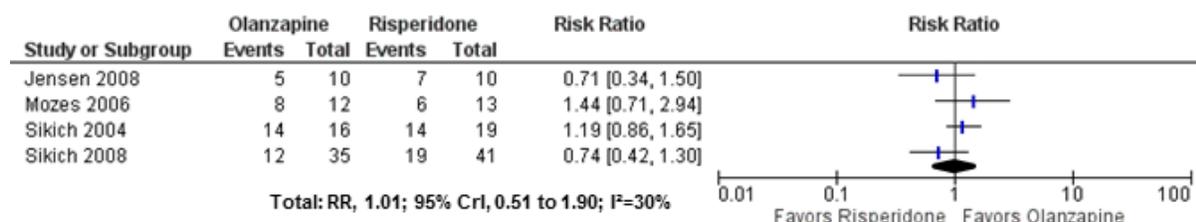
Three meta-analyses were generated for outcomes of schizophrenia symptoms (PANSS total score), response rates, and discontinuation due to lack of efficacy (Figures 22-24). There were no differences between these SGAs for these nonspecific outcomes. Data from the RCT by Jensen et al.⁷⁵ was not sufficient 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 study⁹⁹ 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



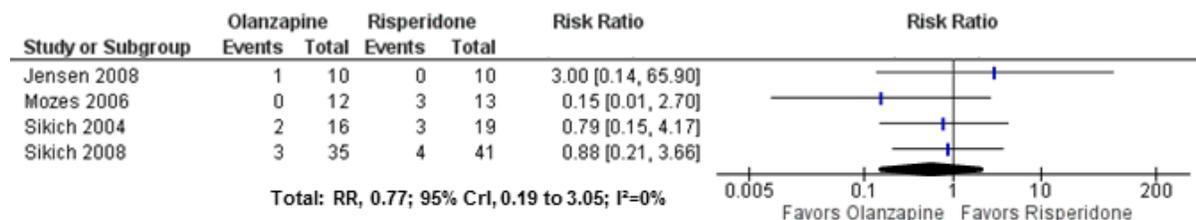
CrI = credible interval; MD = mean difference; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SD = standard deviation

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

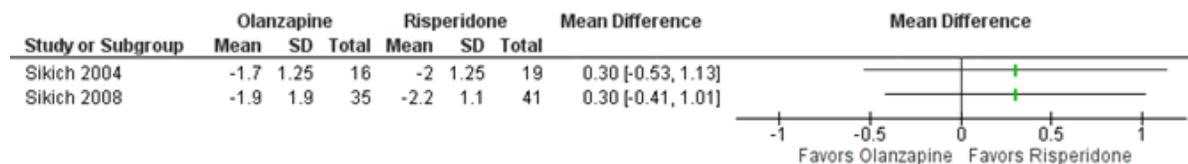


CrI = credible interval; RR = risk ratio

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 RCT⁸⁴ (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 study⁷⁵ 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

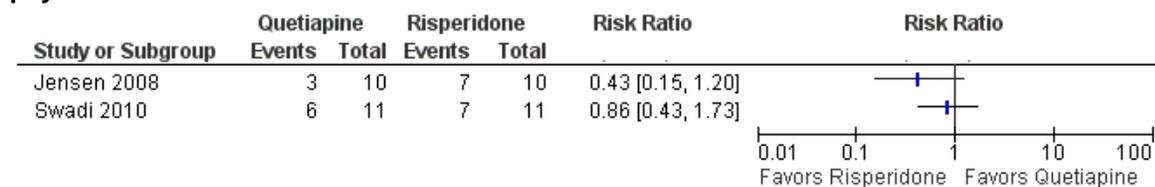
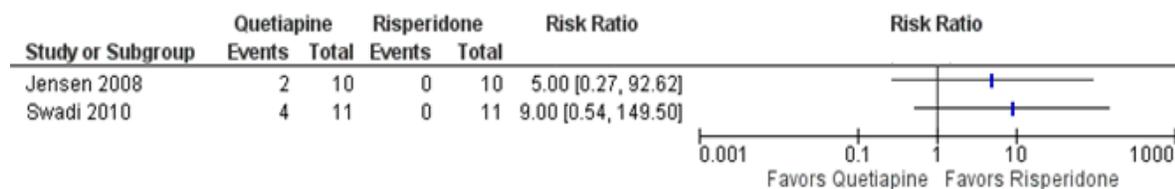


Figure 27. Quetiapine versus risperidone on discontinuation due to lack of efficacy in schizophrenia and related psychosis



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 study⁹⁵ 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.

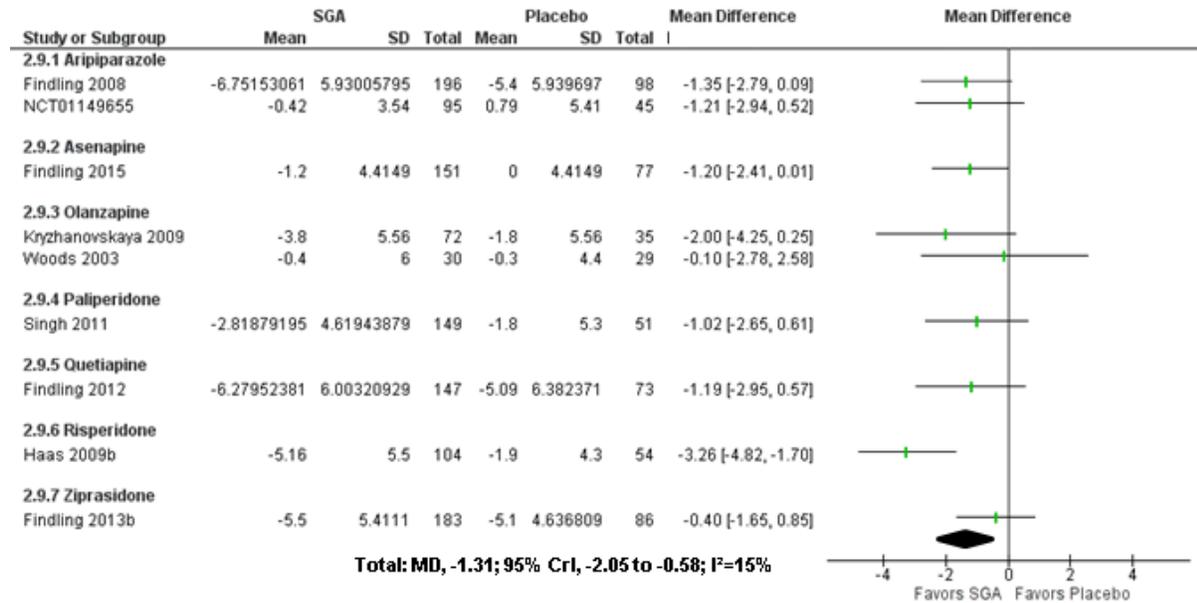
When a study had two or more arms with patients taking different doses of the same drug, we combined data from all arms; the studies in general did not report any difference in effect between doses of the same drug. We realize this strategy may mask a greater or lesser effect when prescribing lower or 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 drug⁹⁵ 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 (NCT01149655⁹⁵) did not change the

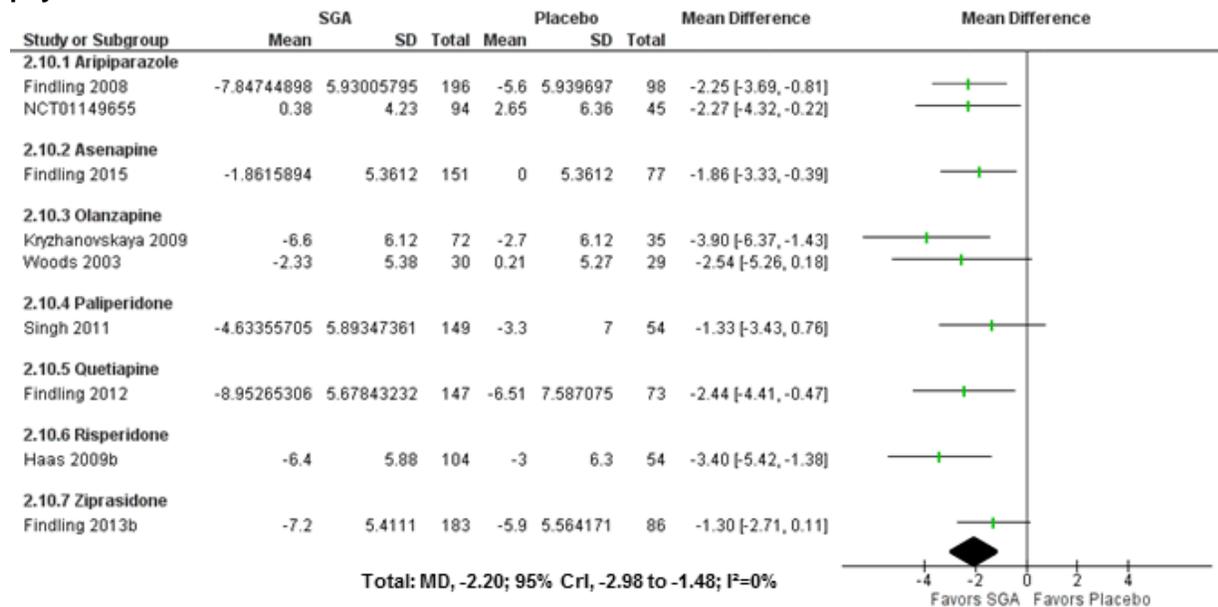
results in a meaningful manner for negative or positive symptoms (MD, -1.41; 95% CrI, -2.38 to -0.51 and MD, -2.19; 95% CrI, -3.18 to -1.31, respectively).

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

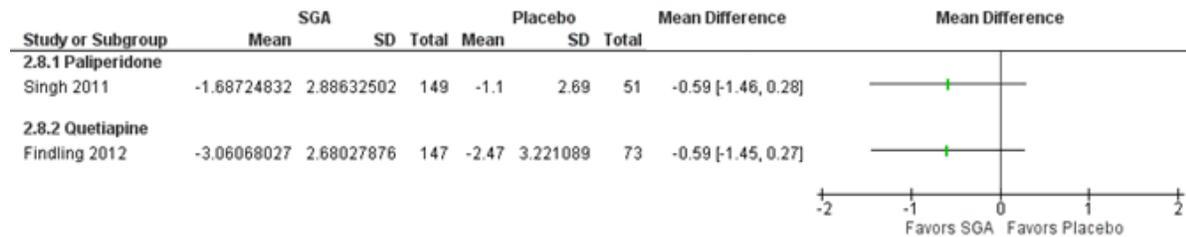
Figure 29. SGAs versus placebo for positive symptoms on PANSS in schizophrenia and related psychosis



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.

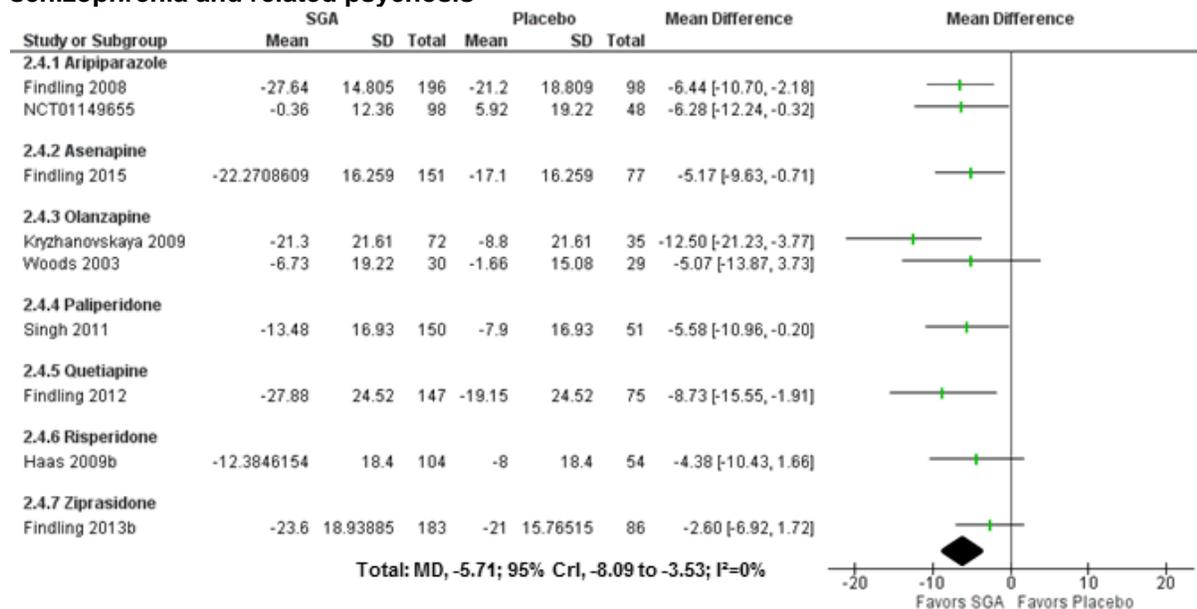
Figure 30. SGAs versus placebo for depressive symptoms on PANSS in schizophrenia and related psychosis



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

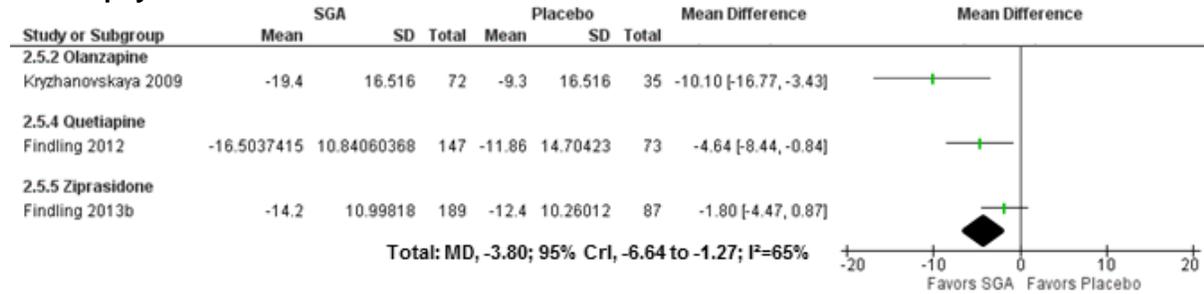


CrI = credible interval; MD = mean difference; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; SGA = second generation antipsychotic

Three RCTs compared SGAs (olanzapine,⁷⁶ ziprasidone,⁷¹ and quetiapine⁷²) 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.

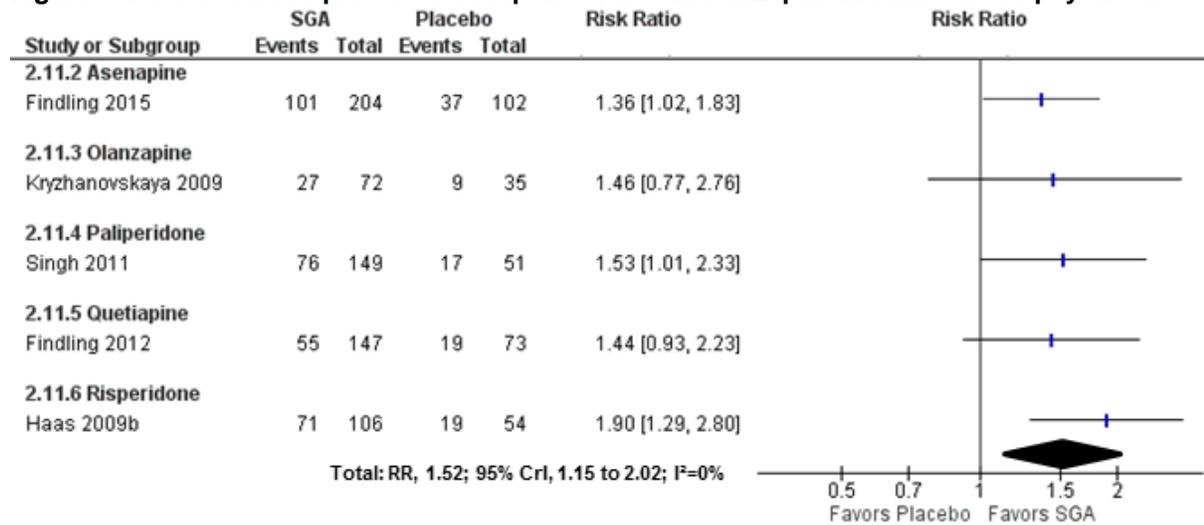
Figure 32. SGAs versus placebo for overall psychiatric symptoms on BPRS in schizophrenia and related psychosis



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

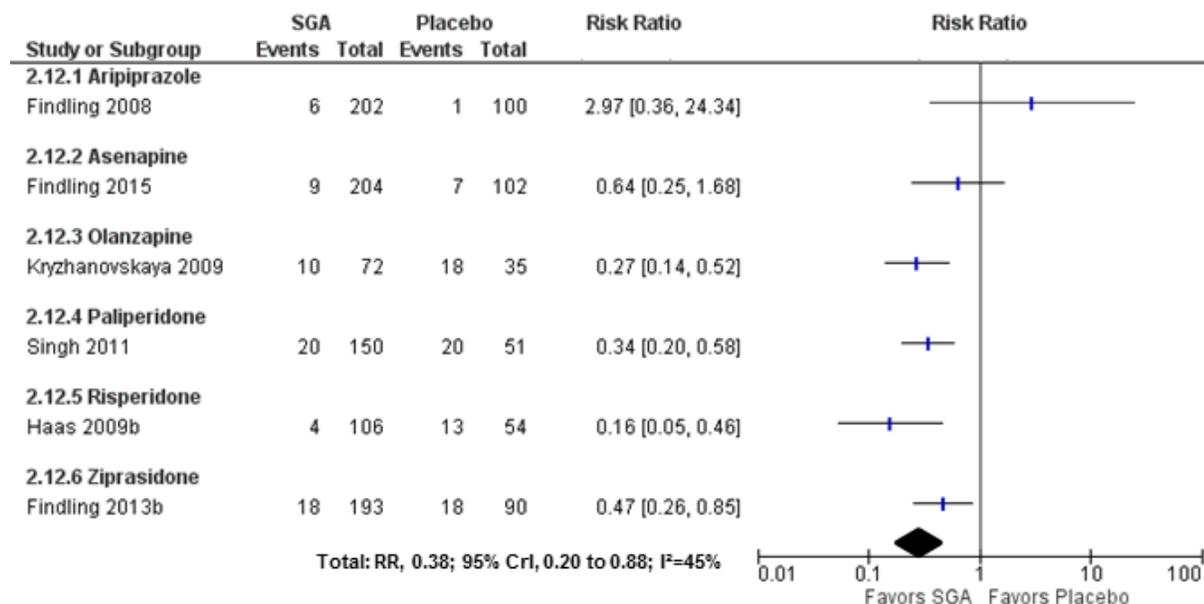
Five RCTs reported response rates for SGAs versus placebo (Figure 33).^{72, 76, 88, 90, 92} The estimated RR was 1.52 (95% CrI, 1.15 to 2.02) showing greater response for SGAs compared with placebo. Data from six RCTs also found the SGAs favorable over placebo for having lower rates of discontinuation 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

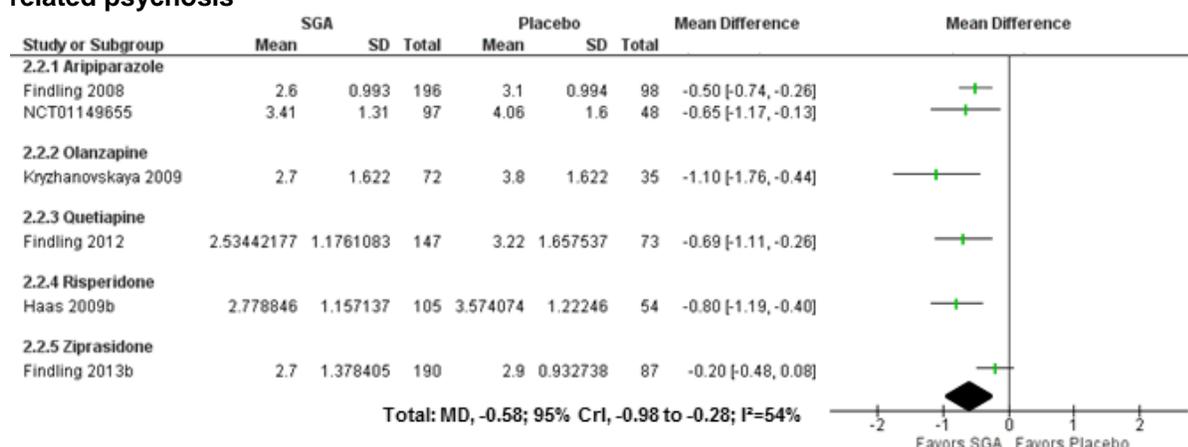
Figure 34. SGAs versus placebo for discontinuation due to lack of efficacy in schizophrenia and related psychosis



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 ziprasidone⁷¹ 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 (NCT01149655⁹⁵) 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

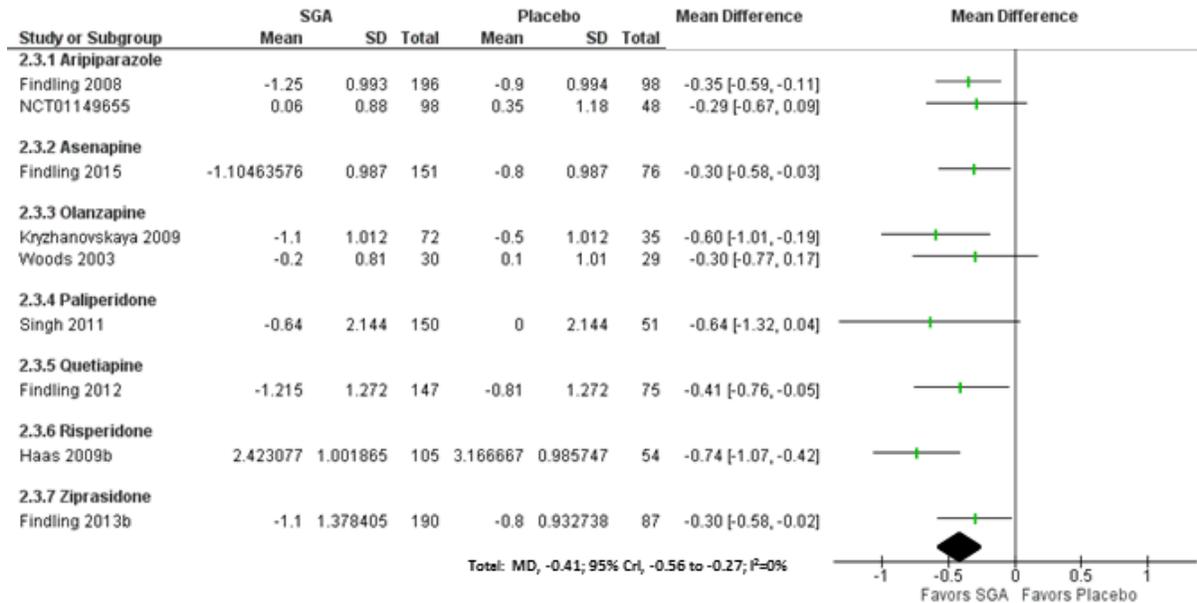


CGI-I = Clinical Global Impression of Improvement; CrI = credible interval; MD = mean difference; SD = standard deviation; SGA = second generation antipsychotic

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 (Woods⁸⁶ and NCT01149655⁹⁵) did not affect the results appreciably (MD, -0.38; 95% CrI, -0.58 to -0.21).

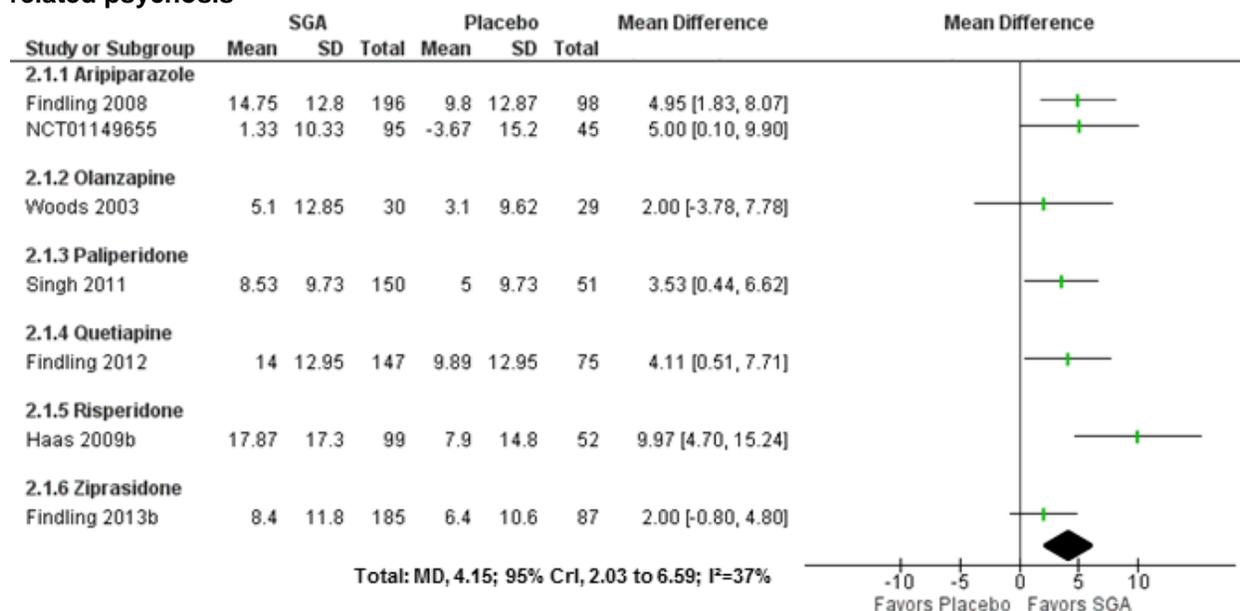
Figure 36. SGAs versus placebo for symptom severity using the CGI-S in schizophrenia and related psychosis



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 ziprasidone⁷¹ 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).

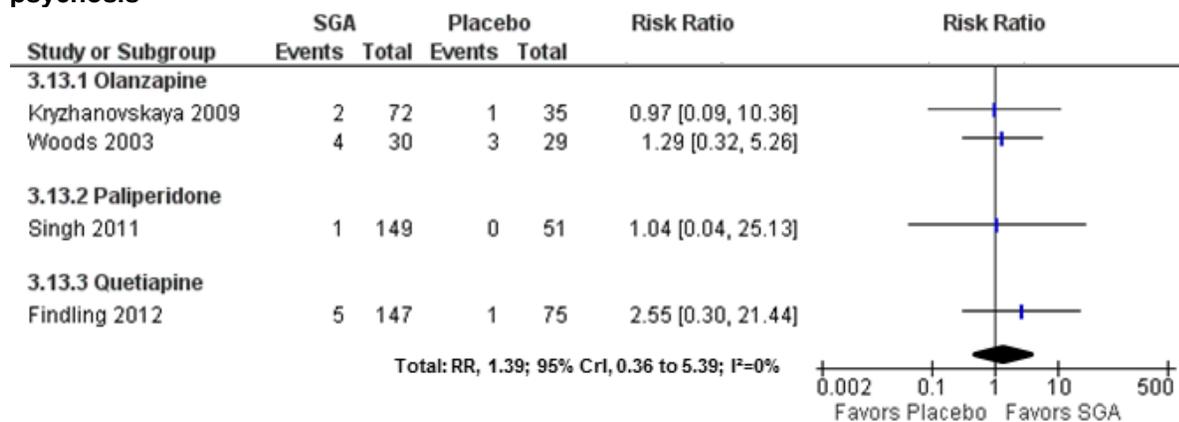
Figure 37. SGAs versus placebo for global functioning using the C-GAS in schizophrenia and related psychosis



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 quetiapine⁷² 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

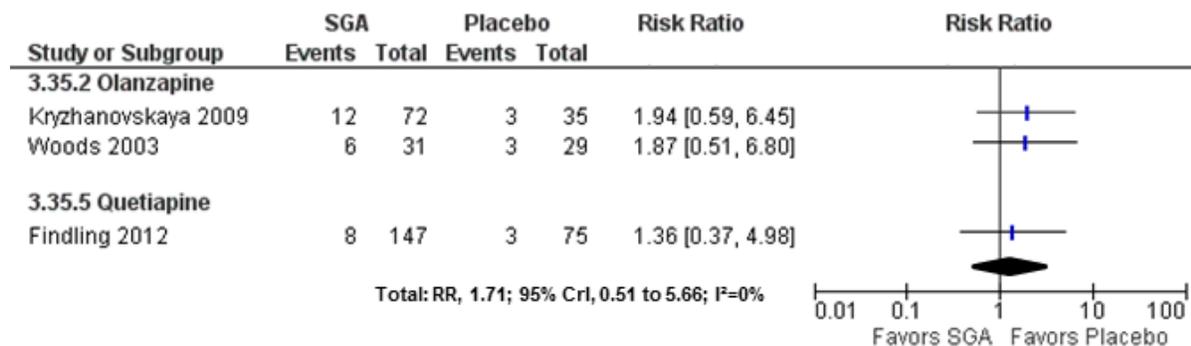


CrI = credible interval; RR = risk ratio; SGA = second-generation antipsychotic

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 cohort¹⁰²): 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 RCT⁹⁴), olanzapine versus quetiapine (one RCT⁶⁷), olanzapine versus risperidone (one RCT⁸¹ and three observational studies^{101, 102, 104}), risperidone versus quetiapine (two observational studies^{101, 104}), clozapine versus other SGAs (one prospective cohort¹⁰²). 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 risperidone⁸⁸): 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

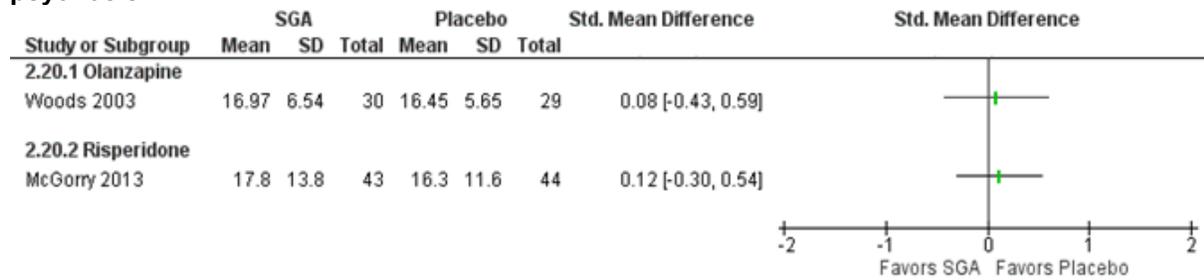
Results on Effectiveness Outcomes From Short- and Long-Term Studies

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 ($p = 0.22$).

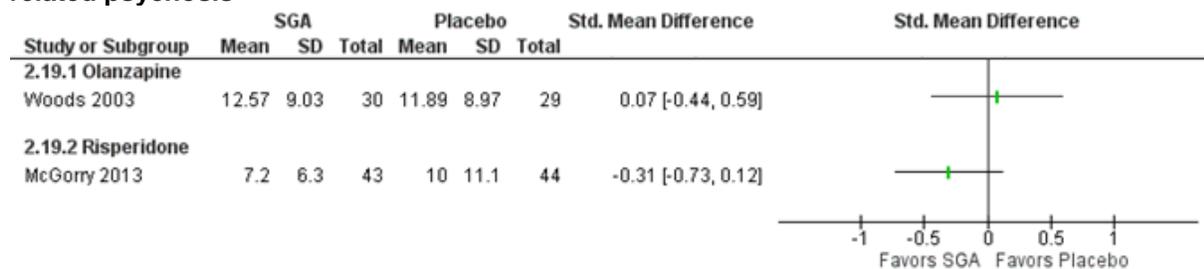
There were no differences between olanzapine and placebo groups for changes in positive symptoms in patients experiencing prodrome ($p = 0.44$).⁸⁶ Figures 40 and 41 present data on negative (PANNS and SANS) and depression (Hamilton Depression Rating Scale and Montgomery-Asberg Depression Rating Scale) 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

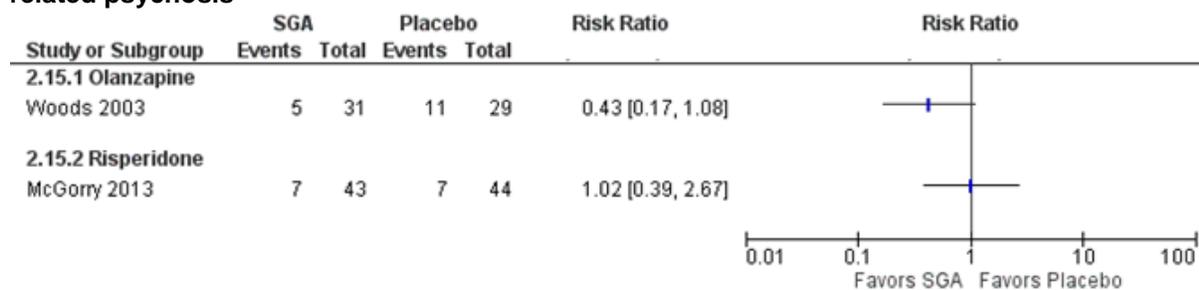


SD = standard deviation; SGA = second-generation antipsychotic

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 $\geq 20\%$ 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

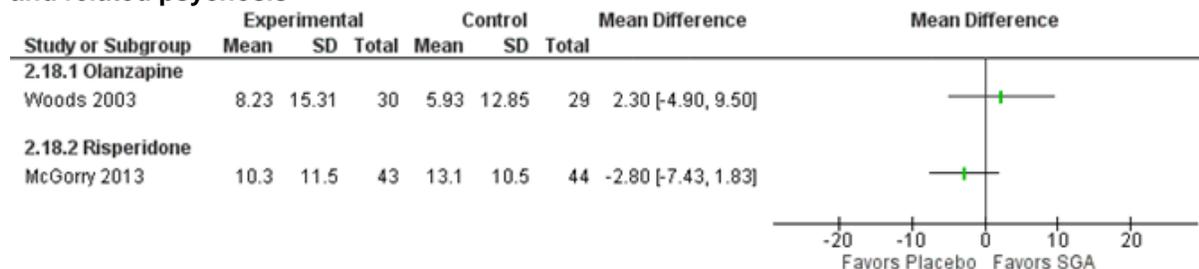


SGA = second-generation antipsychotic

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 ziprasidone⁷¹ or quetiapine⁷² 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 <i>Paliperidone ER vs aripiprazole</i>	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 <i>Haloperidol vs. olanzapine vs. risperidone</i>	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 <i>Haloperidol vs. placebo</i>	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 <i>Olanzapine vs. placebo</i>	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 olanzapine¹¹³ 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 severity.
- **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 ziprasidone⁶⁵): 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 study¹⁰⁶ 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 ADHD¹²¹ 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 Risperidone 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}

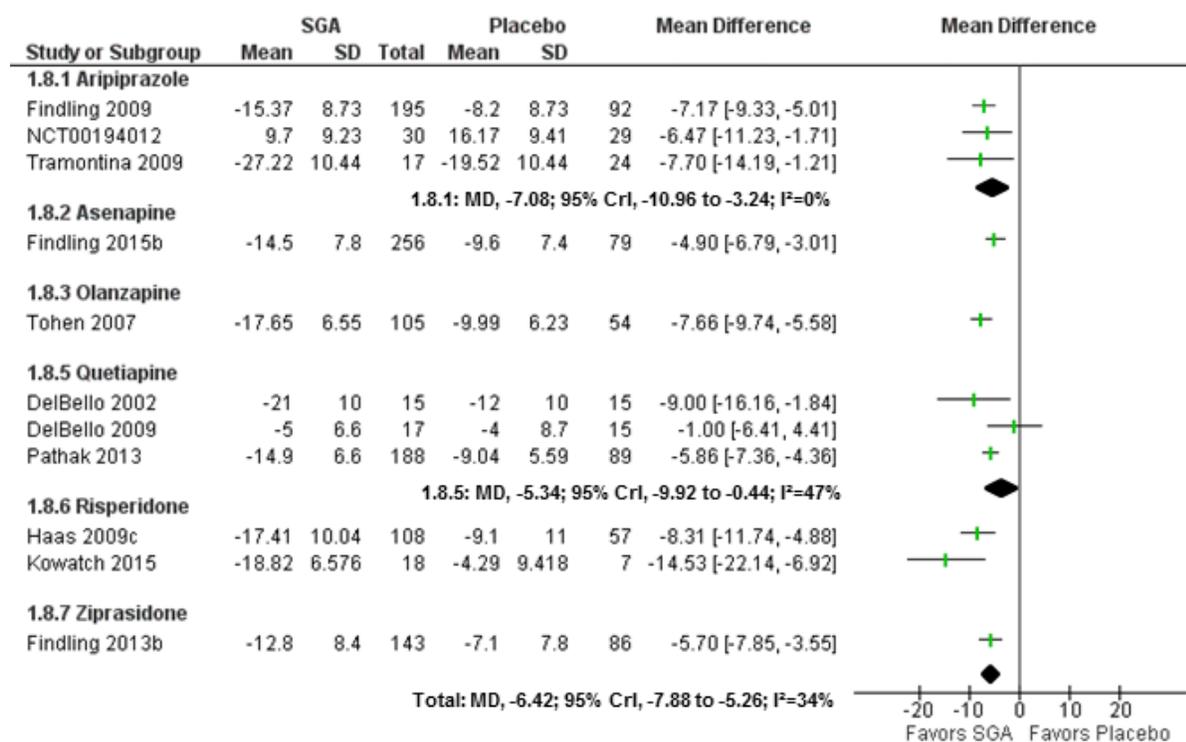
Meta-Analysis for SGAs Versus Placebo in Bipolar Disorder

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 (NCT00194012¹⁰⁶). 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.

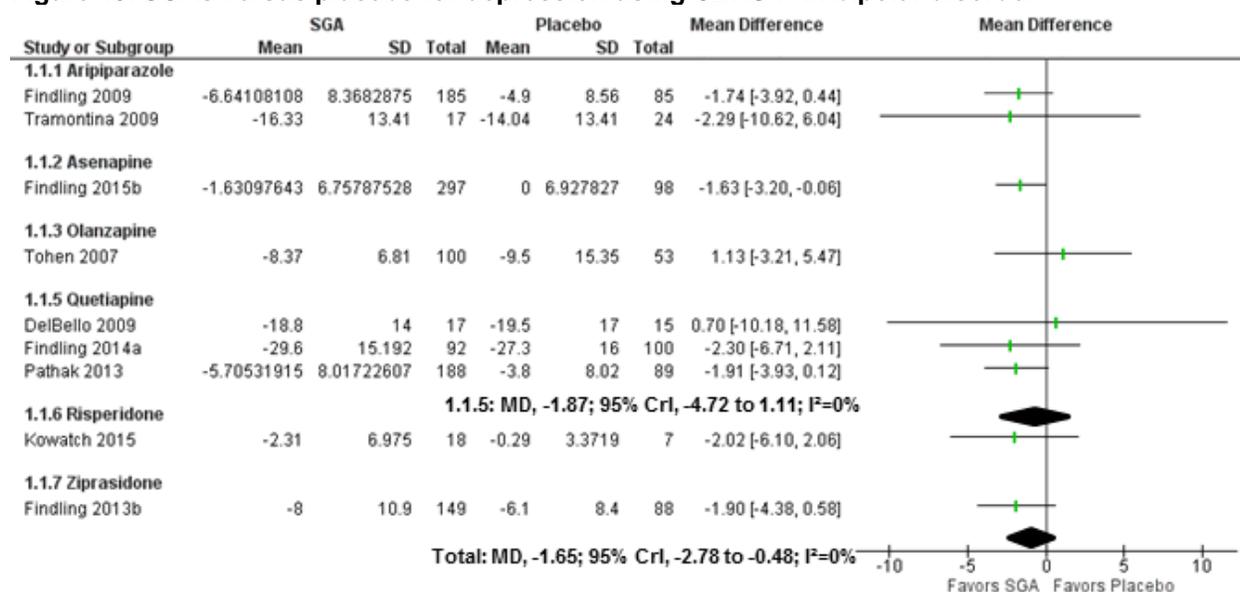
Figure 44. SGAs versus placebo for manic symptoms using YMRS in bipolar disorder



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; I² = 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; I² = 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



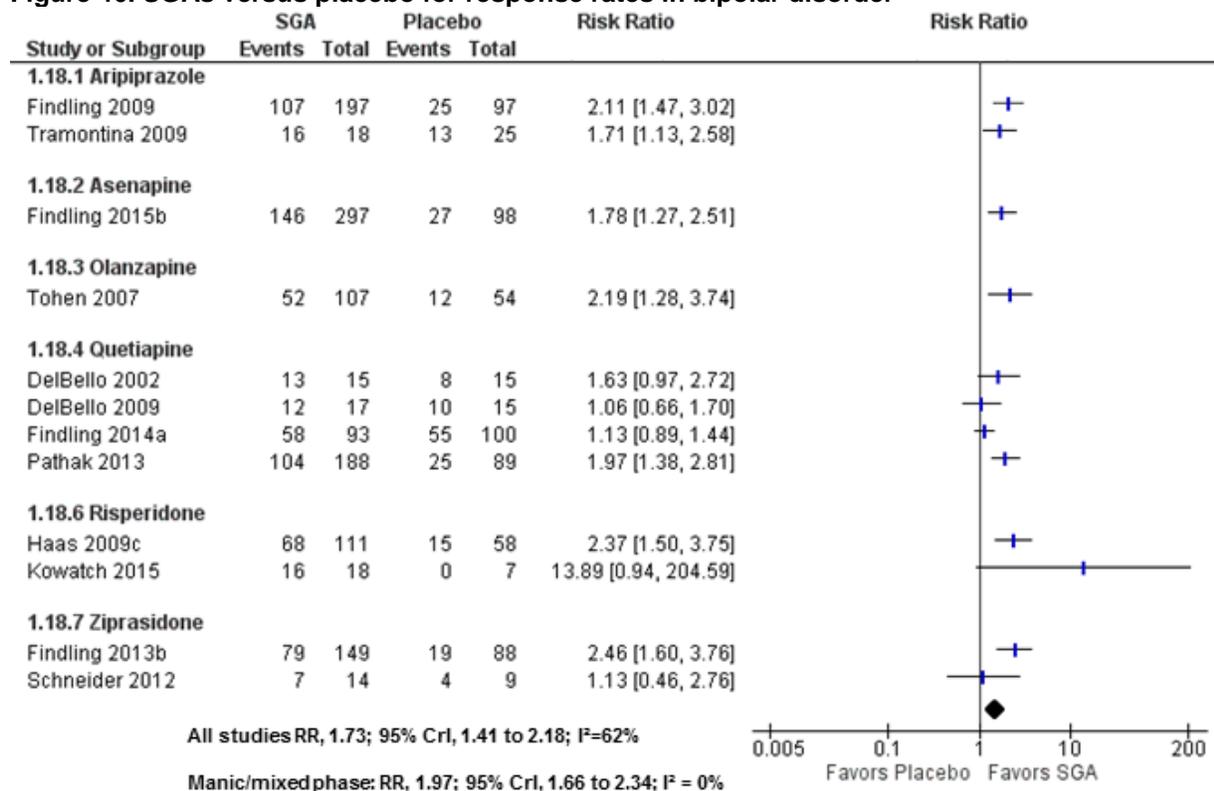
CDRS-R = Children’s Depression Rating Scale-Revised; CrI = credible interval; MD = mean difference; SD = standard deviation; SGA = second-generation antipsychotic

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 (I² = 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 (I²) was reduced from 72 percent to 42 percent.

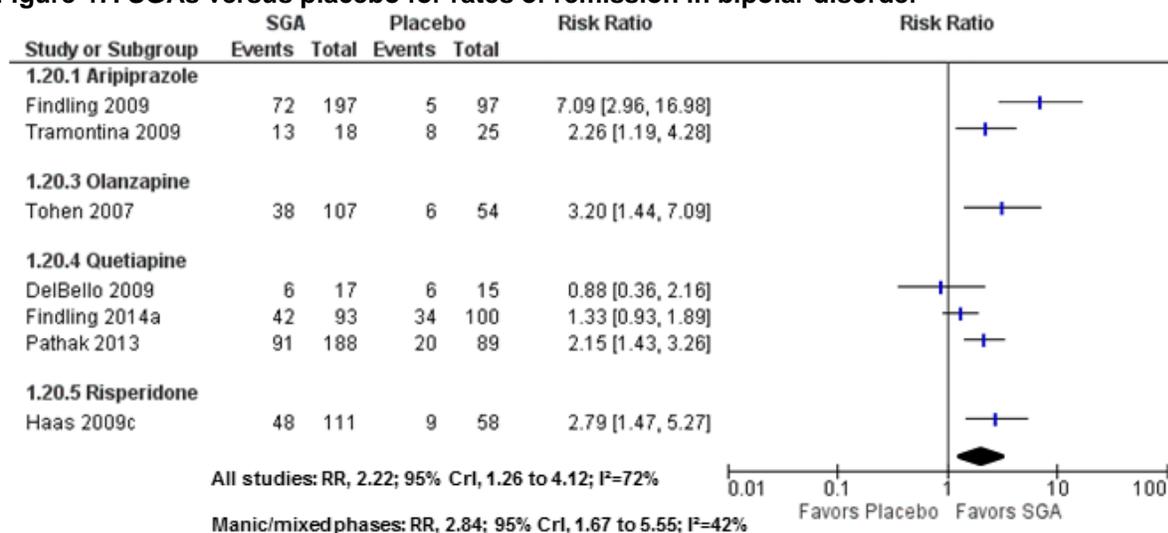
Nine studies provided data for meta-analysis of discontinuation due to lack of efficacy (Figure 48). Results favored SGAs over placebo (RR, 0.37; 95% CrI, 0.23 to 0.61; I² = 0%); there was no effect from removing the DelBello¹¹⁴ and Findling¹⁰⁹ studies. Individual meta-analysis for aripiprazole^{106, 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



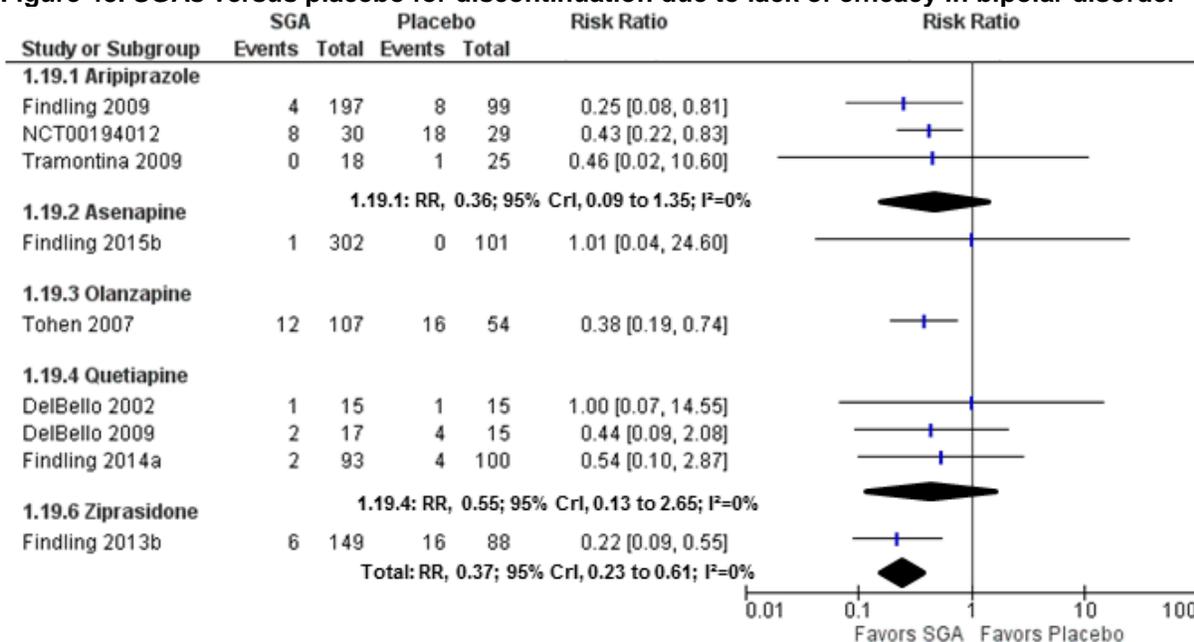
CrI = credible interval; RR = risk ratio; SGA = second-generation antipsychotic

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

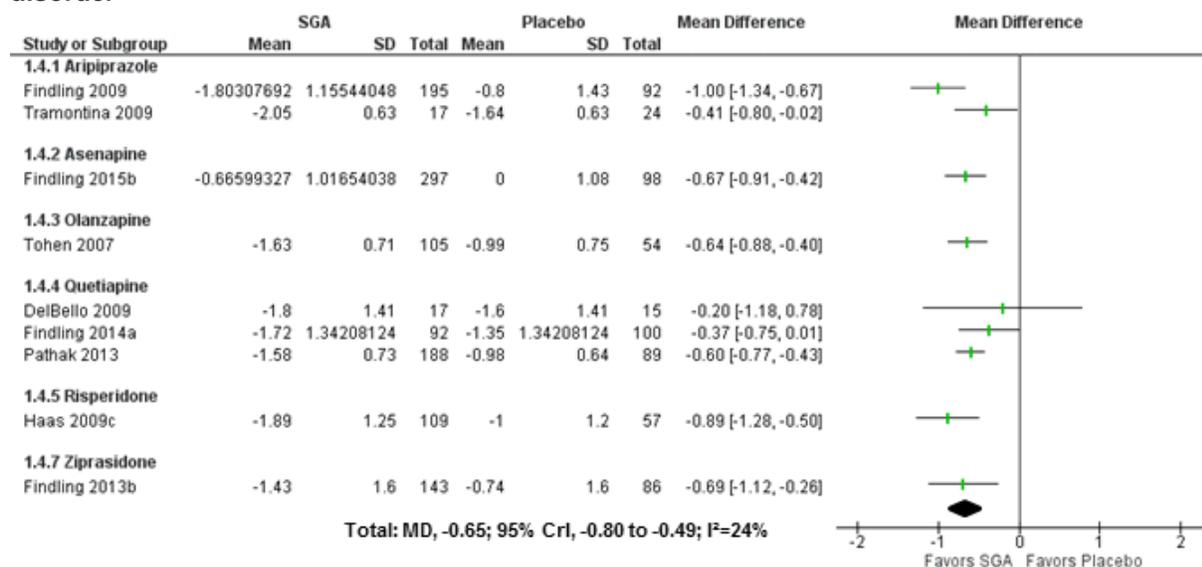


CrI = credible interval; RR = risk ratio; SGA = second-generation antipsychotic

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; I² = 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; I² = 20%).

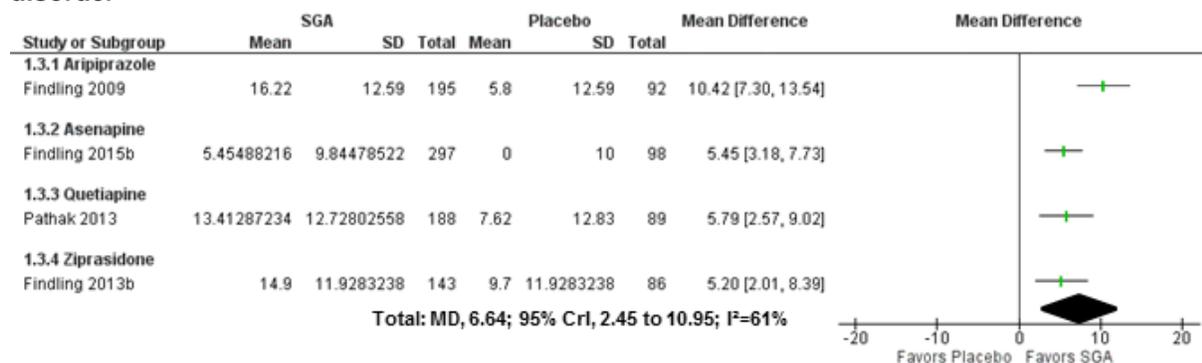
Four studies provided data for SGAs versus placebo on global impressions of functioning, measured using the C-GAS (Figure 50).^{108, 116, 117, 119} The SGAs were favorable over placebo for improving overall functioning (MD, 6.64; 95% CrI, 2.45 to 10.95). There was moderate statistical heterogeneity (I² = 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

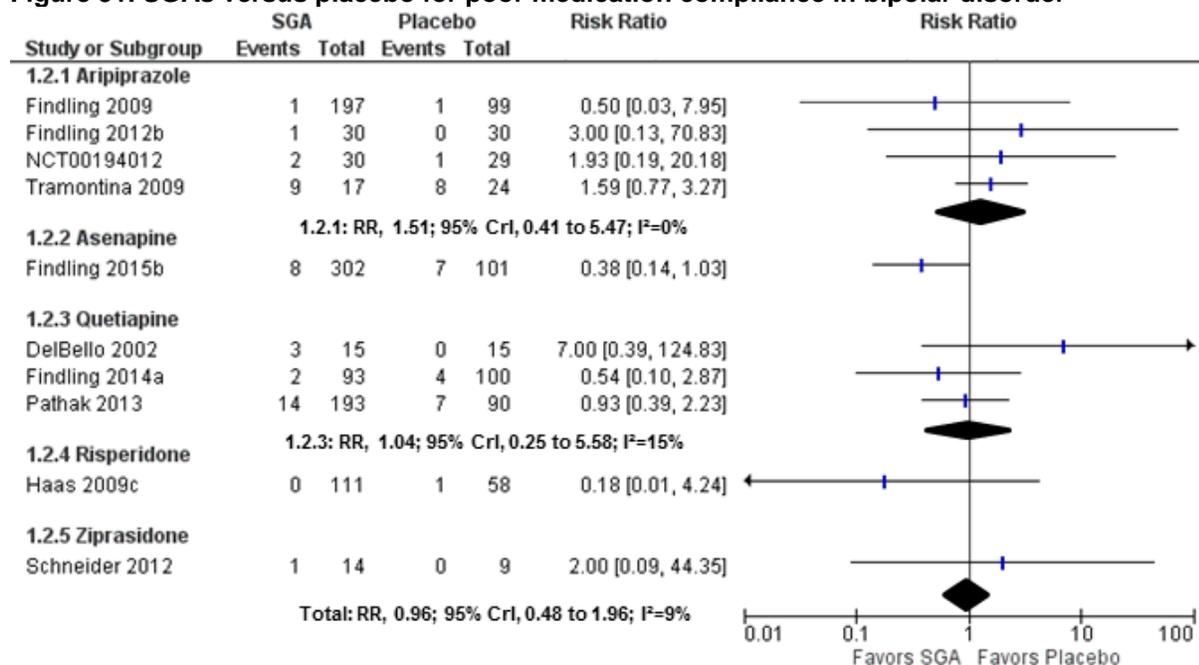
Figure 50. SGAs versus placebo for global impression of functioning using C-GAS in bipolar disorder



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.

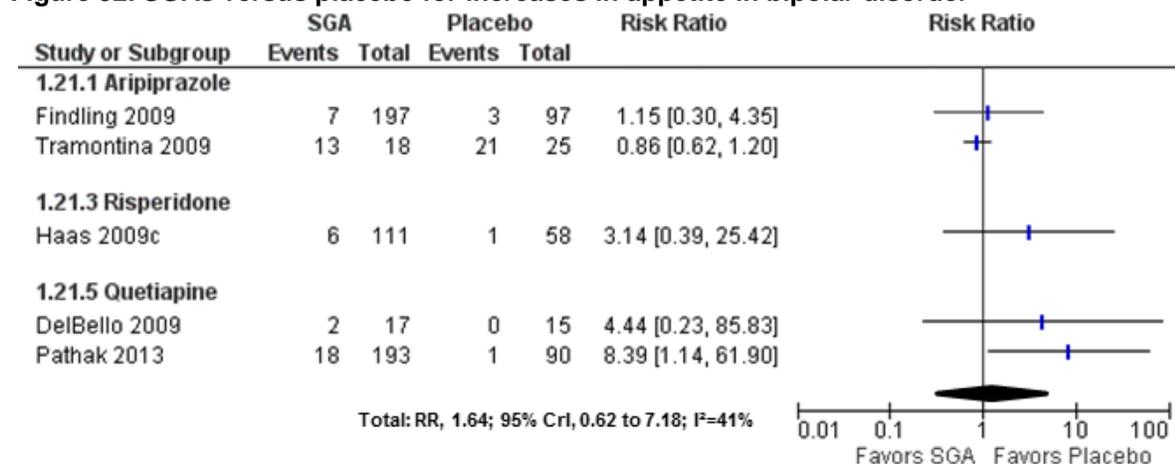
Figure 51. SGAs versus placebo for poor medication compliance in bipolar disorder



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 disorder¹⁰⁶ 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 cohort¹⁰⁷): 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 ziprasidone¹¹⁶): 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 chlorpromazine-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 cyclothymia 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.

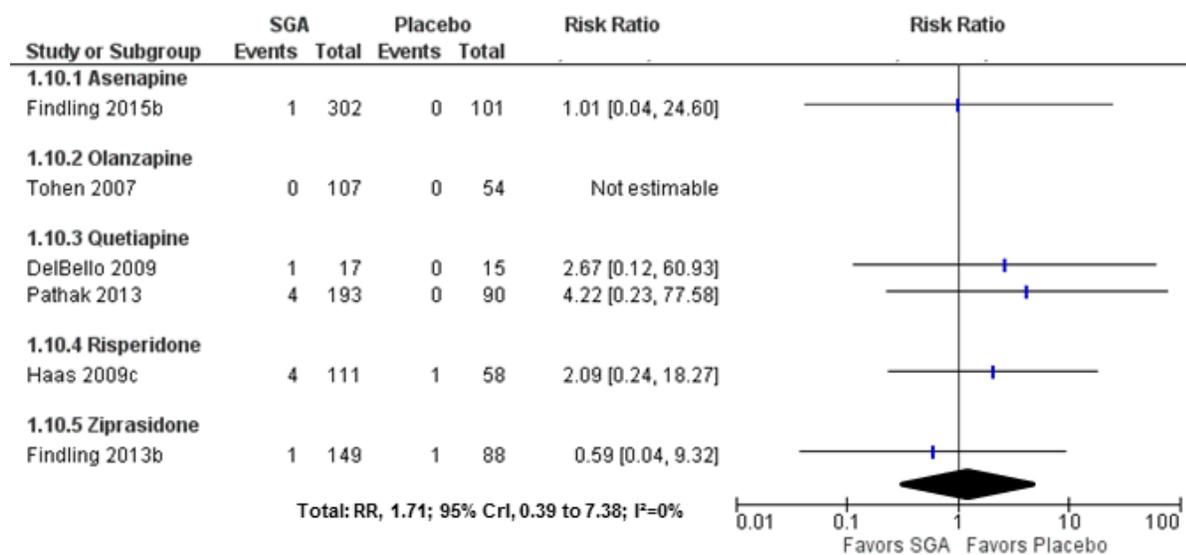
Long-term global impressions and functioning. Low and high doses of aripiprazole significantly favored placebo for global impressions of severity (CGI-BP overall illness; $p < 0.05$) and functioning (CGAS; $p < 0.05$).¹¹⁷ For aripiprazole versus risperidone and quetiapine, no between group differences 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 RCTs¹¹⁶⁻¹¹⁸ 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.

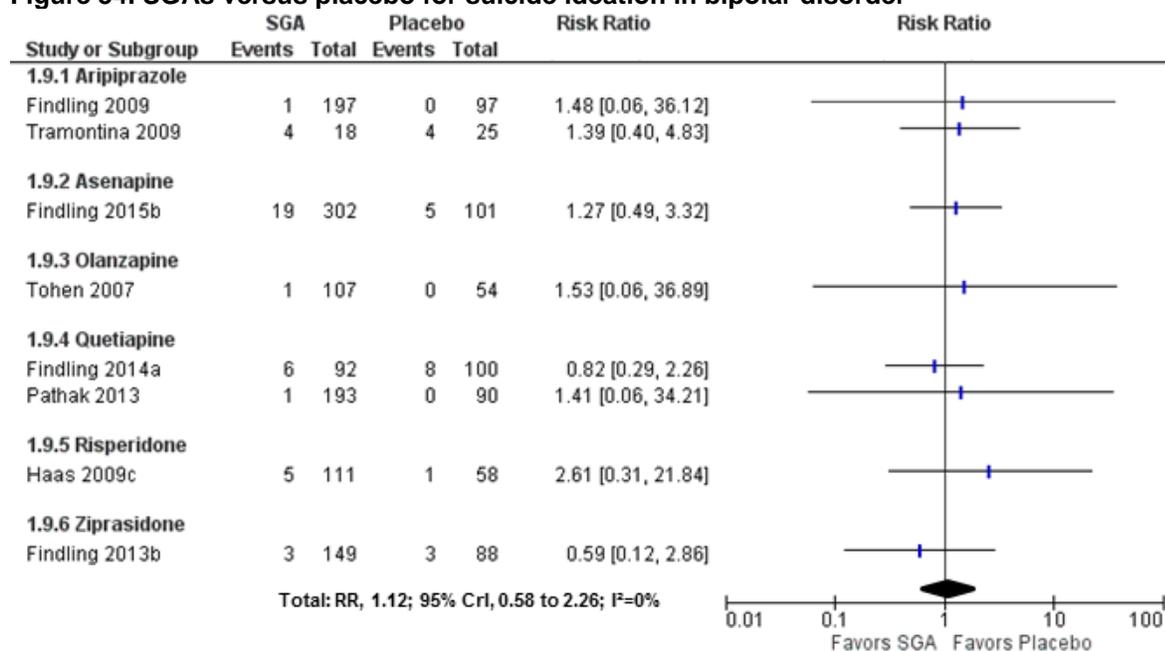
Eight short-term RCTs^{108, 109, 116-121} comparing SGAs with placebo reported rates of suicidal ideation (Figure 54). The pooled estimate showed no significant difference between the groups (RR, 1.12; 95% CrI, 0.58 to 2.26). One study found no difference between ziprasidone and placebo for self-injurious 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 manic¹¹⁷⁻¹¹⁹ and depression¹⁰⁹ 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 study¹²⁰ 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 of 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 <i>Olanzapine versus placebo</i>	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 RCT¹³⁶ 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% G3: 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)	autistic 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	autistic 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 RCT¹²⁴): 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** (aripiprazole¹³¹, lurasidone¹²⁷ and risperidone¹²⁸): 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 study¹⁴¹): 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/day¹³² vs. 1.2¹³⁹ and 1.25-1.75¹²⁸ 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 SGAs¹²⁴ 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 study¹⁴¹ 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.

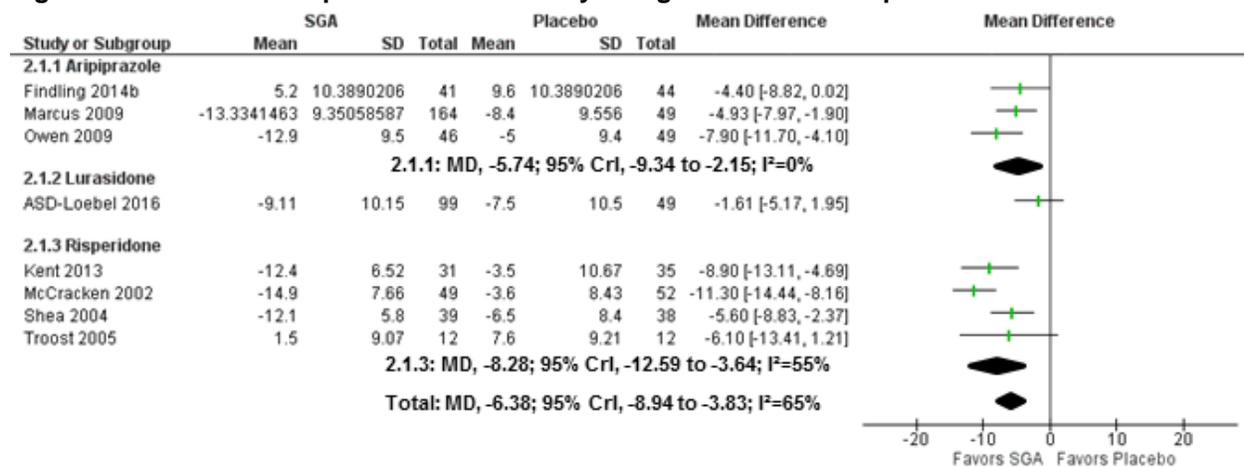
Meta-Analysis for SGAs Versus Placebo in Autism Spectrum Disorders

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 2014b¹²³, RUPP 2005¹³⁸, and Troost 2005¹⁴⁰). 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 aripiprazole¹³¹ and two doses of lurasidone (20 and 60 mg/day),¹²⁷ but for the other study¹²⁸ 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 RCT¹²⁸ 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 2014b¹²³ and Troost 2005¹⁴⁰) 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



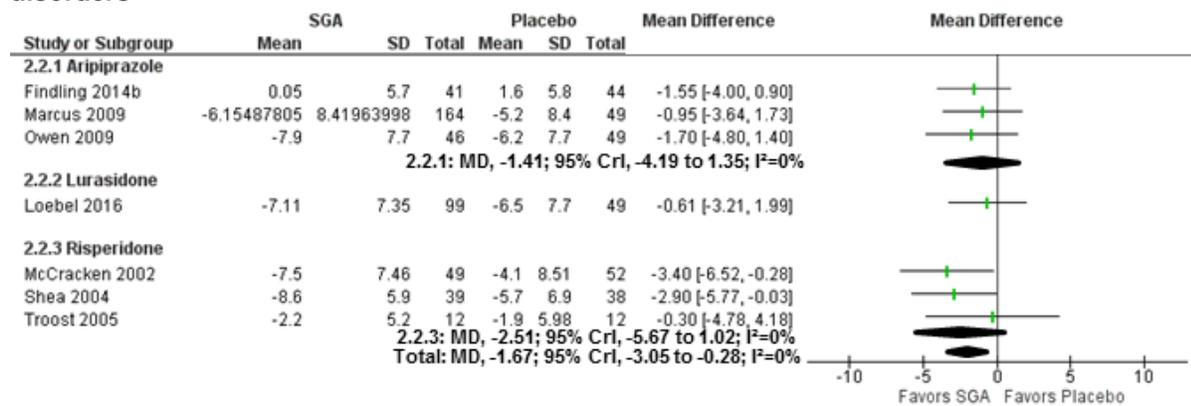
ABC = Aberrant Behavior Checklist; CrI = credible interval; SD = standard deviation; SGA = second-generation antipsychotic; MD = mean difference

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 treatment¹⁴¹ 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

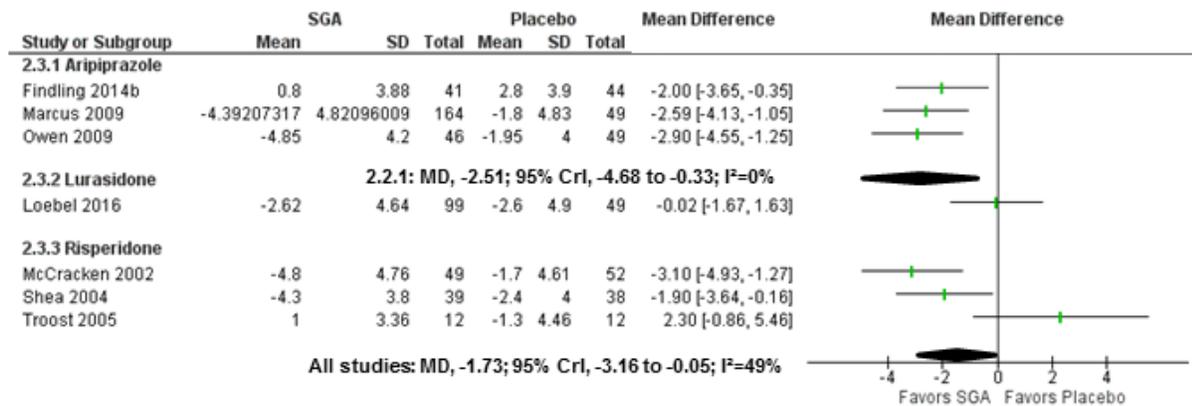
The symptom of inappropriate speech was reduced significantly (MD, -1.04; 95% CrI, -1.83 to -0.26; $I^2 = 39\%$) (Figure 58). Separate meta-analyses for aripiprazole and risperidone failed to show significant benefit for the individual SGAs (aripiprazole: MD, -1.49; 95% CrI, -3.02 to 0.06, and risperidone: 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



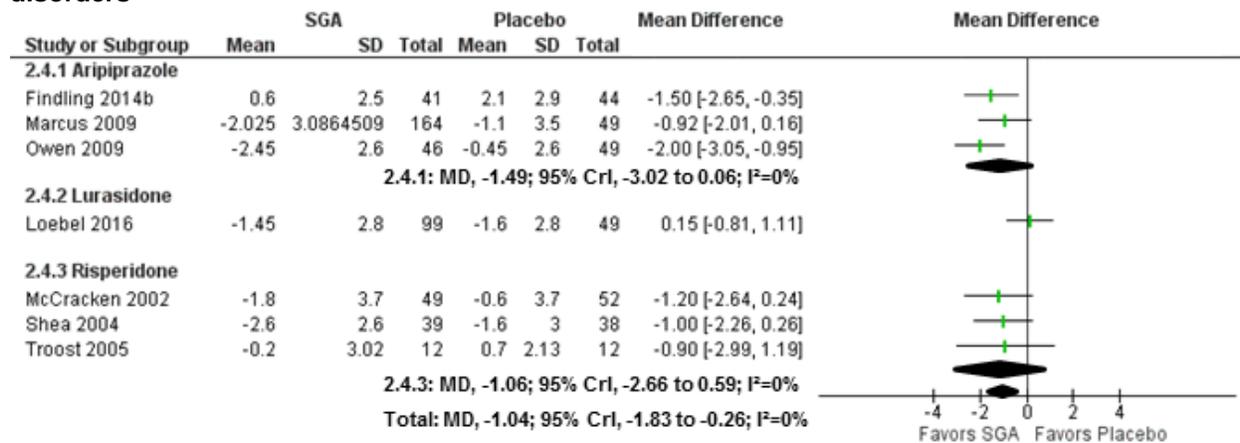
ABC = Aberrant Behavior Checklist; CrI = credible interval; MD = mean difference; SD = standard deviation; SGA = second-generation antipsychotic

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

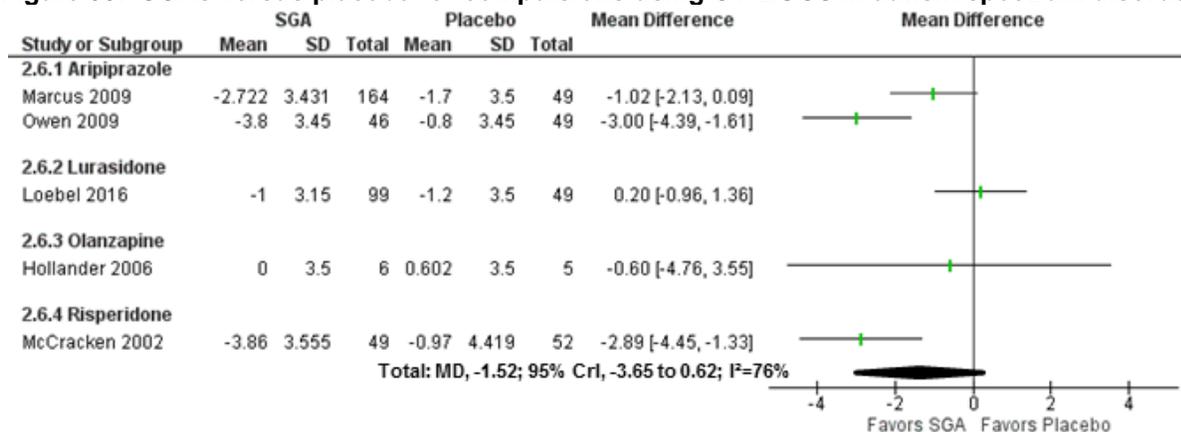
Figure 58. SGAs versus placebo for inappropriate speech using ABC in autism spectrum disorders



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.

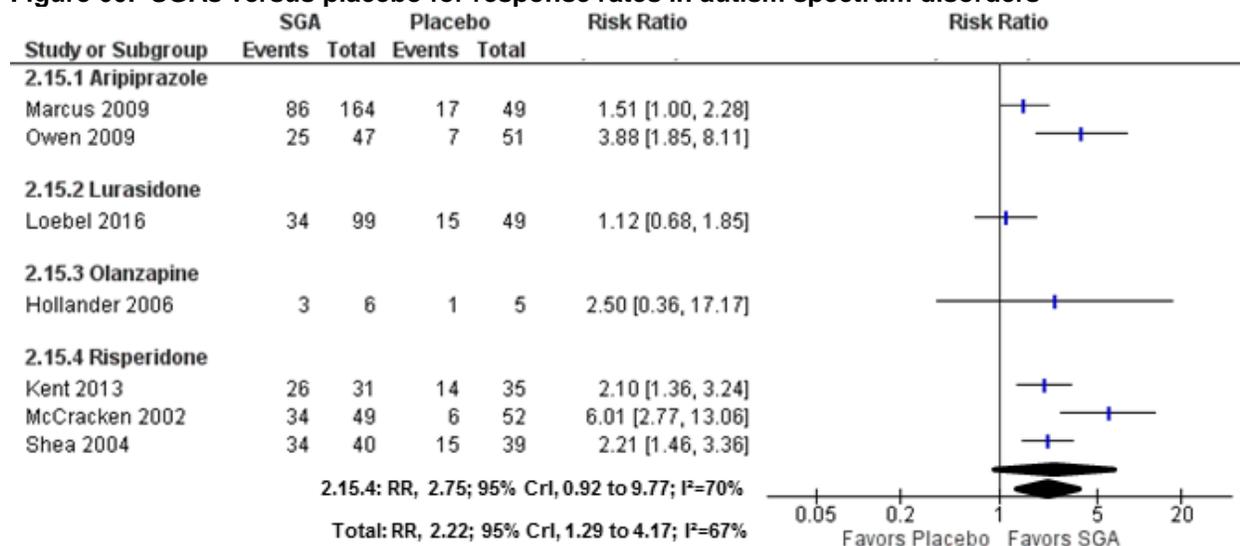
Figure 59. SGAs versus placebo for compulsions using CY-BOCS in autism spectrum disorders



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}

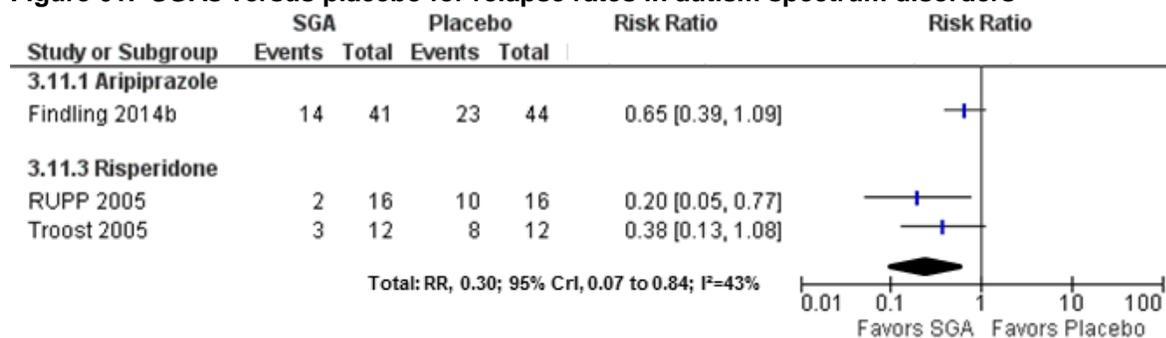
Figure 60. SGAs versus placebo for response rates in autism spectrum disorders



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

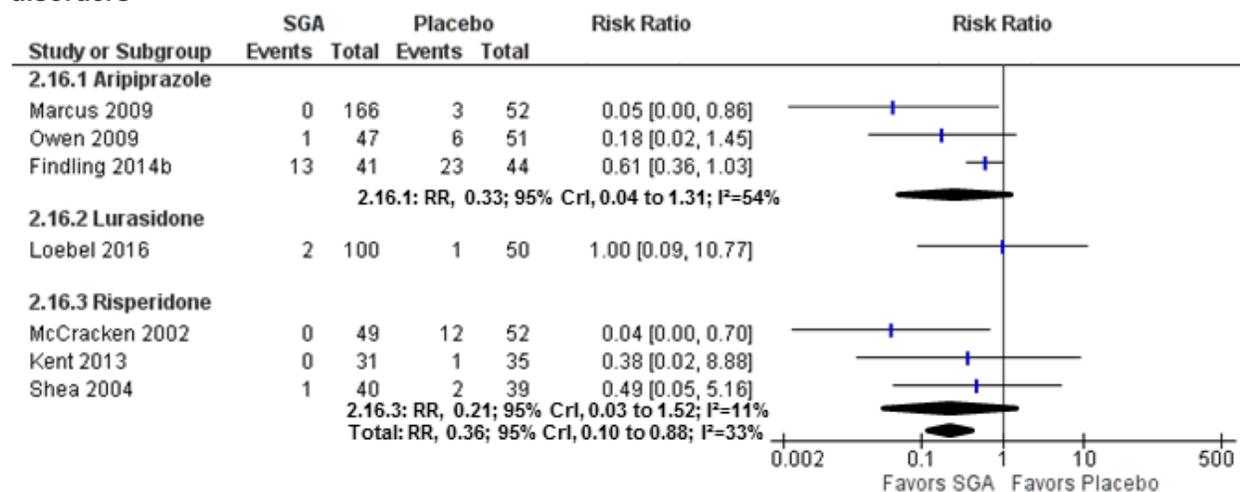
Meta-analysis of relapse rates (based on irritability symptoms and overall clinical impressions) for three RCTs^{123, 138, 140} examining placebo-controlled maintenance of SGAs in patients with ASD found a significant effect favoring maintenance on a SGA compared with placebo (RR, 0.30; 95% CrI, 0.07 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; I² = 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

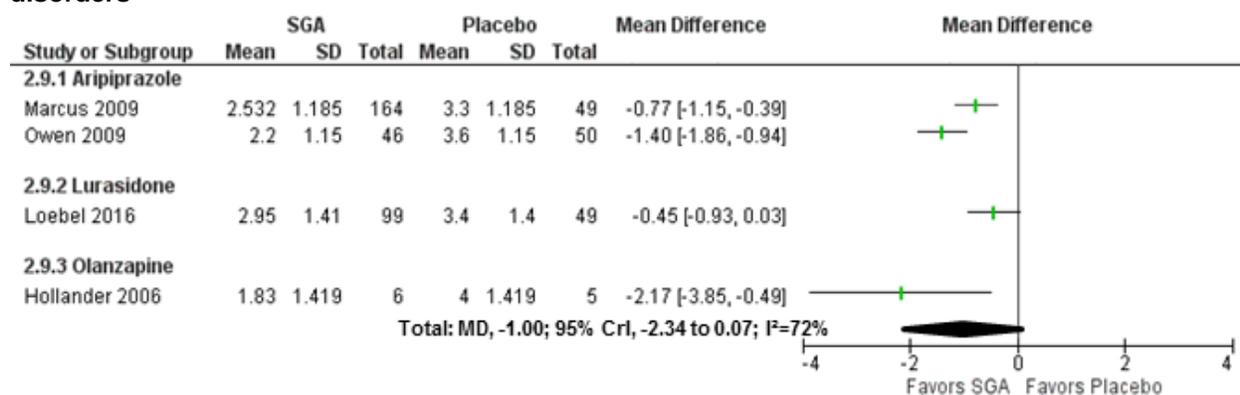
Figure 62. SGAs versus placebo for discontinuation due to lack of efficacy in autism spectrum disorders



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

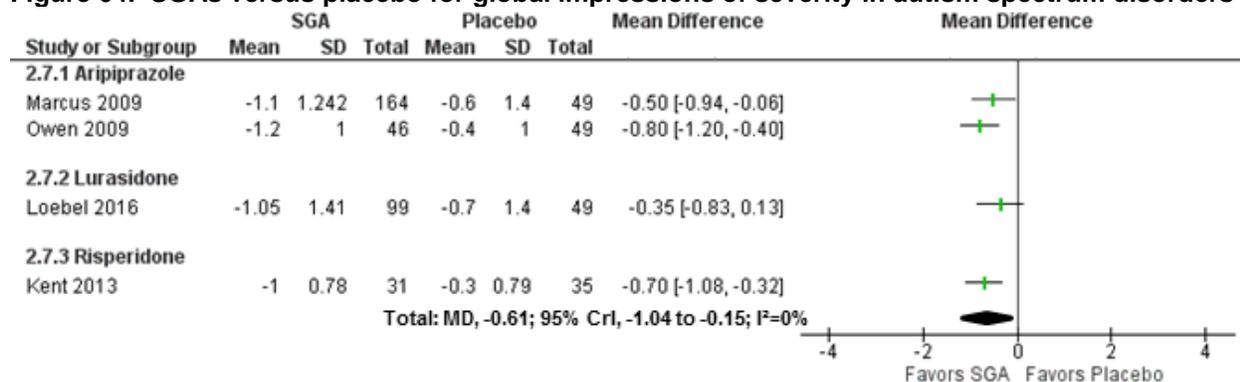
Short-term global impressions. Four RCTs provided data for meta-analyses of SGAs versus placebo for global impressions of improvement^{126, 127, 131, 135} (Figure 63) and severity (Figure 64).^{127, 128, 131, 135} Results found no difference for global improvement (MD, -1.00, 95% CrI, -2.34 to 0.07; I² = 72%) but showed significant improvement for global severity (MD, -0.61; 95% CrI, -1.04 to -0.15; I² = 0%). There was considerable heterogeneity in the results for global improvement likely resulting from the Hollander¹²⁶ 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, 4.5¹²⁸ and 6.5¹³²; 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

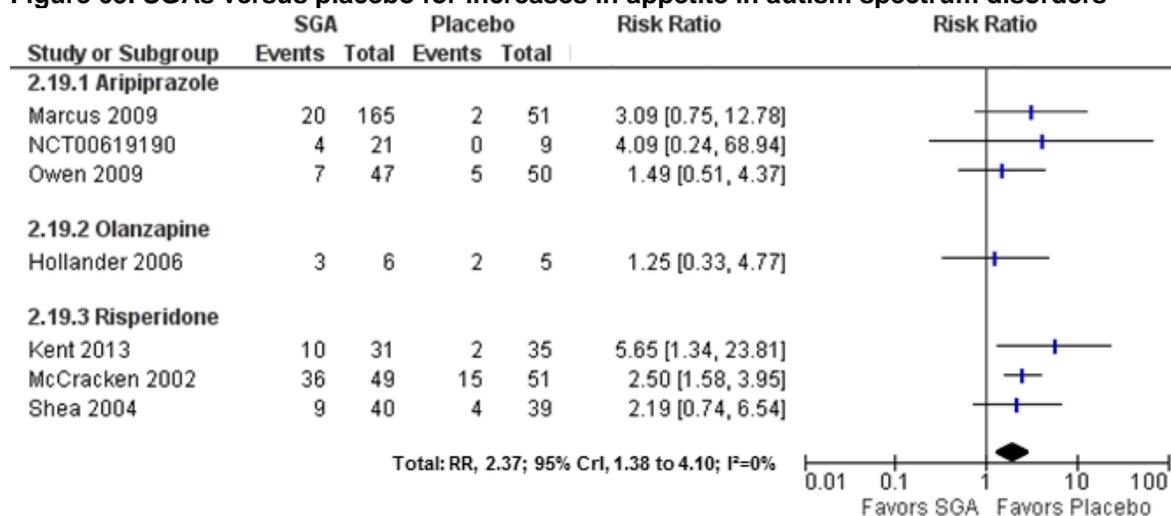
Figure 64. SGAs versus placebo for global impressions of severity in autism spectrum disorders



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 study¹²⁹ (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 ≤ 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/day¹³² vs. 1.2¹³⁹ and 1.25-1.75¹²⁸ 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 RCT¹³³): Global improvement and language was examined between risperidone and haloperidol, but the effects are unknown due to insufficient SOE.
- **FGAs versus FGAs** (one RCT¹³⁶): 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 SGAs¹⁴³ 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 tasks¹³² are not known. The comparative effects of two doses of lurasidone¹²⁷ and three doses of aripiprazole¹³¹ 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 RCTs¹²⁹ 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 RCT¹²⁹ 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 RCT¹³¹ 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 response¹⁴¹ 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 <i>Risperidone vs. placebo</i>	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 <i>Aripiprazole vs. placebo</i>	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 <i>Risperidone vs. placebo</i>	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 <i>Continuous haloperidol vs. discontinuous haloperidol</i>	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 DCD in 7,^{151, 152, 154-158} all trials except one¹⁵⁶ had a large proportion of children with comorbid diagnoses of either DCD 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 DCD 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,^{145, 152, 154, 157, 158} and stimulants were prohibited in three RCTs.^{150, 155, 156}

The duration of treatment ranged from 2 weeks¹⁵² to 6 months¹⁵⁷. 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 RCT¹⁴⁸): 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 quetiapine¹⁵⁵]): 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 study¹⁵³ 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 RCT¹⁵⁰): 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

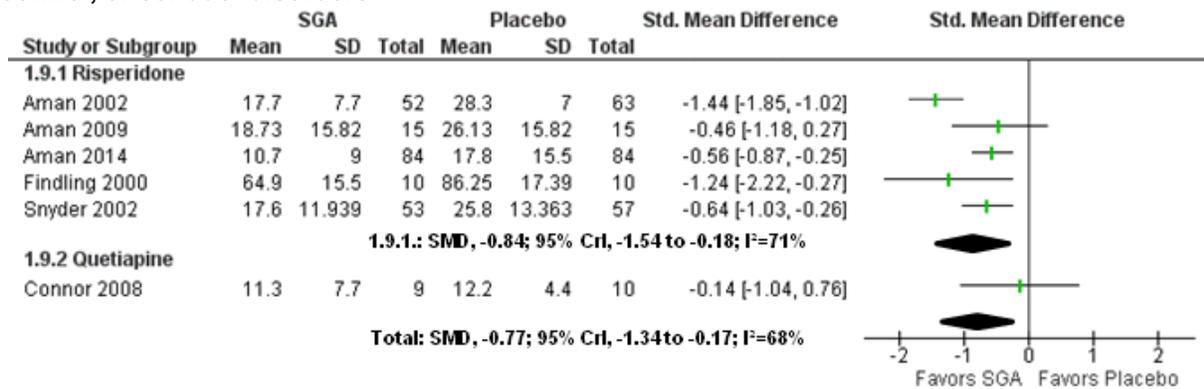
Meta-Analysis for SGAs Versus Placebo in ADHD and/or DICD

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.

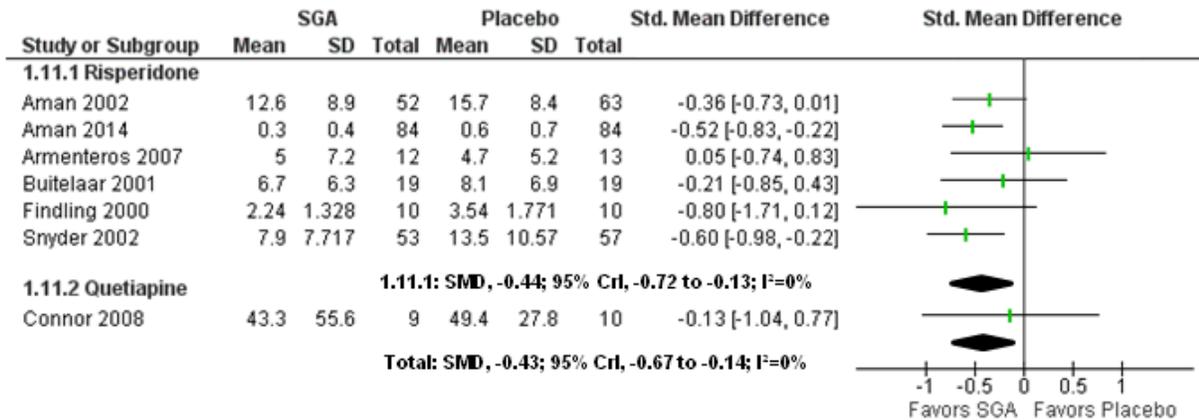
Figure 66. SGAs versus placebo for conduct problems in ADHD and/or disruptive, impulse-control, or conduct disorders



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).

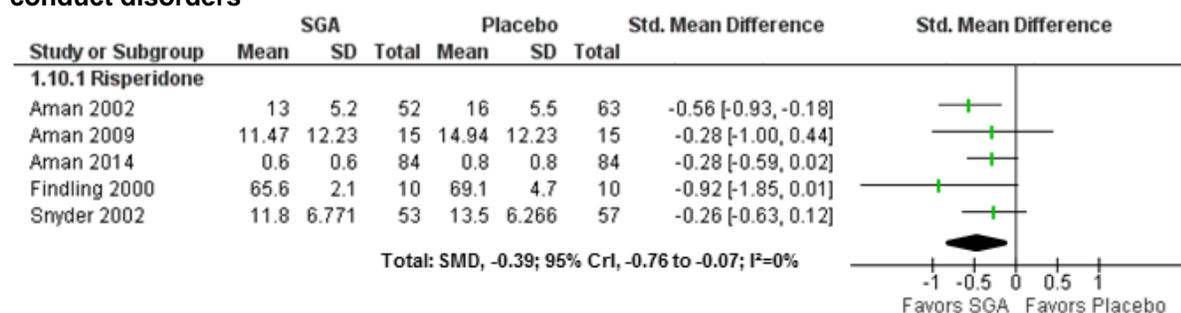
Figure 67. SGAs versus placebo for aggression in ADHD and/or disruptive, impulse-control, or conduct disorders



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-SC4¹⁴⁷ scales. Only the Aman 2002 study¹⁵¹ 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 study¹⁴⁷ administered placebo-controlled risperidone as adjunct treatment, although patients having good response to the “basic” stimulant and parent training were not eligible.

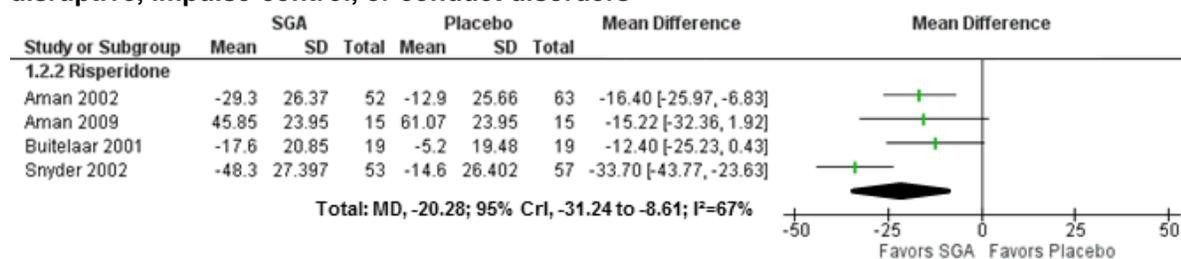
Figure 68. SGAs versus placebo for hyperactivity in ADHD and/or disruptive, impulse-control, or conduct disorders



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

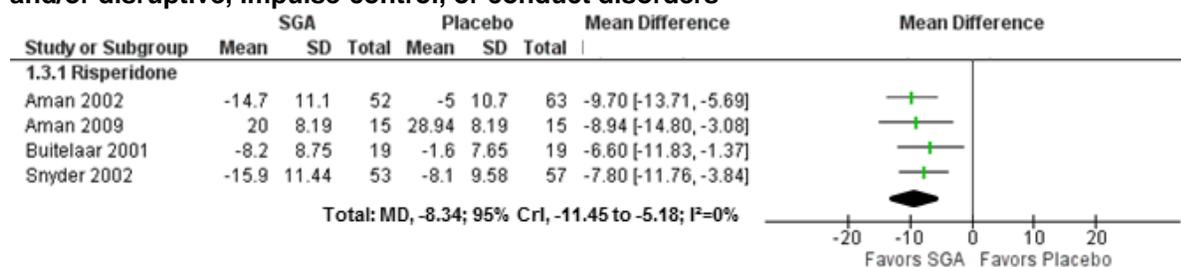
Short-term nonspecific symptoms. Four RCTs^{151, 152, 154, 158} provided data for meta-analyses for aberrant behaviors (Figure 69) and for a combination of hyperactivity and noncompliance symptoms (Figure 70); both were assessed on the ABC using total (range 0-147) and hyperactivity/noncompliance (range 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

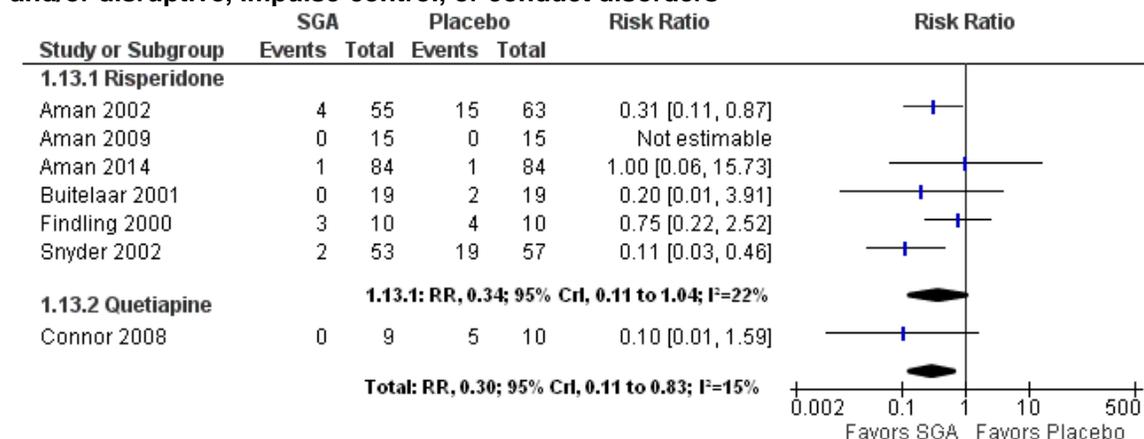
Figure 70. SGAs versus placebo for hyperactivity/noncompliance using ABC subscale in ADHD and/or disruptive, impulse-control, or conduct disorders



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) trial¹⁵² 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).

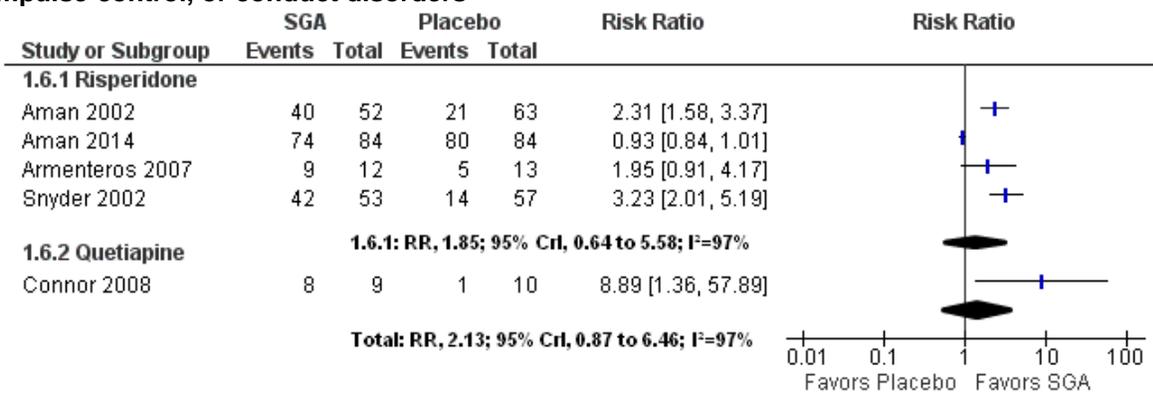
Figure 71. SGAs versus placebo for rates of discontinuation due to lack of efficacy in ADHD and/or disruptive, impulse-control, or conduct disorders



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

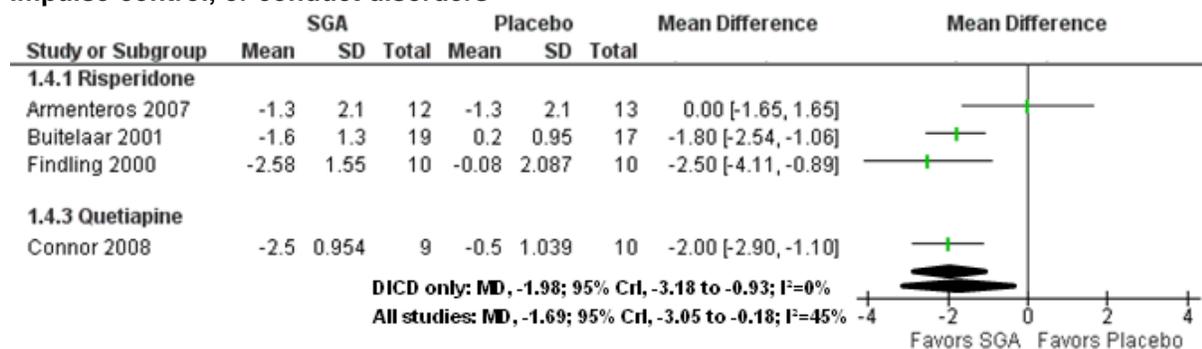
Figure 72. SGAs versus placebo for global impression of improvement in ADHD and/or disruptive, impulse-control, or conduct disorders



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

Four RCTs¹⁵³⁻¹⁵⁶ 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 trial¹⁴⁷ 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

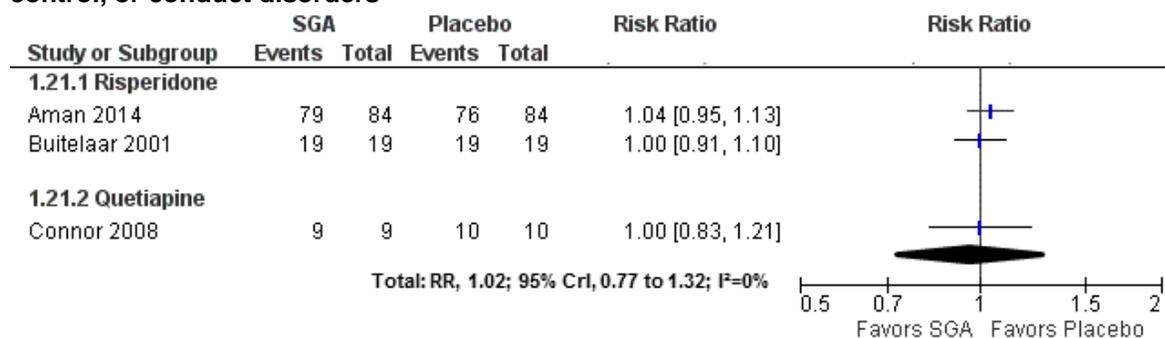
Figure 73. SGAs versus placebo for global impressions of severity in ADHD and/or disruptive, impulse-control, or conduct disorders



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 study¹⁵⁴ 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.

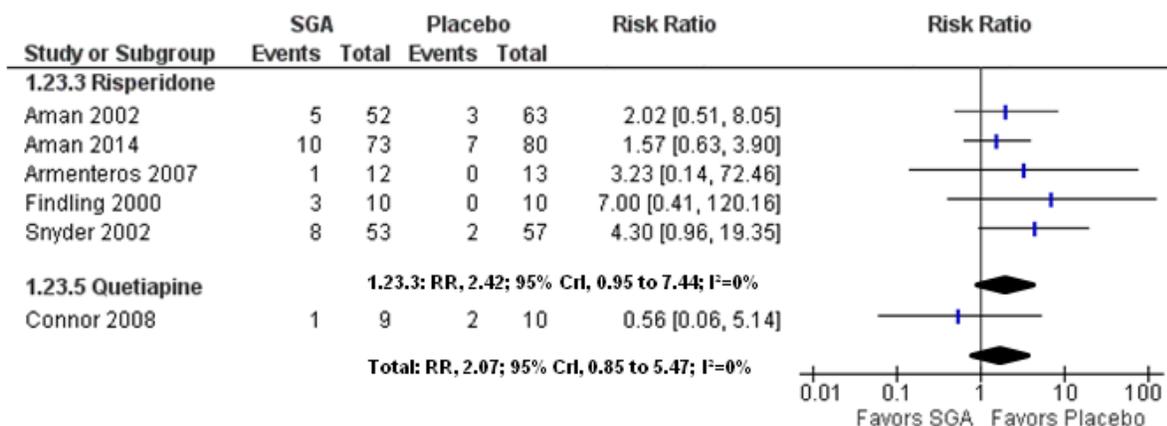
Figure 74. SGAs versus placebo for medication adherence in ADHD and/or disruptive, impulse-control, or conduct disorders



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 RCT¹⁵⁷ 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 study¹⁵³ defined response by ≥ 30 percent reduction in aggression, and found no significant difference between the groups ($p = 0.13$). The other trial's¹⁴⁷ 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 RCT¹⁵⁵ 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 DCD^{151, 152, 154-156, 158}, most studies enrolled a large proportion of children with DCD 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 study¹⁵³ 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 RCT¹⁵⁰ 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 study¹⁴⁶): 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 RCT¹⁵⁰): 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 study¹⁴⁶ was a pooled analysis of data from two RCTs.^{151, 158} One long-term RCT¹⁵⁷ 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 RCT¹⁵⁷ 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 RCT¹⁵⁷ 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 analysis¹⁴⁶ of patient data from the 6-week trials of Aman¹⁵¹ and Snyder¹⁵⁸ 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 RCT¹⁵⁵ 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 RCT¹⁵⁵ 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 RCT¹⁵⁰ 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 analysis¹⁴⁹ of the 6-week Snyder¹⁵⁸ and Aman¹⁵¹ 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 <i>Risperidone vs placebo</i>	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 risperidone to stimulant significantly improved reduction in hyperactivity ($p = 0.0013$). No indication that the effects of risperidone varied with stimulant use.
Buitelaar, 2001 ¹⁵⁴ <i>Risperidone vs placebo</i>	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 <i>Risperidone vs placebo</i>	Regression analysis by age, race, and baseline RAAPP and CGI-S scores	Completion of study RAAPP, CPRS	Age, race, baseline RAAPP score, and baseline CGI-S score was not significantly different between completers and noncompleters. When an adjustment for age was made, no alteration in rating scales scores were observed
Reyes, 2006 ¹⁵⁷ <i>Risperidone vs placebo</i>	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 <i>Risperidone vs placebo</i>	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 RCT¹⁵⁹ 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 RCT¹⁵⁹):** 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 RCT¹⁵⁹ 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 study¹⁶⁰ 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 study¹⁶⁰ 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 study¹⁶³ 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 risperidone¹⁶¹): 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 RCT¹⁶² 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 study¹⁶³ 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 RCT¹⁶¹ 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 RCTs¹⁶⁴⁻¹⁷² and 3 NRCTs¹⁷³⁻¹⁷⁵) 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 study¹⁷⁵ 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 risperidone¹⁶⁴ and with aripiprazole.^{173, 174} One RCT¹⁶⁵ 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 risperidone¹⁷⁰ and ziprasidone¹⁶⁷ 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)	Tourette'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 RCT¹⁶⁶ and one NRCT¹⁷⁵): Tic severity and clinician ratings of global improvement were examined for risperidone versus pimozide¹⁶⁶ 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 RCT¹⁶⁵): 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 ziprasidone¹⁶⁷]): 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 study¹⁶⁵ 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).

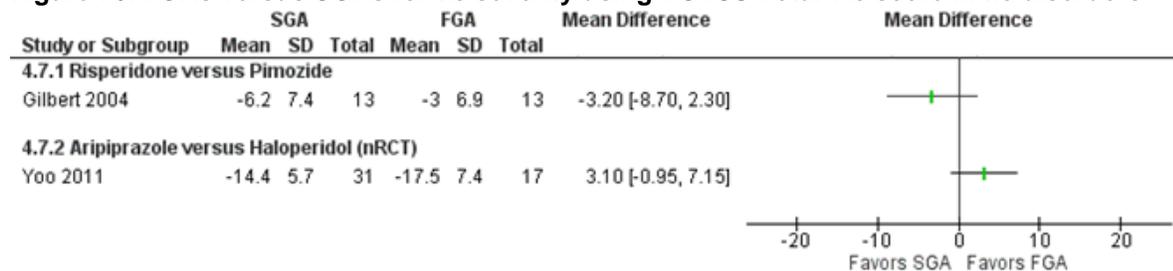
Detailed Analysis

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 RCT¹⁶⁵ 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, $p < 0.05$).

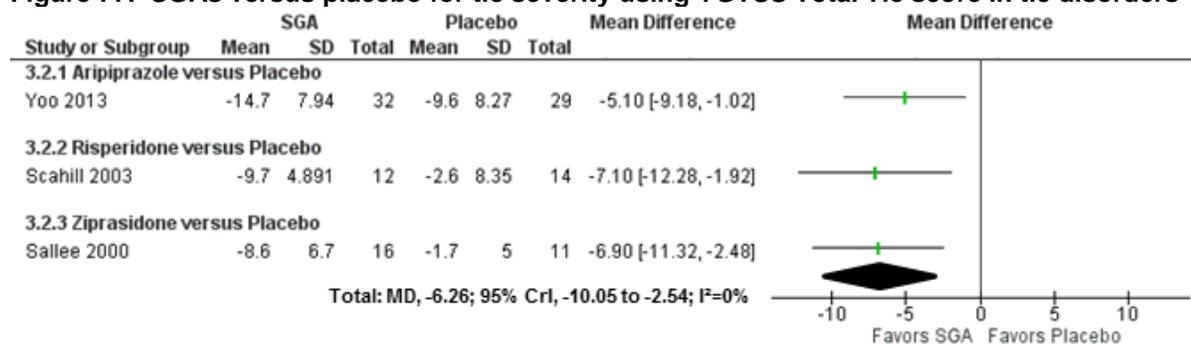
In the RCT¹⁶⁹ comparing haloperidol, pimozide, and no medication, pimozide was similar but haloperidol was inferior to the no medication group on the subscales of working hard, learning, and total academic function (all $p < 0.05$) using the Child Behavior Checklist–Teacher Report Form.

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

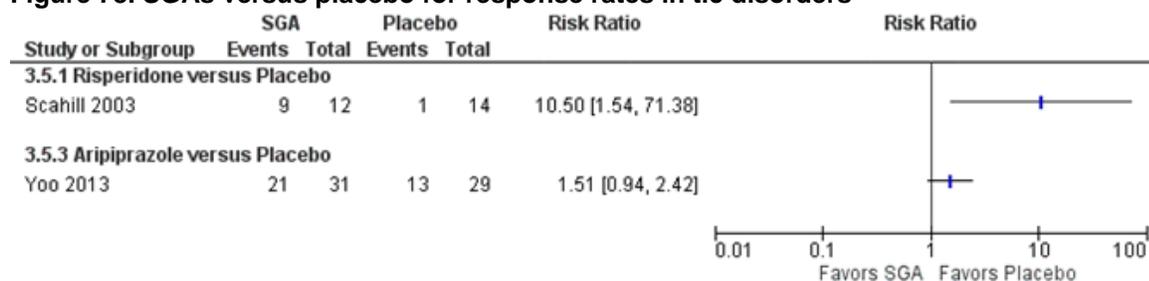
Figure 77. SGAs versus placebo for tic severity using YGTSS Total Tic score in tic disorders



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%; $p = 0.02$).

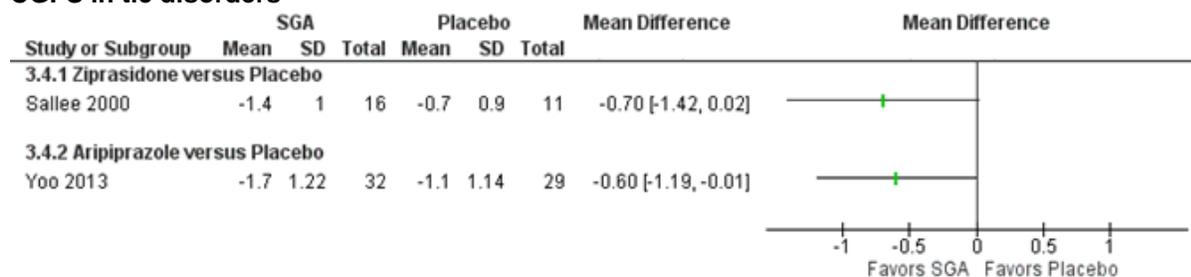
Figure 78. SGAs versus placebo for response rates in tic disorders



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 RCT¹⁷² 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 study¹⁶⁵ 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 RCT¹⁷¹ 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 RCT¹⁶⁹): The effects of pimozide compared with haloperidol for cognitive effects are not known.¹⁶⁹
- **SGAs versus FGAs** (one RCT¹⁶⁵): It is not known if risperidone and aripiprazole differ in their effects on social, emotional, or physical functioning.
- **FGAs versus placebo** (one RCT¹⁷¹): For long-term treatment with pimozide versus placebo, the relative effects on response are unknown.

Detailed Analysis

Long-term nonspecific symptoms. One RCT¹⁷¹ 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 pimozone 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 pimozone 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 <i>Haloperidol vs. pimozone</i>	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 study¹⁷⁸ were persistent behavioral disturbances (e.g., hostility, aggressiveness, irritability, agitation) in children with intellectual impairment and living in residential homes. The other study¹⁷⁷ 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 RCT¹⁷⁸): 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 colleagues¹⁷⁷ (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 trial¹⁷⁹ and 22 observational studies (11 prospective¹⁸⁰⁻¹⁹⁰ and 11 retrospective¹⁹¹⁻²⁰¹) 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 NRCT¹⁷⁹ had high risk of bias. Of the observational studies, thirteen received 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 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 naïve 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% Comorbidities: 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 naïve 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 naïve 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

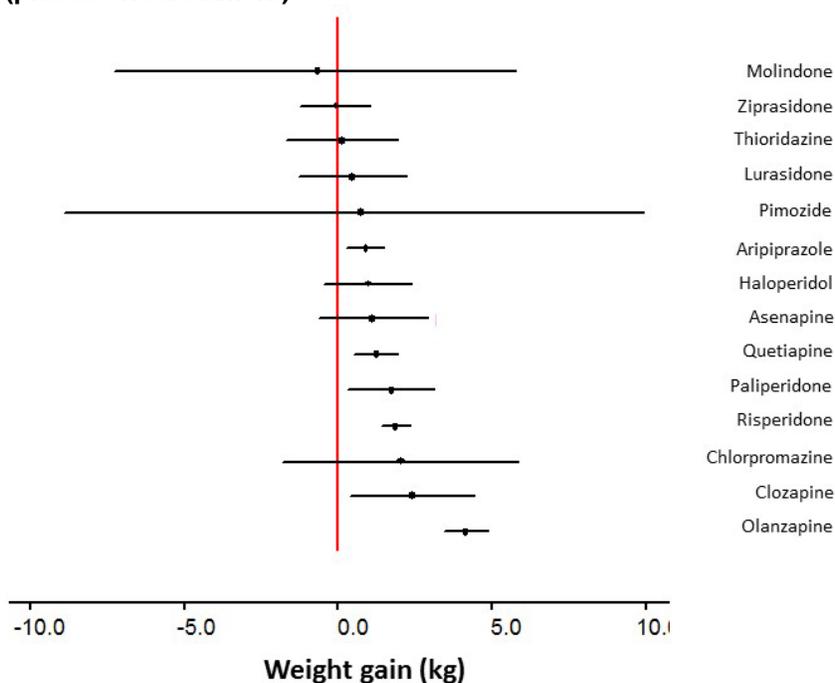
Findings from our analysis for weight gain indicate that patients taking most antipsychotics gain more weight than patients not receiving antipsychotics (Table 29 and Figure 80). Patients taking molindone and ziprasidone may gain less weight on average whereas those receiving olanzapine may gain as much 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, pimozone, 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 pimozone, 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.

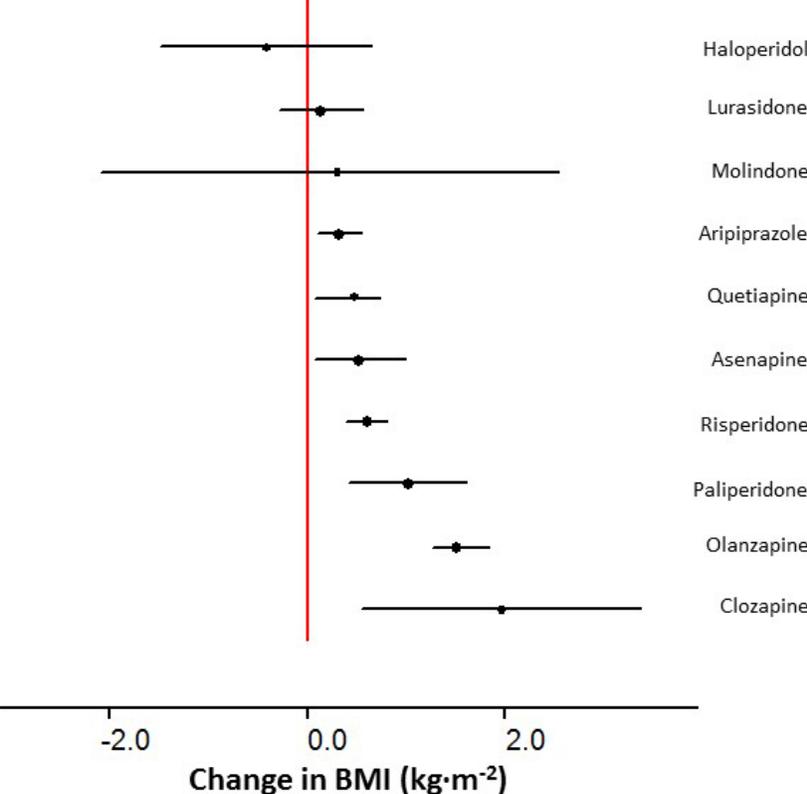
Results of the network meta-analysis for changes in BMI were similar to those for weight gain. The FGAs appear to be relatively less harmful for BMI than for weight (e.g., haloperidol moved from ninth to last place for being worst) but few studies and small samples contributed to the findings for FGAs. 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 antipsychotics 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 RCT⁸¹ (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 RCT⁶⁸ (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 RCT⁷⁷ (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 RCT⁷⁷ (N = 21) comparing haloperidol with clozapine, and an observational study⁹⁹ (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 RCT⁷⁷ (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 RCT⁶⁶ (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 study¹³³ (N = 28) comparing haloperidol with risperidone in autism spectrum disorder (ASD).

Development of diabetes mellitus. A prospective cohort study¹⁰² 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 NRCT¹⁷³ (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·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

^aRisk ratios above 1.0 and positive MD favor SGAs.

^bDowngraded for ROB and imprecision, based on small sample size.

^cDowngraded for ROB.

^dDowngraded 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 RCT¹⁶⁸ (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 RCT¹⁴⁸ (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 RCT⁷⁸ (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 RCT⁶⁷ (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		G2		Relative Effects ^a , Studies
			Events	N	Events	N	
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

^aRRs 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		G2		Relative Effects ^a , Studies	Strength of Evidence; Conclusions
			Events	N	Events	N		
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·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.

^c Downgraded 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·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 study¹⁰⁸ 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 cohort¹⁸⁵): 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 ASD¹³¹) and a prospective cohort study¹⁸⁵ (mixed conditions) compared different doses of aripiprazole. One RCT¹¹⁷ 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 study¹⁸⁵ (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 group¹²⁷, 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 RCT⁹⁰ (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 study⁷⁴ 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 RCT⁶⁵ 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 RCT¹¹⁷ 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		Low Dose		Relative Effects ^a , Studies
	Events	N	Events	N	
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.

^aRR 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		Low dose		Relative Effects ^a , Studies	Strength of Evidence; Conclusions
		events	N	events	N		
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·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·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.

^bDowngraded for ROB and imprecision, because CIs include possibility for clinically relevant benefit for the low dose group.

^cDowngraded for ROB.

^dDowngraded for ROB and imprecision due to small sample sizes.

^eDowngraded for unknown consistency and imprecision from small samples.

^fDowngraded for imprecision, because CIs include possibility for clinically relevant benefit for the low dose group

^gDowngraded 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 RCT¹⁶⁸ (N = 44) reported that 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 thioridazine 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 $\geq 7\%$ 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, $\geq 7\%$ percent weight gain, and somnolence.
 - Compared with placebo, olanzapine probably increases weight gain and BMI, and appears to increase risk for $\geq 7\%$ 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, N 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 QTcB	1, 97 ¹³⁵ 1, 97 ¹³⁵	0 3	47 47	0 0	50 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 QT Prolongation Syncope	2, 631 ^{92, 108} 1, 403 ¹⁰⁸ 1, 403 ¹⁰⁸	3 0 2	453 302 302	0 0 0	178 101 101	
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	Insufficient
	Mortality	3, 395 ^{88, 118, 128}	0	248	0	147	
	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	Insufficient
	Mortality	1, 237 ¹¹⁶	0	149	0	88	
	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 RCT¹⁵⁷ (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 RCT¹⁵⁷ 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 2 0	146 172 19	0 1 0	64 163 20	RR, 12.82; 95% CI, 0.78 to 211.72 ¹¹⁷ RR, 1.90; 95% CI, 0.17 to 20.70 ¹⁵⁷ Not estimable ¹³⁴
	12+ mo	3, 266	0 1 1	30 98 31	0 1 1	30 48 29	Not estimable ¹¹⁰ RR, 0.49; 95% CI, 0.03 to 7.66 ⁹⁵ 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 1	30 98	0 1	30 48	Not estimable ¹¹⁰ RR, 0.49; 95% CI, 0.03 to 7.66 ⁹⁵
Asenapine vs. placebo	<6 mo	2, 709	17 14	302 204	4 3	101 102	RR, 1.42; 95% CI, 0.49 to 4.13 ¹⁰⁸ 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 0	172 19	1 0	163 20	RR, 1.90; 95% CI, 0.17 to 20.70 ¹⁵⁷ 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

^aRR 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% Crl, 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·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% Crl, 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% Crl, 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% Crl, 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% Crl, 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% Crl, 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% Crl, 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% Crl, 0.54 to 1.48 ^{73, 117, 121, 123, 1231, 135, 172}	Moderate; Aripiprazole probably increases slightly ^b
	BMI (kg·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% Crl, 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	-	54	MD, 1.16; 95% CI, 0.93 to 1.39 ¹²⁰	Moderate; Olanzapine probably increases ^b
			-	72	-	34	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- prolactinemi a		2, 268	50	107	1	54	RR, 25.53; 95% CI, 3.58 to 177.76 ¹²⁰	Low; Olanzapine may increase risk ^e
			58	72	6	35	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

^aRisk ratios above 1.0 and positive MD favor placebo.

^bDowngraded for ROB.

^cDowngraded for ROB and imprecision because point estimate and CrI includes clinically significant favor for placebo.

^dDowngraded for ROB and inconsistency.

^eDowngraded 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·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

^aPositive MD favors placebo. We did not combine data from 1 or 2 studies so these results are always presented separately.

^bDowngraded 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)

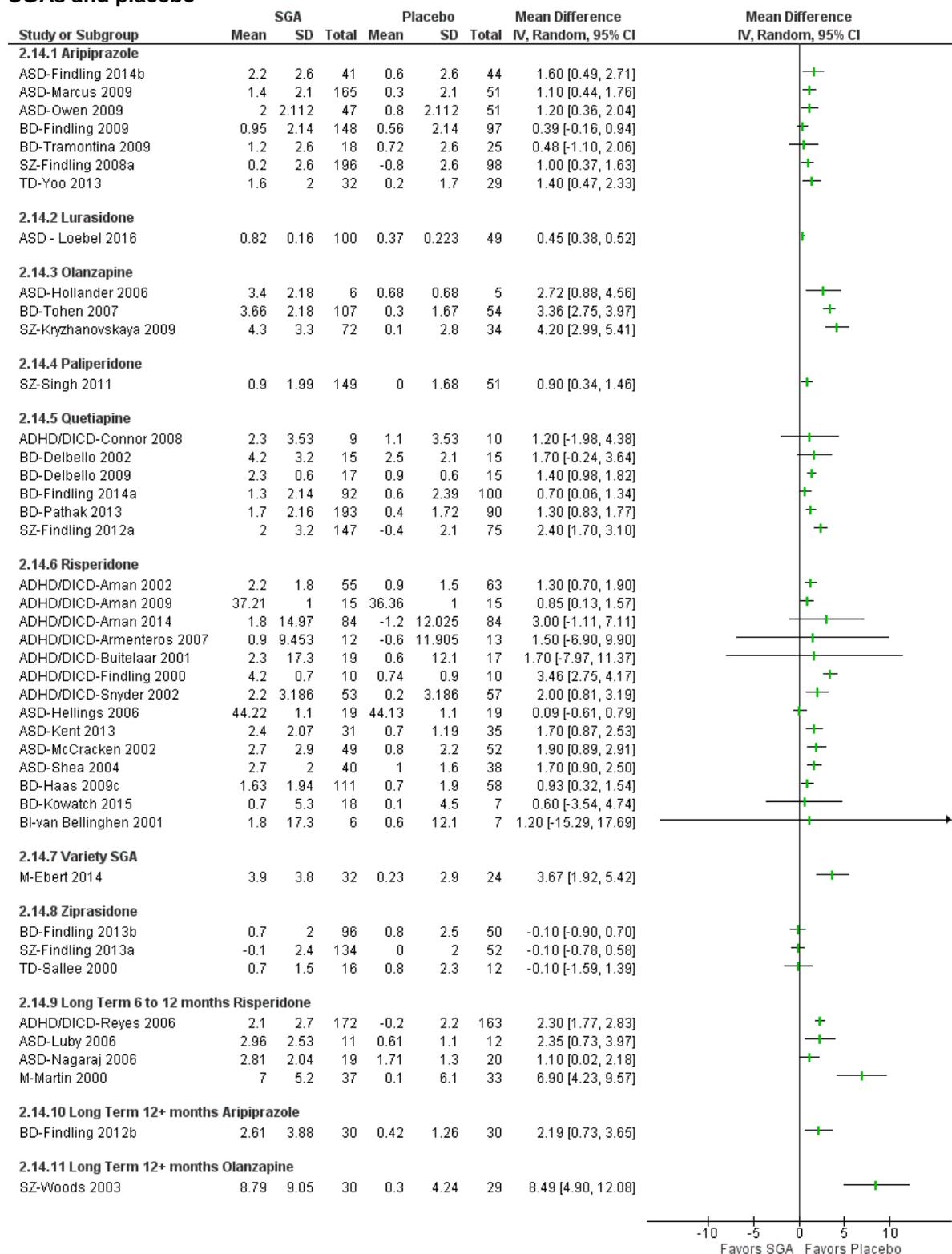
kg = kilograms

*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 $\beta=0.55$; 95% CrI, 0.09 to 1.91) the results of the network meta-analysis were not changed to any meaningful extent.

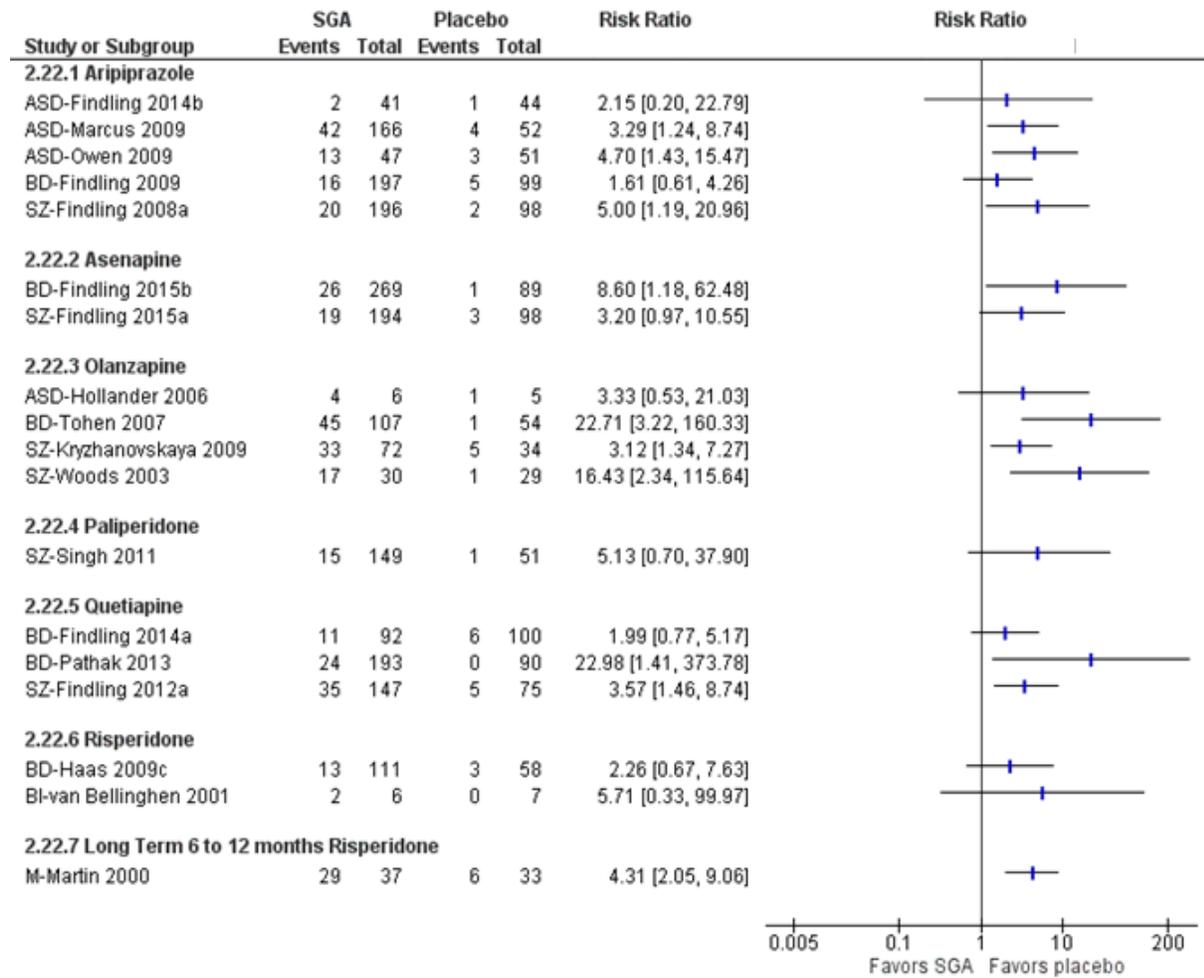
One of our subgroups for this KQ was in relation to treatment condition. Figures 82 to 85 present the data used for our meta-regressions, with each study identified by the condition it studied. Based on observations on these plots, we could not see any trends indicating the effects varied by condition. 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



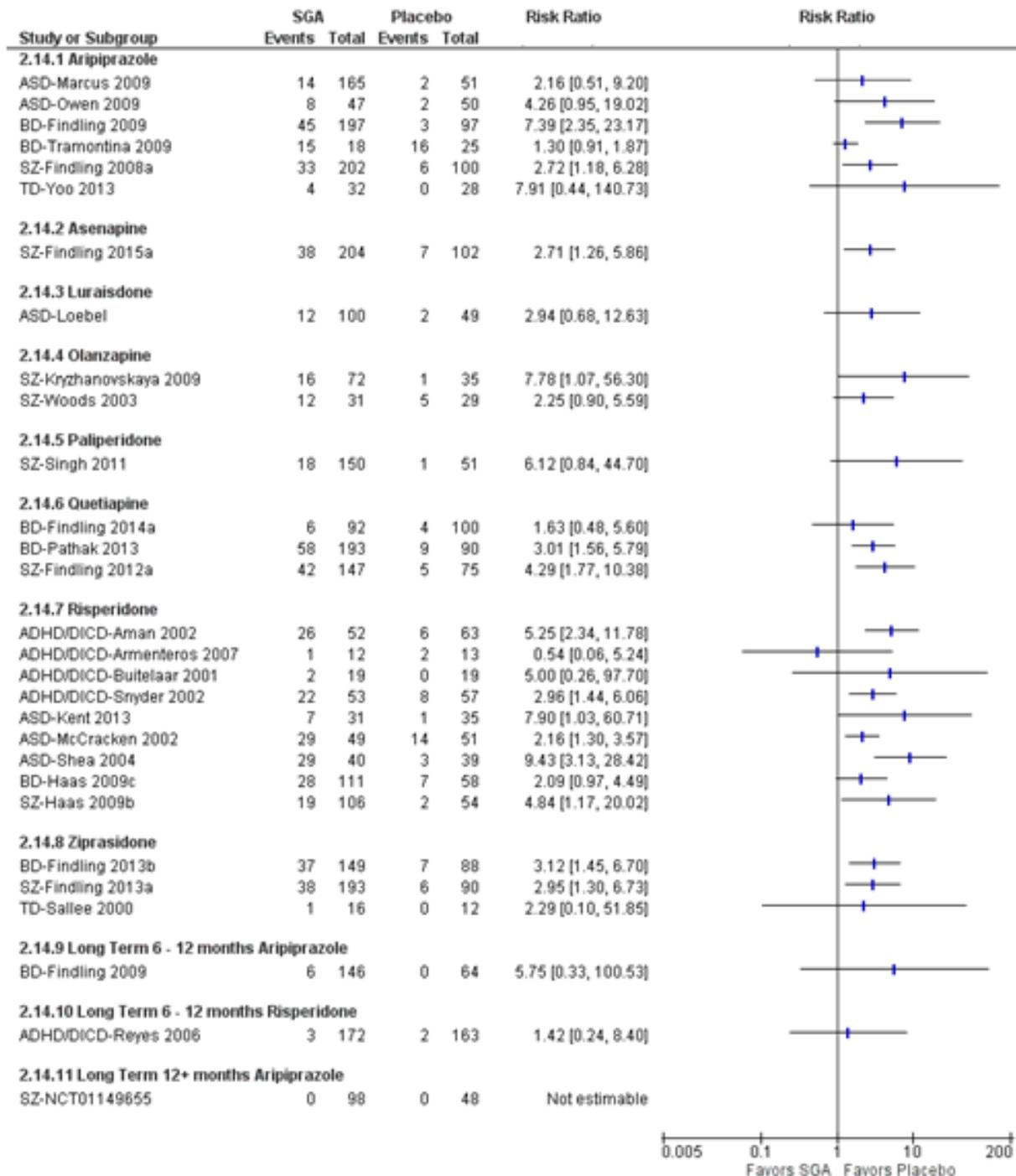
ADHD/DICD = attention deficit hyperactivity disorder, and disruptive, impulse-control, and conduct disorders; ASD = autism spectrum disorders; BI = behavioral issues outside of diagnosis; BD = bipolar disorder; M = mixed conditions; SZ = schizophrenia; TD = tic disorders

Figure 83. Plot of data for weight increase of 7 percent or greater at longest followup for comparisons between SGAs and placebo



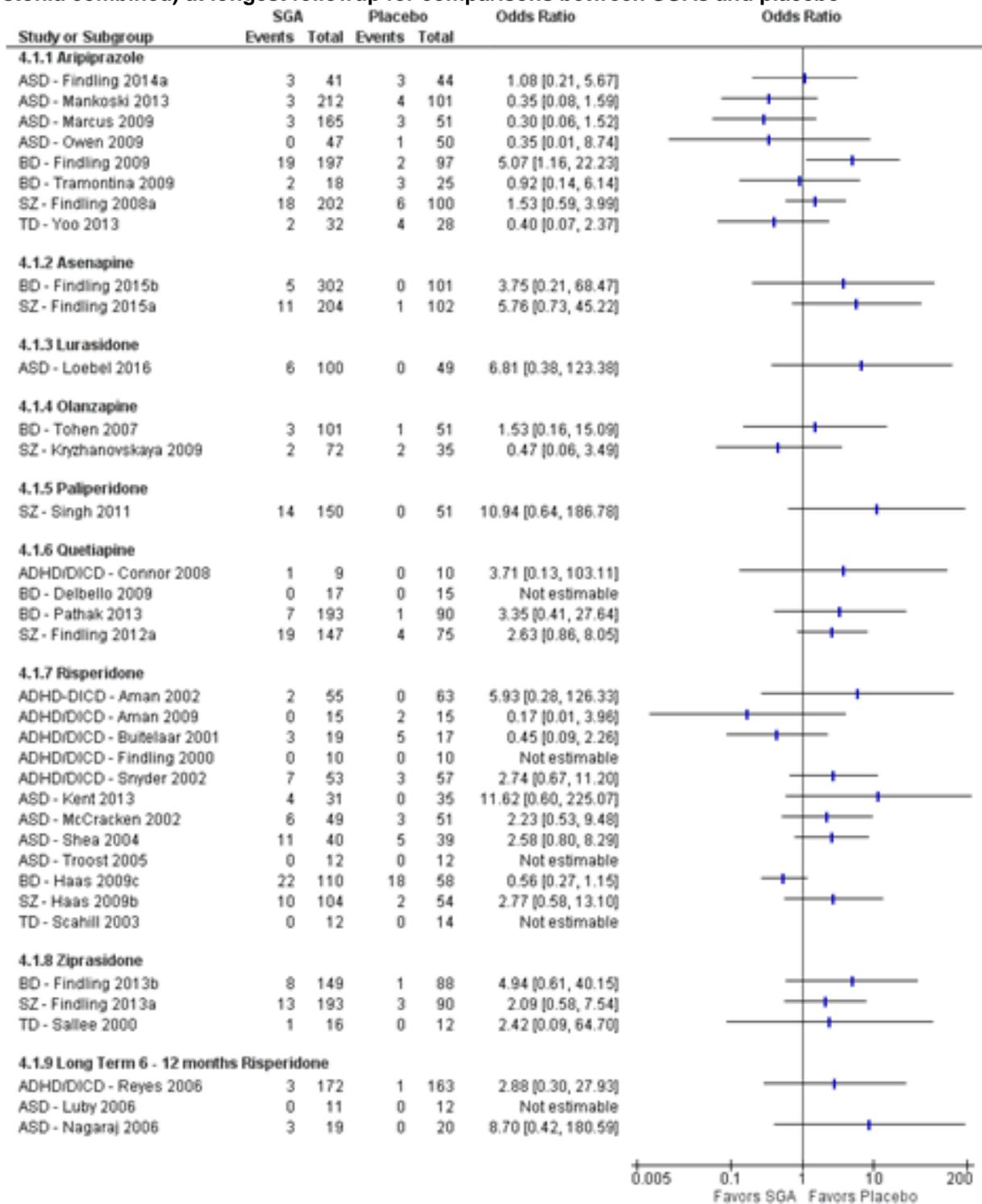
ASD = autism spectrum disorders; BI = behavioral issues outside of diagnosis; BD = bipolar disorder; M = mixed conditions; SZ = schizophrenia

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 quetiapine¹⁸² 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 risperidone¹⁵⁸) 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 associated 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 clozapine¹⁰⁰ found that prolactin levels (and prolactin-related effects⁷⁴) 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 analysis¹⁴⁹ 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 concurrent 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 <i>Haloperidol vs. pimozide vs. placebo</i>	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 <i>Pimozide vs. risperidone</i>	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 <i>Haloperidol vs. olanzapine vs. risperidone</i>	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 $\geq 7\%$ 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 concern about weight gain, males showing an increase in BMI, but females did not.
Wudarsky, 1999 ⁹⁹ <i>Clozapine vs. haloperidol vs. olanzapine</i>	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 <i>Risperidone vs. Olanzapine vs. Quetiapine</i>	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 naïve	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 significantly 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 <i>Quetiapine vs Risperidone vs Olanzapine</i>	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 <i>Olanzapine vs. risperidone</i>	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 <i>Risperidone vs. Olanzapine vs. Quetiapine</i>	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 <i>Low- vs. high-dose aripiprazole</i>	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 <i>Low- vs. high-dose risperidone</i>	Sex and age	Prolactin	The emergence of prolactin-related adverse events was higher in adolescent females than males.
Haas, 2009b ⁸⁸ <i>Low- vs. high-dose risperidone</i>	Sex	Prolactin	Mean change in prolactin levels were higher in females than males.
Wink, 2014 ¹⁴⁴ <i>Risperidone vs. aripiprazole</i>	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 <i>Low- vs. high-dose aripiprazole vs. placebo</i>	Sex	Prolactin	Decreases in prolactin levels were more pronounced for males than for females.
Tramontina, 2009 ¹²¹ <i>Aripiprazole vs. placebo</i>	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 <i>Risperidone (with and without stimulants) vs placebo (with and without stimulants)</i>	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 vomiting (p=0.32) in patients with stimulant.
Aman, 2002 ¹⁵¹ <i>Risperidone vs. placebo</i>	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 <i>Low- vs. high dose risperidone vs. placebo</i>	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 <i>Risperidone vs control</i>	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 <i>Risperidone vs. placebo</i>	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 <i>Risperidone vs placebo</i>	Sex, age, diagnosis, disease severity	Risk for symptom recurrence	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 <i>Risperidone vs. placebo</i>	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 <i>Low- vs. high dose quetiapine vs. placebo</i>	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 increased appetite) 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, doses >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 <i>Antipsychotics cohort</i>	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 <i>Antipsychotic treatment ≥6 mo vs. Antipsychotic naive</i>	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-naïve 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 (DICT). Most RCTs of ADHD and/or DICT 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 DICT, or of patients with ADHD not responding to stimulants; a study¹⁵³ 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 DICT; 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 DICT 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 DICT, or with ADHD and not responding to stimulants. Sensitivity analyses removing the small study¹⁵² 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 aggression¹⁵⁶ 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 $\geq 7\%$ 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 $\geq 7\%$ 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 data²⁰⁴⁻²⁰⁶ and clinician self-reports²⁰⁷ 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-analysis²¹⁰ 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 studies¹¹ 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 than 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 DCD 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 DCD 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 comparisons 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.

References

1. Olfson M, Crystal S, Huang C, et al. Trends in antipsychotic drug use by very young, privately insured children. *J Am Acad Child Adolesc Psychiatry*. 2010 Jan;49(1):13-23. PMID: 20215922.
2. Pathak P, West D, Martin BC, et al. Evidence-based use of second-generation antipsychotics in a state Medicaid pediatric population, 2001-2005. *Psychiatr Serv*. 2010 Feb;61(2):123-9. doi: 10.1176/appi.ps.61.2.123. PMID: 20123816.
3. Zito JM, Safer DJ, de Jong-van den Berg LT, et al. A three-country comparison of psychotropic medication prevalence in youth. *Child Adolesc Psychiatry Ment Health*. 2008;2(1):26. doi: 10.1186/1753-2000-2-26. PMID: 18817536.
4. Zito JM, Safer DJ, Sai D, et al. Psychotropic medication patterns among youth in foster care. *Pediatrics*. 2008 Jan;121(1):e157-63. doi: 10.1542/peds.2007-0212. PMID: 18166534.
5. Olfson M, King M, Schoenbaum M. Treatment of young people with antipsychotic medications in the United States. *JAMA Psychiatry*. 2015 Sep;72(9):867-74. doi: 10.1001/jamapsychiatry.2015.0500. PMID: 26132724.
6. IMS Institute for Healthcare Informatics. *The Use of Medicines in the United States: Review of 2010*. IMS Institute for Healthcare Informatics. NJ, USA: 2011.
7. Crystal S, Olfson M, Huang C, et al. Broadened use of atypical antipsychotics: safety, effectiveness, and policy challenges. *Health Aff (Millwood)*. 2009 Sep-Oct;28(5):w770-81. doi: 10.1377/hlthaff.28.5.w770. PMID: 19622537.
8. Patten SB, Waheed W, Bresee L. A review of pharmacoepidemiologic studies of antipsychotic use in children and adolescents. *Can J Psychiatry*. 2012 Dec;57(12):717-21. PMID: 23228229.
9. Fraguas D, Correll CU, Merchan-Naranjo J, et al. Efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders: comprehensive review of prospective head-to-head and placebo-controlled comparisons. *Eur Neuropsychopharmacol*. 2011 Aug;21(8):621-45. doi: 10.1016/j.euroneuro.2010.07.002. PMID: 20702068.
10. Panagiotopoulos C, Ronsley R, Elbe D, et al. First do no harm: promoting an evidence-based approach to atypical antipsychotic use in children and adolescents. *J Can Acad Child Adolesc Psychiatry*. 2010 May;19(2):124-37. PMID: 20467549.
11. Pringsheim T, Lam D, Ching H, et al. Metabolic and neurological complications of second-generation antipsychotic use in children: a systematic review and meta-analysis of randomized controlled trials. *Drug Saf*. 2011 Aug 1;34(8):651-68. doi: 10.2165/11592020-000000000-00000. PMID: 21751826.
12. Correll CU, Penzner JB, Parikh UH, et al. Recognizing and monitoring adverse events of second-generation antipsychotics in children and adolescents. *Child Adolesc Psychiatr Clin N Am*. 2006 Jan;15(1):177-206. doi: 10.1016/j.chc.2005.08.007. PMID: 16321730.
13. Rettew DC, Greenblatt J, Kamon J, et al. Antipsychotic medication prescribing in children enrolled in Medicaid. *Pediatrics*. 2015 Apr;135(4):658-65. doi: 10.1542/peds.2014-2260. PMID: 25733747.
14. Birnbaum ML, Saito E, Gerhard T, et al. Pharmacoepidemiology of antipsychotic use in youth with ADHD: trends and clinical implications. *Curr Psychiatry Rep*. 2013 Aug;15(8):382. doi: 10.1007/s11920-013-0382-3. PMID: 23881713.
15. Schmid I, Burcu M, Zito JM. Medicaid prior authorization policies for pediatric use of antipsychotic medications. *JAMA*. 2015 Mar 3;313(9):966-8. doi: 10.1001/jama.2015.0763. PMID: 25734740.
16. Findling RL, Drury SS, Jensen PS; American Academy of Child and Adolescent Psychiatry. Practice Parameter for the use of Atypical Antipsychotic Medications in Children and Adolescents. 2012. Available at www.aacap.org
17. Gochman P, Miller R, Rapoport JL. Childhood-onset schizophrenia: the challenge of diagnosis. *Curr Psychiatry Rep*. 2011 Oct;13(5):321-2. doi: 10.1007/s11920-011-0212-4. PMID: 21713647.

18. Remschmidt H, Theisen FM. Schizophrenia and related disorders in children and adolescents. *J Neural Transm Suppl.* 2005;(69):121-41. PMID: 16355606.
19. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* American Psychiatric Association. Washington, DC: Publishing AP; 2013. doi: 10.1176/appi.books.9780890425596.
20. Leibenluft E, Rich BA. Pediatric bipolar disorder. *Annu Rev Clin Psychol.* 2008;4:163-87. doi: 10.1146/annurev.clinpsy.4.022007.141216. PMID: 17716034.
21. Fombonne E. Epidemiological Studies of Pervasive Developmental Disorders. In: Volkmar FP, R.; Klin, A.; Cohen, D., ed *Handbook of autism and pervasive developmental disorders.* Vol. 1. NJ, US: John Wiley & Sons Inc; 2005:42-69.
22. Prevalence of autism spectrum disorders--Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. *MMWR Surveill Summ.* 2012 Mar 30;61(3):1-19. PMID: 22456193.
23. Perou R, Bitsko RH, Blumberg SJ, et al. Mental health surveillance among children--United States, 2005-2011. *MMWR Surveill Summ.* 2013 May 17;62 Suppl 2:1-35. PMID: 23677130.
24. Baird G, Simonoff E, Pickles A, et al. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). *Lancet.* 2006 Jul 15;368(9531):210-5. doi: 10.1016/s0140-6736(06)69041-7. PMID: 16844490.
25. Cury DL, Anagnostou E, Manning-Courtney P, et al. Use of psychotropic medication in children and adolescents with autism spectrum disorders. *Pediatrics.* 2012 Nov;130 Suppl 2:S69-76. doi: 10.1542/peds.2012-0900D. PMID: 23118256.
26. Visser SN, Danielson ML, Bitsko RH, et al. Trends in the parent-report of health care provider-diagnosed and medicated attention-deficit/hyperactivity disorder: United States, 2003-2011. *J Am Acad Child Adolesc Psychiatry.* 2014 Jan;53(1):34-46 e2. doi: 10.1016/j.jaac.2013.09.001. PMID: 24342384.
27. Costello EJ, Foley DL, Angold A. 10-year research update review: the epidemiology of child and adolescent psychiatric disorders: II. Developmental epidemiology. *J Am Acad Child Adolesc Psychiatry.* 2006 Jan;45(1):8-25. doi: 10.1097/01.chi.0000184929.41423.c0. PMID: 16327577.
28. Ruscio AM, Stein DJ, Chiu WT, et al. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Mol Psychiatry.* 2010 Jan;15(1):53-63. doi: 10.1038/mp.2008.94. PMID: 18725912.
29. Diniz JB, Shavitt RG, Fossaluza V, et al. A double-blind, randomized, controlled trial of fluoxetine plus quetiapine or clomipramine versus fluoxetine plus placebo for obsessive-compulsive disorder. *J Clin Psychopharmacol.* 2011 Dec;31(6):763-8. doi: 10.1097/JCP.0b013e3182367aee. PMID: 22020357.
30. Kishi T, Matsuda Y, Iwata N, et al. Antipsychotics for cocaine or psychostimulant dependence: systematic review and meta-analysis of randomized, placebo-controlled trials. *J Clin Psychiatry.* 2013 Dec;74(12):e1169-80. doi: 10.4088/JCP.13r08525. PMID: 24434105.
31. Vergne DE, Anton RF. Aripiprazole: a drug with a novel mechanism of action and possible efficacy for alcohol dependence. *CNS Neurol Disord Drug Targets.* 2010 Mar;9(1):50-4. doi: 10.2174/187152710790966731. PMID: 20201815.
32. Nelson JC, Mankoski R, Baker RA, et al. Effects of aripiprazole adjunctive to standard antidepressant treatment on the core symptoms of depression: a post-hoc, pooled analysis of two large, placebo-controlled studies. *J Affect Disord.* 2010 Jan;120(1-3):133-40. doi: 10.1016/j.jad.2009.06.026. PMID: 19656577.
33. Chen YC, Chen CK, Wang LJ. Quetiapine fumarate augmentation for patients with a primary anxiety disorder or a mood disorder: a pilot study. *BMC Psychiatry.* 2012;12:162. doi: 10.1186/1471-244x-12-162. PMID: 23020711.
34. Cohen JA, Bukstein O, Walter H, et al. Practice parameter for the assessment and treatment of children and adolescents with posttraumatic stress disorder. *J Am Acad Child Adolesc*

- Psychiatry. 2010 Apr;49(4):414-30. PMID: 20410735.
35. Gillberg CH, R.; Steinhausen, H. A Clinician's Handbook of Child and Adolescent Psychiatry. Cambridge: Cambridge University Press; 2006. PMID: PMC2247446.
 36. Sareen J, Cox BJ, Goodwin RD, et al. Co-occurrence of posttraumatic stress disorder with positive psychotic symptoms in a nationally representative sample. *J Trauma Stress*. 2005 Aug;18(4):313-22. doi: 10.1002/jts.20040. PMID: 16281228.
 37. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005 Jun;62(6):593-602. doi: 10.1001/archpsyc.62.6.593. PMID: 15939837.
 38. Kilpatrick DG, Ruggiero KJ, Acierno R, et al. Violence and risk of PTSD, major depression, substance abuse/dependence, and comorbidity: results from the National Survey of Adolescents. *J Consult Clin Psychol*. 2003 Aug;71(4):692-700. doi: 10.1037/0022006X.71.4.692. PMID: 12924674.
 39. Han C, Pae CU, Wang SM, et al. The potential role of atypical antipsychotics for the treatment of posttraumatic stress disorder. *J Psychiatr Res*. 2014 Sep;56:72-81. doi: 10.1016/j.jpsychires.2014.05.003. PMID: 24882700.
 40. Krystal JH, Rosenheck RA, Cramer JA, et al. Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service-related PTSD: a randomized trial. *JAMA*. 2011 Aug 3;306(5):493-502. doi: 10.1001/jama.2011.1080. PMID: 21813427.
 41. Moore JK, Watson HJ, Harper E, et al. Psychotropic drug prescribing in an Australian specialist child and adolescent eating disorder service: a retrospective study. *J Eat Disord*. 2013;1:27. doi: 10.1186/2050-2974-1-27. PMID: 24999406.
 42. Cavanna AE, Servo S, Monaco F, et al. The behavioral spectrum of Gilles de la Tourette syndrome. *J Neuropsychiatry Clin Neurosci*. 2009 Winter;21(1):13-23. doi: 10.1176/appi.neuropsych.21.1.13. PMID: 19359447.
 43. Seida JC, Schouten JR, Mousavi SS, et al. First- and Second-Generation Antipsychotics for Children and Young Adults. Rockville MD; 2012. PMID: 22439156.
 44. Kondo K, O'Neil, M., Mathis, S., McKenna, R., Vander Ley, K., Anderson, J., Helfand, M. Surveillance Report: First and second generation antipsychotics for children and young adults. Rockville, MD: Agency of Healthcare Research and Quality; 2014.
 45. Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: AHRQ; 2014.
 46. First and Second Generation Antipsychotics for Children and Young Adults-Comparative Effectiveness Review Update Protocol. Agency of Healthcare Research and Quality. 2015. <https://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2149>
 47. Higgin JP, Green, S. . Section 6.4.11.1 Search filters The Cochrane Handbook for Systematic Reviews of Interventions The Cochrane Collaboration 2011.
 48. Higgins JP, Green, S. . Section 8. Assessing the risk of bias of included studies Cochrane Handbook for Systematic Reviews of Interventions: The Cochrane Collaboration; 2011.
 49. Berkman ND, Lohr KN, Ansari M, et al. Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville MD; 2008.
 50. Wells G, Shea, B., O'Connell, N., Peterson, J., Welch, V., Losos, M., Tugwell, P. The Newcastle-Ottawa Scale for Assessing the Quality of Nonrandomized Studies in Meta-analyses. Ottawa, ON: Department of Epidemiology and Community Medicine, University of Ottawa 2009.
 51. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med*. 2004 Oct

- 30;23(20):3105-24. doi: 10.1002/sim.1875. PMID: 15449338.
52. Lumley T. Network meta-analysis for indirect treatment comparisons. *Stat Med.* 2002 Aug 30;21(16):2313-24. doi: 10.1002/sim.1201. PMID: 12210616.
 53. Sutton AJ, Abrams KR. Bayesian methods in meta-analysis and evidence synthesis. *Stat Methods Med Res.* 2001 Aug;10(4):277-303. doi: 10.1177/096228010101000404. PMID: 1149141.
 54. Cornell JE, Mulrow CD, Localio R, et al. Random-effects meta-analysis of inconsistent effects: a time for change. *Ann Intern Med.* 2014 Feb 18;160(4). PMID: 24727843.
 55. Golder S, Loke YK, Bland M. Meta-analysis of adverse effects data derived from randomised controlled trials as compared to observational studies: methodological overview. *PLoS Med.* 2011;8(5): e1001026. doi: 10.1371/journal.pmed.1001026. PMID: 21559325.
 56. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997 Sep 13;315(7109):629-34. doi: 10.1136/bmj.315.7109.629. PMID: 9310563.
 57. Veroniki AA, Mavridis D, Higgins J, Salanti G. Characteristics of a loop of evidence that affect detection and estimation of inconsistency: a simulation study *BMC Medical Research Methodology.* 2014;14:106.
 58. Achana FA, Cooper NJ, Bujkiewicz S, et al. Network meta-analysis of multiple outcome measures accounting for borrowing of information across outcomes. *BMC Med Res Methodol.* 2014;14:92. doi: 10.1186/1471-2288-14-92. PMID: 25047164.
 59. Keevil VL, Khaw KT. Overadjustment in regression analyses: considerations when evaluating relationships between body mass index, muscle strength, and body size. *J Gerontol A Biol Sci Med Sci.* 2014 May;69(5):616-7. doi: 10.1093/gerona/glt186. PMID: 24300030.
 60. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol.* 2011 Dec;64(12):1283-93. doi: 10.1016/j.jclinepi.2011.01.012. PMID: 21839614.
 61. Glenton C, Santesso N, Rosenbaum S, et al. Presenting the results of Cochrane systematic reviews to a consumer audience: a qualitative study. *Med Decis Making.* 2010; 30:566-577. doi: 10.1177/0272989X10375853. PMID: 20643912
 62. Biederman J, Mick E. Comparative open-label trial of atypical neuroleptics in children and adolescents with bipolar disorder. *Eur Neuropsychopharmacol.* 2004;14(suppl3):S211-S2. doi: 10.1016/S0924-977X(04)80177-9.
 63. Jefferson AM, Markowitz JS, Brewerton TD. Atypical antipsychotics. *J Am Acad Child Adolesc Psychiatry.* 1998;Vol.37(12):1243-4. doi: 10.1097/00004583-199812000-00004. PMID: 9847493.
 64. Schulz E, Fleischhaker C, Remschmidt HE. Correlated changes in symptoms and neurotransmitter indices during maintenance treatment with clozapine or conventional neuroleptics in adolescents and young adults with schizophrenia. *J Child Adolesc Psychopharmacol.* 1996;6(2):119-31. doi: 10.1089/cap.1996.6.119. PMID: 9231304.
 65. DelBello MP, Versavel M, Ice K, et al. Tolerability of oral ziprasidone in children and adolescents with bipolar mania, schizophrenia, or schizoaffective disorder. *J Child Adolesc Psychopharmacol.* 2008;18(5):491-9. doi: 10.1089/cap.2008.008. PMID: 18928413.
 66. Conus P, Berk M, Cotton SM, et al. Olanzapine or chlorpromazine plus lithium in first episode psychotic mania: An 8-week randomised controlled trial. *European Psychiatry.* 2015;30:975-82.
 67. 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. doi: 10.1007/s00787-009-0749-5. PMID: 19198920.
 68. Berger GE, Proffitt TM, McConchie M, et al. Dosing quetiapine in drug-naive first-episode psychosis: a controlled, double-blind, randomized, single-center study investigating efficacy, tolerability, and safety of 200 mg/day vs. 400 mg/day of quetiapine fumarate in 141 patients aged 15 to 25 years. *J Clin Psychiatry.* 2008;69(11):1702-14. PMID: 19036233.

69. Crocq MA, Guillon MS, Bailey PE, et al. Orally disintegrating olanzapine induces less weight gain in adolescents than standard oral tablets. *Eur Psychiatry*. 2007;22(7):453-4. doi:10.1016/j.eurpsy.2007.06.004. PMID: 17761403.
70. deHaan L, van Bruggen M, Lavalaye J, et al. Subjective experience and D2 receptor occupancy in patients with recent-onset schizophrenia treated with low-dose olanzapine or haloperidol: a randomized, double-blind study. *Am J Psychiatry*. 2003;160(2):303-9. doi: 10.1176/appi.ajp.160.2.303. PMID: 12562577.
71. Findling RL, Cavus I, Pappadopulos E, et al. Ziprasidone in adolescents with schizophrenia: results from a placebo-controlled efficacy and long-term open-extension study. *J Child Adolesc Psychopharmacol*. 2013a Oct;23(8):531-44. doi: 10.1089/cap.2012.0068. PMID: 24111983.
72. Findling RL, McKenna K, Earley WR, et al. Efficacy and safety of quetiapine in adolescents with schizophrenia investigated in a 6-week, double-blind, placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2012a Oct;22(5):327-42. doi: 10.1089/cap.2011.0092. PMID: 23083020.
73. 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*. 2008a;165(11):1432-41. doi: 10.1176/appi.ajp.2008.07061035. PMID: 18765484.
74. Haas M, Eerdekens M, Kushner S, et al. Efficacy, safety and tolerability of two dosing regimens in adolescent schizophrenia: double-blind study. *Br J Psychiatry*. 2009a;194(2):158-64. doi: 10.1192/bjp.bp.107.046177. PMID: 19182179.
75. Jensen JB, Kumra S, Leitten W, et al. A comparative pilot study of second-generation antipsychotics in children and adolescents with schizophrenia-spectrum disorders. *J Child Adolesc Psychopharmacol*. 2008;18(4):317-26. doi: 10.1089/cap.2007.0123. PMID: 18759641.
76. Kryzhanovskaya L, Schulz SC, McDougale C, et al. Olanzapine versus placebo in adolescents with schizophrenia: a 6-week, randomized, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2009;48(1):60-70. doi: 10.1097/CHI.0b013e3181900404. PMID: 19057413.
77. Kumra S, Frazier JA, Jacobsen LK, et al. Childhood-onset schizophrenia. A double-blind clozapine-haloperidol comparison. *Arch Gen Psychiatry*. 1996;53(12):1090-7. doi:10.1001/archpsyc.1996.0183012002005. PMID: 8956674.
78. 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. doi:10.1016/j.biopsych.2007.04.043. PMID: 17651705.
79. Mozes T, Ebert T, Michal SE, et al. An open-label randomized comparison of olanzapine versus risperidone in the treatment of childhood-onset schizophrenia. *J Child Adolesc Psychopharmacol*. 2006;16(4):393-403. doi:10.1089/cap.2006.16.393. PMID: 16958565.
80. Shaw P, Sporn A, Gogtay N, et al. Childhood-onset schizophrenia: A double-blind, randomized clozapine-olanzapine comparison. *Arch Gen Psychiatry*. 2006;63(7):721-30. doi:10.1001/archpsyc.63.7.721. PMID: 16818861.
81. Sikich L, Frazier JA, McClellan J, et al. Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS) study. *Am J Psychiatry*. 2008;165(11):1420-31. doi: 10.1176/appi.ajp.2008.08050756. PMID: 18794207.
82. Sikich L, Hamer RM, Bashford RA, et al. A pilot study of risperidone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial. *Neuropsychopharmacology*. 2004;29(1):133-45. doi:10.1038/sj.npp.1300327 PMID: 14583740.
83. Spencer EK, Campbell M. Children with schizophrenia: diagnosis, phenomenology,

- and pharmacotherapy. *Schizophr Bull.* 1994;20(4):713-25. doi: 10.1093/schbul/20.4.713. PMID: 7701278.
84. Swadi HS, Craig BJ, Pirwani NZ, et al. A trial of quetiapine compared with risperidone in the treatment of first onset psychosis among 15-to 18-year-old adolescents. *Int Clin Psychopharmacol.* 2010;25(1):1-6. doi: 10.1097/YIC.0b013e3283320511. PMID: 19809337.
 85. van Bruggen J, Tijssen J, Dingemans P, et al. Symptom response and side-effects of olanzapine and risperidone in young adults with recent onset schizophrenia. *Int Clin Psychopharmacol.* 2003;18(6):341-6. PMID: 14571154.
 86. Woods SW, Breier A, Zipursky RB, et al. Randomized trial of olanzapine versus placebo in the symptomatic acute treatment of the schizophrenic prodrome. *Biol Psychiatry.* 2003;54(4):453-64. doi:10.1016/S0006-3223(03)00321-4. PMID: 12915290.
 87. Yen YC, Lung F-W, Chong MY. Adverse effects of risperidone and haloperidol treatment in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry.* 2004;Vol.28(2):285-90. doi:10.1016/j.pnpbp.2003.10.006. PMID: 14751424.
 88. Haas M, Unis AS, Armenteros J, et al. A 6-week, randomized, double-blind, placebo-controlled study of the efficacy and safety of risperidone in adolescents with schizophrenia. *J Child Adolesc Psychopharmacol.* 2009b;19(6):611-21. doi: 10.1089/cap.2008.0144. PMID: 20035579.
 89. Johnson & Johnson Pharmaceutical Research & Development. Open-label study to evaluate the safety and pharmacokinetics of single- and multiple-dose extended-release paliperidone in pediatric subjects (10 to 17 years of age) with schizophrenia, schizoaffective disorder, or schizophreniform disorder. (Clinical Study Report). 2011.
 90. Singh J, Robb A, Vijapurkar U, et al. A randomized, double-blind study of paliperidone extended-release in treatment of acute schizophrenia in adolescents. *Biol Psychiatry.* 2011 Dec 15;70(12):1179-87. doi: 10.1016/j.biopsych.2011.06.021. PMID: 21831359.
 91. Buchsbaum MS, Haznedar MM, Aronowitz J, et al. FDG-PET in never-previously medicated psychotic adolescents treated with olanzapine or haloperidol. *Schizophr Res.* 2007 Aug;94(1-3):293-305. doi:10.1016/j.schres.2007.04.027. PMID: 17574821.
 92. Findling RL, Landbloom RP, Mackle M, et al. Safety and Efficacy from an 8 Week Double-Blind Trial and a 26 Week Open-Label Extension of Asenapine in Adolescents with Schizophrenia. *J Child Adolesc Psychopharmacol.* 2015a Jun;25(5):384-96. doi: http://dx.doi.org/10.1089/cap.2015.0027. PMID: 26091193.
 93. 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. *J Clin Psychiatry.* 2013 Apr;74(4):349-56. doi: http://dx.doi.org/10.4088/JCP.12m07785. PMID: 23218022.
 94. Savitz AJ, Lane R, Nuamah I, et al. Efficacy and safety of paliperidone extended release in adolescents with schizophrenia: a randomized, double-blind study. *J Am Acad Child Adolesc Psychiatry.* 2015 Feb;54(2):126-37.e1. doi: http://dx.doi.org/10.1016/j.jaac.2014.11.009. PMID: 25617253.
 95. NCT01149655. Efficacy & Safety Study of Oral Aripiprazole in Adolescents With Schizophrenia. 2015. Available at <https://clinicaltrials.gov/ct2/show/NCT01149655?term=NCT01149655&rank=1>
 96. Gothelf D, Falk B, Singer P, et al. Weight gain associated with increased food intake and low habitual activity levels in male adolescent schizophrenic inpatients treated with olanzapine. *Am J Psychiatry.* 2002;159(6):1055-7. doi: 10.1176/appi.ajp.159.6.1055 PMID: 12042200.
 97. Hrdlicka M, Zedkova I, Blatny M, et al. Weight gain associated with atypical and typical antipsychotics during treatment of adolescent schizophrenic psychoses: A retrospective study. *Neuroendocrinology Lett.* 2009;30(2):256-61. PMID: 19675512.
 98. Kumra S, Jacobsen LK, Lenane M, et al. Childhood-onset schizophrenia: an open-label study of olanzapine in adolescents. *J Am Acad Child Adolesc Psychiatry.*

- 1998;37(4):377-85. doi:10.1097/00004583-199804000-00015. PMID: 9549958.
99. Ratzoni G, Gothelf D, Brand-Gothelf A, et al. Weight Gain Associated with Olanzapine and Risperidone in Adolescent Patients: A Comparative Prospective Study. *J Am Acad Child Adolesc Psychiatry*. 2002;41(3):337-43. doi:10.1097/00004583-200203000-00014 PMID: 11886029.
 100. Wudarsky M, Nicolson R, Hamburger SD, et al. Elevated prolactin in pediatric patients on typical and atypical antipsychotics. *Journal of Child and Adolescent Psychopharmacology*. 9(4).(pp 239-245), 1999. Date of Publication: 1999. 1999(4):239-45.
 101. Castro-Fornieles J, Parellada M, Soutullo CA, et al. Antipsychotic treatment in child and adolescent first-episode psychosis: a longitudinal naturalistic approach. *J Child Adolesc Psychopharmacol*. 2008 Aug;18(4):327-36. doi: <http://dx.doi.org/10.1089/cap.2007.0138>. PMID: 18759642.
 102. Cianchetti C, Ledda MG. Effectiveness and safety of antipsychotics in early onset psychoses: a long-term comparison. *Psychiatry Res*. 2011 Oct 30;189(3):349-56. doi: <http://dx.doi.org/10.1016/j.psychres.2011.03.020>. PMID: 21570128.
 103. O'Donoghue B, Schafer MR, Becker J, et al. Metabolic changes in first-episode early-onset schizophrenia with second-generation antipsychotics. *Early Interv Psychiatry*. 2014 Aug;8(3):276-80. doi: <http://dx.doi.org/10.1111/eip.12083>. PMID: 23968390.
 104. Olfson M, Gerhard T, Huang C, et al. Comparative effectiveness of second-generation antipsychotic medications in early-onset schizophrenia. *Schizophr Bull*. 2012 Jun;38(4):845-53. doi: <http://dx.doi.org/10.1093/schbul/sbq172>. PMID: 21307041.
 105. Schneider MR, Adler CM, Whitsel R, et al. The effects of ziprasidone on prefrontal and amygdalar activation in manic youth with bipolar disorder. *Isr J Psychiatry Relat Sci*. 2012;49(2):112-20. PMID: 22801290.
 106. NCT00194012. Study of Aripiprazole (Abilify) Versus Placebo in Children With Subsyndromal Bipolar Disorder. 2014. Available at <https://clinicaltrials.gov/ct2/show/NCT00194012?term=NCT00194012&rank=1>
 107. Oh J, Chang JG, Lee SB, et al. Comparison of aripiprazole and other atypical antipsychotics for pediatric bipolar disorder: a retrospective chart review of efficacy and tolerability. *Clin Psychopharmacol Neurosci*. 2013 Aug;11(2):72-9. doi: <http://dx.doi.org/10.9758/cpn.2013.11.2.72>. PMID: 24023551.
 108. Findling RL, Landbloom RL, Szegedi A, et al. Asenapine for the Acute Treatment of Pediatric Manic or Mixed Episode of Bipolar I Disorder. *J Am Acad Child Adolesc Psychiatry*. 2015b Dec;54(12):1032-41. doi: 10.1016/j.jaac.2015.09.007. PMID: 26598478.
 109. Findling RL, Pathak S, Earley WR, et al. Efficacy and safety of extended-release quetiapine fumarate in youth with bipolar depression: an 8 week, double-blind, placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2014a Aug;24(6):325-35. doi: <http://dx.doi.org/10.1089/cap.2013.0105>. PMID: 24956042.
 110. Findling RL, Youngstrom EA, McNamara NK, et al. Double-blind, randomized, placebo-controlled long-term maintenance study of aripiprazole in children with bipolar disorder. *J Clin Psychiatry*. 2012b Jan;73(1):57-63. doi: <http://dx.doi.org/10.4088/JCP.11m07104>. PMID: 22152402.
 111. Kowatch RA, Scheffer RE, Monroe E, et al. Placebo-controlled trial of valproic Acid versus risperidone in children 3-7 years of age with bipolar I disorder. *J Child Adolesc Psychopharmacol*. 2015 May;25(4):306-13. doi: <http://dx.doi.org/10.1089/cap.2014.0166>. PMID: 25978742.
 112. Masi G, Milone A, Stawinoga A, et al. Efficacy and Safety of Risperidone and Quetiapine in Adolescents With Bipolar II Disorder Comorbid With Conduct Disorder. *J Clin Psychopharmacol*. 2015 Oct;35(5):587-90. doi: <http://dx.doi.org/10.1097/JCP.0000000000000371>. PMID: 26226481.

113. Biederman J, Mick E, Hammerness P, et al. Open-label, 8-week trial of olanzapine and risperidone for the treatment of bipolar disorder in preschool-age children. *Biol Psychiatry*. 2005; 58(7):589-94. doi:10.1016/j.biopsych.2005.03.019. PMID: 16239162.
114. DelBello MP, Chang K, Welge JA, et al. A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. *Bipolar Disord*. 2009;11(5):483-93. doi: 10.1111/j.1399-5618.2009.00728.x. PMID: 19624387.
115. DelBello MP, Schwiers ML, Rosenberg HL, et al. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. *J Am Acad Child Adolesc Psychiatry*. 2002;41(10):1216-23. doi:10.1097/00004583-200210000-00011 PMID: 12364843.
116. Findling RL, Cavus I, Pappadopulos E, et al. Efficacy, long-term safety, and tolerability of ziprasidone in children and adolescents with bipolar disorder. *J Child Adolesc Psychopharmacol*. 2013b Oct;23(8):545-57. doi: 10.1089/cap.2012.0029. PMID: 24111980.
117. 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. *J Clin Psychiatry*. 2009;70(10):1441-51. doi: 10.4088/JCP.09m05164yel. PMID: 19906348.
118. 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*. 2009c;11(7):687-700. doi: 10.1111/j.1399-5618.2009.00750.x. PMID: 19839994.
119. Pathak S., Findling RL, Earley WR, et al. Efficacy and safety of quetiapine in children and adolescents with mania associated with bipolar I disorder: a 3-week, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2013 Jan;74(1):e100-9. doi: 10.4088/JCP.11m07424. PMID: 23419231.
120. Tohen M, Kryzhanovskaya L, Carlson G, et al. Olanzapine versus placebo in the treatment of adolescents with bipolar mania. *Am J Psychiatry*. 2007;164(10):1547-56. <http://dx.doi.org/10.1176/appi.ajp.2007.06111932> PMID: 17898346.
121. Tramontina S, Zeni CP, Ketzer CR, et al. Aripiprazole in children and adolescents with bipolar disorder comorbid with attention-deficit/hyperactivity disorder: a pilot randomized clinical trial. *J Clin Psychiatry*. 2009;70(5):756-64. doi: 10.4088/JCP.08m04726. PMID: 19389329.
122. Anderson LT, Campbell M, Adams P, et al. The effects of haloperidol on discrimination learning and behavioral symptoms in autistic children. *J Autism Dev Disord*. 1989 Jun;19(2):227-39. PMID: 2663834.
123. Findling RL, Mankoski R, Timko K, et al. A randomized controlled trial investigating the safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric patients with irritability associated with autistic disorder. *J Clin Psychiatry*. 2014b Jan;75(1):22-30. doi: <http://dx.doi.org/10.4088/JCP.13m8500>. PMID: 24502859.
124. Ghanizadeh A, Sahraeizadeh A, Berk M. A head-to-head comparison of aripiprazole and risperidone for safety and treating autistic disorders, a randomized double blind clinical trial. *Child Psychiatry Hum Dev*. 2014a;45(2):185-92. doi: <http://dx.doi.org/10.1007/s10578-013-0390-x>. PMID: 23801256.
125. Hellings JA, Zarccone 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. doi: 10.1007/s10803-006-0078-1 PMID: 16596465.
126. Hollander E, Wasserman S, Swanson EN, et al. A double-blind placebo-controlled pilot study of olanzapine in childhood/adolescent pervasive developmental disorder. *J Child Adolesc Psychopharmacol*. 2006;16(5):541-8. doi:10.1089/cap.2006.16.541. PMID: 17069543.
127. Loebel A, Brams M, Goldman RS, et al. Lurasidone for the treatment of irritability with autistic disorder. *J Autism Dev Disord*. 2016;46:1153-63.
128. Kent JM, Kushner S, Ning X, et al. Risperidone dosing in children and adolescents with autistic disorder: a double-blind, placebo-controlled study. *J Autism Dev*

- Disord. 2013 Aug;43(8):1773-83. doi: 10.1007/s10803-012-1723-5. PMID: 23212807.
129. Luby J, Mrakotsky C, Stalets MM, et al. Risperidone in preschool children with autistic spectrum disorders: an investigation of safety and efficacy. *J Child Adolesc Psychopharmacol.* 2006;16(5):575-87. doi:10.1089/cap.2006.16.575. PMID: 17069546.
 130. Malone RP, Cater J, Sheikh RM, et al. Olanzapine versus haloperidol in children with autistic disorder: an open pilot study. *J Am Acad Child Adolesc Psychiatry.* 2001;40(8):887-94. doi:10.1097/00004583-200108000-00009 PMID: 11501687.
 131. 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 Acad Child Adolesc Psychiatry.* 2009;48(11):1110-9. doi: 10.1097/CHI.0b013e3181b76658. PMID: 19797985.
 132. 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. doi: 10.1056/NEJMoa013171 PMID: 12151468.
 133. 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. PMID: 18080171.
 134. Nagaraj R, Singhi P, Malhi P. Risperidone in children with autism: randomized, placebo-controlled, double-blind study. *J Child Neurol.* 2006;21(6):450-5. doi: 10.1177/08830738060210060801. PMID: 16948927.
 135. 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. doi: 10.1542/peds.2008-3782. PMID: 19948625.
 136. Perry R, Campbell M, Adams P, et al. Long-term efficacy of haloperidol in autistic children: continuous versus discontinuous drug administration. *J Am Acad Child Adolesc Psychiatry.* 1989;28(1):87-92. doi:10.1097/00004583-198901000-00016 PMID: 2914841.
 137. Remington G, Sloman L, Konstantareas M, et al. Clomipramine versus haloperidol in the treatment of autistic disorder: a double-blind, placebo-controlled, crossover study. *J Clin Psychopharmacol.* 2001 Aug;21(4):440-4. PMID: 11476129.
 138. Research Units on Pediatric Psychopharmacology (RUPP). Risperidone treatment of autistic disorder: longer-term benefits and blinded discontinuation after 6 months. *Am J Psychiatry.* 2005;162(7):1361-9. <http://dx.doi.org/10.1176/appi.ajp.162.7.1361> PMID: 15994720.
 139. Shea S, Turgay A, Carroll A, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics.* 2004;114(5):e634-e41. PMID: 15492353.
 140. Troost PW, Lahuis BE, Steenhuis MP, et al. Long-term effects of risperidone in children with autism spectrum disorders: a placebo discontinuation study. *J Am Acad Child Adolesc Psychiatry.* 2005;44(11):1137-44. doi:10.1097/01.chi.0000177055.11229.76 PMID: 16239862.
 141. NCT00619190. Study of Aripiprazole to Treat Children and Adolescents With Autism. 2014. Available at <https://clinicaltrials.gov/ct2/show/NCT00619190?term=00619190&rank=1>
 142. Mankoski R, Stockton G, Manos G, et al. Aripiprazole treatment of irritability associated with autistic disorder and the relationship between prior antipsychotic exposure, adverse events, and weight change. *J Child Adolesc Psychopharmacol.* 2013 Oct;23(8):572-6. doi: <http://dx.doi.org/10.1089/cap.2012.0075>. PMID: 24138011.
 143. Novaes CM, Ponde MP, Freire AC. Control of psychomotor agitation and aggressive behavior in patients with autistic disorder: a retrospective chart review. *Arq Neuropsiquiatr.* 2008;66(3B):646-51. doi: 10.1590/S0004-282X2008000500008. PMID: 18949256.
 144. Wink LK, Early M, Schaefer T, et al. Body mass index change in autism spectrum

- disorders: comparison of treatment with risperidone and aripiprazole. *J Child Adolesc Psychopharmacol*. 2014 Mar;24(2):78-82. doi: <http://dx.doi.org/10.1089/cap.2013.0099>. PMID: 24564519.
145. Troost PW, Althaus M, Lahuus BE, et al. Neuropsychological effects of risperidone in children with pervasive developmental disorders: a blinded discontinuation study. *J Child Adolesc Psychopharmacol*. 2006;16(5):561-73. doi:10.1089/cap.2006.16.561. PMID: 17069545.
 146. Pandina GJ, Bilder R, Harvey PD, et al. Risperidone and cognitive function in children with disruptive behavior disorders. *Biol Psychiatry*. 2007 Aug 1;62(3):226-34. doi:10.1016/j.biopsych.2006.09.036. PMID: 17210137.
 147. 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? *J Am Acad Child Adolesc Psychiatry*. 2014 Jan;53(1):47-60.e1. doi: <http://dx.doi.org/10.1016/j.jaac.2013.09.022>. PMID: 24342385.
 148. Stocks JD, Taneja BK, Baroldi P, et al. A phase 2a randomized, parallel group, dose-ranging study of molindone in children with attention-deficit/hyperactivity disorder and persistent, serious conduct problems. *J Child Adolesc Psychopharmacol*. 2012 Apr;22(2):102-11. doi: <http://dx.doi.org/10.1089/cap.2011.0087>. PMID: 22372512.
 149. Aman MG, Binder C, Turgay A. Risperidone effects in the presence/absence of psychostimulant medicine in children with ADHD, other disruptive behavior disorders, and subaverage IQ. *J Child Adolesc Psychopharmacol*. 2004;14(2):243-54. doi:10.1089/1044546041649020. PMID: 15319021.
 150. Aman MG, Marks RE, Turbott SH, et al. Clinical effects of methylphenidate and thioridazine in intellectually subaverage children. *J Am Acad Child Adolesc Psychiatry*. 1991 Mar;30(2):246-56. doi:10.1097/00004583-199103000-00013. PMID: 2016229.
 151. Aman MG, De SG, 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. doi: <http://dx.doi.org/10.1176/appi.ajp.159.8.1337>. PMID: 12153826.
 152. Aman MG, Hollway JA, Leone S, et al. Effects of risperidone on cognitive-motor performance and motor movements in chronically medicated children. *Res Dev Disabil*. 2009;30(2):386-96. doi:10.1016/j.ridd.2008.07.004. PMID: 18768293.
 153. Armenteros JI, Lewis JE, Davalos M. Risperidone augmentation for treatment-resistant aggression in attention-deficit/hyperactivity disorder: a placebo-controlled pilot study. *J Am Acad Child Adolesc Psychiatry*. 2007(5):558-65. doi:10.1097/chi.0b013e3180323354. PMID: 17450046.
 154. 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. PMID: 11379837.
 155. Connor DF, McLaughlin TJ, Jeffers-Terry M. Randomized controlled pilot study of quetiapine in the treatment of adolescent conduct disorder. *J Child Adolesc Psychopharmacol*. 2008;18(2):140-56. doi:10.1089/cap.2006.0007. PMID: 18439112.
 156. 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. doi:10.1097/00004583-200004000-00021. PMID: 10761354.
 157. Reyes M, Buitelaar J, Toren P, et al. A randomized, double-blind, placebo-controlled study of risperidone maintenance treatment in children and adolescents with disruptive behavior disorders. *Am J Psychiatry*. 2006;163(3):402-10. doi: <http://dx.doi.org/10.1176/appi.ajp.163.3.402>. PMID: 16513860.
 158. Snyder R, Turgay A, Aman M, et al. Effects of risperidone on conduct and disruptive behavior disorders in children with

- subaverage IQs. *J Am Acad Child Adolesc Psychiatry*. 2002;41(9):1026-36. PMID: 12218423.
159. Masi G, Pfanner C, Brovedani P. Antipsychotic augmentation of selective serotonin reuptake inhibitors in resistant tic-related obsessive-compulsive disorder in children and adolescents: a naturalistic comparative study. *J Psychiatr Res*. 2013 Aug;47(8):1007-12. doi: <http://dx.doi.org/10.1016/j.jpsychires.2013.04.003>. PMID: 23664673.
 160. Weisler RH, Khan A, Trivedi MH, et al. Analysis of suicidality in pooled data from 2 double-blind, placebo-controlled aripiprazole adjunctive therapy trials in major depressive disorder. *J Clin Psychiatry*. 2011 Apr;72(4):548-55. doi: <http://dx.doi.org/10.4088/JCP.09m05495gre>. PMID: 20816039.
 161. Hagman J, Gralla J, Sigel E, et al. A double-blind, placebo-controlled study of risperidone for the treatment of adolescents and young adults with anorexia nervosa: a pilot study. *J Am Acad Child Adolesc Psychiatry*. 2011 Sep;50(9):915-24. doi: <http://dx.doi.org/10.1016/j.jaac.2011.06.009>. PMID: 21871373.
 162. Kafantaris V, Leigh E, Hertz S, et al. A placebo-controlled pilot study of adjunctive olanzapine for adolescents with anorexia nervosa. *J Child Adolesc Psychopharmacol*. 2011 Jun;21(3):207-12. doi: <http://dx.doi.org/10.1089/cap.2010.0139>. PMID: 21663423.
 163. Norris ML, Spettigue W, Buchholz A, et al. Olanzapine use for the adjunctive treatment of adolescents with anorexia nervosa. *J Child Adolesc Psychopharmacol*. 2011 Jun;21(3):213-20. doi: <http://dx.doi.org/10.1089/cap.2010.0131>. PMID: 21510781.
 164. Bruggeman R, van der LC, Buitelaar JK, et al. Risperidone versus pimozide in Tourette's disorder: a comparative double-blind parallel-group study. *J Clin Psychiatry*. 2001;62(1):50-6. PMID: 16239162.
 165. Ghanizadeh A, Haghghi A. Aripiprazole versus risperidone for treating children and adolescents with tic disorder: a randomized double blind clinical trial. *Child Psychiatry Hum Dev*. 2014b 01 Oct;45(5):596-603. doi: <http://dx.doi.org/10.1007/s10578-013-0427-1>. PMID: 24343476.
 166. Gilbert DL, Batterson JR, Sethuraman G, et al. Tic reduction with risperidone versus pimozide in a randomized, double-blind, crossover trial. *J Am Acad Child Adolesc Psychiatry*. 2004;Vol.43(2):206-14. doi:10.1097/00004583-200402000-00017. PMID: 14726728.
 167. Sallee FR, Kurlan R, Goetz CG, et al. Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study. *J Am Acad Child Adolesc Psychiatry*. 2000;39(3):292-9. doi:10.1097/00004583-200003000-00010. PMID: 10714048.
 168. Sallee FR, Nesbitt L, Jackson C, et al. Relative efficacy of haloperidol and pimozide in children and adolescents with Tourette's disorder. *Am J Psychiatry*. 1997;154(8):1057-62. <http://dx.doi.org/10.1176/ajp.154.8.1057> PMID: 9247389.
 169. Sallee FR, Sethuraman G, Rock CM. Effects of pimozide on cognition in children with Tourette syndrome: interaction with comorbid attention deficit hyperactivity disorder. *Acta Psychiatr Scand*. 1994;90(1):4-9. doi: 10.1111/j.1600-0447.1994.tb01546.x PMID: 7976448.
 170. Scahill L, Leckman JF, Schultz RT, et al. A placebo-controlled trial of risperidone in Tourette syndrome. *Neurology*. 2003;60(7):1130-5. PMID: 12682319.
 171. Sehgal N. Short-term versus longer term pimozide therapy in Tourette's syndrome: a preliminary study. *Neurology*. 1999;52(4):874-7. PMID: 10078748.
 172. Yoo HK, Joung YS, Lee JS, et al. A multicenter, randomized, double-blind, placebo-controlled study of aripiprazole in children and adolescents with Tourette's disorder. *J Clin Psychiatry*. 2013 Aug;74(8):e772-80. doi: <http://dx.doi.org/10.4088/JCP.12m08189>. PMID: 24021518.
 173. Gulisano M, Cali PV, Cavanna AE, et al. Cardiovascular safety of aripiprazole and pimozide in young patients with Tourette syndrome. *Neurol Sci*. 2011 Dec;32(6):1213-7. doi: <http://dx.doi.org/10.1007/s10072-011-0678-1>. PMID: 21732066.

174. Rizzo R, Eddy CM, Cali P, et al. Metabolic effects of aripiprazole and pimozide in children with Tourette syndrome. *Pediatr Neurol*. 2012 Dec;47(6):419-22. doi: <http://dx.doi.org/10.1016/j.pediatrneurol.2012.08.015>. PMID: 23127261.
175. Yoo HK, Lee JS, Paik KW, et al. Open-label study comparing the efficacy and tolerability of aripiprazole and haloperidol in the treatment of pediatric tic disorders. *Eur Child Adolesc Psychiatry*. 2011 Mar;20(3):127-35. doi: <http://dx.doi.org/10.1007/s00787-010-0154-0>. PMID: 21188439.
176. Storch EA, De Nadai AS, Lewin AB, et al. Defining treatment response in pediatric tic disorders: A signal detection analysis of the yale global tic severity scale. *J Child Adolesc Psychopharmacol*. 2011 01 Dec;21(6):621-7. doi: <http://dx.doi.org/10.1089/cap.2010.0149>. PMID: 2012000755.
177. Omranifard V, Najafi M, Sharbafchi MR, et al. Risperidone as a treatment for childhood habitual behavior. *J Res Pharm Pract*. 2013 Jan;2(1):29-33. doi: <http://dx.doi.org/10.4103/2279-042X.114086>. PMID: 24991601.
178. Van Bellinghen M, De Troch C. Risperidone in the treatment of behavioral disturbances in children and adolescents with borderline intellectual functioning: a double-blind, placebo-controlled pilot trial. *J Child Adolesc Psychopharmacol*. 2001;11(1):5-13. doi:10.1089/104454601750143348. PMID: 11322745.
179. Findling RL, Goldman R, Chiu Y, et al. Pharmacokinetics and tolerability of lurasidone in children and adolescents with psychiatric disorders. *Clinical Therapeutics*. 2015;37:2788-97
180. Ronsley R, Nguyen D, Davidson J, et al. Increased risk of obesity and metabolic dysregulation following 12 months of second-generation antipsychotic treatment in children: A prospective cohort study. *Can J Psychiatr*. 2015;60:441-50.
181. 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. *J Am Acad Child Adolesc Psychiatry*. 2014 Nov;53(11):1179-90. doi:10.1097/JCP.0b013e3181817dd520. PMID: 18626272.
182. Calarge CA, Nicol G, Schlechte JA, et al. Cardiometabolic outcomes in children and adolescents following discontinuation of long-term risperidone treatment. *J Child Adolesc Psychopharmacol*. 2014 Apr;24(3):120-9. doi: <http://dx.doi.org/10.1089/cap.2013.0126>. PMID: 24725198.
183. Correll CU, Manu P, Olshanskiy V, et al. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA*. 2009;302(16):1765-73. doi: 10.1001/jama.2009.1549. PMID: 19861668.
184. Cuerda C, Merchan-Naranjo J, Velasco C, et al. Influence of resting energy expenditure on weight gain in adolescents taking second-generation antipsychotics. *Clin Nutr*. 2011 Oct;30(5):616-23. doi: <http://dx.doi.org/10.1016/j.clnu.2011.03.00>. PMID: 21492975.
185. Findling RL, Kauffman RE, Sallee FR, et al. Tolerability and pharmacokinetics of aripiprazole in children and adolescents with psychiatric disorders: an open-label, dose-escalation study. *J Clin Psychopharmacol*. 2008b;28(4):441-6. doi: 10.1097/JCP.0b013e3181817dd520. PMID: 18626272.
186. 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. doi:10.1089/cap.2006.16.308. PMID: 16768638.
187. Fraguas D, Merchan-Naranjo J, Laita P, et al. Metabolic and hormonal side effects in children and adolescents treated with second-generation antipsychotics. *J Clin Psychiatry*. 2008;69(7):1166-75. PMID: 18588363.
188. Germano E, Italiano D, Lamberti M, et al. ECG parameters in children and adolescents treated with aripiprazole and risperidone. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014 Jun 3;51:23-7. doi: <http://dx.doi.org/10.1016/j.pnpbp.2013.10.020>. PMID: 24211841.
189. Pogge DL, Singer MB, Harvey PD. Rates and predictors of adherence with atypical

- antipsychotic medication: a follow-up study of adolescent inpatients. *J Child Adolesc Psychopharmacol*. 2005 Dec;15(6):901-12. doi:10.1089/cap.2005.15.901. PMID: 16379510.
190. Saito E, Correll CU, Gallelli K, et al. A prospective study of hyperprolactinemia in children and adolescents treated with atypical antipsychotic agents. *J Child Adolesc Psychopharmacol*. 2004;14(3):350-8. doi:10.1089/cap.2004.14.350. PMID: 15650492.
 191. Alacqua M, Trifiro G, Arcoraci V, et al. Use and tolerability of newer antipsychotics and antidepressants: A chart review in a paediatric setting. *Pharm World Sci*. 2008;30(1):44-50. PMID: 17588130.
 192. Bastiaens L. A non-randomized, open study with aripiprazole and ziprasidone for the treatment of aggressive behavior in youth in a community clinic. *Community Ment Health J*. 2009;45(1):73-7. doi: 10.1007/s10597-008-9154-7 PMID: 18597173.
 193. Bobo WV, Cooper WO, Stein CM, et al. Antipsychotics and the risk of type 2 diabetes mellitus in children and youth. *JAMA Psychiatry*. 2013 Oct;70(10):1067-75. doi: <http://dx.doi.org/10.1001/jamapsychiatry.2013.2053>. PMID: 23965896.
 194. Ebert T, Midbari Y, Shmilovitz R, et al. Metabolic effects of antipsychotics in prepubertal children: a retrospective chart review. *J Child Adolesc Psychopharmacol*. 2014 May;24(4):218-22. doi: <http://dx.doi.org/10.1089/cap.2013.0116>. PMID: 24816004.
 195. Friedlander R, Lazar S, Klancnik J. Atypical antipsychotic use in treating adolescents and young adults with developmental disabilities. *Can J Psychiatry*. 2001;46(8):741-5. PMID: 11692977.
 196. Jerrell JM, McIntyre RS. Adverse events in children and adolescents treated with antipsychotic medications. *Hum Psychopharmacol*. 2008 Jun;23(4):283-90. doi: <http://dx.doi.org/10.1002/hup.932>. PMID: 18302312.
 197. Khan RA, Mican LM, Suehs BT. Effects of olanzapine and risperidone on metabolic factors in children and adolescents: a retrospective evaluation. *J Psychiatr Pract*. 2009 Jul;15(4):320-8. doi: <http://dx.doi.org/10.1097/01.pra.0000358319.81307.a5>. PMID: 19625888.
 198. Khan SS, Mican LM. A naturalistic evaluation of intramuscular ziprasidone versus intramuscular olanzapine for the management of acute agitation and aggression in children and adolescents. *J Child Adolesc Psychopharmacol*. 2006;16(6):671-7. doi:10.1089/cap.2006.16.671. PMID: 17201611.
 199. Martin A, Landau J, Leebens P, et al. Risperidone-associated weight gain in children and adolescents: A retrospective chart review. *J Child Adolesc Psychopharmacol*. 2000;10(4):259-68. doi:10.1089/cap.2000.10.259. PMID: 2001041072.
 200. Migliardi G, Spina E, D'Arrigo C, et al. Short- and long-term effects on prolactin of risperidone and olanzapine treatments in children and adolescents. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33(8):1496-501. doi: 10.1016/j.pnpbp.2009.08.009. PMID: 19706318.
 201. Wonodi I, Reeves G, Carmichael D, et al. Tardive dyskinesia in children treated with atypical antipsychotic medications. *Mov Disord*. 2007 Sep 15;22(12):1777-82. doi: 10.1002/mds.21618 PMID: 17580328.
 202. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. *J Clin Psychiatry*. 2004 Feb;65(2):267-72. PMID: 15003083.
 203. Findling RL, Jensen PS. American Academy of Child and Adolescent Psychiatry. Practice Parameter for the use of Atypical Antipsychotic Medications in Children and Adolescents. 2012. Available at www.aacap.org
 204. Edelsohn GA, Parthasarathy M, Terhorst L, et al. Measurement of metabolic monitoring in youth and adult Medicaid recipients prescribed antipsychotics. *J Manag Care Spec Pharm*. 2015 Sep;21(9):769-77, 77a-77cc. doi: 10.18553/jmcp.2015.21.9.769. PMID: 26308224.
 205. Morrato EH, Druss BG, Hartung DM, et al. Small area variation and geographic and

- patient-specific determinants of metabolic testing in antipsychotic users. *Pharmacoepidemiol Drug Saf.* 2011 Jan;20(1):66-75. doi: 10.1002/pds.2062. PMID: 21182154.
206. Morrato EH, Druss B, Hartung DM, et al. Metabolic testing rates in 3 state Medicaid programs after FDA warnings and ADA/APA recommendations for second-generation antipsychotic drugs. *Arch Gen Psychiatry.* 2010 Jan;67(1):17-24. doi: 10.1001/archgenpsychiatry.2009.179. PMID: 20048219.
207. Rodday AM, Parsons SK, Mankiw C, et al. Child and adolescent psychiatrists' reported monitoring behaviors for second-generation antipsychotics. *J Child Adolesc Psychopharmacol.* 2015 May;25(4):351-61. doi: 10.1089/cap.2014.0156. PMID: 25918843.
208. De Hert M, Vancampfort D, Correll CU, et al. Guidelines for screening and monitoring of cardiometabolic risk in schizophrenia: systematic evaluation. *Br J Psychiatry.* 2011 Aug;199(2):99-105. doi: 10.1192/bjp.bp.110.084665. PMID: 21804146.
209. Almandil NB, Liu Y, Murray ML, et al. Weight gain and other metabolic adverse effects associated with atypical antipsychotic treatment of children and adolescents: a systematic review and meta-analysis. *Paediatr Drugs.* 2013 Apr;15(2):139-50. doi: 10.1007/s40272-013-0016-6. PMID: 23519708.
210. Cohen D, Bonnot O, Bodeau N, et al. Adverse effects of second-generation antipsychotics in children and adolescents: a Bayesian meta-analysis. *J Clin Psychopharmacol.* 2012 Jun;32(3):309-16. doi: 10.1097/JCP.0b013e3182549259. PMID: 22544019.
211. 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. doi: 10.1089/cap.2011.0015. PMID: 22166172.
212. Moher D, Pham B, Klassen TP, et al. What contributions do languages other than English make on the results of meta-analyses? *J Clin Epidemiol.* 2000 Sep;53(9):964-72. PMID: 11004423.
213. Pham B, Klassen TP, Lawson ML, Moher D. Language of publication restrictions in systematic reviews gave different results depending on whether the intervention was conventional or complementary. *J Clin Epidemiol.* 2005; 58(8):769-76. PMID: 16086467.
214. Ghanizadeh A. Twice-weekly aripiprazole for treating children and adolescents with tic disorder, a randomized controlled clinical trial. *Ann Gen Psychiatry.* 2016;15:21. PMID: 27579050.
215. Safavi P, Hasanpour-Dehkordi A, AmirAhmadi M. Comparison of risperidone and aripiprazole in the treatment of preschool children with disruptive behavior disorder and attention deficit-hyperactivity disorder: A randomized clinical trial. *J Adv Pharm Technol Res.* 2016;7:43-7. PMID: 27144151.
216. Lamberti M, Siracusano R, Italiano D, et al. Head-to-head comparison of aripiprazole and risperidone in the treatment of ADHD symptoms in children with autistic spectrum disorder and ADHD: a pilot, open-label, randomized controlled study. *Pediatr Drugs.* 2016;18: 319-328. PMID: 27278054.
217. Yoon Y, Wink LK, Pedapati EV, et al. Weight gain effects of second-generation antipsychotic treatment in autism spectrum disorder. *J Child Adolesc Psychopharmacol.* 2016 DOI: 10.1089/cap.2016.0049. PMID: 27389348.

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, 4 th Edition
DSM-IV-TR	Diagnostics and Statistical Manual of Mental Disorders, 4 th Edition, Text Revision
DSM-V	Diagnostics and Statistical Manual of Mental Disorders, 5 th 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·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- (\geq 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 nature³—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 Association 2013.
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 MD 2008.
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 dysregulation 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 dysregulation 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 dysregulation 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 dysregulation 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 dysregulation 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 compulsi* 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 schizo affect*)
 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 tranquill?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 dysregulation 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 dysregulation 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 compulsi* 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 dysregulation 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 schizo affect*).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 xelplion 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(adolescenc* 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 "bipolar" [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

Table C1. Risk of bias assessments for trials

Table C2. Quality assessment ratings for observational studies using Newcastle-Ottawa Scale

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
Omrani 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
<p>Alacqua et al., 2008 ⁹⁶</p> <p>Country: Italy</p> <p>Condition category: Mixed conditions (ADHD, ASD, schizophrenia-related, tics)</p> <p>Funding: NR</p> <p>Newcastle-Ottawa Scale: 6/8 stars</p>	<p>Recruitment dates: Jan 2002 to Dec 2003</p> <p>Study design: Retrospective cohort</p> <p>Diagnostic criteria: DSM-IV</p> <p>Setting: Outpatient/community</p> <p>Inclusion criteria: (1) ≤18 yr, (2) received an incident treatment with atypical antipsychotics or SSRIs during the study period</p> <p>Exclusion criteria: NR</p>	<p>Enrolled: 73 Analyzed: 73 Completed: 50</p> <p>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</p> <p>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</p>	<p>Treatment duration: 3 mo Run-in phase: No Run-in phase duration: NR</p> <p>Permitted drugs: NR</p> <p>Prohibited drugs: NR</p> <p>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</p> <p>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</p> <p>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</p> <p>GROUP 4 Drug name: Risperidone Dosing variability: variable</p>	<p>Benefits: NR</p> <p>Harms: Behavioral issues, dyskinesia, dystonia, dermatologic AE, liver function, hepatic volume, prolactin, prolactin-related AE, sedation, sleepiness, total AE, weight change</p>	<p>Adverse events occurred frequently during first 3 months of treatment with atypical antipsychotics.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		<p>First episode psychosis (n): NR Comorbidities: NR</p> <p>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</p> <p>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</p>	<p>Target dose (mg/day): NR Daily dose (mg/day), mean±SD (range): 2±1.3 Concurrent treatments: NR</p>		
Aman et al., 2014 ⁴	<p>Recruitment dates: August 2008 – November 2012</p> <p>Country: USA</p>	<p>Enrolled: 168 Analyzed: 168 Completed: 137</p>	<p>Treatment duration: 6 wk Run-in phase: Yes</p>	<p>Benefits: NCBRF, ABS, CGI-I, CGI-S, response</p>	<p>Risperidone provided moderate but variable improvement in</p>

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\pmSD (range): 9.03 \pm 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\pmSD (range): 8.75 \pm 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\pmSD (range): 1.7 \pm 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\pmSD (range): 1.9 \pm 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	<p>Recruitment dates: NR</p> <p>Country: USA</p> <p>Condition category: ADHD</p> <p>Funding: NR</p> <p>Risk of bias: Medium (subjective), Medium (objective)</p>	<p>Enrolled: 16 Analyzed: 15 Completed: NR</p> <p>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 naive (n): NR Inpatients (n): NR First episode psychosis (n): NR Comorbidities (n): Borderline intellectual disability (10), mild intellectual disability (4), moderate intellectual disability (1)</p> <p>GROUP 2 N: 16 (crossover)</p>	<p>Treatment duration: 4 wk Run-in phase: Yes Run-in phase duration: 1 wk</p> <p>Permitted drugs: clonidine, lithium</p> <p>Prohibited drugs: NR</p> <p>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)</p> <p>GROUP 2 Drug name: Placebo Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean±SD (range): NR Concurrent treatments: NR</p>	<p>Benefits: ABC, NCBRF Cognitive (MTS, STRM, CPT, GHT)</p> <p>Harms: Dyskinesia, SBP, DBP, pulse</p>	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	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		
		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			

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Aman et al., 2002 ²	<p>Recruitment dates: NR</p> <p>Country: USA</p> <p>Condition category: ADHD</p> <p>Funding: Industry</p> <p>Risk of bias: High (subjective), High (objective)</p> <p>Study design: RCT (parallel)</p> <p>Setting: NR</p> <p>Diagnostic criteria: DSM-IV, NCBRF</p> <p>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</p> <p>Exclusion criteria: (1) dx of PDD, schizophrenia, other psychotic disorders, (2) head injury as a cause</p>	<p>Enrolled: 119 Analyzed: 118 Completed: 118</p> <p>GROUP 1 N: NR Age, mean\pmSD (range): 8.7\pm2.1 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))</p> <p>GROUP 2 N: NR Age, mean\pmSD (range): 8.1\pm2.3 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</p>	<p>Treatment duration: 6 wk Run-in phase: Yes Run-in phase duration: 1 wk</p> <p>Permitted drugs: antihistamines, chloral hydrate, medication for EPS, melatonin, psychostimulants (dose stable for ≥ 30 day before study)</p> <p>Prohibited drugs: anticonvulsants, antidepressants, antipsychotics, carbamazepine, cholinesterase inhibitors, lithium, medications for sleep/anxiety, valproic acid</p> <p>GROUP 1 Drug name: Risperidone Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): 1.2\pm0.6 Concurrent treatments: all groups: methylphenidate hydrochloride (35)</p> <p>GROUP 2 Drug name: Placebo Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): NR Concurrent treatments: see group 1</p>	<p>Benefits: ABC, BPI, CGI-I, NCBRF, VAS-MS Medication adherence, response (CGI)</p> <p>Harms: ECG changes, EPS, prolactin, prolactin-related AE, SAE, sedation, total AE, WAE, weight change</p>	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	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
<p>Risk of bias: Medium (subjective), Medium (objective)</p>	<p>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</p> <p>Exclusion criteria: NR</p>	<p>Diagnostic breakdown (n): ADHD (24), ADD (4), ADD Residual type (1), CD (3)</p> <p>Treatment naïve (n): NR</p> <p>Inpatients (n): 0</p> <p>First episode psychosis (n): NR</p> <p>Comorbidities (n): Significantly subnormal IQ (27), PDD (1)</p> <p>Subjects assigned to three orders of drugs: Thioridazine, methylphenidate, placebo</p>	<p>GROUP 1</p> <p>Drug name: Thioridazine</p> <p>Dosing variability: Fixed</p> <p>Target dose (mg/day): 1.75 mg/kg/day</p> <p>Daily dose (mg/day), mean±SD (range): 1.75 mg/kg/day in 2 daily doses</p> <p>Concurrent treatments: Phenytoin + carbamazepine (2), Phenobarbital +</p> <p>GROUP 2</p> <p>Drug name: Placebo</p> <p>Dosing variability: Fixed</p> <p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean±SD (range): 2 identical placebo capsules per day</p> <p>Concurrent treatments: See group 1</p>		
<p>Anderson et al., 1989⁵</p> <p>Country: USA</p> <p>Condition category: ASD</p> <p>Funding: Non-Industry</p> <p>Risk of bias: High (subjective), Medium (objective)</p>	<p>Recruitment dates: NR</p> <p>Study design: RCT (crossover)</p> <p>Setting: NR</p> <p>Diagnostic criteria: DSM-III</p> <p>Inclusion criteria: (1) Dx of infantile autism using DSM III, made independently by three child psychiatrists</p> <p>Exclusion criteria: (1) Patients with history of</p>	<p>Enrolled: 45</p> <p>Analyzed: 42</p> <p>Completed: 42</p> <p>GROUP 1</p> <p>N: 14</p> <p>Age, mean±SD (range): see below</p> <p>Males %: see below</p> <p>Caucasian %: NR</p> <p>Diagnostic breakdown (n): autistic disorder (all)</p> <p>Treatment naïve (n): NR</p> <p>Inpatients (n): 14</p> <p>First episode psychosis (n): NR</p> <p>Comorbidities: see below</p>	<p>Treatment duration: 14 wk</p> <p>Run-in phase: Yes</p> <p>Run-in phase duration: NR</p> <p>Permitted drugs: NR</p> <p>Prohibited drugs: RN</p> <p>GROUP 1</p> <p>Drug name: Haloperidol, Placebo, Placebo</p> <p>Dosing variability: variable</p> <p>Target dose (mg/day): 4.0</p> <p>Daily dose (mg/day), mean±SD (range): 0.84±0.57</p> <p>Concurrent treatments: NR</p> <p>GROUP 2</p>	<p>Benefits: CPRS, CGI-I, CGI-S, CGI-Efficacy, Conners PTQ, medication adherence</p> <p>Harms: sedation, acute dystonic reaction</p>	<p>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</p>

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	<p>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</p> <p>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</p> <p>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)</p>	<p>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</p> <p>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</p>		functioning, having severe learning difficulties.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Arango et al., 2014 ⁹⁸	Recruitment dates: May 2005 to Feb 2009	Enrolled: 303 Analyzed: 279 Completed: 165 (at 6mo)	Treatment duration: 6 mo Run-in phase: NR Run-in phase duration: NR	Benefits: NA	Close screening and monitoring of cardio-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.
Country: Spain	Study design: Prospective	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	Permitted drugs: NR Prohibited drugs: NR	Harms: Weight (BMI, BMI-z), lipid values, fasting glucose, insulin, blood pressure (systolic/diastolic)	
Condition category: Mixed conditions	Setting: Inpatient/outpatient	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 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)		
Funding: Non-industry	Diagnostic criteria: DSM-IV		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)		
Newcastle-Ottawa Scale: 5/8 stars	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		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)		
		GROUP 3			

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	Recruitment dates: NR Country: Spain Condition category: Schizophrenia and related Funding: Industry, Academic Risk of bias: High (subjective), High (objective)	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	<p>Inpatients (n): all First episode psychosis (n): all Comorbidities: psychosis (all)</p> <p>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)</p>	<p>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 compounds (1), lithium (6), NSAIDs (1)</p>		
Armenteros et al., 2007 ⁷	<p>Recruitment dates: NR</p> <p>Country: USA</p> <p>Condition category: ADHD</p> <p>Funding: Industry</p> <p>Risk of bias: Medium (subjective),</p>	<p>Enrolled: 25 Analyzed: 25 Completed: 23</p> <p>GROUP 1 N: 12 Age, mean±SD (range): 7.3±3.7 Males %: 83.3 Caucasian %: 50 Diagnostic breakdown (n): ADHD + aggressive behavior (12)</p>	<p>Treatment duration: 4 wk Run-in phase: No Run-in phase duration: NR</p> <p>Permitted drugs: current psychostimulants</p> <p>Prohibited drugs: all medications other than current psychostimulants</p> <p>GROUP 1 Drug name: Risperidone</p>	<p>Benefits: CGI-I, CGI-S Medication adherence, response (CAS-P, CAS-T, CGI-I)</p> <p>Harms: Behavioral issues, BMI, somnolence, total AE, WAE, weight change</p>	Compared to placebo, risperidone was modestly effective in combination with psychostimulants for treatment-resistant aggression in ADHD.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Medium (objective)	<p>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</p> <p>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</p>	<p>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)</p> <p>GROUP 2 N: 13 Age, mean\pmSD (range): 8.8\pm3.1 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</p>	<p>Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): 1.1\pm0.6 mg/day Concurrent treatments: all groups: methylphenidate (15), mixed salts amphetamine (10)</p> <p>GROUP 2 Drug name: Placebo Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): 1\pm0.5 mg/day Concurrent treatments: see group 1</p>		
Bastiaens et al., 2009 ⁹⁹	<p>Recruitment dates: Dec 2004 to Sep 2005</p> <p>Country: USA</p> <p>Condition category: Mixed conditions (BP, Schizophrenia, MDD, ASD)</p>	<p>Enrolled: 46 Analyzed: 34 Completed: 34</p> <p>GROUP 1 N: 24 Age, mean\pmSD (range): 11.7\pm2.4 Males %: 83 Caucasian %: NR</p>	<p>Treatment duration: 8.7 wk Run-in phase: No Run-in phase duration: NR</p> <p>Permitted drugs: stable doses of concomitant medications</p> <p>Prohibited drugs: NR</p> <p>GROUP 1</p>	<p>Benefits: NA</p> <p>Harms: Behavioral issues, EPS, sedation, WAE, weight change</p>	<p>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</p>

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)	<p>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</p> <p>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</p>	<p>Comorbidities: MR (0), psychosis (all), SA (28)</p> <p>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</p> <p>Comorbidities: MR (0), psychosis (all), SA (30)</p>	<p>Daily dose (mg/day), mean±SD (range): 200 Concurrent treatments: NR</p> <p>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</p>	<p>somnolence, WAE, weight change</p>	

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	<p>Recruitment dates: NR</p> <p>Study design: RCT (parallel)</p> <p>Setting: Outpatient/community</p> <p>Diagnostic criteria: DSM-IV, K-SADS</p> <p>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</p> <p>Exclusion criteria: (1) any serious, unstable medical illness, (2) history of treatment with both study medications</p>	<p>Enrolled: 31 Analyzed: 31 Completed: 24</p> <p>GROUP 1 N: 15 Age, mean±SD (range): 5.0±0.8 Males %: 67 Caucasian %: 100 Diagnostic breakdown (n): major depression (11), mania (all)</p> <p>Treatment naïve (n): NR Inpatients (n): 0 First episode psychosis (n): NR Comorbidities: ADHD (15), DBD (8)</p> <p>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</p>	<p>Treatment duration: 8 wk Run-in phase: No Run-in phase duration: NR</p> <p>Permitted drugs: benzotropine mesylate (max 2 mg/day), lorazepam (≤2 mg/day)</p> <p>Prohibited drugs: antidepressants, antimanic or mood-stabilizing medications</p> <p>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: benzotropine (1), lorazepam (1)</p> <p>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</p>	<p>Benefits: BPRS, CDRS, YMRS, Response</p> <p>Harms: Behavioral issues, blood pressure, cardiovascular AE, dermatologic AE, glucose, lipid profile, neurologic AE, prolactin, pulse, sedation, weight change</p>	Risperidone 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	Recruitment dates: Jan 1996 to Dec 2007 Country: USA Condition category: Mixed conditions Funding: Non-industry Newcastle-Ottawa Scale: 8/8 stars	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 to 24 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
	<p>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 covariates were unaffected by chronic antipsychotic effects</p> <p>Exclusion criteria: (1) patients with diagnosed conditions for which antipsychotics generally are the only recommended treatment (eg. schizophrenia or related psychoses, organic psychoses, autism, mental retardation, Tourette syndrome, or other tic disorders), (2) patients prescribed clozapine or long-acting injectable preparations, usually indicators of</p>	<p>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)</p>	<p>psychostimulant (4862), α-agonist (2048), benzodiazepine (1818)</p>		

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	<p>Recruitment dates: NR</p> <p>Study design: RCT (parallel)</p> <p>Setting: Outpatient/community</p> <p>Diagnostic criteria: DSM-III-TR</p> <p>Inclusion criteria: (1) 10–65 yr, (2) primary dx of Tourette syndrome (DSM-III-R), (3) ≥ 3 on TSSS and CGI-S</p> <p>Exclusion criteria: NR</p>	<p>Enrolled: 50 Analyzed: 50 Completed: 41</p> <p>GROUP 1 N: 24 Age, mean\pmSD (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)</p> <p>GROUP 2 N: 26 Age, mean\pmSD (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</p>	<p>Treatment duration: 2.8 mo Run-in phase: Yes Run-in phase duration: 2–5 wk</p> <p>Permitted drugs: antiparkinsonian medication and benzodiazepines (discontinued during washout period, limited during treatment)</p> <p>Prohibited drugs: antiparkinsonian medication and benzodiazepines (discontinued during washout period, limited during treatment), psychotropics (within 2 wk prior to and during study)</p> <p>GROUP 1 Drug name: Pimozide Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): 2.9 (1–6) Concurrent treatments: NR</p> <p>GROUP 2 Drug name: Risperidone Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): 3.8 (0.5–6) Concurrent treatments: NR</p>	<p>Benefits: NR Harms: Weight</p>	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	Recruitment dates: NR Country: USA Condition category: Schizophrenia and related Funding: Industry, government Risk of bias: Medium (subjective), NA (objective)	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	Recruitment dates: NR Country: Netherlands Condition category: ADHD Funding: Industry	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
<p>Risk of bias: Medium (subjective), Medium (objective)</p>	<p>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)</p> <p>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</p>	<p>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)</p> <p>GROUP 2 N: 19 Age, mean\pmSD (range): 13.7\pm2 (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)</p>	<p>Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): 2.9 (1.5–4) Concurrent treatments: NR</p> <p>GROUP 2 Drug name: Placebo Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): NR Concurrent treatments: NR</p>	<p>somnolence, total AE, weight change, ESRS</p>	
<p>Calarge et al., 2014¹⁰¹</p> <p>Country: USA</p>	<p>Recruitment dates: NR</p> <p>Study design: Prospective</p>	<p>Enrolled: 108 Analyzed: 101 Completed: 101</p> <p>GROUP 1 N: 74</p>	<p>Treatment duration: 6 mo, followed-up after 1.5 yr Run-in phase: NR Run-in phase duration: NR Permitted drugs: NR</p>	<p>Benefits: NA</p> <p>Harms: Weight (BMI-z), lipid values, glucose, insulin, blood pressure</p>	<p>Discontinuation of risperidone is associated with largely spontaneous resolution of the excessive weight</p>

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 \geq 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\pmSD (range): 13.3 \pm 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\pmSD (range): 12.3 \pm 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\pmSD (range): 13.1 \pm 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\pmSD (range): (mg/kg/d) 0.03 \pm 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\pmSD (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\pmSD (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	Recruitment dates: NR Country: Spain Condition category: Schizophrenia and related Funding: Government Newcastle-Ottawa Scale: 6/8 stars	Enrolled: 110 Analyzed: 60 (only those remaining on same medication) Completed: 60 All patients: 15.5±1.8; Males 67%; White: 86%; 49% drug naïve 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	Recruitment dates: 1990 to 2005 Country: Italy Condition category: Schizophrenia and related Funding: NR Newcastle-Ottawa Scale: 5/8 stars	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	Recruitment dates: Nov 2003 to May 2005 Country: USA	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
<p>Condition category: ADHD</p> <p>Funding: Industry</p> <p>Risk of bias: High (subjective), High (objective)</p>	<p>Study design: RCT (parallel)</p> <p>Setting: Outpatient/community</p> <p>Diagnostic criteria: K-SADS-E</p> <p>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)</p> <p>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 lenticular abnormality or juvenile cataracts, (5) seizure disorder, (6) concurrent administration of any psychoactive medication, (7) pregnant or lactating</p>	<p>GROUP 1</p> <p>N: 9</p> <p>Age, mean\pmSD (range): 13.1\pm1.2 yr</p> <p>Males %: 78%</p> <p>Caucasian %: 78%</p> <p>Diagnostic breakdown: CD with moderate to severe aggression (9)</p> <p>Treatment naïve (n): 2</p> <p>Inpatients (n): NR</p> <p>First episode psychosis (n): NR</p> <p>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)</p> <p>GROUP 2</p> <p>N: 10</p> <p>Age, mean\pmSD (range): 15\pm1.4 yr</p> <p>Males %: 70%</p> <p>Caucasian %: 70%</p> <p>Diagnostic breakdown: CD with moderate to severe aggression (10)</p> <p>Treatment naïve (n): 1</p> <p>Inpatients (n): NR</p> <p>First episode psychosis (n): NR</p> <p>Comorbidities: ADHD (7), DBD (10), depression (3), dysthymia (3), GAD (0), MR (0), OCD (1), panic disorder (0), psychosis (0), PTSD (1)</p>	<p>Permitted drugs: benzotropine</p> <p>Prohibited drugs: psychotropics, rescue medications for aggression</p> <p>GROUP 1</p> <p>Drug name: Quetiapine</p> <p>Dosing variability: variable</p> <p>Target dose (mg/day): 200</p> <p>Daily dose (mg/day), mean\pmSD (range): 294\pm78 (200–600)</p> <p>Concurrent treatments: benzotropine (0)</p> <p>GROUP 2</p> <p>Drug name: Placebo</p> <p>Dosing variability: variable</p> <p>Target dose (mg/day): 200</p> <p>Daily dose (mg/day), mean\pmSD (range): 530\pm245</p> <p>Concurrent treatments: benzotropine (0)</p>	<p>Quality of life (Q-LES-Q), school attendance</p> <p>Harms: Akathisia, Behavioral issues, ECG changes, EPS, prolactin, pulse, SAE, sedation, severity of AE, WAE, weight change, AIMS</p>	<p>further research is required.</p>

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	<p>Recruitment dates: October 2001 and February 2006</p> <p>Country: Australia</p> <p>Condition category: Bipolar</p> <p>Funding: Industry</p> <p>Risk of bias: High (subjective), High (objective)</p>	<p>Enrolled: 98 Analyzed: 83 Completed: 74</p> <p>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</p> <p>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</p> <p>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</p>	<p>Treatment duration: 8 wks Run-in phase: Yes Run-in phase duration: 24 hours</p> <p>Permitted drugs: Benzodiazepines and anticholinergics</p> <p>Prohibited drugs:</p> <p>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</p> <p>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</p>	<p>Benefits: response, remission and symptomatic recovery</p> <p>Harms: weight, extrapyramidal side effects, neutropenia, sedation</p>	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 significant illness; clinically relevant biochemical or hematological abnormalities; pregnancy or lactation; history of epilepsy; drug allergy or hypersensitivity; or non-fluency in English.				
Correll et al., 2009 104	<p>Recruitment dates: Dec 2001 to Sep 2007</p> <p>Study design: Prospective cohort</p> <p>Setting: Inpatient and outpatient</p> <p>Diagnostic criteria: DSM-IV, chart review, discussion with treating clinician, clinical interview</p> <p>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</p>	<p>Enrolled: 312 Analyzed: 257 Completed: 192</p> <p>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</p>	<p>Treatment duration: 2.8 mo Run-in phase: No Run-in phase duration: NR</p> <p>Permitted drugs: co-medications as necessary</p> <p>Prohibited drugs: co-medications as necessary</p> <p>GROUP 1 Drug name: Aripiprazole 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)</p> <p>GROUP 2 Drug name: Olanzapine Dosing variability: variable Target dose (mg/day): NR</p>	<p>Benefits: NR</p> <p>Harms: Fat mass, glucose, insulin resistance, lipid profile, metabolic syndrome, waist circumference, WAE, weight change</p>	<p>First-time SGA medication use was associated with significant weight gain and variable metabolic changes for each medication.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	<p>assessments obtained within 7 day of antipsychotic medication initiation</p> <p>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</p>	<p>Comorbidities: NR</p> <p>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</p> <p>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</p>	<p>Daily dose (mg/day), mean±SD (range): NR</p> <p>Concurrent treatments: anticholinergics (0), antidepressants (10), anxiolytics or hypnotics (3), mood stabilizers (18), none (14), psychostimulants (4), psychotropics (1)</p> <p>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)</p> <p>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)</p>		

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	Recruitment dates: NR Country: France Condition category:	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	<p>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 study was explained</p> <p>Exclusion criteria: (1) Concomitant use of medications that can influence body weight (corticosteroids, 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</p>	<p>Diagnostic breakdown (n): BP (1), brief psychosis/schizophrenia 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)</p> <p>Treatment naïve (n): 10</p> <p>Inpatients (n): NR</p> <p>First episode psychosis (n): NR</p> <p>Comorbidities: NR</p> <p>GROUP 2</p> <p>N: 12</p> <p>Age, mean±SD (range): 16.1±1.3 yr</p> <p>Males %: 66.7</p> <p>Caucasian %: 91.7</p> <p>Diagnostic breakdown (n): BP (4), brief psychosis/schizophrenia 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)</p> <p>Treatment naïve (n): 5</p> <p>Inpatients (n): NR</p> <p>First episode psychosis (n): NR</p> <p>Comorbidities: NR</p>	<p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean±SD (range): NR</p> <p>Concurrent treatments: NR</p> <p>GROUP 2</p> <p>Drug name: Olanzapine</p> <p>Dosing variability: NR</p> <p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean±SD (range): NR</p> <p>Concurrent treatments: NR</p> <p>GROUP 3</p> <p>Drug name: Quetiapine</p> <p>Dosing variability: NR</p> <p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean±SD (range): NR</p> <p>Concurrent treatments: NR</p>		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/schizophrenia 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	Recruitment dates: NR Country: Netherlands Condition category: Schizophrenia and related Funding: Government	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
<p>Risk of bias: High (subjective), High (objective)</p>	<p>admitted to the Adolescent Clinic</p> <p>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</p>	<p>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)</p>	<p>Concurrent treatments: oxazepam (6)</p> <p>GROUP 2 Drug name: Olanzapine Dosing variability: fixed Target dose (mg/day): NR Daily dose (mg/day), mean±SD (range): 7.5 Concurrent treatments: oxazepam (5)</p>		
<p>DelBello et al., 2009¹⁹</p> <p>Country: USA</p> <p>Condition category: Bipolar (depressive)</p> <p>Funding: Industry</p> <p>Risk of bias: High (subjective), High (objective)</p>	<p>Recruitment dates: Mar 2006 to June 2007</p> <p>Study design: RCT (parallel)</p> <p>Setting: Inpatient and outpatient</p> <p>Diagnostic criteria: DSM-IV-TR, WASH-U-KSADS</p> <p>Inclusion criteria: (1) 12–18 yr, (2) dx of bipolar I disorder, depressive episode, (3) screening and baseline CDRS-R score ≥40</p>	<p>Enrolled: 32 Analyzed: 32 Completed: 20</p> <p>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)</p> <p>GROUP 2 N: 15</p>	<p>Treatment duration: 8 wk Run-in phase: Yes Run-in phase duration: NR</p> <p>Permitted drugs: lorazepam (max 4 mg/day days 1–7, 2 mg/day days 8–14)</p> <p>Prohibited drugs: antidepressants (<3 day), anticonvulsants (<3 day), antipsychotics or atomoxetine (<3 day), fluoxetine (<4 wk), psychostimulant (<48 hr)</p> <p>GROUP 1 Drug name: Quetiapine Dosing variability: variable Target dose (mg/day): 600 Daily dose (mg/day), mean±SD (range): 403±133 (300–600)</p>	<p>Benefits: CDRS, CGI-BP, HAM-A, YMRS, response (response, remission, suicide attempt)</p> <p>Harms: Blood pressure, BMI, diabetes, EPS, glucose, LFT, lipid profile, mania, prolactin, pulse, SAE, sedation, tachycardia, WAE, weight change, EPS</p>	<p>Quetiapine monotherapy was no more effective in treating depression in adolescents with bipolar disorder than treatment with placebo.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	<p>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</p>	<p>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)</p>	<p>Concurrent treatments: lorazepam (0)</p> <p>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)</p>		
<p>DelBello et al., 2008¹⁸</p> <p>Country: USA</p> <p>Condition category: Bipolar & schizophrenia-related</p> <p>Funding: Industry</p> <p>Risk of bias: High (subjective), High (objective)</p>	<p>Recruitment dates: NR</p> <p>Study design: RCT (parallel)</p> <p>Setting: Outpatient/community</p> <p>Diagnostic criteria: DSM-IV-TR</p> <p>Inclusion criteria: (1) 10–17 yr, (2) bipolar I disorder (YMRS score ≥17), (3) schizophrenia-related</p>	<p>Enrolled: 63 Analyzed: 63 Completed: 38</p> <p>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</p>	<p>Treatment duration: 3 wk Run-in phase: Yes Run-in phase duration: 24 hr</p> <p>Permitted drugs: benztropine and/or propranolol, lorazepam or similar benzodiazepine</p> <p>Prohibited drugs: antidepressants, mood stabilizers, stimulants</p> <p>GROUP 1 Drug name: Ziprasidone (low) Dosing variability: fixed Target dose (mg/day): 80</p>	<p>Benefits: YMRS, BPRS, CGI-S</p> <p>Harms: Akathisia, behavioral issues, dystonia, ECG changes, EPS (AIMS, SAS, BAS), fatigue, glucose, lipid profile, prolactin, SAE, sedation, somnolence, WAE, weight change</p>	<p>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.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	<p>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</p> <p>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 arrhythmias,</p>	<p>Inpatients (n): NR First episode psychosis (n): NR Comorbidities: MR (0), SA (0)</p> <p>GROUP 2 N: 40 Age, mean\pmSD (range): 13.8 (bipolar), 14.7 (schiz) Males %: 75 Caucasian %: NR Diagnostic breakdown (n): bipolar I (31), schizophrenia or schizoaffective disorder (9) Treatment naïve (n): NR Inpatients (n): NR First episode psychosis (n): NR Comorbidities: MR (0), SA (0)</p>	<p>Daily dose (mg/day), mean\pmSD (range): (20–80) Concurrent treatments: benzotropine (3)</p> <p>GROUP 2 Drug name: Ziprasidone (high) Dosing variability: fixed Target dose (mg/day): 160 Daily dose (mg/day), mean\pmSD (range): (40–160) Concurrent treatments: benzotropine (4)</p>		

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	<p>Recruitment dates: May 2000 to May 2001</p> <p>Country: USA</p> <p>Condition category: Bipolar (manic, mixed)</p> <p>Funding: Industry</p> <p>Risk of bias: Medium (subjective), Medium (objective)</p>	<p>Enrolled: 30 Analyzed: 30 Completed: 22</p> <p>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)</p> <p>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</p>	<p>Treatment duration: 6 wk Run-in phase: Yes Run-in phase duration: NR</p> <p>Permitted drugs: lorazepam (≤2 mg/day for first 14 day)</p> <p>Prohibited drugs: NR</p> <p>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)</p> <p>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)</p>	<p>Benefits: YMRS, Medication adherence, response</p> <p>Harms: Blood cells, blood pressure, ECG changes, prolactin, SAE, sedation, thyroid function, WAE, weight change, EPS (AIMS, BAS, SAS)</p>	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	Recruitment dates: 2011-2012 Country: Israel Condition category: Mixed conditions Funding: NR Newcastle-Ottawa Scale: 5/8 stars	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
		<p>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)</p> <p>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)</p>	<p>GROUP 2 Drug name: Control Dosing variability: NR Target dose (mg/day): NR Daily dose (mg/day), mean±SD (range): NR Concurrent treatments: NR</p>		
Findling et al., 2015b ³⁰	<p>Recruitment dates: Jul 2011 to Sept 2013</p> <p>Country: USA</p> <p>Condition category: Bipolar I (manic, mixed)</p> <p>Funding: Industry</p>	<p>Enrolled: 404 Analyzed: 403 Completed: 350</p> <p>GROUP 1 N: 104 Age, mean±SD (range): 13.7±2.1 yr Males %: 50 Caucasian %: 72.1</p>	<p>Treatment duration: 3 wk Run-in phase: Yes Run-in phase duration: 2-14 d</p> <p>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</p>	<p>Benefits: YMRS, CGI-BP-S, CGAS, CDRS-R, response, suicidal ideation, attempted suicide, psychiatric disorders, worsening of mania, medication adherence</p> <p>Harms: Mortality, somnolence, EPS</p>	<p>All asenapine doses versus placebo were superior based on change in YMRS at day 21. Asenapine was generally well tolerated in patients aged 10 to 17years with bipolar I disorder in manic or mixed states.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
<p>Risk of bias: Low (subjective), Low (objective)</p>	<p>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</p> <p>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</p>	<p>Diagnostic breakdown (n): Manic (40), mixed (64) Treatment naïve (n): 38 Inpatients (n): 0 First episode psychosis (n): NR Comorbidities: ADHD (62)</p> <p>GROUP 2 N: 99 Age, mean\pmSD (range): 13.8\pm2.0 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)</p> <p>GROUP 3 N: 99 Age, mean\pmSD (range): 13.9\pm2.1 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)</p>	<p>diazepam; use of psychostimulants and other ADHD medications, medications to treat extrapyramidal symptoms (EPS; e.g., anticholinergics, short-acting benzodiazepines).</p> <p>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)</p> <p>GROUP 1 Drug name: Asenapine (2.5 mg) Dosing variability: fixed Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): NR Concurrent treatments: Stimulant (29)</p> <p>GROUP 2 Drug name: Asenapine (5 mg) Dosing variability: fixed Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): NR Concurrent treatments: Stimulant (22)</p> <p>GROUP 3 Drug name: Asenapine (10 mg)</p>	<p>(ESRS), akathisia, dystonia, weight gain, BMI, ECG, lipid values, fasting insulin, glucose, prolactin, nausea, orthostatic hypotension related adverse events</p>	<p>Increases in weight and fasting insulin were associated with asenapine.</p>

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	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
	<p>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</p>	<p>First episode psychosis (n): NR</p> <p>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</p>	<p>herbal drugs/dietary supplements for depression, anxiety, and insomnia</p> <p>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)</p> <p>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)</p> <p>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)</p>		
Findling et al., 2014b ²⁸	<p>Recruitment dates: Mar 2011 to Jun 2012</p> <p>Country: USA</p> <p>Condition category: ASD</p> <p>Study design: RCT (parallel)</p> <p>Setting: NR</p>	<p>Enrolled: 85 Analyzed: 82 Completed: 41</p> <p>GROUP 1 N: 41 Age, mean±SD (range): 10.1±2.8 yr</p>	<p>Treatment duration: 16 wk Run-in phase: No Run-in phase duration: NA</p> <p>Permitted drugs: Diphenhydramine for sleep or serious behaviour problems, nonbenzodiazepine sleep aids (eg,</p>	<p>Benefits: ABC-I, CGI-I, CGI-S, PedsQL, CGSQ, relapse, medication adherence</p> <p>Harms: Constipation, EPS (AIMS, BAS,</p>	<p>The safety and efficacy of aripiprazole and risperidone were comparable. The choice between these two medications should</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
<p>Funding: Industry</p> <p>Risk of bias: High (subjective), High (objective)</p>	<p>Diagnostic criteria: DSM-IV-TR, ADI-R</p> <p>Inclusion criteria: (1) Male or 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</p> <p>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 schizophrenia or a current dx of major depressive disorder, pervasive developmental</p>	<p>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</p> <p>GROUP 2 N: 44 Age, mean\pmSD (range): 10.8\pm2.8 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</p>	<p>zolpidem, zaleplon, zopiclone, eszopiclone) for insomnia, and melatonin for insomnia (not permitted to start or make changes to their sleep aid treatment during phase 2)</p> <p>Prohibited drugs: Antipsychotics other than aripiprazole, antidepressants, benzodiazepines, stimulants, α-agonists, mood stabilizers, and atomoxetine</p> <p>GROUP 1 Drug name: Aripiprazole Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): 9.0\pm4.5 [initial of phase 2], 9.7\pm4.9 [end dose at wk 16] Concurrent treatments: NR</p> <p>GROUP 2 Drug name: Placebo Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): 9.5\pm4.2 [initial of phase 2], 10.0\pm4.2 [end dose at wk 16] Concurrent treatments: NR</p>	<p>SAS), akathisia, mortality, lipid profile, glucose, prolactin, sexual maturation</p>	<p>be on the basis of clinical equipoise considering the patient's preference and clinical profile.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	disorder-NOS, Asperger syndrome, Rett syndrome, childhood disintegrative disorder, or fragile X syndrome, (3) history of neuroleptic 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	<p>Recruitment dates: Jan 2009 to Nov 2010</p> <p>Country: USA</p> <p>Condition category: Bipolar I,II (depressed)</p> <p>Funding: Industry</p> <p>Risk of bias: High (subjective), High (objective)</p>	<p>Enrolled: 193 Analyzed: 192 Completed: 144</p> <p>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)</p> <p>GROUP 2 N: 100</p>	<p>Treatment duration: 8 wk Run-in phase: Yes Run-in phase duration: 7-28 d</p> <p>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</p> <p>Prohibited drugs: Adjunctive medications for EPS</p> <p>GROUP 1 Drug name: Quetiapine</p>	<p>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)</p> <p>Harms: somnolence, fatigue, nausea, agitation, EPS (AIMS, BAS, SAS), ECG, transaminase, fasting glucose,</p>	<p>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 depression or MDD. Consistent with studies in adults, quetiapine XR</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	<p>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</p> <p>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, anxiolytic, hypnotic, or other psychoactive drug within 7 days, or fluoxetine within 28 days before baseline,</p>	<p>Age, mean\pmSD (range): 14.0\pm2.1 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)</p>	<p>Dosing variability: variable Target dose (mg/day): 300 Daily dose (mg/day), mean\pmSD (range): mean modal dose, 204.9mg/day Concurrent treatments: Total psychostimulants (20), other (35)</p> <p>GROUP 2 Drug name: Placebo Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): NR Concurrent treatments: psychostimulants (27), other (37)</p>	<p>dyslipidemia, TSH, throxine, prolactin, weight gain, blood pressure, pulse</p>	<p>at the dose range investigated was generally safe and well tolerated in these pediatric patients.</p>

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 item 13 score ≥ 3 at enrollment or randomization, (8) clinically significant deviations from normal reference ranges of clinical laboratory parameters				
Findling, 2013a ²⁵	<p>Recruitment dates: Apr 2006 to Mar 2009 (terminated prematurely)</p> <p>Study design: RCT (parallel)</p> <p>Setting: In- and outpatient</p> <p>Diagnostic criteria: DSM-IV, KID-SCID</p> <p>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</p>	<p>Enrolled: 284 Analyzed: 283 Completed: NR</p> <p>GROUP 1 N: 193 Age, mean\pmSD (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</p> <p>GROUP 2 N: 90 Age, mean\pmSD (range): 15.4 Males %: 69 Caucasian %: 67 Diagnostic breakdown (n): paranoid type (57)</p>	<p>Treatment duration: 6 wk Run-in phase: Yes Run-in phase duration: 14 days</p> <p>Permitted drugs: lorazepam or diazepam, diphenhydramine, zolpidem, benzotropine, anticholinergics, propranolol</p> <p>Prohibited drugs: antipsychotic, mood stabilizers, stimulants, antidepressants, anti-emetics, several antihypertensives</p> <p>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\pmSD (range): 67.8 (<45kg), 129.3 (≥ 45kg) Concurrent treatments: 51%</p> <p>GROUP 2</p>	<p>Benefits: BPRS-A, PANSS, CGI-S, CGI-I, CGAS, health related quality of life (Child Health Questionnaire), suicide, depression</p> <p>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</p>	Oral ziprasidone failed to demonstrate superiority over placebo in adolescents with schizophrenia.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	<p>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</p> <p>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</p>	<p>Treatment naïve (n): NR Inpatients (n): NR First episode psychosis (n): NR</p>	<p>Drug name: Placebo Dosing variability: variable Target dose (mg/day): 60–80 (<45 kg), 120–160 (≥ 45 kg) Daily dose (mg/day), mean\pmSD (range): NR Concurrent treatments: 39%</p>		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	abnormalities, and Fridericia's corrected QT (QTcF) interval \pm 460ms at screening or baseline.				
Findling et al., 2013b ²⁶	<p>Recruitment dates: Jan 2006 to Jul 2007</p> <p>Country: USA</p> <p>Condition category: Bipolar I (manic, mixed)</p> <p>Funding: Industry, non-industry</p> <p>Risk of bias: High (subjective), High (objective)</p>	<p>Enrolled: 238 Analyzed: 229 Completed: 148</p> <p>GROUP 1 N: 149 Age, mean\pmSD (range): 13.2\pm2.4 yr (males), 14.1\pm2.0 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)</p> <p>GROUP 2 N: 88 Age, mean\pmSD (range): 13.5\pm2.0 yr (males), 14.0\pm1.9 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</p>	<p>Treatment duration: 4 wk Run-in phase: Yes Run-in phase duration: 1–10 day</p> <p>Permitted drugs: Lorazepam or a comparable benzodiazepine as required \leq2mg/day. Not to be administered \leq6 hours prior to clinical assessments.</p> <p>Prohibited drugs: Other antipsychotics, lithium and anticonvulsants, stimulants, antidepressants, antiemetics (dopamine antagonists such as prochlorperazine and metoclopramide), treatment with clozapine \leq12 weeks, treatment with a depot antipsychotic \leq4 weeks, treatment with a monoamine oxidase inhibitor \leq2 weeks, or treatment with an investigational agent \leq4 weeks of baseline.</p> <p>GROUP 1 Drug name: Ziprasidone Dosing variability: variable Target dose (mg/day): 60–80 (<45 kg), 120–160 (\geq45 kg) Daily dose (mg/day), mean\pmSD (range): 69.2(<45 kg), 118.8 (\geq45 kg) Concurrent treatments: NR</p> <p>GROUP 2</p>	<p>Benefits: YMRS, CGI-S, CGI-I, CGAS, CDRS-R, suicidal ideation, aggression</p> <p>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</p>	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	Recruitment dates: May 2004 to Nov 2008 Country: USA Condition category: Bipolar I,II, NOS, cyclothymia Funding: Industry Risk of bias: High (subjective), High (objective)	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	Recruitment dates: Oct 2004 to June 2007 Country: Asia, Central and Eastern Europe, South Africa, United States Condition category: Schizophrenia and related Funding: Industry Risk of bias: High (subjective), High (objective)	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/inducers, monoamine oxidase inhibitors, atomoxetine, prophylactic benzotropine 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: BPSd, 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	Recruitment dates: Mar 2005 to Feb 2007 Country: USA Condition category: Bipolar (manic, mixed) Funding: Industry Risk of bias: Medium	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)	<p>disorder with current manic or mixed episodes, with or without psychotic features (DSM-IV), (3) YMRS score ≥ 20</p> <p>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</p>	<p>Inpatients (n): NR First episode psychosis (n): NR Comorbidities: ADHD (48), DBD (28)</p> <p>GROUP 2 N: 99 Age, mean\pmSD (range): 13.3\pm2.3 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)</p> <p>GROUP 3 N: 99 Age, mean\pmSD (range): 13.3\pm2.1 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)</p>	<p>Daily dose (mg/day), mean\pmSD (range): (2–10) Concurrent treatments: NR</p> <p>GROUP 2 Drug name: Aripiprazole (high) Dosing variability: variable Target dose (mg/day): 30 Daily dose (mg/day), mean\pmSD (range): (2–30) Concurrent treatments: NR</p> <p>GROUP 3 Drug name: Placebo Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): NR Concurrent treatments: NR</p>	<p>parkinsonism, prolactin, SAE, somnolence, total AE, WAE, weight change</p>	

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	<p>Recruitment dates: NR</p> <p>Study design: RCT (parallel)</p> <p>Setting: Inpatient and outpatient</p> <p>Diagnostic criteria: DSM-IV, K-SADS-PL</p> <p>Inclusion criteria: (1) 13–17 yr, (2) primary dx of schizophrenia (DSM-IV Axis I, confirmation with K-SADS-PL), (3) baseline PANSS \geq 70</p> <p>Exclusion criteria: (1) current psychiatric comorbidity requiring pharmacology, (2)</p>	<p>Enrolled: 302 Analyzed: 294 Completed: 258</p> <p>GROUP 1 N: 100 Age, mean\pmSD (range): 15.6\pm1.3 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</p> <p>GROUP 2 N: 102</p>	<p>Treatment duration: 6 wk Run-in phase: Yes Run-in phase duration: \geq3 day</p> <p>Permitted drugs: anticholinergics, benzodiazepines</p> <p>Prohibited drugs: antidepressants, atomoxetine, mood stabilizers, other psychotropics, stimulants</p> <p>GROUP 1 Drug name: Aripiprazole (low) Dosing variability: variable Target dose (mg/day): 10 Daily dose (mg/day), mean\pmSD (range): 9.8 (2–10) Concurrent treatments: NR</p> <p>GROUP 2 Drug name: Aripiprazole (high) Dosing variability: variable Target dose (mg/day): 30</p>	<p>Benefits: CGAS, CGI-I, CGI-S, PANSS Health related quality of life (P-QLES-Q), response, suicide</p> <p>Harms: Akathisia, behavioral issues, BMI, dyskinesia, dystonia, ECG changes, EPS, EPS (SAS), glucose, lipid profile, mortality, prolactin, parkinsonism, SAE, somnolence, WAE, weight change</p>	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	Recruitment dates: NR Country: USA Condition category: Mixed conditions Funding: Industry	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	<p>schizophrenia or bipolar</p> <p>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</p>	<p>Diagnostic breakdown (n): schizophrenia (1); bipolar disorder (12); TS (5); ADHD and CD (1); OCD (1); PDD (1)</p> <p>Treatment naïve (n):</p> <p>Inpatients (n):</p> <p>First episode psychosis (n):</p> <p>Comorbidities:</p> <p>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</p> <p>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</p> <p>GROUP 3 N: 6</p>	<p>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)</p> <p>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</p> <p>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</p> <p>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</p>		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	Recruitment dates: NR Country: USA Condition category: ADHD Funding: Industry, Foundation Risk of bias: High (subjective), High (objective)	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: benzotropine 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	Benefits: 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	Recruitment dates: June 2012 to May 2013 Country: USA Condition category: Mixed conditions Funding: Industry Risk of bias: NA (subjective), High (objective)	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 qualitatively 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
	<p>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.</p> <p>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.</p>	<p>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</p> <p>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</p> <p>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</p>	<p>GROUP 2 Drug name: Lurasidone Dosing variability: fixed Target dose (mg/day): 40 Daily dose (mg/day), mean±SD (range): NR Concurrent treatments: NR</p> <p>GROUP 3 Drug name: Lurasidone Dosing variability: fixed Target dose (mg/day): 80 Daily dose (mg/day), mean±SD (range): NR Concurrent treatments: NR</p> <p>GROUP 4 Drug name: Lurasidone Dosing variability: fixed Target dose (mg/day): 120 Daily dose (mg/day), mean±SD (range): NR Concurrent treatments: NR</p> <p>GROUP 5 Drug name: Lurasidone Dosing variability: fixed Target dose (mg/day): 160 Daily dose (mg/day), mean±SD (range): NR Concurrent treatments: NR</p>		<p>concentrations, but with improved tolerability compared with higher doses.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
		<p>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</p> <p>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</p>			
Fleischhaker et al., 2006 ¹⁰⁸	<p>Recruitment dates: NR</p> <p>Country: Germany</p> <p>Condition category: Mixed conditions</p> <p>Funding: NR</p>	<p>Enrolled: 51 Analyzed: 51 Completed: 51</p> <p>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</p>	<p>Treatment duration: 7.4 wk (mean) Run-in phase: No Run-in phase duration: NR</p> <p>Permitted drugs: NR</p> <p>Prohibited drugs: NR</p> <p>GROUP 1 Drug name: Clozapine</p>	<p>Benefits: NR</p> <p>Harms: Akathisia, behavioral issues, bradycardia, blood cells, blood pressure, BMI, constipation, dystonia, dermatologic AE, ECG changes, liver function tachycardia,</p>	<p>Olanzapine caused significant weight gain in children and adolescents, potentially influencing medication compliance and health risk. Clozapine and risperidone were</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Newcastle-Ottawa Scale: 3/8 stars	Inclusion criteria: NR Exclusion criteria: NR	<p>Diagnostic breakdown (n): Schizophrenia (31), PDD (5), AN (1), Cannabis-related disorders (4), AD (3), DBD (3), OCD (2), TD (1) for all groups</p> <p>Inpatients (n): NR</p> <p>First episode psychosis (n): NR</p> <p>Comorbidities (n): NR</p> <p>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</p> <p>Diagnostic breakdown (n): See group 1</p> <p>Inpatients (n): NR</p> <p>First episode psychosis (n): NR</p> <p>Comorbidities (n): NR</p> <p>GROUP 3 N: 19 Age, mean±SD (range): 15.6±2.6 (9.7–19) Males %: 68.4 Caucasian %: NR Treatment naïve (n): NR</p> <p>Diagnostic breakdown (n): See group 1</p> <p>Inpatients (n): NR</p> <p>First episode psychosis (n): NR</p> <p>Comorbidities (n): NR</p>	<p>Dosing variability: variable</p> <p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean±SD (range): 321.9±156.5 (125–600)</p> <p>Concurrent treatments: all groups: amisulpride, biperiden, chlorprotixene, fluboxamine, fluoxetine, haloperidol, imipramine, lactulose, levomepromazine, lorazepam, metixene, metoclopramid, metoprolol, paroxetine, perazine, pimozide, pipamperone, pirenzepine, promethazine</p> <p>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</p> <p>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</p>	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
<p>Fraguas et al., 2008 ¹⁰⁹</p> <p>Country: Spain</p> <p>Condition category: Mixed conditions</p> <p>Funding: Government, Foundation, Other NR</p> <p>Newcastle-Ottawa Scale: 6/8 stars</p>	<p>Recruitment dates: Mar 2005 to Oct 2006</p> <p>Study design: Prospective cohort</p> <p>Setting: Inpatient and outpatient</p> <p>Diagnostic criteria: DSM-IV</p> <p>Inclusion criteria: (1) new prescription of olanzapine, risperidone or quetiapine within 30 days, (2) no history of prior lifetime antipsychotic treatment</p> <p>Exclusion criteria: (1) receiving >1 antipsychotic or needed another antipsychotic during followup</p>	<p>Enrolled: 92 Analyzed: 66 Completed: 66</p> <p>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)</p> <p>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</p>	<p>Treatment duration: 6 mo Run-in phase: No Run-in phase duration: NR</p> <p>Permitted drugs: anticholinergics, antidepressants, benzodiazepines</p> <p>Prohibited drugs: antipsychotics</p> <p>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)</p> <p>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)</p> <p>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)</p>	<p>Benefits: NR</p> <p>Harms: Blood pressure, BMI, glucose, lipid profile, thyroid function, weight change</p>	<p>Metabolic and hormonal adverse events should be carefully monitored when prescribing SGAs.</p>

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	Recruitment dates: NR	Enrolled: 44 Analyzed: 44 Completed: NR	Treatment duration: 6 wk Run-in phase: No Run-in phase duration: NR	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.
Country: Canada Condition category: Mixed conditions Funding: NR Newcastle-Ottawa Scale: 4/8 stars	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	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-	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		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	<p>problems, (3) active files with the mental health sites in the Greater Vancouver area</p> <p>Exclusion criteria: NR</p>	<p>related disorders (3), AD (2), Impulse control disorder (1) for all patients</p> <p>Inpatients (n): NR</p> <p>First episode psychosis (n): NR</p> <p>Comorbidities: Addison's disease (1), hypothyroidism (4), MR (borderline (1), mild (17), moderate (15), severe (9)), Neurodevelopmental syndrome (15), Seizure disorder (9)</p> <p>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</p>	<p>(21), non-SSRI antidepressants (8), SSRIs (9), stimulants (2), tetrabenazine (2)</p> <p>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</p>		
<p>Germano et al., 2014 ¹¹¹</p> <p>Country: Italy</p> <p>Condition category: Mixed</p> <p>Funding: NR</p>	<p>Recruitment dates: Jan 2009-Dec 2012</p> <p>Study design: Prospective</p> <p>Setting: NR</p> <p>Diagnostic criteria: NR</p>	<p>Enrolled: 65 Analyzed: 60 Completed: 60</p> <p>GROUP 1 N: 29 Age, mean±SD (range): See below Males %: See below Caucasian %: NR</p>	<p>Treatment duration: 2 mo Run-in phase: Yes Run-in phase duration: 2 wk</p> <p>Permitted drugs: NR</p> <p>Prohibited drugs: NR</p> <p>GROUP 1 Drug name: Aripiprazole Dosing variability: NR</p>	<p>Benefits: NR</p> <p>Harms: ECG parameters</p>	<p>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.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Newcastle-Ottawa Scale: 5/8 stars	<p>Inclusion criteria: (1) child and adolescent patients, (2) ≤17 yr</p> <p>Exclusion criteria: NR</p>	<p>Diagnostic breakdown (n): See below</p> <p>Treatment naïve (n): See below</p> <p>Inpatients (n): NR</p> <p>First episode psychosis (n): NR</p> <p>Comorbidities: NR</p> <p>GROUP 2</p> <p>N: 31</p> <p>Age, mean±SD (range): See below</p> <p>Males %: See below</p> <p>Caucasian %: NR</p> <p>Diagnostic breakdown (n): See below</p> <p>Treatment naïve (n): See below</p> <p>Inpatients (n): NR</p> <p>First episode psychosis (n): NR</p> <p>Comorbidities: NR</p> <p>Overall age, mean±SD (range): 10.2±2.6 yr</p> <p>Overall Males %: 91.6</p> <p>Overall diagnostic breakdown (n): PDD (22), ODD (12), ADHD (21), MR with psychotic disorder (11), Tourette syndrome and other tic disorders (9)</p> <p>Overall treatment naïve (n): 22</p>	<p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean±SD (range): 7.4±3.1</p> <p>Concurrent treatments: NR</p> <p>GROUP 2</p> <p>Drug name: Risperidone</p> <p>Dosing variability: NR</p> <p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean±SD (range): 1.5±1.0</p> <p>Concurrent treatments: NR</p>		<p>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.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Ghanizadeh et al., 2014a ³²	<p>Recruitment dates: NR</p> <p>Country: Iran</p> <p>Condition category: ASD</p> <p>Funding: Industry/ non-industry</p> <p>Risk of bias: Medium (subjective), Medium (objective)</p>	<p>Enrolled: 59 Analyzed: 59 Completed: 50</p> <p>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</p> <p>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</p> <p>Overall diagnostic breakdown (n): Autism (38), Asperger disorder (8), PDD-NOS (9), childhood disruptive behavior disorder (1)</p>	<p>Treatment duration: 2 mo Run-in phase: NR Run-in phase duration: NR</p> <p>Permitted drugs: Any (with no marked change in dose allowed during the trial and during 2 wk before the trial onset)</p> <p>Prohibited drugs: Antipsychotics</p> <p>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</p> <p>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</p>	<p>Benefits: ABC, CGI-S, CGI-I, discontinuation due to lack of efficacy</p> <p>Harms: Fatigue, constipation, dystonia, dyskinesia, nausea, seizure, agitation, weight</p>	<p>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.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Ghanizadeh et al., 2014b ³³	<p>Recruitment Dates: NR</p> <p>Country: Iran</p> <p>Condition category: Tic disorders</p> <p>Funding: Non-industry</p> <p>Risk of Bias: High (subjective), High (objective)</p>	<p>Enrolled: 60 Analyzed: 60 Completed: 35</p> <p>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</p> <p>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</p>	<p>Treatment duration: 8 weeks Run-in phase: Unclear Run-in phase duration: 2 weeks</p> <p>Permitted drugs: Nortriptyline, Biperiden, Citalopram, Clonidine, Fluvoxamine, Propranolol, Methylphenidate</p> <p>Prohibited drugs: NR</p> <p>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: Nortriptyline (1), Citalopram (1), Clonidine + fluvoxamine + propranolol (1), Methylphenidate (2)</p> <p>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)</p>	<p>Benefits: YGTSS, PedsQL, ADHD RS-IV</p> <p>Harms: Neuromotor effects, metabolic effects, somnolence, exercise intolerance</p>	<p>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. Efficacy and safety of other doses of these medications are recommended. Long term use of the medications needs further studies.</p>
Gilbert et al., 2004 ³⁴	<p>Recruitment dates: NR</p> <p>Country: USA</p> <p>Condition category: Tic disorders</p>	<p>Enrolled: 19 Analyzed: NR Completed: 13</p> <p>GROUP 1 N: 19 (crossover) Age, mean±SD (range): NR Males %: NR Caucasian %: NR</p>	<p>Treatment duration: 8 wk Run-in phase: Yes Run-in phase duration: 2 wk</p> <p>Permitted drugs: NR</p> <p>Prohibited drugs: NR</p> <p>GROUP 1 Drug name: Pimozide</p>	<p>Benefits: CGI-I, TSSR, YGTSS</p> <p>Harms: EPS (ESRS), ECG changes, weight changes</p>	<p>Risperidone was superior to pimozide for tic suppression but it induced weight gain.</p>

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), conduct disorder (1), learning disorder (3), OCD (2), oppositional defiant disorder (2) GROUP 2 N: 19 (crossover) Age, mean±SD (range): NR Males %: NR Caucasian %: NR 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	Recruitment Dates: NR Country: Italy Condition category: Tic disorders Funding: Non-industry Risk of Bias: NA (subjective), Medium (objective)	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	Recruitment dates: Aug 2004 to Dec 2005 Country: India, Russia, Ukraine, USA Condition category: Schizophrenia and related Funding: Industry Risk of bias: High (subjective), High (objective)	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: Propranolol 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 psychotropic 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
	<p>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,</p>	<p>Disorganized (4), Catatonic (0), Residual (0) Treatment naïve (n): NR Inpatients (n): 25 First episode psychosis (n): NR Comorbidities: NR</p> <p>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</p>	<p>oriented or cognitive-behavioral psychotherapy.</p> <p>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</p> <p>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</p> <p>GROUP 3 Drug name: Placebo Dosing variability: fixed Target dose (mg/day): NR Daily dose (mg/day), mean±SD (range): NR Concurrent treatments: NR</p>		
Haas et al., 2009c ³⁸	<p>Recruitment dates: Dec 2003 to Dec 2005</p> <p>Country: USA</p> <p>Condition category: Bipolar (manic, mixed)</p> <p>Study design: RCT (parallel)</p> <p>Setting: Inpatient and outpatient</p>	<p>Enrolled: 170 Analyzed: 169 Completed: 137</p> <p>GROUP 1 N: 50 Age, mean±SD (range): NR (10–17)</p>	<p>Treatment duration: 3 wk Run-in phase: Yes Run-in phase duration: ≤5 day</p> <p>Permitted drugs: medication for EPS; sedatives/hypnotics (run-in and wk 1 only)</p>	<p>Benefits: BPRS, CGI-BP, YMRS, Medication adherence, response, suicide</p> <p>Harms: Behavioral issues, BMI,</p>	<p>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)</p>

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\pmSD (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\pmSD (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\pmSD (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\pmSD (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\pmSD (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	Recruitment dates: Apr 2001 to Mar 2006 Country: Belgium, Bulgaria, Czech Republic, Estonia, Germany, Poland, Romania, USA Condition category: Schizophrenia and related Funding: Industry Risk of bias: High (subjective), High (objective)	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	<p>Recruitment dates: Aug 2004 to Sept 2008</p> <p>Country: USA</p> <p>Condition category: Eating disorders</p> <p>Funding: Non-industry</p> <p>ROB: Medium (subjective), Medium (objective)</p>	<p>Enrolled: 41 Analyzed: 40 Completed: 40</p> <p>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)</p> <p>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</p>	<p>Treatment duration: 9 wk Run-in phase: NR Run-in phase duration: NR</p> <p>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)</p> <p>Prohibited drugs: new psychotropic medications</p> <p>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</p> <p>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</p>	<p>Benefits: EDI-2 DT, EDI-2 BD, ADJ-current, ADJ-desired, CAPT, MASC, suicidal ideation, anxiety, depression</p> <p>Harms: EPS (AIMS, SAS), glucose, lipid profile, prolactin, fatigue, blood pressure</p>	<p>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.</p>
Hellings et al., 2006 ⁴⁰	<p>Recruitment dates: NR</p> <p>Country: USA</p>	<p>Enrolled: 26 Analyzed: 26 Completed: NR</p>	<p>Treatment duration: 5.1 mo (6 wk at each dose)</p> <p>Run-in phase: Yes</p>	<p>Benefits: ABC, CGI-I, PAC, VAS</p>	<p>Compared to placebo, risperidone was more effective in treating</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
<p>Condition category: ASD</p> <p>Funding: Industry, Government</p> <p>Risk of bias: High (subjective), High (objective)</p>	<p>Study design: RCT (crossover)</p> <p>Setting: Outpatient/community</p> <p>Diagnostic criteria: DSM-IV</p> <p>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)</p> <p>Exclusion criteria: (1) previous risperidone hypersensitivity, (2) history of NMS, (3) seizures within the past yr, (4) degenerative brain disease, (5) problematic living situation</p>	<p>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)</p> <p>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</p> <p>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</p>	<p>Run-in phase duration: 5–7 wk</p> <p>Permitted drugs: divalproex, gabapentin (if epilepsy was in remission ≥1 yr)</p> <p>Prohibited drugs: psychotropics, including stimulants</p> <p>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)</p> <p>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</p> <p>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</p>	<p>Harms: NMS, tardive dyskinesia, weight change</p>	<p>problematic behaviors in children and adolescents with MR. Low doses were better tolerated and were equally effective compared to high doses.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Hollander et al., 2006 ⁴¹	<p>Recruitment dates: NR</p> <p>Country: USA</p> <p>Condition category: ASD</p> <p>Funding: Industry</p> <p>Risk of bias: High (subjective), High (objective)</p>	<p>Enrolled: 11 Analyzed: 11 Completed: 8</p> <p>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))</p> <p>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))</p>	<p>Treatment duration: 8 wk Run-in phase: Yes Run-in phase duration: 4 wk</p> <p>Permitted drugs: anticonvulsants (stable dose ≥3 mo), clonidine, chloral hydrate</p> <p>Prohibited drugs: NR</p> <p>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</p> <p>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</p>	<p>Benefits: CGI-I, response (CGI-I, CPRS)</p> <p>Harms: Constipation, EPS (AIMS, BAS, SAS), sedation, weight change</p>	<p>Olanzapine improved global functioning in children and adolescents with PDD, but was associated with a significant risk of weight gain.</p>
Hrdlicka et al., 2009 ¹¹³	<p>Recruitment dates: 1997 to 2007</p> <p>Country: Czech Republic</p> <p>Condition category: Schizophrenia and related</p>	<p>Enrolled: 109 Analyzed: NR Completed: 52</p> <p>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</p>	<p>Treatment duration: 6 wk Run-in phase: No Run-in phase duration: NR</p> <p>Permitted drugs: NR</p> <p>Prohibited drugs: NR</p> <p>GROUP 1 Drug name: Typical (Haloperidol, Perphenazine, Sulpiride) Dosing variability: variable</p>	<p>Benefits: NR</p> <p>Harms: Weight changes</p>	<p>Weight gain did not differ between the groups on typical and atypical antipsychotics.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
<p>Funding: Government, Academic</p> <p>Newcastle-Ottawa Scale: 5/8 stars</p>	<p>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</p> <p>Exclusion criteria: NR</p>	<p>First episode psychosis (n): NR</p> <p>GROUP 2</p> <p>N: 85</p> <p>Age, mean±SD (range): see above</p> <p>Males %: see above</p> <p>Caucasian %: NR</p> <p>Treatment naïve (n): NR</p> <p>Inpatients (n): NR</p> <p>First episode psychosis (n): NR</p>	<p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean±SD (range): Haloperidol 6.8±1.1, Perphenazine 12±6.9, Sulpiride 450±409.3</p> <p>Concurrent treatments: NR</p> <p>GROUP 2</p> <p>Drug name: Atypical (Clozapine, Olanzapine, Risperidone, Ziprasidone)</p> <p>Dosing variability: variable</p> <p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean±SD (range): Clozapine 247.5±118, Olanzapine 15±6.1, Risperidone 2.7±1.3, Ziprasidone 80±0</p> <p>Concurrent treatments: NR</p>		
<p>Jensen et al., 2008 ⁴²</p> <p>Country: USA</p> <p>Condition category: Schizophrenia and related</p> <p>Funding: NR</p> <p>Risk of bias: High (subjective), High (objective)</p>	<p>Recruitment dates: May 2003 to June 2006</p> <p>Study design: RCT (parallel)</p> <p>Setting: Inpatient (most)</p> <p>Diagnostic criteria: DSM-IV, K-SADS</p> <p>Inclusion criteria: (1) 10–18 yr, (2) schizophrenia/schizoaffective disorder, schizopreniform, or psychotic disorder NOS, (3) ≥1 positive or</p>	<p>Enrolled: 30</p> <p>Analyzed: 29</p> <p>Completed: 21</p> <p>GROUP 1</p> <p>N: 10</p> <p>Age, mean±SD (range): 15.3±1.5</p> <p>Males %: 50</p> <p>Caucasian %: 50</p> <p>Diagnostic breakdown (n): psychotic disorder NOS (6), schizophrenia, schizoaffective, schizopreniform disorder (4)</p> <p>Treatment naïve (n): NR</p> <p>Inpatients (n): 9</p> <p>First episode psychosis (n): NR</p>	<p>Treatment duration: 2.8 mo</p> <p>Run-in phase: Yes</p> <p>Run-in phase duration: 2 wk</p> <p>Permitted drugs: diphenhydramine (≤100 mg/day), lorazepam (0.5–2 mg/day)</p> <p>Prohibited drugs: antidepressants, mood stabilizers, and stimulants (discontinued prior to or within first 2 wk of trial)</p> <p>GROUP 1</p> <p>Drug name: Olanzapine</p> <p>Dosing variability: variable</p> <p>Target dose (mg/day): 20</p> <p>Daily dose (mg/day), mean±SD (range): 14±4.6 (5–20)</p>	<p>Benefits: PANSS, CGAS, CGI-S, medication adherence, response</p> <p>Harms: AIMS, SAS, akathisia, behavioral issues, dyskinesia, EPS, mastitis, sedation, WAE, weight change</p>	<p>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.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	<p>negative symptom associated with schizophrenia present throughout the past 2 wk (PANSS)</p> <p>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</p>	<p>Comorbidities: MR (0), psychosis (all)</p> <p>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)</p> <p>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)</p>	<p>Concurrent treatments: anticholinergics (0), dietary counselling, psychoeducation</p> <p>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</p> <p>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,</p>		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
<p>Jerrell et al., 2008 114</p> <p>Country: USA</p> <p>Condition category: Mixed</p> <p>Questions: KQ2, KQ3</p> <p>Funding: Non-industry</p> <p>Newcastle-Ottawa Scale: 6/8 stars</p>	<p>Recruitment dates: Jan 1996 to Dec 2005</p> <p>Study design: Retrospective</p> <p>Setting: Inpatient/outpatient</p> <p>Diagnostic criteria: ICD-9-CM</p> <p>Inclusion criteria: (1) Child and adolescent patients, (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)</p> <p>Exclusion criteria: NR</p>	<p>Enrolled: NA Analyzed: 4140 Completed: 4140</p> <p>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)</p>	<p>Treatment duration: ≥9 mo Run-in phase: NR Run-in phase duration: NR</p> <p>Permitted drugs: NR</p> <p>Prohibited drugs: NR</p> <p>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)</p>	<p>Benefits: NR</p> <p>Harms: Weight gain, type 2 diabetes mellitus, dyslipidemia, hypertension, cardiovascular/cerebrovascular events, orthostatic hypotension/syncope, EPS, seizures, sedation/somnolence, sexual/reproductive</p>	<p>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.</p>
<p>Johnson & Johnson, 2011⁴³</p> <p>Country: NR</p>	<p>Recruitment dates: Mar to Aug 2006</p> <p>Study design: RCT (parallel)</p>	<p>Enrolled: 25 Analyzed: 25 Completed: 24</p> <p>GROUP 1 N: 8</p>	<p>Treatment duration: 7 days Run-in phase: Yes Run-in phase duration: 21 days maximum</p> <p>Permitted drugs: NR</p>	<p>Benefits: NR</p> <p>Harms: total AE, serious AEs, mortality, prolactin, prolactin-related AE,</p>	<p>Pediatric subjects tolerated doses from 4 to 12 mg paliperidone ER (corresponding to weight-adjusted</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
<p>Condition category: Schizophrenia and related</p> <p>Funding: Industry</p> <p>Risk of bias: High (subjective), High (objective)</p>	<p>Setting: NR</p> <p>Diagnostic criteria: DSM-IV-TR</p> <p>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 \leq 3</p> <p>Exclusion criteria: NR</p>	<p>Age, mean\pmSD (range): all groups: 14.6\pm2.2 (10–17)</p> <p>Males %: all groups: 72</p> <p>Caucasian %: all groups: 56</p> <p>Diagnostic breakdown (n): all groups: schizophreniform disorder (8), schizoaffective disorder (7), paranoid (6), undifferentiated (3), disorganized (1)</p> <p>Treatment naïve (n): NR</p> <p>Inpatients (n): NR</p> <p>First episode psychosis (n): NR</p> <p>GROUP 2 N: 9 Age, mean\pmSD (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</p> <p>GROUP 3 N: 8 Age, mean\pmSD (range): see group 1 Males %: see group 1 Caucasian %: see group 1</p>	<p>Prohibited drugs: NR</p> <p>GROUP 1 Drug name: Paliperidone ER Dosing variability: fixed Target dose (mg/day): 0.086 mg/kg/day Daily dose (mg/day), mean\pmSD (range): NR Concurrent treatments: NR</p> <p>GROUP 2 Drug name: Paliperidone ER Dosing variability: fixed Target dose (mg/day): 0.129 mg/kg/day Daily dose (mg/day), mean\pmSD (range): NR Concurrent treatments: NR</p> <p>GROUP 3 Drug name: Paliperidone ER Dosing variability: fixed Target dose (mg/day): 0.171 mg/kg/day Daily dose (mg/day), mean\pmSD (range): NR Concurrent treatments: NR</p>	<p>orthostatic hypotension, ECG changes, EPS scales</p>	<p>doses ranging from 0.086 and 0.171 mg/kg).</p>

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	Recruitment dates: NR Country: USA Condition category: Eating disorders Funding: Industry ROB: Medium (subjective), Medium (objective)	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	<p>Recruitment dates: Dec 2007 to Mar 2010</p> <p>Country: USA</p> <p>Condition category: ASD</p> <p>Funding: Industry</p> <p>Risk of bias: Medium (subjective), Medium (objective)</p>	<p>Enrolled: 96 Analyzed: 96 Completed: 77</p> <p>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</p> <p>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</p> <p>GROUP 3 N: 35 Age, mean±SD (range): NR Males %: 89 Caucasian %: 60 Diagnostic breakdown (n): autistic disorder (all)</p>	<p>Treatment duration: 6 wk Run-in phase: Yes Run-in phase duration: 3 wk</p> <p>Permitted drugs: Anticholinergics, antihistamine, hypnotic, sedative (lorazepam, diphenhydramine)</p> <p>Prohibited drugs: Psychotropic medications for at least 1 week (4 weeks for fluoxetine, 8 weeks for depot medications)</p> <p>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)</p> <p>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)</p> <p>GROUP 3 Drug name: Placebo Dosing variability: NR Target dose (mg/day): NR Daily dose (mg/day), mean±SD (range): NR</p>	<p>Benefits: ABC-I, ABC (other sub scales), CGI-S, CYBOCS, CGI-I, response, aggression</p> <p>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</p>	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: methylphenidate (1), alprazolam (1), melatonin (2)		
Khan et al., 2009 115	Recruitment dates: Sept 2003 to Aug 2005 Country: USA Condition category: Mixed conditions Funding: NR Newcastle-Ottawa Scale: 6/8 stars	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	<p>Treatment naïve (n): NR Inpatients (n): 24 First episode psychosis (n): NR Comorbidities: See below</p> <p>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)</p>			
Khan et al., 2006 116	<p>Recruitment dates: Jan 2003 to Jan 2005</p> <p>Country: USA</p> <p>Condition category: Mixed conditions</p> <p>Funding: NR</p> <p>Newcastle-Ottawa Scale: 4/8 stars</p>	<p>Enrolled: NA Analyzed: 100 Completed: 100</p> <p>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)</p> <p>GROUP 2 N: 50</p>	<p>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</p> <p>Permitted drugs: NR</p> <p>Prohibited drugs: NR</p> <p>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</p>	<p>Benefits: NA</p> <p>Harms: Dermatologic AE, pseudoparkinsonism, sedation</p>	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
	<p>Exclusion criteria: (1) >18 yr, (2) moderate, severe or profound MR, (3) patients who did not receive IM ziprasidone/olanzapine for agitation or aggression during their inpatient stay, (4) patients receiving both IM ziprasidone and olanzapine</p>	<p>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</p>	<p>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</p>		
<p>Kowatch et al., 2015⁴⁶</p> <p>Country: USA</p> <p>Condition category: Bipolar disorder</p> <p>Funding: Non-industry</p> <p>Risk of bias: Medium (subjective), Medium (objective)</p>	<p>Recruitment dates: Sept 2005 to Sept 2010</p> <p>Study design: RCT (parallel)</p> <p>Setting: Outpatient</p> <p>Diagnostic criteria: DSM-IV-TR, K-SADS, PAPA</p> <p>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 [for 3-5 yr]), (4) permitted to have comorbid ADHD</p> <p>Exclusion criteria: (1) Clinically significant or</p>	<p>Enrolled: 25 Analyzed: 25 Completed: 23</p> <p>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%)</p> <p>GROUP 2 N: 7 Age, mean±SD (range): 5.19±1.0 yr Males %: 71 Caucasian %: 71</p>	<p>Treatment duration: 6 wk Run-in phase: Yes Run-in phase duration: 4 wk (aripiprazole/fluoxetine), 2 wk (other psychotropic)</p> <p>Permitted drugs: Oral chlorpromazine in low doses for sleep disturbance and agitation during the first 2 wk of trial</p> <p>Prohibited drugs: Antipsychotic, antidepressant, mood stabilizer/anticonvulsant other than study drug</p> <p>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</p> <p>GROUP 2 Drug name: Placebo Dosing variability: variable</p>	<p>Benefits: YMRS, CGI-I, CDRS, response, irritability</p> <p>Harms: EPS (AIMS, BAS, SAS), ECG, lipid profile, liver function tests, prolactin, insulin, weight (BMI), hematologic values</p>	<p>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.</p>

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, free 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	<p>Recruitment dates: Nov 2002 to Apr 2005</p> <p>Country: Russia, USA</p> <p>Condition category: Schizophrenia and related</p> <p>Funding: Industry</p> <p>Risk of bias: High (subjective), High (objective)</p>	<p>Enrolled: 107 Analyzed: 107 Completed: 64</p> <p>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)</p> <p>GROUP 2 N: 35 Age, mean±SD (range): 16.3±1.6 (13.1–18) Males %: 68.6 Caucasian %: 71.4</p>	<p>Treatment duration: 6 wk Run-in phase: Yes Run-in phase duration: 2–14 day</p> <p>Permitted drugs: anticholinergics (2–6mg/day), benzodiazepines (2 mg/day lorazepam equivalents for ≤3 consecutive days)</p> <p>Prohibited drugs: NR</p> <p>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)</p> <p>GROUP 2 Drug name: Placebo</p>	<p>Benefits: BPRS-C, PANSS, CGI-I, CGI-S, OAS, medication adherence, response, suicide</p> <p>Harm: AIMS, BAS, SAS, BMI, ECG changes, glucose, hepatic enzyme, lipid profile, mortality, prolactin, sedation, schizophrenia, somnolence, WAE, weight change</p>	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
	<p>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</p> <p>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</p>	<p>Treatment naïve (n): 5 Inpatients (n): NR First episode psychosis (n): NR Comorbidities: MR (0), SA (0)</p>	<p>Dosing variability: fixed Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): NR Concurrent treatments: anticholinergics (2), benzodiazepines (18)</p>		

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	<p>Recruitment dates: Sep 2001 to Mar 2006</p> <p>Country: USA</p> <p>Condition category: Schizophrenia and related</p> <p>Funding: NR</p> <p>Risk of bias: High (subjective), High (objective)</p>	<p>Enrolled: 40 Analyzed: 39 Completed: 28</p> <p>GROUP 1 N: 19 Age, mean\pmSD (range): 15.8\pm2.2 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)</p> <p>GROUP 2 N: 21 Age, mean\pmSD (range): 15.5\pm2.1 Males %: 61.9</p>	<p>Treatment duration: 2.8 mo Run-in phase: No Run-in phase duration: NR</p> <p>Permitted drugs: current medications tapered as tolerated (first 4 wk of trial)</p> <p>Prohibited drugs: NR</p> <p>GROUP 1 Drug name: Clozapine Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): 403.1\pm201.8 (50–700) Concurrent treatments: all groups: antidepressants (4), depakote (3), lithium (7), mood stabilizer (6), naltrexone (1), stimulant (1); group 1: n=6</p> <p>GROUP 2 Drug name: Olanzapine (high dose)</p>	<p>Benefits: BPRS, CGAS, CGI-I, CGI-S, SANS, response</p> <p>Harms: Blood cells, BMI, constipation, diabetes, EPS, glucose, lipid profile, prolactin, SAE, WAE, weight change</p>	<p>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.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	<p>on one or more psychotic items on the BRPS)</p> <p>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)</p>	<p>Caucasian %: 28.6</p> <p>Diagnostic breakdown (n): schizoaffective disorder (7), schizophrenia (14)</p> <p>Treatment naïve (n): 0</p> <p>Inpatients (n): NR</p> <p>First episode psychosis (n): 0</p> <p>Comorbidities: MR (0)</p>	<p>Dosing variability: variable</p> <p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean\pmSD (range): 26.2\pm6.5 (10–30)</p> <p>Concurrent treatments: see group 1; group 2: n=11</p>		
<p>Kumra et al., 1998 117</p> <p>Country: USA</p> <p>Condition category: Schizophrenia and related</p> <p>Funding: Industry</p> <p>Newcastle-Ottawa Scale: 5/8 stars</p>	<p>Recruitment dates: NR</p> <p>Study design: Prospective cohort</p> <p>Setting: Inpatient</p> <p>Diagnostic criteria: DSM-III-TR, K-SADS-E</p> <p>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)</p>	<p>Enrolled: 23</p> <p>Analyzed: 23</p> <p>Completed: 21</p> <p>GROUP 1</p> <p>N: 15</p> <p>Age, mean\pmSD (range): 13.6\pm1.5</p> <p>Males %: 53.3</p> <p>Caucasian %: NR</p> <p>Diagnostic breakdown (n): disorganized (8), paranoid (2), undifferentiated (5)</p> <p>Treatment naïve (n): 0</p> <p>Inpatients (n): all</p> <p>First episode psychosis (n): 0</p> <p>GROUP 2</p>	<p>Treatment duration: Clozapine 6 wk, Olanzapine 8 wk</p> <p>Run-in phase: Yes</p> <p>Run-in phase duration: 17.5 day (mean)</p> <p>Permitted drugs: benzodiazepines (<8 mg/day)</p> <p>Prohibited drugs: NR</p> <p>GROUP 1</p> <p>Drug name: Clozapine</p> <p>Dosing variability: variable</p> <p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean\pmSD (range): 317\pm147 (100–600)</p> <p>Concurrent treatments: NR</p> <p>GROUP 2</p>	<p>Benefits: BPRS, SANS, SAPS, response</p> <p>Harms: Behavioral issues, blood cells, constipation, EPS, liver function, seizure, somnolence, tachycardia, weight change</p>	<p>Preliminary data suggested clozapine and olanzapine were efficacious in children and adolescents with treatment-refractory schizophrenia.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	<p>premorbid Full Scale IQ >70</p> <p>Exclusion criteria: (1) any significant unstable neurological or medical disorder, (2) current serious suicidal risk, (3) active alcohol or drug abuse</p>	<p>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</p>	<p>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)</p>		
<p>Kumra et al., 1996⁴⁸</p> <p>Country: USA</p> <p>Condition category: Schizophrenia and related</p> <p>Funding: NR</p> <p>Risk of bias: High (subjective), High (objective)</p>	<p>Recruitment dates: NR</p> <p>Study design: RCT (parallel)</p> <p>Setting: Inpatient</p> <p>Diagnostic criteria: DSM-III-TR, K-SADS, DICA-R</p> <p>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</p> <p>Exclusion criteria: (1) neurologic or medical disease</p>	<p>Enrolled: 21 Analyzed: 21 Completed: 17</p> <p>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</p> <p>GROUP 2 N: 10 Age, mean±SD (range): 14.4±2.9 Males %: 50 Caucasian %: NR Diagnostic breakdown (n): disorganized (5), undifferentiated (5)</p>	<p>Treatment duration: 6 wk Run-in phase: Yes Run-in phase duration: 6 wk</p> <p>Permitted drugs: group 1: benzotropine mesylate (≤6 mg/day); group 2: identical placebo; all: atenolol, antibiotics, anticonvulsants</p> <p>Prohibited drugs: NR</p> <p>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</p> <p>GROUP 2 Drug name: Clozapine Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean±SD (range): 176±149 (25–525)</p>	<p>Benefits: BPRS-C, CGAS, CGI-I, SANS, SAPS,</p> <p>Harms: Blood cells, blood pressure, EPS (SAS, AIMS), drowsiness, hepatic enzyme, NMS, seizure, tachycardia, weight</p>	<p>Clozapine was more effective in controlling positive and negative symptoms in treatment-refractory childhood onset schizophrenia than haloperidol.</p>

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	Recruitment dates: Sept 2013 to Nov 2014 Country: USA Condition category: ASD Funding: Industry Risk of Bias: Medium (subjective, Medium (objective)	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, benzotropine, 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	Recruitment dates: Nov 1999 to Nov 2002 Country: USA Condition category: ASD Funding: Industry Risk of bias: Medium (subjective), Low (objective)	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	Recruitment dates: NR Country: USA 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
<p>Condition category: ASD</p> <p>Funding: Industry</p> <p>Risk of bias: High (subjective), Medium (objective)</p>	<p>Setting: Inpatient and outpatient</p> <p>Diagnostic criteria: DSM-IV</p> <p>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</p> <p>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</p>	<p>N: 6</p> <p>Age, mean\pmSD (range): 7.3\pm1.9 (5–10.1)</p> <p>Males %: 66.7</p> <p>Caucasian %: 66.7</p> <p>Diagnostic breakdown (n): autistic disorder (5), PDD NOS (1)</p> <p>Treatment naïve (n): NR</p> <p>Inpatients (n): NR</p> <p>First episode psychosis (n): NR</p> <p>Comorbidities: MR (mild (1), moderate (2), severe (3))</p> <p>GROUP 2</p> <p>N: 6</p> <p>Age, mean\pmSD (range): 8.5\pm2.4 (4.9–11.8)</p> <p>Males %: 66.7</p> <p>Caucasian %: 50</p> <p>Diagnostic breakdown (n): autistic disorder (all)</p> <p>Treatment naïve (n): NR</p> <p>Inpatients (n): NR</p> <p>First episode psychosis (n): NR</p> <p>Comorbidities: MR (mild (0), moderate (3), severe (2))</p>	<p>Prohibited drugs: NR</p> <p>GROUP 1</p> <p>Drug name: Haloperidol</p> <p>Dosing variability: variable</p> <p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean\pmSD (range): 1.4\pm0.7 (0.5–2.5)</p> <p>Concurrent treatments: NR</p> <p>GROUP 2</p> <p>Drug name: Olanzapine</p> <p>Dosing variability: variable</p> <p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean\pmSD (range): 7.9\pm2.5 (5–10)</p> <p>Concurrent treatments: NR</p>	<p>Harms: Dermatologic AE, EPS (AIMS, SAS), EPS, fatigue, tachycardia, weight changes</p>	<p>placebo-controlled and long-term studies are needed.</p>
<p>Mankoski et al., 2013¹¹⁸ (see Marcus 2009 & Owen 2009)</p> <p>Country: USA</p> <p>Condition category: ASD</p>	<p>Study design: Retrospective (pooled analysis), evaluate impact of prior antipsychotic exposure (PAE) on safety and tolerability outcomes in pediatric subjects receiving aripiprazole treatment</p>	<p>Enrolled: NA</p> <p>Analyzed: 313</p> <p>Completed: NA</p> <p>GROUP 1</p> <p>N: 176</p> <p>Age, mean\pmSD (range): see below</p> <p>Males %: see below</p> <p>Caucasian %: NR</p>	<p>GROUP 1</p> <p>Drug name: Aripiprazole (antipsychotic naïve)</p> <p>Dosing variability: NR</p> <p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean\pmSD (range): NR</p> <p>Concurrent treatments: NR</p> <p>GROUP 2</p>	<p>Benefits: ABC-I, CGI-S</p> <p>Harms: NA</p>	<p>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</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Funding: Industry Newcastle-Ottawa Scale: 6/8 stars		<p>Diagnostic breakdown (n): NR</p> <p>Treatment naïve (n): 176</p> <p>Inpatients (n): NR</p> <p>First episode psychosis (n): NA</p> <p>Comorbidities: NR</p> <p>GROUP 2 N: 80 Age, mean±SD (range): see below Males %: see below Caucasian %: NR</p> <p>Diagnostic breakdown (n): NR</p> <p>Treatment naïve (n): 80</p> <p>Inpatients (n): NR</p> <p>First episode psychosis (n): NA</p> <p>Comorbidities: NR</p> <p>GROUP 3 N: 36 Age, mean±SD (range): see below Males %: see below Caucasian %: NR</p> <p>Diagnostic breakdown (n): NR</p> <p>Treatment naïve (n): 0</p> <p>Inpatients (n): NR</p> <p>First episode psychosis (n): NA</p> <p>Comorbidities: NR</p> <p>GROUP 4 N: 21 Age, mean±SD (range): see below</p>	<p>Drug name: Placebo (antipsychotic naïve)</p> <p>Dosing variability: NR</p> <p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean±SD (range): NR</p> <p>Concurrent treatments: NR</p> <p>GROUP 3 Drug name: Aripiprazole (PAE)</p> <p>Dosing variability: NR</p> <p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean±SD (range): NR</p> <p>Concurrent treatments: NR</p> <p>GROUP 4 Drug name: Placebo (PAE)</p> <p>Dosing variability: NR</p> <p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean±SD (range): NR</p> <p>Concurrent treatments: NR</p>		<p>receiving placebo. Changes in metabolic parameters in antipsychotic naïve subjects receiving aripiprazole treatment were small and similar to those in subjects receiving placebo.</p>

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	Recruitment dates: June 2006 to Jun 2008 Country: USA Condition category: ASD Funding: Industry Risk of bias: High (subjective), High (objective)	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, benzotropine 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), benzotropine (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 associated with autistic disorder.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	<p>(5) stable nonpharmacologic therapy</p> <p>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 an abnormal laboratory test result considered clinically significant, (7) antipsychotic treatment resistant, (8) known allergy or hypersensitivity to aripiprazole</p>	<p>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</p> <p>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</p>	<p>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), benzotropine (1), hypnotics and sedatives (1)</p> <p>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)</p> <p>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)</p>		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Martin et al., 2000 119	<p>Recruitment dates: 1998</p> <p>Country: USA</p> <p>Condition category: Mixed conditions</p> <p>Funding: Non--industry</p> <p>Newcastle-Ottawa Scale: 6/8 stars</p>	<p>Enrolled: NA Analyzed: 70 Completed: 70</p> <p>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</p> <p>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</p>	<p>Treatment duration: ≥6 mo Run-in phase: Yes Run-in phase duration: 4 wk</p> <p>Permitted drugs: NR</p> <p>Prohibited drugs: NR</p> <p>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), α₂ agonist (8), traditional neuroleptic (0)</p> <p>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), α₂ agonist (6), traditional neuroleptic (9)</p>	<p>Benefits: NR</p> <p>Harms: Weight (BMI, BMI z-score)</p>	<p>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.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Masi et al., 2015 ⁵⁵	<p>Recruitment dates: Jan 2013 to Jan 2014</p> <p>Country: Italy</p> <p>Condition category: Bipolar II (hypomanic)</p> <p>Funding: Industry</p> <p>Risk of bias: High (subjective), High (objective)</p>	<p>Enrolled: 24 Analyzed: 22 Completed: 22</p> <p>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)</p> <p>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)</p>	<p>Treatment duration: 12 wk Run-in phase: NR Run-in phase duration: NR (all treatment naïve)</p> <p>Permitted drugs: Methylphenidate at stable dose in 1 patient in risperidone group</p> <p>Prohibited drugs: Psychotropics≤6mo</p> <p>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</p> <p>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</p>	<p>Benefits: YMRS, CGI-S, CGAS, HDRS, HAM-A, MOAS, response</p> <p>Harms: BMI, prolactin, somnolence, fatigue, EPS, ECG</p>	<p>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 of QTc prolongation, should be cautiously considered in the context of the limited time of the study.</p>
Masi et al., 2013 ⁵⁴	<p>Recruitment Dates: NR</p>	<p>Enrolled: 69 Analyzed: 69 Completed: 69</p>	<p>Treatment duration: ≥ 12 wk Run-in phase: NR Run-in phase duration: NR</p>	<p>Benefits: C-GAS, CGI-S, CGI-I, response</p>	<p>In tic-related pediatric OCD, augmentation of</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
<p>Country: Italy</p> <p>Condition category: OCD</p> <p>Funding: No funding provided</p> <p>Risk of Bias: High (subjective), Medium (objective)</p>	<p>Study design: NRCT (parallel)</p> <p>Diagnostic criteria: DSM-IV, K-SADS-PL (OCD), DSM-IV-TR (Tic)</p> <p>Setting: Outpatient</p> <p>Inclusion criteria: Diagnosis of OCD, CGI score ≥ 4 and C-GAS score ≤ 60. Comorbid tic disorder, ≥ 40 on YGTSS, non-responder to SSRI</p> <p>Exclusion criteria: Diagnosis of mental retardation, PDD, schizophrenia</p>	<p>GROUP 1: N: 35 Age, mean\pmSD (range): 13.3\pm2.2 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)</p> <p>GROUP 2: N: 34 Age, mean\pmSD (range): 13.9\pm2.5 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)</p>	<p>Permitted drugs: SSRI</p> <p>Prohibited drugs: NR</p> <p>GROUP 1 Drug name: Risperidone Dosing variability: Variable Target dose (mg/day): 3 mg/day Daily dose (mg/day), mean\pmSD (range): 1.7\pm0.8 (0.5-3) mg/day Concurrent treatments: SSRI (35), mood stabilizers (3), stimulants (1), psychotherapy (20)</p> <p>GROUP 2: Drug name: Aripiprazole Dosing variability: Variable Target dose (mg/day): 12.5 mg/day Daily dose (mg/day), mean\pmSD (range): 8.9\pm3.1 (2.5-12.5) mg/day Concurrent treatments: SSRI (34), mood stabilizers (1), stimulants (1), psychotherapy (14)</p>	<p>Harms: Weight, sedation, tremors</p>	<p>SSRIs with risperidone or aripiprazole was tolerated and effective in about half of the patients who did not respond to SSRIs alone.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
<p>McCracken et al., 2002⁵⁶</p> <p>Country: USA</p> <p>Condition category: ASD</p> <p>Funding: Industry, Government, Foundation</p> <p>Risk of bias: Medium (subjective), Medium (objective)</p>	<p>Recruitment dates: Jun 1999 to Apr 2001</p> <p>Study design: RCT (parallel)</p> <p>Setting: Inpatient and outpatient</p> <p>Diagnostic criteria: DSM-IV, ADI-R</p> <p>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</p>	<p>Enrolled: 101 Analyzed: 101 Completed: 80</p> <p>GROUP 1 N: 49 Age, mean\pmSD (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))</p> <p>GROUP 2 N: 52 Age, mean\pmSD (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))</p>	<p>Treatment duration: 8 wk Run-in phase: Yes Run-in phase duration: 1–4 wk</p> <p>Permitted drugs: anticonvulsants (constant dose ≥ 4 wk and seizure-free for ≥ 6 mo), benzotropine</p> <p>Prohibited drugs: antihistamines, ceterazine, erythromycin, metoclopramide, pseudoephedrine, and any drug that may impact risperidone concentrations or lead to drug interactions; psychotropics</p> <p>GROUP 1 Drug name: Risperidone Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): 1.8\pm0.7 (0.5–3.5) Concurrent treatments: anticonvulsants (2)</p> <p>GROUP 2 Drug name: Placebo Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): 2.4\pm0.6 (0.5–3.5) Concurrent treatments: anticonvulsants (2)</p>	<p>Benefits: ABC, CYBOCS, CGI-I, CGI-S, RFRLRS, VAS, AIMS, Cognitive, medication adherence, patient, parent/care provider reported outcomes (diet/intake, sleep), response</p> <p>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</p>	<p>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.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	<p>IQ test, (10) inpatients or outpatients</p> <p>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</p>				
McGorry et al., 2013 ⁵⁷	<p>Recruitment dates: August 2000 to May 2006</p> <p>Country: Australia</p> <p>Condition category: Schizophrenia and related</p> <p>Funding: Industry</p> <p>Study design: RCT (parallel)</p> <p>Setting: Outpatient</p> <p>Diagnostic criteria: Ultra-high risk: (1) the presence of attenuated (subthreshold) psychotic symptoms</p>	<p>Enrolled: 87 Analyzed: NR Completed: 56</p> <p>GROUP 1 N: 43 Age, mean\pmSD (range): 17.6\pm3.0 Males %: 35 Caucasian %: NR Treatment naïve (n): 100 Inpatients (n): 0 First episode psychosis (n): UHR</p>	<p>Treatment duration: 52 wk Run-in phase: NA Run-in phase duration: NA</p> <p>Permitted drugs: NR</p> <p>Prohibited drugs: mood-stabilizing medications</p> <p>GROUP 1 Drug name: Cognitive therapy + risperidone Dosing variability: variable Target dose (mg/day): up to 2mg/day</p>	<p>Benefits: BPRS, SANS, GAF, HDRS, quality of life, transition rates</p> <p>Harms: UKU</p>	<p>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.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Risk of bias: High (subjective), High (objective)	<p>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</p> <p>Inclusion criteria: 14-30 yrs; see above criteria</p> <p>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-</p>	<p>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</p>	<p>Daily dose (mg/day), mean±SD (range): NR Concurrent treatments: NR</p> <p>GROUP 2 Drug name: Cognitive therapy + placebo Dosing variability: NR Target dose (mg/day): NR Daily dose (mg/day), mean±SD (range): 0 Concurrent treatments: NR</p>		

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	Recruitment dates: NR Country: Turkey Condition category: ASD Funding: Industry Risk of bias: Medium (subjective), Medium (objective)	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	Recruitment dates: NR Country: Israel Condition category: Schizophrenia and related	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
<p>Funding: No funding</p> <p>Risk of bias: High (subjective), High (objective)</p>	<p>Diagnostic criteria: DSM-IV, K-SADS</p> <p>Inclusion criteria: (1) hospitalized childhood-onset schizophrenic children</p> <p>Exclusion criteria: (1) MR</p>	<p>Caucasian %: NR</p> <p>Diagnostic breakdown (n): disorganized schizophrenia (3), paranoid schizophrenia (2), schizophreniform disorder (6), unspecified schizoprehenia (1)</p> <p>Treatment naïve (n): NR</p> <p>Inpatients (n): all</p> <p>First episode psychosis (n): NR</p> <p>Comorbidities: ADHD (2), familial mediterranean fever (1), MR (0), tic disorder (1)</p> <p>GROUP 2</p> <p>N: 13</p> <p>Age, mean±SD (range): 10.7±1.4 (8.8–13.3)</p> <p>Males %: 38.5</p> <p>Caucasian %: NR</p> <p>Diagnostic breakdown (n): disorganized schizophrenia (4), paranoid schizophrenia (4), schizophreniform disorder (4), unspecified schizoprehenia (1)</p> <p>Treatment naïve (n): NR</p> <p>Inpatients (n): all</p> <p>First episode psychosis (n): NR</p> <p>Comorbidities: ADHD (1), epilepsy (2), MR (0), neurofibromatosis (1), OCD (3)</p>	<p>GROUP 1</p> <p>Drug name: Olanzapine</p> <p>Dosing variability: variable</p> <p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean±SD (range): 8.2±4.4 (2.5–20)</p> <p>Concurrent treatments: biperiden (2), carbamazepine (2), citalopram (1), colchicine (1), methylphenidate (2), promethizine (2), valproic acid (1)</p> <p>GROUP 2</p> <p>Drug name: Risperidone</p> <p>Dosing variability: variable</p> <p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean±SD (range): 1.6±1 (0.3–4.5)</p> <p>Concurrent treatments: biperiden (4), citalopram (2), fluoxetine (1), phenytoin (1), promethizine (1), valproic acid (1)</p>		
Nagaraj et al., 2006 ⁶⁰	Recruitment dates: Jan 2002 to Dec 2003	<p>Enrolled: 40</p> <p>Analyzed: 39</p> <p>Completed: 39</p>	<p>Treatment duration: 6 mo</p> <p>Run-in phase: Yes</p> <p>Run-in phase duration: ≥1 mo</p>	<p>Benefits: CARS, CGAS, response (CARS, CGAS,</p>	<p>Risperidone improved global functioning and</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
<p>Country: India</p> <p>Condition category: ASD</p> <p>Funding: Industry, Academic</p> <p>Risk of bias: Low (subjective), Low (objective)</p>	<p>Study design: RCT (parallel)</p> <p>Setting: Outpatient/community</p> <p>Diagnostic criteria: DSM-IV</p> <p>Inclusion criteria: (1) ≤12 yr, (2) autism (DSM-IV)</p> <p>Exclusion criteria: (1) severe MR, (2) any significant coexisting disease or illness, (3) severe malnutrition</p>	<p>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)</p> <p>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)</p>	<p>Permitted drugs: antiepileptics</p> <p>Prohibited drugs: no other drugs permitted</p> <p>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</p> <p>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</p>	<p>Global Impression of Parents)</p> <p>Harms: Dyskinesia, sedation, weight change</p>	<p>social responsiveness, reduced hyperactivity and aggression, and was well tolerated in children with autism.</p>
<p>NCT00194012, 2013⁶¹</p> <p>Country: USA</p> <p>Condition category: Bipolar</p> <p>Funding:</p>	<p>Recruitment dates: August 2004-May 2012</p> <p>Study design: RCT</p> <p>Setting: Outpatient</p>	<p>Enrolled: 59 Analyzed: NR Completed: 21 (15 Group 1; 6 Group 2)</p> <p>GROUP 1 N: 30 Age, mean±SD (range): <18 yr (all) Males %: 66.7</p>	<p>Treatment duration: 12 wk, plus 6 wk open label extension</p> <p>Run-in phase: NR</p> <p>Run-in phase duration: NR</p> <p>Permitted drugs: NR</p> <p>Prohibited drugs: psychotropic agents taken <1 wk of baseline (2</p>	<p>Benefits: YMRS</p> <p>Harms: AEs (major and minor)</p>	<p>NR</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Industry, Institution (hospital) Risk of bias: High (subjective). High (objective)	<p>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</p> <p>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</p> <p>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</p>	<p>Caucasian %: NR Treatment naïve (n): NR Inpatients (n): None First episode psychosis (n): NR</p> <p>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</p>	<p>wk for fluoxetine; 3 days for psychostimulants)</p> <p>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</p> <p>GROUP 2 Drug name: Placebo Dosing variability: NR Target dose (mg/day): NR Daily dose (mg/day), mean±SD (range): NR Concurrent treatments: NR</p>		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	<p>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</p>				

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	<p>females, not using an adequate birth control</p>				
<p>NCT00619190, 2013 ¹²¹</p> <p>Country: USA</p> <p>Condition category: ASD</p> <p>Funding: Institution (University)</p> <p>Newcastle-Ottawa Scale: 4/8</p>	<p>Recruitment dates: NR</p> <p>Study design: Controlled before-after study</p> <p>Setting: NR</p> <p>Diagnostic criteria: NR</p> <p>Inclusion criteria: NR</p> <p>Exclusion criteria: NR</p>	<p>Enrolled: 30 Analyzed: Completed: 29</p> <p>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</p> <p>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</p>	<p>Treatment duration: 12 wk Run-in phase: NR Run-in phase duration: NR</p> <p>Permitted drugs: NR</p> <p>Prohibited drugs: NR</p> <p>GROUP 1 Drug name: Aripiprazole Dosing variability: 1-30 mg Target dose (mg/day): NR Daily dose (mg/day), mean±SD (range): NR Concurrent treatments: NR</p> <p>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</p>	<p>Benefits: ABC-I, CGI-S, ABC-Lethargy/Social Withdrawal</p> <p>Harms: AEs (major and minor)</p>	
<p>NCT01149655, 2014 ⁶²</p> <p>Country: Multiple countries</p> <p>Condition category: Schizophrenia and related</p> <p>Funding: Industry (pharmaceutical)</p>	<p>Recruitment dates: July 2011-Dec 2013</p> <p>Study design: RCT</p> <p>Setting: Outpatient</p> <p>Diagnostic criteria: DSM-IV-TR diagnosis of schizophrenia</p> <p>Inclusion Criteria:</p>	<p>Enrolled: 146 Analyzed: Completed: 21 (15 (group 1), 6 (group 2))</p> <p>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</p>	<p>Treatment duration: 52 wk Run-in phase: Yes (stabilized on 10-30 mg/day of aripiprazole prior to randomization) Run-in phase duration: NR</p> <p>Permitted drugs: NR</p> <p>Prohibited drugs: NR</p> <p>GROUP 1 Drug name: Aripiprazole Dosing variability: 10-30 mg/day</p>	<p>Benefits: Relapse Rate (CGI-I/S, PANSS, hospitalization, suicide ideation, violent/aggressive behavior), % exacerbation or relapse/impending relapse, % responders, % achieved remission,</p>	

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Risk of bias: High (subjective). High (objective)	<p>(1) schizophrenia, (2) hx of illness \geq6 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.</p> <p>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 \leq30 days prior to screening, (8) DSM-IV-TR criteria for substance dependence \leq180</p>	<p>Inpatients (n): NR First episode psychosis (n): NR</p> <p>GROUP 2 N: 48 Age, mean\pmSD (range): 15.6\pm1.1 (males), 15.3\pm1.0 (females) Males %: 70.8 Caucasian %: NR Treatment naïve (n): 0 Inpatients (n): NR First episode psychosis (n): NR</p>	<p>Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): NR Concurrent treatments: NR</p> <p>GROUP 2 Drug name: Placebo Dosing variability: NR Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): NR Concurrent treatments: NR</p>	<p>% discontinued, CGAS</p> <p>Harms: AEs (minor and serious)</p>	

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 \geq 4.0 mIU/L), known hypothyroidism or hyperthyroidism (unless stabilized with medication for \geq 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	Recruitment dates: Jan 2000 to Dec 2006	Enrolled: 86 Analyzed: 86 Completed: 86	Treatment duration: 2 wk for weight outcomes Run-in phase: NR Run-in phase duration: NR	Benefits: CDI, MASC, EDI-2DT, EDI-2BD	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
Country: Canada	Study design: Retrospective	GROUP 1 N: 43 Age, mean\pmSD (range): 14.4 \pm 1.9 yr Males %: 0 Caucasian %: NR	Permitted drugs: SSRI/SNRI (17), benzodiazepine (3) (at the time of olanzapine initiation)	Harms: change in body composition (weight, BMI), dyslipidemia, liver function test, sedation, rebound weight loss and increased psychological stress after initial discontinuation of olanzapine	
Condition category: Eating disorders (Anorexia nervosa)	Setting: inpatient and outpatient	Diagnostic breakdown (n): ANR (29), ANBP (2), EDNOS-R (12)	Prohibited drugs: NR		
Funding: Non-industry	Diagnostic criteria: DSM-IV	Diagnostic breakdown (n): ANR (29), ANBP (2), EDNOS-R (12)	GROUP 1 Drug name: Olanzapine Dosing variability: flexible Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): [median (IQR)] 5.0 (3.75-7.5)		
Newcastle-Ottawa Scale: 7/8 stars	Inclusion criteria: (1) 10-17 yr, (2) female, (3) diagnosed with AN or EDNOS according to DSM-IV	Treatment naïve (n): NR Inpatients (n): 35 First episode psychosis (n): NR			

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	<p>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</p>	<p>Comorbidities: Anxiety (29), depression (26), obsessive compulsive disorder (3)</p> <p>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)</p>	<p>Concurrent treatments: SSRI/SNRI (17), benzodiazepine (3)</p> <p>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</p>		<p>during the entire course of treatment, regardless of the patient's absolute weight.</p>
<p>Novaes et al., 2008 ¹²³</p> <p>Country: Brazil</p> <p>Condition category: ASD</p> <p>Funding: Foundation</p> <p>Newcastle-Ottawa Scale: 8/8 stars</p>	<p>Recruitment dates: Jan 2001 to June 2006</p> <p>Study design: Retrospective cohort</p> <p>Setting: Outpatient/community</p> <p>Diagnostic criteria: DSM-IV</p> <p>Inclusion criteria: (1) ASD, (2) behavioral disturbances (psychomotor aggression or agitation)</p>	<p>Enrolled: NA Analyzed: 26 Completed: 26</p> <p>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)</p>	<p>Treatment duration: 17 mo (mean) Run-in phase: No Run-in phase duration: NR</p> <p>Permitted drugs: NR Prohibited drugs: NR</p> <p>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</p>	<p>Benefits: Response (CGI-I)</p> <p>Harms: NR</p>	<p>SGAs appeared to reduce agitation and aggression in patients with ASD.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Exclusion criteria: NR		<p>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</p> <p>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</p> <p>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</p>	<p>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</p> <p>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</p> <p>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)</p>		

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
O'Donoghue et al., 2014 ¹²⁴	Recruitment dates: January 2001 to August 2005 Country: Austria Condition category: Schizophrenia and related Funding: NR Newcastle-Ottawa Scale: 3/8 stars	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	Recruitment dates: Jan 2010 to Oct 2011 Country: South Korea Condition category: Bipolar I, II, NOS Funding: NR Newcastle-Ottawa Scale: 6/8 stars	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
	<p>IV diagnosis of bipolar I disorder, bipolar II disorder, bipolar disorder, and bipolar affective disorder</p> <p>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</p>	<p>First episode psychosis (n): NR</p> <p>Comorbidities: See below</p> <p>GROUP 2</p> <p>N: 65</p> <p>Age, mean±SD (range): 11.46±3.95 yr</p> <p>Males %: 76.9</p> <p>Caucasian %: NR</p> <p>Diagnostic breakdown (n): NR</p> <p>Treatment naïve (n): NR</p> <p>Inpatients (n): 0</p> <p>First episode psychosis (n): NR</p> <p>Comorbidities: See below</p> <p>Overall comorbidities: ADHD (50), tic related disorders (17), conduct disorders and ODD (5), autism spectrum disorder (12)</p>	<p>Concurrent treatments: See below</p> <p>GROUP 2</p> <p>Drug name: Others</p> <p>Dosing variability: NR</p> <p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean±SD (range): Risperidone (1.46±1.08), quetiapine (207.46±200.53), paliperidone (4.50±2.12)</p> <p>Concurrent treatments: See below</p> <p>Overall concurrent treatments: mood stabilizers (20), methylphenidate (34), atomoxetine (12), antidepressants (27)</p>		<p>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.</p>
<p>Olfson et al., 2012¹²⁶</p> <p>Country: USA</p> <p>Condition category: Schizophrenia and related</p> <p>Funding: Government</p>	<p>Recruitment dates: Medicaid claims file 2001-2005</p> <p>Study design: Retrospective cohort</p> <p>Setting: Inpatients (<10%) and outpatients</p> <p>Diagnostic criteria: ICD-9-CM</p>	<p>Enrolled: 1745</p> <p>Analyzed: 1745</p> <p>Completed: NA</p> <p>GROUP 1</p> <p>N: 805</p> <p>Age, mean±SD (range): NR</p> <p>Males %: 62</p> <p>Caucasian %: 38</p> <p>Treatment naïve (n): 805</p> <p>Inpatients (n):</p>	<p>Treatment duration:</p> <p>Run-in phase:</p> <p>Run-in phase duration:</p> <p>Permitted drugs: None</p> <p>Prohibited drugs: None</p> <p>GROUP 1</p> <p>Drug name: Risperidone</p> <p>Dosing variability:</p> <p>Target dose (mg/day):</p>	<p>Benefits: Medication adherence (all-cause discontinuation), psychiatric hospital admission</p> <p>Harms: NR</p>	<p>The results suggest that rapid antipsychotic medication discontinuation and psychiatric hospital admission are common in the community treatment of early-onset schizophrenia.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Newcastle-Ottawa Scale: 7/8 stars	<p>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</p> <p>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</p>	<p>First episode psychosis (n): NR</p> <p>GROUP 2 N: 382 Age, mean±SD (range): NR Males %: 69 Caucasian %: 38 Treatment naïve (n): 382 Inpatients (n): First episode psychosis (n): NR</p> <p>GROUP 3 N: 260 Age, mean±SD (range): NR Males %: 52 Caucasian %: 48 Treatment naïve (n): 260 Inpatients (n): First episode psychosis (n): NR</p> <p>GROUP 4 N: 173 Age, mean±SD (range): NR Males %: 55 Caucasian %: 42 Treatment naïve (n): 173 Inpatients (n): First episode psychosis (n): NR</p> <p>GROUP 5 N: 125</p>	<p>Daily dose (mg/day), mean±SD (range): Concurrent treatments:</p> <p>GROUP 2 Drug name: Olanzapine Dosing variability: Target dose (mg/day): Daily dose (mg/day), mean±SD (range): Concurrent treatments:</p> <p>GROUP 3 Drug name: Quetiapine Dosing variability: Target dose (mg/day): Daily dose (mg/day), mean±SD (range): Concurrent treatments:</p> <p>GROUP 4 Drug name: Aripiprazole Dosing variability: Target dose (mg/day): Daily dose (mg/day), mean±SD (range): Concurrent treatments:</p> <p>GROUP 5 Drug name: Ziprasidone Dosing variability: Target dose (mg/day): Daily dose (mg/day), mean±SD (range): Concurrent treatments:</p>		

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	Recruitment dates: 2009 Country: Iran Condition category: Behavioral issues Funding: Institution (University) Risk of bias: High (subjective), NA (objective)	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 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.				

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Owen et al., 2009 ⁶⁴	<p>Recruitment dates: June 2006 to April 2008</p> <p>Country: USA</p> <p>Condition category: ASD</p> <p>Funding: Industry</p> <p>Risk of bias: Medium (subjective), Low (objective)</p>	<p>Enrolled: 164 Analyzed: 98 Completed: 75</p> <p>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</p> <p>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</p>	<p>Treatment duration: 8 wk Run-in phase: Yes Run-in phase duration: ≤6 wk</p> <p>Permitted drugs: anxiolytics, benzotropine or propranolol, diphenhydramine (≤50 mg/day), psychotropic medication, sleep aids</p> <p>Prohibited drugs: antidepressants, antipsychotics, anxiolytics, mood stabilizers, neuroleptics, psychostimulants (washout ≥4 day), fluoxetine, olanzapine/fluoxetine (washout ≥4 wk before screen visit)</p> <p>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</p> <p>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</p>	<p>Benefits: ABC, CYBOCS, CGI-I, CGI-S, PedsQL, CGSQ, response (ABC-I, CGI-I), suicide</p> <p>Harms: EPS (AIMS, BAS, SAS), fatigue, glucose, lipid profile, prolactin, LDL, total cholesterol, HDL, somnolence, aggression, total AE, weight change</p>	<p>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 behaviour, or a combination of these symptoms.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Pandina et al., 2007 ¹²⁷ (see Aman 2002, Snyder 2002)	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	<p>Enrolled: NA Analyzed: 228 Completed: NA</p> <p>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)</p> <p>GROUP 2 N: 88 Age, mean±SD (range): 8.4 yr Males %: 77 Caucasian %: 68</p>	<p>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</p> <p>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</p>	<p>Benefits: continuous performance task (CPT), VLT-C</p> <p>Harms: NA</p>	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	Recruitment dates: Aug 2004 to Jul 2006 Country: USA Condition category: Bipolar I (manic) Funding: Industry Risk of bias: High (subjective), High (objective)	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, benzotropine Prohibited drugs: Prophylactic use of benzotropine 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	Recruitment dates: NR Country: USA Condition category: ASD Funding: Industry, Government, Foundation Risk of bias: High (subjective), High (objective)	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 autistic children. Drug efficacy was not diminished 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	Recruitment dates: NR Country: USA Condition category: Mixed conditions Funding: NR Newcastle-Ottawa Scale: 6/8 stars	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	Recruitment dates: Jan 2000 to Aug 2000 Country: Israel Condition category: Schizophrenia and related Funding: Government, Foundation Newcastle-Ottawa Scale: 3/8 stars	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	Adolescents 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	Recruitment dates: NR Country: Canada Condition category: ASD Funding: Non-industry Risk of bias: High (subjective), High (objective)	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, arrhythmias	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	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 (MVL, 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	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
Country: Italy					

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	Recruitment dates: Feb 2009 to Mar 2012 Country: Canada Study design: Prospective Cohort Condition category: Mixed conditions Funding: Industry Newcastle-Ottawa Scale: 4/8 stars	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 identification and treatment of metabolic side effects.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	medications known to affect metabolism.	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	Recruitment dates: NR Country: USA Condition category: ASD Funding: Industry/ Non-industry Risk of bias: Medium (subjective), Medium (objective) 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: anticonvulsant 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	
		<p>Treatment naïve (n): see below</p> <p>Inpatients (n): NR</p> <p>First episode psychosis (n): NR</p> <p>Comorbidities: see below</p> <p>Overall age, mean±SD (range): 9.0±2.5 yr</p> <p>Overall males %: 86.8</p> <p>Caucasian %: 60.5</p> <p>Overall treatment naïve (n): 7</p> <p>Overall comorbidities: IQ average (2), IQ borderline (5), MR (27)</p>				
Saito et al., 2004 131	<p>Recruitment dates: Sept 2001 to Mar 2003</p> <p>Country: USA</p> <p>Condition category: Mixed conditions</p> <p>Funding: Government</p> <p>Newcastle-Ottawa Scale: 6/8 stars</p>	<p>Study design: Prospective cohort</p> <p>Setting: Inpatient/outpatient</p> <p>Diagnostic criteria: NR</p> <p>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</p>	<p>Enrolled: 40</p> <p>Analyzed: 40</p> <p>Completed: 40</p> <p>GROUP 1</p> <p>N: 13</p> <p>Age, mean±SD (range): all groups: 13.4±3.4 (5–18)</p> <p>Males %: all groups: 55</p> <p>Caucasian %: NR</p> <p>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)</p> <p>Treatment naïve (n): NR</p> <p>Inpatients (n): NR</p> <p>First episode psychosis (n): NR</p>	<p>Treatment duration: 11.2 wk</p> <p>Run-in phase: Yes</p> <p>Run-in phase duration: 1 mo.</p> <p>Permitted drugs: NR</p> <p>Prohibited drugs: NR</p> <p>GROUP 1</p> <p>Drug name: Olanzapine</p> <p>Dosing variability: variable</p> <p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean±SD (range): 7.8±4.2</p> <p>Concurrent treatments: all groups: divalproex sodium (7), lithium (5), SSRI (11), stimulants (9), benzodiazepines (3), alpha-adrenergic agonists (3)</p> <p>GROUP 2</p> <p>Drug name: Quetiapine</p> <p>Dosing variability: variable</p> <p>Target dose (mg/day): NR</p>	<p>Benefits: NA</p> <p>Harms: prolactin, prolactin-related AEs</p>	<p>Prolactin levels were significantly increased in children and adolescents treated with risperidone, compared to those treated with olanzapine or quetiapine.</p>

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	Recruitment dates: NR Country: USA Condition category: Tic disorders Funding: Industry	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 adolescents with Tourette syndrome, and may also be an effective anti-tic medication.

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
<p>Risk of bias: Medium (subjective), Medium (objective)</p>	<p>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</p> <p>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</p>	<p>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)</p> <p>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)</p>	<p>Target dose (mg/day): NR Daily dose (mg/day), mean±SD (range): 28.2±9.6 Concurrent treatments: NR</p> <p>GROUP 2 Drug name: Placebo Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean±SD (range): NR Concurrent treatments: NR</p>		
<p>Sallee et al., 1997⁷²</p> <p>Country: USA</p> <p>Condition category: Tic disorders</p> <p>Funding: Industry, Government</p>	<p>Recruitment dates: NR</p> <p>Study design: RCT (crossover)</p> <p>Setting: Outpatient/community</p> <p>Diagnostic criteria: DSM-III-TR, K-SADS-P</p> <p>Inclusion criteria: (1) principal DSM-III-R dx</p>	<p>Enrolled: 22 Analyzed: 22 Completed: 22</p> <p>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</p>	<p>Treatment duration: 6 wk Run-in phase: Yes Run-in phase duration: >2 wk</p> <p>Permitted drugs: diphenhydramine hydrochloride</p> <p>Prohibited drugs: adjunctive treatment, anticholinergics, concomitant medications</p> <p>GROUP 1 Drug name: Haloperidol Dosing variability: variable</p>	<p>Benefits: CGAS, CGI-S Medication adherence, response</p> <p>Harms: Akathisia, akinesia, behavioral issues, electrocardiovascular, EPS (AIMS, ESRS), prolactin, treatment limiting AE, WAE, weight change</p>	<p>Pimozide is superior to haloperidol for controlling symptoms of Tourette syndrome in children and adolescents.</p>

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	Recruitment dates: NR Country: USA Condition category: Tic disorders	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
<p>Funding: Foundation</p> <p>Risk of bias: Medium (subjective), Medium (objective)</p>	<p>Diagnostic criteria: DSM-III-TR, TSGS</p> <p>Inclusion criteria: (1) consecutive outpatient children who met DSM-III-R criteria for Tourette syndrome and severity criteria using the TSGS</p> <p>Exclusion criteria: NR</p>	<p>Caucasian %: NR Diagnostic breakdown (n): NR Treatment naïve (n): NR Inpatients (n): NR First episode psychosis (n): NR Comorbidities: ADHD (6)</p> <p>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)</p>	<p>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</p> <p>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</p>		
<p>Savitz et al., 2015⁷⁴</p> <p>Country: India, Romania, Russia, Slovakia, Spain, Ukraine, and the United States</p> <p>Condition category: Schizophrenia and related</p> <p>Funding: Industry</p>	<p>Recruitment dates: November 2009 to June 2012</p> <p>Study design: RCT (parallel)</p> <p>Setting: Inpatient and outpatient</p> <p>Diagnostic criteria: DSM-IV</p> <p>Inclusion criteria: (1) 12-17 yr, (2) body weight ≥ 29kg, (3) diagnosis of</p>	<p>Enrolled: 228 Analyzed: 226 Completed: 174</p> <p>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</p> <p>GROUP 2</p>	<p>Treatment duration: 8wk acute, 18 wk maintenance Run-in phase: Yes Run-in phase duration: ≤3 wks</p> <p>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 extrapyramidal symptoms</p>	<p>Benefits: PANSS, maintenance of stability, CGI-S, response</p> <p>Harms: AIMS, BAS, SAS, any AE, C-SSRS, prolactin, weight, ECG, glucose, insulin, lipids</p>	<p>Paliperidone ER did not demonstrate superiority to aripiprazole in treating adolescent schizophrenia.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
<p>Risk of bias: Medium (subjective), Medium (objective)</p>	<p>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 suboptimal current treatment</p> <p>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</p>	<p>N: 114 Age, mean\pmSD (range): 15.4\pm1.5 Males %: 67 Caucasian %: 77 Treatment naive (n): 11 Inpatients (n): 68 (at screening) First episode psychosis (n): 0</p>	<p>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</p> <p>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\pmSD (range): 6.75\pm1.8 Concurrent treatments: anti-EPS medications or antihistamines (26%)</p> <p>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\pmSD (range): 11.6\pm3.0 Concurrent treatments: anti-EPS medications or antihistamines (25%)</p>		

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	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\pmSD (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\pmSD (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\pmSD (range): 2.5 \pm 0.9 Concurrent treatments: NR GROUP 2 Drug name: Placebo Dosing variability: variable Target dose (mg/day): 3 Daily dose (mg/day), mean\pmSD (range): 3.3 \pm 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	Recruitment dates: NR	Enrolled: 23 Analyzed: 17 Completed: 11	Treatment duration: 4 wk Run-in phase: Yes Run-in phase duration: NR	Benefits: YMRS, response, medication adherence	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.
Country: USA	Study design: RCT (parallel)	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)	Permitted drugs: NR Prohibited drugs: NR	Harms: NR	
Condition category: Bipolar I (manic, mixed)	Setting: 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: benzotropine (1), lorazepam (1)		
Funding: Industry	Diagnostic criteria: DSM-IV-TR, K-SADS-PL		GROUP 2 Drug name: Placebo Dosing variability: NR Target dose (mg/day): NR Daily dose (mg/day), mean±SD (range): NR Concurrent treatments: NR		
Risk of bias: High (subjective), High (objective)	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				

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	Recruitment dates: Oct 1993 to Nov 1995 Country: USA Condition category: Tic disorders Funding: Industry, Government, Foundation Risk of bias: Medium (subjective), NA (objective)	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	Recruitment dates: Jan 1998 to June 2005 Country: USA	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
<p>Condition category: Schizophrenia and related</p> <p>Funding: NR</p> <p>Risk of bias: Medium (subjective), Medium (objective)</p>	<p>Setting: Inpatient</p> <p>Diagnostic criteria: DSM-IV, K-SADS, medical and school record review, interview with child and parents</p> <p>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)</p> <p>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)</p>	<p>Age, mean\pmSD (range): 11.7\pm2.3</p> <p>Males %: 66.7</p> <p>Caucasian %: 58.3</p> <p>Treatment naïve (n): 0</p> <p>Inpatients (n): all</p> <p>First episode psychosis (n): 0</p> <p>Comorbidities: ADHD (4), anxiety disorders (6), MR (0)</p> <p>GROUP 2</p> <p>N: 13</p> <p>Age, mean\pmSD (range): 12.8\pm2.4</p> <p>Males %: 53.8</p> <p>Caucasian %: 53.8</p> <p>Treatment naïve (n): 0</p> <p>Inpatients (n): all</p> <p>First episode psychosis (n): 0</p> <p>Comorbidities: ADHD (3), anxiety disorders (1), MR (0)</p>	<p>Prohibited drugs: NR</p> <p>GROUP 1</p> <p>Drug name: Clozapine</p> <p>Dosing variability: variable</p> <p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean\pmSD (range): 327\pm113 (150–500)</p> <p>Concurrent treatments: diphenhydramine hydrochloride (4), guanfacine hydrochloride (1), lorazepam (2), sedatives (4), ≤ 4 hr specialized education, recreational and occupational therapy</p> <p>GROUP 2</p> <p>Drug name: Olanzapine</p> <p>Dosing variability: variable</p> <p>Target dose (mg/day): NR</p> <p>Daily dose (mg/day), mean\pmSD (range): 18.1\pm4.3</p> <p>Concurrent treatments: clomipramine hydrochloride (1), diphenhydramine hydrochloride (6), lorazepam (3), sedatives (3), valproate sodium (2), ≤ 4 hr specialized education, recreational and occupational therapy</p>	<p>blood pressure, constipation, dermatologic AE, ECG changes, STESS, AIMS, SAS, lipid profile, seizure, sleepiness, somnolence, tachycardia, weight change, BMI change</p>	
<p>Shea et al., 2004⁷⁹</p> <p>Country: Canada</p>	<p>Recruitment dates: NR</p>	<p>Enrolled: 80</p> <p>Analyzed: 79</p> <p>Completed: 72</p>	<p>Treatment duration: 8 wk</p> <p>Run-in phase: No</p> <p>Run-in phase duration: NR</p>	<p>Benefits: ABC, NCBRF, VAS-MS Response (ABC-I, CGI-C)</p>	<p>In children with ASD, risperidone was well tolerated and efficacious in</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
<p>Condition category: ASD</p> <p>Funding: Industry</p> <p>Risk of bias: Medium (subjective), Medium (objective)</p>	<p>Study design: RCT (parallel)</p> <p>Setting: Outpatient/community</p> <p>Diagnostic criteria: DSM-IV</p> <p>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</p> <p>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</p>	<p>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)</p> <p>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)</p>	<p>Permitted drugs: anticholinergics, anticonvulsants and/or medications for sleep or anxiety (constant dose ≥30 days before enrolment), medications for preexisting organic disorders</p> <p>Prohibited drugs: α-2 antagonists, antidepressants, antipsychotics, cholinesterase inhibitors, clonidine, guanfacine, lithium, naltrexone, psychostimulants</p> <p>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)</p> <p>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)</p>	<p>Harms: Anorexia, behavioral issues, blood pressure, constipation, EPS (ESRS), fatigue, hyperkinesias, pulse, SAE, somnolence, tachycardia, tardive dyskinesia, total AE, WAE, weight change</p>	<p>the treatment of autism associated behavioral symptoms.</p>

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	<p>Recruitment dates: Feb 2002 to May 2006</p> <p>Country: USA</p> <p>Condition category: Schizophrenia and related</p> <p>Funding: Government</p> <p>Risk of bias: Low (subjective), Low (objective)</p>	<p>Enrolled: 116 Analyzed: NR Completed: 70</p> <p>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)</p> <p>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</p>	<p>Treatment duration: 8 wk (10.1 mo extension) Run-in phase: Yes Run-in phase duration: 2 wk</p> <p>Permitted drugs: antidepressants or non-antipsychotic mood stabilizers (≥4 wk prior to study entry); anticholinergics, benzodiazepines, propranolol (concomitant); thymoleptics (maintenance phase)</p> <p>Prohibited drugs: NR</p> <p>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%)</p> <p>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%),</p>	<p>Benefits: BPRS-C, CGI-I, CGI-S, CAFAS, PANSS, medication adherence, response, suicide</p> <p>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</p>	Risperidone 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
	<p>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</p>	<p>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)</p> <p>GROUP 3 N: 42 Age, mean\pmSD (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)</p>	<p>benztropine (14%), mood stabilizers (2), propranolol (11%)</p> <p>GROUP 3 Drug name: Risperidone Dosing variability: variable Target dose (mg/day): 6 Daily dose (mg/day), mean\pmSD (range): 2.8\pm1.4 (0.5–6) Concurrent treatments: antidepressants (5), benzodiazepines (41%), benztropine (34%), mood stabilizers (4), propranolol (7%)</p>		
Sikich et al., 2004 ⁸⁰	<p>Recruitment dates: Nov 1997 to May 2001</p> <p>Country: USA</p> <p>Condition category:</p>	<p>Enrolled: 50 Analyzed: 50 Completed: 32</p> <p>GROUP 1 N: 15 Age, mean\pmSD (range): 15.4\pm2.2</p>	<p>Treatment duration: 8 wk Run-in phase: Yes Run-in phase duration: 1–2 wk</p> <p>Permitted drugs: amantadine (200 mg/day), antidepressants and mood stabilizers (if taken ≥ 4 wk preceding study entry or if clinically</p>	<p>Benefits: BPRS-C, CPRS, CGI-I, CGI-S, response, medication adherence</p> <p>Harms: Withdrawal due to AEs, akathisia, BMI, constipation,</p>	<p>Risperidone and olanzapine were effective in acutely reducing symptoms in psychotic youth.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
Schizophrenia and related	<p>Diagnostic criteria: DSM-IV, K-SADS-P</p> <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</p> <p>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</p>	<p>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</p> <p>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</p> <p>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</p>	<p>significant affective symptoms persisted after 4 wk of study treatment), benzotropine (1–3 mg/day), lorazepam (0.5–3 mg/day), propranolol (20–60 mg/day), trihexyphenidyl (4–6 mg/day)</p> <p>Prohibited drugs: NR</p> <p>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), benzotropine/trihexyphenidyl (7), bupropion (4), citalopram (1), gabapentin (1), lithium (1), lorazepam (3), paroxetine (1), sertraline (3), valproate (2), venlafaxine (1), inpatient or residential treatment (9)</p> <p>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: benzotropine/trihexyphenidyl (5), bupropion (2), carbamazepine (1), fluoxetine (2), fluvoxamine (1), lithium (1), lorazepam (1), paroxetine (1), propranolol (2), sertraline (1), valproate (1), inpatient or residential treatment (10)</p>	<p>dermatologic AE, dystonia, ECG changes, EPS, SAS, AIMS, tardive dyskinesias, glucose, lipid profile, prolactin, prolactin-related AE, sedation, WAE, weight changes, white blood cells</p>	

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	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 (benztropine, biperiden), lorazepam (rescue) Prohibited drugs: alcohol, antipsychotics, antidepressants, drugs of abuse, lithium, psychostimulants, anticonvulsants, sedatives, cholinesterase inhibitors 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
	<p>based on medical history, physical examination, ECG, and laboratory test results</p> <p>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</p>	<p>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</p> <p>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</p>	<p>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)</p> <p>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)</p> <p>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)</p>		
Snyder et al., 2002 ⁸³	<p>Recruitment dates: NR</p> <p>Study design: RCT (parallel)</p>	<p>Enrolled: 110 Analyzed: 110 Completed: 85</p> <p>GROUP 1 N: 53</p>	<p>Treatment duration: 6 wk Run-in phase: Yes Run-in phase duration: 1 wk</p> <p>Permitted drugs: stable doses (≥30 days prior to study) of anticholinergics, antihistamines,</p>	<p>Benefits: ABC, BPI, CGI-I, CGI-S, NCBRF, VAS Medication adherence</p>	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
<p>Condition category: ADHD</p> <p>Funding: Foundation</p> <p>Risk of bias: High (subjective), High (objective)</p>	<p>Setting: Inpatient and outpatient</p> <p>Diagnostic criteria: DSM-IV, VABS</p> <p>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</p> <p>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)</p>	<p>Age, mean\pmSD (range): 8.6\pm0.3 (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)</p> <p>GROUP 2 N: 57 Age, mean\pmSD (range): 8.8\pm0.3 (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)</p>	<p>chloral hydrate, medication for preexisting medical conditions, melatonin, psychostimulants (comorbid ADHD)</p> <p>Prohibited drugs: no other medication permitted</p> <p>GROUP 1 Drug name: Risperidone Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): 1\pm0.1 SE (0.4–3.8) Concurrent treatments: NR</p> <p>GROUP 2 Drug name: Placebo Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean\pmSD (range): NR Concurrent treatments: NR</p>	<p>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</p>	

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	Recruitment dates: Sep 1989 to May 1991	Enrolled: 16 Analyzed: 16 Completed: 16	Treatment duration: 8 wk Run-in phase: Yes Run-in phase duration: 2 wk	Benefits: BPRS-C, CGI-I, CGI-S, CPRS Harms: Drowsiness, dystonia	Haloperidol improved the target psychotic symptoms in children with schizophrenia.
Country: USA	Study design: RCT (crossover)	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	Permitted drugs: NR Prohibited drugs: NR		
Condition category: Schizophrenia and related	Setting: Inpatient		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		
Funding: Industry, Government	Diagnostic criteria: DSM-III-TR, DICA-R		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		
Risk of bias: Medium (subjective), Medium (objective)	Inclusion criteria: (1) actively psychotic prepubertal patients, (2) 5–11 yr, (3) admitted to the Bellevue Hospital Children's Inpatient Psychiatric Unit, (4) schizophrenia	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			
	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				
Stocks et al., 2012 ⁸⁵	Recruitment dates: October 2008 – September 2009	Enrolled: 78 Analyzed: 78 Completed: 55	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
Country: USA		GROUP 1			

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
<p>Condition category: ADHD</p> <p>Funding: Industry</p> <p>Risk of bias: High (subjective), High (objective)</p>	<p>Study design: RCT (parallel)</p> <p>Setting: outpatient</p> <p>Diagnostic criteria: K-SADS-PL, DSM-IV-TR</p> <p>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</p> <p>Exclusion criteria: Current or lifetime diagnosis of BP, PTSD, personality disorder, psychotic disorder, currently meeting diagnostic criteria for major depressive disorder,</p>	<p>N: 20</p> <p>Age, mean\pmSD (range): 8.5\pm1.88 yr</p> <p>Males %: 95%</p> <p>Caucasian %: 55%</p> <p>Diagnostic breakdown (n): ADHD (20)</p> <p>Treatment naïve (n): NR</p> <p>Inpatients (n): 0</p> <p>First episode psychosis (n): 0</p> <p>Comorbidities (n): Asthma (5), CD (2), Enuresis (4), Insomnia (1), ODD (6), Seasonal allergies (2)</p> <p>GROUP 2</p> <p>N: 19</p> <p>Age, mean\pmSD (range): 9.4\pm1.98 yr</p> <p>Males %: 84.2%</p> <p>Caucasian %: 57.9%</p> <p>Diagnostic breakdown (n): ADHD (19)</p> <p>Treatment naïve (n): NR</p> <p>Inpatients (n): 0</p> <p>First episode psychosis (n): 0</p> <p>Comorbidities (n): Asthma (3), CD (2), Eczema (3), Enuresis (3), Environmental allergies (1), Insomnia (2), ODD (7), Seasonal allergies (1)</p> <p>GROUP 3</p> <p>N: 19</p> <p>Age, mean\pmSD (range): 8.8\pm2.12 yr</p>	<p>Permitted drugs: methylphenidate, amphetamine, benzotropine</p> <p>Prohibited drugs: other antipsychotics, antidepressants, hypnotics, anticonvulsants, antihypertensives, antihistamines</p> <p>GROUP 1</p> <p>Drug name: Molindone hydrochloride</p> <p>Dosing variability: Fixed</p> <p>Target dose (mg/day): <30 kg: 5 mg/day; ≥ 30 kg: 10 mg/day</p> <p>Daily dose (mg/day), mean\pmSD (range): <30 kg: 5 mg/day; ≥ 30 kg: 10 mg/day</p> <p>Concurrent treatments: Stable dose of FDA approved psychostimulant (methylphenidate or amphetamine)</p> <p>GROUP 2</p> <p>Drug name: Molindone hydrochloride</p> <p>Dosing variability: Fixed</p> <p>Target dose (mg/day): <30 kg: 10 mg/day; ≥ 30 kg: 20 mg/day</p> <p>Daily dose (mg/day), mean\pmSD (range): <30 kg: 10 mg/day; ≥ 30 kg: 20 mg/day</p> <p>Concurrent treatments: Stable dose of FDA approved psychostimulant (methylphenidate or amphetamine)</p> <p>GROUP 3</p> <p>Drug name: Molindone hydrochloride</p> <p>Dosing variability: Fixed</p>	<p>Harms: Somnolence, metabolic effects, neuromotor effects, infection, prolactin related events</p>	<p>efficacy results suggest that molindone produces dose-related behavioral improvements over 9-12 weeks.</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	OCD, PDD or other AD as primary disorder	<p>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)</p> <p>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)</p>	<p>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)</p> <p>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)</p>		
Swadi et al., 2010 ⁸⁶	<p>Recruitment dates: NR</p> <p>Country: New Zealand</p> <p>Condition category:</p>	<p>Enrolled: 22 Analyzed: 22 Completed: 22</p> <p>GROUP 1 N: 11 Age, mean±SD (range): NR</p>	<p>Treatment duration: 6 wk Run-in phase: No Run-in phase duration: NR</p> <p>Permitted drugs: NR</p> <p>Prohibited drugs: NR</p>	<p>Benefits: BPRS, PANSS, response (BPRS, CGI-S, HAM-D, PANSS, YMRS)</p> <p>Harms: Blood pressure, SAS, BAS, AIMS, glucose, lipid</p>	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	Diagnostic criteria: DSM-IV	Males %: 54.5 Caucasian %: NR Treatment naïve (n): 11 Inpatients (n): all First episode psychosis (n): 11 Comorbidities: 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	profile, liver function, prolactin, sedation, weight change	
Funding: Industry	Inclusion criteria: (1) <19 yr, (2) first onset psychotic disorder or a mood disorder with psychotic features	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 Comorbidities: SUD (0)	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		
Risk of bias: High (subjective), High (objective)	Exclusion criteria: (1) alcohol or substance dependence not in full remission, (2) prior treatment with atypical antipsychotic drugs				
Tohen et al., 2007 ⁸⁷	Recruitment dates: Nov 2002 to May 2005	Enrolled: 161 Analyzed: 161 Completed: 120	Treatment duration: 3 wk Run-in phase: Yes Run-in phase duration: 2–14 day	Benefits: CDRS, CGI-BP (overall, mania, depression subscales), ADHS IV, OAS, YMRS (total+item analysis), HRQoL(subscales); Olsen 2012, response, suicide	Olanzapine was more effective in treating adolescents with bipolar mania and placebo; however, it resulted in significantly greater weight gain.
Country: Puerto Rico, USA	Study design: RCT (parallel)	GROUP 1 N: 107 Age, mean±SD (range): 15.1±1.3 Males %: 57	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)		
Condition category: Bipolar disorder	Setting: Inpatient and outpatient	Caucasian %: 66.4 Diagnostic breakdown (n): mixed (61), psychotic features (22), rapid cycling (25)	Prohibited drugs: anticholinergics	Harms: Bipolar exacerbation, blood cells, blood pressure, BMI, ECG changes, EPS (AIMS, BAS, SAS), glucose, hepatic enzyme, lipid profile, mortality, prolactin, prolactin-	
Funding: Industry	Diagnostic criteria: DSM-IV-TR, K-SADS-PL	Diagnostic breakdown (n): mixed (61), psychotic features (22), rapid cycling (25) Treatment naïve (n): NR Inpatients (n): NR First episode psychosis (n): NR Comorbidities: ADHD (45), DBD (37)	GROUP 1 Drug name: Olanzapine Dosing variability: variable Target dose (mg/day): NR		
Risk of bias: Medium (subjective), Medium (objective)	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				

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	<p>the Adolescent Structured YMRS</p> <p>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</p>	<p>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)</p>	<p>Daily dose (mg/day), mean±SD (range): 8.9 (2.5–20) Concurrent treatments: anticholinergics (4.7%), benzodiazepines (12.1%)</p> <p>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%)</p>	<p>related AE, pulse, SAE, weight change</p>	
<p>Tramontina et al., 2009⁸⁸</p> <p>Country: Brazil</p> <p>Condition category: Bipolar disorder</p> <p>Funding: Industry, Government, Hospital</p> <p>Risk of bias: Low (subjective), Low (objective)</p>	<p>Recruitment dates: Jan 2005 to Nov 2007</p> <p>Study design: RCT (parallel)</p> <p>Setting: Outpatient/community</p> <p>Diagnostic criteria: DSM-IV, K-SADS-E</p> <p>Inclusion criteria: (1) 8–17 yr, (2) DSM IV bipolar I or II disorder comorbid with ADHD, (3) clear reports of</p>	<p>Enrolled: 43 Analyzed: 43 Completed: 41</p> <p>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</p>	<p>Treatment duration: 6 wk Run-in phase: No Run-in phase duration: NR</p> <p>Permitted drugs: NR</p> <p>Prohibited drugs: NR</p> <p>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</p> <p>GROUP 2</p>	<p>Benefits: CDRS, CGI-S, CMRS-P, YMRS, medication adherence, response, suicide</p> <p>Harms: Akathisia, behavioral issues, dermatologic AE, dyskinesia, EPS, fatigue, seizure, somnolence, weight change</p>	<p>Aripiprazole was effective in decreasing mania symptoms and improving global functioning without resulting in severe adverse events or weight gain.</p>

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\pmSD (range): 12.2 \pm 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\pmSD (range): 15 \pm 3.2 (10–20) Concurrent treatments: none		
Troost et al., 2005 ⁸⁹	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\pmSD (range): 9.4 \pm 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\pmSD (range): 1.9 \pm 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
	<p>or a combination of these, (3) 5–17 yr, (4) weight ≥15 kg, (5) mental age ≥18 mo</p> <p>Exclusion criteria: (1) children on effective psychotropic drug treatment for disruptive behavior</p>	<p>Comorbidities: MR (2)</p> <p>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)</p>	<p>Concurrent treatments: stimulants (1), stimulant and anticonvulsant (1)</p> <p>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)</p>		
Van Bellinghen et al., 2001 ⁹⁰	<p>Recruitment dates: NR</p> <p>Country: Belgium</p> <p>Condition category: Behavioral issues</p> <p>Funding: Industry</p> <p>Risk of bias: Medium (subjective), Medium (objective)</p>	<p>Enrolled: 13 Analyzed: 13 Completed: 13</p> <p>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)</p> <p>GROUP 2 N: 7 Age, mean±SD (range): NR (7–14) Males %: 42.9 Caucasian %: NR</p>	<p>Treatment duration: 4 wk Run-in phase: No Run-in phase duration: NR</p> <p>Permitted drugs: antiepileptics</p> <p>Prohibited drugs: NR</p> <p>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)</p> <p>GROUP 2 Drug name: Placebo Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean±SD (range): NR Concurrent treatments: NR</p>	<p>Benefits: ABC, CGI-I, PAC, VAS</p> <p>Harms: Parkinsonism, pulse, somnolence, total AE, weight change, EP disorder (ESRS)</p>	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	Recruitment dates: NR	Enrolled: 44 Analyzed: 42 Completed: NR	Treatment duration: Olanzapine 9.8 wk, Risperidone 6.7 wk Run-in phase: No Run-in phase duration: NA	Benefits: PANSS, medication adherence, response	Symptom response was similar in the olanzapine and risperidone groups.
Country: Netherlands	Study design: RCT (parallel)	GROUP 1 N: 18	Permitted drugs: NR	Harms: BAS, SAS, AIMS, akathisia, parkinsonism, prolactin, prolactin-related AE, sedation, seizure, sexual dysfunction, somnolence, tachycardia, tardive dyskinesia, weight change	
Condition category: Schizophrenia and related	Setting: Inpatient	Age, mean±SD (range): 21.0±2.8	Prohibited drugs: antipsychotics		
Funding: Industry, Government	Diagnostic criteria: DSM-IV	Males %: 72 Caucasian %: NR	GROUP 1 Drug name: Olanzapine Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean±SD (range): 15.6±4 (5–30) Concurrent treatments: anticholinergics (2),		
	Inclusion criteria: (1) 16–28 yr, (2) first or second psychotic episode according to DSM-IV criteria of schizophrenia,	Treatment naïve (n): NR Inpatients (n): NR First episode psychosis (n): 16 GROUP 2 N: 26			

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
<p>Risk of bias: High (subjective), High (objective)</p>	<p>schizophreniform or schizoaffective disorder, (3) actively symptomatic at study entry (PANSS score of moderate or higher on items for delusions, conceptual disorganization, or hallucinations)</p> <p>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</p>	<p>Age, mean±SD (range): 20.6±3.0 Males %: 85 Caucasian %: NR Treatment naïve (n): NR Inpatients (n): NR First episode psychosis (n): 22</p>	<p>antidepressants (0), benzodiazepines (7), mood stabilizers (0)</p> <p>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)</p>		
<p>Weisler et al., 2011¹³²</p> <p>Country: USA</p>	<p>Recruitment Dates: NR</p> <p>Study design: Observational (pooled analysis of 2 trials)</p>	<p>Enrolled: 35 Analyzed: 35 Completed: 35</p> <p>GROUP 1: N: 16 Age, mean±SD (range):</p>	<p>Treatment duration: 6 wk Run-in phase: No Run-in phase duration: NA</p> <p>Permitted drugs: Escitalopram, fluoxetine, paroxetine CR, sertraline, venlafaxine XR</p>	<p>Benefits: suicide-related events and ideation</p> <p>Harms: NR</p>	<p>Adjunctive aripiprazole treatment represents a generally safe and relatively well-tolerated and efficacious treatment</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
<p>Condition category: Depression</p> <p>Funding: Industry</p> <p>Newcastle-Ottawa Scale: 6/8 stars</p>	<p>Diagnostic criteria: DSM-IV-TR</p> <p>Setting: outpatients</p> <p>Inclusion criteria: Outpatients 18-65 yr (only looking at subgroup ≤ 25 yr here), major depressive episode ≥ 8 wk, inadequate response to ≥ 1 historical antidepressant</p> <p>Exclusion criteria: Significant risk of committing suicide during course of trial</p>	<p>≤ 25 yr</p> <p>Males %: NR</p> <p>Caucasian %: NR</p> <p>Diagnostic breakdown (n): NR</p> <p>Treatment naïve (n): 0</p> <p>Inpatients (n): 0</p> <p>First episode psychosis (n): NR</p> <p>Comorbidities (n): NR</p> <p>GROUP 2:</p> <p>N: 19</p> <p>Age, mean\pmSD (range): ≤ 25 yr</p> <p>Males %: NR</p> <p>Caucasian %: NR</p> <p>Diagnostic breakdown (n): NR</p> <p>Treatment naïve (n): 0</p> <p>Inpatients (n): 0</p> <p>First episode psychosis (n): NR</p> <p>Comorbidities (n): NR</p>	<p>Prohibited drugs: NR</p> <p>GROUP 1</p> <p>Drug name: Aripiprazole</p> <p>Dosing variability: Variable</p> <p>Target dose (mg/day): 15 mg/day (paroxetine or fluoxetine) or 20 mg/day (all other patients)</p> <p>Daily dose (mg/day), mean\pmSD (range): NR</p> <p>Concurrent treatments: Escitalopram, fluoxetine, paroxetine CR, sertraline, venlafaxine XR</p> <p>GROUP 2:</p> <p>Drug name: Placebo</p> <p>Dosing variability: Variable</p> <p>Target dose (mg/day): NA</p> <p>Daily dose (mg/day), mean\pmSD (range): NA</p> <p>Concurrent treatments: Escitalopram, fluoxetine, paroxetine CR, sertraline, venlafaxine XR</p>	<p>Benefits: CGI-I</p> <p>Harms: Weight change (BMI, BMI-z)</p>	<p>option for patients with MDD who had an inadequate response to standard antidepressant medication.</p>
<p>Wink et al., 2014 133</p> <p>Country: USA</p> <p>Condition category: ASD</p> <p>Funding: Industry/ non-industry</p> <p>Newcastle-Ottawa Scale: 7/8 stars</p>	<p>Recruitment dates: July 2004 to Apr 2012</p> <p>Study design: Retrospective</p> <p>Setting: NR</p> <p>Diagnostic criteria: DSM-IV-TR</p> <p>Inclusion criteria: (1) 2-20 yr, (2) meets DSM-IV-TR criteria for ASD diagnosis, (3)</p>	<p>Enrolled: 142</p> <p>Analyzed: 142</p> <p>Completed: NR</p> <p>GROUP 1</p> <p>N: 72</p> <p>Age, mean\pmSD (range): 8.41\pm3.59yr</p> <p>Males %: 83.3</p> <p>Caucasian %: 77.8</p> <p>Diagnostic breakdown (n): Autistic disorder (40), PDD-NOS (29), Asperger's disorder (3)</p> <p>Treatment naïve (n): NR</p>	<p>Treatment duration: Risperidone (2.37\pm2.55 yr), Aripiprazole (1.47\pm1.21 yr)</p> <p>Run-in phase: NR</p> <p>Run-in phase duration: NR</p> <p>Permitted drugs: NR</p> <p>Prohibited drugs: NR</p> <p>GROUP 1</p> <p>Drug name: Risperidone</p> <p>Dosing variability: variable</p> <p>Target dose (mg/day): NR</p>	<p>Benefits: CGI-I</p> <p>Harms: Weight change (BMI, BMI-z)</p>	<p>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</p>

Study	Study Characteristics	Participant Characteristics	Treatment Characteristics	Outcomes Reported	Author Conclusions
	<p>subjects treated at the Christian Sarkine Autism Treatment Center (CSATC)</p> <p>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</p>	<p>Inpatients (n): NR First episode psychosis (n): NR Comorbidities: intellectual disability (34)</p> <p>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)</p>	<p>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)</p> <p>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)</p>		the results of such a study.
<p>Wonodi et al., 2007¹³⁴</p> <p>Country: USA</p> <p>Condition category: Mixed conditions</p> <p>Funding: Non-industry</p> <p>Newcastle-Ottawa Scale: 8/8 stars</p>	<p>Recruitment dates: NR</p> <p>Study design: Retrospective</p> <p>Setting: Inpatient/outpatient</p> <p>Diagnostic criteria: NR</p> <p>Inclusion criteria: All children (5-18 yr) already receiving or likely to be prescribed antipsychotic</p>	<p>Enrolled: 424 Analyzed: 198 Completed: 198</p> <p>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</p>	<p>Treatment duration: ≥6mo Run-in phase: NR Run-in phase duration: NR</p> <p>Permitted drugs: NR</p> <p>Prohibited drugs: NR</p> <p>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)</p>	<p>Benefits: NR</p> <p>Harms: Tardive dyskinesia</p>	<p>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</p>

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	Recruitment dates: Jan 1998 to July 2001 Country: Canada, USA Condition category: Schizophrenia and related Funding: Industry, Government Risk of bias: High (subjective), High (objective)	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, benzotropine 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), propranolol 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
	<p>communicate with investigator, (5) informed consent/assent</p> <p>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) pregnant or lactating, (8) took nonprotocol psychotropic medications</p>	Comorbidities: SA (9)	<p>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)</p>		
<p>Wudarsky et al., 1999¹³⁵</p> <p>Country: USA</p> <p>Condition category: Schizophrenia and related</p> <p>Funding: NR</p> <p>Newcastle-Ottawa Scale: 7/8 stars</p>	<p>Recruitment dates: NR</p> <p>Study design: Prospective cohort</p> <p>Setting: Outpatient/community</p> <p>Diagnostic criteria: DSM-IV, DSM-III-TR, structured interviews</p> <p>Inclusion criteria: (1) DSM dx of schizophrenia, (2) resistant to treatment with two different FGAs</p>	<p>Enrolled: 47 Analyzed: 47 Completed: NR</p> <p>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</p> <p>GROUP 2 N: 22</p>	<p>Treatment duration: 6 wk Run-in phase: Yes Run-in phase duration: 3 wk</p> <p>Permitted drugs: NR</p> <p>Prohibited drugs: NR</p> <p>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</p> <p>GROUP 2 Drug name: Clozapine</p>	<p>Benefits: NR</p> <p>Harms: Prolactin</p>	<p>Mean prolactin levels were significantly elevated after 6 weeks of treatment with haloperidol, clozapine, and olanzapine in patients with childhood-onset schizophrenia.</p>

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	Dosing variability: variable Target dose (mg/day): NR Daily dose (mg/day), mean±SD (range): 325.4±211 Concurrent treatments: NR		
		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	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	Recruitment dates: NR Country: Taiwan Condition category: Schizophrenia and related Funding: Hospital Risk of bias: High (subjective), High (objective)	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	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	Benefits: PANSS Harms: NR	Risperidone was superior to haloperidol in improving negative symptoms and better tolerated during the treatment of schizophrenia.
	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	GROUP 2 N: 6 (≤24 yr) Age, mean±SD (range): 20.7 (20–22) Males %: 66.7 Caucasian %: NR Treatment naïve (n): 0	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		

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	Recruitment Dates: August 2008 – April 2010 Country: South Korea Condition category: Tic disorders Funding: Industry Risk of Bias: High (subjective), High (objective)	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
	<p>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.</p>				
Yoo et al., 2011 ⁹⁴	<p>Recruitment Dates: August 2005 – March 2007</p> <p>Country: South Korea</p> <p>Condition category: Tic disorders</p> <p>Funding: NR</p> <p>Study design: NRCT (parallel)</p> <p>Diagnostic criteria: DSM-IV, Total tic scores ≥ 22 on Korean version of YGTSS</p>	<p>Enrolled: 48 Analyzed: 48 Completed: 37</p> <p>GROUP 1: N: 31 Age, mean\pmSD (range): 11.2\pm3.5 (6-18) yr Males %: 71% Caucasian %: NR</p>	<p>Treatment duration: 8 wk Run-in phase: Yes Run-in phase duration: Drug free for 2 wk before study entry</p> <p>Permitted drugs: NR</p> <p>Prohibited drugs: NR</p> <p>GROUP 1 Drug name: Aripiprazole</p>	<p>Benefits: YGTSS, CGI-I, CGI-S</p> <p>Harms: ESRS, AE checklist</p>	<p>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</p>

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\pmSD (range): 8.6 \pm 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\pmSD (range): 10.6 \pm 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\pmSD (range): 1.9 \pm 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 Impressions-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)

References

1. Aman MG, Marks RE, Turbott SH, et al. Clinical effects of methylphenidate and thioridazine in intellectually subaverage children. *J Am Acad Child Adolesc Psychiatry*. 1991;30(2):246-56. PMID: 2016229.
2. Aman MG, De SG, 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. PMID: 12153826.
3. Aman MG, Hollway JA, Leone S, et al. Effects of risperidone on cognitive-motor performance and motor movements in chronically medicated children. *Res Dev Disabil*. 2009;30(2):386-96. PMID: 18768293.
4. 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? *J Am Acad Child Adolesc Psychiatry*. 2014;53(1):47-60.e1. PMID: 24342385.
5. Anderson LT, Campbell M, Adams P, et al. The effects of haloperidol on discrimination learning and behavioral symptoms in autistic children. *J Autism Dev Disord*. 1989;19(2):227-39. PMID: 2663834.
6. 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. PMID: 19198920.
7. Armenteros JL, Lewis JE, Davalos M. Risperidone augmentation for treatment-resistant aggression in attention-deficit/hyperactivity disorder: a placebo-controlled pilot study. *J Am Acad Child Adolesc Psychiatry*. 2007(5):558-65. PMID: 17450046.
8. Berger GE, Proffitt TM, McConchie M, et al. Dosing quetiapine in drug-naive first-episode psychosis: a controlled, double-blind, randomized, single-center study investigating efficacy, tolerability, and safety of 200 mg/day vs. 400 mg/day of quetiapine fumarate in 141 patients aged 15 to 25 years. *J Clin Psychiatry*. 2008;69(11):1702-14. PMID: 19036233.
9. Biederman J, Mick E, Hammerness P, et al. Open-label, 8-week trial of olanzapine and risperidone for the treatment of bipolar disorder in preschool-age children. *Biol Psychiatry*. 2005;58(7):589-94. PMID: 16239162.
10. Bruggeman R, Van Der LC, Buitelaar JK, et al. Risperidone versus pimozide in tourette's disorder: a comparative double-blind parallel-group study. *J Clin Psychiatry*. 2001;62(1):50-6. PMID: 11235929.
11. Buchsbaum MS, Haznedar MM, Aronowitz J, et al. FDG-PET in never-previously medicated psychotic adolescents treated with olanzapine or haloperidol. *Schizophr Res*. 2007;94(1-3):293-305. PMID: 17574821.
12. 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. PMID: 11379837.
13. Connor DF, McLaughlin TJ, Jeffers-Terry M. Randomized controlled pilot study of quetiapine in the treatment of adolescent conduct disorder. *J Child Adolesc Psychopharmacol*. 2008;18(2):140-56. PMID: 18439112.
14. Conus P, Berk M, Cotton SM, et al. Olanzapine or chlorpromazine plus lithium in first episode psychotic mania: An 8-week randomised controlled trial. *Eur Psychiatry*. 2015;30(8):975-82. PMID: 26485297.
15. Crocq MA, Guillon MS, Bailey PE, et al. Orally disintegrating olanzapine induces less weight gain in adolescents than standard oral tablets. *Eur Psychiatry*. 2007;22(7):453-4. PMID: 17761403.
16. de Haan L, Van Bruggen M, Lavalaye J, et al. Subjective experience and d2 receptor occupancy in patients with recent-onset schizophrenia treated with low-dose olanzapine or haloperidol: a randomized, double-blind study. *Am J Psychiatry*. 2003;160(2):303-9. PMID: 12562577.

17. Delbello MP, Schwiers ML, Rosenberg HL, et al. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. *J Am Acad Child Adolesc Psychiatry*. 2002;41(10):1216-23. PMID: 12364843.
18. Delbello MP, Versavel M, Ice K, et al. Tolerability of oral ziprasidone in children and adolescents with bipolar mania, schizophrenia, or schizoaffective disorder. *J Child Adolesc Psychopharmacol*. 2008;18(5):491-9. PMID: 18928413.
19. Delbello MP, Chang K, Welge JA, et al. A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. *Bipolar Disord*. 2009;11(5):483-93. PMID: 19624387.
20. 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. PMID: 10761354.
21. 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*. 2008a;165(11):1432-41. PMID: 18765484.
22. 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. *J Clin Psychiatry*. 2009;70(10):1441-51. PMID: 19906348.
23. Findling RL, Mckenna K, Earley WR, et al. Efficacy and safety of quetiapine in adolescents with schizophrenia investigated in a 6-week, double-blind, placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2012a Oct;22(5):327-42. PMID: 23083020.
24. Findling RL, Youngstrom EA, Mcnamara NK, et al. Double-blind, randomized, placebo-controlled long-term maintenance study of aripiprazole in children with bipolar disorder. *J Clin Psychiatry*. 2012b;73(1):57-63. PMID: 22152402.
25. Findling RL, Cavus I, Pappadopulos E, et al. Ziprasidone in adolescents with schizophrenia: Results from a placebo-controlled efficacy and long-term open-extension study. *J Child Adolesc Psychopharmacol*. 2013a;23(8):531-44. PMID: 24111983.
26. Findling RL, Cavus I, Pappadopulos E, et al. Efficacy, long-term safety, and tolerability of ziprasidone in children and adolescents with bipolar disorder. *J Child Adolesc Psychopharmacol*. 2013b;23(8):545-57. PMID: 24111980.
27. Findling RL, Pathak S, Earley WR, et al. Efficacy and safety of extended-release quetiapine fumarate in youth with bipolar depression: an 8 week, double-blind, placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2014b;24(6):325-35. PMID: 24956042.
28. Findling RL, Mankoski R, Timko K, et al. A randomized controlled trial investigating the safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric patients with irritability associated with autistic disorder. *J Clin Psychiatry*. 2014b;75(1):22-30. PMID: 24502859.
29. Findling RL, Landbloom RP, Mackle M, et al. Safety and efficacy from an 8 week double-blind trial and a 26 week open-label extension of asenapine in adolescents with schizophrenia. *J Child Adolesc Psychopharmacol*. 2015a;25(5):384-96. PMID: 26091193.
30. Findling RL, Landbloom RL, Szegedi A, et al. Asenapine for the acute treatment of pediatric manic or mixed episode of bipolar I disorder. *J Am Acad Child Adolesc Psychiatry*. 2015b;54(12):1032-41. PMID: 26598478.
31. Findling RL, Goldman R, Chiu YY, et al. Pharmacokinetics and tolerability of lurasidone in children and adolescents with psychiatric disorders. *Clin Ther*. 2015;37(12):2788-97. PMID: 26631428.
32. Ghanizadeh A, Sahraeizadeh A, Berk M. A head-to-head comparison of aripiprazole and risperidone for safety and treating autistic disorders, a randomized double blind clinical trial. *Child Psychiatry Hum Dev*. 2014a;45(2):185-92. PMID: 23801256.

33. Ghanizadeh A, Haghghi A. Aripiprazole versus risperidone for treating children and adolescents with tic disorder: a randomized double blind clinical trial. *Child Psychiatry Hum Dev.* 2014b;45(5):596-603. PMID: 24343476.
34. Gilbert DL, Batterson JR, Sethuraman G, et al. Tic reduction with risperidone versus pimozide in a randomized, double-blind, crossover trial. *J Am Acad Child Adolesc Psychiatry.* 2004;43(2):206-14. PMID: 14726728.
35. Gulisano M, Cali PV, Cavanna AE, et al. Cardiovascular safety of aripiprazole and pimozide in young patients with tourette syndrome. *Neurol Sci.* 2011;32(6):1213-7. PMID: 21732066.
36. Haas M, Eerdekens M, Kushner S, et al. Efficacy, safety and tolerability of two dosing regimens in adolescent schizophrenia: double-blind study. *Br J Psychiatry.* 2009a;194(2):158-64. PMID: 19182179.
37. Haas M, Unis AS, Armenteros J, et al. A 6-week, randomized, double-blind, placebo-controlled study of the efficacy and safety of risperidone in adolescents with schizophrenia. *J Child Adolesc Psychopharmacol.* 2009b;19(6):611-21. PMID: 20035579.
38. 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.* 2009c;11(7):687-700. PMID: 19839994.
39. Hagman J, Gralla J, Sigel E, et al. A double-blind, placebo-controlled study of risperidone for the treatment of adolescents and young adults with anorexia nervosa: a pilot study. *J Am Acad Child Adolesc Psychiatry.* 2011;50(9):915-24. PMID: 21871373.
40. 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. PMID: 16596465.
41. Hollander E, Wasserman S, Swanson EN, et al. A double-blind placebo-controlled pilot study of olanzapine in childhood/adolescent pervasive developmental disorder. *J Child Adolesc Psychopharmacol.* 2006;16(5):541-8. PMID: 17069543.
42. Jensen JB, Kumra S, Leitten W, et al. A comparative pilot study of second-generation antipsychotics in children and adolescents with schizophrenia-spectrum disorders. *J Child Adolesc Psychopharmacol.* 2008;18(4):317-26. PMID: 18759641.
43. Johnson & Johnson Pharmaceutical Research & Development. Open-label study to evaluate the safety and pharmacokinetics of single- and multiple-dose extended-release paliperidone in pediatric subjects (10 to 17 years of age) with schizophrenia, schizoaffective disorder, or schizophreniform disorder. 2011. http://filehosting.pharmacm.com/DownloadService.ashx?client=CTR_JNJ_6051&studyid=473&filename=CR002371_CSR.pdf. Accessed September 28, 2015.
44. Kafantaris V, Leigh E, Hertz S, et al. A placebo-controlled pilot study of adjunctive olanzapine for adolescents with anorexia nervosa. *J Child Adolesc Psychopharmacol.* 2011;21(3):207-12. PMID: 21663423.
45. Kent JM, Kushner S, Ning X, et al. Risperidone dosing in children and adolescents with autistic disorder: a double-blind, placebo-controlled study. *J Autism Dev Disord.* 2013;43(8):1773-83. PMID: 23212807.
46. Kowatch RA, Scheffer RE, Monroe E, et al. Placebo-controlled trial of valproic acid versus risperidone in children 3-7 years of age with bipolar I disorder. *J Child Adolesc Psychopharmacol.* 2015;25(4):306-13. PMID: 25978742.
47. Kryzhanovskaya L, Schulz SC, Mcdougale C, et al. Olanzapine versus placebo in adolescents with schizophrenia: a 6-week, randomized, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry.* 2009;48(1):60-70. PMID: 19057413.

48. Kumra S, Frazier JA, Jacobsen LK, et al. Childhood-onset schizophrenia. A double-blind clozapine-haloperidol comparison. *Arch Gen Psychiatry*. 1996;53(12):1090-7. PMID: 8956674.
49. 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. PMID: 17651705.
50. Loebel A, Brams M, Goldman RS, et al. Lurasidone for the treatment of irritability associated with autistic disorder. *J Autism Dev Disord*. 2016;46(4):1153-63. PMID: 26659550.
51. Luby J, Mrakotsky C, Stalets MM, et al. Risperidone in preschool children with autistic spectrum disorders: an investigation of safety and efficacy. *J Child Adolesc Psychopharmacol*. 2006;16(5):575-87. PMID: 17069546.
52. Malone RP, Cater J, Sheikh RM, et al. Olanzapine versus haloperidol in children with autistic disorder: an open pilot study. *J Am Acad Child Adolesc Psychiatry*. 2001;40(8):887-94. PMID: 11501687.
53. 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 Acad Child Adolesc Psychiatry*. 2009;48(11):1110-9. PMID: 19797985.
54. Masi G, Pfanner C, Brovedani P. Antipsychotic augmentation of selective serotonin reuptake inhibitors in resistant tic-related obsessive-compulsive disorder in children and adolescents: a naturalistic comparative study. *J Psychiatr Res*. 2013;47(8):1007-12. PMID: 23664673.
55. Masi G, Milone A, Stawinoga A, et al. Efficacy and safety of risperidone and quetiapine in adolescents with bipolar II disorder comorbid with conduct disorder. *J Clin Psychopharmacol*. 2015;35(5):587-90. PMID: 26226481.
56. 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. PMID: 12151468.
57. 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. *J Clin Psychiatry*. 2013;74(4):349-56. PMID: 23218022.
58. 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. PMID: 18080171.
59. Mozes T, Ebert T, Michal SE, et al. An open-label randomized comparison of olanzapine versus risperidone in the treatment of childhood-onset schizophrenia. *J Child Adolesc Psychopharmacol*. 2006;16(4):393-403. PMID: 16958565.
60. Nagaraj R, Singhi P, Malhi P. Risperidone in children with autism: randomized, placebo-controlled, double-blind study. *J Child Neurol*. 2006;21(6):450-5. PMID: 16948927.
61. NCT00194012. Study of aripiprazole (abilify) versus placebo in children with subsyndromal bipolar disorder. In: *ClinicalTrials.gov*. Bethesda, MD: National Library of Medicine (US); 2013. [cited: 2016 Apr 13]. <https://clinicaltrials.gov/ct2/show/NCT00194012>. NLM Identifier: NCT00194012.
62. NCT01149655. Efficacy & safety study of oral aripiprazole in adolescents with schizophrenia. 2014. In: *ClinicalTrials.gov*. Bethesda, MD: National Library of Medicine (US); 2013. [cited: 2016 Apr 13]. <https://clinicaltrials.gov/ct2/show/NCT01149655>. NML Identifier: NCT01149655.
63. Omranifard V, Najafi M, Sharbafchi MR, et al. Risperidone as a treatment for childhood habitual behavior. *J Res Pharm Pract*. 2013;2(1):29-33. PMID: 24991601.
64. 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.

65. Pathak S., Findling RL, Earley WR, et al. Efficacy and safety of quetiapine in children and adolescents with mania associated with bipolar I disorder: a 3-week, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2013;74(1):e100-9. PMID: 23419231.
66. Perry R, Campbell M, Adams P, et al. Long-term efficacy of haloperidol in autistic children: continuous versus discontinuous drug administration. *J Am Acad Child Adolesc Psychiatry*. 1989;28(1):87-92. PMID: 2914841.
67. Remington G, Sloman L, Konstantareas M, et al. Clomipramine versus haloperidol in the treatment of autistic disorder: a double-blind, placebo-controlled, crossover study. *J Clin Psychopharmacol*. 2001;21(4):440-4. PMID: 11476129.
68. Reyes M, Buitelaar J, Toren P, et al. A randomized, double-blind, placebo-controlled study of risperidone maintenance treatment in children and adolescents with disruptive behavior disorders. *Am J Psychiatry*. 2006;163(3):402-10. PMID: 16513860.
69. Rizzo R, Eddy CM, Cali P, et al. Metabolic effects of aripiprazole and pimozide in children with tourette syndrome. *Pediatr Neurol*. 2012;47(6):419-22. PMID: 23127261.
70. Research Units on Pediatric Psychopharmacology Autism N. Risperidone treatment of autistic disorder: Longer-term benefits and blinded discontinuation after 6 months. *Am J Psychiatry*. 2005;162(7):1361-9. PMID: 15994720.
71. Sallee FR, Sethuraman G, Rock CM. Effects of pimozide on cognition in children with tourette syndrome: Interaction with comorbid attention deficit hyperactivity disorder. *Acta Psychiatr Scand*. 1994;90(1):4-9. PMID: 7976448.
72. Sallee FR, Nesbitt L, Jackson C, et al. Relative efficacy of haloperidol and pimozide in children and adolescents with tourette's disorder. *Am J Psychiatry*. 1997;154(8):1057-62. PMID: 9247389.
73. Sallee FR, Kurlan R, Goetz CG, et al. Ziprasidone treatment of children and adolescents with tourette's syndrome: a pilot study. *J Am Acad Child Adolesc Psychiatry*. 2000;39(3):292-9. PMID: 10714048.
74. Savitz AJ, Lane R, Nuamah I, et al. Efficacy and safety of paliperidone extended release in adolescents with schizophrenia: a randomized, double-blind study. *J Am Acad Child Adolesc Psychiatry*. 2015;54(2):126-37.e1. PMID: 25617253.
75. Scahill L, Leckman JF, Schultz RT, et al. A placebo-controlled trial of risperidone in tourette syndrome. *Neurology*. 2003;60(7):1130-5. PMID: 12682319.
76. Schneider MR, Adler CM, Whitsel R, et al. The effects of ziprasidone on prefrontal and amygdalar activation in manic youth with bipolar disorder. *Isr J Psychiatry Relat Sci*. 2012;49(2):112-20. PMID: 22801290.
77. Sehgal N. Short-term versus longer term pimozide therapy in tourette's syndrome: a preliminary study. *Neurology*. 1999;52(4):874-7. PMID: 10078748.
78. Shaw P, Sporn A, Gogtay N, et al. Childhood-onset schizophrenia: a double-blind, randomized clozapine-olanzapine comparison. *Arch Gen Psychiatry*. 2006;63(7):721-30. PMID: 16818861.
79. Shea S, Turgay A, Carroll A, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics*. 2004;114(5):e634-e41. PMID: 15492353.
80. Sikich L, Hamer RM, Bashford RA, et al. A pilot study of risperidone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial. *Neuropsychopharmacology*. 2004;29(1):133-45. PMID: 14583740.
81. Sikich L, Frazier JA, McClellan J, et al. Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (teoss) study. *Am J Psychiatry*. 2008;165(11):1420-31. PMID: 18794207.

82. Singh J, Robb A, Vijapurkar U, et al. A randomized, double-blind study of paliperidone extended-release in treatment of acute schizophrenia in adolescents. *Biol Psychiatry*. 2011 Dec 15;70(12):1179-87. PMID: 21831359.
83. Snyder R, Turgay A, Aman M, et al. Effects of risperidone on conduct and disruptive behavior disorders in children with subaverage iqs. *J Am Acad Child Adolesc Psychiatry*. 2002;41(9):1026-36. PMID: 12218423.
84. Spencer EK, Campbell M. Children with schizophrenia: Diagnosis, phenomenology, and pharmacotherapy. *Schizophr Bull*. 1994;20(4):713-25. PMID: 7701278.
85. Stocks JD, Taneja BK, Baroldi P, et al. A phase 2a randomized, parallel group, dose-ranging study of molindone in children with attention-deficit/hyperactivity disorder and persistent, serious conduct problems. *J Child Adolesc Psychopharmacol*. 2012;22(2):102-11. PMID: 22372512.
86. Swadi HS, Craig BJ, Pirwani NZ, et al. A trial of quetiapine compared with risperidone in the treatment of first onset psychosis among 15-to 18-year-old adolescents. *Int Clin Psychopharmacol*. 2010;25(1):1-6. PMID: 19809337.
87. Tohen M, Kryzhanovskaya L, Carlson G, et al. Olanzapine versus placebo in the treatment of adolescents with bipolar mania. *Am J Psychiatry*. 2007;164(10):1547-56. PMID: 17898346.
88. Tramontina S, Zeni CP, Ketzer CR, et al. Aripiprazole in children and adolescents with bipolar disorder comorbid with attention-deficit/hyperactivity disorder: a pilot randomized clinical trial. *J Clin Psychiatry*. 2009;70(5):756-64. PMID: 19389329.
89. Troost PW, Lahuis BE, Steenhuis MP, et al. Long-term effects of risperidone in children with autism spectrum disorders: a placebo discontinuation study. *J Am Acad Child Adolesc Psychiatry*. 2005;44(11):1137-44. PMID: 16239862.
90. Van Bellinghen M, De Troch C. Risperidone in the treatment of behavioral disturbances in children and adolescents with borderline intellectual functioning: a double-blind, placebo-controlled pilot trial. *J Child Adolesc Psychopharmacol*. 2001;11(1):5-13. PMID: 11322745.
91. Van Bruggen J, Tijssen J, Dingemans P, et al. Symptom response and side-effects of olanzapine and risperidone in young adults with recent onset schizophrenia. *Int Clin Psychopharmacol*. 2003;18(6):341-6. PMID: 14571154.
92. Woods SW, Breier A, Zipursky RB, et al. Randomized trial of olanzapine versus placebo in the symptomatic acute treatment of the schizophrenic prodrome. *Biol Psychiatry*. 2003;54(4):453-64. PMID: 12915290.
93. Yen YC, Lung F-W, Chong MY. Adverse effects of risperidone and haloperidol treatment in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2004;28(2):285-90. PMID: 14751424.
94. Yoo HK, Lee JS, Paik KW, et al. Open-label study comparing the efficacy and tolerability of aripiprazole and haloperidol in the treatment of pediatric tic disorders. *Eur Child Adolesc Psychiatry*. 2011 ;20(3):127-35. PMID: 21188439.
95. Yoo HK, Joung YS, Lee JS, et al. A multicenter, randomized, double-blind, placebo-controlled study of aripiprazole in children and adolescents with tourette's disorder. *J Clin Psychiatry*. 2013;74(8):e772-80. PMID: 24021518.
96. Alacqua M, Trifiro G, Arcoraci V, et al. Use and tolerability of newer antipsychotics and antidepressants: a chart review in a paediatric setting. *Pharm World Sci*. 2008;30(1):44-50. PMID: 17588130.
97. Aman MG, Binder C, Turgay A. Risperidone effects in the presence/absence of psychostimulant medicine in children with adhd, other disruptive behavior disorders, and subaverage IQ. *J Child Adolesc Psychopharmacol*. 2004;14(2):243-54. PMID: 15319021.

98. 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. *J Am Acad Child Adolesc Psychiatry*. 2014;53(11):1179-90,90.e1-4. PMID: 25440308.
99. Bastiaens L. A non-randomized, open study with aripiprazole and ziprasidone for the treatment of aggressive behavior in youth in a community clinic. *Community Men Health J*. 2009;45(1):73-7. PMID: 18597173.
100. Bobo WV, Cooper WO, Stein CM, et al. Antipsychotics and the risk of type 2 diabetes mellitus in children and youth. *JAMA Psychiatry*. 2013;70(10):1067-75. PMID: 23965896.
101. Calarge CA, Nicol G, Schlechte JA, et al. Cardiometabolic outcomes in children and adolescents following discontinuation of long-term risperidone treatment. *J Child Adolesc Psychopharmacol*. 2014;24(3):120-9. PMID: 24725198.
102. Castro-Fornieles J, Parellada M, Soutullo CA, et al. Antipsychotic treatment in child and adolescent first-episode psychosis: a longitudinal naturalistic approach. *J Child Adolesc Psychopharmacol*. 2008;18(4):327-36. PMID: 18759642.
103. Cianchetti C, Ledda MG. Effectiveness and safety of antipsychotics in early onset psychoses: a long-term comparison. *Psychiatry Res*. 2011;189(3):349-56. PMID: 21570128.
104. Correll CU, Manu P, Olshanskiy V, et al. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA*. 2009;302(16):1765-73. PMID: 19861668.
105. Cuerda C, Merchan-Naranjo J, Velasco C, et al. Influence of resting energy expenditure on weight gain in adolescents taking second-generation antipsychotics. *Clin Nutr*. 2011;30(5):616-23. PMID: 21492975.
106. Ebert T, Midbari Y, Shmilovitz R, et al. Metabolic effects of antipsychotics in prepubertal children: a retrospective chart review. *J Child Adolesc Psychopharmacol*. 2014;24(4):218-22. PMID: 24816004.
107. Findling RL, Kauffman RE, Sallee FR, et al. Tolerability and pharmacokinetics of aripiprazole in children and adolescents with psychiatric disorders: an open-label, dose-escalation study. *J Clin Psychopharmacol*. 2008b;28(4):441-6. PMID: 18626272.
108. 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. PMID: 16768638.
109. Fraguas D, Merchan-Naranjo J, Laita P, et al. Metabolic and hormonal side effects in children and adolescents treated with second-generation antipsychotics. *J Clin Psychiatry*. 2008;69(7):1166-75. PMID: 18588363.
110. Friedlander R, Lazar S, Klancnik J. Atypical antipsychotic use in treating adolescents and young adults with developmental disabilities. *Can J Psychiatry*. 2001;46(8):741-5. PMID: 11692977.
111. Germano E, Italiano D, Lamberti M, et al. ECG parameters in children and adolescents treated with aripiprazole and risperidone. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014;51:23-7. PMID: 24211841.
112. Gothelf D, Falk B, Singer P, et al. Weight gain associated with increased food intake and low habitual activity levels in male adolescent schizophrenic inpatients treated with olanzapine. *Am J Psychiatry*. 2002;159(6):1055-7. PMID: 12042200.
113. Hrdlicka M, Zedkova I, Blatny M, et al. Weight gain associated with atypical and typical antipsychotics during treatment of adolescent schizophrenic psychoses: a retrospective study. *Neuroendocrinology Lett*. 2009;30(2):256-61. PMID: N/A.
114. Jerrell JM, Mcintyre RS. Adverse events in children and adolescents treated with antipsychotic medications. *Hum Psychopharmacol*. 2008;23(4):283-90. PMID: 18302312.
115. Khan RA, Mican LM, Suehs BT. Effects of olanzapine and risperidone on metabolic factors in children and adolescents: a retrospective evaluation. *J Psychiatr Pract*. 2009;15(4):320-8. PMID: 19625888.

116. Khan SS, Mican LM. A naturalistic evaluation of intramuscular ziprasidone versus intramuscular olanzapine for the management of acute agitation and aggression in children and adolescents. *J Child Adolesc Psychopharmacol*. 2006;16(6):671-7. PMID: 17201611.
117. Kumra S, Jacobsen LK, Lenane M, et al. Childhood-onset schizophrenia: An open-label study of olanzapine in adolescents. *J Am Acad Child Adolesc Psychiatry*. 1998;37(4):377-85. PMID: 9549958.
118. Mankoski R, Stockton G, Manos G, et al. Aripiprazole treatment of irritability associated with autistic disorder and the relationship between prior antipsychotic exposure, adverse events, and weight change. *J Child Adolesc Psychopharmacol*. 2013;23(8):572-6. PMID: 24138011.
119. Martin A, Landau J, Leebens P, et al. Risperidone-associated weight gain in children and adolescents: a retrospective chart review. *J Child Adolesc Psychopharmacol*. 2000;10(4):259-68. PMID: 11191686.
120. Migliardi G, Spina E, D'arrigo C, et al. Short- and long-term effects on prolactin of risperidone and olanzapine treatments in children and adolescents. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33(8):1496-501. PMID: 19706318.
121. NCT00619190. Study of aripiprazole to treat children and adolescents with autism. 2013. In: *ClinicalTrials.gov*. Bethesda, MD: National Library of Medicine (US); 2013. [cited: 2016 Apr 13]. <https://clinicaltrials.gov/ct2/show/NCT00619190>. NLM Identifier: NCT00619190.
122. Norris ML, Spettigue W, Buchholz A, et al. Olanzapine use for the adjunctive treatment of adolescents with anorexia nervosa. *J Child Adolesc Psychopharmacol*. 2011;21(3):213-20. PMID: 21510781.
123. Novaes CM, Ponde MP, Freire AC. Control of psychomotor agitation and aggressive behavior in patients with autistic disorder: A retrospective chart review. *Arq Neuropsiquiatr*. 2008;66(3B):646-51. PMID: 18949256.
124. O'donoghue B, Schafer MR, Becker J, et al. Metabolic changes in first-episode early-onset schizophrenia with second-generation antipsychotics. *Early Interv Psychiatry*. 2014;8(3):276-80. PMID: 23968390.
125. Oh J, Chang JG, Lee SB, et al. Comparison of aripiprazole and other atypical antipsychotics for pediatric bipolar disorder: A retrospective chart review of efficacy and tolerability. *Clin Psychopharmacol Neurosci*. 2013;11(2):72-9. PMID: 24023551.
126. Olfson M, Gerhard T, Huang C, et al. Comparative effectiveness of second-generation antipsychotic medications in early-onset schizophrenia. *Schizophr Bull*. 2012;38(4):845-53. PMID: 21307041.
127. Pandina GJ, Bilder R, Harvey PD, et al. Risperidone and cognitive function in children with disruptive behavior disorders. *Biol Psychiatry*. 2007;62(3):226-34. PMID: 17210137.
128. Pogge DL, Singer MB, Harvey PD. Rates and predictors of adherence with atypical antipsychotic medication: a follow-up study of adolescent inpatients. *J Child Adolesc Psychopharmacol*. 2005;15(6):901-12. PMID: 16379510.
129. Ratzoni G, Gothelf D, Brand-Gothelf A, et al. Weight gain associated with olanzapine and risperidone in adolescent patients: a comparative prospective study. *J Am Acad Child Adolesc Psychiatry*. 2002;41(3):337-43. PMID: 11886029.
130. Ronsley R, Nguyen D, Davidson J, et al. Increased risk of obesity and metabolic dysregulation following 12 months of second-generation antipsychotic treatment in children: a prospective cohort study. *Can J Psychiatry*. 2015;60(10):441-50. PMID: 26720191.
131. Saito E, Correll CU, Gallelli K, et al. A prospective study of hyperprolactinemia in children and adolescents treated with atypical antipsychotic agents. *J Child Adolesc Psychopharmacol*. 2004;14(3):350-8. PMID: 15650492.

132. Weisler RH, Khan A, Trivedi MH, et al. Analysis of suicidality in pooled data from 2 double-blind, placebo-controlled aripiprazole adjunctive therapy trials in major depressive disorder. *J Clin Psychiatry*. 2011;72(4):548-55. PMID: 20816039.
133. Wink LK, Early M, Schaefer T, et al. Body mass index change in autism spectrum disorders: comparison of treatment with risperidone and aripiprazole. *J Child Adolesc Psychopharmacol*. 2014;24(2):78-82. PMID: 24564519.
134. Wonodi I, Reeves G, Carmichael D, et al. Tardive dyskinesia in children treated with atypical antipsychotic medications. *Mov Disord*. 2007;22(12):1777-82. PMID: 17580328.
135. Wudarsky M, Nicolson R, Hamburger SD, et al. Elevated prolactin in pediatric patients on typical and atypical antipsychotics. *J Child Adolesc*

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. <i>Journal of the American Academy of Child & Adolescent Psychiatry</i> . 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. <i>Journal of the American Academy of Child & Adolescent Psychiatry</i> , 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. <i>Am J Psychiatry</i> 2002;159(8):1337-46.	Aman M, Findling A, Derivan U. Risperidone versus placebo for severe conduct disorder in children with mental retardation. <i>Int J Neuropsychopharmacol</i> 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. <i>Annual Meeting of the American Psychiatric Association; 2001.</i>
	Aman MG, Findling RL. Effects of risperidone on the behavior of children with subaverage IQ's and conduct disorder or oppositional defiant disorder. <i>155th Annual Meeting of the American Psychiatric Association; 2002.</i>
	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. <i>Clin Ther</i> 2006;28(5):794-800.
	Findling RL, Aman MG, Eerdeken M, et al. Long-term, open-label study of risperidone in children with severe disruptive behaviors and below-average IQ. <i>Am J Psychiatry</i> 2004;161(4):677-84.
	Turgay A. Risperidone in children with disruptive behavior disorder and ADHD. <i>154th Annual Meeting of the American Psychiatric Association; 2001.</i>
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? <i>Journal of the American Academy of Child & Adolescent Psychiatry</i> . 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. <i>Journal of Child & Adolescent Psychopharmacology</i> , 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. <i>Journal of the American Academy of Child & Adolescent Psychiatry</i> . 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. <i>Eur Child Adolesc Psychiatry</i> 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. <i>Schizophr Bull</i> 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. <i>Journal of the American Academy of Child & Adolescent Psychiatry</i> . 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. <i>Revista de Psiquiatria y Salud Mental</i> . 2012;5(4), 217-228.
	Garcia-Amador, M, Merchn-Naranjo, J, Tapia, C, et al. Neurological Adverse Effects of Antipsychotics in Children and Adolescents. <i>Journal of Clinical Psychopharmacology</i> . 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. <i>J Clin Psychiatry</i> 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.
Castro-Fornieles J, Parellada M, Soutullo CA, et al. Antipsychotic treatment in child and adolescent first-episode psychosis: A longitudinal naturalistic approach. <i>Journal of Child & Adolescent Psychopharmacology</i> . 2008 Aug;18(4):327-36. PMID: 18759642.	Noguera A, Ballesta P, Baeza I, et al. Twenty-four months of antipsychotic treatment in children and adolescents with first psychotic episode: discontinuation and tolerability. <i>Journal of Clinical Psychopharmacology</i> . 2013;33(4), 463-471.
Correll CU, Manu P, Olshanskiy V, et al. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. <i>JAMA - Journal of the American Medical Association</i> 302(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. <i>Journal of the American Academy of Child & Adolescent Psychiatry</i> . 2015; 54(9), 718-727.e713.
Findling RL, McNamara NK, Branicky LA, et al. A double-blind pilot study of risperidone in the treatment of conduct disorder. <i>J Am Acad Child Adolesc Psychiatry</i> 2000;39(4):509-16.	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. <i>Journal of Child & Adolescent Psychopharmacology</i> . 2009; 19(5), 563-573.
	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. <i>Schizophrenia Research. Abstracts of The VIIIth International Congress on Schizophrenia Research</i> ; Santa Fe, NM; 1999:17-21.
	Findling RL. Risperidone in children with conduct disorder. <i>Eur Neuropsychopharmacol</i> 1999:S358
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. <i>Am J Psychiatry</i> 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). <i>European Neuropsychopharmacology</i> . 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. <i>J Child Adolesc Psychopharmacol</i> 2010;20(1):33-8.
	Center for Drug Evaluation and Research. Otsuka Pharmaceutical. NDA# 021-436, 021-713, 021-729, 021-866. October 2007. http://www.accessdata.fda.gov .
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. <i>Journal of Clinical Psychiatry</i> . 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. <i>Journal of Affective Disorders</i> . 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. <i>Bipolar Disorders</i> . 2013 15(2), 138-149.

Main Publication	Associated Publications
	<p>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. <i>Journal of Child & Adolescent Psychopharmacology</i>. 2011;21(4), 359-364.</p> <p>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. <i>Journal of Child & Adolescent Psychopharmacology</i>. 2013; 23(2), 72-79.</p>
<p>Fleischhaker C, Heiser P, Hennighausen K, et al. Clinical drug monitoring in child and adolescent psychiatry: side effects of atypical neuroleptics. <i>J Child Adolesc Psychopharmacol</i> 2006;16(3):308-16.</p>	<p>Fleischhaker C, Heiser P, Hennighausen K, et al. Weight gain associated with clozapine, olanzapine and risperidone in children and adolescents. <i>J Neural Transm</i> 2007;114(2):273-80.</p> <p>Fleischhaker C, Heiser P, Hennighausen K, et al. Weight gain in children and adolescents during 45 weeks treatment with clozapine, olanzapine and risperidone. <i>J Neural Transm</i> 2008;115(11):1599-608.</p>
<p>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. <i>Bipolar Disord</i> 2009;11(7):687-700.</p>	<p>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. <i>Johnson & Johnson Pharmaceutical Research</i>; 2010.</p>
<p>Hellings JA, Zarcone JR, Reese RM, et al. A crossover study of risperidone in children, adolescents and adults with mental retardation. <i>J Autism Dev Disord</i> 2006;36(3):401-11.</p>	<p>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 <i>J Child Adolesc Psychopharmacol</i> 2001;11(3):229-38.</p> <p>Hellings JA, Zarcone JR, Valdovinos MG, et al. Risperidone-induced prolactin elevation in a prospective study of children, adolescents, and adults with mental retardation and pervasive developmental disorders. <i>J Child Adolesc Psychopharmacol</i> 2005;15(6):885-92.</p> <p>Zarcone JR, Hellings JA, Crandall K, et al. Effects of risperidone on aberrant behavior of persons with developmental disabilities: a double-blind crossover study using multiple measures. <i>Am J Ment Retard</i> 2001;106(6):525-38.</p>
<p>Jerrell JM, McIntyre RS. Adverse events in children and adolescents treated with antipsychotic medications. <i>Hum</i>. 2008 Jun;23(4):283-90. PMID: 18302312.</p>	<p>Jerrell JM, Hwang TL, Livingston TS. Neurological adverse events associated with antipsychotic treatment in children and adolescents. <i>Journal of Child Neurology</i>. 2008;23(12), 1392-1399.</p>
	<p>Jerrell JM. Adverse events associated with psychotropic treatment in African American children and adolescents. <i>Journal of the National Medical Association</i>. 2010;102(5), 375-383.</p>
<p>Kryzhanovskaya L, Schulz SC, McDougle C, et al. Olanzapine versus placebo in adolescents with schizophrenia: a 6-week, randomized, double-blind, placebo-controlled trial. <i>J Am Acad Child Adolesc Psychiatry</i> 2009;48(1): 60-70.</p>	<p>Olanzapine versus placebo in the treatment of adolescents with schizophrenia. <i>Clinical Study Summary: Study F1D-MC-HGIN</i>, Summary ID# 4066. 1-49. Eli Lilly and co.; April 2007. Available at http://www.lillytrials.com/results/Zyprexa.pdf.</p> <p>Center for Drug Evaluation and Research. Eli Lilly and Company. NDA# 020592. July 2008. http://www.accessdata.fda.gov.</p>
<p>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. <i>Biol Psychiatry</i> 2008;63(5):524-9.</p>	<p>Kumra S, Kranzler H, Gerbino-Rosen G, et al. Clozapine versus "high-dose" olanzapine in refractory early-onset schizophrenia: an open-label extension study. <i>J Child Adolesc Psychopharmacol</i> 2008;18(4):307-16.</p>
<p>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. <i>J Am</i></p>	<p>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. <i>The Primary Care Companion to CNS Disorders</i>. 2011; 13(1).</p>

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. <i>Clinical Therapeutics</i> . 2012; 34(4), 980-992.
McCracken JT, McGough J, Shah B, et al. Risperidone in children with autism and serious behavioral problems. <i>N Engl J Med</i> 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. <i>J Child Adolesc Psychopharmacol</i> 2005;15(6):869–84.
	Aman MG, Hollway JA, McDougle CJ, et al. Cognitive effects of risperidone in children with autism and irritable behavior. <i>J Child Adolesc Psychopharmacol</i> 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. <i>Biol Psychiatry</i> 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. <i>J Am Acad Child Adolesc Psychiatry</i> 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. <i>Journal of Child & Adolescent Psychopharmacology</i> . 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. <i>J Intellect Dev Disabil</i> 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. <i>Am J Psychiatry</i> 2004;161(6):1125–7.
	McDougle CJ, Scahill L, Aman MG, et al. Risperidone for the core symptom domains of autism: results from the study by the autism network of the research units on pediatric psychopharmacology. <i>Am J Psychiatry</i> 2005;162(6):1142–8.
	Scahill L, McCracken J, McDougle CJ, et al. Methodological issues in designing a multisite trial of risperidone in children and adolescents with autism. <i>J Child Adolesc Psychopharmacol</i> 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. <i>Journal of Clinical Psychiatry</i> . 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. <i>Australian & New Zealand Journal of Psychiatry</i> . 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. <i>Journal of Clinical Psychiatry</i> . 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. <i>Eur Child Adolesc Psychiatry</i> 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. <i>Eur Child Adolesc Psychiatry</i> 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. <i>Pediatrics</i> . 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. <i>The Primary Care Companion to CNS Disorders</i> . 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. <i>Clinical Therapeutics</i> . 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. <i>Journal of the J Am Acad Child Adolesc Psychiatry</i> 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. <i>J Neural Transm</i> 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. <i>Am J Psychiatry</i> 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. <i>J Child Adolesc Psychopharmacol</i> 2005;15(6):869–84.
Reyes M, Buitelaar J, Toren P, et al. A randomized, double-blind, placebo-controlled study of risperidone maintenance treatment in children and adolescents with disruptive behavior disorders. <i>Am J Psychiatry</i> 2006;163(3):402–10.	Haas M, Karcher K, Pandina GJ. Treating disruptive behavior disorders with risperidone: a 1-year, open-label safety study in children and adolescents. <i>J Child Adolesc Psychopharmacol</i> 2008;18(4):337–46. Pandina GJ, Zhu Y, Cornblatt B. Cognitive function with long-term risperidone in children and adolescents with disruptive behavior disorder. <i>Journal of Child & Adolescent Psychopharmacology</i> . 2009; 19(6), 749-756.
Sallee FR, Sethuraman G, Rock CM. Effects of pimozide on cognition in children with Tourette syndrome: interaction with comorbid attention deficit hyperactivity disorder. <i>Acta Psychiatr Scand</i> 1994;90(1):4–9.	Sallee FR, Rock CM, Head LA. Cognitive effects of neuroleptic use in children with Tourette syndrome. In: Richardson, Mary Ann, editors: <i>Use of neuroleptics in children</i> . Washington, DC; 1996. p.171–184.
Sallee FR, Nesbitt L, Jackson C, et al. Relative efficacy of haloperidol and pimozide in children and adolescents with Tourette disorder. <i>Am J Psychiatry</i> 1997;154(8):1057–62.	Sallee FR, Dougherty D, Sethuraman G, et al. Prolactin monitoring of haloperidol and pimozide treatment in children with Tourette syndrome. <i>Biol Psychiatry</i> 1996;40(10):1044–50.
Sallee FR, Kurlan R, Goetz CG, et al. Ziprasidone treatment of children and adolescents with Tourette syndrome: a pilot study. <i>J Am Acad Child Adolesc Psychiatry</i> 2000;39(3):292–9.	Chappell P, Sallee F. The tolerability and efficacy of ziprasidone in the treatment of children and adolescents with Tourette syndrome. 9th Congress of the Association of European Psychiatrists; Copenhagen; 1998.
Shea S, Turgay A, Carroll A, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. <i>Pediatrics</i> 2004;114(5):e634–41.	Pandina GJ, Bossie CA, Youssef E, et al. Risperidone improves behavioral symptoms in children with autism in a randomized, double-blind, placebo-controlled trial. <i>J Autism Dev Disord</i> 2007;37(2):367–73.
Sikich L, Frazier JA, McClellan J, et al. Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS) study. <i>Am J Psychiatry</i> 2008;165(11):1420–31.	Findling RL, Johnson JL, McClellan J, et al. Double-blind maintenance safety and effectiveness findings from the Treatment of Early-Onset Schizophrenia Spectrum (TEOSS) Study. <i>J Am Acad Child Adolesc Psychiatry</i> 2010;49(6):583–94. Frazier JA, McClellan J, Findling RL, et al. Treatment of early-onset schizophrenia spectrum disorders (TEOSS): demographic and clinical characteristics. <i>J Am Acad Child Adolesc Psychiatry</i> 2007;46(8):979–88. McClellan J, Sikich L, Findling RL, et al. Treatment of early-onset schizophrenia spectrum disorders (TEOSS): rationale, design, and methods. <i>J Am Acad Child Adolesc Psychiatry</i> 2007;46(8):969–78.
Singh J, Robb A, Vijapurkar, U, et al. A randomized, double-blind study of paliperidone extended-release in treatment of acute schizophrenia in adolescents. <i>Biol Psychiatry</i> . 2011; 70(12): 1179-1187.	Center for Drug Evaluation and Research. Johnson and Johnson. NDA# 022264. February 2009. http://www.accessdata.fda.gov .
Snyder R, Turgay A, Aman M, et al. Effects of risperidone on conduct and disruptive behavior disorders in children with subaverage IQs. <i>J Am</i>	Turgay A, Binder C, Snyder R, et al. Long-term safety and efficacy of risperidone for the treatment of disruptive behavior disorders in children with subaverage IQs. <i>Pediatrics</i> 2002;110(3):e34–46.

Main Publication	Associated Publications
Acad Child Adolesc Psychiatry 2002;41(9):1026–36.	Turgay A. Risperidone in children with disruptive behavior disorder and ADHD. 155th Annual Meeting of the American Psychiatric Association; 2002.
Spencer EK, Campbell M. Children with schizophrenia: diagnosis, phenomenology, and pharmacotherapy. Schizophr Bull 1994;20(4):713–25.	Spencer EK, Kafantaris V, Padron-Gayol MV, et al. Haloperidol in schizophrenic children: early findings from a study in progress. Psychopharmacol Bull 1992;28(2):183–6.
	Spencer EK, Alpert M, Pouget ER. Scales for the assessment of neuroleptic response in schizophrenic children: specific measures derived from the CPRS. Psychopharmacol Bull 1994;30(2):199–202.
	Spencer EK, Kafantaris V, Padron-Gayol MV, et al. Haloperidol in hospitalized schizophrenic children. In: Richardson, Mary Ann, editors: Use of neuroleptics in children. Washington, DC; 1996. p. 67–83.
Tohen M, Kryzhanovskaya L, Carlson G, et al. Olanzapine versus placebo in the treatment of adolescents with bipolar mania. Am J Psychiatry 2007;164(10):1547–56.	Olsen BT, Ganocy SJ, Bitter SM, et al. Health-related quality of life as measured by the child health questionnaire in adolescents with bipolar disorder treated with olanzapine. Comprehensive Psychiatry. 2012; 53(7), 1000-1005.
	Robertson-Plouch C. Olanzapine useful in adolescent mania. Academy of Adolescent and Child Psychiatry 2006;31(12):727.
	Tohen M, Kryzhanovskaya L, Carlson G, et al. Olanzapine in the treatment of acute mania in adolescents with bipolar I disorder: a 3-week randomized double-blind placebo-controlled study. Neuropsychopharmacol 2005;7:S176.
	Center for Drug Evaluation and Research. Eli Lilly and Company. NDA# 020592. July 2008. http://www.accessdata.fda.gov .
	Olanzapine versus placebo in the treatment of mania in Adolescents with bipolar 1 disorder. Clinical Study Summary: Study F1D-MC-HGIU, Summary ID# 4360. 1-46. Eli Lilly and co.; February 2007. Available at http://www.lillytrials.com/results/Zyprexa.pdf .
Troost PW, Lahuis BE, Steenhuis MP, et al. Long-term effects of risperidone in children with autism spectrum disorders: a placebo discontinuation study. J Am Acad Child Adolesc Psychiatry 2005;44(11):1137–44.	Troost PW, Althaus M, Lahuis BE, et al. Neuropsychological effects of risperidone in children with pervasive developmental disorders: a blinded discontinuation study. J Child Adolesc Psychopharmacol 2006;16(5):561–73.
van Bruggen J, Tijssen J, Dingemans P, et al. Symptom response and side-effects of olanzapine and risperidone in young adults with recent onset schizophrenia. Int Clin Psychopharmacol 2003;18(6):341–6.	Lavalaye J, Linszen DH, Booij J, et al. Dopamine D2 receptor occupancy by olanzapine or risperidone in young patients with schizophrenia. Psychiatry Res 1999;92(1):33–44.
Woods SW, Breier A, Zipursky RB, et al. Randomized trial of olanzapine versus placebo in the symptomatic acute treatment of the schizophrenic prodrome. Biol Psychiatry 2003;54(4):453–64.	Hawkins KA, Keefe RS, Christensen BK, et al. Neuropsychological course in the prodrome and first episode of psychosis: findings from the PRIME North America Double Blind Treatment Study. Schizophr Res 2008;105(1–3):1–9.
	Keefe RS, Perkins DO, Gu H, et al. A longitudinal study of neurocognitive function in individuals at-risk for psychosis. Schizophr Res 2006;88(1–3):26–35.
	McGlashan TH, Zipursky RB, Perkins D, et al. The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis: study rationale and design. Schizophr Res 2003;61(1):7–18.
	McGlashan TH, Zipursky RB, Perkins D, et al. Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. Am J Psychiatry 2006;(5):790–9.

Main Publication

Associated Publications

Miller TJ, Zipursky RB, Perkins D, et al. The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis: baseline characteristics of the "prodromal" sample. *Schizophr Res* 2003;61(1):19–30.

Appendix F. Excluded Studies

1. Adler BA, Wink LK, Early M, et al. Drug-refractory aggression, self-injurious behavior, and severe tantrums in autism spectrum disorders: a chart review study. *Autism*. 2015;19(1):102-6. DOI: 10.1177/1362361314524641. PMID: 24571823. EXCLUDE: Study Design.
2. Adelugba O, Mela M, Haq I. Involuntary treatment of psychiatric inpatients certified under the Saskatchewan Mental Health Services Act in a secure forensic psychiatric treatment center. *Med Sci Law*. 2015;55(2):113-20. PMID: 2464420. EXCLUDE: Age
3. Adis Medical W. Effective treatment of attention-deficit hyperactivity disorder also helps control symptoms of comorbid oppositional defiant disorder. *Drugs and Ther Perspect*. 2016;32(3):104-9. doi: <http://dx.doi.org/10.1007/s40267-015-0269-y>. PMID: 20160145075. EXCLUDE: Publication Type.
4. Anderson VM, Goldstein ME, Kydd RR, et al. Extensive gray matter volume reduction in treatment-resistant schizophrenia. *Int J Neuropsychopharmacology*. 2015;18(7):pyv016. doi: <http://dx.doi.org/10.1093/ijnp/pyv016>. PMID: 25716781. EXCLUDE: Age.
5. Akkaya C, Sarandol A, Cangur S, et al. Retrospective database analysis on the effectiveness of typical and atypical antipsychotic drugs in an outpatient clinic setting. *Hum Psychopharmacol*. 2007;22(8):515-28. DOI: 10.1002/hup.882. PMID: 17868197. EXCLUDE: Age.
6. Alessi NE. Ziprasidone in autism. *J Am Acad Child Adol Psychiatry*. 2003;42(6):622-3. DOI: <http://dx.doi.org/10.1097/01.CHI.0000046853.56865.10>. PMID: 12921465. EXCLUDE: Publication Type.
7. Alfaro CL, Wudarsky M, Nicolson R, et al. Correlation of antipsychotic and prolactin concentrations in children and adolescents acutely treated with haloperidol, clozapine, or olanzapine. *J Child Adol Psychopharmacol*. 2002;12(2):83-91. PMID: 12188977. EXCLUDE: Study Design.
8. Archie S, Zangeneh-Kazemi A, Akhtar-Danesh N. First-episode affective psychosis and lipid monitoring: Survival analysis of the first abnormal lipid test. *Early Interv Psychiatry*. 2015;9(6):507-11. doi: <http://dx.doi.org/10.1111/eip.12180>. PMID: 2014754223. EXCLUDE: Age.
9. Aman M, Buitelaar J, Smedt GD, et al. Pharmacotherapy of disruptive behavior and item changes on a standardized rating scale: pooled analysis of risperidone effects in children with subaverage IQ. *J Child Adol Psychopharmacol*. 2005;15(2):220-32. DOI:10.1089/cap.2005.15.220. PMID: 15910206. EXCLUDE: Outcomes.
10. Aman M, Rettiganti M, Nagaraja HN, et al. Tolerability, safety, and benefits of risperidone in children and adolescents with autism: 21-month follow-up after 8-week placebo-controlled trial. *J Child Adol Psychopharmacol*. 2015;25(6):482-93. doi: <http://dx.doi.org/10.1089/cap.2015.0005>. PMID: 26262903. EXCLUDE: Intervention.
11. Aman MG, Kasper W, Manos G, et al. Line-item analysis of the Aberrant Behavior Checklist: results from two studies of aripiprazole in the treatment of irritability associated with autistic disorder. *J Child Adol Psychopharmacol*. 2010;20(5):415-22. doi: <http://dx.doi.org/10.1089/cap.2009.0120>. PMID: 20973712. EXCLUDE: Outcomes.
12. Aman MG, White AJ. Thioridazine dose effects with reference to stereotypic behavior in mentally retarded residents. *J Autism Dev Disord*. 1988;18(3):355-66. doi: <http://dx.doi.org/10.1007/BF02212192>. PMID: 1988228303. EXCLUDE: Intervention.
13. Amann BL, Pogarell O, Mergl R, et al. EEG abnormalities associated with antipsychotics: a comparison of quetiapine, olanzapine, haloperidol and healthy subjects. *Hum Psychopharmacol*. 2003;18(8):641-6. DOI: 10.1002/hup.537. PMID: 14696024. EXCLUDE: Age.
14. Andrade SE, Lo JC, Roblin D, et al. Antipsychotic medication use among children and risk of diabetes mellitus. *Pediatrics*. 2011;128(6):1135-41. DOI: <http://dx.doi.org/10.1542/peds.2011-0855>. PMID: 22106077.

EXCLUDE: Intervention.

15. Andrezina R, Josiassen RC, Marcus RN, et al. Intramuscular aripiprazole for the treatment of acute agitation in patients with schizophrenia or schizoaffective disorder: a double-blind, placebo-controlled comparison with intramuscular haloperidol. *Psychopharmacology*. 2006;188(3):281-92. PMID: 16953381. EXCLUDE: Age.
16. Apiquian R, Fresan A, Herrera K, et al. Minimum effective doses of haloperidol for the treatment of first psychotic episode: a comparative study with risperidone and olanzapine. *Int J Neuropsychopharmacol*. 2003;6(4):403-8. PMID: 14604455. EXCLUDE: Age.
17. Arato M, O'Connor R, Meltzer HY, et al. A 1-year, double-blind, placebo-controlled trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: the Ziprasidone Extended Use in Schizophrenia (ZEUS) study. *Int Clin Psychopharmacol*. 2002;17(5):207-15. PMID: 12177583. EXCLUDE: Age.
18. Aripiprazole and adolescent schizophrenia: a simple neuroleptic. No comparison with standard neuroleptic in adolescents. *Prescrire Int*. 2009;18(104):251. PMID: 20025091. EXCLUDE: Publication Type.
19. Aripiprazole and adolescent schizophrenia: a simple neuroleptic. No comparison with standard neuroleptic in adolescents. *Prescrire Int*. 2009;18(104):251. PMID: 20025091. EXCLUDE: Publication Type.
20. Aripiprazole at adult doses effective in youths with schizophrenia. *Brown University Child & Adolescent Psychopharmacology Update*. 2008;10(11):1-7. PMID: N/A. EXCLUDE: Outcomes.
21. Aripiprazole effective in treating irritability in autistic youth. *Brown University Child & Adolescent Psychopharmacology Update*. 2010;12(2):4-5. PMID: N/A. EXCLUDE: Publication Type.
22. Armour A, Gottschlich MM, Khoury J, et al. A randomized, controlled prospective trial of zolpidem and haloperidol for use as sleeping agents in pediatric burn patients. *J Burn Care Res*. 2008;29(1):238-47. doi: PMID: 18182928. EXCLUDE: Diagnosis.
23. Arranz B, San L, Duenas RM, et al. Lower weight gain with the orally disintegrating olanzapine than with standard tablets in first-episode never treated psychotic patients. *Hum Psychopharmacol*. 2007;22(1):11-5. PMID: 17191265. EXCLUDE: Age.
24. Arvanitis LA, Miller BG. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *The Seroquel Trial 13 Study Group. Biol Psychiatry*. 1997;42(4):233-46. PMID: 9270900. EXCLUDE: Age.
25. Atmaca M, Kuloglu M, Tezcan E, et al. Quetiapine is not associated with increase in prolactin secretion in contrast to haloperidol. *Arch Med Res*. 2002;33(6):562-5. PMID: 12505103. EXCLUDE: Age.
26. Atmaca M, Kuloglu M, Tezcan E, et al. Quetiapine augmentation in patients with treatment resistant obsessive-compulsive disorder: a single-blind, placebo-controlled study. *Int Clin Psychopharmacol*. 2002;17(3):115-9. PMID: 11981352. EXCLUDE: Age.
27. Attard A, Olofinjana O, Cornelius V, et al. Paliperidone palmitate long-acting injection--prospective year-long follow-up of use in clinical practice. *Acta Psychiatr Scand*. 2014;130(1):46-51. PMID: 24117209. EXCLUDE: Study Design.
28. Azorin JM, Spiegel R, Remington G, et al. A double-blind comparative study of clozapine and risperidone in the management of severe chronic schizophrenia. *Am J Psychiatr*. 2001;158(8):1305-13. PMID: 11481167. EXCLUDE: Age.
29. Bachmann CJ, Gebhardt S, Lehr D, et al. Subjective and biological weight-related parameters in adolescents and young adults with schizophrenia spectrum disorder under clozapine or olanzapine treatment. *Z Kinder Jugendpsychiatr Psychother*. 2012;40(3):151-8. PMID: 22532107. EXCLUDE: Study Design.
30. Bai YM, Chen TT, Wu B, et al. A comparative efficacy and safety study of long-acting risperidone injection and risperidone oral tablets among hospitalized patients: 12-week randomized, single-blind study. *Pharmacopsychiatry*. 2006;39(4):135-41. PMID: 16900609. EXCLUDE: Age.

31. Baker RW, Kinon BJ, Maguire GA, et al. Effectiveness of rapid initial dose escalation of up to forty milligrams per day of oral olanzapine in acute agitation. *J Clin Psychopharmacol.* 2003;23(4):342-8. PMID: 12920409. EXCLUDE: Age.
32. Baldessarini RJ, Hennen J, Wilson M, et al. Olanzapine versus placebo in acute mania: treatment responses in subgroups. *J Clin Psychopharmacol.* 2003;23(4):370-6. PMID: 12920413. EXCLUDE: Age.
33. Bali V, Kamble PS, Aparasu RR. Predictors of concomitant use of antipsychotics and stimulants and its impact on stimulant persistence in pediatric attention deficit hyperactivity disorder. *J Manag Care Spec Pharm.* 2015;21(6):486-98. PMID: 26011550. EXCLUDE: Outcomes.
34. Bartzokis G, Lu PH, Nuechterlein KH, et al. Differential effects of typical and atypical antipsychotics on brain myelination in schizophrenia.[Erratum appears in *Schizophr Res.* 2008;99(1-3):379]. *Schizophr Res.* 2007;93(1-3):13-22. PMID: 17407804. EXCLUDE: Age.
35. Battaglia J, Moss S, Rush J, et al. Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study. *Am J Emerg Med.* 1997;15(4):335-40. PMID: 9217519. EXCLUDE: Age.
36. Bauer M, Thase ME, Liu S, et al. Analysis of potentially predictive factors of efficacy of adjunct extended-release quetiapine fumarate in patients with major depressive disorder. *J Psychopharmacol.* 2015;29(5):565-74. PMID: 25257148. EXCLUDE: Age.
37. Beasley CM, Jr., Sutton VK, Hamilton SH, et al. A double-blind, randomized, placebo-controlled trial of olanzapine in the prevention of psychotic relapse. *J Clin Psychopharmacol.* 2003;23(6):582-94. PMID: 14624189. EXCLUDE: Age.
38. Beasley CM, Jr., Sutton VK, Taylor CC, et al. Is quality of life among minimally symptomatic patients with schizophrenia better following withdrawal or continuation of antipsychotic treatment? *J Clin Psychopharmacol.* 2006;26(1):40-4. PMID: 16415704.
39. Beasley CM, Jr., Tollefson G, Tran P, et al. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology.* 1996;14(2):111-23. PMID: 8822534. EXCLUDE: Age.
40. Beer F, Heinrich H, Springer S, et al. Quetiapine in the treatment of psychotic adolescents: a case series of 23 patients with severe early onset psychosis. *World J Biol Psychiatr.* 2007;8(1):38-41. PMID: 17366348. EXCLUDE: Study Design.
41. Berling I, Isbister GK. Prolonged QT Risk Assessment in Antipsychotic Overdose Using the QT Nomogram. *Ann Emerg Med.* 2015;66(2):154-64. PMID: 25639523. EXCLUDE: Age.
42. Berman RM, Fava M, Thase ME, et al. Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. *CNS Spectr.* 2009;14(4):197-206. PMID: 19407731. EXCLUDE: Age.
43. Berwaerts J, Liu Y, Gopal S, et al. Efficacy and Safety of the 3-Month Formulation of Paliperidone Palmitate vs Placebo for Relapse Prevention of Schizophrenia: A Randomized Clinical Trial. *JAMA Psychiatry.* 2015;72(8):830-9. PMID: 25820612. EXCLUDE: Age.
44. Bhowmik D, Aparasu RR, Rajan SS, et al. The utilization of psychopharmacological treatment and medication adherence among Medicaid enrolled children and adolescents with bipolar depression. *J Affect Disord.* 2013;150(2):424-9. PMID: 23747210. EXCLUDE: Intervention.
45. Bhowmik D, Aparasu RR, Rajan SS, et al. Risk of manic switch associated with antidepressant therapy in pediatric bipolar depression. *J Child Adol Psychopharmacol.* 2014;24(10):551-61. PMID: 25470655. EXCLUDE: Intervention.
46. Berk M, Tiller JW, Zhao J, et al. Effects of asenapine in bipolar I patients meeting proxy criteria for moderate-to-severe mixed major depressive episodes: a post hoc analysis. *J Clin Psychiatr.* 2015;76(6):728-34. PMID: 25612216. EXCLUDE: Age.

47. Berling I, Isbister GK. Prolonged QT Risk Assessment in Antipsychotic Overdose Using the QT Nomogram. *Ann Emerg Med.* 2015;66(2):154-64. PMID: 25639523. EXCLUDE: Age.
48. Berwaerts J, Liu Y, Gopal S, et al. Efficacy and Safety of the 3-Month Formulation of Paliperidone Palmitate vs Placebo for Relapse Prevention of Schizophrenia: A Randomized Clinical Trial. *JAMA Psychiatry.* 2015;72(8):830-9. PMID: 25820612. EXCLUDE: Age.
49. Biederman J, Hammerness P, Doyle R, et al. Risperidone treatment for ADHD in children and adolescents with bipolar disorder. *Neuropsychiatr Dis Treat.* 2008;4(1B):203-7. PMID: 18728799. EXCLUDE: Study Design.
50. Biederman J, McDonnell MA, Wozniak J, et al. Aripiprazole in the treatment of pediatric bipolar disorder: a systematic chart review. *CNS Spectr.* 2005;10(2):141-8. PMID: 15685125. EXCLUDE: Study Design.
51. Biederman J, Mick E. Comparative open-label trial of atypical neuroleptics in children and adolescents with bipolar disorder. *Eur Neuropsychopharmacol.* 2004;14(suppl3):S211-S2. PMID: N/A. EXCLUDE: Publication Type.
52. Bildik T, Ozbaran NB, Kose S, et al. Gunluk uygulamada ayaktan tedavi goren bir ergen hasta populasyonunda aripiprazolun etkinlik ve tolerabilitesi. [Effectiveness and tolerability of aripiprazole in a real-world outpatient population of youth]. *Klinik Psikofarmakoloji Bulteni.* 2012;22(3):225-34. PMID: 2012576016. EXCLUDE: Study Design.
53. Bissada H, Tasca GA, Barber AM, et al. Olanzapine in the treatment of low body weight and obsessive thinking in women with anorexia nervosa: a randomized, double-blind, placebo-controlled trial. *Am J Psychiatr.* 2008;165(10):1281-8. PMID: 18558642. EXCLUDE: Age.
54. Bishop JR, Reilly JL, Harris MS, et al. Pharmacogenetic associations of the type-3 metabotropic glutamate receptor (GRM3) gene with working memory and clinical symptom response to antipsychotics in first-episode schizophrenia. *Psychopharmacology.* 2015;232(1):145-54. PMID: 25096017. EXCLUDE: Age.
55. Bitter I, Dossenbach MR, Brook S, et al. Olanzapine versus clozapine in treatment-resistant or treatment-intolerant schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatr.* 2004;28(1):173-80. PMID: 14687871. EXCLUDE: Age.
56. Blader JC. Pharmacotherapy and postdischarge outcomes of child inpatients admitted for aggressive behavior. *J Clin Psychopharmacol.* 2006;26(4):419-25. PMID: 16855463. EXCLUDE: Intervention.
57. Blankenship K, Erickson CA, Stigler KA, et al. Aripiprazole for irritability associated with autistic disorder in children and adolescents aged 6-17 years. *Pediatr Health.* 2010;4(4):375-81. PMID: 21359119. EXCLUDE: Publication Type.
58. Blasi G, Selvaggi P, Fazio L, et al. Variation in Dopamine D2 and Serotonin 5-HT2A Receptor Genes is Associated with Working Memory Processing and Response to Treatment with Antipsychotics. *Neuropsychopharmacology.* 2015;40(7):1600-8. PMID: 25563748. EXCLUDE: Diagnosis.
59. Blin O, Azorin JM, Bouhours P. Antipsychotic and anxiolytic properties of risperidone, haloperidol, and methotrimeprazine in schizophrenic patients. *J Clin Psychopharmacol.* 1996;16(1):38-44. PMID: 8834417. EXCLUDE: Age.
60. Bobes J, Gibert J, Ciudad A, et al. Safety and effectiveness of olanzapine versus conventional antipsychotics in the acute treatment of first-episode schizophrenic inpatients. *Prog Neuropsychopharmacol Biol Psychiatr.* 2003;27(3):473-81. PMID: 12691783. EXCLUDE: Age.
61. Bogenschutz MP, George Nurnberg H. Olanzapine versus placebo in the treatment of borderline personality disorder. *J Clin Psychiatr.* 2004;65(1):104-9. PMID: 14744178. EXCLUDE: Age.
62. Bola JR, Mosher LR. At issue: predicting drug-free treatment response in acute psychosis from the Soteria project. *Schizophr Bull.* 2002;28(4):559-75. PMID: 12795491. EXCLUDE: Study Design.

63. Bola JR, Mosher LR. Treatment of acute psychosis without neuroleptics: two-year outcomes from the Soteria project. *J Nerv Ment Dis.* 2003;191(4):219-29. PMID: 12695732.
EXCLUDE: Intervention.
64. Bondolfi G, Dufour H, Patris M, et al. Risperidone versus clozapine in treatment-resistant chronic schizophrenia: a randomized double-blind study. The Risperidone Study Group. *Am J Psychiatr.* 1998;155(4):499-504. PMID: 9545995.
EXCLUDE: Age.
65. Booth C, Brown AS, Carico H. Male eating disorders: An update on an underrecognized population. *U.S. Pharmacist.* 2015;40(10):52-6. PMID: 2015453748.
EXCLUDE: Publication Type.
66. Borison RL, Arvanitis LA, Miller BG. ICI 204,636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. U.S. SEROQUEL Study Group. *J Clin Psychopharmacol.* 1996;16(2):158-69. PMID: 8690831.
EXCLUDE: Age.
67. Borison RL, Diamond B, Pathiraja A, et al. Pharmacokinetics of risperidone in chronic schizophrenic patients. *Psychopharmacol Bull.* 1994;30(2):193-7. PMID: 7530379.
EXCLUDE: Age.
68. Bornstein RA, Yang V. Neuropsychological performance in medicated and unmedicated patients with Tourette's disorder. *Am J Psychiatr.* 1991;148(4):468-71. DOI: PMID: 1672484.
EXCLUDE: Intervention.
69. Borovcanin M, Jovanovic I, Dejanovic SD, et al. Increase systemic levels of IL-23 as a possible constitutive marker in schizophrenia. *Psychoneuroendocrinology.* 2015;56:143-7. PMID: 25827958.
EXCLUDE: Age.
70. Boter H, Peuskens J, Libiger J, et al. Effectiveness of antipsychotics in first-episode schizophrenia and schizophreniform disorder on response and remission: an open randomized clinical trial (EUFEST). *Schizophr Res.* 2009;115(2-3):97-103. PMID: 19819114.
EXCLUDE: Age.
71. Bowden CL, Grunze H, Mullen J, et al. A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *J Clin Psychiatr.* 2005;66(1):111-21. PMID: 15669897.
EXCLUDE: Age.
72. Breier A, Meehan K, Birkett M, et al. A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. *Arch Gen Psychiatr.* 2002;59(5):441-8. PMID: 11982448.
EXCLUDE: Age.
73. Broerse A, Crawford TJ, den Boer JA. Differential effects of olanzapine and risperidone on cognition in schizophrenia? A saccadic eye movement study. *J Neuropsychiatry Clin Neurosc.* 2002;14(4):454-60. PMID: 12426415.
EXCLUDE: Age.
74. Buck TR, Viskochil J, Farley M, et al. Psychiatric comorbidity and medication use in adults with autism spectrum disorder. *J Autism Dev Disord.* 2014;44(12):3063-71. DOI: PMID: 2485538.
EXCLUDE: Study Design.
75. Butterfield MI, Becker ME, Connor KM, et al. Olanzapine in the treatment of post-traumatic stress disorder: a pilot study. *Int Clin Psychopharmacol.* 2001;16(4):197-203. PMID: 11459333.
EXCLUDE: Age.
76. Byerly MJ, Nakonezny PA, Bettcher BM, et al. Sexual dysfunction associated with second-generation antipsychotics in outpatients with schizophrenia or schizoaffective disorder: an empirical evaluation of olanzapine, risperidone, and quetiapine. *Schizophr Res.* 2006;86(1-3):244-50. PMID: 16730951.
EXCLUDE: Age.
77. Caicedo C, Williams SH. Risperidone improves behavior in children with autism. *J Fam Pract.* 2002 Nov;51(11):915. PMID: 12485538.
EXCLUDE: Publication Type.
78. Calabrese JR, Keck PE, Jr., Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatr.* 2005;162(7):1351-60. PMID: 15994719.
EXCLUDE: Age.
79. Calarge CA, Acion L, Kuperman S, et al. Weight gain and metabolic abnormalities during extended risperidone treatment in children and adolescents. *J*

- Child Adolesc Psychopharmacol. 2009;19(2):101-9. PMID: 19364288. EXCLUDE: Study Design.
80. Calarge CA, Burns TL, Schlechte JA, et al. Longitudinal examination of the skeletal effects of selective serotonin reuptake inhibitors and risperidone in boys. *J Clin Psychiatr.* 2015;76(5):607-13. PMID: 26035190. EXCLUDE: Intervention.
81. Bressington D, Stock J, Hulbert S, et al. A retrospective observational study of the effectiveness of paliperidone palmitate on acute inpatient hospitalization rates. *Int Clin Psychopharmacol.* 2015;30(4):230-6. PMID: 25882381. EXCLUDE: Age.
82. Bridler R, Haberle A, Muller ST, et al. Psychopharmacological treatment of 2195 in-patients with borderline personality disorder: A comparison with other psychiatric disorders. *Euro Neuropsychopharmacology.* 2015;25(6):763-72. PMID: 25907249. EXCLUDE: Diagnosis.
83. Brown R, James A. Practical pharmacotherapy in child psychiatry: An update. *Adv Psychiatr Treat.* 2015;21(6):387-95. PMID: 2015540704. EXCLUDE: Publication Type.
84. Bruno A, Zoccali RA, Abenavoli E, et al. Augmentation of clozapine with agomelatine in partial-responder schizophrenia: a 16-week, open-label, uncontrolled pilot study. *J Clin Psychopharmacol.* 2014;34(4):491-4. PMID: 24911437. EXCLUDE: Age.
85. Calarge CA, Nicol G, Xie D, et al. Correlates of weight gain during long-term risperidone treatment in children and adolescents. *Child Adolesc Psychiatr Ment Health.* 2012;6(1):21. PMID: 22643087. EXCLUDE: Study Design.
86. Caldwell MF, Malterer M, Umstead D, et al. A retrospective evaluation of adjunctive risperidone treatment in severely behaviorally disordered boys receiving psychosocial treatment. *J Child Adolesc Psychopharmacol.* 2008;18(1):34-43. DOI: PMID: 18294087. EXCLUDE: Outcomes.
87. Camm AJ, Karayal ON, Meltzer H, et al. Ziprasidone and the corrected QT interval: a comprehensive summary of clinical data. *CNS Drugs.* 2012;26(4):351-65. PMID: 22452529. EXCLUDE: Age.
88. Campbell M, Adams P, Perry R, et al. Tardive and withdrawal dyskinesia in autistic children: a prospective study. *Psychopharmacol Bull.* 1988;24(2):251-5. PMID: 3212157. EXCLUDE: Study Design.
89. Campbell M, Armenteros JL, Malone RP, et al. Neuroleptic-related dyskinesias in autistic children: a prospective, longitudinal study. *J Am Acad Child Adolesc Psychiatr.* 1997;36(6):835-43. PMID: 9183140. EXCLUDE: Study Design.
90. Campbell M, Locascio JJ, Choroco MC, et al. Stereotypies and tardive dyskinesia: abnormal movements in autistic children. *Psychopharmacol Bull.* 1990;26(2):260-6. PMID: 2236468. EXCLUDE: Study Design.
91. Canuso CM, Dirks B, Carothers J, et al. Randomized, double-blind, placebo-controlled study of paliperidone extended-release and quetiapine in inpatients with recently exacerbated schizophrenia. *Am J Psychiatr.* 2009;166(6):691-701. PMID: 19411369. EXCLUDE: Age.
92. Carey PD, Vythilingum B, Seedat S, et al. Quetiapine augmentation of SRIs in treatment refractory obsessive-compulsive disorder: a double-blind, randomised, placebo-controlled study. *BMC Psychiatry.* 2005;5:5. PMID: 15667657. EXCLUDE: Age.
93. Carlson GA, Lavelle J, Bromet EJ. Medication treatment in adolescents vs. adults with psychotic mania. *J Child Adolesc Psychopharmacol.* 1999;9(3):221-31. PMID: 10521014. EXCLUDE: Intervention.
94. Carrasco JL, Gutierrez M, Gomez JC, et al. Treatment of severely psychotic inpatients with schizophrenia: olanzapine versus other antipsychotic drugs. *Int Clin Psychopharmacol.* 2002;17(6):287-95. PMID: 12409682. EXCLUDE: Age.
95. Calver L, Drinkwater V, Gupta R, et al. Droperidol v. haloperidol for sedation of aggressive behaviour in acute mental health: randomised controlled trial. *Br J*

- Psychiatr. 2015;206(3):223-8. doi: PMID: 25395689.
EXCLUDE: Age.
96. Centorrino F, Masters GA, Talamo A, et al. Metabolic syndrome in psychiatrically hospitalized patients treated with antipsychotics and other psychotropics. *Hum Psychopharmacol*. 2012;27(5):521-6. PMID: 22996619.
EXCLUDE: Publication Type.
97. Chang JS, Hwang SS, Yi SH, et al. Evaluating subjective domains of antipsychotic-induced adverse effects using heart rate variability. *Psychiatry Clin Neurosci*. 2015;69(5):283-91. PMID: 25066617.
EXCLUDE: Age.
98. Chappell P, Sallee F. The tolerability and efficacy of ziprasidone in the treatment of children and adolescents with Tourette's syndrome [abstract]. 11th European College of Neuropsychopharmacology Congress; Paris, France. 1998:P2.017. <http://onlinelibrary.wiley.com/doi/10.1002/9781118154763.ch327>.
EXCLUDE: Publication Type.
99. Chaves C, Marque CR, Maia-de-Oliveira JP, et al. Effects of minocycline add-on treatment on brain morphometry and cerebral perfusion in recent-onset schizophrenia. *Schizophr Res*. 2015;161(2-3):439-45. PMID: 25497439.
EXCLUDE: Age.
100. Chen VCH, Liao YT, Lai TJ, et al. Survival analysis of the use of first and second generation antipsychotics among patients suffering schizophrenia: A nationwide population-based cohort study. *Schizophr Res*. 2015;169(1-3):406-11. PMID: 20151062335.
EXCLUDE: Intervention.
101. Chen JX, Su YA, Bian QT, et al. Adjunctive aripiprazole in the treatment of risperidone-induced hyperprolactinemia: A randomized, double-blind, placebo-controlled, dose-response study. *Psychoneuroendocrinology*. 2015;58:130-40. PMID: 25981348.
EXCLUDE: Age.
102. Chiu CC, Chen KP, Liu HC, et al. The early effect of olanzapine and risperidone on insulin secretion in atypical-naïve schizophrenic patients. *J Clin Psychopharmacol*. 2006;26(5):504-7. PMID: 16974193.
EXCLUDE: Age.
103. Chouinard G. A placebo-controlled clinical trial of remoxipride and chlorpromazine in newly admitted schizophrenic patients with acute exacerbation. *Acta Psychiatr Scand Suppl*. 1990;358:111-9. PMID: 1978469.
EXCLUDE: Age.
104. Chrzanowski WK, Marcus RN, Torbeyns A, et al. Effectiveness of long-term aripiprazole therapy in patients with acutely relapsing or chronic, stable schizophrenia: a 52-week, open-label comparison with olanzapine. *Psychopharmacology*. 2006;189(2):259-66. PMID: 17058105.
EXCLUDE: Age.
105. Chue P, Eerdeken M, Augustyns I, et al. Comparative efficacy and safety of long-acting risperidone and risperidone oral tablets. *European Neuropsychopharmacology*. 2005;15(1):111-7. PMID: 15572280.
EXCLUDE: Age.
106. Citrome L, Volavka J, Czobor P, et al. Efficacy of ziprasidone against hostility in schizophrenia: Post hoc analysis of randomized, open-label study data. *J Clin Psychiatry*. 2006;67(4):638-42. PMID: 16669729.
EXCLUDE: Age.
107. Ciudad A, Olivares JM, Bousono M, et al. Improvement in social functioning in outpatients with schizophrenia with prominent negative symptoms treated with olanzapine or risperidone in a 1 year randomized, open-label trial. *Progr Neuropsychopharmacol Biol Psychiatry*. 2006;30(8):1515-22. PMID: 16820255.
EXCLUDE: Age.
108. Clozapine more effective than high-dose olanzapine in early-onset schizophrenia. *Brown University Child & Adolescent Psychopharmacology Update*. 2007;9(10):1-4. PMID: 105971262.
EXCLUDE: Outcomes.
109. Clozapine versus olanzapine for COS. *Brown University Child & Adolescent Psychopharmacology Update*. 2006;8(9):4. PMID: 106223379.
EXCLUDE: Publication Type.
110. Cohen BM, Lipinski JF, Wateraux C. A fixed dose study of the plasma concentration and clinical effects of thioridazine and its major metabolites. *Psychopharmacology*. 1989;97(4):481-8. PMID: 2498945.
EXCLUDE: Age.

111. Cohen LS. Quetiapine in treatment-resistant obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*. 2003;42(6):623-4. PMID: 12921466.
EXCLUDE: Study Design.
112. Coley KC, Carter CS, DaPos SV, et al. Effectiveness of antipsychotic therapy in a naturalistic setting: a comparison between risperidone, perphenazine, and haloperidol. *J Clin Psychiatry*. 1999;60(12):850-6. PMID: 10665632.
EXCLUDE: Age.
113. Conley RR, Kelly DL, Nelson MW, et al. Risperidone, quetiapine, and fluphenazine in the treatment of patients with therapy-refractory schizophrenia. *Clin Neuropharmacol*. 2005;28(4):163-8. PMID: 16062094.
EXCLUDE: Age.
114. Connor DF, Fletcher KE, Wood JS. Neuroleptic-related dyskinesias in children and adolescents. *J Clin Psychiatry*. 2001;62(12):967-74. PMID: 11780878.
EXCLUDE: Intervention.
115. Consoli A, Brunelle J, Bodeau N, et al. Medication use in adolescents treated in a French psychiatric setting for acute manic or mixed episode. *J Canadian Acad Child Adolesc Psychiatry*. 2009;18(3):231-8. PMID: 19718424.
EXCLUDE: Study Design.
116. Cookson J, Keck PE, Jr., Ketter TA, et al. Number needed to treat and time to response/remission for quetiapine monotherapy efficacy in acute bipolar depression: evidence from a large, randomized, placebo-controlled study. *Int Clin Psychopharmacol*. 2007;22(2):93-100. PMID: 17293709.
EXCLUDE: Age.
117. Cooper SJ, Tweed J, Raniwalla J, et al. A placebo-controlled comparison of zotepine versus chlorpromazine in patients with acute exacerbation of schizophrenia. *Acta Psychiatr Scand*. 2000;101(3):218-25. PMID: 10721870.
EXCLUDE: Age.
118. Coraci LM. Atypical neuroleptic response in non-psychotic adolescents [Ph.D.]. Ann Arbor: Fairleigh Dickinson University; 2008.
EXCLUDE: Study Design.
119. Coraci LM. Atypical neuroleptic response in non-psychotic adolescents. *Dissertation Abstracts International: Section B: The Sciences and Engineering*. 2009;69(7-B).
EXCLUDE: Study Design.
120. Correll CU. Antipsychotic medications. <http://dx.doi.org/login.ezproxy.library.ualberta.ca/10.1176/appi.books.9781615370306.md38>. Dulcan, Mina K [Ed]. 2016.
EXCLUDE: Publication Type.
121. Correia CT, Almeida JP, Santos PE, et al. Pharmacogenetics of risperidone therapy in autism: association analysis of eight candidate genes with drug efficacy and adverse drug reactions. *Pharmacogenomics J*. 2010;10(5):418-30. PMID: 19997080.
EXCLUDE: Study Design.
122. Correll CU, Zhao J, Carson W, et al. Early antipsychotic response to aripiprazole in adolescents with schizophrenia: predictive value for clinical outcomes. *J Am Acad Child Adolesc Psychiatry*. 2013;52(7):689-98.e3. PMID: 23800482.
EXCLUDE: Intervention.
123. Corrigan MH, Gallen CC, Bonura ML, et al. Effectiveness of the selective D4 antagonist sonepiprazole in schizophrenia: a placebo-controlled trial. *Biol Psychiatry*. 2004;55(5):445-51. PMID: 15023570.
EXCLUDE: Age.
124. Cote AT, Devlin AM, Panagiotopoulos C. Initial screening of children treated with second-generation antipsychotics points to an association between physical activity and insulin resistance. *Pediatr Exe Sci*. 2014;26(4):455-62. PMID: 103912834.
EXCLUDE: Study Design.
125. Court A, Mulder C, Kerr M, et al. Investigating the effectiveness, safety and tolerability of quetiapine in the treatment of anorexia nervosa in young people: a pilot study. *J Psychiatr Res*. 2010;44(15):1027-34. PMID: 20447652.
EXCLUDE: Age.
126. Covington L, Cola PA. Clozapine vs. Haloperidol: antipsychotic effects on sexual function in schizophrenia. *Sex Disabil*. 2000;18(1):41-8. PMID: N/A.
EXCLUDE: Age.
127. Crespo-Facorro B, Carrasco-Marin E, Perez-Iglesias R, et al. Interleukin-12 plasma levels in drug-naive patients with a first episode of psychosis: Effects of antipsychotic drugs. *Psychiatry Res*. 2008;158(2):206-16. PMID: 18243335.

EXCLUDE: Age.

128. Crespo-Facorro B, Perez-Iglesias R, Ramirez-Bonilla M, et al. A practical clinical trial comparing haloperidol, risperidone, and olanzapine for the acute treatment of first-episode nonaffective psychosis. *J Clin Psychiatry*. 2006;67(10):1511-21. PMID: 17107241.

EXCLUDE: Age.

129. Cressman AM, Macdonald EM, Huang A, et al. Prescription stimulant use and hospitalization for psychosis or mania: A population-based study. *J Clin Psychopharmacol*. 2015;35(6):667-71. PMID: 2015466252.

EXCLUDE: Intervention.

130. Cuesta MJ, Jalon EG, Campos MS, et al. Cognitive effectiveness of olanzapine and risperidone in first-episode psychosis. *Br J Psychiatry*. 2009;194(5):439-45. PMID: 19407274.

EXCLUDE: Age.

131. Curran MP. Aripiprazole in the treatment of irritability associated with autistic disorder in paediatric patients: profile report. *CNS Drugs*. 2011 Sep 1;25(9):801-2. PMID: 21870890.

EXCLUDE: Publication Type.

132. Curran MP. Aripiprazole: in the treatment of irritability associated with autistic disorder in pediatric patients. *Paediatr Drugs*. 2011;13(3):197-204. PMID: 21500873.

EXCLUDE: Publication Type.

133. Currier GW, Chou JC, Feifel D, et al. Acute treatment of psychotic agitation: a randomized comparison of oral treatment with risperidone and lorazepam versus intramuscular treatment with haloperidol and lorazepam. *J Clin Psychiatry*. 2004;65(3):386-94. PMID: 15096079.

EXCLUDE: Age.

134. Curtis J, Henry C, Watkins A, et al. Metabolic abnormalities in an early psychosis service: a retrospective, naturalistic cross-sectional study. *Early Interv Psychiatry*. 2011;5(2):108-14. PMID: 21470374.

EXCLUDE: Study Design.

135. Cutler AJ, Kalali AH, Weiden PJ, et al. Four-week, double-blind, placebo- and ziprasidone-controlled trial of iloperidone in patients with acute exacerbations of schizophrenia. *J Clin Psychopharmacol*. 2008;28(2 Suppl 1):S20-8. PMID: 18334909.

EXCLUDE: Age.

136. Czobor P, Volavka J, Meibach RC. Effect of risperidone on hostility in schizophrenia. *J Clin Psychopharmacol*. 1995;15(4):243-9. PMID: 7593706.

EXCLUDE: Age.

137. Daglas R, Cotton SM, Allott K, et al. A single-blind, randomised controlled trial on the effects of lithium and quetiapine monotherapy on the trajectory of cognitive functioning in first episode mania: A 12-month follow-up study. *Eur Psychiatr*. 2016;31:20-8. PMID: 26655594.

EXCLUDE: Intervention.

138. Daniel DG, Currier GW, Zimbroff DL, et al. Efficacy and safety of oral aripiprazole compared with haloperidol in patients transitioning from acute treatment with intramuscular formulations. *J Psychiatr Pract*. 2007;13(3):170-7. PMID: 17522560.

EXCLUDE: Age.

139. Daniel DG, Zimbroff DL, Potkin SG, et al. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. Ziprasidone Study Group.

Neuropsychopharmacology. 1999;20(5):491-505. PMID: 10192829.

EXCLUDE: Age.

140. Davidson M, Galderisi S, Weiser M, et al. Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: a randomized, open-label clinical trial (EUFEST). [Erratum appears in *Am J Psychiatry*. 2009 Jun;166(6):731]. *Am J Psychiatry*. 2009;166(6):675-82. PMID: 19369319.

EXCLUDE: Age.

141. de Haan L, van Amelsvoort T, Rosien K, et al. Weight loss after switching from conventional olanzapine tablets to orally disintegrating olanzapine tablets. *Psychopharmacology*. 2004;175(3):389-90. PMID: 15322727.

EXCLUDE: Age.

142. De Hert M, Schreurs V, Sweers K, et al. Typical and atypical antipsychotics differentially affect long-term incidence rates of the metabolic syndrome in first-episode patients with schizophrenia: a retrospective chart review. *Schizophr Res*. 2008;101(1-3):295-303. PMID: 18299188.

EXCLUDE: Age.

143. de Hoogd S, Overbeek WA, Heerdink ER, et al. Differences in body mass index z-scores and weight status in a Dutch pediatric psychiatric population with and without use of second-generation antipsychotics. *J Child Adolesc Psychopharmacol*. 2012;22(2):166-73. PMID: 22506734. EXCLUDE: Study Design.
144. Degrauw RS, Li JZ, Gilbert DL. Body mass index changes and chronic neuroleptic drug treatment for Tourette syndrome. *Pediatr Neurol*. 2009;41(3):183-190. PMID: 19664533. EXCLUDE: Intervention.
145. Delate T, Kauffman YS, Botts SR, et al. Metabolic monitoring in commercially insured pediatric patients newly initiated to take a second-generation antipsychotic. *JAMA Pediatr*. 2014;168(7):679-81. PMID: 24796974. EXCLUDE: Intervention.
146. DelBello M, Detke HC, Landry J, et al. Safety and efficacy of olanzapine/fluoxetine combination versus placebo in patients aged 10 to 17 in the acute treatment of major depressive episodes associated with bipolar I disorder. *Neuropsychopharmacology*. 2012;S99-s100. DOI: 10.1016/j.jaac.2014.12.012. EXCLUDE: Publication Type.
147. DelBello M, Versave M, Ice K, et al. An open-label study of ziprasidone in pediatric patients with bipolar disorder: safety, tolerability, efficacy, and functional outcomes. *Bipolar Disord*. 2006;27. <http://onlinelibrary.wiley.com/doi/10.1111/j.1530-0267.2006.00725.x>. EXCLUDE: Publication Type.
148. Detke HC, DelBello MP, Landry J, et al. Olanzapine/Fluoxetine combination in children and adolescents with bipolar I depression: a randomized, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2015;54(3):217-24. PMID: 25721187. EXCLUDE: Intervention.
149. Dion Y, Annable L, Sandor P, et al. Risperidone in the treatment of tourette syndrome: a double-blind, placebo-controlled trial. *J Clin Psychopharmacol*. 2002;22(1):31-9. PMID: 11799340. EXCLUDE: Age.
150. Dowling Bruun R. Subtle and underrecognized side effects of neuroleptic treatment in children with Tourette's disorder. *Am J Psychiatry*. 1988;145(5):621-4. PMID: 2895987. EXCLUDE: Publication Type.
151. Edelsohn GA, Parthasarathy M, Terhorst L, et al. Measurement of metabolic monitoring in youth and adult medicaid recipients prescribed antipsychotics. *J Manag Care Pharm*. 2015;21(9):769-77. PMID: 2015499690. EXCLUDE: Diagnosis.
152. Effects of quetiapine on adolescent conduct disorder. *Brown University Child & Adolescent Psychopharmacology Update*. 2008;10(7):3-4. PMID: 105796599. EXCLUDE: Publication Type.
153. Effects of risperidone on cognitive function in children with disruptive behaviors. *Brown University Child & Adolescent Psychopharmacology Update*. 2007;9(9):4-5. PMID: 105969211. EXCLUDE: Publication Type.
154. Elbe D, Barr AM, Honer WG, et al. Managing ADHD and disruptive behaviour disorders with combination psychostimulant and antipsychotic treatment. *J Psychiatry and Neurosci*. 2014;39(3):32-3. PMID: 24758945. EXCLUDE: Publication Type.
155. El-Missiry A, Elbatrawy A, El-Missiry M, et al. Comparing cognitive functions in medication adherent and non-adherent patients with schizophrenia. *J Psychiatric Res*. 2015;70:106-12. doi: PMID: 2015432869. EXCLUDE: Age.
156. Emsley RA. Risperidone in the treatment of first-episode psychotic patients: a double-blind multicenter study. *Risperidone Working Group. Schizophr Bull*. 1999;25(4):721-9. PMID: 10667742. EXCLUDE: Age.
157. Emsley RA, Raniwalla J, Bailey PJ, et al. A comparison of the effects of quetiapine ('seroquel') and haloperidol in schizophrenic patients with a history of and a demonstrated, partial response to conventional antipsychotic treatment. *PRIZE Study Group. Int Clin Psychopharmacol*. 2000;15(3):121-31. PMID: 10870870. EXCLUDE: Age.
158. Endicott J, Paulsson B, Gustafsson U, et al. Quetiapine monotherapy in the treatment of depressive episodes of bipolar I and II disorder: Improvements in quality of life and quality of sleep. *J Affect Disord*. 2008;111(2-3):306-19. PMID: 18774180. EXCLUDE: Age.

159. Endicott J, Rajagopalan K, Minkwitz M, et al. A randomized, double-blind, placebo-controlled study of quetiapine in the treatment of bipolar I and II depression: improvements in quality of life. *Int Clin Psychopharmacol.* 2007;22(1):29-37. PMID: 17159457. EXCLUDE: Age.
160. Ercan ES, Ardic UA, Ercan E, et al. A promising preliminary study of aripiprazole for treatment-resistant childhood obsessive-compulsive disorder. *J Child Adolesc Psychopharmacol.* 2015;25(7):580-4. PMID: 26375768. EXCLUDE: Intervention.
161. Erzegovesi S, Guglielmo E, Siliprandi F, et al. Low-dose risperidone augmentation of fluvoxamine treatment in obsessive-compulsive disorder: a double-blind, placebo-controlled study. *Eur Neuropsychopharmacol.* 2005;15(1):69-74. PMID: 15572275. EXCLUDE: Age.
162. Esbensen AJ, Greenberg JS, Seltzer MM, et al. A longitudinal investigation of psychotropic and non-psychotropic medication use among adolescents and adults with autism spectrum disorders. *J Autism Dev Disord.* 2009;39(9):1339-49. PMID: 19434487. EXCLUDE: Outcomes.
163. Fakra E, Khalfa S, Da Fonseca D, et al. Effect of risperidone versus haloperidol on emotional responding in schizophrenic patients. *Psychopharmacology.* 2008;200(2):261-72. PMID: 18575849. EXCLUDE: Age.
164. Farag M, Stern JS, Simmons H, et al. Serial pharmacological prescribing practices for tic management in Tourette syndrome. *Hum Psychopharmacology.* 2015;30(6):435-41. PMID: 2015333020. EXCLUDE: Age.
165. Farmer CA, Brown NV, Gadow KD, et al. Comorbid symptomatology moderates response to risperidone, stimulant, and parent training in children with severe aggression, disruptive behavior disorder, and attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol.* 2015;25(3):213-24. PMID: 25885011. EXCLUDE: Outcomes.
166. Faulkner MJ. Factors contributing to weight gain in children who take atypical antipsychotics: University of New Mexico; 2013.
- EXCLUDE: Publication Type.
167. Fava M, Wisniewski SR, Thase ME, et al. Metabolic assessment of aripiprazole as adjunctive therapy in major depressive disorder: a pooled analysis of 2 studies. *J Clin Psychopharmacol.* 2009;29(4):362-7. PMID: 19593176. EXCLUDE: Age.
168. Fedorenko OY, Loonen AJ, Lang F, et al. Association study indicates a protective role of phosphatidylinositol-4-phosphate-5-kinase against tardive dyskinesia. *Int J Neuropsychopharmacol.* 2015;18(6):PMID: 25548108. EXCLUDE: Age.
169. Fervaha G, Takeuchi H, Lee J, et al. Antipsychotics and amotivation. *Neuropsychopharmacology.* 2015;40(6):1539-48. PMID: 25567425. EXCLUDE: Age.
170. Findling R, Chiu YY, Silva R, et al. Pharmacokinetic and safety evaluation of lurasidone in pediatric patients with psychiatric disorders. *Schizophr Bull.* 2015;S31. EXCLUDE: Diagnosis.
171. Findling RL, Daneman D. Prolactin levels during long-term risperidone treatment in children and adolescents: A reanalysis of data. *J Clin Psychiatr.* 2016;77(2):e155-e70. PMID: 20160192775. EXCLUDE: Publication Type.
172. Findling R, DelBello M, Wang P, et al. Safety and efficacy of ziprasidone in pediatric bipolar disorder. *Eur Neuropsychopharmacol.* 2009;S682-s3. PMID: N/A. EXCLUDE: Publication Type.
173. Findling RL, Frazier JA, Gerbino-Rosen G, et al. Is there a role for clozapine in the treatment of children and adolescents? *J Am Acad Child Adolesc Psychiatry.* 2007;46(3):423-8. PMID: 17314729. EXCLUDE: Publication Type.
174. Findling RL, Pathak S, Earley WR, et al. Safety, tolerability, and efficacy of quetiapine in youth with schizophrenia or bipolar I disorder: a 26-week, open-label, continuation study. *J Child Adolesc Psychopharmacol.* 2013;23(7):490-501. PMID: 24024534. EXCLUDE: Study Design.
175. 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. PMID: 18765484. EXCLUDE: Duplicate.
176. 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. *J Affect Disord*. 2012;143(1-3):231-5. PMID: 23044285. EXCLUDE: Outcomes.
177. Fleischhacker WW, McQuade RD, Marcus RN, et al. A double-blind, randomized comparative study of aripiprazole and olanzapine in patients with schizophrenia. *Biol Psychiatry*. 2009;65(6):510-7. PMID: 18986646. EXCLUDE: Age.
178. Foley DL, Mackinnon A, Morgan VA, et al. Effect of age, family history of diabetes, and antipsychotic drug treatment on risk of diabetes in people with psychosis: a population-based cross-sectional study. *The Lancet. Psychiatry*. 2015;2(12):1092-8. PMID: 26477242. EXCLUDE: Age.
179. Fraguas D, Llorente C, Rapado-Castro M, et al. Attitude toward antipsychotic medication as a predictor of antipsychotic treatment discontinuation in first-episode early-onset psychosis. *Rev Psiquiatr Salud Ment*. 2008;1(1):10-7. PMID: 23040428. EXCLUDE: Outcomes.
180. Frazier JA, Giuliano AJ, Johnson JL, et al. Neurocognitive outcomes in the treatment of early-onset schizophrenia spectrum disorders study. *J Am Acad Child Adolesc Psychiatry*. 2012;51(5):496-505. PMID: 22525956. EXCLUDE: Intervention.
181. Frazier TW, Youngstrom EA, Haycook T, et al. Effectiveness of medication combined with intensive behavioral intervention for reducing aggression in youth with autism spectrum disorder. *J Child Adolesc Psychopharmacol*. 2010;20(3):167-77. PMID: 20578929. EXCLUDE: Intervention.
182. Fusar-Poli P, Frascarelli M, Valmaggia L, et al. Antidepressant, antipsychotic and psychological interventions in subjects at high clinical risk for psychosis: OASIS 6-year naturalistic study. *Psychol Med*. 2015;45(6):1327-39. PMID: 25335776. EXCLUDE: Age.
183. Gaebel W, Moller HJ, Buchkremer G, et al. Pharmacological long-term treatment strategies in first episode schizophrenia--study design and preliminary results of an ongoing RCT within the German Research Network on Schizophrenia. *Eur Arch Psychiatry Clin Neurosci*. 2004;254(2):129-40. PMID: 15146342. EXCLUDE: Age.
184. Gagiano C, Read S, Thorpe L, et al. Short- and long-term efficacy and safety of risperidone in adults with disruptive behavior disorders. *Psychopharmacology*. 2005;179(3):629-36. PMID: 15668818. EXCLUDE: Age.
185. Gallego JA, Robinson DG, Sevy SM, et al. Time to treatment response in first-episode schizophrenia: should acute treatment trials last several months? *J Clin Psychiatry*. 2011;72(12):1691-6. PMID: 21939612. EXCLUDE: Age.
186. Galler A, Bollow E, Meusers M, et al. Comparison of glycemic and metabolic control in youth with type 1 diabetes with and without antipsychotic medication: analysis from the nationwide German/Austrian Diabetes Survey (DPV). *Diabetes Care*. 2015;38(6):1051-7. PMID: 25784664. EXCLUDE: Intervention.
187. Garakani A, Martinez JM, Marcus S, et al. A randomized, double-blind, and placebo-controlled trial of quetiapine augmentation of fluoxetine in major depressive disorder. *Int Clin Psychopharmacol*. 2008;23(5):269-75. PMID: 18703936. EXCLUDE: Age.
188. Gardner DM, Abidi S, Ursuliak Z, et al. Incidence of oculogyri crisis and long-term outcomes with second-generation antipsychotics in a first-episode psychosis program. *J Clin Psychopharmacol*. 2015;35(6):715-8. PMID: 2015466234. EXCLUDE: Age.
189. Gearing RE, Charach A. Medication adherence for children and adolescents with first-episode psychosis following hospitalization. *Eur Child Adolesc Psychiatry*. 2009;18(10):587-95. PMID: 19381709. EXCLUDE: Intervention.
190. Geddes JR, Gardiner A, Rendell J, et al. Comparative evaluation of quetiapine plus lamotrigine combination versus quetiapine monotherapy (and folic acid versus placebo) in bipolar depression (CEQUEL): A 2 x 2 factorial randomised trial.

- Lancet Psychiatry. 2016;3(1):31-9. PMID: 20151042200.
EXCLUDE: Age.
191. Ghaziuddin N, Merchant C, Dopp R, et al. A naturalistic study of suicidal adolescents treated with an SSRI: Suicidal ideation and behavior during 3-month post-hospitalization period. *Asian J Psychiatry*. 2014;11:13-9. PMID: 2014724645.
EXCLUDE: Intervention.
192. Gitlin M, Nuechterlein K, Subotnik KL, et al. Clinical outcome following neuroleptic discontinuation in patients with remitted recent-onset schizophrenia. *Am J Psychiatry*. 2001;158(11):1835-42. PMID: 11691689.
EXCLUDE: Age.
193. Godleski LS, Goldsmith LJ, Vieweg WV, et al. Switching from depot antipsychotic drugs to olanzapine in patients with chronic schizophrenia. *J Clin Psychiatry*. 2003;64(2):119-22. PMID: 12633119.
EXCLUDE: Age.
194. Gomez JC, Sacristan JA, Hernandez J, et al. The safety of olanzapine compared with other antipsychotic drugs: results of an observational prospective study in patients with schizophrenia (EFESO Study). *Pharmacoepidemiologic Study of Olanzapine in Schizophrenia. J Clin Psychiatry*. 2000;61(5):335-43. PMID: 10847307.
EXCLUDE: Age.
195. Gonzalez-Heydrich J, Raches D, Wilens TE, et al. Retrospective study of hepatic enzyme elevations in children treated with olanzapine, divalproex, and their combination. *J Am Acad Child Adolesc Psychiatry*. 2003;42(10):1227-33. PMID: 14560173.
EXCLUDE: Study Design.
196. Green AI, Lieberman JA, Hamer RM, et al. Olanzapine and haloperidol in first episode psychosis: two-year data. *Schizophr Res*. 2006;86(1-3):234-43. PMID: 16887334.
EXCLUDE: Age.
197. Green AI, Tohen MF, Hamer RM, et al. First episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol. *Schizophr Res*. 2004;66(2-3):125-35. PMID: 15061244.
EXCLUDE: Age.
198. Goldberg PH, Martin P, Biernacki C, et al. Treatments for pediatric bipolar disorder. Nathan, Peter E [Ed]. 2015. Exclude: Publication Type.
199. Goldstein ME, Anderson VM, Pillai A, et al. Glutamatergic neurometabolites in clozapine-responsive and -resistant schizophrenia. *Int J Neuropsychopharmacol*. 2015;18(6) PMID: 25603859.
EXCLUDE: Age.
200. Gonzalez-Rodriguez A, Studerus E, Spitz A, et al. Gender differences in the psychopathology of emerging psychosis. *Isr J Psychiatry Relat Sci*. 2014;51(2):85-92. PMID: 25372557.
EXCLUDE: Age.
201. Green WH, Padron-Gayol M, Hardesty AS, et al. Schizophrenia with childhood onset: a phenomenological study of 38 cases. *J Am Acad Child Adolesc Psychiatry*. 1992;31(5):968-76. PMID: 1400132.
EXCLUDE: Outcomes.
202. Greenhill LL, Halperin JM, Barmack J. Cognitive effects of neuroleptic treatment in children with conduct disorder. Richardson, Mary Ann [Ed]. 1996.
EXCLUDE: Publication Type.
203. Guler AS, Yazgan Y, Pelin AU. Dikkat eksikligi hiperaktivite bozuklugu olan cocuklarda otizm spektrumuna ozgu ozellikler ve risperidon kullanim kararini belirleyen faktorler. [Autistic traits and factors related to a clinical decision to use risperidone in children with attention deficit hyperactivity disorder]. *Bull Clin Psychopharmacol*. 2014;24(4):333-41. DOI: <http://dx.doi.org/10.5455/bcp.20140616123454>. PMID: N/A.
EXCLUDE: Study Design.
204. Gunther T, Herpertz-Dahlmann B, Jolles J, et al. The influence of risperidone on attentional functions in children and adolescents with attention-deficit/hyperactivity disorder and co-morbid disruptive behavior disorder. *J Child Adolesc Psychopharmacol*. 2006;16(6):725-35. PMID: 17201616.
EXCLUDE: Intervention.
205. Gurpegui M, Alvarez E, Bousoño M, et al. Effect of olanzapine or risperidone treatment on some cognitive functions in a one-year follow-up of schizophrenia outpatients with prominent negative symptoms. *Eur Neuropsychopharmacol*. 2007;17(11):725-34. PMID: 17543505.
EXCLUDE: Age.

206. Haas M, Eerdeken M, Kushner S, et al. Efficacy, safety and tolerability of two dosing regimens in adolescent schizophrenia: double-blind study. *Br J Psychiatry*. 2009;194(2):158-64. PMID: 19182179. EXCLUDE: Duplicate.
207. Haas M, Unis AS, Armenteros J, et al. A 6-week, randomized, double-blind, placebo-controlled study of the efficacy and safety of risperidone in adolescents with schizophrenia. *J Child Adolesc Psychopharmacol*. 2009;19(6):611-21. PMID: 20035579. EXCLUDE: Duplicate.
208. Habibi N, Dodangi N, Nazeri A. Efficacy and Safety of Aripiprazole for Treatment of Irritability in Children with Autistic Disorder: An Open-Label Study. *Iran J Med Sci*. 2015;40(6):548-9 2p. PMID: 110966669. EXCLUDE: Publication Type.
209. Hamilton SH, Revicki DA, Genduso LA, et al. Olanzapine versus placebo and haloperidol: quality of life and efficacy results of the North American double-blind trial. *Neuropsychopharmacology*. 1998;18(1):41-9. PMID: 9408917. EXCLUDE: Age.
210. Haro JM, Novick D, Suarez D, et al. Antipsychotic treatment discontinuation in previously untreated patients with schizophrenia: 36-month results from the SOHO study. *J Psychiatr Res*. 2009;43(3):265-73. PMID: 18644606. EXCLUDE: Age.
211. Harrigan EP, Miceli JJ, Anziano R, et al. A randomized evaluation of the effects of six antipsychotic agents on QTC, in the absence and presence of metabolic inhibition. *J Clin Psychopharmacol*. 2004;24(1):62-9. PMID: 14709949. EXCLUDE: Age.
212. Harvey PD, Green MF, McGurk SR, et al. Changes in cognitive functioning with risperidone and olanzapine treatment: a large-scale, double-blind, randomized study. *Psychopharmacology*. 2003;169(3-4):404-11. PMID: 12590356. EXCLUDE: Age.
213. Harvey PD, Patterson TL, Potter LS, et al. Improvement in social competence with short-term atypical antipsychotic treatment: a randomized, double-blind comparison of quetiapine versus risperidone for social competence, social cognition, and neuropsychological functioning. *Am J Psychiatry*. 2006;163(11):1918-25. PMID: 17074943. EXCLUDE: Age.
214. Hassan M, Madhavan SS, Kalsekar ID, et al. Comparing adherence to and persistence with antipsychotic therapy among patients with bipolar disorder. *Ann Pharmacother*. 2007;41(11):1812-8. PMID: 17925501. EXCLUDE: Age.
215. Hayes RD, Downs J, Chang CK, et al. The effect of clozapine on premature mortality: an assessment of clinical monitoring and other potential confounders. *Schizophr Bull*. 2015;41(3):644-55. PMID: 25154620. EXCLUDE: Age.
216. Heresco-Levy U, Greenberg D, Lerer B, et al. Trial of maintenance neuroleptic dose reduction in schizophrenic outpatients: two-year outcome. *J Clin Psychiatry*. 1993;54(2):59-62. PMID: 8095259. EXCLUDE: Age.
217. Hellings JA, Jadhav M, Jain S, et al. Low Dose Loxapine: Neuromotor Side Effects and Tolerability in Autism Spectrum Disorders. *J Child Adolesc Psychopharmacol*. 2015;25(8):618-24. PMID: 2015481269. EXCLUDE: Intervention.
218. Hoekstra PJ, Troost PW, Lahuis BE, et al. Risperidone-induced weight gain in referred children with autism spectrum disorders is associated with a common polymorphism in the 5-hydroxytryptamine 2C receptor gene. *J Child Adolesc Psychopharmacol*. 2010;20(6):473-7. PMID: 21186965. EXCLUDE: Study Design.
219. Honer WG, Kopala LC, Rabinowitz J. Extrapyramidal symptoms and signs in first-episode, antipsychotic exposed and non-exposed patients with schizophrenia or related psychotic illness. *J Psychopharmacol*. 2005;19(3):277-85. PMID: 15888513. EXCLUDE: Age.
220. Hong IS, Bishop JR. Anticholinergic use in children and adolescents after initiation of antipsychotic therapy. *Ann Pharmacother*. 2010;44(7-8):1171-80. PMID: 20587746. EXCLUDE: Outcomes.
221. Hongkaew Y, Ngamsamut N, Puangpetch A, et al. Hyperprolactinemia in Thai children and adolescents with autism spectrum disorder treated with

- risperidone. *Neuropsychiatr Dis Treat*. 2015;11:191-6. PMID: 25653528.
EXCLUDE: Study Design.
- 222.Howland RH. Use of atypical antipsychotics in children and adolescents. *J Psychosoc Nurs Ment Health Serv*. 2005;43(8):15-8. PMID: 16149723.
EXCLUDE: Publication Type.
- 223.Huang YS, Yeh CB, Tang CS, et al. Effectiveness of aripiprazole in adolescents and young adults with schizophrenia spectrum disorders: comparison of first-episode to recurrent psychosis. *Early Interv Psychiatry*. 2013;7(1):89-93. PMID: 22816371.
EXCLUDE: Study Design.
- 224.Hughenoltz GW, Heerdink ER, Meijer WE, et al. Reasons for switching between antipsychotics in daily clinical practice. *Pharmacopsychiatry*. 2005;38(3):122-4. PMID: 15902582.
EXCLUDE: Age.
- 225.Hughenoltz GW, Heerdink ER, Nolen WA, et al. Less medication switching after initial start with atypical antipsychotics. *Eur Neuropsychopharmacol*. 2004;14(1):1-5. PMID: 14659981.
EXCLUDE: Age.
- 226.Huq ZU, Investigators R-G. A trial of low doses of risperidone in the treatment of patients with first-episode schizophrenia, schizophreniform disorder, or schizoaffective disorder. *J Clin Psychopharmacol*. 2004;24(2):220-4. PMID: 15206670.
EXCLUDE: Age.
- 227.Ingole S, Belorkar NR, Waradkar P, et al. Comparison of effects of olanzapine and risperidone on body mass index and blood sugar level in schizophrenic patients. *Indian J Physiol Pharmacol*. 2009;53(1):47-54. PMID: 19810576.
EXCLUDE: Age.
- 228.Iqbal E, Mallah R, Jackson RG, et al. Identification of adverse drug events from free text electronic patient records and information in a large mental health case register. *PLoS ONE [Electronic Resource]*. 2015;10 (8) (no pagination)(e0134208)
EXCLUDE: Intervention.
- 229.Jain S, Andridge R, Hellings JA. Loxapine for reversal of antipsychotic-induced metabolic disturbances: A chart review. *J Autism Dev Disord*. 2016;46(4):1344-53. doi: <http://dx.doi.org/10.1007/s10803-015-2675-3>.
EXCLUDE: Intervention.
- 230.Jakubovski E, Carlson JP, Bloch MH. Prognostic subgroups for remission, response, and treatment continuation in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial. *J Clin Psychiatr*. 2015;76(11):1535-45. PMID: 26581028.
EXCLUDE: Age.
- 231.Jalota R, Bond C, Jose RJ. Quetiapine and the development of the metabolic syndrome. *QJM*. 2015;108(3):245-7. PMID: 22908317.
EXCLUDE: Study Design.
- 232.Jarskog LF, Lowy MT, Grove RA, et al. A Phase II study of a histamine H3 receptor antagonist GSK239512 for cognitive impairment in stable schizophrenia subjects on antipsychotic therapy. *Schizophr Res*. 2015;164(1-3):136-42. PMID: 25728831.
EXCLUDE: Age.
- 233.Jaselskis CA, Cook EH, Jr., Fletcher KE, et al. Clonidine treatment of hyperactive and impulsive children with autistic disorder. *J Clin Psychopharmacol*. 1992;12(5):322-7. PMID: 1479049.
EXCLUDE: Intervention.
- 234.Jefferson AM, Markowitz JS, Brewerton TD. Atypical antipsychotics. *J Am Acad Child Adolesc Psychiatry*. 1998;37(12):1243-4.
EXCLUDE: Publication Type.
- 235.Jerrell JM. Pharmacotherapy in the community-based treatment of children with bipolar I disorder. *Hum Psychopharmacol*. 2008;23(1):53-9. PMID: 17957821.
EXCLUDE: Intervention.
- 236.Jerrell JM. Neurological and cardiovascular adverse events associated with antimanic treatment in children and adolescents. *CNS Neurosci Ther*. 2010;16(1):25-31. PMID: 19769597.
EXCLUDE: Intervention.
- 237.Jerrell JM, Tripathi A, Rizvi AA, et al. The risk of developing type 2 diabetes mellitus associated with psychotropic drug use in children and adolescents: a retrospective cohort analysis. *Prim Care Companion CNS Disord*. 2012;14(1). PMID: 22690363.
EXCLUDE: Study Design.
- 238.Jiao F, Zhang X, Wang J. Clinical observation on treatment of Tourette syndrome in Chinese children by clonidine adhesive patch. *Eur J Paediatr Neurology*. 2016;20(1):80-4. PMID: 26602699.
EXCLUDE: Intervention.

239. Jing Y. Health outcomes assessment for children and adolescents with bipolar disorder treated with and without atypical antipsychotics [Ph.D.]. Ann Arbor: University of Cincinnati; 2009.
EXCLUDE: Unable to Retrieve.
240. Jones PB, Barnes TR, Davies L, et al. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Arch Gen Psychiatry*. 2006;63(10):1079-87. PMID: 17015810.
EXCLUDE: Age.
241. Joshi G, Biederman J, Wozniak J, et al. Response to second generation antipsychotics in youth with comorbid bipolar disorder and autism spectrum disorder. *CNS Neurosci Ther*. 2012;18(1):28-33.. PMID: 21114638.
EXCLUDE: Intervention.
242. Joshi G, Mick E, Wozniak J, et al. Impact of obsessive-compulsive disorder on the antimanic response to olanzapine therapy in youth with bipolar disorder. *Bipolar Disord*. 2010;12(2):196-204. PMID: 20402712.
EXCLUDE: Study Design.
243. Joshi G, Petty C, Wozniak J, et al. A prospective open-label trial of quetiapine monotherapy in preschool and school age children with bipolar spectrum disorder. *J Affect Disord*. 2012;136(3):1143-53. PMID: 22035648.
EXCLUDE: Study Design.
244. Joshi G, Petty C, Wozniak J, et al. A prospective open-label trial of paliperidone monotherapy for the treatment of bipolar spectrum disorders in children and adolescents. *Psychopharmacology*. 2013;227(3):449-58. PMID: 23397049.
EXCLUDE: Intervention.
245. Joshi PT, Hamel L, Joshi AR, et al. Use of droperidol in hospitalized children. *J Am Acad Child Adolesc Psychiatry*. 1998;37(2):228-30. PMID: 9473921.
EXCLUDE: Study Design.
246. Joyce C, Witcher R, Herrup E, et al. Evaluation of the Safety of Quetiapine in Treating Delirium in Critically Ill Children: A Retrospective Review. *J Child & Adolesc Psychopharmacol*. 2015;25(9):666-70. PMID: 26469214.
EXCLUDE: Diagnosis.
247. Juven-Wetzler A, Fostick L, Cwikel-Hamzany S, et al. Treatment with Ziprasidone for schizophrenia patients with OCD. *Eur Neuropsychopharmacol*. 2014;24(9):1454-62. PMID: 25048540.
EXCLUDE: Age.
248. Kahn RS, Fleischhacker WW, Boter H, et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet*. 2008;371(9618):1085-97. PMID: 18374841.
EXCLUDE: Age.
249. Kalkan Ucar S, Ozbaran B, Demiral N, et al. Clinical overview of children with mucopolysaccharidosis type III A and effect of Risperidone treatment on children and their mothers psychological status. *Brain Dev*. 2010;32(2):156-61. PMID: 19217229.
EXCLUDE: Diagnosis.
250. Kampman KM, Pettinati H, Lynch KG, et al. A pilot trial of olanzapine for the treatment of cocaine dependence. *Drug Alcohol Depend*. 2003;70(3):265-73. PMID: 12757964.
EXCLUDE: Age.
251. Kane JM, Detke HC, Naber D, et al. Olanzapine long-acting injection: a 24-week, randomized, double-blind trial of maintenance treatment in patients with schizophrenia. *Am J Psychiatry*. 2010;167(2):181-9. PMID: 20008947.
EXCLUDE: Age.
252. Kane JM, Eerdeken M, Lindenmayer JP, et al. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. *Am J Psychiatry*. 2003;160(6):1125-32. PMID: 12777271.
EXCLUDE: Age.
253. Kane JM, Skuban A, Ouyang J, et al. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. *Schizophr Res*. 2015;164(1-3):127-35. PMID: 25682550.
EXCLUDE: Age.
254. Kapur S, Arenovich T, Agid O, et al. Evidence for onset of antipsychotic effects within the first 24 hours of treatment. *Am J Psychiatry*. 2005;162(5):939-46. PMID: 15863796.
EXCLUDE: Age.
255. Karagianis J, Grossman L, Landry J, et al. A randomized controlled trial of the effect of sublingual orally disintegrating olanzapine versus oral

- olanzapine on body mass index: the PLATYPUS Study.[Erratum appears in Schizophr Res. 2011;133(1-3):266]. Schizophr Res. 2009;113(1):41-8. PMID: 19535229.
EXCLUDE: Age.
- 256.Karaman MG, Ozdemir E, Yurteri N, et al. Risperidone and serum lipid profile changes in child and adolescent patients. Neurol Psychiatry Brain Res. 2011;17(1):16-20. PMID: N/A
EXCLUDE: Study Design.
- 257.Kass E, Posner JE, Greenhill LL. Pharmacological treatments for attention-deficit/hyperactivity disorder and disruptive behavior disorders. Nathan, Peter E [Ed]. 2015.
EXCLUDE: Publication Type.
- 258.Kaster TS, de Jesus D, Radhu N, et al. Clozapine potentiation of GABA mediated cortical inhibition in treatment resistant schizophrenia. Schizophr Res. 2015;165(2-3):157-62. PMID: 25957485.
EXCLUDE: Age.
- 259.Kaur H, Jajodia A, Grover S, et al. Genetic variations of PIP4K2A confer vulnerability to poor antipsychotic response in severely ill schizophrenia patients. 2014;9(7):e102556. PMID: 25025909.
EXCLUDE: Age.
- 260.Keck P, Jr., Buffenstein A, Ferguson J, et al. Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. Psychopharmacology. 1998;140(2):173-84. PMID: 9860108.
EXCLUDE: Age.
- 261.Keck PE, Orsulak PJ, Cutler AJ, et al. Aripiprazole monotherapy in the treatment of acute bipolar I mania: a randomized, double-blind, placebo- and lithium-controlled study. J Affect Disord. 2009;112(1-3):36-49. PMID: 18835043.
EXCLUDE: Age.
- 262.Keck PE, Jr., Reeves KR, Harrigan EP, et al. Ziprasidone in the short-term treatment of patients with schizoaffective disorder: results from two double-blind, placebo-controlled, multicenter studies. J Clin Psychopharmacol. 2001;21(1):27-35. PMID: 11199944.
EXCLUDE: Age.
- 263.Keefe RS, Seidman LJ, Christensen BK, et al. Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. Am J Psychiatry. 2004;161(6):985-95.PMID: 15169686.
EXCLUDE: Age
- 264.Keefe RSE. The longitudinal course of cognitive impairment in schizophrenia: An examination of data from premorbid through posttreatment phases of illness. J Clin Psychiatr. 2014;75(Suppl 2):8-13.
EXCLUDE: Publication Type.
- 265.Keefe RS, Young CA, Rock SL, et al. One-year double-blind study of the neurocognitive efficacy of olanzapine, risperidone, and haloperidol in schizophrenia. Schizophr Res. 2006;81(1):1-15. PMID: 16202565.
EXCLUDE: Age.
- 266.Keefe RSE. The longitudinal course of cognitive impairment in schizophrenia: An examination of data from premorbid through posttreatment phases of illness. J Clin Psychiatr. 2014;75(Suppl 2):8-13. doi: <http://dx.doi.org/10.4088/JCP.13065su1.02>.
EXCLUDE: Publication Type.
- 267.Keinanen J, Mantere O, Kieseppa T, et al. Early insulin resistance predicts weight gain and waist circumference increase in first-episode psychosis--A one year follow-up study. Schizophr Res. 2015;169(1-3):458-63. PMID: 26589392.
EXCLUDE: Age.
- 268.Kelly AC, Sheitman BB, Hamer RM, et al. A naturalistic comparison of the long-term metabolic adverse effects of clozapine versus other antipsychotics for patients with psychotic illnesses. J Clin Psychopharmacol. 2014;34(4):441-5. PMID: 24943389.
EXCLUDE: Age.
- 269.Kelly DL, Conley RR, Love RC, et al. Weight gain in adolescents treated with risperidone and conventional antipsychotics over six months. J Child Adolesc Psychopharmacol. 1998;8(3):151-9. PMID: 9853689.
EXCLUDE: Diagnosis.
- 270.Kelly DL, Love RC, MacKowick M, et al. Atypical antipsychotic use in a state hospital inpatient adolescent population. J Child Adolesc Psychopharmacol. 2004;14(1):75-85. PMID: 15142394.
EXCLUDE: Study Design.
- 271.Kemp DE, Correll CU, Tohen M, et al. Associations among obesity, acute weight gain, and response to treatment with olanzapine in adolescent

- schizophrenia. *J Child Adolesc Psychopharmacol*. 2013;23(8):522-30. PMID: 24111982.
EXCLUDE: Outcomes.
272. Kent JM, Hough D, Singh J, et al. An open-label extension study of the safety and efficacy of risperidone in children and adolescents with autistic disorder. *J Child Adolesc Psychopharmacol*. 2013;23(10):676-86. PMID: 24350813.
EXCLUDE: Study Design.
273. Kerwin R, Millet B, Herman E, et al. A multicentre, randomized, naturalistic, open-label study between aripiprazole and standard of care in the management of community-treated schizophrenic patients Schizophrenia Trial of Aripiprazole: (STAR) study. *Eur Psychiatry*. 2007;22(7):433-43. PMID: 17555947.
EXCLUDE: Age.
274. Kessing LV, Hansen HV, Christensen EM, et al. Do young adults with bipolar disorder benefit from early intervention? *J Affect Disord*. 2014;152-154:403-8. PMID: 24268595.
EXCLUDE: Intervention.
275. Ketter TA, Jones M, Paulsson B. Rates of remission/euthymia with quetiapine monotherapy compared with placebo in patients with acute mania. *J Affect Disord*. 2007;100 Suppl 1:S45-53. PMID: 17383011.
EXCLUDE: Age
276. Khamker N. First episode schizophrenia. *SAFP*. 2015;57(5):29-33. PMID: 2015520958.
EXCLUDE: Publication Type.
277. Khanna S, Rosen J, Blevins D, et al. Psychosis and catatonia after dancing with a dangerous partner. *Current Psychiatry*. 2015;14(11):58-63. PMID: 20160122672.
EXCLUDE: Publication Type.
278. Khodaie-Ardakani MR, Khosravi M, Zarinpard R, et al. A Placebo-Controlled Study of Raloxifene Added to Risperidone in Men with Chronic Schizophrenia. *Acta Med Irani*. 2015;53(6):337-45. PMID: 26069170.
EXCLUDE: Age.
279. Kilian R, Dietrich S, Toumi M, et al. Quality of life in persons with schizophrenia in out-patient treatment with first- or second-generation antipsychotics. *Acta Psychiatr Scand*. 2004;110(2):108-18. PMID: 15233711.
EXCLUDE: Age.
280. Kim JH, Kim D, Marder SR. Time to rehospitalization of clozapine versus risperidone in the naturalistic treatment of comorbid alcohol use disorder and schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32(4):984-8. PMID: 18262321.
EXCLUDE: Age.
281. King DJ, Link CG, Kowalczyk B. A comparison of bid and tid dose regimens of quetiapine (Seroquel) in the treatment of schizophrenia. *Psychopharmacology*. 1998;137(2):139-46. PMID: 9630000.
EXCLUDE: Age.
282. Kinon BJ, Kane JM, Johns C, et al. Treatment of neuroleptic-resistant schizophrenic relapse. *Psychopharmacol Bull*. 1993;29(2):309-14. PMID: 7904762.
EXCLUDE: Age.
283. Kinon BJ, Stauffer VL, Kollack-Walker S, et al. Olanzapine versus aripiprazole for the treatment of agitation in acutely ill patients with schizophrenia. *J Clin Psychopharmacol*. 2008;28(6):601-7. PMID: 19011427.
EXCLUDE: Age.
284. Kinon BJ, Volavka J, Stauffer V, et al. Standard and higher dose of olanzapine in patients with schizophrenia or schizoaffective disorder: a randomized, double-blind, fixed-dose study. *J Clin Psychopharmacol*. 2008;28(4):392-400. PMID: 18626265.
EXCLUDE: Age.
285. Klein RG. Thioridazine effects on the cognitive performance of children with attention-deficit hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 1990;1(4):1990-1.
EXCLUDE: Language.
286. Kluge M, Schuld A, Himmerich H, et al. Clozapine and olanzapine are associated with food craving and binge eating: results from a randomized double-blind study. *J Clin Psychopharmacol*. 2007;27(6):662-6. PMID: 18004133.
EXCLUDE: Age.
287. Knegtering R, Castelein S, Bous H, et al. A randomized open-label study of the impact of quetiapine versus risperidone on sexual functioning. *J Clin Psychopharmacol*. 2004;24(1):56-61. PMID: 14709948.
EXCLUDE: Age.

288. Kompoliti K, Stebbins GT, Goetz CG, et al. Association between antipsychotics and body mass index when treating patients with tics. *J Child Adolesc Psychopharmacol.* 2010;20(4):277-81. PMID: 20807065. EXCLUDE: Age.
289. Kopala LC, Good KP, Honer WG. Extrapyramidal signs and clinical symptoms in first-episode schizophrenia: response to low-dose risperidone. *J Clin Psychopharmacol.* 1997;17(4):308-13. PMID: 9241011. EXCLUDE: Age.
290. Kordon A, Wahl K, Koch N, et al. Quetiapine addition to serotonin reuptake inhibitors in patients with severe obsessive-compulsive disorder: a double-blind, randomized, placebo-controlled study. *J Clin Psychopharmacol.* 2008;28(5):550-4. PMID: 18794652. EXCLUDE: Age.
291. Kowatch RA, Sethuraman G, Hume JH, et al. Combination pharmacotherapy in children and adolescents with bipolar disorder. *Biol Psychiatry.* 2003;53(11):978-84. PMID: 12788243. EXCLUDE: Intervention.
292. Krakowski M, Czobor P, Citrome L. Weight gain, metabolic parameters, and the impact of race in aggressive inpatients randomized to double-blind clozapine, olanzapine or haloperidol. *Schizophr Res.* 2009;110(1-3):95-102. PMID: 19269139. EXCLUDE: Age.
293. Kraus JE, Sheitman BB, Cook A, et al. Olanzapine versus risperidone in newly admitted acutely ill psychotic patients. *J Clin Psychiatry.* 2005;66(12):1564-8. PMID: 16401158. EXCLUDE: Age.
294. Kristensen D, Hageman I, Bauer J, et al. Antipsychotic polypharmacy in a treatment-refractory schizophrenia population receiving adjunctive treatment with electroconvulsive therapy. *J ECT.* 2013;29(4):271-6. PMID: 23859980. EXCLUDE: Study Design.
295. Kryzhanovskaya LA, Robertson-Plouch CK, Xu W, et al. The safety of olanzapine in adolescents with schizophrenia or bipolar I disorder: a pooled analysis of 4 clinical trials. [Erratum appears in *J Clin Psychiatry* 2009;70(12):1729]. *J Clin Psychiatry.* 2009;70(2):247-58. DOI: 10.4088/JCP.08m03538 PMID: 19210948. EXCLUDE: Publication Type.
296. Kubik P. New indication: Asenapine for pediatric bipolar. *Curr Psychiatr.* 2015;14(8):60-1. PMID: NA. EXCLUDE: Publication Type.
297. Kumar SR, Sinha VK, Tikka SK, et al. Gamma activity model for treatment-resistant bipolar psychotic mania. *Indian J Pharmacol.* 2015;47(2):215-8. PMID: 25878386. EXCLUDE: Age.
298. Kumari V, Ettinger U, Lee SE, et al. Common and distinct neural effects of risperidone and olanzapine during procedural learning in schizophrenia: a randomised longitudinal fMRI study. *Psychopharmacology.* 2015;232(17):3135-47. PMID: 25980483. EXCLUDE: Age.
299. Kumra S, Frazier JA, Jacobsen LK, et al. Childhood-onset schizophrenia: A double-blind clozapine-haloperidol comparison. Hertzog, Margaret E [Ed]. 1998. EXCLUDE: Publication Type.
300. Kumra S, Jacobsen LK, Rapoport JL. Childhood-Onset Schizophrenia - A Double-Blind Clozapine Trial (DUP). 149th Annual Meeting of the American Psychiatric Association. New York, New York, USA. 4-9th May, 1996. <http://onlinelibrary.wiley.com/doi/10.1002/9781118154211.ch348>. EXCLUDE: Publication Type.
301. Kuperman S, Calarge C, Kolar A, et al. An open-label trial of aripiprazole in the treatment of aggression in male adolescents diagnosed with conduct disorder. *Ann Clin Psychiatry.* 2011;23(4):270-6. PMID: 22073384. EXCLUDE: Study Design.
302. Lage MJ, Hassan MK. The relationship between antipsychotic medication adherence and patient outcomes among individuals diagnosed with bipolar disorder: a retrospective study. *Ann Gen Psychiatry.* 2009;8:9. PMID: 105380351. EXCLUDE: Age.
303. Lambert M, Conus P, Schimmelmann BG, et al. Comparison of olanzapine and risperidone in 367 first-episode patients with non-affective or affective psychosis: results of an open retrospective medical record study. *Pharmacopsychiatry.* 2005;38(5):206-13. PMID: 16189747. EXCLUDE: Age.

- 304.Lasich A. Attention deficit hyperactivity disorder and co-morbidity: a clinic study. *South Afr J Child Adolesc Psychiatry*. 1992;4(1):8-12. DOI: <http://dx.doi.org/10.1080/16826108.1992.9631475>. PMID: N/A
EXCLUDE: Publication Type.
- 305.Lahon K, Shetty HM, Paramel A, et al. Adverse drug reaction monitoring of antipsychotics, antidepressants and mood stabilizers in the psychiatric outpatient unit of a teaching hospital - A retrospective study. *Int J Pharma and Bio Sci*. 2012;3(1):P470-P8. PMID: 2014902008.
EXCLUDE: Age.
- 306.Lauriello J, Lambert T, Andersen S, et al. An 8-week, double-blind, randomized, placebo-controlled study of olanzapine long-acting injection in acutely ill patients with schizophrenia.[Erratum appears in *J Clin Psychiatry*. 2011 Aug;72(8):1157]. *J Clin Psychiatry*. 2008;69(5):790-9. PMID: 18452346.
EXCLUDE: Age.
- 307.Lauriello J, McEvoy JP, Rodriguez S, et al. Long-acting risperidone vs. placebo in the treatment of hospital inpatients with schizophrenia. *Schizophr Res* 2005 1;72(2-3):249-58. PMID: 15560969.
EXCLUDE: Age.
- 308.Latoo J, Omodunbi O, Hindley D, et al. Physical health of people with severe mental illness: Don't just screen... intervene! *British Journal of Medical Practitioners*. 2015;8 (3) (no pagination)(a821) PMID: 2015441730.
EXCLUDE: Intervention.
- 309.LeBlanc JC, Binder CE, Armenteros JL, et al. Risperidone reduces aggression in boys with a disruptive behaviour disorder and below average intelligence quotient: analysis of two placebo-controlled randomized trials. *Int Clin Psychopharmacol*. 2005;20(5):275-83. PMID: 16096518.
EXCLUDE: Outcomes.
- 310.Lee BH, Hong JP, Hwang JA, et al. Alterations in plasma vascular endothelial growth factor levels in patients with schizophrenia before and after treatment. *Psychiatr Res*. 2015;30;228(1):95-9. PMID: 25977072.
EXCLUDE: Age.
- 311.Lee CS, Williamson LR, Martin SE, et al. Adverse events in very young children prescribed psychotropic medications: preliminary findings from an acute clinical sample. *J Child Adolesc Psychopharmacol*. 2015;25(6):509-13. PMID: 26262905.
EXCLUDE: Intervention.
- 312.Lejeune J, Larmo I, Chrzanowski W, et al. Oral risperidone plus oral lorazepam versus standard care with intramuscular conventional neuroleptics in the initial phase of treating individuals with acute psychosis. *Int Clin Psychopharmacol*. 2004;19(5):259-69. PMID: 15289699.
EXCLUDE: Age.
- 313.Lepping P, Freudenmann RW. Delusional infestation. Merrick, Joav [Ed]. 2015.
EXCLUDE: Publication Type.
- 314.Levine SZ, Kodesh A, Goldberg Y, et al. Initial severity and efficacy of risperidone in autism: Results from the RUPP trial. *Eur Psychiatr*. 2016;32:16-20. PMID: 20160180335.
EXCLUDE: outcomes
- 315.Lewis SW, Barnes TR, Davies L, et al. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. *Schizophr Bull*. 2006;32(4):715-23. PMID: 16540702.
EXCLUDE: Age.
- 316.Lewis SW, Davies L, Jones PB, et al. Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment. *Health Technol Assess*. 2006;10(17):iii-iv, ix-xi, 1-165. PMID: 16707074.
EXCLUDE: Age.
- 317.Lieberman JA, Phillips M, Gu H, et al. Atypical and conventional antipsychotic drugs in treatment-naive first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. *Neuropsychopharmacology*. 2003;28(5):995-1003. PMID: 12700715.
EXCLUDE: Age.
- 318.Lieberman JA, Tollefson G, Tohen M, et al. Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. *Am J Psychiatry*. 2003;160(8):1396-404. PMID: 12900300.
EXCLUDE: Age.
- 319.Liu W, Yu H, Jiang B, et al. The predictive value of baseline NAA/Cr for treatment response of first-

- episode schizophrenia: A 1H MRS study. *Neurosci Lett*. 2015;600:199-205. PMID: 26099422.
EXCLUDE: Age.
- 320.Liu X, Kubilis P, Xu D, et al. Psychotropic drug utilization in children with concurrent attention-deficit/hyperactivity disorder and anxiety. *J Anxiety Disord*. 2014;28(6):530-6. PMID: 24981018.
EXCLUDE: Study Design.
- 321.Locascio JJ, Malone RP, Small AM, et al. Factors related to haloperidol response and dyskinesias in autistic children. *Psychopharmacol Bull*. 1991;27(2):119-26. PMID: 1924657.
EXCLUDE: Language.
- 322.Long-term treatment with risperidone yields benefits in treating disruptive behavior disorders. *Brown University Child & Adolescent Psychopharmacology Update*. 2006;8(5):1. PMID: 106343185.
EXCLUDE: Publication Type.
- 323.Loze JY, Pikalov A, Baker R, et al. Effects of aripiprazole on glucose, lipids and weight in adolescent patients: a pooled analysis of 2 clinical trials. *Eur Neuropsychopharmacol*. 2009:S689-s90. <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/749/CN-01008749/frame.html>.
EXCLUDE: Outcomes.
- 324.Lyseng-Williamson KA. Paliperidone extended release: a guide to its use in schizophrenia in adolescents aged >15 years. *Drugs Ther Perspect*. 2014;30(11):380-5. DOI: <http://dx.doi.org/10.1007/s40267-014-0157-x>. PMID: N/A.
EXCLUDE: Publication Type.
- 325.Macfadden W, Adler CM, Turkoz I, et al. Adjunctive long-acting risperidone in patients with bipolar disorder who relapse frequently and have active mood symptoms. *BMC Psychiatry*. 2011;11:171. PMID: 22034906.
EXCLUDE: Age.
- 326.Maldari LA. The treatment of adolescent psychiatric inpatients with atypical neuroleptics: an investigation of cognitive change, functional outcome and satisfaction. *Diss Abst Int: Section B: The Sciences and Engineering* 2008;69(6-B).
EXCLUDE: Study Design.
- 327.Malla A, Norman R, Scholten D, et al. A comparison of two novel antipsychotics in first episode non-affective psychosis: one-year outcome on symptoms, motor side effects and cognition. *Psychiatry Res*. 2004 15;129(2):159-69. PMID: 15590043.
EXCLUDE: Age.
- 328.Mancini C, Van Ameringen M, Patterson B, et al. Trichotillomania in youth: a retrospective case series. *Depress Anxiety*. 2009;26(7):661-5. PMID: 19496078.
EXCLUDE: Intervention.
- 329.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. *J Child Adolesc Psychopharmacol*. 2011;21(4):359-64. PMID: 21823911.
EXCLUDE: Outcomes.
- 330.Marcus RN, Owen R, Manos G, et al. Aripiprazole in the treatment of irritability in pediatric patients (aged 6-17 years) with autistic disorder: results from a 52-week, open-label study. *J Child Adolesc Psychopharmacol*. 2011;21(3):229-36. PMID: 21663425.
EXCLUDE: Study Design.
- 331.Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials.[Erratum appears in *J Clin Psychiatry*. 1998 Apr;59(4):200]. *J Clin Psychiatry*. 1997;58(12):538-46. PMID: 9448657.
EXCLUDE: Age.
- 332.Marder SR, Glynn SM, Wirshing WC, et al. Maintenance treatment of schizophrenia with risperidone or haloperidol: 2-year outcomes. *Am J Psychiatry*. 2003;160(8):1405-12. PMID: 12900301.
EXCLUDE: Age.
- 333.Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. *Am J Psychiatry*. 1994;151(6):825-35. PMID: 7514366.
EXCLUDE: Age.
- 334.Margari L, Matera E, Craig F, et al. Tolerability and safety profile of risperidone in a sample of children and adolescents. *Int Clin Psychopharmacol*. 2013;28(4):177-83. PMID: 23689836.
EXCLUDE: Study Design.
- 335.Margari L, Matera E, Petruzzelli MG, et al. Prolactin variations during risperidone therapy in a sample of drug-naïve children and adolescents. *Int Clin Psychopharmacol*. 2015;30(2):103-8. PMID: 25514607.
EXCLUDE: Intervention.

336. Marsanic VB, Dodig-Curkovic K, Juretic Z. Outpatient treatment of children and adolescents with antipsychotic drugs in Croatia. *Nord J Psychiatry*. 2012;66(1):2-7. PMID: 21306199. EXCLUDE: Study Design.
337. Martin Otano L, Barbadillo Izquierdo L, Galdeano Mondragon A, et al. After six months of anti-psychotic treatment: Is the improvement in mental health at the expense of physical health? *Rev Psiquiatr Salud Ment*. 2013;6(1):26-32. PMID: 23084806. EXCLUDE: Age.
338. Masi G, Millepiedi S, Perugi G, et al. Pharmacotherapy in paediatric obsessive-compulsive disorder: a naturalistic, retrospective study. *CNS Drugs*. 2009;23(3):241-52. PMID: 19320532. EXCLUDE: Intervention.
339. Masi G, Milone A, Canepa G, et al. Olanzapine treatment in adolescents with severe conduct disorder. *Eur Psychiatry*. 2006;21(1):51-7. PMID: 16487906. EXCLUDE: Study Design.
340. Masi G, Milone A, Manfredi A, et al. Combined pharmacotherapy-multimodal psychotherapy in children with Disruptive Behavior Disorders. *Psychiatr Res*. 2016;238:8-13. doi: PMID: 20160222674. EXCLUDE: Intervention.
341. Matsunaga H, Nagata T, Hayashida K, et al. A long-term trial of the effectiveness and safety of atypical antipsychotic agents in augmenting SSRI-refractory obsessive-compulsive disorder. *J Clin Psychiatry*. 2009;70(6):863-8. PMID: 19422759. EXCLUDE: Age.
342. Matsuura Y, Fujino H, Hashimoto R, et al. Standing postural instability in patients with schizophrenia: Relationships with psychiatric symptoms, anxiety, and the use of neuroleptic medications. *Gait Posture*. 2015;41(3):847-51. PMID: 25813604. EXCLUDE: Age.
343. Martsenkovsky I, Martsenkovska I, Martsenkovskyi D. Risperidon and atomoxetine in the treatment of several and challenging behaviors in children with PDD. *Eur Psychiatr*; 2015. p. 195. EXCLUDE: Intervention.
344. McDougle CJ, Goodman WK, Leckman JF, et al. Haloperidol addition in fluvoxamine-refractory obsessive-compulsive disorder. A double-blind, placebo-controlled study in patients with and without tics. *Arch Gen Psychiatry*. 1994;51(4):302-8. PMID: 8161290. EXCLUDE: Age.
345. McEvoy JP, Hogarty GE, Steingard S. Optimal dose of neuroleptic in acute schizophrenia. A controlled study of the neuroleptic threshold and higher haloperidol dose. *Arch Gen Psychiatry*. 1991;48(8):739-45. PMID: 1883257. EXCLUDE: Age.
346. McEvoy JP, Johnson J, Perkins D, et al. Insight in first-episode psychosis. *Psychol Med*. 2006;36(10):1385-93. PMID: 16740175. EXCLUDE: Age.
347. McEvoy JP, Lieberman JA, Perkins DO, et al. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. *Am J Psychiatry*. 2007;164(7):1050-60. PMID: 17606657. EXCLUDE: Age.
348. McIntyre RS, Cohen M, Zhao J, et al. Asenapine versus olanzapine in acute mania: a double-blind extension study. [Erratum appears in *Bipolar Disord*. 2010 Feb;12(1):112]. *Bipolar Disord*. 2009;11(8):815-26. PMID: 19832806. EXCLUDE: Age.
349. McIntyre RS, Cohen M, Zhao J, et al. A 3-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states. [Erratum appears in *Bipolar Disord*. 2010 May;12(3):350]. *Bipolar Disord*. 2009;11(7):673-86. PMID: 19839993. EXCLUDE: Age.
350. McIntyre RS, Mancini DA, Srinivasan J, et al. The antidepressant effects of risperidone and olanzapine in bipolar disorder. *Can J Clin Pharmacol*. 2004;11(2):e218-26. PMID: 15520475. EXCLUDE: Age.
351. Meltzer HY, Alphas L, Green AI, et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). [Erratum appears in *Arch Gen Psychiatry*. 2003;60(7):735]. *Arch Gen Psychiatry*. 2003;60(1):82-91. PMID: 12511175. EXCLUDE: Age.
352. Meltzer HY, Bobo WV, Roy A, et al. A randomized, double-blind comparison of clozapine and high-dose

- olanzapine in treatment-resistant patients with schizophrenia. *J Clin Psychiatry*. 2008;69(2):274-85. PMID: 18232726. EXCLUDE: Age.
353. Menard ML, Thummler S, Auby P, et al. Preliminary and ongoing French multicenter prospective naturalistic study of adverse events of antipsychotic treatment in naive children and adolescents. *Child & Adolescent Psychiatry & Mental Health*. [Electronic Resource]. 2014;8:18. PMID: 24991232. EXCLUDE: Study Design.
354. Menard ML, Thummler S, Giannitelli M, et al. Incidence of adverse events in antipsychotic-naive children and adolescents treated with antipsychotic drugs: a French multicentre naturalistic study protocol (ETAPE). *BMJ Open*. 2016;6(4):e011020. PMID: 27053275. EXCLUDE: Publication Type.
355. 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. *Rev Psiquiatr Salud Ment*. 2012;5(4):217-28. PMID: 23021294. EXCLUDE: Publication Type.
356. Meyer N, Gee S, Whiskey E, et al. Optimizing outcomes in clozapine rechallenge following neutropenia: a cohort analysis. *J Clin Psychiatr*. 2015;76(11):e1410-6. PMID: 26646037. EXCLUDE: Age.
357. Mick E, Biederman J. Risperidone for the treatment of ADHD in children with bipolar disorder. 158th Annual Meeting of the American Psychiatric Association; 2005 May 21-26; Atlanta, GA. 2005 <http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2125.2005.01410.x>. PMID: 16111111. EXCLUDE: Study Design.
358. Midbari Y, Ebert T, Kosov I, et al. Hematological and cardiometabolic safety of clozapine in the treatment of very early onset schizophrenia: a retrospective chart review. *J Child Adolesc Psychopharmacol*. 2013;23(8):516-21. PMID: 24111981. EXCLUDE: Intervention.
359. Miller DD, Caroff SN, Davis SM, et al. Extrapyramidal side-effects of antipsychotics in a randomised trial. *Br J Psychiatry*. 2008;193(4):279-88. PMID: 18827289. EXCLUDE: Age.
360. Moeller KE, Shireman TI, Liskow BI. Relapse rates in patients with schizophrenia receiving aripiprazole in comparison with other atypical antipsychotics. *J Clin Psychiatry*. 2006;67(12):1942-7. PMID: 17194273. EXCLUDE: Age.
361. Moilanen J, Haapea M, Miettunen J, et al. Characteristics of subjects with schizophrenia spectrum disorder with and without antipsychotic medication - A 10-year follow-up of the Northern Finland 1966 Birth Cohort study. *Eur Psychiatry*. 2013;28(1):53-8. PMID: 21920710. EXCLUDE: Publication Type.
362. Mojtabai R, Lavelle J, Gibson PJ, et al. Atypical antipsychotics in first admission schizophrenia: medication continuation and outcomes. *Schizophr Bull*. 2003;29(3):519-30. PMID: 14609245. EXCLUDE: Age.
363. Moller HJ, Johnson S, Mateva T, et al. Evaluation of the feasibility of switching from immediate release quetiapine to extended release quetiapine fumarate in stable outpatients with schizophrenia. *Int Clin Psychopharmacol*. 2008;23(2):95-105. PMID: 18301124. EXCLUDE: Age.
364. Moller HJ, Riedel M, Jager M, et al. Short-term treatment with risperidone or haloperidol in first-episode schizophrenia: 8-week results of a randomized controlled trial within the German Research Network on Schizophrenia. *Int J Neuropsychopharmacol*. 2008;11(7):985-97. PMID: 18466670. EXCLUDE: Age.
365. Moon KT. Bipolar disorder I in children: Which treatment works best? *Am Fam Physician*. 2012;86(9):848-53. PMID: N/A. EXCLUDE: Publication Type.
366. Moosavi SM, Ahmadi M, Mojtabadi D, et al. Comparison of Quetiapine and Risperidone in Treatment of Acute Psychosis: A Double-Blind, Randomized-Controlled Study. *Glob J Health Sci*. 2015;7(5):359-63. PMID: 26156901. EXCLUDE: Age.
367. Moreno C, Merchan-Naranjo J, Alvarez M, et al. Metabolic effects of second-generation antipsychotics in bipolar youth: comparison with other psychotic and nonpsychotic diagnoses. *Bipolar Disord*. 2010;12(2):172-84. PMID: 20402710. EXCLUDE: Intervention.

368. Morrato EH, Parks J, Campagna EJ, et al. Comparative effectiveness of injectable paliperidone palmitate versus oral atypical antipsychotics: early postmarketing evidence. *J Comp Eff Res*. 2015;4(2):89-99. PMID: 25251693. EXCLUDE: Age.
369. Mullen J, Jibson MD, Sweitzer D. A comparison of the relative safety, efficacy, and tolerability of quetiapine and risperidone in outpatients with schizophrenia and other psychotic disorders: the quetiapine experience with safety and tolerability (QUEST) study. *Clin Ther*. 2001;23(11):1839-54. PMID: 11768836. EXCLUDE: Age.
370. Mullins CD, Obeidat NA, Cuffel BJ, et al. Risk of discontinuation of atypical antipsychotic agents in the treatment of schizophrenia. *Schizophr Res*. 2008;98(1-3):8-15. PMID: 17596914. EXCLUDE: Age.
371. Murphy AL, Gardner DM, Kisely S, et al. A qualitative study of antipsychotic medication experiences of youth. *J Can Acad Child Adolesc Psychiatry*. 2015;24(1):61-9. PMID: 26336383. EXCLUDE: Study Design.
372. Mutlu C, Sukran Uneri O, Tanidir C, et al. Agresif ve yıkıcı davranışsal belirtileri olan okul öncesi çocuklarda risperidon kullanımı [Risperidone use in preschool children with aggressive and destructive behavioral symptoms]. *Anadolu Psikiyatri Dergisi*. 2015;16(3):212-9. DOI: 10.5455/apd.167083. PMID: N/A. EXCLUDE: Language.
373. Naber D, Riedel M, Klimke A, et al. Randomized double blind comparison of olanzapine vs. clozapine on subjective well-being and clinical outcome in patients with schizophrenia. *Acta Psychiatr Scand*. 2005;111(2):106-15. PMID: 15667429. EXCLUDE: Age.
374. Naguy A, At-Tajali A. Ziprasidone monotherapy for Tourette syndrome with comorbid ADHD. *Afr J Psychiatry (South Africa)*. 2015;18(SpecialIssue):1-2. PMID: 2015508318. EXCLUDE: Publication Type.
375. Nahshoni E, Spitzer S, Berant M, et al. QT interval and dispersion in very young children treated with antipsychotic drugs: a retrospective chart review. *J Child Adolesc Psychopharmacol*. 2007;17(2):187-94. PMID: 17489713. EXCLUDE: Intervention.
376. Nair NP. Therapeutic equivalence of risperidone given once daily and twice daily in patients with schizophrenia. The Risperidone Study Group. *J Clin Psychopharmacol*. 1998;18(2):103-10. PMID: 9555595. EXCLUDE: Age.
377. Nakamura M, Ogasa M, Guarino J, et al. Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2009;70(6):829-36. PMID: 19497249. EXCLUDE: Age.
378. Newcomer JW, Campos JA, Marcus RN, et al. A multicenter, randomized, double-blind study of the effects of aripiprazole in overweight subjects with schizophrenia or schizoaffective disorder switched from olanzapine. *J Clin Psychiatry*. 2008;69(7):1046-56. PMID: 18605811. EXCLUDE: Age.
379. Newcomer JW, Ratner RE, Eriksson JW, et al. A 24-week, multicenter, open-label, randomized study to compare changes in glucose metabolism in patients with schizophrenia receiving treatment with olanzapine, quetiapine, or risperidone. *J Clin Psychiatry*. 2009;70(4):487-99. DOI: PMID: 19358783. EXCLUDE: Age.
380. Ngai YF, Sabatini P, Nguyen D, et al. Quetiapine treatment in youth is associated with decreased insulin secretion. *J Clin Psychopharmacol*. 2014;34(3):359-64. PMID: 24633003. EXCLUDE: Study Design.
381. Nielsen RE, Laursen MF, Lammers Vernal D, et al. Risk of diabetes in children and adolescents exposed to antipsychotics: A nationwide 12-year case-control study. *J Am Acad Child Adolesc Psychiatry*. 2014;53(9):971-9.e6. PMID: 25151420. EXCLUDE: Intervention.
382. Norris ML, Spettigue W, Buchholz A, et al. Factors influencing research drug trials in adolescents with anorexia nervosa. *Brunner-Mazel Eating Disorders Monograph Series*. 2010;18(3):210-7. PMID: 20419525. EXCLUDE: Study Design.
383. Noto C, Ota VK, Gouvea ES, et al. Effects of risperidone on cytokine profile in drug-naive first-episode psychosis. *Int J Neuropsychopharmacol*. 2015;18(4) PMID: 25522386. EXCLUDE: Age.

384. Nuechterlein KH, Green MF, Calkins ME, et al. Attention/vigilance in schizophrenia: performance results from a large multi-site study of the Consortium on the Genetics of Schizophrenia (COGS). *Schizophr Res.* 2015;163(1-3):38-46. PMID: 25749017. EXCLUDE: Age
385. Nussbaum L, Gradinaru R, Andreescu N, et al. The response to atypical antipsychotic drugs in correlation with the cyp2d6 genotype: clinical implications and perspectives. *Farmacia.* 2014;62(6):1191-201. PMID: N/A. EXCLUDE: Intervention.
386. Okazaki M, Adachi N, Akanuma N, et al. Do antipsychotic drugs increase seizure frequency in epilepsy patients? *Eur Neuropsychopharmacol.* 2014;24(11):1738-44. PMID: 25453222. EXCLUDE: Age.
387. Ono S, Suzuki Y, Fukui N, et al. GIPR Gene Polymorphism and Weight Gain in Patients With Schizophrenia Treated With Olanzapine. *J Neuropsychiatr Clin Neurosci.* 2015;27(2):162-4. PMID: 25321336. EXCLUDE: Age.
388. Oosthuizen P, Emsley R, Jadri Turner H, et al. A randomized, controlled comparison of the efficacy and tolerability of low and high doses of haloperidol in the treatment of first-episode psychosis. *Int J Neuropsychopharmacol.* 2004;7(2):125-31. PMID: 15003147. EXCLUDE: Age.
389. Opjordsmoen S, Melle I, Friis S, et al. Stability of medication in early psychosis: a comparison between second-generation and low-dose first-generation antipsychotics. *Early Int Psychiatry.* 2009;3(1):58-65. PMID: 21352176. EXCLUDE: Age.
390. Padala PR, Madison J, Monnahan M, et al. Risperidone monotherapy for post-traumatic stress disorder related to sexual assault and domestic abuse in women. *Int Clin Psychopharmacol.* 2006;21(5):275-80. PMID: 16877898. EXCLUDE: Age.
391. Pae CU, Kim JJ, Lee CU, et al. Rapid versus conventional initiation of quetiapine in the treatment of schizophrenia: a randomized, parallel-group trial. *J Clin Psychiatry.* 2007;68(3):399-405. PMID: 17388709. EXCLUDE: Age.
392. Pae CU, Nassir Ghaemi S, Kim TS, et al. Rapid titration versus conventional titration of quetiapine in the treatment of bipolar mania: a preliminary trial. *Int Clin Psychopharmacol.* 2005;20(6):327-30. PMID: 16192842. EXCLUDE: Age.
393. Pae CU, Nassir Ghaemi S, Patkar A, et al. Adjunctive risperidone, olanzapine and quetiapine for the treatment of hospitalized patients with bipolar I disorder: a retrospective study. *Prog Neuropsychopharmacol Biol Psychiatry.* 2006;30(7):1322-5. PMID: 16631294. EXCLUDE: Age.
394. Pae CU, Serretti A, Chiesa A, et al. Immediate versus gradual suspension of previous treatments during switch to aripiprazole: results of a randomized, open label study. *Eur Neuropsychopharmacol.* 2009;19(8):562-70. PMID: 19442491. EXCLUDE: Age.
395. Paixao MJ. Atypical antipsychotics for disruptive behavior disorders in children and youths. *Am J Nurs.* 2013;113(6):60. PMID: 23702768. EXCLUDE: Publication Type.
396. Pan PY, Lee MS, Yeh CB. The efficacy and safety of once-daily quetiapine extended release in patients with schizophrenia switched from other antipsychotics: an open-label study in Chinese population. *BMC Psychiatry.* 2015;15:1. PMID: 25609320. EXCLUDE: Age.
397. Pandina GJ, Revicki DA, Kleinman L, et al. Psychometric evaluation of a patient-rated troubling symptom scale for generalized anxiety disorder clinical trials. *Psychopharmacol Bull.* 2008;41(3):68-90. PMID: 18779777. EXCLUDE: Age.
398. Patel JK, Buckley PF, Woolson S, et al. Metabolic profiles of second-generation antipsychotics in early psychosis: findings from the CAFE study. *Schizophr Res.* 2009;111(1-3):9-16. PMID: 19398192. EXCLUDE: Age.
399. Patel NC, DelBello MP, Keck PE, Jr., et al. Ethnic differences in maintenance antipsychotic prescription among adolescents with bipolar disorder. *J Child Adolesc Psychopharmacol.* 2005;15(6):938-46. PMID: 16379514. EXCLUDE: Intervention.

400. Patel NC, Dorson PG, Edwards N, et al. One-year rehospitalization rates of patients discharged on atypical versus conventional antipsychotics. *Psychiatric Serv.* 2002;53(7):891-3. PMID: 12096177.
EXCLUDE: Age.
401. Patel NC, Kistler JS, James EB, et al. A retrospective analysis of the short-term effects of olanzapine and quetiapine on weight and body mass index in children and adolescents. *Pharmacotherapy.* 2004;24(7 D):824-30. PMID: 15303445.
EXCLUDE: Diagnosis.
402. Patkar AA, Peindl K, Mago R, et al. An open-label, rater-blinded, augmentation study of aripiprazole in treatment-resistant depression. *Prim Care Companion J Clin Psychiatry.* 2006;8(2):82-7. PMID: 16862232.
EXCLUDE: Age.
403. Pavuluri MN, Henry DB, Carbray JA, et al. A one-year open-label trial of risperidone augmentation in lithium nonresponder youth with preschool-onset bipolar disorder. *J Child Adolesc Psychopharmacol.* 2006;16(3):336-50. PMID: 16768641.
EXCLUDE: Study Design.
404. Perez-Iglesias R, Crespo-Facorro B, Amado JA, et al. A 12-week randomized clinical trial to evaluate metabolic changes in drug-naive, first-episode psychosis patients treated with haloperidol, olanzapine, or risperidone. *J Clin Psychiatry.* 2007;68(11):1733-40. PMID: 18052567. EXCLUDE: Age.
405. Perez-Iglesias R, Crespo-Facorro B, Martinez-Garcia O, et al. Weight gain induced by haloperidol, risperidone and olanzapine after 1 year: findings of a randomized clinical trial in a drug-naive population. *Schizophr Res.* 2008;99(1-3):13-22. PMID: 18053689.
EXCLUDE: Age.
406. Perez-Iglesias R, Mata I, Pelayo-Teran JM, et al. Glucose and lipid disturbances after 1 year of antipsychotic treatment in a drug-naive population. *Schizophr Res.* 2009;107(2-3):115-21. PMID: 18993033.
EXCLUDE: Age.
407. Perez-Iglesias R, Vazquez-Barquero JL, Amado JA, et al. Effect of antipsychotics on peptides involved in energy balance in drug-naive psychotic patients after 1 year of treatment. *J Clin Psychopharmacol.* 2008;28(3):289-95. PMID: 18480685.
EXCLUDE: Age.
408. Perry CM. Paliperidone extended release: in adolescents with schizophrenia. *Paediatr Drugs.* 2012;14(6):417-27. PMID: 23050744.
EXCLUDE: Publication Type.
409. Perry R, Pataki C, Munoz-Silva DM, et al. Risperidone in children and adolescents with pervasive developmental disorder: pilot trial and follow-up. *J Child Adolesc Psychopharmacol.* 1997;7(3):167-79. PMID: 9466234.
EXCLUDE: Publication Type.
410. Peuskens J, Van Baelen B, De Smedt C, et al. Effects of risperidone on affective symptoms in patients with schizophrenia. *Int Clin Psychopharmacol.* 2000;15(6):343-9. PMID: 11110010.
EXCLUDE: Age.
411. 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. *Aust NZ J Psychiatry.* 2009;43(9):818-29. PMID: 19670055.
EXCLUDE: Publication Type.
412. Pijnenborg GH, Timmerman ME, Derks EM, et al. Differential effects of antipsychotic drugs on insight in first episode schizophrenia: Data from the European First-Episode Schizophrenia Trial (EUFEST). *Eur Neuropsychopharmacol.* 2015;25(6):808-16. PMID: 25907250.
EXCLUDE: Age.
413. Pisano S, Catone G, Pascotto A, et al. Second generation antipsychotics in adolescent anorexia nervosa: a new hypothesis of eligibility criteria. *J Child Adolesc Psychopharmacol.* 2014;24(5):293-5. PMID: 24827862
EXCLUDE: Study Design.
414. Piscitelli SC, Frazier JA, McKenna K, et al. Plasma clozapine and haloperidol concentrations in adolescents with childhood-onset schizophrenia: association with response. *J Clin Psychiatry.* 1994;55 Suppl B:94-7. PMID: 7961584.
EXCLUDE: Outcomes.
415. Podobnik J, Foller Podobnik I, Grgic N, et al. The effect of add-on treatment with quetiapine on measures of depression, aggression, irritability and suicidal tendencies in children and adolescents. *Psychopharmacology.* 2012;220(3):639-41. PMID: 22173852.
EXCLUDE: Diagnosis.

416. Pogge DL, Young K, Insalaco B, et al. Use of atypical antipsychotic medications in adolescent psychiatric inpatients: a comparison with inpatients who did not receive antipsychotic medications during their stay. *Int J Clin Pract*. 2007;61(6):896-902. PMID: 17504351. EXCLUDE: Study Design.
417. Post RM, Leverich GS, Kupka R, et al. Clinical correlates of sustained response to individual drugs used in naturalistic treatment of patients with bipolar disorder. *Compr Psychiatry*. 2016;66:146-56. PMID: 20160224122. EXCLUDE: Age.
418. Post RM. Treatment of Bipolar Depression: Evolving Recommendations. *Psychiatr Clin North Am*. 2016;39(1):11-33. PMID: 20160123691. EXCLUDE: Publication Type.
419. Potkin SG, Gharabawi GM, Greenspan AJ, et al. A double-blind comparison of risperidone, quetiapine and placebo in patients with schizophrenia experiencing an acute exacerbation requiring hospitalization. *Schizophr Res*. 2006;85(1-3):254-65. PMID: 16797162. EXCLUDE: Age.
420. Potkin SG, Thyrum PT, Alva G, et al. The safety and pharmacokinetics of quetiapine when coadministered with haloperidol, risperidone, or thioridazine. *J Clin Psychopharmacol*. 2002;22(2):121-30. PMID: 11910256. EXCLUDE: Age.
421. Potkin SG, Weiden PJ, Loebel AD, et al. Remission in schizophrenia: 196-week, double-blind treatment with ziprasidone vs. haloperidol. *Int J Neuropsychopharmacol*. 2009;12(9):1233-48. PMID: 19419595. EXCLUDE: Age.
422. Potvin S, Aubin G, Stip E. Antipsychotic-induced parkinsonism is associated with working memory deficits in schizophrenia-spectrum disorders. *Eur Arch Psychiatry Clin Neurosci*. 2015;265(2):147-54. PMID: 24925606. EXCLUDE: Age.
423. Pozzi M, Cattaneo D, Baldelli S, et al. Therapeutic drug monitoring of second-generation antipsychotics in pediatric patients: An observational study in real-life settings. *Eur J Clin Pharmacol*. 2016;72(3):285-93. doi: PMID: 2015552239. EXCLUDE: outcomes
424. Preskorn SH. Prediction of individual response to antidepressants and antipsychotics: an integrated concept. *Dialogues Clin Neurosci*. 2014;16(4):545-54. PMID: 25733958. EXCLUDE: Publication Type.
425. Preval H, Klotz SG, Southard R, et al. Rapid-acting IM ziprasidone in a psychiatric emergency service: a naturalistic study. *Gen Hosp Psychiatry*. 2005;27(2):140-4. PMID: 15763126. EXCLUDE: Age.
426. Pribylova L, Kolek M, Vesela S, et al. De novo cost-utility analysis of oral paliperidone in the treatment of schizoaffective disorder. *J Psychiatr Res*. 2015;70:33-7. PMID: 2015432861. EXCLUDE: Age.
427. Pringsheim T, Pearce M. Complications of antipsychotic therapy in children with tourette syndrome. *Pediatr Neurol*. 2010;43(1):17-20. DOI: <http://dx.doi.org/10.1016/j.pediatrneurol.2010.02.01>. EXCLUDE: Study Design.
428. Purdon SE, Woodward N, Lindborg SR, et al. Procedural learning in schizophrenia after 6 months of double-blind treatment with olanzapine, risperidone, and haloperidol. *Psychopharmacology*. 2003;169(3-4):390-7. PMID: 12827347. EXCLUDE: Age.
429. Questions remain about use of newer antipsychotics in pediatric population. *Brown University Psychopharmacology Update*. 2009;20(1):1-7. PMID: 105598357. EXCLUDE: Publication Type.
430. Quetiapine equal to placebo for teen bipolar depression. *Brown University Child & Adolescent Psychopharmacology Update*. 2009;11(9):4-5. PMID: 105418595. EXCLUDE: Publication Type.
431. Quetiapine versus risperidone in first-onset adolescent psychosis. *Brown University Child & Adolescent Psychopharmacology Update*. 2010;12(2):5-6. PMID: 105306061. EXCLUDE: Outcomes.
432. Quetiapine vs. risperidone in psychosis. *Brown University Child & Adolescent Psychopharmacology Update*. 2009;11(12):4-5. PMID: 105259630. EXCLUDE: Outcomes.
433. Quintana H, Wilson MS, 2nd, Purnell W, et al. An open-label study of olanzapine in children and

- adolescents with schizophrenia. *J Psychiatr Pract*. 2007;13(2):86-96. PMID: 17414684.
EXCLUDE: Study Design.
434. Rabinowitz J, Harvey PD, Eerdeken M, et al. Premorbid functioning and treatment response in recent-onset schizophrenia. *Br J Psychiatry*. 2006;189:31-5. PMID: 16816303.
EXCLUDE: Age.
435. Rabinowitz J, Werbeloff N, Caers I, et al. Determinants of antipsychotic response in schizophrenia: implications for practice and future clinical trials. *J Clin Psychiatry*. 2014;75(4):e308-16. PMID: 24813414.
EXCLUDE: Age.
436. Rahman A, Mican LM, Fischer C, et al. Evaluating the incidence of leukopenia and neutropenia with valproate, quetiapine, or the combination in children and adolescents. *Ann Pharmacother*. 2009;43(5):822-30. PMID: 19401471.
EXCLUDE: Diagnosis.
437. Rani FA, Byrne P, Cranswick N, et al. Mortality in children and adolescents prescribed antipsychotic medication: a retrospective cohort study using the UK general practice research database. *Drug Saf*. 2011;34(9):773-81. PMID: 21830839.
EXCLUDE: Study Design.
438. Rani FA, Byrne PJ, Murray ML, et al. Paediatric Atypical Antipsychotic Monitoring Safety (PAMS) study: pilot study in children and adolescents in secondary- and tertiary-care settings. *Drug Saf*. 2009;32(4):325-33. PMID: 19388723.
EXCLUDE: Diagnosis.
439. Rapoport J, Kumra S, Jacobsen LK. The spectrum of extrapyramidal symptoms in children and young adults conference abstract. 150th Annual Meeting of the American Psychiatric Association. San Diego, California, USA. 17-22 May, 1997. 1997 <http://onlinelibrary.wiley.com/doi/10.1002/ajcp.10001>. PMID: 11971414.
EXCLUDE: Publication Type.
440. Ravindran A, Silverstone P, Lacroix D, et al. Risperidone does not affect steady-state pharmacokinetics of divalproex sodium in patients with bipolar disorder. *Clin Pharmacokinet*. 2004;43(11):733-40. PMID: 15301577.
EXCLUDE: Age.
441. Reed E, Vance A, Luk E, et al. Single and combined psychotropic medication use in a child and adolescent mental health service. *Aust NZ J Psychiatry*. 2004;38(4):204-11. PMID: 15038798.
EXCLUDE: Intervention.
442. Reich DB, Winternitz S, Hennen J, et al. A preliminary study of risperidone in the treatment of posttraumatic stress disorder related to childhood abuse in women. *J Clin Psychiatry*. 2004;65(12):1601-6. PMID: 15641864.
EXCLUDE: Age.
443. Remschmidt H, Schulz E, Martin PDM. An open trial of clozapine in thirty-six adolescents with schizophrenia. *J Child Adolesc Psychopharmacol*. 1994;4(1):31-41. PMID: 1994156335.
EXCLUDE: Publication Type.
444. Ren XS, Qian S, Lee AF, et al. Treatment persistence: a comparison among patients with schizophrenia who were initiated on atypical antipsychotic agents. *J Clin Pharmacy Ther*. 2006;31(1):57-65. PMID: 16476121.
EXCLUDE: Age.
445. Reyes M, Croonenberghs J, Augustyns I, et al. Long-term use of risperidone in children with disruptive behavior disorders and subaverage intelligence: efficacy, safety, and tolerability. *J Child Adolesc Psychopharmacol*. 2006;16(3):260-72. PMID: 16768634.
EXCLUDE: Study Design.
446. Reyes M, Olah R, Csaba K, et al. Long-term safety and efficacy of risperidone in children with disruptive behaviour disorders. Results of a 2-year extension study. *Eur Child Adolesc Psychiatry*. 2006;15(2):97-104. PMID: 16523250.
EXCLUDE: Study Design.
447. Riedel M, Muller N, Spellmann I, et al. Efficacy of olanzapine versus quetiapine on cognitive dysfunctions in patients with an acute episode of schizophrenia. *Eur Arch Psychiatry Clin Neurosci*. 2007;257(7):402-12. PMID: 17629725.
EXCLUDE: Age.
448. Ritchie B, Norris ML. QTc prolongation associated with atypical antipsychotic use in the treatment of adolescent-onset anorexia nervosa. *J Can Acad Child Adolesc Psychiatry*. 2009;18(1):60-3. PMID: 19270852.
EXCLUDE: Study Design.

- 449.Ritsner MS, Gibel A. The effectiveness and predictors of response to antipsychotic agents to treat impaired quality of life in schizophrenia: a 12-month naturalistic follow-up study with implications for confounding factors, antidepressants, anxiolytics, and mood stabilizers. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006;30(8):1442-52. PMID: 16842897. EXCLUDE: Age.
- 450.Robertson MM, Scull DA, Eapen V, et al. Risperidone in the treatment of Tourette syndrome: a retrospective case note study. *J Psychopharmacol*. 1996;10(4):317-20. PMID: 22302981. EXCLUDE: Study Design.
- 451.Robinson DG, Gallego JA, John M, et al. A Randomized Comparison of Aripiprazole and Risperidone for the Acute Treatment of First-Episode Schizophrenia and Related Disorders: 3-Month Outcomes. *Schizophr Bull*. 2015;41(6):1227-36. PMID: 2015496122. EXCLUDE: Age.
- 452.Robles O, Zabala A, Bombin I, et al. Cognitive efficacy of quetiapine and olanzapine in early-onset first-episode psychosis. *Schizophr Bull*. 2011;37(2):405-15. PMID: 19706697. EXCLUDE: Duplicate.
- 453.Rojo LE, Gaspar PA, Silva H, et al. Metabolic syndrome and obesity among users of second generation antipsychotics: A global challenge for modern psychopharmacology. *Pharmacol Res*. 2015;101:74-85. PMID: 2015322038. EXCLUDE: Publication Type.
- 454.Roke Y, Buitelaar JK, Boot AM, et al. Risk of hyperprolactinemia and sexual side effects in males 10-20 years old diagnosed with autism spectrum disorders or disruptive behavior disorder and treated with risperidone. *J Child Adolesc Psychopharmacol*. 2012;22(6):432-9. PMID: 23234586. EXCLUDE: Study Design.
- 455.Roke Y, van Harten PN, Buitelaar JK, et al. Antipsychotic-induced hyperprolactinemia and testosterone levels in boys. *Horm Res Pediatr*. 2012;77(4):235-40. PMID: 22538969. EXCLUDE: Study Design.
- 456.Roke Y, van Harten PN, Buitelaar JK, et al. Bone mineral density in male adolescents with autism spectrum disorders and disruptive behavior disorder with or without antipsychotic treatment. *Eur J Endocrinol*. 2012;167(6):855-63. PMID: 23011870. EXCLUDE: Study Design.
- 457.Rothbaum BO, Killeen TK, Davidson JR, et al. Placebo-controlled trial of risperidone augmentation for selective serotonin reuptake inhibitor-resistant civilian posttraumatic stress disorder. *J Clin Psychiatry*. 2008;69(4):520-5. PMID: 18278987. EXCLUDE: Age.
- 458.Ruan L, Hu S, Huang M, et al. Efficacy and safety of long-acting risperidone on early onset schizophrenia in adolescent patients. *Afr J Pharmacy Pharmacol*. 2010;4(5):184-92. PMID: N/A EXCLUDE: Study Design.
- 459.Rybakowski JK, Vansteelandt K, Remlinger-Molenda A, et al. Extrapyramidal symptoms during treatment of first schizophrenia episode: results from EUFEST. *Eur Neuropsychopharmacol*. 2014;24(9):1500-5. PMID: 25085534. EXCLUDE: Age.
- 460.Sacchetti E, Galluzzo A, Valsecchi P, et al. Ziprasidone vs clozapine in schizophrenia patients refractory to multiple antipsychotic treatments: the MOZART study. *Schizophr Res*. 2009;110(1-3):80-9. PMID: 19269791. EXCLUDE: Age.
- 461.Sacchetti E, Galluzzo A, Valsecchi P, et al. Ziprasidone vs clozapine in schizophrenia patients refractory to multiple antipsychotic treatments: the MOZART study.[Erratum appears in *Schizophr Res*. 2010 Aug;121(1-3)281 Note: multiple investigator names added]. *Schizophr Res*. 2009;113(1):112-21. PMID: 19606529. EXCLUDE: Age.
- 462.Sachs GS, Grossman F, Ghaemi SN, et al. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. *Am J Psychiatry*. 2002;159(7):1146-54. PMID: 12091192. EXCLUDE: Age.
- 463.Safa M, Sadr S, Delfan B, et al. Metabolic effects of olanzapine and risperidone in patients with psychotic disorders. *Int J Psychiatry Clin Pract*. 2008;12(4):299-302. PMID: 24937718. EXCLUDE: Age.
- 464.Safety concerns prompt changes to study of drugs for early-onset schizophrenia. *Brown University Child & Adolescent Psychopharmacology Update*. 2007;9(10):1-7. PMID: 105971263. Language: English. EXCLUDE: Outcomes.

465. Saljoughian M. Atypical antipsychotics: safety and use in pediatric patients. *U.S. Pharmacist*. 2015;40(5) PMID: N/A.
EXCLUDE: Publication Type.
466. Sallee FR, Miceli JJ, Tensfeldt T, et al. Single-dose pharmacokinetics and safety of ziprasidone in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 2006;45(6):720-8. PMID: 16721322.
EXCLUDE: Study Design.
467. Sallee FR, Nesbit L, Jackson C. Double-blind, controlled comparison of haloperidol and pimozide in children with Gilles de la Tourette's Syndrome. 149th Annual Meeting of the American Psychiatric Association; 1996 May 4-9; New York. 1996:0199. <http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2214.1996.tb01999.x>
EXCLUDE: Publication Type.
468. Saloner B, Matone M, Kreider AR, et al. Second-generation antipsychotic use among stimulant-using children, by organization of Medicaid mental health. *Psychiatr Serv*. 2014;65(12):1458-64. PMID: 25179737.
EXCLUDE: Publication Type.
469. Salpekar JA, Joshi PT, Axelson DA, et al. Depression and Suicidality Outcomes in the Treatment of Early Age Mania Study. *J Am Acad Child Adolesc Psychiatry*. 2015;54(12):999-1007.e4. PMID: 26598475.
EXCLUDE: Intervention.
470. Sandor P, Musisi S, Moldofsky H, et al. Tourette syndrome: a follow-up study. *J Clin Psychopharmacol*. 1990;10(3):197-9. PMID: 2115892.
EXCLUDE: Age.
471. Sanford M, Keating GM. Aripiprazole: in adolescents with schizophrenia. *Paediatr Drugs*. 2007;9(6):419-23. PMID: 18052412.
EXCLUDE: Publication Type.
472. Scahill L, Sukhodolsky DG, Anderberg E, et al. Sensitivity of the modified Children's Yale-Brown Obsessive Compulsive Scale to detect change: Results from two multi-site trials. *Autism*. 2016;20(2):145-52. PMID: 25882391.
EXCLUDE: Intervention.
473. Scheidemantel T, Korobkova I, Rej S, et al. Asenapine for bipolar disorder. *Neuropsychiatr Dis Treat*. 2015;11:3007-17. PMID: 26674884.
EXCLUDE: Publication Type.
474. Schulz E, Fleischhaker C, Remschmidt HE. Correlated changes in symptoms and neurotransmitter indices during maintenance treatment with clozapine or conventional neuroleptics in adolescents and young adults with schizophrenia. *J Child Adolesc Psychopharmacol*. 1996;6(2):119-31. PMID: 9231304.
EXCLUDE: Intervention.
475. Scott EM, Hermens DF, White D, et al. Body mass, cardiovascular risk and metabolic characteristics of young persons presenting for mental healthcare in Sydney, Australia. *BMJ Open*. 2015;5(3):e007066. PMID: 25818274.
EXCLUDE: Publication Type.
476. Sernyak MJ, Desai R, Stolar M, et al. Impact of clozapine on completed suicide. *Am J Psychiatry*. 2001;158(6):931-7. PMID: 2001216017.
EXCLUDE: Age.
477. Shahrivar Z, Alaghband-Rad J, Mahmoudi Gharraie J, et al. The efficacy of an integrated treatment in comparison with treatment as usual in a group of youths with first-episode psychosis. *Neuropsychiatr Enfance Adolesc*. 2012:S284-s5. PMID: N/A
EXCLUDE: Intervention.
478. Shapira NA, Ward HE, Mandoki M, et al. A double-blind, placebo-controlled trial of olanzapine addition in fluoxetine-refractory obsessive-compulsive disorder. *Biol Psychiatry*. 2004;55(5):553-5. PMID: 15023585.
EXCLUDE: Age.
479. Shapiro AK, Shapiro E, Fulop G. Pimozide treatment of tic and Tourette disorders. *Pediatrics*. 1987;79(6):1032-9. PMID: 3295739.
EXCLUDE: Publication Type.
480. Shapiro E, Shapiro AK, Fulop G, et al. Controlled study of haloperidol, pimozide and placebo for the treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry*. 1989;46(8):722-30. PMID: 2665687.
EXCLUDE: Age.
481. Sharma PS, Kongasseri S, Praharaj SK. Outcome of mood stabilizer discontinuation in bipolar disorder after 5 years of euthymia. *J Clin Psychopharmacol*. 2014;34(4):504-7. PMID: 24943387.
EXCLUDE: Age.
482. Shaygannejad V, Khatoonabadi SAR, Shafiei B, et al. Olanzapine versus haloperidol: Which can control stuttering better? *Int J Preventive Med*. 2013;4:S270-

- S3. PMID: 2015433931.
EXCLUDE: Diagnosis.
483. Sheehan DV, McElroy SL, Harnett-Sheehan K, et al. Randomized, placebo-controlled trial of risperidone for acute treatment of bipolar anxiety. *J Affect Disord.* 2009;115(3):376-85. PMID: 19042026.
EXCLUDE: Age.
484. Sikich L, Frazier JA, McClellan J, et al. Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS) study. [Erratum appears in *Am J Psychiatry.* 2008 Nov;165(11):1495]. *Am J Psychiatry.* 2008;165(11):1420-31. PMID: 18794207.
EXCLUDE: Duplicate.
485. Sikirica V, Pliszka SR, Betts KA, et al. Impact of atypical antipsychotic use among adolescents with attention-deficit/hyperactivity disorder. *Am J Manag Care.* 2014;20(9):711-21. PMID: 25365746.
EXCLUDE: Intervention.
486. Silva RR, Malone RP, Anderson LT, et al. Haloperidol withdrawal and weight changes in autistic children. *Psychopharmacol Bull.* 1993;29(2):287-91. PMID: 8290679.
EXCLUDE: Study Design.
487. Simpson GM, Glick ID, Weiden PJ, et al. Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. *Am J Psychiatry.* 2004;161(10):1837-47. PMID: 15465981.
EXCLUDE: Age.
488. Sinclair T, Beckman D, Cobb M, et al. Obesity rates and psychotropic medication use: differences between a juvenile detained and committed populations in an urban setting. *J Forensic Psychol Pract.* 2014;14(3):213-20. DOI: <http://dx.doi.org/10.1080/15228932.2014.918477>. PMID: N/A
EXCLUDE: Study Design.
489. Singer MB. Variables related to compliance with neuroleptic medication in adolescent psychiatric patients after discharge from a psychiatric hospitalization. *Diss Abstr Int: Section B: The Sciences and Engineering.* 2003;63(9-B). PMID: N/A.
EXCLUDE: Publication Type.
490. Sloman L, Remington G, Konstantareas M, et al. Haloperidol versus clomipramine in autistic disorder. 151st Annual Meeting of the American Psychiatric Association; 1998 May 30 - Jun 4; Toronto. 1998 <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/668/CN-00284668/frame.html>. PMID: N/A.
EXCLUDE: Publication Type.
491. Smith DH. Thematic issue on child and adolescent psychiatry. *Can Child Adolesc Psychiatr Rev / La Revue canadienne de psychiatrie.* 2015;60(10):415-6.
EXCLUDE: Publication Type.
492. Smulevich AB, Khanna S, Eerdeken M, et al. Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol. *Eur Neuropsychopharmacol.* 2005;15(1):75-84. PMID: 15572276.
EXCLUDE: Age.
493. Sohn M. The off-label use of atypical antipsychotics and its impact on Attention Deficit/Hyperactivity Disorder (ADHD). *Dissertation Abstracts International: Section B: Sci Eng.* 2015;76(4-B E).
EXCLUDE: Diagnosis.
494. Sohn M, Talbert J, Blumenschein K, et al. Atypical antipsychotic initiation and the risk of type II diabetes in children and adolescents. *Adv Pharmacoepidemiol Drug Saf.* 2015;24(6):583-91. PMID: 25808613.
EXCLUDE: outcomes
495. Sohn M. The off-label use of atypical antipsychotics and its impact on attention deficit/hyperactivity disorder (ADHD) [Ph.D.]. *Ann Arbor: University of Kentucky;* 2014. PMID: N/A.
EXCLUDE: Diagnosis.
496. Soria-Saucedo R, Walter HJ, Cabral H, et al. Receipt of Evidence-Based Pharmacotherapy and Psychotherapy Among Children and Adolescents With New Diagnoses of Depression. *Psychiatr Serv.* 2016;67(3):316-23. PMID: 26725295.
EXCLUDE: Intervention.
497. Souza VB, Moura Filho FJ, Souza FG, et al. Cataract occurrence in patients treated with antipsychotic drugs. *Rev Bras Psiquiatr.* 2008;30(3):222-6. PMID: 18833422.
EXCLUDE: Age.
498. Spivak B, Shabash E, Sheitman B, et al. The effects of clozapine versus haloperidol on measures of impulsive aggression and suicidality in chronic

- schizophrenia patients: an open, nonrandomized, 6-month study. *J Clin Psychiatry*. 2003;64(7):755-60. PMID: 12934974.
EXCLUDE: Age.
- 499.Srihari VH, Tek C, Kucukgoncu S, et al. First-Episode Services for Psychotic Disorders in the U.S. Public Sector: A Pragmatic Randomized Controlled Trial. *Psychiatr Serv*. 2015;66(7):705-12. PMID: 25639994.
EXCLUDE: Age.
- 500.Staller JA. Intramuscular ziprasidone in youth: a retrospective chart review. *J Child Adolesc Psychopharmacol*. 2004;14(4):590-2. PMID: 15662151.
EXCLUDE: Study Design.
- 501.Staller JA. Psychopharmacologic treatment of aggressive preschoolers: a chart review. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(1):131-5. PMID: 17007977.
EXCLUDE: Study Design.
- 502.Stefanovic V, Mihajlovic G, Nenadovic M, et al. The effect of antipsychotic drugs on nonspecific inflammation markers in the first episode of schizophrenia. *Vojnosanit Pregl*. 2015;72(12):1085-92. PMID: 26898032.
EXCLUDE: Age.
- 503.Steinhausen H-C, Helenius D. "The association between medication for attention-deficit/hyperactivity disorder and cancer": Correction. *J Child Adolesc Psychopharmacol*. 2014;24(2):107-8.
EXCLUDE: Publication Type.
- 504.Stentebjerg-Olesen M, Ganocy SJ, Findling RL, et al. Early response or nonresponse at week 2 and week 3 predict ultimate response or nonresponse in adolescents with schizophrenia treated with olanzapine: results from a 6-week randomized, placebo-controlled trial. *Eur Child Adolesc Psychiatry*. 2015;24(12):1485-96. PMID: 26032132
EXCLUDE: Study Design.
- 505.Stentebjerg-Olesen M, Jeppesen P, Pagsberg AK, et al. Early nonresponse determined by the clinical global impressions scale predicts poorer outcomes in youth with schizophrenia spectrum disorders naturalistically treated with second-generation antipsychotics. *J Child Adolesc Psychopharmacol*. 2013;23(10):665-75. PMID: 24266529.
EXCLUDE: Study Design.
- 506.Stevens JR, Kymissis PI, Baker AJL. Elevated prolactin levels in male youths treated with risperidone and quetiapine. *J Child Adolesc Psychopharmacol*. 2005;15(6):893-900. PMID: 16379509.
EXCLUDE: Study Design.
- 507.Stoklosa J, Rose AB, Liebson ES, et al. Intensely Suicidal Behavior with a First Manic Episode. *Harv Rev Psychiatry*. 2015;23(4):288-95. PMID: 20160065262.
EXCLUDE: Publication Type.
- 508.Straiton ML, Powell K, Reneflot A, et al. Managing Mental Health Problems Among Immigrant Women Attending Primary Health Care Services. *Health Care Women Int*. 2016;37(1):118-39 22p. PMID: 111902586.
EXCLUDE: Age.
- 509.Strous RD, Kupchik M, Roitman S, et al. Comparison between risperidone, olanzapine, and clozapine in the management of chronic schizophrenia: a naturalistic prospective 12-week observational study. *Hum Psychopharmacol*. 2006;21(4):235-43. PMID: 16783815.
EXCLUDE: Age.
- 510.Study of risperidone with autistic children finds no detrimental cognitive effects. *Brown University Child & Adolescent Psychopharmacology Update*. 2008;10(9):3-4. PMID: 105681306.
EXCLUDE: Publication Type.
- 511.Subotnik KL, Casaus LR, Ventura J, et al. Long-Acting Injectable Risperidone for Relapse Prevention and Control of Breakthrough Symptoms After a Recent First Episode of Schizophrenia. A Randomized Clinical Trial. *JAMA Psychiatr*. 2015;72(8):822-9PMID: 26107752.
EXCLUDE: Age.
- 512.Sun X, Hamer R, McEvoy J. Asenapine once daily versus twice daily: impact on patient acceptance in a randomized, open-label, 14-day clinical trial. *J Clin Psychiatr*; 2015;992-3.
EXCLUDE: Age.
- 513.Sundar Raj M, Prasath M, Adalarasu K. Autism spectrum disorder. *Int J Pharm Technol*. 2015;7(2):8638-47. PMID: 2015453923.
EXCLUDE: Publication Type.
- 514.Svestka J, Synek O, Tomanova J, et al. Differences in the effect of second-generation antipsychotics on prolactinaemia: six weeks open-label trial in female

- in-patients. *Neuroendocrinol Lett.* 2007;28(6):881-8. PMID: 18063941. EXCLUDE: Age.
515. Sylvia LG, Thase ME, Reilly-Harrington NA, et al. Psychotherapy use in bipolar disorder: Association with functioning and illness severity. *Aust N Z J Psychiatry.* 2015;49(5):453-61. PMID: 25680360. EXCLUDE: Age.
516. Swanson JW, Swartz MS, Elbogen EB. Effectiveness of atypical antipsychotic medications in reducing violent behavior among persons with schizophrenia in community-based treatment. *Schizophr Bull.* 2004;30(1):3-20. PMID: 15176758. EXCLUDE: Age.
517. Swanson JW, Swartz MS, Van Dorn RA, et al. Comparison of antipsychotic medication effects on reducing violence in people with schizophrenia. *Br J Psychiatry.* 2008;193(1):37-43. PMID: 18700216. EXCLUDE: Age.
518. Takahashi S, Suzuki M, Uchiyama M. One-year follow-up of serum prolactin level in schizophrenia patients treated with blonanserin: A case series. *Psychiatry Investig.* 2015;12(4):566-8. PMID: 2015502075. EXCLUDE: Publication Type.
519. Tasca GA, Keating L, Maxwell H, et al. Predictors of treatment acceptance and of participation in a randomized controlled trial among women with anorexia nervosa. *Eur Eat Disord Rev.* 2012;20(2):155-61. PMID: 21751299. EXCLUDE: Study Design
520. Taylor D, Hanssens L, Loze JY, et al. Preference of medicine and patient-reported quality of life in community-treated schizophrenic patients receiving aripiprazole vs standard of care: results from the STAR study. *Eur Psychiatry.* 2008;23(5):336-43. PMID: 18423987. EXCLUDE: Age.
521. Taylor DM, Douglas-Hall P, Olofinjana B, et al. Reasons for discontinuing clozapine: matched, case-control comparison with risperidone long-acting injection. *Br J Psychiatry.* 2009;194(2):165-7. PMID: 19182180. EXCLUDE: Age.
522. Taylor M, Turner M, Watt L, et al. Atypical antipsychotics in the real world--a naturalistic comparative outcome study. *Scott Med J.* 2005;50(3):102-6. PMID: 16163994. EXCLUDE: Age.
523. TEOSS: maintenance safety and effectiveness findings. *Brown University Child & Adolescent Psychopharmacology Update.* 2010;12(7):3-4. PMID: 105045864. EXCLUDE: Outcomes.
524. Thase ME, Macfadden W, Weisler RH, et al. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *J Clin Psychopharmacol.* 2006;600-9. PMID: 17110817 EXCLUDE: Age.
525. Thase ME, Youakim JM, Skuban A, et al. Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: a phase 3, randomized, placebo-controlled study in patients with inadequate response to antidepressants. *J Clin Psychiatr.* 2015;76(9):1224-31. PMID: 26301701. EXCLUDE: Age.
526. Thase ME, Youakim JM, Skuban A, et al. Adjunctive brexpiprazole 1 and 3 mg for patients with major depressive disorder following inadequate response to antidepressants: a phase 3, randomized, double-blind study. *J Clin Psychiatr.* 2015;76(9):1232-40. PMID: 26301771. EXCLUDE: Age.
527. Tiihonen J, Wahlbeck K, Lonnqvist J, et al. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. *BMJ.* 2006;333(7561):224-7. PMID: 16825203. EXCLUDE: Age.
528. Tobiasova Z, van der Lingen KH, Scahill L, et al. Risperidone-related improvement of irritability in children with autism is not associated with changes in serum of epidermal growth factor and interleukin-13. *J Child Adoles Psychopharmacol.* 2011;21(6):555-64. PMID: 22070180. EXCLUDE: Outcomes.
529. Tohen M, Bowden CL, Smulevich AB, et al. Olanzapine plus carbamazepine v. carbamazepine alone in treating manic episodes. *Br J Psychiatry.* 2008;192(2):135-43. PMID: 18245032. EXCLUDE: Age.
530. Tohen M, Jacobs TG, Grundy SL, et al. Efficacy of olanzapine in acute bipolar mania: a double-blind,

- placebo-controlled study. The Olanzapine HGGW Study Group.[Erratum appears in Arch Gen Psychiatry 2002;59(1):91]. Arch Gen Psychiatry. 2000;57(9):841-9. PMID: 10986547.
EXCLUDE: Age.
531. Tohen M, Kryzhanovskaya L, Carlson G, et al. Efficacy of olanzapine for the treatment of acute mania in subtypes of adolescent patients: A 3-week randomized double-blind placebo controlled study. Bipolar Disord. 2006;26.
<http://onlinelibrary.wiley.com/doi/10.1111/j.1533-5017.2006.00644.x>
EXCLUDE: Duplicate.
532. Tohen M, Sanger TM, McElroy SL, et al. Olanzapine versus placebo in the treatment of acute mania. Olanzapine HGGW Study Group. Am J Psychiatry. 1999;156(5):702-9. PMID: 10327902.
EXCLUDE: Age.
533. Tohen M, Vieta E, Goodwin GM, et al. Olanzapine versus divalproex versus placebo in the treatment of mild to moderate mania: a randomized, 12-week, double-blind study. J Clin Psychiatry. 2008;69(11):1776-89. PMID: 19014751.
EXCLUDE: Age.
534. Tollefson GD, Beasley CM, Jr., Tran PV, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry. 1997;154(4):457-65. PMID: 9090331.
EXCLUDE: Age.
535. Tollefson GD, Sanger TM. Negative symptoms: a path analytic approach to a double-blind, placebo- and haloperidol-controlled clinical trial with olanzapine. Am J Psychiatry. 1997;154(4):466-74. PMID: 9090332.
EXCLUDE: Age.
536. Torniainen M, Mittendorfer-Rutz E, Tanskanen A, et al. Antipsychotic treatment and mortality in schizophrenia. Schizophr Bull. 2015;41(3):656-63. PMID: 25422511. Exclude: Age.
537. Torres JJ, Kozicky J, Popuri S, et al. 12-month longitudinal cognitive functioning in patients recently diagnosed with bipolar disorder. Bipolar Disord. 2014;16(2):159-71. PMID: 24636366.
EXCLUDE: Intervention.
538. Treating first psychotic episode in adolescents. Brown University Child & Adolescent Psychopharmacology Update. 2009;11(4):3-4. PMID: 105495563.
EXCLUDE: Outcomes.
539. Tsay ME, Klein-Schwartz W, Anderson B. Toxicity and clinical outcomes of paliperidone exposures reported to U.S. Poison Centers. Clin Toxicol. 2014;52(3):207-13. PMID: 22364403.
EXCLUDE: Study Design.
540. Turkel SB, Jacobson J, Munzig E, et al. Atypical antipsychotic medications to control symptoms of delirium in children and adolescents. J Child Adolesc Psychopharmacol. 2012;22(2):126-30. PMID: 22364403.
EXCLUDE: Diagnosis.
541. Tyrer P, Oliver-Africano P, Romeo R, et al. Neuroleptics in the treatment of aggressive challenging behaviour for people with intellectual disabilities: a randomised controlled trial (NACHBID). Health Technol Assess. 2009;13(21):iii-iv, ix-xi, 1-54. PMID: 19397849.
EXCLUDE: Age.
542. Urben S, Baumann P, Barcellona S, et al. Cognitive efficacy of quetiapine in early-onset first-episode psychosis: a 12-week open label trial. Psychiatr Q. 2012;83(3):311-24. PMID: 22101738.
EXCLUDE: Intervention.
543. Uttley L, Kearns B, Ren S, et al. Aripiprazole for the treatment and prevention of acute manic and mixed episodes in bipolar I disorder in children and adolescents: a NICE single technology appraisal. Pharmacoeconomics. 2013;31(11):981-90. PMID: 24092620.
EXCLUDE: Publication Type.
544. van Nimwegen LJ, de Haan L, van Beveren NJ, et al. Effect of olanzapine and risperidone on subjective well-being and craving for cannabis in patients with schizophrenia or related disorders: a double-blind randomized controlled trial. Can J Psychiatry. 2008;53(6):400-5. PMID: 18616861.
EXCLUDE: Age.
545. van Wattum PJ, Fabius C, Roos C, et al. Polypharmacy reduction in youth in a residential treatment center leads to positive treatment outcomes and significant cost savings. J Child Adolesc Psychopharmacol. 2013;23(9):620-7. PMID: 24251644.
EXCLUDE: Intervention.

546. Vanden Borre R, Vermote R, Buttiens M, et al. Risperidone as add-on therapy in behavioural disturbances in mental retardation: a double-blind placebo-controlled cross-over study. *Acta Psychiatr Scand.* 1993;87(3):167-71. PMID: 7682029. EXCLUDE: Age.
547. Vazquez-Bourgon J, Arranz MJ, Mata I, et al. Serotonin transporter polymorphisms and early response to antipsychotic treatment in first episode of psychosis. *Psychiatry Res.* 2010;175(3):189-94. PMID: 20031235. EXCLUDE: Age.
548. Velligan DI, Carroll C, Lage MJ, et al. Outcomes of medicaid beneficiaries with schizophrenia receiving clozapine only or antipsychotic combinations. *Psychiatr Serv.* 2015;66(2):127-33. PMID: 25321616. EXCLUDE: Age.
549. Ventura J, Subotnik KL, Gitlin MJ, et al. Negative symptoms and functioning during the first year after a recent onset of schizophrenia and 8 years later. *Schizophr Res.* 2015;161(2-3):407-13. PMID: 25499044. EXCLUDE: Age.
550. Vernal DL, Kapoor S, Al-Jadiri A, et al. Outcome of youth with early-phase schizophrenia-spectrum disorders and psychosis not otherwise specified treated with second-generation antipsychotics: 12 week results from a prospective, naturalistic cohort study. *J Child Adolesc Psychopharmacol.* 2015;25(7):535-47. PMID: 26375767. EXCLUDE: Intervention.
551. Vesper FH, Vesper BD, McMullan JT, et al. Risperidone versus haloperidol, in combination with lorazepam, in the treatment of acute agitation and psychosis: a pilot, randomized, double-blind, placebo-controlled trial. *J Psychiatr Pract.* 2006;12(2):103-8. PMID: 16728906. EXCLUDE: Age.
552. Vieta E, Bourin M, Sanchez R, et al. Effectiveness of aripiprazole v. haloperidol in acute bipolar mania: double-blind, randomised, comparative 12-week trial. *Br J Psychiatry.* 2005;187:235-42. PMID: 16135860. EXCLUDE: Age.
553. Vieta E, Suppes T, Eggens I, et al. Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). *J Affect Disord.* 2008;109(3):251-63. PMID: 18579216.
- EXCLUDE: Age.
554. Vik-Mo AO, Birkenaes AB, Ferno J, et al. Increased expression of lipid biosynthesis genes in peripheral blood cells of olanzapine-treated patients. *Int J Neuropsychopharmacol.* 2008;11(5):679-84. PMID: 18241359. EXCLUDE: Age.
555. Villari V, Rocca P, Fonzo V, et al. Oral risperidone, olanzapine and quetiapine versus haloperidol in psychotic agitation. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008;32(2):405-13. PMID: 17900775. EXCLUDE: Age.
556. Volavka J, Czobor P, Sheitman B, et al. Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. [Erratum appears in *Am J Psychiatry* 2002;159(12):2132]. *Am J Psychiatry.* 2002;159(2):255-62. PMID: 11823268. EXCLUDE: Age.
557. Voruganti LP, Awad AG, Parker G, et al. Cognition, functioning and quality of life in schizophrenia treatment: results of a one-year randomized controlled trial of olanzapine and quetiapine. *Schizophr Res.* 2007;96(1-3):146-55. PMID: 17728106. EXCLUDE: Age.
558. Vulink NC, Denys D, Fluitman SB, et al. Quetiapine augments the effect of citalopram in non-refractory obsessive-compulsive disorder: a randomized, double-blind, placebo-controlled study of 76 patients. *J Clin Psychiatry.* 2009;70(7):1001-8. PMID: 19497245. EXCLUDE: Age.
559. Walkup JT, Wagner KD, Miller L, et al. Treatment of Early-Age Mania: Outcomes for Partial and Nonresponders to Initial Treatment. *J Am Acad Child Adolesc Psychiatry.* 2015 Dec;54(12):1008-19. PMID: 26598476. EXCLUDE: Intervention.
560. Wang J, Hu MR, Guo XF, et al. Cognitive effects of atypical antipsychotic drugs in first-episode drug-naive schizophrenic patients. *Neural Regen Res.* 2013;8(3):277-86. PMID: 2015864151. EXCLUDE: Age.
561. Waugaman RM. Potential lower efficacy of molindone among first-generation antipsychotics.

- Am J Psychiatry. 2009;166(4):491. PMID: 19339370.
EXCLUDE: Publication Type.
562. Weiden PJ, Daniel DG, Simpson G, et al. Improvement in indices of health status in outpatients with schizophrenia switched to ziprasidone. *J Clin Psychopharmacol.* 2003;23(6):595-600. PMID: 14624190.
EXCLUDE: Age.
563. Weiden PJ, Schooler NR, Weedon JC, et al. A randomized controlled trial of long-acting injectable risperidone vs continuation on oral atypical antipsychotics for first-episode schizophrenia patients: initial adherence outcome. *J Clin Psychiatry.* 2009;70(10):1397-406. PMID: 19906343.
EXCLUDE: Age.
564. Weight gain and metabolic changes in children and adolescents treated with atypical antipsychotics. *Drug Benefit Trends.* 2009;21(11):358. PMID: 2010089448.
EXCLUDE: Publication Type.
565. Weiser M, Shneider-Beeri M, Nakash N, et al. Improvement in cognition associated with novel antipsychotic drugs: a direct drug effect or reduction of EPS? *Schizophr Res.* 2000;46(2-3):81-9. PMID: 11120419.
EXCLUDE: Age.
566. Weiss M, Panagiotopoulos C, Giles L, et al. A naturalistic study of predictors and risks of atypical antipsychotic use in an attention-deficit/hyperactivity disorder clinic. *J Child Adolesc Psychopharmacol.* 2009;19(5):575-82. PMID: 19877982.
EXCLUDE: Study Design.
567. West AE, Celio CI, Henry DB, et al. Child Mania Rating Scale-Parent Version: a valid measure of symptom change due to pharmacotherapy. *J Affect Disord.* 2011;128(1-2):112-9. PMID: 20858565.
EXCLUDE: Intervention.
568. West AE, Weinstein SM, Celio CI, et al. Co-morbid disruptive behavior disorder and aggression predict functional outcomes and differential response to risperidone versus divalproex in pharmacotherapy for pediatric bipolar disorder. *J Child Adolesc Psychopharmacol.* 2011;21(6):545-53. PMID: 22136096.
EXCLUDE: Intervention.
569. Wetterling T, Mussigbrodt HE. Weight gain: side effect of atypical neuroleptics? *J Clin Psychopharmacol.* 1999;19(4):316-21. PMID: 10440458.
EXCLUDE: Age.
570. Wilhelm S, Schacht A, Wagner T. Use of antipsychotics and benzodiazepines in patients with psychiatric emergencies: results of an observational trial. *BMC Psychiatry.* 2008;8:61. PMID: 18647402.
EXCLUDE: Age.
571. Winter HR, Earley WR, Hamer-Maansson JE, et al. Steady-state pharmacokinetic, safety, and tolerability profiles of quetiapine, norquetiapine, and other quetiapine metabolites in pediatric and adult patients with psychotic disorders. *J Child Adolesc Psychopharmacol.* 2008;18(1):81-98. PMID: 18294091.
EXCLUDE: Study Design.
572. Wright P, Birkett M, David SR, et al. Double-blind, placebo-controlled comparison of intramuscular olanzapine and intramuscular haloperidol in the treatment of acute agitation in schizophrenia. *Am J Psychiatry.* 2001;158(7):1149-51. PMID: 11431240.
EXCLUDE: Age.
573. Wu JQ, Chen DC, Tan YL, et al. Cognitive impairments in first-episode drug-naïve and chronic medicated schizophrenia: MATRICS consensus cognitive battery in a Chinese Han population. *Psychiatr Res.* 2016;238:196-202. PMID: 20160162360.
EXCLUDE: Age.
574. Wunderink L, Nienhuis FJ, Sytema S, et al. Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. *J Clin Psychiatry.* 2007;68(5):654-61. PMID: 17503973.
EXCLUDE: Age.
575. Yatham LN, Paulsson B, Mullen J, et al. Quetiapine versus placebo in combination with lithium or divalproex for the treatment of bipolar mania. *J Clin Psychopharmacol.* 2004:599-606. PMID: 15538120.
EXCLUDE: Age.
576. Young AH, Oren DA, Lowy A, et al. Aripiprazole monotherapy in acute mania: 12-week randomised placebo- and haloperidol-controlled study. *Br J Psychiatry.* 2009;194(1):40-8. PMID: 19118324.
EXCLUDE: Age.
577. Youngstrom E, Zhao J, Mankoski R, et al. Item level patterns of response of aripiprazole for the acute treatment of pediatric bipolar I disorder.

- Neuropsychopharmacology. 2010;S170. DOI: 10.1038/npp.2010.216. PMID: N/A.
EXCLUDE: Publication Type.
578. Younis IR, Laughren TP, Wang Y, et al. An integrated approach for establishing dosing recommendations: paliperidone for the treatment of adolescent schizophrenia. *J Clin Psychopharmacol.* 2013;33(2):152-6. PMID: 23422374.
EXCLUDE: Publication Type.
579. Yu AP, Atanasov P, Ben-Hamadi R, et al. Resource utilization and costs of schizophrenia patients treated with olanzapine versus quetiapine in a Medicaid population. *Value Health.* 2009;12(5):708-15. PMID: 19508658.
EXCLUDE: Age.
580. Yung A, Amminger P, Berger G, et al. Randomized controlled trial of antipsychotic and cognitive therapy in young people at ultra-high risk of psychosis. *Early Interv Psychiatry.* 2012;11. PMID: 21034687
EXCLUDE: Publication Type.
581. Zarcone JR, Lindauer SE, Morse PS, et al. Effects of risperidone on destructive behavior of persons with developmental disabilities: III. Functional analysis. *Am J Ment Retard.* 2004;109(4):310-21. PMID: 15176916.
EXCLUDE: Age.
582. Zedkova I, Dudova I, Urbanek T, et al. Onset of action of atypical and typical antipsychotics in the treatment of adolescent schizophrenic psychoses. *Neuroendocrinol Lett.* 2011;32(5):667-70. PMID: 22167144.
EXCLUDE: Intervention.
583. Zeni CP, Tramontina S, Ketzer CR, et al. Methylphenidate combined with aripiprazole in children and adolescents with bipolar disorder and attention-deficit/hyperactivity disorder: a randomized crossover trial. *J Child Adolesc Psychopharmacol.* 2009;19(5):553-61. PMID: 19877980.
EXCLUDE: Intervention.
584. Zhang H, Li H, Liu Y, et al. Safety and efficacy of paliperidone extended-release in chinese patients with schizophrenia: A 24-week, open-label extension of a randomized, double-blind, placebo-controlled study. *Neuropsychiatr Dis Treat.* 2016;12:69-77
PMID: 20160049641.
EXCLUDE: Age.
585. Zhang JP, Robinson DG, Gallego JA, et al. Association of a Schizophrenia Risk Variant at the DRD2 Locus with Antipsychotic Treatment Response in First-Episode Psychosis. *Schizophr Bull.* 2015;41(6):1248-55. PMID: 2015496131.
EXCLUDE: Age.
586. Zheng Y, Zhang Z-J, Han X-M, et al. A proprietary herbal medicine (5- Ling Granule) for Tourette syndrome: a randomized controlled trial. *J Child Psychol Psychiatr.* 2016;57(1):74-83 10p. PMID: 111554275.
EXCLUDE: Intervention.
587. Zink M, Kuwilsky A, Krumm B, et al. Efficacy and tolerability of ziprasidone versus risperidone as augmentation in patients partially responsive to clozapine: a randomised controlled clinical trial. *J Psychopharmacol.* 2009;23(3):305-14. PMID: 18562423.
EXCLUDE: Age.
588. Zipursky RB, Christensen BK, Daskalakis Z, et al. Treatment response to olanzapine and haloperidol and its association with dopamine D receptor occupancy in first-episode psychosis. *Can J Psychiatry.* 2005;50(8):462-9. PMID: 16127964.
EXCLUDE: Age.
589. Zong X, Hu M, Li Z, et al. N-acetylaspartate reduction in the medial prefrontal cortex following 8 weeks of risperidone treatment in first-episode drug-naive schizophrenia patients. *Sci Rep.* 2015;5:9109. PMID: 25778460.
EXCLUDE: Age.
590. Zuddas A, Di Martino A, Muglia P, et al. Long-term risperidone for pervasive developmental disorder: efficacy, tolerability, and discontinuation. *J Child Adolesc Psychopharmacol.* 2000;10(2):79-90. PMID: 10933118.
EXCLUDE: Study Design.

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**

Figure G1. Weight network analysis star plot

Figure G2. Weight inconsistency factor plot

Figure G3. BMI network analysis star plot

Figure G4. BMI inconsistency factor plot

Table G1. Pairwise comparisons from network meta-analysis for weight gain

Table G2. Pairwise comparisons from network meta-analysis for BMI

Table G3. Findings for GAE: FGA vs SGA

Table G4. Findings for GAE: FGA vs FGA

Table G5. Findings for GAE: SGA vs SGA

Table G6. Findings for GAE: Dose comparisons - aripiprazole

Table G7. Findings for GAE: Dose comparisons - asenapine

Table G8. Findings for GAE: Dose comparisons - lurasidone

Table G9. Findings for GAE: Dose comparisons - paliperidone

Table G10. Findings for GAE: Dose comparisons - quetiapine

Table G11. Findings for GAE: Dose comparisons - risperidone

Table G12. Findings for GAE: Dose comparisons - ziprasidone

Table G13. Findings for GAE: FGA vs placebo

Table G14. Findings for GAE: SGA vs placebo

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:

$$Y_i \sim N(\delta_i, V_i) \quad i = 1, \dots, Nstud$$

$$\delta_i \sim N(d, \tau^2)$$

$$d \sim N(0, 10000)$$

$$\tau \sim Uniform(0, m)$$

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:

$$Y_i \sim N(\delta_i + \beta x_i, V_i) \quad i = 1, \dots, N_{stud}$$

Where β is the regression coefficient and x_i is the value of the covariate of the i th 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:

$$\delta_{(j,b,k)} \sim N(d_{(b,k)}, \sigma^2) \sim N(d_{(P,k)} - d_{(P,b)}); j=1, \dots, N_{stud}; b, k=1, \dots, N_{treat} \quad b < k$$

$$d_{(P,k)} \sim N(0, 10000); k=2, \dots, N_{treat}$$

$$\sigma \sim \text{Unif}(0, m)$$

In this model $\delta_{(j,b,k)}$ 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 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
      }
    }
}
```

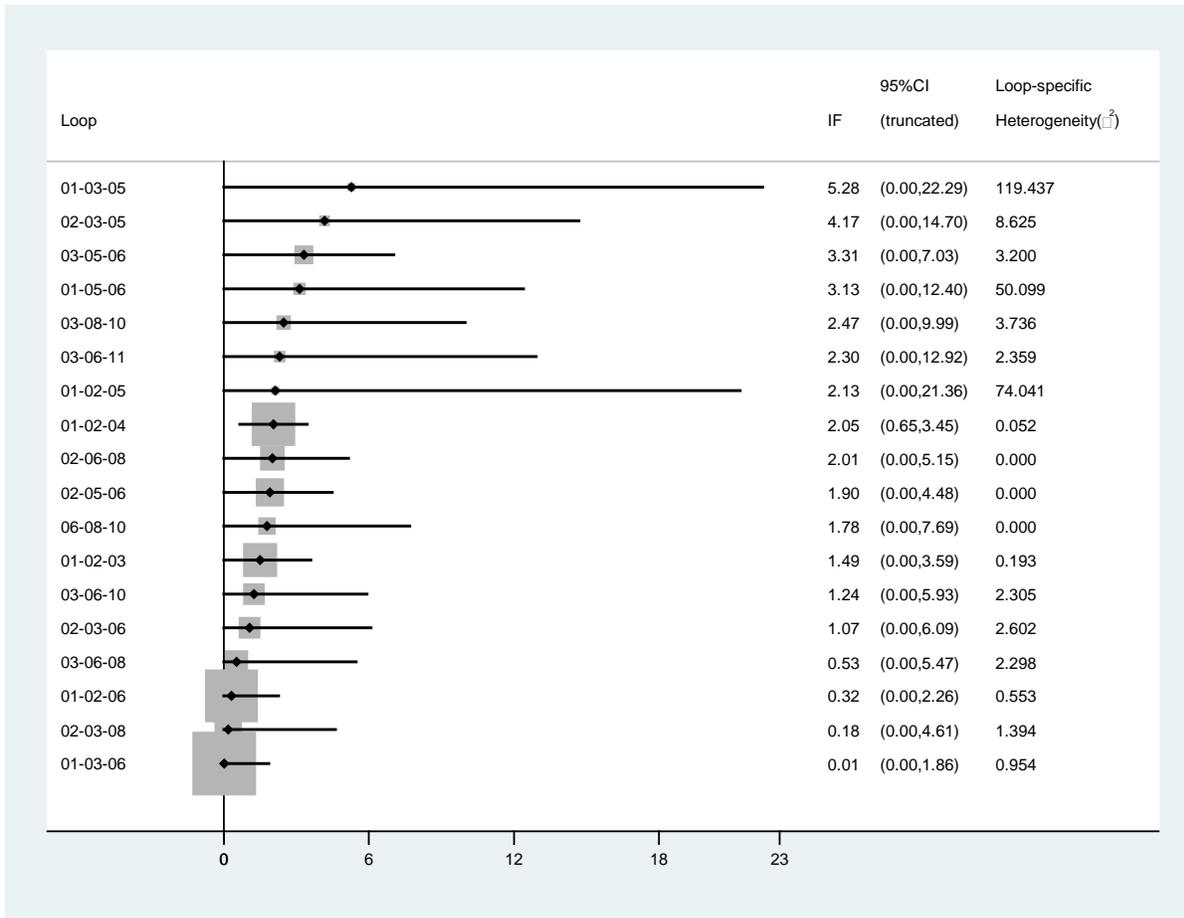
NT=no. treatments, NS=no. studies;
 # NB : set up M vectors each r[,]. n[,.] and t[,.], where M is the Maximum number of treatments
 # per trial in the dataset. In this dataset M is 3.

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 8 NA	3.9	1.047445873	1.1	1.166726189	NA	NA	3	6	
7.2	6.5375 4.9 NA 3	5.322445026	3.6	6.30005291	NA	NA	3	6	8	
4.3	2.444885287 NA 2	4.6	4.634670071	NA	NA	NA	NA	6	8	NA
4.5	4.315693262 NA 2	2.7	6.784462291	NA	NA	NA	NA	6	9	NA
1.9	4.118012423 NA 2	1	4.118012423	NA	NA	NA	NA	6	9	NA
1.28	0.246777685 NA 2	1.68	0.333243949	NA	NA	NA	NA	2	8	NA
0.94	0.871367786 NA 2	0.9	2.045993646	NA	NA	NA	NA	8	10	NA
4.4	0.559016994 10 NA	3.6	0.360555128	2.1	1.511857892	NA	NA	3	6	
3.4	1.449568901 NA 2	5	1.549193338	NA	NA	NA	NA	3	10	NA
87	3.983368201 NA 2	76.3	3.633286285	NA	NA	NA	NA	3	10	NA
3.6	1.109400392 NA 2	3.8	1.732050808	NA	NA	NA	NA	3	10	NA
4.48	0.377790328 3 5	8.6	0.59491596	6.11	0.594794082	5.38	0.272345413	2		
3.2	1.309068371 2	2.2	0.96 NA	NA	NA	NA	3	6	NA	NA
2.24	0.654368062 NA 2	1.96	0.599319381	NA	NA	NA	NA	3	6	NA
5.27	0.889582789 NA 2	1	0.353009043	NA	NA	NA	NA	3	6	NA
5.78	0.937700282 NA 2	4.45	0.956666667	NA	NA	NA	NA	3	6	NA
3.6	0.981155781 2	4.5	1.3 NA	NA	NA	NA	3	6	NA	NA
11.52	1.370369061 6 NA	6.27	1.428018267	7.08	0.742220803	NA	NA	3	5	
16.2	3.111269837 10 NA	7.2	1.67600716	9.5	2.685268453	NA	NA	3	6	
11.1	1.744133022 6 NA	2.5	1.388044188	5	1.023363439	NA	NA	3	5	
11.1	1.553160549 11 NA	11	1.287485552	7.6	3.06740933	NA	NA	3	6	
15.5	1.529705854 NA 2	5.4	1.388044188	NA	NA	NA	NA	3	5	NA
-0.2	0.172317299 NA 2	2.1	0.20587307	NA	NA	NA	NA	1	6	NA
0.61	0.317542648 NA 2	2.96	0.762823702	NA	NA	NA	NA	1	6	NA
1.71	0.290688837 NA 2	2.81	0.468008097	NA	NA	NA	NA	1	6	NA
0.1	1.061873701 NA 2	7	0.854874734	NA	NA	NA	NA	1	6	NA
0.42	0.230043474 NA 2	2.61	0.708387841	NA	NA	NA	NA	1	2	NA
0.3	0.787348234 NA 2	8.79	1.652296382	NA	NA	NA	NA	1	3	NA
0.4	0.404605071 NA 2	2.3	0.360011161	NA	NA	NA	NA	2	4	NA
36.36	0.312420657 NA 2	37.21	0.312420657	NA	NA	NA	NA	1	6	NA
33.61	0.229797012 NA 2	33.74	0.229797012	NA	NA	NA	NA	1	13	NA
0.6	2.934681063 NA 2	2.3	3.968892196	NA	NA	NA	NA	1	6	NA
44.13	0.252357307 NA 2	44.22	0.252357307	NA	NA	NA	NA	1	6	NA
0.56	0.265434332 NA 2	0.95	0.163576992	NA	NA	NA	NA	1	2	NA
0.48	0.156220839 NA 2	1.6	0.117388809	NA	NA	NA	NA	1	12	NA

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

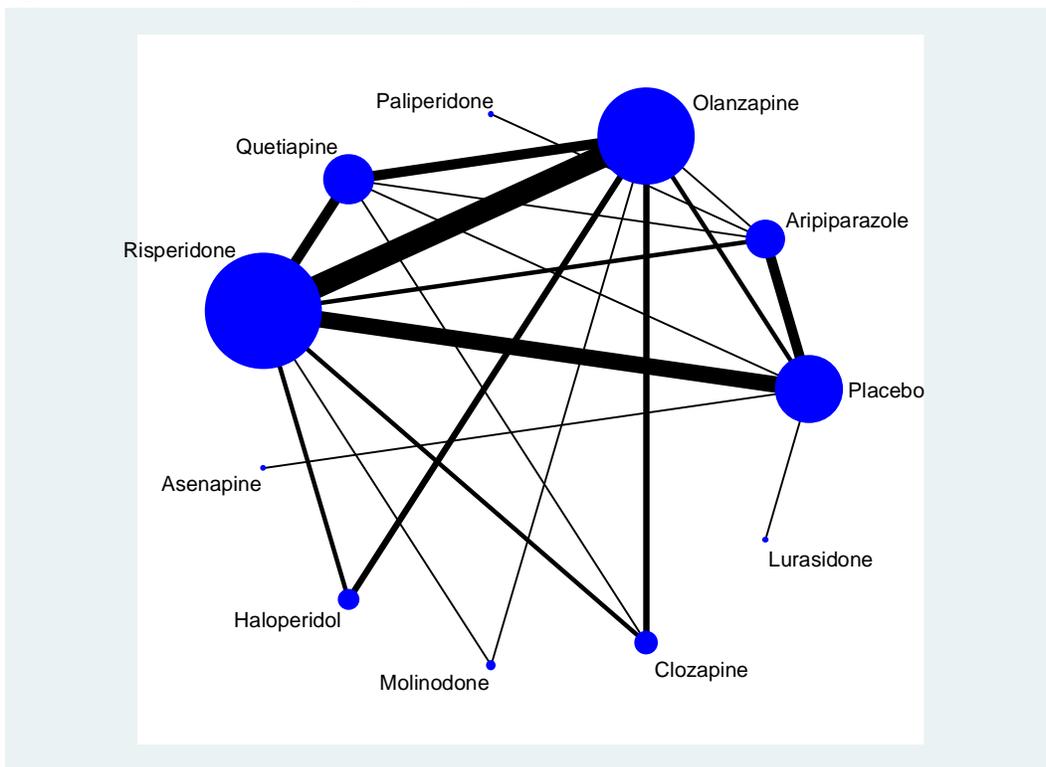
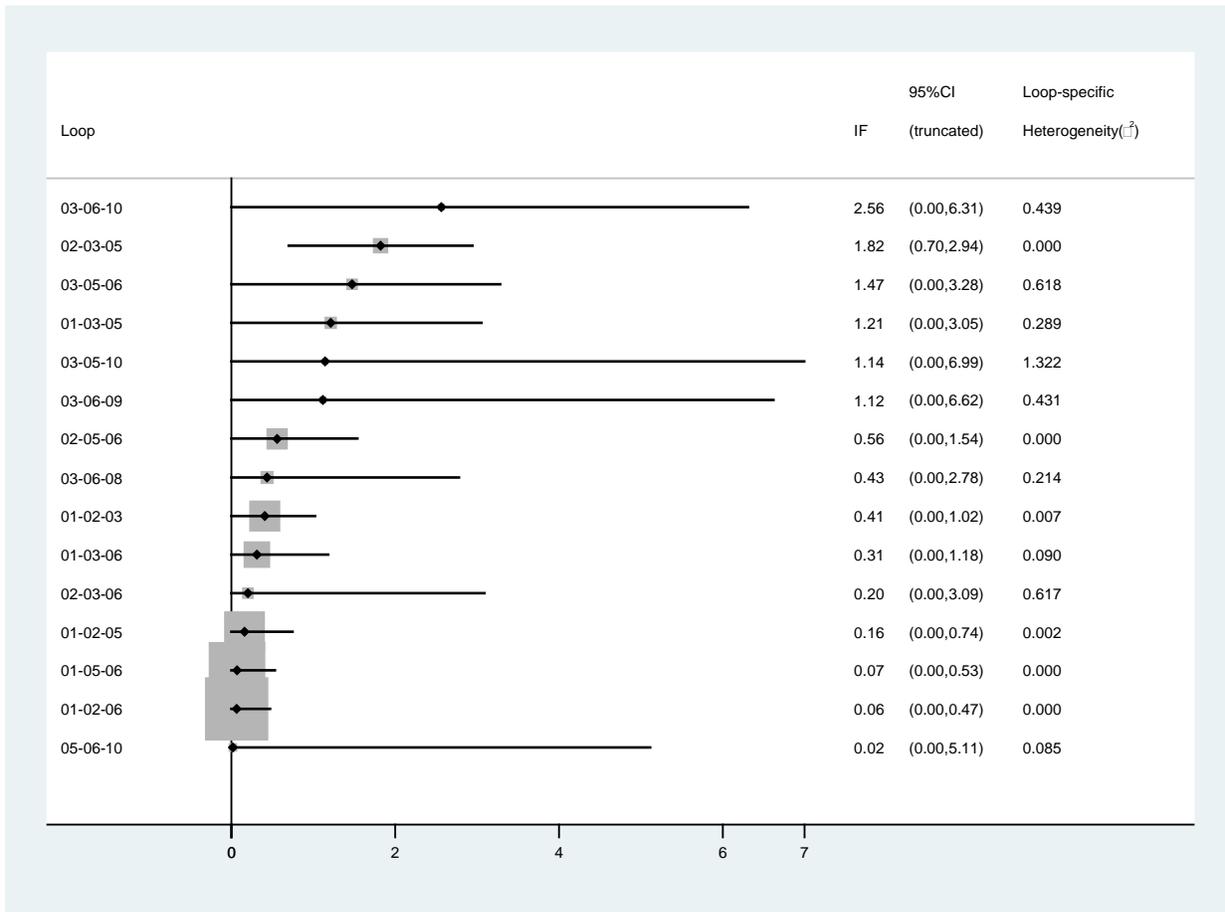


Figure G4. BMI inconsistency factor plot



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 comparisons 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	20	15	21	RR, 1.19; 95% CI, 0.56 to 1.65 ¹
			17	20	13	13	RR, 0.86; 95% CI, 0.70 to 1.07 ¹
	AE limiting treatment	6, 343	39	163	23	180	RR, 1.82; 95% CrI, 0.90 to 4.42 ^{1-3, 68}
		2, 50					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	10	NA	13	MD, -3.50; 95% CI, -10.24 to 3.24 ¹
			NA	10	NA	21	MD, -3.40; 95% CI, -9.92 to 3.12 ¹
	BMI (kg·m ⁻²)	7, 236	NA	73	NA	163	MD, -1.57; 95% CrI, -2.49 to -0.53 ^{1, 3, 4, 13}
	BMI (kg·m ⁻²) (6to<12)	2, 54	NA	10	NA	13	MD, -0.70; 95% CI, -3.08 to 1.68 ¹
			NA	10	NA	21	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·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·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·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	0	19	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	6	0	6	RR, 3.00; 95% CI, 0.15 to 61.74 ⁶
			4	7	3	19	RR, 3.62; 95% CI, 1.07 to 12.27 ⁴
	Akathisia	2, 57	3	7	0	19	RR, 17.50; 95% CI, 1.01 to 301.78 ⁴
			2	15	2	16	RR, 1.07; 95% CI, 0.17 to 6.64 ³
	Dystonia	2, 57	2	7	0	19	RR, 12.50; 95% CI, 0.67 to 232.59 ⁴
			2	15	0	16	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·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	6	6	6	RR, 0.38; 95% CI, 0.14 to 1.06 ⁶
			1	8	19	21	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	7	9	19	RR, 0.90; 95% CI, 0.34 to 2.41 ⁴	
		14	15	15	16	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	0	17	Not estimable ⁴
			7	15	5	19	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	7	1	17	RR, 7.29; 95% CI, 0.91 to 58.61 ⁴
			2	15	0	19	RR, 6.25; 95% CI, 0.32 to 121.14 ³
	Dystonia	2, 58	2	7	1	17	RR, 4.86; 95% CI, 0.52 to 45.32 ⁴
			2	15	0	19	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·m ⁻²)	2, 51	NA	4	NA	21	MD, -1.00; 95% CI, -2.47 to 0.47 ⁴
			NA	7	NA	19	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	7	3	17	RR, 2.43; 95% CI, 0.64 to 9.24 ⁴
			14	15	17	19	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	15	4	19	RR, 1.27; 95% CI, 0.38 to 4.24 ³	
		6	20	6	21	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·m ⁻²)	1, 55	NA	20	NA	35	MD, -2.05; 95% CI, -2.73 to -1.37 ¹
	BMI (kg·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·m ⁻²)	1, 61	NA	20	NA	41	MD, -1.15; 95% CI, -1.87 to -0.43 ¹
	BMI (kg·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·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·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. pimozone	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·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·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·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·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					
	Akathisia (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·m ⁻²)	1, 226	NA	114	NA	112	MD, -0.50; 95% CI, -0.74 to -0.26 ¹⁹
	BMI (kg·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
	Akathisia (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·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
	Akathisia (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·m ⁻²)	1, 215	NA	47	NA	168	MD, -0.25; 95% CI, -0.62 to 0.12 ¹⁸
	BMI (kg·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·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·m ⁻²)	3, 87	NA	40	NA	47	MD, -0.66; 95% CrI, -2.59 to 1.23 ²⁷⁻²⁹
	BMI (kg·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	2	2	24	RR, 1.67; 95% CI, 0.10 to 27.14 ²⁶	
				0	15	7	10	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·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·m ⁻²)	1, 30	NA	15	NA	15	MD, -0.20; 95% CI, -0.77 to 0.37 ²⁹
	BMI (kg·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·m ⁻²)	3, 232	NA	116	NA	116	MD, 1.36; 95% CrI, -0.29 to 3.40 ^{18, 35, 36}
	BMI (kg·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·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·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	16	6	19	RR, 1.78; 95% CI, 0.81 to 3.93 ²⁹	
		3	12	13	19	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·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·m ⁻²)	3, 463	NA	116	NA	347	MD, 0.04; 95% CrI, -1.34 to 1.20 ^{18, 35, 36}
	BMI (kg·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·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·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)	
		Count	N	Count	N	Count	N	Count	N	Count	N	Count	N
	Findling 2008a(1) ⁴⁹ Findling 2008b(2) ⁵⁰ Findling 2009(3) ⁵¹ Marcus 2009(4) ⁵²			10 mg/day				20 mg/day		25 mg/day		30mg/day	
		5 mg/day		10 mg/day		15 mg/day						30mg/day	
				10 mg/day								30 mg/day	
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	-	-	5	100	-	-	-	-	-	-	12	102
	3	-	-	8	98	-	-	-	-	-	-	11	99
	3 (6to<12)	-	-	1	75	-	-	-	-	-	-	2	71
	4	1	52	2	59	0	54	-	-	-	-	-	-
Dystonia	1	-	-	4	100	-	-	-	-	-	-	2	102
	2	-	-	-	-	-	-	1	8	1	7	0	6
	3	-	-	0	98	-	-	-	-	-	-	5	99
	3 (6to<12)	-	-	2	75	-	-	-	-	-	-	1	71
Somnolence	1	-	-	11	100	-	-	-	-	-	-	22	102
	2	-	-	-	-	1	8	0	7	1	6	-	-
	3	-	-	19	98	-	-	-	-	-	-	27	99
	3 (6to<12)	-	-	5	75	-	-	-	-	-	-	1	71
4	4	52	5	59	5	54	-	-	-	-	-	-	
Sedation	2	-	-	-	-	-	-	0	8	0	7	1	6
	3	-	-	2	98	-	-	-	-	-	-	0	99
	4	9	52	17	59	13	54	-	-	-	-	-	-
		Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N
BMI (kg·m ⁻²)	1	-	-	0.0(0.8)	99	-	-	-	-	-	-	0.0(0.8)	97
	3	-	-	0.2(0.8)	75	-	-	-	-	-	-	0.3(1.1)	72
	4	0.6 (0.2)	52	0.6(0.2)	59	0.8 (0.2)	59	-	-	-	-	-	-
Weight (kg)	1	-	-	0.0(2.1)	100	-	-	-	-	-	-	0.2(2.3)	102
	2	-	-	-	-	-	-	-0.2(2.5)	8	0.9(2.3)	7	0.4(1.8)	6
	3	-	-	0.8(1.7)	75	-	-	-	-	-	-	1.1(2.3)	73
	3 (6to<12)	-	-	6.5(NR)	75	-	-	-	-	-	-	6.6(NR)	71
4	1.3 (2.2)	53	1.3	59	1.5(2.2)	54	-	-	-	-	-	-	

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	
		Count	N	Count	N	Count	N
	Findling 2015a(1) ⁵³ Findling 2015b(2) ⁵⁴	5 mg/day 5 mg/day		10 mg/day 10 mg/day		20 mg/day	
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·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		40 mg		60mg		80 mg		120 mg		160 mg	
		Count	N	Count	N	Count	N	Count	N	Count	N	Count	N
Any AE	1	4	20	17	25	-	-	17	19	24	25	16	16
	2	35	49			38	51						
AE limiting treatment	1	0	20	3	25	-	-	5	19	1	25	0	16
	2	2	49			2	51						
Akathisia	2	3	49			3	51						
Dystonia	1	0	20	0	25	-	-	0	19	4	25	2	16
Sedation	1	0	20	3	25	-	-	5	19	7	25	4	16
	2	3	49			1	51						
Somnolence	1	0	20	11	25	-	-	7	19	16	25	10	16
	2	3	49			9	51						
		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			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		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		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	86	132	-	-	93	125	-	-
	2	-	-	41	55	-	-	39	51
	3	-	-	45	50	-	-	58	61
	4	18	30	27	31	-	-	-	-
AE limiting treatment	1	6	132	-	-	5	125	-	-
	2	-	-	3	55	-	-	4	51
	3	-	-	3	50	-	-	10	61
	4	0	30	1	31	-	-	-	-
≥7% increase in weight	3	-	-	7	50	-	-	6	61
Hyperprolactinemia	1	55	132	-	-	70	125	-	-
Prolactin-related events	1	2	132	-	-	7	125	-	-
	2	-	-	0	55	-	-	0	51
	3	-	-	2	50	-	-	3	61
	4	0	30	1	31	-	-	-	-
Any EPS	1	13	132	-	-	41	125	-	-
	2	-	-	18	55	-	-	20	51
	3	-	-	4	50	-	-	15	61
Akathisia	1	2	132	-	-	11	125	-	-
Dystonia	1	8	132	-	-	23	125	-	-
Somnolence	2	-	-	13	55	-	-	6	51
	3	-	-	21	50	-	-	34	61
	4	0	30	7	31	-	-	-	-
Sedation	3	-	-	10	50	-	-	13	61
	4	1	30	8	31	-	-	-	-
		Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N
BMI (kg·m ⁻²)	2	-	-	0.36(NR)	55	-	-	0.48(NR)	51
	3	-	-	0.7(0.9)	50	-	-	0.5(0.9)	61
	4	0.4(0.7)	30	1.1(1.35)	31	-	-	-	-
Weight (kg)	1	1.7	132	-	-	3.2(3.49)	125	-	-
	2	-	-	1.3(NR)	55	-	-	1.5(NR)	51
	3	-	-	1.9(1.7)	50	-	-	1.4(2.4)	61
	4	1.2	30	2.4(2.07)	31	-	-	-	-

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	
		Count	N	Count	N
	Delbello 2008(1) ⁶⁵	80 mg/day		160 mg/day	
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·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·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·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·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·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·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·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·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
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·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·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·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·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·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·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·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·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

References

1. Sikich L, Frazier JA, McClellan J, et al. Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (teoss) study. *Am J Psychiatry*. 2008;165(11):1420-31. PMID: 18794207.
2. Yoo HK, Lee JS, Paik KW, et al. Open-label study comparing the efficacy and tolerability of aripiprazole and haloperidol in the treatment of pediatric tic disorders. *Eur Child Adolesc Psychiatry*. 2011;20(3):127-35. PMID: 21188439.
3. Sikich L, Hamer RM, Bashford RA, et al. A pilot study of risperidone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial. *Neuropsychopharmacology*. 2004;29(1):133-45. PMID: 14583740.
4. Ratzoni G, Gothelf D, Brand-Gothelf A, et al. Weight gain associated with olanzapine and risperidone in adolescent patients: a comparative prospective study. *J Am Acad Child Adolesc Psychiatry*. 2002;41(3):337-43. PMID: 11886029.
5. Cianchetti C, Ledda MG. Effectiveness and safety of antipsychotics in early onset psychoses: a long-term comparison. *Psychiatry Res*. 2011;189(3):349-56. PMID: 21570128.
6. Malone RP, Cater J, Sheikh RM, et al. Olanzapine versus haloperidol in children with autistic disorder: an open pilot study. *J Am Acad Child Adolesc Psychiatry*. 2001;40(8):887-94. PMID: 11501687.
7. Yoo HK, Joung YS, Lee JS, et al. A multicenter, randomized, double-blind, placebo-controlled study of aripiprazole in children and adolescents with tourette's disorder. *J Clin Psychiatry*. 2013;74(8):e772-80. PMID: 24021518.
8. 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. PMID: 18080171.
9. Bruggeman R, Van Der LC, Buitelaar JK, et al. Risperidone versus pimozide in tourette's disorder: a comparative double-blind parallel-group study. *J Clin Psychiatry*. 2001;62(1):50-6. PMID: 11235929.
10. Gilbert DL, Batterson JR, Sethuraman G, et al. Tic reduction with risperidone versus pimozide in a randomized, double-blind, crossover trial. *J Am Acad Child Adolesc Psychiatry*. 2004;43(2):206-14. PMID: 14726728.
11. Ebert T, Midbari Y, Shmilovitz R, et al. Metabolic effects of antipsychotics in prepubertal children: a retrospective chart review. *J Child Adolesc Psychopharmacol*. 2014;24(4):218-22. PMID: 24816004.
12. Kumra S, Frazier JA, Jacobsen LK, et al. Childhood-onset schizophrenia. A double-blind clozapine-haloperidol comparison. *Arch Gen Psychiatry*. 1996;53(12):1090-7. PMID: 8956674.
13. Gothelf D, Falk B, Singer P, et al. Weight gain associated with increased food intake and low habitual activity levels in male adolescent schizophrenic inpatients treated with olanzapine. *Am J Psychiatry*. 2002;159(6):1055-7. PMID: 12042200.
14. Wudarsky M, Nicolson R, Hamburger SD, et al. Elevated prolactin in pediatric patients on typical and atypical antipsychotics. *J Child Adolesc Psychopharmacol*. 1999(4):239-45. PMID: 10630453.
15. Yen YC, Lung F-W, Chong MY. Adverse effects of risperidone and haloperidol treatment in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2004;28(2):285-90. PMID: 14751424.
16. Perry R, Campbell M, Adams P, et al. Long-term efficacy of haloperidol in autistic children: continuous versus discontinuous drug administration. *J Am Acad Child Adolesc Psychiatry*. 1989;28(1):87-92. PMID: 2914841.
17. Sallee FR, Nesbitt L, Jackson C, et al. Relative efficacy of haloperidol and pimozide in children and adolescents with tourette's disorder. *Am J Psychiatry*. 1997;154(8):1057-62. PMID: 9247389.

18. Correll CU, Manu P, Olshanskiy V, et al. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA*. 2009;16(16):1765-73. PMID: 19861668.
19. Savitz AJ, Lane R, Nuamah I, et al. Efficacy and safety of paliperidone extended release in adolescents with schizophrenia: a randomized, double-blind study. *J Am Acad Child Adolesc Psychiatry*. 2015;54(2):126-37.e1. PMID: 25617253.
20. Oh J, Chang JG, Lee SB, et al. Comparison of aripiprazole and other atypical antipsychotics for pediatric bipolar disorder: a retrospective chart review of efficacy and tolerability. *Clin*. 2013;11(2):72-9. PMID: 24023551.
21. Masi G, Pfanner C, Brovedani P. Antipsychotic augmentation of selective serotonin reuptake inhibitors in resistant tic-related obsessive-compulsive disorder in children and adolescents: a naturalistic comparative study. *J Psychiatr Res*. 2013;47(8):1007-12. PMID: 23664673.
22. Ghanizadeh A, Haghghi A. Aripiprazole versus risperidone for treating children and adolescents with tic disorder: a randomized double blind clinical trial. *Child Psychiatry Hum Dev*. 2014b;45(5):596-603. PMID: 24343476.
23. Ghanizadeh A, Sahraeizadeh A, Berk M. A head-to-head comparison of aripiprazole and risperidone for safety and treating autistic disorders, a randomized double blind clinical trial. *Child Psychiatry Hum Dev*. 2014a;45(2):185-92. PMID: 23801256.
24. Wink LK, Early M, Schaefer T, et al. Body mass index change in autism spectrum disorders: comparison of treatment with risperidone and aripiprazole. *J Child Adolesc Psychopharmacol*. 2014;24(2):78-82. PMID: 24564519.
25. Bastiaens L. A non-randomized, open study with aripiprazole and ziprasidone for the treatment of aggressive behavior in youth in a community clinic. *Community Ment Health J*. 2009(1):73-7. PMID: 18597173.
26. Alacqua M, Trifiro G, Arcoraci V, et al. Use and tolerability of newer antipsychotics and antidepressants: a chart review in a paediatric setting. *Pharm World Sci*. 2008;30(1):44-50. PMID: 17588130.
27. Shaw P, Sporn A, Gogtay N, et al. Childhood-onset schizophrenia: a double-blind, randomized clozapine-olanzapine comparison. *Arch Gen Psychiatry*. 2006;63(7):721-30. PMID: 16818861.
28. 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. PMID: 17651705.
29. 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. PMID: 16768638.
30. Hrdlicka M, Zedkova I, Blatny M, et al. Weight gain associated with atypical and typical antipsychotics during treatment of adolescent schizophrenic psychoses: a retrospective study. *Neuroendocrinology Lett*. 2009;30(2):256-61. PMID: N/A.
31. Kumra S, Jacobsen LK, Lenane M, et al. Childhood-onset schizophrenia: an open-label study of olanzapine in adolescents. *J Am Acad Child Adolesc Psychiatry*. 1998;37(4):377-85. PMID: 9549958.
32. Castro-Fornieles J, Parellada M, Soutullo CA, et al. Antipsychotic treatment in child and adolescent first-episode psychosis: a longitudinal naturalistic approach. *J Child Adolesc Psychopharmacol*. 2008;18(4):327-36. PMID: 18759642.
33. 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. PMID: 19198920.
34. Jensen JB, Kumra S, Leitten W, et al. A comparative pilot study of second-generation antipsychotics in children and adolescents with schizophrenia-spectrum disorders. *J Child Adolesc Psychopharmacol*. 2008;18(4):317-26. PMID: 18759641.

35. 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. *J Am Acad Child Adolesc Psychiatry*. 2014;53(11):1179-90. PMID: 25440308.
36. Fraguas D, Merchan-Naranjo J, Laita P, et al. Metabolic and hormonal side effects in children and adolescents treated with second-generation antipsychotics. *J Clin Psychiatry*. 2008;69(7):1166-75. PMID: 18588363.
37. Cuerda C, Merchan-Naranjo J, Velasco C, et al. Influence of resting energy expenditure on weight gain in adolescents taking second-generation antipsychotics. *Clin Nutr*. 2011;30(5):616-23. PMID: 21492975.
38. Saito E, Correll CU, Gallelli K, et al. A prospective study of hyperprolactinemia in children and adolescents treated with atypical antipsychotic agents. *J Child Adolesc Psychopharmacol*. 2004;14(3):350-8. PMID: 15650492.
39. Friedlander R, Lazar S, Klancnik J. Atypical antipsychotic use in treating adolescents and young adults with developmental disabilities. *Can J Psychiatry*. 2001;46(8):741-5. PMID: 11692977.
40. Mozes T, Ebert T, Michal SE, et al. An open-label randomized comparison of olanzapine versus risperidone in the treatment of childhood-onset schizophrenia. *J Child Adolesc Psychopharmacol*. 2006;16(4):393-403. PMID: 16958565.
41. Van Bruggen J, Tijssen J, Dingemans P, et al. Symptom response and side-effects of olanzapine and risperidone in young adults with recent onset schizophrenia. *Int Clin Psychopharmacol*. 2003;18(6):341-6. PMID: 14571154.
42. Biederman J, Mick E, Hammerness P, et al. Open-label, 8-week trial of olanzapine and risperidone for the treatment of bipolar disorder in preschool-age children. *Biol Psychiatry*. 2005;58(7):589-94. PMID: 16239162.
43. Pogge DL, Singer MB, Harvey PD. Rates and predictors of adherence with atypical antipsychotic medication: A follow-up study of adolescent inpatients. *J Child Adolesc Psychopharmacol*. 2005;15(6):901-12. PMID: 16379510.
44. Crocq MA, Guillon MS, Bailey PE, et al. Orally disintegrating olanzapine induces less weight gain in adolescents than standard oral tablets. *Eur Psychiatry*. 2007;22(7):453-4. PMID: 17761403.
45. Khan RA, Mican LM, Suehs BT. Effects of olanzapine and risperidone on metabolic factors in children and adolescents: a retrospective evaluation. *J Psychiatr Pract*. 2009 Jul;15(4):320-8. PMID: 19625888.
46. Migliardi G, Spina E, D'arrigo C, et al. Short- and long-term effects on prolactin of risperidone and olanzapine treatments in children and adolescents. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33(8):1496-501. PMID: 19706318.
47. Masi G, Milone A, Stawinoga A, et al. Efficacy and safety of risperidone and quetiapine in adolescents with bipolar II disorder comorbid with conduct disorder. *J Clin Psychopharmacol*. 2015;35(5):587-90. PMID: 26226481.
48. Swadi HS, Craig BJ, Pirwani NZ, et al. A trial of quetiapine compared with risperidone in the treatment of first onset psychosis among 15-to 18-year-old adolescents. *Int Clin Psychopharmacol*. 2010;25(1):1-6. PMID: 19809337.
49. 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*. 2008a;165(11):1432-41. PMID: 18765484.
50. Findling RL, Kauffman RE, Sallee FR, et al. Tolerability and pharmacokinetics of aripiprazole in children and adolescents with psychiatric disorders: an open-label, dose-escalation study. *J Clin Psychopharmacol*. 2008b;28(4):441-6. PMID: 18626272.

51. 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. *J Clin Psychiatry*. 2009;70(10):1441-51. PMID: 19906348.
52. 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 Acad Child Adolesc Psychiatry*. 2009;48(11):1110-9. PMID: 19797985.
53. Findling RL, Landbloom RP, Mackle M, et al. Safety and efficacy from an 8 week double-blind trial and a 26 week open-label extension of asenapine in adolescents with schizophrenia. *J Child Adolesc Psychopharmacol*. 2015a;25(5):384-96. PMID: 26091193.
54. Findling RL, Landbloom RL, Szegedi A, et al. Asenapine for the acute treatment of pediatric manic or mixed episode of bipolar I disorder. *J Am Acad Child Adolesc Psychiatry*. 2015b;54(12):1032-41. PMID: 26598478.
55. Stocks JD, Taneja BK, Baroldi P, et al. A phase 2a randomized, parallel group, dose-ranging study of molindone in children with attention-deficit/hyperactivity disorder and persistent, serious conduct problems. *J Child Adolesc Psychopharmacol*. 2012;22(2):102-11. PMID: 22372512.
56. Johnson & Johnson Pharmaceutical Research & Development. Open-label study to evaluate the safety and pharmacokinetics of single- and multiple-dose extended-release paliperidone in pediatric subjects (10 to 17 years of age) with schizophrenia, schizoaffective disorder, or schizophreniform disorder. 2011. http://filehosting.pharmacm.com/DownloadService.ashx?client=CTR_JNJ_6051&studyid=473&filename=CR002371_CSR.pdf. Accessed September 28, 2015.
57. Singh J, Robb A, Vijapurkar U, et al. A randomized, double-blind study of paliperidone extended-release in treatment of acute schizophrenia in adolescents. *Biol Psychiatry*. 2011;70(12):1179-87. PMID: 21831359.
58. Berger GE, Proffitt TM, Mcconchie M, et al. Dosing quetiapine in drug-naive first-episode psychosis: A controlled, double-blind, randomized, single-center study investigating efficacy, tolerability, and safety of 200 mg/day vs. 400 mg/day of quetiapine fumarate in 141 patients aged 15 to 25 years. *J Clin Psychiatry*. 2008;69(11):1702-14. PMID: 19036233.
59. Findling RL, Mckenna K, Earley WR, et al. Efficacy and safety of quetiapine in adolescents with schizophrenia investigated in a 6-week, double-blind, placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2012a;22(5):327-42. PMID: 23083020.
60. Pathak S., Findling RL, Earley WR, et al. Efficacy and safety of quetiapine in children and adolescents with mania associated with bipolar I disorder: a 3-week, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2013;74(1):e100-9. PMID: 23419231.
61. Haas M, Eerdeken M, Kushner S, et al. Efficacy, safety and tolerability of two dosing regimens in adolescent schizophrenia: double-blind study. *Br J Psychiatry*. 2009a;194(2):158-64. PMID: 19182179.
62. Haas M, Unis AS, Armenteros J, et al. A 6-week, randomized, double-blind, placebo-controlled study of the efficacy and safety of risperidone in adolescents with schizophrenia. *J Child Adolesc Psychopharmacol*. 2009b;19(6):611-21. PMID: 20035579.
63. 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*. 2009c;11(7):687-700. PMID: 19839994.
64. Kent JM, Kushner S, Ning X, et al. Risperidone dosing in children and adolescents with autistic disorder: a double-blind, placebo-controlled study. *J Autism Dev Disord*. 2013;43(8):1773-83. PMID: 23212807.

65. Delbello MP, Versavel M, Ice K, et al. Tolerability of oral ziprasidone in children and adolescents with bipolar mania, schizophrenia, or schizoaffective disorder. *J Child Adolesc Psychopharmacol*. 2008;18(5):491-9. PMID: 18928413.
66. Remington G, Sloman L, Konstantareas M, et al. Clomipramine versus haloperidol in the treatment of autistic disorder: a double-blind, placebo-controlled, crossover study. *J Clin Psychopharmacol*. 2001;21(4):440-4. PMID: 11476129.
67. Anderson LT, Campbell M, Adams P, et al. The effects of haloperidol on discrimination learning and behavioral symptoms in autistic children. *J Autism Dev Disord*. 1989;19(2):227-39. PMID 2663834.
68. Conus P, Berk M, Cotton SM, et al. Olanzapine or chlorpromazine plus lithium in first episode psychotic mania: An 8-week randomised controlled trial. *Eur Psychiatry*. 2015;30(8):975-82. PMID: 26485297.
69. Findling RL, Goldman R, Chiu YY, et al. Pharmacokinetics and tolerability of lurasidone in children and adolescents with psychiatric disorders. *Clin Ther*. 2015;37(12):2788-97. PMID: 26631428.
70. Loebel A, Brams M, Goldman RS, et al. Lurasidone for the treatment of irritability associated with autistic disorder. *J Autism Dev Discord*. 2016;46(4):1153-63. PMID: 26659550.
71. Ronsley R, Nguyen D, Davidson J, et al. Increased risk of obesity and metabolic dysregulation following 12 months of second-generation antipsychotic treatment in children: a prospective cohort study. *Can J Psychiatry*. 2015;60(10):441–50. PMID: 26720191