

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

Key Findings:

- Key Question 1: Strength of evidence regarding second-generation antipsychotics (SGAs) and improvement in mania scores may have increased from low to moderate, so that conclusion is possibly out of date. Strength of evidence regarding risperidone and reduction in problem behavior may have increased. The original CER included no studies of SGAs for anorexia nervosa; we found four that met inclusion criteria.
- Key Question 2: All conclusions for this question, on adverse events, are up to date.
- Key Question 3: All conclusions are up to date.
- Key Question 4: All conclusions are up to date.

Summary Decision

This CER's priority for updating is **Low**

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Contents

1. Introduction.....	1
2. Methods.....	1
2.1 Literature Searches	1
2.2 Study selection	1
2.3 Expert Opinion	1
2.4 Check for qualitative and quantitative signals	1
2.5 Compilation of Findings and Conclusions.....	2
2.6 Determining Priority for Updating.....	2
3. Results	3
3.1 Search	3
3.2 Expert Opinion	3
3.3 Identifying qualitative and quantitative signals	3
References	9
Appendix A. Search Methodology	12
Appendix B. Evidence Table	24
Appendix C. Questionnaire Matrix	29
Table	
Table 1: Summary Table	4

1. Introduction

Comparative Effectiveness Review (CER) #39 was originally released in February, 2012.¹ Therefore, our surveillance assessment began in August, 2012. At that time, we contacted experts involved in the original CER to request their opinions as to whether the conclusions had changed. We also conducted an updated electronic literature search. Every month since the CER's original release, we received any applicable warnings from the U.S. Food and Drug Administration (FDA), Health Canada, and UK Medicines and Healthcare products Regulatory Agency (MHRA) on the included medications.

2. Methods

2.1 Literature Searches

We conducted a limited literature search covering January 1, 2011 to August 25, 2012, using the identical search strategy used for the original report. This search included five high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and the New England Journal of Medicine) and four specialty journals (Journal of Clinical Psychiatry, Journal of Children & Adolescent Psychopharmacology, Journal of the American Academy of Child & Adolescent Psychiatry, and American Journal of Psychiatry). The specialty journals were those most highly represented among the references for the original report. This search resulted in 59 titles / abstracts to review.

We then conducted a full search of Pubmed and Psycinfo using the same terms. This search found the same 59 titles/ abstracts plus 509 additional. Appendix A includes the search strategy.

2.2 Study selection

We used the same inclusion and exclusion criteria as the original CER.

2.3 Expert Opinion

We shared the conclusions of the original report with eight experts in the field (including the original project leader, original technical expert panel (TEP) members, original peer reviewers, and a suggested field 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 back. Appendix C shows the questionnaire matrix that was sent to the experts.

2.4 Check for qualitative and quantitative 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 was also conducted for adverse events including extrapyramidal symptoms (EPC) weight gain, dyslipidemia, sedation, and prolactin-related events. We looked for both quantitative and qualitative signals.

2.5 Compilation of Findings and Conclusions

For this assessment we constructed a summary table that includes the key questions, the original conclusions, the findings of the new literature search, the expert assessments, and any FDA reports that pertained to each key question. We categorized whether the conclusions need updating using a 4-category scheme:

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

We used 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 still valid.
- 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 substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably 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.

2.6 Determining Priority for Updating

We used the following two criteria in making our final conclusion for this CER:

- How much of the CER is possibly, probably, or certainly out of date?
- How out of date is that portion of the CER? For example, would the potential changes to the conclusions involve refinement of original estimates or do the potential changes mean

some therapies are no longer favored or may not exist? Is the portion of the CER that is probably or certainly out of date an issue of safety (a drug withdrawn from the market, a black box warning) or the availability of a new drug within class (the latter being less of a signal to update than the former)?

3. Results

3.1 Search

The literature search identified 568 titles. After title and abstract review, we selected 55 for full text review. The remaining titles / abstracts were rejected because they were editorials, letters, animal studies, individual case reports, or did not include topics of interest.

Upon full text review, 36 articles were rejected because they did not meet the original CER inclusion criteria. For example, three were descriptions of utilization patterns, some reviewed studies already included in the CER, some studies included only adult patients, and some studies had no control or comparison group. The remaining 19 studies were abstracted into an evidence table (Appendix B).²⁻²⁰

3.2 Expert Opinion

We shared the conclusions of the original report with eight experts in the field (including the original project leader, original technical expert panel (TEP) members, original peer reviewers, and a suggested field 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. The original project leader was out on leave.

The two experts felt all the conclusions were either up to date or did not know. They did not suggest that any conclusion might be out of date.

3.3 Identifying qualitative and quantitative signals

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, and the recommendations of the Southern California Evidence-based Practice Center (SCEPC) regarding the need for update.

In general, the vast majority of the new studies we identified reflected the conclusions of the original CER. The only exception is that the original CER identified no studies of anorexia nervosa that met their inclusion criteria. We identified Two RCTs, one CCT, and one retrospective cohort study of adolescent girls with this condition.

Table 1: Summary Table

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
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>One RCT of risperidone vs risperidone plus parent training found the combination group had significantly higher VABS socialization and communication scores than drug alone.²</p>	<p>Not reported</p>	<p>1 expert thought that CGI scores improved in the included studies of aripiprazole. The other expert did not know if the conclusion was still valid.</p>	<p>Conclusion is up to date.</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>No new studies comparing antipsychotics with placebo or active tx for ADHD were identified.</p>	<p>Not reported</p>	<p>1 expert felt the conclusion was up to date, the other did not know.</p>	<p>Conclusion is up to date.</p>
<p>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).</p>	<p>A new meta-analysis of 17 RCTs⁷ using the reduction in Young Mania Rating Scale (YMRS) scores as outcome showed much larger 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.</p> <p>One new RCT found risperidone superior to both lithium and divalproex in children with bipolar disorder after 6 weeks.¹¹</p>	<p>Not reported</p>	<p>Both experts felt the conclusion was up to date.</p>	<p>Conclusion possibly out of date regarding strength of evidence.</p>

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
<p>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).</p>	<p>One new RCT found that 3, 6, and 12 mg doses of paliperidone extended release were superior to placebo in adolescents with schizophrenia.¹⁵ One new small cohort of adolescents with schizophrenia or schizoaffective disorder found that long-term, clozapine is more effective than haloperidol, risperidone, and olanzapine.¹⁹ One large retrospective cohort found a trend toward shorter time to improvement with SGAs compared to FGAs; differences among SGAs were not significant.¹²</p>	<p>Not reported</p>	<p>1 expert felt the conclusion was up to date, the other did not know.</p>	<p>Conclusion up to date.</p>
<p>Five studies provided evidence on symptom improvement in Tourette syndrome. SGAs were favored over placebo for tics (moderate strength of evidence).</p>	<p>One open label trial found no difference in efficacy between aripiprazole and haloperidol.¹³</p>	<p>Not reported</p>	<p>Both experts felt the conclusion was up to date.</p>	<p>Conclusion up to date.</p>
<p>Four studies examined improvement for behavioral issues. One study found greater improvement in autistic symptoms with risperidone than placebo (low strength of evidence).</p>	<p>A new systematic review¹⁴ of 6 RCTs found risperidone superior to placebo in reducing problem behavior in children with intellectual disabilities.</p>	<p>Not reported</p>	<p>Both experts felt the conclusion was up to date.</p>	<p>Conclusion possibly out of date.</p>
<p>None of the included studies examined obsessive compulsive disorder, post-traumatic stress disorder, or anorexia nervosa</p>	<p>We found 2 RCTs^{8,20}, one CCT⁶, and one retrospective cohort study⁹ of SGAs in adolescent girls with anorexia nervosa. An RCT and CCT found no difference between</p>	<p>Not reported</p>	<p>Both experts did not know.</p>	<p>Conclusion is out of date.</p>

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
	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.			
Key Question 2. Adverse Events				
<p>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.</p> <p>For all comparisons of different FGAs or FGA with placebo, evidence was insufficient to draw a conclusion for adverse events.</p>	<p>An open label trial of aripiprazole vs haloperidol in children with tic disorders EPS were more frequent in the haloperidol group at 4 weeks.¹³ 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.¹⁸ One RCT in children with bipolar disorder found that weight gain was greater with risperidone than lithium or divalproex.¹¹</p>	Not reported	1 expert felt the conclusion was up to date, the other did not know.	Conclusion is up to date.
<p>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). Table C presents outcomes and comparisons for which the strength of evidence was low.</p>	<p>A systematic review³ 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.</p>	Not reported	Both experts felt the conclusion was up to date.	Conclusion is up to date.
<p>Adverse events were reported in 36 studies comparing SGAs with placebo. For nearly all outcomes and comparisons, the placebo</p>	<p>Adverse events were reported in five new studies compared SGAs with placebo. Findings echo those in the original CER,</p>		Both experts felt the conclusion was up to date.	Conclusion is up to date.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
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 prolactinrelated adverse event (moderate strength of evidence).	with SGA groups reporting more weight gain, sedation, headache, and fatigue.			
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.	Not reported	1 expert felt the conclusion was up to date, the other did not know.	Conclusion is up to date.
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).	We found no new studies of medication adherence in PDD or ADHD patients.	Not reported	1 expert felt the conclusion was up to date, the other did not know.	Conclusion is up to date.
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 ⁵ 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.	Not reported	Both experts felt the conclusion was up to date.	Conclusion is up to date.
22 studies provided data on a variety of	We found no new studies of schizophrenic patients reporting	Not reported	1 expert felt the conclusion was up to date, the other did not know.	Conclusion is up to date.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
<p>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>adherence or suicide-related behaviors.</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 whether there was a significant association between subpopulations and outcomes and the direction of this association.</p>	<p>Secondary analysis⁴ of an RCT on bipolar patients included in the original CER¹⁷ 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>Not reported</p>	<p>Both experts felt the conclusion was up to date.</p>	<p>Conclusion is up to date.</p>

Legend: ADHD= Attention Deficit Hyperactivity Disorder; ASD=Autism Spectrum Disorder; BMI=Body Mass Index; CCT=Case Controlled Trial; CGI=Clinical Global Impressions; DBD=Disruptive Behavior Disorder; FGAs=First-Generation Antipsychotics; PDD= Pervasive Developmental Disorders; RCT=Randomized Controlled Trial; SCEPC=Southern California Evidence-based Practice Center; SGA=Second-Generation Antipsychotics; YMRC=Young Mania Rating Scale

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Appendices

Appendix A: Search Methodology

Appendix B: Evidence Tables

Appendix C: Questionnaire Matrix

Appendix A. Search Methodology

SEARCH #1 (Run 8/7/2012):

DATABASE SEARCHED & TIME PERIOD COVERED:

Medline – 2011-8/2012

LANGUAGE: English

SEARCH STRATEGY:

1. exp Child Development Disorders, Pervasive/
2. Child behavior disorders/
3. (child adj1 development adj1 disorder*).tw.
4. Asperger Syndrome/
5. (asperger* adj1 (syndrome or disorder)).tw.
6. Autistic Disorder/
7. (autism* or (autistic adj1 disorder*) or kanner* syndrome).tw.
8. Rett Syndrome/
9. (((rett or retts) adj1 (syndrome or disorder)) or cerebroatrophic hyperammonemia*).tw.
10. Schizophrenia, Childhood/
11. (child* adj2 schizophrenia*).tw.
12. aggression/
13. aggression.tw.
14. psychomotor agitation/
15. ((psychomotor adj1 (agitation or restlessness or hyperactivity or excitement)) or akathisia).tw.
16. "sleep initiation and maintenance disorders"/
17. ((sleep adj2 disorder*) or insomnia*).tw.
18. mood disorders/
19. ((mood or affective) adj1 disorder*).tw.
20. impulsive behavior/
21. (impulsive adj1 behavior?).tw.
22. borderline personality disorder/
23. (borderline adj1 personality adj1 disorder*).tw.
24. personality disorders/
25. (affective adj2 dysregulation).tw.
26. ((\$behavioral adj2 dyscontrol) or (impulsive-behavioral adj2 deregulation)).tw.
27. (mood adj2 lability).tw.
28. (irritable or irritability).tw.
29. Self-Injurious Behavior/
30. (self-injurious behavior?r or self-mutilating behavior?r or self mutilation or self-destructive behavior?r or deliberate self-harm or parasuicide).tw.
31. antisocial personality disorder/
32. "Attention Deficit and Disruptive Behavior Disorders"/
33. Attention Deficit Disorder with Hyperactivity/
34. ((attention adj deficit adj disorder) or hyperkinetic syndrome or adhd).tw.
35. Conduct Disorder/
36. (conduct adj disorder*).tw.

37. Childhood Disintegrative Disorder.tw.
38. "Pervasive Developmental Disorder Not Otherwise Specified".tw.
39. (atypical adj1 autism).tw.
40. Oppositional Defiant Disorder.tw.
41. "Disruptive Behavior Disorder Not Otherwise Specified".tw.
42. Schizophrenia/
43. Schizophrenia, Catatonic/
44. Schizophrenia, Disorganized/
45. Schizophrenia, Paranoid/
46. ((catatonic or disorganized or paranoid) adj schizophrenia).tw.
47. Psychotic Disorders/
48. ((Psychotic or schizoaffective or schizophreniform) adj disorder).tw.
49. (brief reactive psychoses or psychoses).tw.
50. first episode schizophrenia.tw.
51. (prodromal and schizophrenic).tw.
52. Schizotypal Personality Disorder/
53. (schizotypal personality disorder or ((borderline or pseudoneurotic or pseudopsychopathic or incipient or latent) adj2 schizophrenia)).tw.
54. Bipolar Disorder/
55. (((bipolar or manic) adj (disorder or psychoses or depression)) or mania*).tw.
56. "Depressive Disorder, Major"/ and (refractory or chronic or resistant).ti,ab.
57. Depression/ and (refractory or chronic or resistant).ti,ab.
58. Depressive Disorder/
59. ((depressive adj (disorder or neuroses or syndrome*)) or ((endogenous or neurotic or unipolar) adj depression*)).tw.
60. Obsessive-Compulsive Disorder/
61. (OCD or anankastic personalit* or (obsessive compulsive adj (disorder* or neuroses*)) or (obsessivecompulsive adj (disorder* or neuroses*))).tw.
62. exp anorexia nervosa/
63. ((anorexia adj nervosa*) or anorexia*).tw.
64. exp stress disorders, post-traumatic/
65. ((chronic or acute or delayed onset) and (post-traumatic adj stress adj disorder*)).tw.
66. ((posttraumatic or post-traumatic or post traumatic) adj (neuroses or disorder)).tw.
67. ptsd.tw.
68. exp tourette syndrome/
69. (\$tourette* adj (syndrome or disorder or disease)).tw.
70. (tic adj disorder).tw.
71. (multiple adj motor adj vocal adj tic adj disorder).tw.
72. or/1-71
73. exp Antipsychotic Agents/
74. exp Tranquilizing Agents/
75. ((first or 1st) adj generation adj antipsychotic*).tw.
76. azaperone/
77. 1649-18-9.rm.
78. (Atsaperoni or Azaperon or Azaperona or Azaperone or Azaperonum or Eucalmyl or Fluoperidol or NSC 170976 or R 1929 or R-1929 or Sedaperone or Stresnil or Suicalm).mp.
79. Butyrophenones/ad, to, tu, ct, po, ae
80. Clopenthixol/

81. 982-24-1.m.
82. (Chlorpenthixol or Clopenthixol or Clopenthixolum or Sordinol or Zuclopenthixol).mp.
83. chlorpromazine/
84. 50-53-3.m.
85. (Aminazin or Aminazine or Ampliactil or BC 135 or Chlorpromazine or Chlorpromazinum or Clorpromazina or Chlor-Promanyl or Chlorpromados or Chlorderazin or Chlorpromazin or Contomin or Elmarin or Esmind or Fenactil or Fenaktyl or HL 5746 or Largactil or Largactilothiazine or Megaphen or Largactyl or Klooripromatsiini or Klorpromazin or 6 Copin or Trinicalm Forte or Diminex Balsamico Juven Tos or Largatrex or Phenactyl or Proma or Promactil or Promazil or Prozil or Psychozine or Sanpron or Thorazine or Torazina or Wintermin).mp.
86. Chlorprothixene/
87. 113-59-7.m.
88. (Chlorprothixene or Chlorprothixen or Chlorprothixenum or Chlorprotixen or Chlorprotixene or Clorprotisene or Clorprotixeno or Laractan or Paxyl or Rentovet or Taractan or Tarasan or Traquilan or Trictal or Truxal or Truxaletten or Truxil or Vetacalm).mp.
89. Dibenzoxazepines/ad, to, tu, ct, po, ae
90. Droperidol/
91. 548-73-2.m.
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.
93. Flupenthixol/
94. 2709-56-0.m.
95. (Depixol or Emergil or Fluanxol or Flupenthixol or Flupentixol or Flupentixolum or Fluxanxol or Siplaril or Siplarol).mp.
96. fluphenazine/
97. 69-23-8.m.
98. (Dapotum or Elinol or Flufenazina or Fluofenazine or Fluphenazine or Fluorphenazine or Fluphenazinum or Ftorphenazine or Moditen or Pacinol or Sevinol or Siqualon or Triflumethazine or Valamina or Vespazine).mp.
99. haloperidol/
100. 52-86-8.m.
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 Serenefl or Sernas or Sernel or Serenase or Ulcolind or Uliolind or Vesalium).mp.
102. Indoles/ad, to, tu, ct, po, ae
103. Lithium carbonate/

104. 554-13-2.rn.
105. (Camcolit or Candamide or Carbolith or Carbonic acid lithium salt or dilithium salt or Eskalith or Eutimin or Hypnorex or Limas or Lithium or Liskonum or Litard or Lithane or Lithea or Lithicarb or Lithinate or Lithionate or Lithotabs or Liticar or Manialith or Maniprex or Micalith or Neurolepsin or Pfi-lithium or Phasal or Plenur or Priadel or Quilonorm or Teralithe).mp.
106. loxapine/
107. 1977-10-2.rn.
108. (Clozapine or CL 62362 or Dibenzacepin or Dibenzaozepine or Hydrofluoride 3170 or LW 3170 or Lossapina or Loksapiini or Loxapin or Loxapina or Loxapine or Loxapinum or Oxilapine or Loxapac or SUM 3170 or Loxitane or Desconex).mp.
109. Methiothepin/
110. 20229-30-5.rn.
111. (Methiothepin or metitepine or Methiothepine or Methiothepin maleate or Metitepina or Metitepinum).mp.
112. Methotrimeprazine/
113. 60-99-1.rn.
114. (Dedoran or Hirnamin or Hirnamine or Levomepromazine or Levomepromazin or Levomepromazina or 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 Levolam or Nozinan or Sinogan or Tisercin or Veractil).mp.
115. molindone/
116. 7416-34-4.rn.
117. (Molindona or Molindone or Molindonum).mp.
118. Penfluridol/
119. 26864-56-2.rn.
120. (Penfluridol or Penfluridolum or Semap).mp.
121. Perazine/
122. 84-97-9.rn.
123. (Pemazine Dimalonate or Peragal or Perazin or Perazine or Perazinum or Taxilan).mp.
124. perphenazine/
125. 58-39-9.rn.
126. (Chlorperphenazine or Chlorpiprazine or Decentan or Emesinal or Etaperazin or Etaperazine or Ethaperazine or Etrafon or F-mon or Fentazin or Mutabon or Perfenazin or Perfenazina or Perfenazinas or Perfenazine or Perphenazin or Perphenazine or Perfenazyna or Perphenazinum or Pertriptyl or Sch 3940 or Thilatazin or Tranquisan or Trifaron or Trilafon or Trilifan or Triptafen or Triphenot or Triavil).mp.
127. Phenothiazines/ad, to, tu, ct, po, ae [Administration & Dosage, Toxicity, Therapeutic Use, Contraindications, Poisoning, Adverse Effects]
128. Pimozide/
129. 2062-78-4.rn.
130. (Antalon or Opiran or Orap or Pimotsidi or Pimozid or Pimozida or Pimozidas or Pimozide or Pimozidum or Pimozyd).mp.

131. Prochlorperazine/
132. 58-38-8.m.
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 Mitil or Prochlorpemazine or Prochlorperazinum or Prochlorperazina or Prochlorperazine or Proklooriperatsiini or Prokloorperazin or Prorazin or Phenothiazine or Seratil or Stemetil or Tementil or Temetid).mp.
134. Promazine/
135. 58-40-2.m.
136. (Ampazine or Berophen or Esparin or Liranol or Neo-Hibernex or Prazin or Sparine or Sinophenin or Promazine hydrochloride or Protactyl or Promatsiini or Promazin or Promazine or Promazinum or Propazinum or Prazine or Promwill or Protactyl or Romtiazin or Sinophenin or Talofen or Talofen or Tomil or Verophen).mp.
137. Raclopride/
138. 84225-95-6.m.
139. (raclopride or racloprida or raclopridum or raklopid or raklopridl).mp.
140. Spiperone/
141. 749-02-0.m.
142. (E 525 or Espiperona or Spiperone or Spiperonum or Spiroperidol or Spiropitan).mp.
143. thioridazine/
144. 50-52-2.m.
145. (Aldazine or Dazithin or Detril or Elperil or Mallorol or Malloryl or Melleril or Meleril or Mellaril or Mellerets or Mellerette or Melleretten or Melleril or Sonapax or Thioridazin or Thioridazine or Thioridazinum or Tioridatsiini or Tioridazin or Tioridazina or Tioridazinas).mp.
146. Thiothixene/
147. 5591-45-7.m.
148. (Navane or Navaron or Orbinamon or Thiothixene or Tiotikseeni or Tiotixen or Tiotixeno or Tiotixenum or Thixit or Tiotixene).mp.
149. Thioxanthenes/ad, to, tu, ct, po, ae
150. Tiapride/
151. 51012-32-9.m.
152. (Betaprid or Delpral or Doparid or Etilis or Equilium or Italiprid or Luxoben or Normagit or Porfanil or Serepid or Tiacob or Tiapridal or Tiapride).mp.
153. Trifluoperidol/
154. 749-13-3.m.
155. (Flumoperone or Psicoperidol or Psychoperidol or Trifluoperidol or Trifluoperidoli or Trifluoperidolum or Triperidol or Trisedil or Trisedyl).mp.
156. Trifluoperazine/
157. 117-89-5.m.
158. (Cuait D or Cuait N or eskazine or flupazine or Jatrosom or Jalonac or Parstelin or Parmodalin or stelazine

or Stelabid or Stelapar or Sycot or Terfluzine or Trifluoperazine or Trifluoperazini Hydrochloridum or triftazin or Trinicalm Forte or Trinicalm Plus).mp.
159. Triflupromazine/
160. 146-54-3.rn.
161. (Adazine or Fluopromazine or Phenothiazine or Psyquil or Siquil or Triflupromazina or Triflupromazine or Trifluopromazine or Vesprin or Vetame).mp.
162. Zuclopenthixol/
163. 53772-83-1.rn.
164. (Cisordinol or Clopixol or Ciatyl-Z or Clopenthixol or Clopentixol or Sedanxol or Zuclopenthixolum or Zuclopenthixol or Zuclopenthixol or Zuklopenthixol).mp.
165. or/73-164
166. (atypical adj antipsychotic*).tw.
167. ((second or 2nd) adj generation adj antipsychotic*).tw.
168. ((third or 3rd) adj generation adj antipsychotic*).tw.
169. Amisulpride.tw.
170. 71675-85-9.rn.
171. (Aminosultopride or Amisulprida or Amisulpridum or Solian or Sulpitac).mp.
172. aripiprazole.tw.
173. 129722-12-9.rn.
174. (Abilitat or Abilify or Aripiprazole or Discmelt or OPC 31 or OPC 14597).mp.
175. Asenapine.tw.
176. 65576-45-6.rn.
177. EINECS 265-829-4.mp.
178. Blonanserin.tw.
179. 132810-10-7.rn.
180. AD 5423.mp.
181. Clotiapine.tw.
182. 2058-52-8.rn.
183. (Clothiapine or Clotiapina or Clotiapinum or Dibenzothiazepine or Etumina or Etumine or Entumin or Etomine or Entumine or HF 2159 or LW 2159 or "BRN 0568276").mp.
184. clozapine/
185. 5786-21-0.rn.
186. (Clozapin or Clozapina or Clozapine or Clozapinum or Clorazil or Clozaril or FazaClo or Leponex or LX 100-129 or Zaponex).mp.
187. Diazepine.tw.
188. 12688-68-5.rn.
189. Dibenzazepines/ad, to, tu, ct, po, ae
190. Dibenzothiazepines/ct, ad, to, tu, ae, po
191. Fluvoxamine/
192. (54739-18-3 or 61718-82-9).rn.
193. (dumirox or DU23000 or Fluvoxamina or fluvoxamine or Fluvoaminum or Fluvoxamine Maleate or Fevarin or Luvox or SME 3110).mp.
194. Iloperidone.tw.
195. 133454-47-4.rn.
196. (Fanapt or HP 873 or Zomaril).mp.

197. Isoxazoles/ad, to, tu, ct, po, ae
198. Mesoridazine/
199. 5588-33-0.rn.
200. (Calodal or Lidanar or Lidanil or Mesoridazina or Mesoridazine or Mesoridazinum or Serentil or THD-2-SO).mp.
201. mosapramine.tw.
202. 89419-40-9.rn.
203. (Closipramine or Cremin or Mosapramina).mp.
204. olanzapine.tw.
205. 132539-06-1.rn.
206. (Zyprexa or Olantsapiini or Olanzapin or Olanzapina or Olanzapinum or Olansek or Zalasta or Zypadhera).mp.
207. paliperidone.tw.
208. 144598-75-4.rn.
209. (9-Hydroxyrisperidone or Invega or R 76477 or RO76477).mp.
210. Perospirone.tw.
211. 150915-41-6.rn.
212. (lullan or perospirone hydrochloride).mp.
213. Piperidines/ad, to, tu, ct, po, ae
214. Piperazines/ad, tu, to, ct, po, ae
215. Pirenzepine/tu, ad, to, ct, po, ae
216. Pyrimidinones/ad, to, tu, ct, po, ae
217. quetiapine.tw.
218. 111974-69-7.rn.
219. (Co-Quetiapine or HSDB 7557 or Seroquel).mp.
220. Quinolones/to, po, ct, ad, tu, ae
221. Remoxipride/
222. 80125-14-0.rn.
223. (FLA 731 or Remoxiprida or Remoxipride or Remoxipridum).mp.
224. Risperidone/
225. 106266-06-2.rn.
226. (Apexidone or Psychodal or Risperdal or Risperidona or Risperidone or Risperidonum or Risperin or Risperilept or Rispolin or Spiron).mp.
227. Sertindole.tw.
228. 106516-24-9.rn.
229. (Lu 23-174 or Sertindol or Serdolect or Sertindolum).mp.
230. Sulpiride/
231. 15676-16-1.rn.
232. (Ablit or Aiglonyl or Alimoral or Calmoiflorine 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 Omiryil or Omperan or Ozoderpin or Psicocen or Pyrkappl or Sernevin or Splotin or Stamonevrol or Sulparex or Sulpirid or Sulpirida or Sulpiride or Sulpiridum or Sulpor or Suprium or Sulpyrid or Trilan or Valirem or Zemorcon).mp.
233. Thiazoles/ad, th, ct, po, to, ae

234. Zotepine.tw.
235. 26615-21-4.rn.
236. (Lodepin or Nipolept or Zotepina or Zotepinum or Zoleptil).mp.
237. ziprasidone.tw.
238. 146939-27-7.rn.
239. Zeldox.mp.
240. or/73-74,166-239
241. or/165,240
242. and/72,241
243. randomized controlled trial.pt.
244. controlled clinical trial.pt.
245. randomi?ed.ab.
246. placebo.ab.
247. drug therapy.fs.
248. randomly.ab.
249. trial.ab.
250. groups.ab.
251. or/243-250
252. (humans not (animals and humans)).sh,hw.
253. 251 and 252
254. cohort studies/
255. followup studies/
256. longitudinal studies/
257. prospective studies/
258. Retrospective Studies/
259. Case-Control Studies/
260. (cohort\$ or longitudinal or retrospective or prospective or followup or case-control).tw.
261. or/254-260
262. 261 and 252
263. exp infant/
264. exp child/
265. exp adolescent/
266. exp pediatrics/
267. (\$child\$ or adolescen\$ or p*ediatic\$).tw.
268. or/263-267
269. and/242,253,268
270. and/242,262,268
271. and/242,253
272. and/242,262
273. or/271-272
274. limit 273 to "all child (0 to 18 years)"
275. or/269-270
276. or/274-275
277. limit 276 to (english language and yr="2011 -Current")
278. limit 273 to "young adult (19 to 24 years)"
279. exp Young Adult/
280. (young adj adult*).tw.
281. ((college or university) adj2 (age or student*)).tw.
282. students/
283. or/279-282
284. and/242,253,283

285. and/242,262,283
286. or/284-285
287. or/278,286
288. limit 287 to (english language and yr="2011 -Current")
289. 277 or 288
290. (editorial or letter or comment).pt. or case reports/
291. 289 not 290

NUMBER OF ITEMS RETRIEVED: 472

SEARCH #2 (Run 8/14/2012):
DATABASE SEARCHED & TIME PERIOD COVERED:
PsycInfo – 2011-8/2012

LANGUAGE: English
Limits: 2011-; peer reviewed

SEARCH STRATEGY:

(DE pervasive developmental disorders OR DE behavioral disorders OR child N1 development N1 disorder* OR DE aspergers syndrome OR Asperger N1 (syndrome OR disorder) OR DE autism OR autism* OR (autistic N1(syndrome or disorder) OR kanner* syndrome OR DE rett syndrome OR ((rett OR retts) N1(syndrome OR disorder)) OR “cerebroatrophic hyperammonemia”) OR DE childhood schizophrenia OR child* N2 schizophrenia OR DE aggressiveness OR DE aggressive behavior OR aggression OR “psychomotor agitation” OR ((psychomotor N1 (agitation OR restlessness OR hyperactivity OR excitement)) OR akathisia OR “sleep initiation disorder*” OR “sleep maintenance disorder*” OR (sleep N2 disorder*) OR insomnia OR DE affective disorders OR ((mood OR affective) N1 disorder*) OR DE impulsiveness OR impulsive* N1 behavior OR DE borderline personality disorder OR borderline N1 personality N1 disorder OR DE personality disorders OR affective N2 dysregulation OR ((behavioral N2 dyscontrol) or (impulsive-behavioral N2 deregulation)) OR mood N2 lability OR irritable OR irritability OR DE self injurious behavior OR “self injurious behavior*” OR “self-mutilating behavior*” OR “self-destructive behavior*” OR “deliberate self harm” OR parasuicide OR DE antisocial personality disorder OR DE Attention Deficit Disorder OR DE Behavior Problems OR DE attention deficit Disorder with hyperactivity OR ((attention N1 deficit N1 disorder) OR adhd OR “hyperkinetic syndrome”) OR DE conduct disorder OR Conduct N1 disorder OR “childhood disintegrative disorder” OR “pervasive developmental disorder not otherwise specified” OR atypical N1 autism OR “Oppositional defiant disorder” OR “disruptive behavior disorder not otherwise specified” OR DE schizophrenia OR DE catatonic schizophrenia OR DE paranoid schizophrenia OR (catatonic OR disorganized OR paranoid) N1 schizophrenia OR DE psychosis OR ((psychotic OR schizoaffective OR schizophreniform) N1 disorder) OR “brief reactive psychosis” OR “brief reactive psychoses” OR “first episode schizophrenia” OR (prodrom\$ AND schizophren\$) OR DE schizotypal personality disorder OR (“schizotypal personality disorder” OR (borderline OR pseudoneurotic OR pseudopsychopathic OR incipient OR latent) N2 schizophrenia) OR DE bipolar disorder OR (((bipolar OR manic) N1 (disorder OR psychosis OR psychoses OR depression)) OR mania*) OR DE Major Depression AND (refractory OR chronic OR resistant) OR ((depressive N1 (disorder OR neuroses OR syndrome*)) OR ((endogenous OR neurotic OR unipolar) N1

depression*)) OR DE obsessive compulsive disorder OR
(OCD OR “anankastic personalit*” OR (“Obsessive compulsive” N1 (disorder* OR neuros*)) OR
(obsessivecompulsive N1 (disorder* OR neuros*)) OR DE anorexia nervosa OR
((anorexia N1 nervosa*) OR anorexia*) OR DE posttraumatic stress disorder OR
((chronic or acute or “delayed onset”) AND (post-traumatic N1 stress N1 disorder*))
OR ((posttraumatic OR post-traumatic OR post traumatic N1 (neuroses OR disorder))
OR pstd OR DE Tourette syndrome OR tic N1 disorder OR(multiple N1 motor N1 vocal N1 tic N1
disorder))

AND

(DE neuroleptic drugs OR DE tranquilizing drugs OR “first generation antipsychotic” OR “1st generation
antipsychotic” OR azaperone OR atsaperoini OR azaperon OR azaperona OR azaperone OR azaperonum
OR eucalmyl OR fluoperidol OR sedaperone OR stresnil OR suicalm OR butyrophenones OR

Clopenthixol

OR chlorpenthixol OR clopenthixol OR clopenthixolum OR sordinol OR zucloperthixol OR
chlorpromazine OR 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 OR Chlorprothixene
OR 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 OR Dibenzoxazepines OR Droperidol OR
Dehydrobenzoperidol or Dehydrobenzperidol or Deidrobenzperidolo or Dridol or Droleptan or
Droperidol or Droperidoli or Droperidolis or Droperidolum or Disifelit or Halkan or Inapsin or Inapsine
or Inopsin or Thalamonal or Nilperidol or Properidol or Sintodril or Vetkalm OR Flupenthixol OR
Depixol or Emergil or Fluaxol or Flupenthixol or Flupentixol or Flupentixolum or Fluxanxol or Siplaril
or Siplarol OR fluphenazine OR 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 OR haloperidol OR Aldo or Aloperidin or Aloperidol or
Aloperidolo or Brotopon or Dozic or Einalon S or Eukystol or Fortunan or Galoperidol or Haldol or
Halojust or Halopal or Haloperidol or Haloperidoli or Haloperidolis or Haloperidolu or Halopoidol or
Serenace or Halopidol or Haloper or Halperon or Keselan or Lealgin or Linton or Mixidol or Peluces or
Pernox or Serenace or Serenefl or Sernas or Sernel or Serenase or Ulcolind or Uliolind or Vesalium OR
Indoles OR Lithium carbonate OR 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 OR
loxapine OR Cloxazepine or CL 62362 or Dibenzacepin or Dibenzoazepine or Hydrofluoride 3170 or LW
3170 or Lossapina or Loksapiini or Loxapin or Loxapina or Loxapine or Loxapinum or Oxilapine or
Loxapac or SUM 3170 or Loxitane or Desconex OR Methiothepin OR Methiothepin or metitepine or
Methiothepine or Methiothepin maleate or Metitepina or Metitepinum OR Methotrimprazine OR
Dedoran or Hirnamin or Hirnamine or Levomepromazine or Levomepromazin or Levomepromazina or
Levopromazioni or Levomepromazinum or Levoprome or Levotomin or Mepromazine or
Methotrimprazine or Neurocil or Neozine or Nirvan or Nocinan or Momizan or Nozinane or Sinogan or
Levolam or Nozinan or Sinogan or Tisercin or Veractil OR molindone OR Molindona or Molindone or
Molindonum OR Penfluridol OR Penfluridol or Penfluridolum or Semap OR Perazine OR Pemazine
Dimalonate or Peragal or Perazin or Perazine or Perazinum or Taxilan OR perphenazine
ORChlorperphenazine 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 OR Phenothiazines OR Pimozide OR Antalón or Opiran or Orap or Pimotsidi or Pimozid or Pimozida or Pimozidas or Pimozide or Pimozidum or Pimozyd OR Prochlorperazine OR 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 OR Promazine OR 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 OR Raclopride OR raclopride or racloprida or raclopridum or rakloprid or raklopridil OR Spiperone OR E 525 or Espiperona or Spiperone or Spiperonum or Spiroperidol or Spiropitan OR thioridazine OR 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 OR Thiothixene OR Navane or Navaron or Orbinamon or Thiothixene or Tiotikseeni or Tiotixen or Tiotixeno or Tiotixenum or Thixit or Tiotixene OR Thioxanthenes OR Tiapride OR Betaprid or Delpral or Doparid or Etilen or Equilium or Italiprid or Luxoben or Normagit or Porfanil or Sereprid or Tiacob or Tiapridal or Tiapride OR Trifluoperidol OR Flumoperone or Psicoperidol or Psychoperidol or Trifluoperidol or Trifluoperidoli or Trifluoperidolum or Triperidol or Trisedil or Trisedyl OR Trifluoperazine OR Cuait D or Cuait N or eskazine or flupazine or Jatrosom or Jalonac or Parstelin or Parmodalín or stelazine or Stelabid or Stelapar or Sycot or Terfluzine or Trifluoperazine or Trifluoperazini Hydrochloridum or triftazin or Trinicalm Forte or Trinicalm Plus OR Triflupromazine OR Adazine or Fluopromazine or Phenothiazine or Psyquil or Siquil or Triflupromazina or Triflupromazine or Trifluopromazine or Vesprin or Vetame OR Zuclopenthixol OR Cisordinol or Clopixol or Ciatyl-Z or Clopenthixol or Clopenthixol or Sedanaxol or Zuclopenthixolum or Zuclopenthixol or Zuclopenthixol or Zuklopenthixol OR Atypical N1 antipsychotic*OR “second generation antipsychotic” OR “2nd generation antipsychotic” OR “third generation antipsychotic” OR “3rd generation antipsychotic” OR Amisulpride OR Aminosultopride or Amisulprida or Amisulpridum or Solian or Sulpitac OR aripiprazole OR Abilitat or Abilify or Aripiprazole or Discmelt or OPC 31 or OPC 14597 OR Asenapine OR Blonanserin OR Clotiapine OR Clotiapine or Clotiapina or Clotiapium or Dibenzothiazepine or Etumina or Etumine or Entumin or Etumine or Entumine or HF 2159 or LW 2159 or "BRN 0568276" OR clozapine OR Clozapin or Clozapina or Clozapine or Clozapinum or Clorazil or Clozaril or FazaClo or Leponex or LX 100-129 or Zaponex OR Diazepine OR Dibenzazepines OR Dibenzothiazepines OR Fluvoxamine OR dumirox or DU23000 or Fluvoxamina or fluvoxamine or Fluvoaminum or Fluvoxamine Maleate or Fevarin or Luvox OR Iloperidone OR Fanapt or HP 873 or Zomaril OR Isoxazoles OR Mesoridazine OR Calodal or Lidanar or Lidanil or Mesoridazina or Mesoridazine or Mesoridazinum or Serentil or THD-2-SO OR mosapramine OR Clospipramine or Cremin or Mosapramina OR olanzapine OR Zyprexa or Olantsapiini or Olanzapin or Olanzapina or Olanzapinum or Olansek or Zalasta or Zypadhera OR paliperidone OR 9-Hydroxyrisperidone or Invega or R 76477 or RO76477 OR Perospirone OR lullan or perospirone hydrochloride OR Piperidines OR Piperazines OR Pirenzepine OR Pyrimidinones OR quetiapine OR Co-Quetiapine or HSDB 7557 or Seroquel OR Quinolones OR Remoxipride OR FLA 731 or Remoxiprida or Remoxipride or Remoxipridum OR Risperidone OR Apexidone or Psychodal or Risperdal or Risperidona or Risperidone or Risperidonum or Risperin or Risperilept or Rispolin or Spiron OR Sertindole OR Lu 23-174 or Sertindol or Serdolect or Sertindolum OR Sulpiride OR 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 OR Thiazoles OR Zotepine OR Lodepin or Nipolept or Zotepina or Zotepinum or Zoleptil OR ziprasidone OR Zeldox)

AND

“Randomized controlled trial” OR “clinical trial” OR AB randomized OR AB randomized OR AB placebo OR “drug therapy” OR AB randomly OR AB trial OR AB groups OR cohort OR longitudinal OR retrospective OR prospective OR follow-up OR case-control

AND

Child* or adolescen* or pediatric* OR paediatric* or youth or “young adult” OR student* OR “college age”

NUMBER OF ITEMS RETRIEVED: 179

Total citations: 472(Medline) + 96(Psycinfo after removing dups & case studies)= 568 results

Appendix B. Evidence Table

Author, Year	Study Design	Country	Population	Intervention Category	Specific Intervention	Setting / Duration / F/u	Outcomes
Kafantaris, 2011 ⁸	RCT	US	20 girls aged 12 to 21 with anorexia nervosa	Atypical antipsychotics	Olanzapine vs Placebo	Eating disorder program: inpatient, day tx, or outpatient, 10 weeks	Change in BMI did not differ significantly between groups
Attia, 2011 ²⁰	RCT	US, Canada	23 patients aged ≥ 16 with anorexia nervosa	Atypical antipsychotics	Olanzapine vs Placebo	Outpatient, 8 weeks	Olanzapine patients gained more weight than placebo. Differences in psych measures were not significant. Sedation was more frequent with the drug.
Norris, 2011 ⁹	Retrospective cohort	Canada	86 girls aged 10 to 17 years with anorexia nervosa	Atypical antipsychotics	Olanzapine vs Usual care	Hospital eating disorder program, minimum 2 weeks	Olanzapine patients had greater illness severity at baseline, making conclusions impossible to draw
Hagman, 2011 ⁶	CCT	US	N = 40 females 12 to 21 years old with anorexia nervosa	Atypical antipsychotics	Risperidone vs Placebo	Residential eating disorders program, 9 weeks	No difference between groups in change in BMI
Findling, 2012 ⁵	RCT - Maintenance phase	US	N = 60, aged 4 to 9 with bipolar disorder	Atypical antipsychotics	Aripiprazole vs Placebo	Outpatient, 72 weeks	Aripiprazole patients had significantly longer time to mood event (median 6.14 weeks) than placebo patients (2.29 weeks). Drug group had more stomach pain,

Author, Year	Study Design	Country	Population	Intervention Category	Specific Intervention	Setting / Duration / F/u	Outcomes
							increase appetite, and headaches.
Liu, 2011 ⁷	Systematic review	Various	2,666 children & adolescents with bipolar disorder	Mood stabilizers, anticonvulsants, atypical antipsychotics, naturopathics	Lithium, Divalproex, Carbamazepine, Lamotrigine, Oxcarbazepine, Topiramate, Aripiprazole, Olanzapine, Quetiapine, Risperidone, Ziprasidone, Omega 3	17 RCTs & 29 open label trials	A meta-analysis of RCTs using the reduction in Young Mania Rating Scale (YMRS) scores as outcome showed much larger effects for atypicals (-16.8 points) compared to mood stabilizers (-10.99 points) and anticonvulsants (-11.03 points). Differences among atypicals were not statistically significant.
West, 2011 ⁴	RCT - Secondary analysis of Pavuluri, 2011 ¹⁷	US	N=65, aged 8 to 18 with bipolar disorder	Atypical vs FGA	Risperidone vs Divalproex	Outpatient, 6 weeks	Subjects with disruptive behavior disorder (DBD) had greater improvements in manic symptoms in response to risperidone, while subjects without DBD improved with either drug.
Geller, 2012 ¹¹	RCT	US	279 patients aged 6 to 15 with bipolar disorder	Atypicals, Mood stabilizers	Risperidone vs Lithium vs Divalproex	Outpatient, 8 weeks	Response rates were significantly higher with risperidone (68.5%) compared to lithium (35.6%) or divalproex (24.0%). Weight gain was greater

Author, Year	Study Design	Country	Population	Intervention Category	Specific Intervention	Setting / Duration / F/u	Outcomes
							with risperidone than the other two drugs.
Unwin, 2011 ¹⁴	Systematic review	UK	459 patients aged 5 to 18 with problem behavior and intellectual disabilities	Atypical antipsychotics	Risperidone vs Placebo	6 RCTs	All studies found risperidone superior to placebo in reducing problem behavior. Mean weight gain for risperidone groups was 2.3kg. Other common adverse events were somnolence, fatigue, and headache. 3 RCTs had open label 2 year f/u: 35% of patients had dropped out or were lost to f/u.
Scahill, 2012 ²	RCT	US	N=124, aged 4 to 14 with PDD + Serious behavior problems	Atypical antipsychotics	Risperidone vs Risperidone + Parent Training	Home, 24 weeks	Combination group had significantly higher VABS socialization and communication scores than drug alone.
Maayan, 2011 ³	Systematic review	Various	Children & Adolescents with Bipolar, Schizophrenia, ASD, or Disruptive behavior	Atypical antipsychotics	Olanzapine, Clozapine, Risperidone, Quetiapine, Aripiprazole	34 RCTs, 16 cohort studies	Weight gain: Olanzapine 3.8 - 16.2 kg, Clozapine 1.9 - 9.5 kg, Risperidone 1.9 - 7.2 kg, Quetiapine 2.3 - 6.1 kg, Aripiprazole 0 - 4.4 kg greater weight gain in ASD,

Author, Year	Study Design	Country	Population	Intervention Category	Specific Intervention	Setting / Duration / F/u	Outcomes
							disruptive behavior patients, perhaps due to less prior exposure to atypicals
Yung, 2011 ¹⁰	RCT	Australia	115 adolescents at ultra high risk for psychosis	Atypical antipsychotics	Cognitive therapy + risperidone vs cognitive therapy + placebo vs supportive therapy + placebo	Personal Assessment & Crisis Evaluation (PACE) Outpatient Center, 6 months	There were no significant differences between groups regarding number of patients developing psychotic disorder or any secondary measures.
Robles, 2011 ¹⁶	RCT	Spain	50 patients aged 12 to 18 with early onset psychosis	Atypical antipsychotics	Quetiapine vs Olanzapine	Hospital at baseline, then outpatient, 6 months	Neither group made significant gains in cognitive performance, which was the focus of this paper
Singh, 2011 ¹⁵	RCT	India, Russia, Ukraine, Romania, US	200 patients aged 12 to 17 with schizophrenia	Atypical antipsychotics	3 weight-based doses of paliperidone extended release vs placebo	Outpatient, hospitalization optional, 6 weeks	With weight-based tx, only the medium dose lead to significant improvement in symptoms. 3, 6, and 12 mg actual dose strengths were superior to placebo. Adverse events including somnolence, akathisia, tremor, insomnia and headache were dose related.
Cianchetti, 2011 ¹⁹	Cohort	Italy	47 patients aged 10 to 17	Atypical antipsychotics,	Aripiprazole, Olanzapine,	Outpatient, 3 years	Long-term, clozapine is more

Author, Year	Study Design	Country	Population	Intervention Category	Specific Intervention	Setting / Duration / F/u	Outcomes
			with schizophrenia or schizoaffective disorder	FGAs	Quetiapine, Risperidone, Clozapine, Haloperidol		effective than haloperidol, risperidone and olanzapine.
Zedkova, 2011 ¹²	Retrospective cohort	Czech Republic	296 adolescents with schizophrenia and other psychotic disorders	Atypical antipsychotics, FGAs	Aripiprazole, Olanzapine, Quetiapine, Risperidone, Ziprasidone, Clozapine, Haloperidol, Perphenazine, Suspirod	University dept of child psychiatry	Significant trend toward shorter time to first improvement with atypicals; differences among atypicals were not statistically significant.
Yoo, 2011 ¹³	Open label clinical trial	South Korea	48 patients aged 6 to 15 with tic disorders	Atypical antipsychotics, FGAs	Aripiprazole vs Haloperidol	Outpatient, 8 weeks	There we no significant between group effects or interactions; both groups improved. Extrapyramidal symptoms were higher in the haloperidol group at 4 weeks.
Gulisano, 2011 ¹⁸	Cohort	Italy	50 patients aged 6 to 18 with Tourette's Syndrome	Atypical antipsychotics, FGAs	Aripiprazole vs pimozide	Outpatient, 2 years	Adverse events focus: At equal doses, aripiprazole has safer cardiovascular profile, with a lower frequency of QTc prolongation

Legend: ADHD= Attention Deficit Hyperactivity Disorder; ASD=Autism Spectrum Disorder; BMI=Body Mass Index; CCT=Case Controlled Trial; CGI=Clinical Global Impressions; DBD=Disruptive Behavior Disorder; FGAs=First-Generation Antipsychotics; PDD= Pervasive Developmental Disorders; RCT=Randomized Controlled Trial; SCEPC=Southern California Evidence-based Practice Center; SGAs=Second-Generation Antipsychotics; YMRC=Young Mania Rating Scale

Appendix C. Questionnaire Matrix

Surveillance and Identification of Triggers for Updating Systematic Reviews for the EHC Program

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

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
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>	<input type="checkbox"/>	<p>New Evidence:</p>	<input type="checkbox"/>
<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>	<input type="checkbox"/>	<p>New Evidence:</p>	<input type="checkbox"/>

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
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).	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
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).	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
Five studies provided evidence on symptom improvement in Tourette syndrome. SGAs were favored over placebo for tics (moderate strength of evidence).	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
Four studies examined improvement for behavioral issues. One study found greater improvement in autistic symptoms with risperidone than placebo (low strength of evidence).	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
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	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
<p>avored 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.</p> <p>For all comparisons of different FGAs or FGA with placebo, evidence was insufficient to draw a conclusion for adverse events.</p>			
<p>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). Table C presents outcomes and comparisons for which the strength of evidence was low.</p>	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<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 prolactinrelated adverse event (moderate strength of evidence).</p>	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
Key Question 3: Short- and long-term outcomes			
<p>The findings for other short- and long-term outcomes are presented separately for each condition in Table D. The evidence was</p>		New Evidence:	

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
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.	<input type="checkbox"/>		<input type="checkbox"/>
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).	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
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).	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
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	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
studies on behavioral issues. The evidence was insufficient for all of the outcomes and comparisons examined in these studies.			
Key Question 4: Subpopulations			
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.	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
Are there new data that could inform the key questions that might not be addressed in the conclusions?			