

AHRQ Comparative Effectiveness Review Surveillance Program

CER #39: First & second generation antipsychotics for children and young adults

Original Release Date: February, 2012

Surveillance Report: November, 2012

Surveillance Report: October, 2014

Summary of Key Findings from Surveillance Reports:

- For Key Question 1, studies were identified suggesting that conclusions related to the effectiveness of Second Generation Antidepressants (SGA) for anorexia nervosa are out of date, that conclusions related to the comparative effectiveness of First Generation Antidepressants (FGA) and SGAs are possibly out of date, that the conclusion of no difference between SGAs and placebo for aggression is possibly out of date, that the strength of evidence (SOE) for SGAs and improvement on mania scales may possibly increase from low to moderate, and the SOE regarding risperidone and reduction in problem behavior may have increased.
- For Key Question 2, conclusions related to cardiovascular events and weight gain, and the tolerability of molidone hydrochloride are possibly out of date, and the SOE for additional adverse events may possibly increase from moderate to high.
- For Key Question 3, the conclusion on the safety and tolerability of FGAs vs. SGAs is possibly out of date.
- For Key Question 4, conclusions related to individuals with comorbid disorders are possibly out of date.

Signal Assessment: The signals examined in this surveillance assessment suggest that the original CER is possibly out of date.

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Conflict of Interest:

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

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Introduction

The purpose of the surveillance process for the EPC Program is to decide if and when a systematic review is in need of updating. Approximately 25 systematic reviews are selected for surveillance annually based on popularity, use in obtaining continuing medical education certificates, potential impact for changing the field, and use in clinical practice guidelines.

Comparative Effectiveness Review (CER) #39 titled “First- and Second- Generation Antipsychotics for Children and Young Adults” was published in February, 2012.¹ Surveillance assessment was completed in November, 2012 at which time the CER’s priority for updating was low.² The CER was again selected for surveillance assessment based on popularity, potential impact, and other measures of use collected as of June, 2013.³

The key questions for the original CER are as follows:

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

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

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

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

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

- Response rates with corresponding dose, duration of response, remission, relapse, speed of response and time to discontinuation of medication.
- Growth and maturation.
- Cognitive and emotional development.

- Suicide-related behaviors or death by suicide.
- Medication adherence and persistence.
- School performance and attendance.
- Work-related functional capacity.
- Patient insight into illness.
- Patient-, parent-, or care provider-reported outcomes, including levels of physical activity or inactivity and diet (e.g., caloric intake, food preferences).
- Health-related quality of life.
- Legal or justice system interaction (e.g., arrests, detention).
- Health care system utilization (e.g., protective services, social services).
- “Outcomes that matter” to children, youth, young adults, and their families. These *functional* outcomes may reflect a developmental perspective.

Key Question 4: Do the effectiveness and risks of FGAs and SGAs vary in differing subpopulations, including:

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

Our surveillance assessment began in June, 2014. We conducted an electronic search for literature published since the most recent surveillance report search date. After completing a scan of this literature to identify evidence potentially related to the key questions in this CER, we contacted experts involved in the original CER to request their opinions as to whether the conclusions had changed.

Methods

Prior Surveillance

A surveillance report for the original CER was released in November, 2012, and included a search for relevant literature published between January 2011 and August 2012, expert opinion, and a search of FDA reports.² The findings from this report are included in our assessment.

Literature Searches

We conducted two literature searches of PubMed and PsycINFO covering August 2012 to June 2014, using the identical search strategy used for the original report¹ and searching for studies published since the end date of the most recent surveillance search.

The first search was conducted to assess a signal for the potential to update. This search included the same nine journals selected for the prior surveillance assessments plus an additional two high-impact journals (PLoS Medicine and Cochrane Database of Systematic Reviews) and three specialty journals (Pediatrics, Archives of General Psychiatry, and Archives of Clinical Psychiatry). The journal selection process included selecting journals from among the top 10 journals from relevant specialty subject areas (Appendix A) and among those most highly represented among the references for the original report (Appendix B). The included journals were seven high-impact general medical interest journals (The BMJ, New England Journal of Medicine, Lancet, JAMA, PLoS Medicine, Annals of Internal Medicine and Cochrane Database of Systematic Reviews) and seven specialty journals (American Journal of Psychiatry, Pediatrics, Archives of General Psychiatry, Archives of Clinical Psychiatry, Journal of Clinical Psychiatry, Journal of Child and Adolescent Psychopharmacology, and Journal of the American Academy of Child and Adolescent Psychiatry). The second search was conducted to assess the volume of literature and size of a potential systematic review. The second search included a full search of Pubmed and PsycINFO. The search strategy is reported in Appendix C.

Study Selection

Using the same inclusion and exclusion criteria as the original CER (see Appendix D), one investigator reviewed the titles and abstracts of the 14 high-impact journal search results (Appendix E).

To calculate the expected number of included studies based on the total number of studies resulting from the full search, a random sample of 200 titles and abstracts resulting from the full search were reviewed for inclusion.

Expert Opinion

We shared the conclusions of the original report and most recent surveillance assessment, findings from the literature analysis, and the newly identified studies with seven experts in the field (original peer reviewers, technical expert panel members [TEP] and a local expert) to request their assessment of the need to update the report and their recommendations of any relevant new studies. Two subject matter experts responded to our request. Appendix F shows the forms that were sent to the experts. Note that the British Journal of Medicine and Journal of Clinical Psychiatry were added to the included list of searched journals after summaries were shared with expert reviewers. Consequently, expert reviewers did not receive information on the two articles²²⁻²³ meeting inclusion criteria that were published in these journals.

Horizon Scanning High-Impact Potential

The AHRQ Healthcare Horizon Scanning System identifies emerging health care technologies and innovations with the potential to impact health care for AHRQ's 14 priority conditions.⁴ We reviewed the Depression and Other Mental Health Disorders section to identify new potentially high-impact interventions related to the key questions in this CER. Potentially high impact interventions were considered in the final assessment of the need to update.

FDA Black Box Warnings

We searched the FDA MedWatch online database website for black box warnings relevant to the key questions in this CER.

Check for Qualitative Signals

The authors of the original CER conducted meta-analyses on the efficacy of second-generation antipsychotics (SGAs) for pervasive developmental disorders (PDD), attention deficit hyperactivity disorder (ADHD), bipolar disorder, schizophrenia, and Tourette's syndrome. Meta-analyses were also conducted for adverse events including extrapyramidal symptoms (EPC) weight gain, dyslipidemia, sedation, and prolactin-related events. We compared the conclusions of the included abstracts to the conclusions of the original CER and surveillance reports, and assessed expert opinions to identify qualitative signals to update.

Compilation of Findings and Conclusions

For this assessment we constructed a summary table (Appendix G) that includes the key questions, the conclusions from the original CER and most recent surveillance assessment, findings of the new literature search, and the expert assessments that pertained to each key question. Because we did not find any FDA black box warnings relevant to the key questions in this CER, we did not include a column for this in the summary table. We categorized whether the conclusions need updating using a 3-category scheme:

- Original conclusion is still valid and this portion of the CER is likely not in need of updating
- Original conclusion is possibly out of date and this portion of the CER may need updating
- Original conclusion is out of date.

We considered the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as likely not in need of updating.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

Signal Assessment for Updating

We used the following considerations in our assessment of the need to update this CER:

- **Strong signal:** A report is considered to have a strong signal for updating if new evidence is identified that clearly renders conclusions from the original report out of date, such as the addition or removal of a drug or device from the market or a new FDA boxed warning.
- **Medium signal:** A report is considered to have a medium signal for updating when new evidence is identified which may change the conclusions from the original report. This may occur when abstract review and expert assessment indicates that some conclusions from the original report may be out of date, or when it is unclear from abstract review how new evidence may impact the findings from the original report. In this case, full-text review and data abstraction may be needed to more clearly classify a signal.
- **Weak signal:** A report is considered to have a weak signal for updating if little or no new evidence is identified that would change the conclusions from the original report. This may occur when little to no new evidence is identified, or when some new evidence is identified but it is clear from abstract review and expert assessment that the new evidence is unlikely to change the conclusions of the original report.

Results

Prior Surveillance

Prior surveillance of the topic included 19 studies and consultation with two subject matter experts, and concluded that for Key Question 1, the strength of evidence regarding second-generation antipsychotics (SGAs) and improvement in mania scores may have increased from low to moderate and was possibly out of date, and that the strength of evidence regarding risperidone and reduction in problem behavior may have also increased from low to moderate, and was possibly out of date. In addition, the original report found no studies examining SGAs for anorexia nervosa. The prior surveillance assessment identified four studies that met inclusion criteria and deemed this conclusion out of date. All other original CER conclusions were determined to be up to date.²

Literature Searches

The literature search identified 870 titles, with 59 from the 14 selected high profile general medical and specialty journals (Appendix E). After title and abstract review, 40 studies were rejected because they did not meet the original CER inclusion criteria (see Appendix D). The remaining 19 studies⁵⁻²³ were examined for potential to change the results of the original review. From the remaining 811 titles, a random sample of 200 was reviewed for inclusion. 4.5% of the titles met criteria for inclusion, for an expected total of 37 studies.

Horizon Scanning

We identified one intervention, *Cortisol antagonist (mifepristone, Korlym) for treatment of psychotic depression*. The high impact potential for this intervention is on the lower end of the high-impact-potential range, and is not closely related to any of the key questions for this CER. Thus, we did not identify a relevant high-impact potential intervention for this CER.

FDA Black Box Warnings

We did not find any FDA black box warnings relevant to the key questions in this CER.

Expert Opinion

We shared the conclusions of the original report with seven experts in the field (original peer reviewers, original technical expert panel (TEP) members and a local expert) to request their assessment of the need to update the report and their recommendations of any relevant new studies. Two subject matter experts responded. Appendix F shows the forms that were sent to the experts.

The two experts each identified at least one report conclusion they felt was out of to date. One reviewer felt that there were likely unpublished studies related to the key questions, but did not know of specific details (see Appendix G).

Identifying Qualitative Signals

Appendix G shows the original key questions, the conclusions of the original report and the most recent surveillance report, the results of the literature, the experts' assessments, and the recommendations of the Scientific Resource Center (SRC) regarding the need for update.

Many of the studies we identified had the potential to change the conclusions in the original CER. The original report concluded that Second-Generation Antipsychotics (SGAs) were favored over First-Generation Antipsychotics (FGAs) for symptom improvement in patients with schizophrenia or schizophrenia-related psychosis¹. We identified a systematic review⁵ that examined five RCTs and found no difference on the Brief Psychiatric Rating Scale (BPRS), and another study that found no significant differences between molindone, olanzapine, and risperidone on neurocognitive functioning in patients with schizophrenia, but that SGAs were associated with modest improvements in neurocognitive function⁶. In addition, we also found studies reporting no difference between ziprasidone and placebo on the BPRS-A⁷, that quetiapine at 400 and 800 mg/day is effective over placebo on the PANSS⁸, and that early response to aripiprazole was the best predictor for later symptom improvement in adolescents⁹. For children and adolescents with ADHD, the original CER concluded no difference between placebo and aggression for SGAs²; however, we identified both a meta-analysis¹⁰ that found limited evidence to support the efficacy of SGAs for reducing aggression, and a study¹¹, which found reductions on the NCBRF-TIQ, with 5-40 mg of molindone hydrochloride. In children with bipolar disorder, the original CER concluded a low strength of evidence favoring SGAs over placebo for mania. We identified one RCT reporting greater reductions on the YMRS for ziprasidone vs. placebo⁸, and another study found greater improvements on the YMRS for quetiapine over placebo in participants aged 10-17.²² For children with pervasive developmental disorders, the original CER concluded that SGAs were favored over placebo for children with autism, and we identified a meta-analysis of two RCTs which similarly found aripiprazole to be more effective than placebo.¹² Finally, the original CER concluded that SGAs were more effective for symptom reduction in children and adolescents with Tourette's Disorder. Congruently, we identified one placebo-controlled trial of children and adolescents 6-18 comparing aripiprazole to placebo found greater tic reduction on the Yale Global Tic Severity Scale for aripiprazole.²³

Related to adverse events, we identified a study examining weight and metabolic changes associated with 24+ weeks of olanzapine found the magnitude of changes in weight and lipid parameters to be greater in adolescents as compared with adults.¹³ No evidence comparing weight gain by age group was included in the original report. Other findings include a study that found ziprasidone to be generally well tolerated

with a neutral weight and metabolic profile⁸; another that found no clinically significant changes in BMI, liver enzymes or fasting lipids or glucose associated with SGAs²¹; and a study reporting that Olanzapine-related weight gain was not associated with clinical outcomes¹⁴. We also identified a systematic review which found that fewer adolescents receiving SGAs as compared with FGAs left studies early due to adverse events⁵; a study reporting that risperidone was associated with hyperprolactinemia and demised sexual functioning in pubertal boys with ASD and DBD¹⁵; another study that found no significant cardiac events associated with aripiprazole¹⁶; that molindone hydrochloride was generally well tolerated¹¹; and that aripiprazole was associated with more somnolence, sedation, fatigue, extrapyramidal disorder, drooling, and weight gain in antipsychotic naïve children and adolescents than those with prior antipsychotic exposure.¹⁷

We identified a study examining Tourette's Disorder (TD) with comorbid ADHD, which concluded that aripiprazole was an effective treatment for TD, but only moderately effective for ADHD¹⁸; that the combined use of olanzapine and atomoxetine was effective in reductions on the ADHD-RS and the Modified Overt Aggression Scale (MOAS) in children with ADHD and comorbid disruptive disorders¹⁹; and that among adolescents with bipolar disorder and comorbid conduct disorder, quetiapine effectively reduced CGI-S and C-GAS scores in 55% of participants, with non-responders more frequently male and frequently also had comorbid ADHD²⁰.

Finally, although no studies meeting the inclusion criteria for the original CER were identified, newer antipsychotics such as lurasidone, asenapine, and iloperidone are SGAs that have been approved by the FDA in the last five years for use in adults 18 and older diagnosed with some of the conditions included in the original CER. They are not currently approved for use in children and adolescents. This report includes young adults up to age 24; thus, there is likely existing literature relevant to the key questions for young adults 19-24.

Signal Assessment for Updating

The SRC recommendation based on the results of the prior surveillance assessment, recent literature, FDA boxed warning information, horizon scanning, ongoing clinical trials, and expert assessment is that:

- Key Question 1: Conclusions on the effectiveness of SGAs for anorexia nervosa are out of date due to no studies included in the original CER, and four studies found in the previous surveillance. Conclusions on comparative effectiveness of FGAs vs. SGAs possibly out of date due to a systematic review which found no difference between FGAs and SGAs on the BPRS, and a systematic review of 13 RCTs which found no difference between FGAs and SGAs in five RCTs. The conclusion of no difference between SGAs and placebo for aggression are possibly out of date due to a study which found limited evidence supporting the efficacy of SGAs over placebo. In addition, the strength of evidence (SOE) for SGAs and improvement on mania scores may be out of date, with a possible change from low to moderate.
- Key Question 2: Conclusions comparing adverse events for FGAs and SGAs may be out of date due to original CER findings of insufficient evidence related to cardiovascular events and weight gain, and a new study which found molindone hydrochloride to be well tolerated. In addition, the conclusions are possibly out of date with regard to weight gain, with a new study indicating greater weight gain and lipid changes in adolescents vs. adults, and a study which found that ziprasidone had a neutral weight profile. In addition, the SOE regarding other adverse events may possibly have increased from moderate to high, due to the large number of supporting studies.
- Key Question 3: Conclusion on the safety and tolerability of FGAs vs. SGAs is possibly out of date, due to a systematic review of 13 RCTs that found that in 3 RCTs, SGAs may be better tolerated than FGAs.

- Key Question 4: Conclusions related to individuals with comorbid disorders are possibly out of date based on studies found on subjects with ADHD with comorbid disruptive disorders, Tourette's Disorder with comorbid ADHD, and bipolar disorder with comorbid conduct disorder.

The signal to update this report is medium, suggesting that the conclusions in the original CER are possibly out of date.

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Appendices

Appendix A: Top 10 Journals

Appendix B: Most Cited Journals from Original Systematic Review

Appendix C: Original Search Strategy

Appendix D: Inclusion and Exclusion Criteria from Original Systematic Review

Appendix E: Literature Search Results

Appendix F: Questionnaire Sent to Expert Reviewers

Appendix G: Summary Table

Appendix A. Top 10 Journals

In the Journal Citation Reports database, the science and social science sections were searched by subject area discipline(s) for each surveillance reports topic area. For each subject area discipline, the list was constructed by selecting the top 10 journals from the 5 year citation impact factor average list. Selected citations were downloaded in .csv format.

Behavioral Sciences:

1. Behavioral & Brain Sciences
2. Trends in Cognitive Sciences
3. Neuroscience & Biobehavioral Reviews
4. Advances in the Study of Behavior
5. Cognitive, Affective, & Behavioral Neuroscience
6. Frontiers in Behavioral Neuroscience
7. Cortex
8. Autism Research
9. Neuropsychologia
10. Biological Psychology

Developmental Psychology:

1. Journal of the American Academy of Child Psychiatry
2. Developmental Review
3. Development and Psychopathology
4. Journal of Child Psychology and Psychiatry
5. Child Development
6. Autism Research
7. Developmental Science
8. Developmental Psychology
9. Journal of Autism and Developmental Disorders
10. Journal of Abnormal Child Psychology

Psychiatry:

1. Archives of General Psychiatry
2. The American Journal of Psychiatry
3. Molecular Psychiatry
4. Biological Psychiatry
5. Schizophrenia Bulletin
6. Neuropsychopharmacology
7. Journal of the American Academy of Child Psychiatry
8. The British Journal of Psychiatry
9. Journal of Psychiatry & Neuroscience
10. World Psychiatry

Psychology:

1. Annual Review of Psychology
2. Psychological Bulletin
3. Annual Review of Clinical Psychology
4. Psychological Review
5. Social Cognitive and Affective Neuroscience
6. Journal of Child Psychology and Psychiatry
7. Psychological Medicine
8. Psychotherapy and Psychosomatics
9. Cognitive Psychology
10. Health Psychology

Top 10 General Medical:

1. New England Journal of Medicine
2. Lancet
3. Journal of the American Medical Association
4. PLoS Medicine
5. Annals of Internal Medicine
6. The BMJ
7. Archives of Internal Medicine
8. Canadian Medical Association Journal
9. Cochrane Database of Systematic Reviews
10. BMC Medicine

Pediatrics Top 10:

1. Journal of the American Academy of Child Psychiatry
2. Pediatrics
3. Archives of Pediatric & Adolescent Medicine
4. Journal of Pediatrics – US
5. Developmental Disabilities Research Reviews
6. Journal of Adolescent Health
7. Seminars in Fetal and Neonatal Medicine
8. Archives of Disease in Childhood – Fetal and Neonatal Edition
9. The Pediatric Infectious Disease Journal
10. Developmental Medicine & Child Neurology

Appendix B. Most Cited Journals from Original Systematic Review

Journal	Citations
Journal of the American Academy of Child and Adolescence Psychiatry	17
Journal of Child and Adolescent Psychopharmacology	15
The American Journal of Psychiatry	9
Journal of Clinical Psychiatry	6
Biological Psychiatry	3
The British Journal of Psychiatry	3
European Child & Adolescent Psychiatry	3
Journal of Clinical Epidemiology	3
Journal of the American Medical Association	3
Archives of General Psychiatry	2
Bipolar Disorder	2
Child & Adolescent Psychiatric Clinics of North America	2
Child and Adolescent Psychiatry and Mental Health	2
International Clinical Psychopharmacology	2
Neurology	2
Pediatrics	2
Progress in Neuro-Psychopharmacology & Biological Psychiatry	2
Research in Developmental Disabilities	2
Schizophrenia Bulletin	2

Appendix C. Original Search Strategy

Top Journals used for surveillance of this topic:

- Annals of Internal Medicine
- British Medical Journal
- Journal of the American Medical Association
- Lancet
- New England Journal of Medicine
- PLoS Medicine
- Cochrane Database of Systematic Reviews
- American Journal of Psychiatry
- Pediatrics
- Archives of General Psychiatry
- Archives of Clinical Psychiatry
- Journal of Clinical Psychiatry
- Journal of Child and Adolescent Psychopharmacology
- Journal of the American Academy of Child and Adolescence Psychiatry

Run 06/19/2014	
Ovid MEDLINE and Ovid OLDMEDLINE	
Original Search Strategy	<ol style="list-style-type: none"> 1 exp Child Development Disorders, Pervasive/ (20767) 2 Child behavior disorders/ (18411) 3 (child adj1 development adj1 disorder*).tw. (8) 4 Asperger Syndrome/ (1521) 5 (asperger* adj1 (syndrome or disorder)).tw. (1647) 6 Autistic Disorder/ (16183) 7 (autism* or (autistic adj1 disorder*) or kanner* syndrome).tw. (21153) 8 Rett Syndrome/ (1890)

9 (((rett or retts) adj1 (syndrome or disorder)) or cerebroatrophic hyperammonemia*).tw. (91)
 10 Schizophrenia, Childhood/ (1472)
 11 (child* adj2 schizophrenia*).tw. (858)
 12 aggression/ (26646)
 13 aggression.tw. (19652)
 14 psychomotor agitation/ (3532)
 15 ((psychomotor adj1 (agitation or restlessness or hyperactivity or excitement)) or akathisia).tw. (2041)
 16 "sleep initiation and maintenance disorders"/ (8837)
 17 ((sleep adj2 disorder* or insomnia*).tw. (24090)
 18 mood disorders/ (10833)
 19 ((mood or affective) adj1 disorder*).tw. (23583)
 20 impulsive behavior/ (5387)
 21 (impulsive adj1 behavio?r).tw. (825)
 22 borderline personality disorder/ (4977)
 23 (borderline adj1 personality adj1 disorder*).tw. (4036)
 24 personality disorders/ (14491)
 25 (affective adj2 dysregulation).tw. (161)
 26 ((\$behavioral adj2 dyscontrol) or (impulsive-behavioral adj2 deregulation)).tw. (112)
 27 (mood adj2 lability).tw. (171)
 28 (irritable or irritability).tw. (16656)
 29 Self-Injurious Behavior/ (4871)
 30 (self-injurious behavio?r or self-mutilating behavio?r or self mutilation or self-destructive behavio?r or deliberate self-harm or parasuicide).tw. (3959)
 31 antisocial personality disorder/ (7794)
 32 "Attention Deficit and Disruptive Behavior Disorders"/ (2072)
 33 Attention Deficit Disorder with Hyperactivity/ (20268)
 34 ((attention adj deficit adj disorder) or hyperkinetic syndrome or adhd).tw. (15761)
 35 Conduct Disorder/ (2265)
 36 (conduct adj disorder*).tw. (3547)
 37 Childhood Disintegrative Disorder.tw. (62)
 38 "Pervasive Developmental Disorder Not Otherwise Specified".tw. (298)
 39 (atypical adj1 autism).tw. (89)
 40 Oppositional Defiant Disorder.tw. (1236)
 41 "Disruptive Behavior Disorder Not Otherwise Specified".tw. (6)
 42 Schizophrenia/ (82074)
 43 Schizophrenia, Catatonic/ (525)

44 Schizophrenia, Disorganized/ (508)
 45 Schizophrenia, Paranoid/ (3645)
 46 ((catatonic or disorganized or paranoid) adj schizophrenia).tw. (1308)
 47 Psychotic Disorders/ (32187)
 48 ((Psychotic or schizoaffective or schizophreniform) adj disorder).tw. (4995)
 49 (brief reactive psychoses or psychoses).tw. (8416)
 50 first episode schizophrenia.tw. (1094)
 51 (prodromal and schizophrenic).tw. (892)
 52 Schizotypal Personality Disorder/ (2168)
 53 (schizotypal personality disorder or ((borderline or pseudoneurotic or pseudopsychopathic or incipient or latent) adj2 schizophrenia)).tw. (683)
 54 Bipolar Disorder/ (31399)
 55 (((bipolar or manic) adj (disorder or psychoses or depression)) or mania*).tw. (22151)
 56 "Depressive Disorder, Major"/ and (refractory or chronic or resistant).ti,ab. (2004)
 57 Depression/ and (refractory or chronic or resistant).ti,ab. (7601)
 58 Depressive Disorder/ (58330)
 59 ((depressive adj (disorder or neuroses or syndrome*)) or ((endogenous or neurotic or unipolar) adj depression*)).tw. (20796)
 60 Obsessive-Compulsive Disorder/ (11273)
 61 (OCD or anankastic personalit* or (obsessive compulsive adj (disorder* or neuros*)) or (obsessivecompulsive adj (disorder* or neuros*))).tw. (10055)
 62 exp anorexia nervosa/ (10687)
 63 ((anorexia adj nervosa*) or anorexia*).tw. (22474)
 64 exp stress disorders, post-traumatic/ (21087)
 65 ((chronic or acute or delayed onset) and (post-traumatic adj stress adj disorder*)).tw. (949)
 66 ((posttraumatic or post-traumatic or post traumatic) adj (neuroses or disorder)).tw. (66)
 67 ptsd.tw. (12510)
 68 exp tourette syndrome/ (3553)
 69 (Tourette* adj (syndrome or disorder or disease)).tw. (3809)
 70 (tic adj disorder).tw. (424)
 71 (multiple adj motor adj vocal adj tic adj disorder).tw. (0)
 72 or/1-71 (441689)
 73 exp Antipsychotic Agents/ (121515)
 74 exp Tranquilizing Agents/ (200951)
 75 ((first or 1st) adj generation adj antipsychotic*).tw. (488)
 76 azaperone/ (136)
 77 1649-18-9.rm. (0)

- 78 (Atsaperoni or Azaperon or Azaperona or Azaperone or Azaperonum or Eucalmyl or Fluoperidol or NSC 170976 or R 1929 or R-1929 or Sedaperone or Stresnil or Suicalm).mp. (231)
- 79 Butyrophenones/ad, to, tu, ct, po, ae (634)
- 80 Clopenthixol/ (372)
- 81 982-24-1.rn. (372)
- 82 (Chlorpenthixol or Clopenthixol or Clopenthixolum or Sordinol or Zuclopenthixol).mp. (507)
- 83 chlorpromazine/ (15893)
- 84 50-53-3.rn. (0)
- 85 (Aminazin or Aminazine or Ampliactil or BC 135 or Chlorpromazine or Chlorpromazinum or Clorpromazina or Chlor-Promanyl or Chlorpromados or Chlorderazin or Chlorpromazin or Contomin or Elmarin or Esmind or Fenactil or Fenaktyl or HL 5746 or Largactil or Largactilothiazine or Megaphen or Largactyl or Klooripromatsiini or Klorpromazin or 6 Copin or Trinicalm Forte or Diminex Balsamico Juven Tos or Largatrex or Phenactyl or Proma or Promactil or Promazil or Prozil or Psychozine or Sanpron or Thorazine or Torazina or Wintermin).mp. (20424)
- 86 Chlorprothixene/ (564)
- 87 113-59-7.rn. (0)
- 88 (Chlorprothixene or Chlorprothixen or Chlorprothixenum or Chlorprotixen or Chlorprotixene or Clorprotisene or Clorprotixeno or Laractan or Paxyl or Rentovet or Taractan or Tarasan or Traquilan or Trictal or Truxal or Truxaletten or Truxil or Vetacalm).mp. (751)
- 89 Dibenzoxazepines/ad, to, tu, ct, po, ae (302)
- 90 Droperidol/ (1918)
- 91 548-73-2.rn. (0)
- 92 (Dehydrobenzoperidol or Dehydrobenzperidol or Deidrobenezperidolo or Dridol or Droleptan or Droperidol or Droperidoli or Droperidolis or Droperidolum or Disifelit or Halkan or Inapsin or Inapsine or Inopsin or Thalamonal or Nilperidol or Properidol or Sintodril or Vetkalm).mp. (2828)
- 93 Flupenthixol/ (875)
- 94 2709-56-0.rn. (0)
- 95 (Depixol or Emergil or Fluanxol or Flupenthixol or Flupentixol or Flupentixolum or Fluxanxol or Siplaril or Siplarol).mp. (1418)
- 96 fluphenazine/ (2309)
- 97 69-23-8.rn. (0)
- 98 (Dapotum or Elinol or Flufenazina or Fluofenazine or Fluphenazine or Fluorphenazine or Fluphenazinum or Ftorphenazine or Moditen or Pacinol or Sevinol or Siqualon or Triflumethazine or Valamina or Vespazine).mp. (3082)
- 99 haloperidol/ (14763)
- 100 52-86-8.rn. (0)
- 101 (Aldo or Aloperidin or Aloperidol or Aloperidolo or Brootoxon or Dozic or Einalon S or Eukystol or Fortunan or Galoperidol or Haldol or Halojust or Halopal or Haloperidol or Haloperidoli or Haloperidolis or Haloperidolu or Halopoidol or

Serenace or Halopidol or Haloper or Halperon or Keselan or Lealgin or Linton or Mixidol or Peluces or Pernox or Serenace or Sereneff or Sernas or Sernel or Serenase or Ulcolind or Uliolind or Vesalium).mp. (22865)

102 Indoles/ad, to, tu, ct, po, ae (9771)

103 Lithium carbonate/ (2702)

104 554-13-2.rn. (0)

105 (Camcolit or Candamide or Carbolith or Carbonic acid lithium salt or dilithium salt or Eskalith or Eutimin or Hypnorex or Limas or Lithium or Liskonum or Litard or Lithane or Lithea or Lithicarb or Lithinate or Lithionate or Lithotabs or Liticar or Manialith or Maniprex or Micalith or Neurolepsin or Pfi-lithium or Phasal or Plenur or Priadel or Quilonorm or Teralithe).mp. (39486)

106 loxapine/ (258)

107 1977-10-2.rn. (0)

108 (Clozapine or CL 62362 or Dibenzacepin or Dibenzoazepine or Hydrofluoride 3170 or LW 3170 or Lossapina or Loksapiini or Loxapin or Loxapina or Loxapine or Loxapinum or Oxilapine or Loxapac or SUM 3170 or Loxitane or Desconex).mp. (428)

109 Methiothepin/ (393)

110 20229-30-5.rn. (0)

111 (Methiothepin or metitepine or Methiothepine or Methiothepin maleate or Metitepina or Metitepinum).mp. (993)

112 Methotrimeprazine/ (686)

113 60-99-1.rn. (0)

114 (Dedoran or Hirnamin or Hirnamine or Levomepromazine or Levomepromazin or Levomepromazina or Levopromazoni or Levomepromazinum or Levoprome or Levotomin or Mepromazine or Methotrimeprazine or Neurocil or Neozine or Nirvan or Nocinan or Momizan or Nozinane or Sinogan or Levolum or Nozinan or Sinogan or Tisercin or Veractil).mp. (985)

115 molindone/ (138)

116 7416-34-4.rn. (0)

117 (Molindona or Molindone or Molindonum).mp. (224)

118 Penfluridol/ (149)

119 26864-56-2.rn. (0)

120 (Penfluridol or Penfluridolum or Semap).mp. (230)

121 Perazine/ (150)

122 84-97-9.rn. (0)

123 (Pemazine Dimalonate or Peragal or Perazin or Perazine or Perazinum or Taxilan).mp. (239)

124 perphenazine/ (1437)

125 58-39-9.rn. (0)

126 (Chlorperphenazine or Chlorpiprazine or Decentan or Emesinal or Etaperazin or Etaperazine or Ethaperazine or Etrafon or F-mon or Fentazin or Mutabon or Perfenazin or Perfenazina or Perfenazinas or Perfenazine or Perphenazin or Perphenazine or Perfenazyna or Perphenazinum or Pertriptyl or Sch 3940 or Thilatazin or Tranquisan or Trifaron or Trilafon or Trilifan or

Triptafen or Triphenot or Triavil).mp. (1911)
 127 Phenothiazines/ad, to, tu, ct, po, ae [Administration & Dosage, Toxicity, Therapeutic Use, Contraindications, Poisoning, Adverse Effects] (2776)
 128 Pimozide/ (1726)
 129 2062-78-4.rn. (0)
 130 (Antalon or Opiran or Orap or Pimotsidi or Pimozid or Pimozida or Pimozidas or Pimozide or Pimozidum or Pimozyd).mp. (2482)
 131 Prochlorperazine/ (950)
 132 58-38-8.rn. (0)
 133 (Apo-Prochlorazine or Capazine or Chlormepazine or Compazine or Compro or Dhaperazine or Emelent or Kronocin or Nipodal or Novamin or Nu-Prochlor or Meterazin or Meterazine or Mital or Prochlorpemazine or Prochlorperazinum or Prochlorperazina or Prochlorperazine or Proklooriperatsiini or Proklorperazin or Prorazin or Phenothiazine or Seratil or Stemetil or Tementil or Temetid).mp. (6245)
 134 Promazine/ (973)
 135 58-40-2.rn. (0)
 136 (Ampazine or Berophen or Esparin or Liranol or Neo-Hibernex or Prazin or Sparine or Sinophenin or Promazine hydrochloride or Protactyl or Promatsiini or Promazin or Promazine or Promazinum or Propazinum or Prazine or Promwill or Protactyl or Romtiazin or Sinophenin or Talofen or Talofen or Tomil or Verophen).mp. (1332)
 137 Raclopride/ (1605)
 138 84225-95-6.rn. (0)
 139 (raclopride or racloprida or raclopridum or rakloprid or raklopridl).mp. (2487)
 140 Spiperone/ (2811)
 141 749-02-0.rn. (0)
 142 (E 525 or Espiperona or Spiperone or Spiperonum or Spiroperidol or Spiropitan).mp. (4368)
 143 thioridazine/ (2196)
 144 50-52-2.rn. (0)
 145 (Aldazine or Dazithin or Detril or Elperil or Mallorol or Malloryl or Melleril or Meleril or Mellaril or Mellerets or Mellerette or Melleretten or Melleril or Sonapax or Thioridazin or Thioridazine or Thioridazinum or Tioridatsiini or Tioridazin or Tioridazina or Tioridazinas).mp. (3019)
 146 Thiothixene/ (332)
 147 5591-45-7.rn. (0)
 148 (Navane or Navaron or Orbinamon or Thiothixene or Tiotikseeni or Tiotixen or Tiotixeno or Tiotixenum or Thixit or Tiotixene).mp. (459)
 149 Thioxanthenes/ad, to, tu, ct, po, ae (414)
 150 Tiapride/ (7)
 151 51012-32-9.rn. (7)

152 (Betaprid or Delpral or Doparid or Etilis or Equilium or Italiprid or Luxoben or Normagit or Porfanil or Sereprid or Tiacob or Tiapridal or Tiapride).mp. (440)

153 Trifluoperidol/ (162)

154 749-13-3.rn. (0)

155 (Flumoperone or Psicoperidol or Psychoperidol or Trifluoperidol or Trifluoperidoli or Trifluoperidolum or Triperidol or Trisedil or Trisedyl).mp. (224)

156 Trifluoperazine/ (3389)

157 117-89-5.rn. (0)

158 (Cuait D or Cuait N or eskazine or flupazine or Jatrosom or Jalonac or Parstelin or Parmodalin or stelazine or Stelabid or Stelapar or Sycot or Terfluzine or Trifluoperazine or Trifluoperazini Hydrochloridum or triftazin or Trinicalm Forte or Trinicalm Plus).mp. (4982)

159 Triflupromazine/ (288)

160 146-54-3.rn. (0)

161 (Adazine or Fluopromazine or Phenothiazine or Psyquil or Siquil or Triflupromazina or Triflupromazine or Trifluopromazine or Vesprin or Vetame).mp. (5428)

162 Zuclopenthixol/ (372)

163 53772-83-1.rn. (0)

164 (Cisordinol or Clopixon or Ciatyl-Z or Clopenthixol or Clopentixol or Sedanxol or Zuclopenthixolum or Zuclopentixol or Zuclopenthixol or Zuklopentixol).mp. (500)

165 or/73-164 (242429)

166 (atypical adj antipsychotic*).tw. (7573)

167 ((second or 2nd) adj generation adj antipsychotic*).tw. (1805)

168 ((third or 3rd) adj generation adj antipsychotic*).tw. (22)

169 Amisulpride.tw. (792)

170 71675-85-9.rn. (0)

171 (Aminosultopride or Amisulprida or Amisulpridum or Solian or Sulpitac).mp. (12)

172 aripiprazole.tw. (2269)

173 129722-12-9.rn. (0)

174 (Abilitat or Abilify or Aripiprazole or Discmelt or OPC 31 or OPC 14597).mp. (2456)

175 Asenapine.tw. (182)

176 65576-45-6.rn. (0)

177 EINECS 265-829-4.mp. (0)

178 Blonanserin.tw. (66)

179 132810-10-7.rn. (45)

180 AD 5423.mp. (10)

181 Clotiapine.tw. (34)

182 2058-52-8.rn. (0)
 183 (Clothiapine or Clotiapina or Clotiapinum or Dibenzothiazepine or Etumina or Etumine or Entumin or Etomine or Entumine or HF 2159 or LW 2159 or "BRN 0568276").mp. (107)
 184 clozapine/ (6772)
 185 5786-21-0.rn. (0)
 186 (Clozapin or Clozapina or Clozapine or Clozapinum or Clorazil or Clozaril or FazaClo or Leponex or LX 100-129 or Zaponex).mp. (10014)
 187 Diazepine.tw. (538)
 188 12688-68-5.rn. (0)
 189 Dibenzazepines/ad, to, tu, ct, po, ae (1420)
 190 Dibenzothiazepines/ct, ad, to, tu, ae, po (1947)
 191 Fluvoxamine/ (1706)
 192 (54739-18-3 or 61718-82-9).rn. (0)
 193 (dumirox or DU23000 or Fluvoxamina or fluvoxamine or Fluvoaminum or Fluvoxamine Maleate or Fevarin or Luvox or SME 3110).mp. (2580)
 194 Iloperidone.tw. (126)
 195 133454-47-4.rn. (73)
 196 (Fanapt or HP 873 or Zomaril).mp. (14)
 197 Isoxazoles/ad, to, tu, ct, po, ae (2802)
 198 Mesoridazine/ (126)
 199 5588-33-0.rn. (0)
 200 (Calodal or Lidanar or Lidanil or Mesoridazina or Mesoridazine or Mesoridazinum or Serentil or THD-2- SO).mp. (224)
 201 mosapramine.tw. (17)
 202 89419-40-9.rn. (0)
 203 (Clospipramine or Cremin or Mosapramina).mp. (2)
 204 olanzapine.tw. (6174)
 205 132539-06-1.rn. (4483)
 206 (Zyprexa or Olantsapiini or Olanzapin or Olanzapina or Olanzapinum or Olansek or Zalasta or Zypadhera).mp. (161)
 207 paliperidone.tw. (432)
 208 144598-75-4.rn. (373)
 209 (9-Hydroxyrisperidone or Invega or R 76477 or RO76477).mp. (217)
 210 Perospirone.tw. (118)
 211 150915-41-6.rn. (0)
 212 (lullan or perospirone hydrochloride).mp. (11)
 213 Piperidines/ad, to, tu, ct, po, ae (10643)
 214 Piperazines/ad, tu, to, ct, po, ae (18338)

215	Pirenzepine/tu, ad, to, ct, po, ae (1554)
216	Pyrimidinones/ad, to, tu, ct, po, ae (1619)
217	quetiapine.tw. (3091)
218	111974-69-7.rn. (0)
219	(Co-Quetiapine or HSDB 7557 or Seroquel).mp. (133)
220	Quinolones/to, po, ct, ad, tu, ae (3740)
221	Remoxipride/ (238)
222	80125-14-0.rn. (0)
223	(FLA 731 or Remoxiprida or Remoxipride or Remoxipridum).mp. (367)
224	Risperidone/ (5035)
225	106266-06-2.rn. (0)
226	(Apexidone or Psychodal or Risperdal or Risperidona or Risperidone or Risperidonum or Risperin or Risperilept or Rispolin or Spiron).mp. (7732)
227	Sertindole.tw. (399)
228	106516-24-9.rn. (212)
229	(Lu 23-174 or Sertindol or Serdolect or Sertindolum).mp. (25)
230	Sulpiride/ (3715)
231	15676-16-1.rn. (0)
232	(Abilit or Aiglonyl or Alimoral or Calmoflorine or Championyl or Darleton or Desmenat or Dobren or Dogmatil or Dogmatyl or Dolmatil or Eclorion or Eglonil or Eglonyl or Enimon or Equilid or Eusulpid or Fardalan or Fidelan or Guastil or Isnamide or Kylistro or Lisopiride or Mariastel or Meresa or Miradol or Mirbanil or Neogama or Normum or Nufarol or Omiryl or Omperan or Ozoderpin or Psicocen or Pyrkappl or Sernevin or Splotin or Stamonevrol or Sulparex or Sulpirid or Sulpirida or Sulpiride or Sulpiridum or Sulpor or Suprium or Sulpyrid or Trilan or Valirem or Zemorcon).mp. (5788)
233	Thiazoles/ad, th, ct, po, to, ae (3942)
234	Zotepine.tw. (251)
235	26615-21-4.rn. (0)
236	(Lodepin or Nipolept or Zotepina or Zotepinum or Zoleptil).mp. (2)
237	ziprasidone.tw. (1454)
238	146939-27-7.rn. (0)
239	Zeldox.mp. (5)
240	or/73-74,166-239 (243803)
241	or/165,240 (282973)
242	and/72,241 (56268)
243	randomized controlled trial.pt. (376264)
244	controlled clinical trial.pt. (88551)
245	randomi?ed.ab. (354841)

246 placebo.ab. (154906)
 247 drug therapy.fs. (1707329)
 248 randomly.ab. (214452)
 249 trial.ab. (307931)
 250 groups.ab. (1364020)
 251 or/243-250 (3366504)
 252 (humans not (animals and humans)).sh,hw. (12031341)
 253 251 and 252 (2428068)
 254 cohort studies/ (167683)
 255 followup studies/ (496498)
 256 longitudinal studies/ (86467)
 257 prospective studies/ (367890)
 258 Retrospective Studies/ (494255)
 259 Case-Control Studies/ (183337)
 260 (cohort\$ or longitudinal or retrospective or prospective or followup or case-control).tw. (985551)
 261 or/254-260 (1865014)
 262 261 and 252 (1689918)
 263 exp infant/ (937374)
 264 exp child/ (1545664)
 265 exp adolescent/ (1610430)
 266 exp pediatrics/ (43604)
 267 (\$child\$ or adolescen\$ or p*ediatric\$).tw. (1196928)
 268 or/263-267 (3126486)
 269 and/242,253,268 (8310)
 270 and/242,262,268 (2080)
 271 and/242,253 (42373)
 272 and/242,262 (7398)
 273 or/271-272 (43123)
 274 limit 273 to "all child (0 to 18 years)" (8271)
 275 or/269-270 (8543)
 276 or/274-275 (8543)
 277 limit 276 to (english language and yr="2011 -Current") (1018)
 278 limit 273 to "young adult (19 to 24 years)" (1741)
 279 exp Young Adult/ (361888)
 280 (young adj adult*).tw. (58531)
 281 ((college or university) adj2 (age or student*)).tw. (21610)

	282 students/ (34553) 283 or/279-282 (448386) 284 and/242,253,283 (1793) 285 and/242,262,283 (766) 286 or/284-285 (1853) 287 or/278,286 (1853) 288 limit 287 to (english language and yr="2011 -Current") (924) 289 277 or 288 (1465) 290 (editorial or letter or comment).pt. or case reports/ (2858976) 291 289 not 290 (1259)
Date Limits	292 limit 291 to ed=20120801-20140620 (780)
Journal Limits	293 "new england journal of medicine".jn. (70962) 294 lancet.jn. (128756) 295 jama.jn. (65459) 296 "plos medicine public library of science".jn. (2616) 297 "annals of internal medicine".jn. (29725) 298 "cochrane database of systematic reviews".jn. (10848) 299 "american journal of psychiatry".jn. (23875) 300 pediatrics.jn. (31653) 301 pediatrics.jn. (31653) 302 pediatrics.jn. (31653) 303 "archives of general psychiatry".jn. (8254) 304 "archives of general psychiatry".jn. (8254) 305 "journal of child & adolescent psychopharmacology".jn. (1353) 306 "journal of the american academy of child & adolescent psychiatry".jn. (5609) 307 "journal of the american academy of child & adolescent psychiatry".jn. (5609) 308 british medical journal.jn. (97340) 309 bmj.jn. (61963) 310 "journal of clinical psychiatry".jn (9688) 311 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 (492331)
	312 292 and 311 (66)

Appendix D. Inclusion and Exclusion Criteria from Original Systematic Review

Our inclusion/exclusion criteria were developed in consultation with the Technical Expert Panel (TEP). Criteria are summarized below.

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

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

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

Original inclusion/exclusion criteria extracted from Effective Health Care Program, CER #39, *First- and Second- Generation Antipsychotics for Children and Young Adults*, p.15

Appendix E. Literature Search Results

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Appendix F. Questionnaire Sent to Expert Reviewers

AHRQ Comparative Effectiveness Review Surveillance Program

Reviewer Form

Title of Original Review: First & second generation antipsychotics for children and young adults

[Link to Report](#)

Name of Reviewer: _____

Instructions:

The AHRQ Scientific Resource Center (SRC) periodically conducts surveillance of published AHRQ reviews to assist with prioritization of reports for updating. One part of this process includes soliciting expert review of our synthesis of recently published literature and any identified FDA black box warnings.

The attached document includes a table highlighting the conclusions from the original report, conclusions from a surveillance review conducted in 2012, and our synthesis of the recently published literature. Abstracts from relevant literature are included at the end of the attached document. If you would like a list of our full search results, please let us know.

Please review the table in the attached document and provide responses to the questions for each key question below. The primary goal of this review is to identify any missing studies, drugs, interventions, or devices; and ensure the accuracy of our synthesis of the recently published literature.

Key Question 1:

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

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

Prior Surveillance Assessment (November 2012):

- Strength of evidence regarding SGAs and improvement in mania scores may have increased from low to moderate
- Strength of evidence regarding risperidone and reduction in problem may have increased
- The original CER found no studies of SGAs for anorexia nervosa; four were found.

SRC Literature Analysis:

- The original CER concluded that SGAs were favored over FGAs for symptom improvement in patients with schizophrenia or schizophrenia-related psychosis. A recent systematic review concluded no difference between SGAs and FGAs on the Brief Psychiatric Rating Scale (BPRS). See attached table for more details.

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

Key Question 2:

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

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

Prior Surveillance Assessment (November 2012):

- All conclusions were up to date

SRC Literature Analysis:

- One study found that the magnitude of changes in weight and lipid parameters associated with 24+ weeks of olanzapine were greater in adolescents as compared with adults. See attached table for more details.

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Key Question 3:

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

- Response rates with corresponding dose, duration of response, remission, relapse, speed of response and time to discontinuation of medication.
- Growth and maturation.
- Cognitive and emotional development.
- Suicide-related behaviors or death by suicide.
- Medication adherence and persistence.
- School performance and attendance.
- Work-related functional capacity.
- Patient insight into illness.

- Patient-, parent-, or care provider-reported outcomes, including levels of physical activity or inactivity and diet (e.g., caloric intake, food preferences).
- Health-related quality of life.
- Legal or justice system interaction (e.g., arrests, detention).
- Health care system utilization (e.g., protective services, social services).
- “Outcomes that matter” to children, youth, young adults, and their families. These *functional* outcomes may reflect a developmental perspective.

Prior Surveillance Assessment (November 2012):

- All conclusions were up to date

SRC Literature Analysis:

- A systematic review found that fewer adolescents receiving SGAs as compared with FGAs left studies early due to adverse events

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

Key Question 4:

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

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

Prior Surveillance Assessment (November 2012):

- All conclusions were up to date

SRC Literature Analysis:

- A study of adolescents with Tourette’s Disorder (TD) and comorbid ADHD concluded that aripiprazole was an effective treatment for TD, but only moderately effective for ADHD
- The use of olanzapine and atomoxetine was effective in reductions on the ADHD-RS and the Modified Overt Aggression Scale (MOAS) in children with ADHD and comorbid disruptive disorders
- Among adolescents with bipolar disorder and comorbid conduct disorder, quetiapine effectively reduced CGI-S and C-GAS scores in 55% of participants, with non-responders more frequently male and frequently also had comorbid ADHD
- Aripiprazole was associated with more somnolence, sedation, fatigue, extraqprymidial disorder, drooling, and weight gain in antipsychotic naïve children and adolescents than those with prior antipsychotic exposure

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Original Review Conclusions and Literature Analysis

Title of Original Review: First- and Second- Generation Antipsychotics for Children and Young Adults

[Link to Report](#)

The conclusions from the original report, conclusions from a prior surveillance assessment and an analysis of recent literature identified by the Scientific Resource Center (SRC) are summarized below. Abstracts are provided for included literature at the end of the document.

Conclusions From Original Review	Conclusions from Prior Surveillance Assessment (Nov 2012)	SRC Literature Analysis (October 2014)
Key Question 1: Disorder-specific and nonspecific symptoms.		
A total of 11 studies examining pervasive developmental disorders (PDD) reported measures of symptom improvement. No significant difference was observed between FGAs and SGAs for autistic symptoms. SGAs were favored over placebo for autistic and obsessive-compulsive symptoms, but no difference was found for on the clinical global impressions (CGI) scale. The strength of evidence for these findings was low.	One RCT of risperidone vs risperidone plus parent training found the combination group had significantly higher VABS socialization and communication scores than drug alone.	A new meta-analysis of 2 RCTs found larger effects on the Aberrant Behavior Checklist (ABC) irritability, hyperactivity, and stereotypy subscales for aripiprazole vs. placebo for children/youths with ASD (Ching & Pringsheim, 2012).
Eight studies reported the effects of antipsychotics on symptoms in ADHD and disruptive behavior disorders. SGAs were superior to placebo on various measures of behavior symptoms and on the CGI (moderate strength of evidence). There was no difference between SGAs and placebo for aggression or anxiety (low strength of evidence).	No new studies comparing antipsychotics with placebo or active tx for ADHD were identified.	One new meta-analysis (Loy et al., 2012) comparing SGAs to placebo found limited evidence to support the efficacy of SGAs in reducing aggression (-6.49 points on the ABD irritability scale) and conduct problems (-8.61 points on the NCBRF-CP) with possible maintenance of effect up to six months. An open label randomized dosage trial of children of molindone hydrochloride with ADHD and persistent serious conduct problems found that doses between 5-40 mg produces improvements on the NCBRF-TIQ conduct problem subscale, the CGI-S, and SNAP-IV, with greatest improvements seen at 40mg (Stocks et al., 2012).
Eleven studies on bipolar disorders reported symptom improvement. SGAs were favored over placebo on the CGI (moderate strength of	A new meta-analysis of 17 RCTs using the reduction in Young Mania Rating Scale (YMRS) scores as outcome showed much larger	One new RCT (Findling, et al., 2012) found greater reductions on the YMRS for ziprasidone vs. placebo.

Conclusions From Original Review	Conclusions from Prior Surveillance Assessment (Nov 2012)	SRC Literature Analysis (October 2014)
evidence). Studies showed no significant difference for depression and a significant difference for mania favoring SGAs over placebo (low strength of evidence).	effects for SGAs (-16.8 points) compared to mood stabilizers (-10.99 points) and anticonvulsants (-11.03 points). Differences among SGAs were not statistically significant. One new RCT found risperidone superior to both lithium and divalproex in children with bipolar disorder after 6 weeks.	
25 studies reported symptom improvement in patients with schizophrenia or schizophrenia-related psychosis. SGAs were favored over placebo for the CGI and positive and negative symptoms (moderate strength of evidence). SGAs were significantly favored over FGAs on the CGI (low strength of evidence). No significant difference was found between clozapine and olanzapine or olanzapine and risperidone for the CGI or positive and negative symptoms (low strength of evidence).	One new RCT found that 3, 6, and 12 mg doses of paliperidone extended release were superior to placebo in adolescents with schizophrenia. One new small cohort of adolescents with schizophrenia or schizoaffective disorder found that long-term, clozapine is more effective than haloperidol, risperidone, and olanzapine. One large retrospective cohort found a trend toward shorter time to improvement with SGAs compared to FGAs; differences among SGAs were not significant.	One new systematic review of 13 RCTs (Kumar et al., 2013) found no difference between FGAs and SGAs on the Brief Psychiatric Rating Scale (BPRS) in 5 RCTs. Adolescents responded better to standard vs. lower dose of risperidone; however, lower doses of aripiprazole and ziprasidone may be equally effective. No convincing evidence supporting a difference in the effectiveness of FGAs vs. SGAs. One new RCT found no difference between ziprasidone and placebo on the BPRS-A (Findling, et al., 2013), and another RCT found quetiapine at 400 and 800 mg/day to be effective over placebo in PANSS score reductions (Findling et al., 2012). One RCT compared the effect of molidone, olanzapine, and risperidone on neurocognitive functioning and found no significant difference between medications; however, treatment with SGAs was associated with modest improvements in measures of neurocognitive function (Frazier et al., 2012). A post-hoc analysis of an RCT comparing aripiprazole to placebo in adolescents found that early response (by week 3) had the best predictive power for later symptom improvement (Cornell et al., 2013)
Five studies provided evidence on symptom improvement in Tourette syndrome. SGAs were	One open label trial found no difference in efficacy between aripiprazole and haloperidol.	No new research was found

Conclusions From Original Review	Conclusions from Prior Surveillance Assessment (Nov 2012)	SRC Literature Analysis (October 2014)
favored over placebo for tics (moderate strength of evidence).		
Four studies examined improvement for behavioral issues. One study found greater improvement in autistic symptoms with risperidone than placebo (low strength of evidence).	A new systematic review of 6 RCTs found risperidone superior to placebo in reducing problem behavior in children with intellectual disabilities	No new research was found
None of the included studies examined obsessive compulsive disorder, post-traumatic stress disorder, or anorexia nervosa.	We found 2 RCTs, one CCT, and one retrospective cohort study of SGAs in adolescent girls with anorexia nervosa. An RCT and CCT found no difference between drug and placebo groups in BMI change. One RCT found that olanzapine patients gained more weight than placebo patients at 8 weeks. The cohort study did not control for illness severity so made conclusions difficult	No new research was found
Key Question 2. Adverse Events		
Twelve studies provided adverse-events data for FGAs versus SGAs. For extrapyramidal symptoms, SGAs were significantly favored over haloperidol (low strength of evidence). Haloperidol was favored over olanzapine for weight/body composition (low strength of evidence). All other adverse events were not significant (low strength of evidence) or had insufficient evidence. For all comparisons of different FGAs or FGA with placebo, evidence was insufficient to draw a conclusion for adverse events.	An open label trial of aripiprazole vs haloperidol in children with tic disorders EPS were more frequent in the haloperidol group at 4 weeks. A cohort study in children with Tourette's syndrome found aripiprazole had a safer cardiovascular profile than pimozide, with a lower frequency of QTc prolongation. One RCT in children with bipolar disorder found that weight gain was greater with risperidone than lithium or divalproex.	An open label study of molindone hydrochloride in children found treatment to be well tolerated – common side effects included somnolence, weight increase, akathisia, sedation, and abdominal pain (Stocks et al., 2012).
25 studies compared the adverse event profiles of various SGAs. Risperidone was favored over olanzapine for dyslipidemia (moderate strength of evidence). Olanzapine was favored over risperidone for prolactin-related events (moderate strength of evidence). Both quetiapine and risperidone were favored over olanzapine for weight/body composition (moderate strength of evidence).	A systematic review focusing on adverse events in children & adolescents using SGAs found weight gain was higher with olanzapine than other SGAs, and lowest with aripiprazole. There was greater weight gain in ASD and disruptive behavior patients, perhaps due to less prior exposure to SGAs.	No new research was found

Conclusions From Original Review	Conclusions from Prior Surveillance Assessment (Nov 2012)	SRC Literature Analysis (October 2014)
<p>Adverse events were reported in 36 studies comparing SGAs with placebo. For nearly all outcomes and comparisons, the placebo group experienced significantly fewer adverse events than the group receiving SGAs. One exception to this trend was a significant effect in favor of aripiprazole for prolactin related adverse event (moderate strength of evidence)</p>	<p>Adverse events were reported in five new studies compared SGAs with placebo. Findings echo those in the original CER, with SGA groups reporting more weight gain, sedation, headache, and fatigue.</p>	<p>One review (Ching & Pringsheim, 2012) found increased weight gain and higher risk ratios for sedation and tremor associated with aripiprazole as compared with placebo.</p> <p>One RCT found ziprasidone to be generally well-tolerated with an overall neutral weight and metabolic profile, with common adverse events being sedation, somnolence, headache, and insomnia (Findling, et al., 2012), and another found similar common adverse events, with no clinically significant changes in movement disorder scales, BMI, liver enzymes, or fasting lipids or glucose (Findling et al., 2013).</p> <p>One study examining weight and metabolic changes associated with 24+ weeks of olanzapine found the magnitude of changes in weight and lipid parameters to be greater in adolescents as compared with adults (Kryzhanovskaya, et al., 2012). Another study found that Olanzapine-related weight gain was not independently associated with symptomatic outcome when controlling for treatment duration (Kemp, et al., 2013).</p> <p>One study (Roke, et al., 2012) found that risperidone was associated with hyperprolactinemia and diminished sexual dysfunction in pubertal boys with ASD and DBD.</p> <p>A study examining the effects of aripiprazole on ECGs in children and adolescents found no significant cardiac effects (Ho et al., 2012).</p>

Conclusions From Original Review	Conclusions from Prior Surveillance Assessment (Nov 2012)	SRC Literature Analysis (October 2014)
Key Question 3: Short- and long-term outcomes		
The findings for other short- and long-term outcomes are presented separately for each condition in Table D. The evidence was rated as insufficient to draw conclusions for health-related quality of life, involvement with the legal system, and other patient-, parent-, or care provider-reported outcomes for all conditions.	We found no new studies reporting on quality of life or involvement with the legal system.	No new research was found
Short- and long-term outcomes were reported in nine studies examining pervasive developmental disorders (PDD) and in eight studies examining ADHD and disruptive behavior disorders. Medication adherence was not significantly different	We found no new studies of medication adherence in PDD or ADHD patients	No new research was found
Eleven bipolar studies provided data for other outcomes. Medication adherence was significantly better for placebo than for SGAs (low strength of evidence). SGAs and placebo did not significantly differ for suicide-related behaviors (moderate strength of evidence).	We found no new studies of bipolar patients reporting adherence or suicide-related behaviors. We found one-long term (72 weeks) RCT reporting on the maintenance phase (Findling, 2012). Patients were randomized to either taper off aripiprazole or placebo. Patients tapering off the drug had significantly longer time to “mood event” than those on placebo.	No new research was found
22 studies provided data on a variety of short- and long-term outcomes for patients with schizophrenia and related psychosis. The studies found no significant difference in medication adherence between FGAs and SGAs, olanzapine and quetiapine, olanzapine and risperidone, or SGAs and placebo (low strength of evidence). Similarly, SGAs and placebo did not differ in suicide-related behaviors (low strength of evidence). Other outcomes were reported by four studies on Tourette syndrome and two studies on behavioral issues. The evidence was insufficient for all of the outcomes and comparisons examined in these studies.	We found no new studies of schizophrenic patients reporting adherence or suicide-related behaviors.	One new systematic review of 13 RCTs comparing FGAs to SGAs (Kumar, et al., 2013) found that fewer adolescents receiving SGAs left the studies (3 RCTs) due to adverse events.

Conclusions From Original Review	Conclusions from Prior Surveillance Assessment (Nov 2012)	SRC Literature Analysis (October 2014)
Key Question 4: Subpopulations		
<p>36 studies compared outcomes across various patient subpopulations. Sex and age were examined most frequently. Overall, few studies identified differences in the results across subpopulations. Few associations between the patient or clinical variables and outcomes were supported by more than one study. Studies frequently had discordant conclusions in whether there was a significant association between subpopulations and outcomes and the direction of this association.</p>	<p>Secondary analysis of an RCT on bipolar patients included in the original CER found that patients with disruptive behavior disorder (DBD) had greater improvements in manic symptoms in response to risperidone, while patients without DBD improved with either risperidone or divalproex.</p>	<p>One prospective cohort open label study found the combined use of olanzapine and atomoxetine to be effective in reductions on the ADHD-RS and the Modified Overt Aggression Scale (MOAS) in children and adolescents with ADHD and comorbid disruptive disorders (Holzer, et al., 2013).</p> <p>A study examining Tourette’s Disorder with comorbid ADHD found aripiprazole to be an effective treatment for TD, but only moderately effective for ADHD symptomology (Masi, et al., 2012).</p> <p>A study of quetiapine in adolescents with Bipolar disorder with comorbid CD found that 55% of participants showed significant improvements on the CGI-S and C-GAS. Non-responders were more frequently male and had comorbid ADHD (Masi, et al., 2013).</p> <p>A study comparing antipsychotic naïve (AN) children and adolescents to those with prior antipsychotic exposure (PAE) found that aripiprazole was associated with more somnolence, sedation, fatigue, extrapyramidal disorder, drooling, and weight gain in AN than PAE (Mankoski, et al., 2013).</p>

Legend: FGA = first generation antidepressant; SGA = second generation antidepressant; ADHD = attention deficit hyperactivity disorder; CGI = clinical global impressions-improvement

Abstracts from Relevant Literature

Ching, H. and Pringsheim, T. 2012.

Aripiprazole for autism spectrum disorders (ASD). Cochrane Database of Systematic Reviews.

BACKGROUND: Autism spectrum disorders (ASD) include Autistic Disorder, Asperger's Disorder and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). Irritability related to ASD has been treated with antipsychotics. Aripiprazole, a third generation atypical antipsychotic, is a relatively new drug that has a unique mechanism of action different from other antipsychotics. OBJECTIVES: To determine the safety and efficacy of aripiprazole for individuals with ASD. SEARCH METHODS: We searched the following databases on 4th May 2011: Cochrane Central Register of Controlled Trials (CENTRAL) (2011, Issue 2), MEDLINE (1948 to April Week 3 2011), EMBASE (1980 to 2011 Week 17), PsycINFO (1887 to current), CINAHL (1937 to current), WorldCat, ZETOC, Autism Data, Conference Proceedings Index-S, Conference Proceedings Index -SSH, ClinicalTrials.gov, and WHO ICTRP. We searched for records published in 1990 or later, as this was the year aripiprazole became available. SELECTION CRITERIA: Randomized controlled trials of aripiprazole versus placebo for the treatment of individuals with a diagnosis of ASD. DATA COLLECTION AND ANALYSIS: Two review authors independently collected, evaluated, and analyzed data. We performed meta-analysis for primary and secondary outcomes, when possible. MAIN RESULTS: Two randomized controlled trials with similar methodology have evaluated the use of aripiprazole for a duration of eight weeks in 316 children with ASD. The included trials had a low risk of bias. Although we searched for studies across age groups, only studies in children and youths were found. Meta-analysis of study results revealed a mean improvement of 6.17 points on the Aberrant Behavior Checklist (ABC) irritability subscale, 7.93 points on the ABC hyperactivity subscale, and 2.66 points in the stereotypy subscale in children treated with aripiprazole relative to children treated with a placebo. In terms of adverse side effects, children treated with aripiprazole had a greater increase in weight with a mean increase of 1.13 kg relative to placebo, and had a higher risk ratio for sedation (RR 4.28) and tremor (RR 10.26). AUTHORS' CONCLUSIONS: Evidence from two randomized controlled trials suggests that aripiprazole can be effective in treating some behavioral aspects of ASD in children. After treatment with aripiprazole, children showed less irritability, hyperactivity, and stereotypies (repetitive, purposeless actions). Notable side effects must be considered, however, such as weight gain, sedation, drooling, and tremor. Longer studies of aripiprazole in individuals with ASD would be useful to gain information on long-term safety and efficacy.

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Correll, C.U., Zhao, J., Carson, W., Marcus, R., McQuade, R., Forbes, R.A., and Mankoski, R. 2013.

Early antipsychotic response to aripiprazole in adolescents with schizophrenia: predictive value for clinical outcomes. Journal of the American Academy of Child & Adolescent Psychiatry.

OBJECTIVE: In adults with chronic schizophrenia, most symptom decreases occur in the first few weeks of antipsychotic treatment, and nonresponse at week 2 predicts a later nonresponse. The trajectory of antipsychotic response and the predictive value of early antipsychotic effects were investigated for ultimate outcome in adolescent schizophrenia, where such data are still lacking. METHOD: This post hoc analysis of a 6-week, randomized, double-blinded trial of aripiprazole (n = 196) versus placebo (n = 98) evaluated if adolescents 13 to 17 years old with schizophrenia exhibited substantial symptomatic improvement to aripiprazole in the first few treatment weeks and whether early response (ER) versus early nonresponse (ENR) predicted clinically relevant outcomes. ER decreased at least 20% and ENR decreased less than 20% in Positive and Negative Syndrome Scale (PANSS) total score at week 2 (ER2/ENR2) or 3 (ER3/ENR3). Ultimate response decreased at least 40% in PANSS score. RESULTS: Nearly 50% of the PANSS decrease was achieved by week 2 and up to 75% by week 3. ER2/ER3 subjects showed significantly greater improvement than ENR subjects in PANSS total score, PANSS positive and negative subscale scores, and functionally relevant outcomes. In general, ER3 had better sensitivity, specificity, and positive and negative predictive values than ER2 for predicting ultimate response. ER2 subjects were 8.8 times (95% confidence interval 4.0-19.4) and ER3 subjects were 8.6 times (95% confidence interval 4.5-16.6) more likely to achieve remission at week 6 (p < .0001) than ENR2 and ENR3 subjects, respectively, although adverse events were similar. CONCLUSIONS: Like adults with chronic schizophrenia, adolescents with early-phase schizophrenia exhibited most symptomatic improvement early during aripiprazole treatment, with week 3 improvements having the best predictive power. Although requiring extension, these results may inform clinical decision making. Clinical trial registration information-Aripiprazole in Adolescents with Schizophrenia, <http://clinicaltrials.gov/>, NCT00102063. Copyright 2013 American Academy of Child and Adolescent Psychiatry. Published by Elsevier Inc. All rights reserved. in this age range is insufficient when considered alone but is consistent with the data in the population of children with ASD.

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Findling, R.L. Cavus, I. Pappadopulos, E. Vanderburg, D.G. Schwartz, J.H. Gundapaneni, B.K. and Delbello, M.P. 2013. Ziprasidone in adolescents with schizophrenia: results from a placebo-controlled efficacy and long-term open-extension study. Journal of Child & Adolescent Psychopharmacology.

OBJECTIVE: The purpose of this study was to evaluate the short- and long-term efficacy, safety, and tolerability of ziprasidone in adolescents with schizophrenia. METHODS: Subjects ages 13-17 years with schizophrenia (American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 4th ed. [DSM-IV]) were enrolled in a 6 week, randomized, double-blind, placebo-controlled multicenter trial (RCT) followed by a 26 week open-label extension study (OLE). Subjects were randomized in a 2:1 ratio to flexible-dose oral ziprasidone (40-160 mg/day, based on weight) or placebo. Primary end-point was change from baseline in Brief Psychiatric Rating Scale-Anchored (BPRS-A) total score. Safety assessments included adverse events, vital signs, laboratory measures, electrocardiograms, weight and body mass index, and movement disorder ratings. RESULTS: Planned interim analysis for the primary end-point in the RCT resulted in early termination of both studies because of futility. In the RCT, 283 subjects received ziprasidone (n=193) or placebo (n=90). In the intent-to-treat analysis population, the least squares mean (SE) BPRS-A score decrease from baseline at week 6 was not significantly different (p=0.15; -14.16 [0.78] for ziprasidone and -

12.35 [1.05] for placebo). Per-protocol analysis was significant ($p=0.02$). In the OLE, 221 subjects entered the OLE and received ziprasidone for a median of 99 days. The mean (SD) change in BPRS-A score from end of RCT to end of OLE (last observation carried forward) was -6.9 (8.9). The most common treatment-emergent adverse events ($> 10\%$) for all causalities during the RCT were somnolence and extrapyramidal disorders, and during OLE was somnolence only. No subjects had Fridericia's corrected QT (QTcF) > 500 ms in the RCT or OLE phases. One completed suicide occurred during the OLE phase. For RCT and OLE, no clinically significant changes were reported in metabolic indices and laboratory measures. CONCLUSIONS: Ziprasidone failed to separate from placebo in treatment of schizophrenia in adolescents. Ziprasidone was generally well tolerated with an overall neutral weight and metabolic profile. Clinical Trials Registry: NCT00257192 and NCT00265382 at ClinicalTrials.gov.

Findling, R.L., Cavus, I., Pappadopulos, E., Vanderburg, D.G., Schwartz, J.H., Gundapaneni, B.K., and Delbello, M.P. 2013. Efficacy, long-term safety, and tolerability of ziprasidone in children and adolescents with bipolar disorder. Journal of Child & Adolescent Psychopharmacology.

OBJECTIVE: The purpose of this study was to evaluate the short- and long-term efficacy and safety of ziprasidone in children and adolescents with bipolar I disorder. METHODS: Subjects 10-17 years of age with a manic or mixed episode associated with bipolar I disorder participated in a 4 week, randomized, double-blind, placebo-controlled multicenter trial (RCT) followed by a 26 week open-label extension study (OLE). Subjects were randomized 2:1 to initially receive flexible-dose ziprasidone (40-160 mg/day, based on weight) or placebo. Primary outcome was the change in Young Mania Rating Scale (YMRS) scores from baseline. Safety assessments included weight and body mass index (BMI), adverse events (AEs), vital signs, laboratory measures, electrocardiograms, and movement disorder ratings. RESULTS: In the RCT, 237 subjects were treated with ziprasidone ($n=149$; mean age, 13.6 years) or placebo ($n=88$; mean age, 13.7 years). The estimated least squares mean changes in YMRS total (intent-to-treat population) were -13.83 (ziprasidone) and -8.61 (placebo; $p=0.0005$) at RCT endpoint. The most common AEs in the ziprasidone group were sedation (32.9%), somnolence (24.8%), headache (22.1%), fatigue (15.4%), and nausea (14.1%). In the OLE, 162 subjects were enrolled, and the median duration of treatment was 98 days. The mean change in YMRS score from the end of the RCT to the end of the OLE (last observation carried forward) was -3.3 (95% confidence interval, -5.0 to -1.6). The most common AEs were sedation (26.5%), somnolence (23.5%), headache (22.2%), and insomnia (13.6%). For both the RCT and the OLE, no clinically significant mean changes in movement disorder scales, BMI z-scores, liver enzymes, or fasting lipids and glucose were observed. One subject on ziprasidone in the RCT and none during the OLE had Fridericia-corrected QT interval (QTcF) > 460 ms. CONCLUSION: These results demonstrate that ziprasidone is efficacious for treating children and adolescents with bipolar disorder. Ziprasidone was generally well tolerated with a neutral metabolic profile. Clinical Trials Registry: NCT00257166 and NCT00265330 at ClinicalTrials.gov.

Findling, R.L., McKenna, K., Earley, W.R., Stankowski, J. and Pathak, S. 2012.

Efficacy and safety of quetiapine in adolescents with schizophrenia investigated in a 6-week, double-blind, placebo-controlled trial. Journal of Child & Adolescent Psychopharmacology.

OBJECTIVE: The purpose of this study was to evaluate the efficacy and safety of acute quetiapine monotherapy in adolescents with schizophrenia. METHODS: Patients ages 13-17 years with an American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR) diagnosis of schizophrenia and a Positive and Negative Syndrome Scale (PANSS) total score >60 were randomized to 6 weeks of quetiapine (400 or 800mg/day) or placebo treatment. The primary efficacy measure was change in PANSS total score from baseline to day 42. Safety endpoints included adverse events and assessments of clinical chemistry values, suicidality, and extrapyramidal symptoms. RESULTS: The intent-to-treat population included 220 patients. Least-squares mean change in PANSS total score from baseline to endpoint was -27.31 with quetiapine 400mg/day, -28.44 with quetiapine 800mg/day, and -19.15 with placebo (p=0.043 and 0.009 for quetiapine 400 and 800mg/day, respectively, vs. placebo; mixed-model, repeated-measures analysis). Several secondary efficacy outcomes, including Clinical Global Impressions-Improvement score, supported the primary outcome measure in demonstrating significantly greater improvement in quetiapine groups than in the placebo group. Mean changes in body weight at day 42 were 2.2kg and 1.8kg for quetiapine 400 and 800mg/day, respectively, and -0.4kg for placebo. Mean changes in certain clinical chemistry parameters, including total cholesterol and triglycerides, were numerically greater in the quetiapine groups than in the placebo group. Adverse events associated with quetiapine were mostly mild to moderate in intensity and were consistent with its known profile in adults with schizophrenia. CONCLUSIONS: In this 6-week study of adolescent patients, quetiapine at doses of 400 and 800mg/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 in adult and adolescent populations. Clinical trial registration information: Quetiapine Fumarate (SEROQUEL()) Compared to Placebo in the Treatment of Adolescent Patients With Schizophrenia (ANCHOR 112). Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00090324?term=quetiapine+112&rank=1>.

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Frazier, J.A. Giuliano, A.J. Johnson, J.L. Yakutis, L. Youngstrom, E.A. Breiger, D. Sikich, L. Findling, R.L. McClellan, J. Hamer, R.M. Vitiello, B. Lieberman, J.A. and Hooper, S.R. 2012

Neurocognitive outcomes in the treatment of early-onset schizophrenia spectrum disorders study. Journal of the American Academy of Child & Adolescent Psychiatry.

OBJECTIVE: To assess neurocognitive outcomes following antipsychotic intervention in youth enrolled in the National Institute of Mental Health (NIMH)-funded Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS). METHOD: Neurocognitive functioning of youth (ages 8

to 19 years) with schizophrenia or schizoaffective disorder was evaluated in a four-site, randomized, double-blind clinical trial comparing molindone, olanzapine, and risperidone. The primary outcomes were overall group change from baseline in neurocognitive composite and six domain scores after 8 weeks and continued treatment up to 52 weeks. Age and sex were included as covariates in all analyses. RESULTS: Of 116 TEOSS participants, 77 (66%) had post-baseline neurocognitive data. No significant differences emerged in the neurocognitive outcomes of the three medication groups. Therefore, the three treatment groups were combined into one group to assess overall neurocognitive outcomes. Significant modest improvements were observed in the composite score and in three of six domain scores in the acute phase, and in four of six domain scores in the combined acute and maintenance phases. Partial correlation analyses revealed very few relationships among Positive and Negative Syndrome Scale (PANSS) baseline or change scores and neurocognition change scores. CONCLUSIONS: Antipsychotic intervention in youth with early-onset schizophrenia spectrum disorders (EOSS) led to modest improvement in measures of neurocognitive function. The changes in cognition were largely unrelated to baseline symptoms or symptom change. Small treatment effect sizes, easily accounted for by practice effects, highlight the critical need for the development of more efficacious interventions for the enduring neurocognitive deficits seen in EOSS. Clinical trial registry information-Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS); <http://www.clinicaltrials.gov>; NCT00053703. Copyright 2012 American Academy of Child and Adolescent Psychiatry. Published by Elsevier Inc. All rights reserved.

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Ho, J.G., Caldwell, R.L., McDougle, C.J., Orsagh-Yentis, D.K., Erickson, C.A., Posey, D.J., and Stigler, K.A. 2012. The effects of aripiprazole on electrocardiography in children with pervasive developmental disorders. Journal of Child & Adolescent Psychopharmacology.

OBJECTIVES: Psychotropic medications, including the atypical antipsychotics, have historically been scrutinized for cardiac effects and risk of sudden death. Aripiprazole is an atypical antipsychotic approved for pediatric use in schizophrenia, bipolar I disorder, and autistic disorder. Adult studies have evaluated aripiprazole's effects on electrocardiograms, but no pediatric studies have been published to date. METHODS: Electrocardiographic data were collected from children and adolescents participating in a 14-week, prospective, open-label study (n=25) of aripiprazole for irritability in pervasive developmental disorder not otherwise specified and Asperger's disorder. A 12-lead electrocardiogram was obtained at the baseline and end point visits. The electrocardiograms were evaluated for abnormal findings, and the PR, QRS, QT(c), and RR intervals were recorded. The QT interval was corrected using Bazett's, United States Food and Drug Administration (FDA) Pharmacology Division, and Fridericia's formulas. RESULTS: Twenty-four subjects received both baseline and posttreatment electrocardiograms. The mean age was 8.6 years (range 5-17 years). The average final aripiprazole dose was 7.8mg/day (range 2.5-15mg/day). There were no significant differences noted with the PR, QRS, RR, and QT(c) intervals after aripiprazole therapy. Also, there was no significant correlation between the dose given and the percent change in the QT(c). No post-treatment QT(c) exceeded 440ms. CONCLUSIONS: To our knowledge, this is the first systematic evaluation of the cardiac effects of aripiprazole in children and adolescents. The results are consistent with previously published literature in adults

that aripiprazole has no significant cardiac effects and can be deemed a low risk for causing sudden death. It will be important to confirm these findings in a randomized controlled trial.

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Holzer, B., Lopes, V., and Lehman, R. 2013.

Combination use of atomoxetine hydrochloride and olanzapine in the treatment of attention-deficit/hyperactivity disorder with comorbid disruptive behavior disorder in children and adolescents 10-18 years of age. Journal of Child & Adolescent Psychopharmacology.

OBJECTIVE: The aim of this study was to assess the use of atomoxetine and olanzapine in combination to treat attention-deficit/hyperactivity disorder (ADHD) and comorbid disruptive behaviors in children and adolescents 10-18 years of age. METHODS: Eleven subjects ages 10-18 received open-label atomoxetine and olanzapine for a 10 week treatment period. Patients were assessed at baseline, 2 weeks, 4 weeks, 6 weeks, and 10 weeks (posttreatment). ADHD improvement was measured through the ADHD Rating Scale (ADHD-RS) (Investigator and Parent ratings). Aggression was measured through the Modified Overt Aggression Scale (MOAS). RESULTS: The combined use of atomoxetine and olanzapine resulted in statistically significant improvement in ADHD symptoms and overt aggression from baseline to posttreatment. As evidenced by a 33% reduction in symptoms on the ADHD-RS-I and the MOAS, 73% of patients were considered responders to ADHD treatment, whereas 55% responded to treatment for aggression. Both medications were generally well tolerated. Olanzapine treatment was associated with significant weight gain. Patients gained, on average, 3.9 kg throughout the treatment period. CONCLUSIONS: These data provide initial evidence that combination use of atomoxetine and olanzapine for the treatment of ADHD and comorbid disruptive behaviors was effective in reducing ADHD symptoms and aggressive behavior in a 10 week treatment period.

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Kemp, D.E., Correll, C.U., Tohen, M., Delbello, M.P., Ganocy, S.J., Findling, R.L. and Chang, K.2013.

Associations among obesity, acute weight gain, and response to treatment with olanzapine in adolescent schizophrenia. Journal of Child & Adolescent Psychopharmacology.

OBJECTIVE: The purpose of this study was to investigate associations between body weight and illness characteristics, including weight gain and therapeutic efficacy, in adolescents with schizophrenia. METHODS: Adolescents ages 13-17 years (n = 107) with American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) schizophrenia enrolled in a 6 week, double-blind, placebo-controlled trial comparing olanzapine and placebo. Therapeutic response was assessed by the Brief Psychiatric Rating Scale for Children (BPRS-C). Secondary outcomes included the Clinical Global Impressions-Severity (CGI-S) scale and Positive and Negative Syndrome Scale (PANSS). Obesity was defined as sex-/age-adjusted body mass index (BMI) > 95th percentile. Linear regression was used to analyze the relationship

between weight gain and psychiatric symptom improvement; logistic regression was conducted to identify predictors of baseline obesity. RESULTS: Weight gain was significantly correlated with greater BPRS-C reduction among olanzapine-treated subjects ($r = -0.31$, $p < 0.01$), whereas a trend was observed among placebo-treated subjects ($r = -0.31$, $p = 0.08$). However, this relationship became nonsignificant when analyses were controlled for duration of olanzapine treatment ($p = 0.12$), and a treatment by weight gain interaction did not emerge in a repeated-measures mixed model analysis that included time in the study ($t = 1.27$, $p = 0.21$). Additionally, weight gain $> 7\%$ was not significantly associated with response or remission. Among 17 adolescents (16%) with obesity at study entry, obesity was not significantly associated with endpoint BPRS-C illness severity. However, girls ($p = 0.03$), individuals hospitalized within the past year ($p = 0.02$), and those with less severe overall ($p = 0.03$) and negative symptoms ($p = 0.003$) according to the CGI-S and PANSS negative subscale, respectively, were more likely to be obese at baseline. CONCLUSION: Baseline obesity was associated with lower illness severity, which could be mediated by greater treatment adherence, leading to more weight gain. Olanzapine-related weight gain was not independently associated with symptomatic outcome when controlling for treatment duration. Additional studies are needed to extend these findings to other disorders and medications.

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Kryzhanovskaya, L.A., Xu, W., Millen, B.A., Acharya, N., Jen, K.Y., and Osuntokun, O. 2012.

Comparison of long-term (at least 24 weeks) weight gain and metabolic changes between adolescents and adults treated with olanzapine. Journal of Child & Adolescent Psychopharmacology.

OBJECTIVE: The purpose of these analyses was to compare the weight and other metabolic changes between adolescents and adults during long-term (at least 24 weeks) olanzapine treatment. METHOD: The adult database included 86 studies with 12,425 patients with schizophrenia, schizoaffective disorder, depression, borderline personality disorder, or bipolar I disorder; the adolescent database comprised six studies with 489 patients with schizophrenia, schizoaffective disorder, borderline personality disorder, bipolar I disorder, or prodromal psychosis. Patients who had at least 24 weeks of olanzapine exposure ($N = 4,280$ from adult database and $N = 179$ from adolescent database) were analyzed in this study. Weight data were collected for all patients, fasting glucose and lipids data were collected in some patients. For weight gain, data in 34.5% adults (4,280/12,425) and 36.6% adolescents (179/489) were analyzed while for glucose and lipids, data in 8.4% (1,038/12,425) adults and 24.9% adolescents (122/489) were analyzed. Adult patients were treated with oral (5-20 mg/day) or depot formulations (doses equivalent to oral doses of 5-20 mg/day) of olanzapine and adolescent patients were treated with oral olanzapine (2.5-20 mg/day). The incidences of potentially clinically significant categorical changes in weight and metabolic parameters were calculated with a 95% confidence interval (CI). Nonoverlapping 95% CIs were considered as indicating a statistically significant difference. Weight, lipid, and glucose change comparisons are summarized. RESULTS: The mean age for adolescents and adults was 15.8 and 38.8, respectively. The percentage of the male population was similar for both adults (58.5%) and adolescents (62.8%). The median duration of the follow-up period was 201 days for adolescent database and 280 days for adult database. The mean weight gain from baseline to endpoint in adolescents was 11.24 kg when compared with 4.81 kg in adults. The 95% CI for adolescents (10.1, 12.4) and adults (4.57, 5.04) are not overlapping, which indicates that the difference between adolescents and adults is

statistically significant. The percentage of olanzapine-treated adolescents with > 7% mean weight gain was 89.4% compared with 55.4% in adults (Number need to harm [NNH]=3). Mean changes from baseline to endpoint were also greater for adolescents than for adults in fasting total cholesterol (5.49 mg/dL vs. 2.06 mg/dL), LDL (5.41 mg/dL vs. 0.49 mg/dL), and triglycerides (20.49 mg/dL vs. 16.72 mg/dL), but overlapping 95% CIs were observed for all lipid parameters. Mean changes from baseline to endpoint in fasting glucose values were similar between adolescents and adults (3.13 mg/dL vs. 3.95 mg/dL). However, the incidence of treatment-emergent significant glucose changes was greater in adults. Among olanzapine-treated adults and adolescents, 8.9% and 0.9% experienced a shift from normal to high and 12.5% and 3.3% experienced a shift from normal/impaired glucose tolerance (IGT) to high fasting glucose, respectively. The incidence of IGT to high elevations in glucose was greater in adolescents, but overlapping 95% CI was observed. CONCLUSIONS: The types of metabolic changes during the long-term olanzapine treatment in adolescents were similar to those observed in adults. However, the magnitude of changes in weight and lipid parameters was greater in adolescents. Patients should receive regular monitoring of weight, fasting blood glucose, and lipid profile at the beginning of, and periodically during, treatment with olanzapine.

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*Kumar, A. Datta, S. Wright, S.D. Furtado, V.A. and Russell, P.S. 2013.
Atypical antipsychotics for psychosis in adolescents. Cochrane Database of Systematic Reviews.*

BACKGROUND: Schizophrenia often presents in adolescence, but current treatment guidelines are based largely on studies of adults with psychosis. Over the past decade, the number of studies on treatment of adolescent-onset psychosis has increased. The current systematic review collates and critiques evidence obtained on the use of various atypical antipsychotic medications for adolescents with psychosis. OBJECTIVES: To investigate the effects of atypical antipsychotic medications in adolescents with psychosis. We reviewed in separate analyses various comparisons of atypical antipsychotic medications with placebo or a typical antipsychotic medication or another atypical antipsychotic medication or the same atypical antipsychotic medication but at a lower dose. SEARCH METHODS: We searched the Cochrane Schizophrenia Group Register (October 2011), which is based on regular searches of BIOSIS, CENTRAL, CINAHL, EMBASE, MEDLINE and PsycINFO. We inspected references of all identified studies and contacted study authors and relevant pharmaceutical companies to ask for more information. SELECTION CRITERIA: We included all relevant randomised controlled trials (RCTs) that compared atypical antipsychotic medication with placebo or another pharmacological intervention or with psychosocial interventions, standard psychiatric treatment or no intervention in children and young people aged 13 to 18 years with a diagnosis of schizophrenia, schizoaffective disorder, acute and transient psychoses or unspecified psychosis. We included studies published in English and in other languages that were available in standardised databases. DATA COLLECTION AND ANALYSIS: Review authors AK and SSD selected the studies, rated the quality of the studies and performed data extraction. For dichotomous data, we estimated risk ratios (RRs) with 95% confidence intervals (CIs) using a fixed-effect model. When possible, for binary data presented in the 'Summary of findings' table, we calculated illustrative comparative risks. We summated continuous data using the mean difference (MD). Risk of bias was assessed for included studies. MAIN RESULTS: We included 13 RCTs, with a total of 1112 participants. We found no

data on service utilisation, economic outcomes, behaviour or cognitive response. Trials were classified into the following groups. 1. Atypical antipsychotics versus placebo: Only two studies compared one atypical antipsychotic medication with placebo. In one study, the number of non-responders treated with olanzapine was not different from the number treated with placebo (1 RCT, n = 107, RR 0.84, 95% CI 0.65 to 1.10); however, significantly more (57% vs 32%) people left the study early (1 RCT, n = 107, RR 0.56, 95% CI 0.36 to 0.87) from the placebo group compared with the olanzapine group. With regard to adverse effects, young people treated with aripiprazole had significantly lower serum cholesterol compared with those given placebo (1 RCT, n = 302, RR 3.77, 95% CI 1.88 to 7.58). 2. Atypical antipsychotics versus typical antipsychotics: When the findings of all five trials comparing atypical antipsychotic medications with a typical antipsychotic medication were collated, no difference in the mean end point Brief Psychiatric Rating Scale (BPRS) score was noted between the two arms (5 RCTs, n = 236, MD -1.08, 95% CI -3.08 to 0.93). With regard to adverse effects, the mean end point serum prolactin concentration was much higher than the reference range for treatment with risperidone, olanzapine and molindone in one of the studies. However, fewer adolescents who were receiving atypical antipsychotic medications left the study because of adverse effects (3 RCTs, n = 187, RR 0.65, 95% CI 0.36 to 1.15) or for any reason (3 RCTs, n = 187, RR 0.62, 95% CI 0.39 to 0.97). 3. One atypical antipsychotic versus another atypical antipsychotic: The mean end point BPRS score was not significantly different for people who received risperidone compared with those who received olanzapine; however, the above data were highly skewed. Overall no difference was noted in the number of people leaving the studies early because of any adverse effects between each study arm in the three studies comparing olanzapine and risperidone (3 RCTs, n = 130, RR 1.15, 95% CI 0.44 to 3.04). Specific adverse events were not reported uniformly across the six different studies included in this section of the review; therefore it was difficult to do a head-to-head comparison of adverse events for different atypical antipsychotic medications. 4. Lower-dose atypical antipsychotic versus standard/higher-dose atypical antipsychotic: Three studies reported comparisons of lower doses of the atypical antipsychotic medication with standard/higher doses of the same medication. One study reported better symptom reduction with a standard dose of risperidone as compared with a low dose (1 RCT, n = 257, RR -8.00, 95% CI -13.75 to -2.25). In another study, no difference was reported in the number of participants not achieving remission between the group receiving 10 mg/d and those who received 30 mg/d of aripiprazole (1 RCT, n = 196, RR 0.84, 95% CI 0.48 to 1.48). Similarly in the other study, authors reported no statistically significant difference in clinical response between the two groups receiving lower-dose (80 mg/d) and higher-dose (160 mg/d) ziprasidone, as reflected by the mean end point BPRS score (1 RCT, n = 17, MD -4.40, 95% CI -19.20 to 10.40).

AUTHORS' CONCLUSIONS: No convincing evidence suggests that atypical antipsychotic medications are superior to typical medications for the treatment of adolescents with psychosis. However, atypical antipsychotic medications may be more acceptable to young people because fewer symptomatic adverse effects are seen in the short term. Little evidence is available to support the superiority of one atypical antipsychotic medication over another, but side effect profiles are different for different medications. Treatment with olanzapine, risperidone and clozapine is often associated with weight gain. Aripiprazole is not associated with increased prolactin or with dyslipidaemia. Adolescents may respond better to standard-dose as opposed to lower-dose risperidone, but for aripiprazole and ziprasidone, lower doses may be equally effective. Future trials should ensure uniform ways of reporting.

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Loy, J.H., Merry, S.N., Hetrick, S.E. and Stasiak, K. 2012.

Atypical antipsychotics for disruptive behaviour disorders in children and youths. Cochrane Database of Systematic Reviews.

BACKGROUND: Disruptive behaviour disorders include conduct disorder, oppositional defiant disorder and disruptive behaviour not otherwise specified. Attention deficit hyperactivity disorder (ADHD) is frequently associated with disruptive behaviour disorders. The difficulties associated with disruptive behaviour disorders are demonstrated through aggression and severe behavioural problems. These often result in presentation to psychiatric services and may be treated with medications such as atypical antipsychotics. There is increasing evidence of a significant rise in the use of atypical antipsychotics for treating disruptive behaviour disorders in child and adolescent populations. **OBJECTIVES:** To evaluate the effect and safety of atypical antipsychotics, compared to placebo, for treating disruptive behaviour disorders in children and youths. **SEARCH METHODS:** We searched the following databases in August 2011: CENTRAL (2011, Issue 3), MEDLINE (1948 to August Week 1), EMBASE (1980 to 2011 Week 32), PsycINFO (1806 to August Week 2 2011), CINAHL (1937 to current), ClinicalTrials.gov (searched 15 August 2011), Australian New Zealand Clinical Trials Registry (ANZCTR) (searched 15 August 2011), CenterWatch (searched 15 August 2011) and ICTRP (searched 15 August 2011). **SELECTION CRITERIA:** We included randomised controlled trials with children and youths up to and including the age of 18, in any setting, with a diagnosis of a disruptive behaviour disorder. We included trials where participants had a comorbid diagnosis of attention deficit hyperactivity disorder, major depression or an anxiety disorder. **DATA COLLECTION AND ANALYSIS:** Two review authors independently selected the studies and disagreements were resolved by discussion. Two review authors extracted data independently. One review author entered data into Review Manager software and another checked it. We contacted trial authors for information about adverse effects and to provide missing data. **MAIN RESULTS:** We included eight randomised controlled trials, spanning 2000 to 2008. Seven assessed risperidone and one assessed quetiapine. Three of the studies were multicentre. Seven trials assessed acute efficacy and one assessed time to symptom recurrence over a six-month maintenance period. We performed meta-analyses for the primary outcomes of aggression, conduct problems and weight changes but these were limited by the available data as different trials reported either mean change scores (average difference) or final/post-intervention raw scores and used different outcome measures. We also evaluated each individual trial's treatment effect size where possible, using Hedges'. For aggression, we conducted two meta-analyses. The first included three trials (combined $n = 238$) using mean difference (MD) on the Aberrant Behaviour Checklist (ABC) Irritability subscale. Results yielded a final mean score with treatment that was 6.49 points lower than the post-intervention mean score with placebo (95% confidence interval (CI) -8.79 to -4.19). The second meta-analysis on aggression included two trials (combined $n = 57$) that employed two different outcome measures (Overt Aggression Scale (modified) (OAS-M) and OAS, respectively) and thus we used a standardised mean difference. Results yielded an effect estimate of -0.18 (95% CI -0.70 to 0.34), which was statistically non-significant. We also performed two meta-analyses for conduct problems. The first included two trials (combined $n = 225$), both of which employed the Nisonger Child Behaviour Rating Form - Conduct Problem subscale (NCBRF-CP). The results yielded a final mean score with treatment that was 8.61 points lower than that with placebo (95% CI -11.49 to -5.74). The second meta-analysis on conduct problems included two trials (combined $n = 36$), which used the Conners' Parent Rating Scale - Conduct Problem subscale (CPRS-CP). Results yielded a mean score with treatment of 12.67 lower than with placebo (95% CI -37.45 to 12.11), which was a statistically non-significant result. With respect to the side effect of weight gain, a

meta-analysis of two studies (combined n = 138) showed that participants on risperidone gained on average 2.37 kilograms more than those in the placebo group over the treatment period (MD 2.37; 95% CI 0.26 to 4.49). For individual trials, there was a range of effect sizes (ranging from small to large) for risperidone reducing aggression and conduct problems. The precision of the estimate of the effect size varied between trials.

AUTHORS' CONCLUSIONS: There is some limited evidence of efficacy of risperidone reducing aggression and conduct problems in children aged 5 to 18 with disruptive behaviour disorders in the short term. For aggression, the difference in scores of 6.49 points on the ABC Irritability subscale (range 0 to 45) may be clinically significant. For conduct problems, the difference in scores of 8.61 points on the NCBRF-CP (range 0 to 48) is likely to be clinically significant. Caution is required due to the limitations of the evidence and the small number of relevant high-quality studies. The findings from the one study assessing impact in the longer term suggest that the effects are maintained to some extent (small effect size) for up to six months. Inadequately powered studies produced non-significant results. The evidence is restricted by heterogeneity of the population (including below average and borderline IQ), and methodological issues in some studies, such as use of enriched designs and risk of selection bias. No study addressed the issue of pre-existing/concurrent psychosocial interventions, and comorbid stimulant medication and its dosage was only partially addressed. There is currently no evidence to support the use of quetiapine for disruptive behaviour disorders in children and adolescents. It is uncertain to what degree the efficacy found in clinical trials will translate into real life clinical practice. Participants in the studies were recruited from clinical services but those who agree to take part in the clinical trials are a subset of the overall population presenting for care. There are no research data for children under five years of age. Further high-quality research is required with large samples of clinically representative youths and long-term follow-up to replicate current findings.

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Mankoski, R. Stockton, G. Manos, G. Marler, S. McQuade, R. Forbes, R.A. and Marcus, R. 2013.

Aripiprazole treatment of irritability associated with autistic disorder and the relationship between prior antipsychotic exposure, adverse events, and weight change. Journal of Child and Adolescent Psychopharmacology.

OBJECTIVE: The purpose of this study was to evaluate the impact of prior antipsychotic exposure (PAE) on safety and tolerability outcomes in pediatric subjects receiving aripiprazole treatment. **METHODS:** This study was a post-hoc analysis of pooled data from two 8-week, double-blind, randomized, placebo-controlled studies evaluating aripiprazole for the treatment of irritability in pediatric subjects with autistic disorder, aged 6-17 years. Subjects were stratified by PAE; adverse events (AEs), and changes in weight, and metabolic measures were evaluated. For subjects receiving aripiprazole, regardless of PAE, baseline weight, age, gender, and symptom severity were evaluated in a regression model predicting body weight change. **RESULTS:** Of 316 randomized subjects, 259 (82.0%) were antipsychotic naive (AN) and 57 (18.0%) had a PAE. Aripiprazole-treated AN subjects were more likely than PAE subjects to report somnolence (11.9% vs. 2.8%), sedation (22.7% vs. 11.1%), or fatigue (17.0% vs. 13.9%). Rates of extrapyramidal disorder and drooling, but not akathisia or tremor, were marginally higher in AN subjects. Overall, 10.8% of aripiprazole-treated AN subjects had at least one AE leading to discontinuation compared with 8.3% of aripiprazole-treated PAE subjects. AN subjects receiving aripiprazole had a larger change in weight from baseline to endpoint compared with those receiving placebo

(1.9 vs. 0.7 kg; treatment difference 1.2 kg, 95% CI: 0.5, 1.9) than PAE subjects receiving aripiprazole compared with subjects receiving placebo (0.4 vs. -0.4 kg; treatment difference 0.9 kg, 95% CI: -0.6, 2.4). Regression analysis identified that younger subjects with higher baseline weight z-score were at highest risk for weight gain. There were no significant changes in metabolic measures compared with placebo in either group. CONCLUSIONS: Weight gain was more pronounced in AN subjects and more likely to occur in younger subjects with a higher baseline weight z-score. AN subjects were more likely to experience AEs related to somnolence. However, based on discontinuations rates from AEs, overall tolerability was good for both AN and PAE groups. Clinical trial registration: Study of aripiprazole in the treatment of children and adolescents with autistic disorder. Registry: www.clinicaltrials.gov . Identifiers: NCT00332241 and NCT00337571.

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Masi, G., Gagliano, A., Siracusano, R., Berlofffa, S., Calarese, T., Ilardo, G., Pfanner, C., Magazu, A. and Cedro, C. 2012. Aripiprazole in children with Tourette's disorder and co-morbig attention-deficit/hyperactivity disorder: a 12-week, open-label, preliminary study. Journal of Child & Adolescent Psychopharmacology.

Tourette's disorder (TD) in children and adolescents is frequently co-morbid with attention-deficit/hyperactivity disorder (ADHD). Dopamine-blockers are the first line treatment for TD, whereas dopamine-agonists, such as stimulants, are the gold-standard in the treatment of ADHD. These contrasting effects supported concerns about the risk that stimulants for treating ADHD may trigger or worsen co-morbid tics. Aripiprazole, a partial dopamine agonist, acts as an antagonist at dopamine D2 receptors in hyperdopaminergic conditions and displays agonist properties under hypodopaminergic conditions. The present study describes the use of aripiprazole (10.0 + 4.8 mg/day) in a consecutive group of 28 patients with a primary diagnosis of TD and co-morbid ADHD, combined subtype. The Yale Global Tic Severity Scale (YGTSS) and the ADHD-Rating Scale (ADHD-RS-IV) were used as primary outcome measures and both significantly improved (p<0.001) after the treatment. Global measures of severity (Clinical Global Impressions-Severity) and of functional impairment (Children's Global Assessment Scale) also significantly improved during the treatment (p<0.001). At the YGTSS there was a reduction of 42.5%, in motor tics, of 47.9% in phonic tics (44.7% for the combined scores), and of 32.3% in tic impairment. Nineteen patients (67.9%) had a reduction of at least 50% of the YGTSS score (motor+phonic tics). The improvement at the ADHD-RS-IV score was 22.5%, 12 patients (42.8%) presented an improvement of 30%, but only 2 (7.1%) an improvement greater than 50%. Using a logistic regression model, a reduction of at least 30% in ADHD-RS-IV score was more likely to occur in the obsessive-compulsive disorder co-morbid group. Aripiprazole was well tolerated and none of the patients discontinued medication because of side effects. In summary, aripiprazole resulted in an effective treatment for TD, but it was only moderately effective on co-occurring ADHD symptomatology. Our preliminary data suggest that aripiprazole may represent a possible therapeutic option, among other possible monotherapies addressing both tics and ADHD.

Masi, G., Pisano, S., Pfanner, C., Milone, A. and Manfredi, A. 2013.

Quetiapine monotherapy in adolescents with bipolar disorder comorbid with conduct disorder. Journal of Child & Adolescent Psychopharmacology.

Bipolar Disorders (BD) are often comorbid with disruptive behaviour disorders (DBDs) (oppositional-defiant disorder or conduct disorder), with negative implications on treatment strategy and outcome. The aim of this study was to assess the efficacy of quetiapine monotherapy in adolescents with BD comorbid with conduct disorder (CD). A consecutive series of 40 adolescents (24 males and 16 females, age range 12-18 years, mean age 14.9 + 2.0 years), diagnosed with a clinical interview (Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version [K-SADS-PL]) according to American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR) criteria were included. All the patients were treated with quetiapine monotherapy (mean final dose 258 + 124mg/day, range 100-600mg/day). At the end-point (3 months), 22 patients (55.0%) were responders (Clinical Global Impressions-Improvement [CGI-I] score of 1 or 2 and CGI-Severity [CGI-S] < 3 and improvement of at least 30% Children's Global Assessment Scale [C-GAS] during 3 consecutive months). Both CGI-S and C-GAS significantly improved ($p < 0.0001$). Nine out of the 16 patients with suicidality (56.3%) had a reduction in this severe symptom during the follow-up. Nonresponders were more frequently males, and more frequently had an attention-deficit/hyperactivity disorder (ADHD) comorbidity. Eight patients (20.0%) experienced moderate to severe sedation and eight (20.0%) experienced increased appetite and weight gain. In these severely impaired adolescents, quetiapine monotherapy was well tolerated and effective in >50% of the patients.

AN subjects were more likely to experience AEs related to somnolence. However, based on discontinuations rates from AEs, overall tolerability was good for both AN and PAE groups. Clinical trial registration: Study of aripiprazole in the treatment of children and adolescents with autistic disorder. Registry: www.clinicaltrials.gov . Identifiers: NCT00332241 and NCT00337571.

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Roke, Y., Buitelaar, J.K., Boot, A.M., Tenback, D. and Van Harten, P.N. 2012.

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. Journal of Child & Adolescent Psychopharmacology.

OBJECTIVE: The aim of this study was to investigate the long-term treatment effects of risperidone on prolactin levels and prolactin-related side effects in pubertal boys with autism spectrum disorders (ASD) and disruptive behavior disorders (DBD).METHOD: Physical healthy 10-20-year-old males with ASD (n=89) and/ or DBD (n=9) chronically treated (mean 52 months, range 16-126 months) with risperidone (group 1, n=51) or

not treated with any antipsychotic (group 2, n=47) were recruited to this observational study from the child psychiatry outpatient clinic. Morning non-fasting serum prolactin levels were measured and prolactin-related side effects were assessed by means of questionnaires and physical examination. Group differences were tested with Student's t, chi(2), Fisher exact, and Mann-Whitney tests, and logistic regression analysis, according to the type and distribution of data. RESULTS: Hyperprolactinemia was present in 47% of subjects in group 1 but only in 2% of subjects in group 2 (odds ratio 71.9; 95% CI, 7.7; 676.3). Forty-six percent of subjects in group 1 had asymptomatic hyperprolactinemia. Current risperidone dose and 9-OH risperidone plasma level were significant predictors of hyperprolactinemia (p=0.035 and p=0.03, respectively). Gynecomastia and sexual dysfunction were present in 43% and 14% of the subjects in group 1, respectively, compared with 21% and 0% of subjects in group 2 (p=0.05 and p=0.01). Gynecomastia was not significantly associated with hyperprolactinemia. CONCLUSIONS: Hyperprolactinemia is a common side effect in young males treated over the long term with risperidone. Young males treated with risperidone are more likely to report diminished sexual functioning than are those not treated with antipsychotics.

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Stocks, J.D., Taneja, B.K., Baroldi, P. and Findling, R.L. 2012.

A phase 2a randomized, parallel group, dose-ranging study of molindone in children with attention-deficit/hyperactivity disorder and persistent, serious conduct problems. Journal of Child & Adolescent Psychopharmacology.

OBJECTIVE: To evaluate safety and tolerability of four doses of immediate-release molindone hydrochloride in children with attention-deficit/hyperactivity disorder (ADHD) and serious conduct problems. METHODS: This open-label, parallel-group, dose-ranging, multicenter trial randomized children, aged 6-12 years, with ADHD and persistent, serious conduct problems to receive oral molindone thrice daily for 9-12 weeks in four treatment groups: Group 1-10 mg (5 mg if weight <30 kg), group 2-20 mg (10 mg if <30 kg), group 3-30 mg (15 mg if <30 kg), and group 4-40 mg (20 mg if <30 kg). The primary outcome measure was to evaluate safety and tolerability of molindone in children with ADHD and serious conduct problems. Secondary outcome measures included change in Nisonger Child Behavior Rating Form-Typical Intelligence Quotient (NCBRF-TIQ) Conduct Problem subscale scores, change in Clinical Global Impressions-Severity (CGI-S) and -Improvement (CGI-I) subscale scores from baseline to end point, and Swanson, Nolan, and Pelham rating scale-revised (SNAP-IV) ADHD-related subscale scores. RESULTS: The study randomized 78 children; 55 completed the study. Treatment with molindone was generally well tolerated, with no clinically meaningful changes in laboratory or physical examination findings. The most common treatment-related adverse events (AEs) included somnolence (n=9), weight increase (n=8), akathisia (n=4), sedation (n=4), and abdominal pain (n=4). Mean weight increased by 0.54 kg, and mean body mass index by 0.24 kg/m². The incidence of AEs and treatment-related AEs increased with increasing dose. NCBRF-TIQ subscale scores improved in all four treatment groups, with 34%, 34%, 32%, and 55% decreases from baseline in groups 1, 2, 3, and 4, respectively. CGI-S and SNAP-IV scores improved over time in all treatment groups, and CGI-I scores improved to the greatest degree in group 4. CONCLUSIONS: Molindone at doses of

5-20 mg/day (children weighing <30 kg) and 20-40 mg (> 30 kg) was well tolerated, and preliminary efficacy results suggest that molindone produces dose-related behavioral improvements over 9-12 weeks. Additional double-blind, placebo-controlled trials are needed to further investigate molindone in this pediatric population.

Appendix G: Summary Table

Conclusions From CER Executive Summary	Conclusions from Most Recent Surveillance Assessment (Nov 2012 – Link to Paper)	SRC Literature Search (October 2014)	Expert Opinion	Conclusion from SRC
Key Question 1: Disorder-specific and nonspecific symptoms.				
<p>A total of 11 studies examining pervasive developmental disorders (PDD) reported measures of symptom improvement. No significant difference was observed between FGAs and SGAs for autistic symptoms. SGAs were favored over placebo for autistic and obsessive-compulsive symptoms, but no difference was found for on the clinical global impressions (CGI) scale. The strength of evidence for these findings was low.</p>	<p>Conculsion is up to date</p>	<p>A new meta-analysis by Ching and Pringsheim of two RCTs found larger effects on the Aberrant Behavior Checklist (ABC) irritability, hyperactivity, and sterotypy subscales for aripiprazole vs. placebo for children/youths with ASD¹².</p>	<p>One reviewer noted that there were probably unpublished studies conducted by the sponsor, but was unaware of specific results.</p>	<p>The original conclusions are still valid, with the possibility of an increase in SOE given the Ching & Pringsheim meta-analysis¹².</p>
<p>Eight studies reported the effects of antipsychotics on symptoms in ADHD and disruptive behavior disorders. SGAs were superior to placebo on various measures of behavior symptoms and on the CGI (moderate strength of evidence). There was no difference between SGAs and placebo for aggression or anxiety (low strength of evidence).</p>	<p>Conclusion is up to date</p>	<p>One new meta-analysis comparing SGAs to placebo found limited evidence to support the efficacy of SGAs in reducing aggression (-6.49 points on the ABC irritability scale) and conduct problems (-8.61 points on the NCBRF-CP) with possible maintenance of effect up to six months.¹⁰</p> <p>An open label randomized dosage trial of children of molindone hydrochloride with ADHD and persistent serious conduct problems found that doses between 5-</p>	<p>One reviewer noted that there were probably unpublished studies conducted by the sponsor, but was unaware of specific results.</p>	<p>This conclusion is possibly out of date with regard to SGAs vs. placebo for aggression.^{10,11}</p>

Conclusions From CER Executive Summary	Conclusions from Most Recent Surveillance Assessment (Nov 2012 – Link to Paper)	SRC Literature Search (October 2014)	Expert Opinion	Conclusion from SRC
		40 mg produces improvements on the NCBRF-TIQ conduct problem subscale, the CGI-S, and SNAP-IV, with greatest improvements seen at 40mg. ¹¹		
Eleven studies on bipolar disorders reported symptom improvement. SGAs were favored over placebo on the CGI (moderate strength of evidence). Studies showed no significant difference for depression and a significant difference for mania favoring SGAs over placebo (low strength of evidence).	Conclusion possibly out of date regarding strength of evidence	One new RCT found greater reductions on the YMRS for ziprasidone vs. placebo ⁸ , and another study found greater improvements on the YMRS for quetiapine over placebo in participants aged 10-17. ²²	One reviewer noted the findings of the prior surveillance and highlighted the study which found SGAs superior to lithium and anticonvulsants in reducing YMRS scores. The other reviewer noted that there were probably unpublished studies conducted by the sponsor, but was unaware of specific results.	This conclusion is probably out of date with regard to SOE for SGAs vs. placebo for mania.
25 studies reported symptom improvement in patients with schizophrenia or schizophrenia-related psychosis. SGAs were favored over placebo for the CGI and positive and negative symptoms (moderate strength of evidence). SGAs were significantly favored over FGAs on the CGI (low strength of evidence). No significant difference was found between clozapine and olanzapine or olanzapine and risperidone for the CGI or positive and negative	Conclusion is up to date	One new systematic review of 13 RCTs found no difference between FGAs and SGAs on the Brief Psychiatric Rating Scale (BPRS) in 5 RCTs. ⁵ Adolescents responded better to standard vs. lower dose of risperidone; however, lower doses of aripiprazole and ziprasidone may be equally effective. No convincing evidence supporting a difference in the effectiveness of FGAs	One reviewer noted that there were probably unpublished studies conducted by the sponsor, but was unaware of specific results.	This conclusion is possibly out of date with regard to new findings related FGSs vs. SGAs for schizophrenia.

Conclusions From CER Executive Summary	Conclusions from Most Recent Surveillance Assessment (Nov 2012 – Link to Paper)	SRC Literature Search (October 2014)	Expert Opinion	Conclusion from SRC
symptoms (low strength of evidence).		<p>vs SGAs.</p> <p>One new RCT found no difference between ziprasidone and placebo on the BPRS-A⁷, and another RCT found quetiapine at 400 and 800mg/day to be effective over placebo in PANSS score reductions.⁸</p> <p>One RCT compared the effect of molindone, olanzapine, and risperidone on neurocognitive functioning and found no significant differences between medications; however, treatment with SGAs was associated with modest improvements in measures of neurocognitive function.⁶</p> <p>A post-hoc analysis of an RCT comparing aripiprazole to placebo in adolescents found that early response (by week 3) had the best predictive power for later symptom improvement.⁹</p>		
Five studies provided evidence on symptom improvement in Tourette syndrome. SGAs were favored over placebo for tics (moderate strength of evidence).	Conclusion possibly out of date	One placebo-controlled trial of children and adolescents 6-18 comparing aripiprazole to placebo found greater tic reduction on the Yale Global Tic Severity Scale	One reviewer noted that there were probably unpublished studies conducted by the sponsor, but was unaware of specific results.	Original conclusion is still valid and this portion of the report does not need updating.

Conclusions From CER Executive Summary	Conclusions from Most Recent Surveillance Assessment (Nov 2012 – Link to Paper)	SRC Literature Search (October 2014)	Expert Opinion	Conclusion from SRC
None of the included studies examined obsessive compulsive disorder, post-traumatic stress disorder, or anorexia nervosa.	Conclusion is out of date	for aripiprazole. ²³ No new research was found	One reviewer noted that there were probably unpublished studies conducted by the sponsor, but was unaware of specific results.	This conclusion is out of date with regard to findings related SGAs for anorexia nervosa identified in the prior surveillance.
Key Question 2: Adverse Events				
Twelve studies provided adverse-events data for FGAs versus SGAs. For extrapyramidal symptoms, SGAs were significantly favored over haloperidol (low strength of evidence). Haloperidol was favored over olanzapine for weight/body composition (low strength of evidence). All other adverse events were not significant (low strength of evidence) or had insufficient evidence. For all comparisons of different FGAs or FGA with placebo, evidence was insufficient to draw a conclusion for adverse events.	Conclusion is up to date	An open label study of molindone hydrochloride in children found treatment to be well tolerated – common side effects included somnolence, weight increase, akathisia, sedation, and abdominal pain. ¹¹	One reviewer noted that there were probably unpublished studies conducted by the sponsor, but was unaware of specific results.	This conclusion is possibly out of date with regard to findings in the prior surveillance related to cardiovascular events (found in prior surveillance) and weight gain, as well as new findings related to adverse events for molindone hydrochloride.
25 studies compared the adverse event profiles of various SGAs. Risperidone was favored over olanzapine for dyslipidemia (moderate strength of evidence). Olanzapine was favored over risperidone for prolactin-related events (moderate strength of evidence). Both quetiapine and	Conclusion is up to date	No new research was found	One reviewer noted that there were probably unpublished studies conducted by the sponsor, but was unaware of specific results.	Original conclusion is still valid and this portion of the original report does not need updating.

Conclusions From CER Executive Summary	Conclusions from Most Recent Surveillance Assessment (Nov 2012 – Link to Paper)	SRC Literature Search (October 2014)	Expert Opinion	Conclusion from SRC
risperidone were favored over olanzapine for weight/body composition (moderate strength of evidence).				
Adverse events were reported in 36 studies comparing SGAs with placebo. For nearly all outcomes and comparisons, the placebo group experienced significantly fewer adverse events than the group receiving SGAs. One exception to this trend was a significant effect in favor of aripiprazole for prolactin related adverse events (moderate strength of evidence).	Conclusion is up to date	<p>One review found increased weight gain and higher risk ratios for sedation and tremor associated with aripiprazole as compared with placebo¹², and a 10-week RCT found significant weight gain, and increases in BMI and waist circumference.²³</p> <p>One RCT found ziprasidone to be generally well tolerated with an overall neutral weight and metabolic profile, with common adverse events being sedation, somnolence, headache, and insomnia.⁸ and another found similar common adverse events, with no clinically significant changes in movement disorder scales, BMI, liver enzymes, or fasting lipids or glucose.²¹</p> <p>One study examining weight and metabolic changes associated with 24+ weeks of olanzapine found the magnitude of changes in weight and lipid parameters</p>	<p>One reviewer noted that the evidence is pointing to increased risk for weight gain in antipsychotic naïve children and youth treated with aripiprazole.¹²</p> <p>The other reviewer noted that there were probably unpublished studies conducted by the sponsor, but was unaware of specific results.</p>	This conclusion is possibly out of date with regard to new evidence indicating greater weight and lipid changes associated with olanzapine in adolescents vs. adults, and for weight gain related to ziprasidone. Possible SOE increases due to the number of studies supporting other original report conclusions.

Conclusions From CER Executive Summary	Conclusions from Most Recent Surveillance Assessment (Nov 2012 – Link to Paper)	SRC Literature Search (October 2014)	Expert Opinion	Conclusion from SRC
		<p>to be greater in adolescents as compared with adults.¹³</p> <p>Another study found that Olanzapine-related weight gain was not independently associated with symptomatic outcome when controlling for treatment duration.¹⁴</p> <p>Another study found mild to moderate adverse events related to weight and cholesterol for quetiapine over a three-week period.²²</p> <p>One study found that risperidone was associated with hyperprolactinemia and demised sexual function in pubertal boys with ASD and DBD.¹⁵</p> <p>A study examining the effects of aripiprazole on ECGs in children and adolescents found no significant cardiac effects.¹⁶</p>		
Key Question 3: Short- and long-term outcomes				

Conclusions From CER Executive Summary	Conclusions from Most Recent Surveillance Assessment (Nov 2012 – Link to Paper)	SRC Literature Search (October 2014)	Expert Opinion	Conclusion from SRC
<p>The findings for other short- and long-term outcomes are presented separately for each condition in Table D. The evidence was rated as insufficient to draw conclusions for health-related quality of life, involvement with the legal system, and other patient-, parent-, or care provider–reported outcomes for all conditions.</p>	<p>Conclusion is up to date</p>	<p>No new research was found</p>	<p>The two experts did not know of any additional studies, and either believed the original report to be up to date or did not know.</p>	<p>Original conclusion is still valid and this portion of the original report does not need updating.</p>
<p>Short- and long-term outcomes were reported in nine studies examining pervasive developmental disorders (PDD) and in eight studies examining ADHD and disruptive behavior disorders. Medication adherence was not significantly different between SGAs and placebo for both conditions (low strength of evidence).</p>	<p>Conclusion is up to date</p>	<p>No new research was found</p>	<p>The two experts did not know of any additional studies, and either believed the original report to be up to date or did not know.</p>	<p>Original conclusion is still valid and this portion of the original report does not need updating.</p>
<p>Eleven bipolar studies provided data for other outcomes. Medication adherence was significantly better for placebo than for SGAs (low strength of evidence). SGAs and placebo did not significantly differ for suicide-related behaviors (moderate strength of evidence).</p>	<p>Conclusion is up to date</p>	<p>No new research was found</p>	<p>The two experts did not know of any additional studies, and either believed the original report to be up to date or did not know.</p>	<p>Original conclusion is still valid and this portion of the original report does not need updating.</p>

Conclusions From CER Executive Summary	Conclusions from Most Recent Surveillance Assessment (Nov 2012 – Link to Paper)	SRC Literature Search (October 2014)	Expert Opinion	Conclusion from SRC
<p>22 studies provided data on a variety of short- and long-term outcomes for patients with schizophrenia and related psychosis. The studies found no significant difference in medication adherence between FGAs and SGAs, olanzapine and quetiapine, olanzapine and risperidone, or SGAs and placebo (low strength of evidence). Similarly, SGAs and placebo did not differ in suicide-related behaviors (low strength of evidence).</p> <p>Other outcomes were reported by four studies on Tourette syndrome and two studies on behavioral issues. The evidence was insufficient for all of the outcomes and comparisons examined in these studies.</p>	<p>Conclusion is up to date</p>	<p>One new systematic review of 13 RCTs comparing FGAs to SGAs found that fewer adolescents receiving SGAs left the studies (3 RCTs) due to adverse events.⁵</p>	<p>One reviewer highlighted the review by Kumar et al.⁵, which concluded that SGAs appear to be better tolerated than FGAs.</p>	<p>This conclusion is probably out of date with regard to new findings related to the tolerability of FGAs vs. SGAs.</p>
Key Question 4: Subpopulations				
<p>36 studies compared outcomes across various patient subpopulations. Sex and age were examined most frequently. Overall, few studies identified differences in the results across subpopulations. Few associations between the patient or clinical variables and outcomes were supported by more than one study. Studies frequently had discordant conclusions in</p>	<p>Conclusion is up to date</p>	<p>One prospective cohort open label study found the combined use of olanzapine and atomoxetine to be effective in reductions on the ADHD-RS and the Modified Overt Aggression Scale (MOAS) in children and adolescents with ADHD and comorbid disruptive disorders.¹⁹</p>	<p>The two experts did not know of any additional studies, and either believed the original report to be up to date or did not know.</p>	<p>This conclusion is probably out of date with regard to numerous new studied identified addressing subpopulations related to comorbidity, sex, etc.</p>

Conclusions From CER Executive Summary	Conclusions from Most Recent Surveillance Assessment (Nov 2012 – Link to Paper)	SRC Literature Search (October 2014)	Expert Opinion	Conclusion from SRC
<p>whether there was a significant association between subpopulations and outcomes and the direction of this association.</p>		<p>A study examining Tourette’s Disorder with comorbid ADHD found aripiprazole to be an effective treatment for TD, but only moderately effective for ADHD symptomology.¹⁸</p> <p>A study of Bipolar disorder with comorbid CD found that 55% of participants showed significant improvements on the CGI-S and C-GAS. Non responders were more frequently male and had comorbid ADHD.²⁰</p> <p>A study comparing antipsychotic naïve (AN) participants to those with prior antipsychotic exposure (PAE) found that aripiprazole was associated with more somnolence, sedation, fatigue, extrapyramidal disorder, drooling, and weight gain in AN than PAE.¹⁷</p>		

Legend: FGAs = first generation antipsychotics; SGAs = second generation antipsychotics; RCT = randomized controlled trial; VABS = Vineland adaptive behavior scale; ASD = autism spectrum disorder; SOE = strength of evidence; ADHD = attention-deficit/hyperactivity disorder; NCBRF= Nisonger child behavior rating scale; SNAP-IV = Swanson, Nolan and Pehlam Scale IV; PANSS = positive and negative syndrome scale; CCT = controlled clinical trial; BMI = body mass index; EPS = extrapyramidal symptom; QTc = QT interval corrected for heart rate; CER = comparative effectiveness report; DBD = disruptive behavior disorder; ECGs = electrocardiograms; TD = tourette’s disorder; CD = conduct disorder; C-GAS = children’s global assessment scale; CGI-S = clinical global impressions – severity