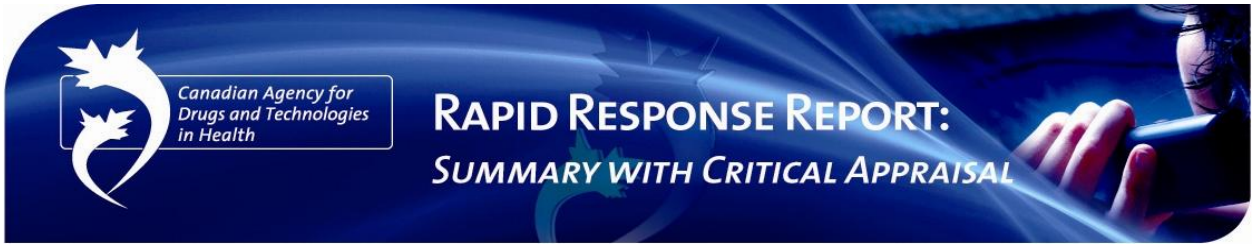

TITLE: Antipsychotics for Pediatric Patients: A Review of the Clinical Efficacy, Safety, and Guidelines

DATE: 17 December 2012

CONTEXT AND POLICY ISSUES

Antipsychotic drugs are widely used to treat a variety of psychiatric disorders. These drugs are commonly divided into two categories: first generation antipsychotics (FGA) or typical antipsychotics and second generation antipsychotics (SGA) or atypical antipsychotics.[1] FGA includes drugs such as haloperidol, loxapine, thiothixene, and thioridazine. SGA includes drugs such as aripiprazole, clozapine, olanzapine, quetiapine, risperidone and ziprasidone. These drugs are available in Canada, except for thioridazine which has been discontinued.[2] These drugs are used to alleviate psychotic symptoms but they are associated with a number of adverse effects such as extrapyramidal side effects (EPS), weight gain, and sedation. Generally, compared with FGAs, the SGAs are associated with lower risk of motor side effects but higher risk of weight gain, elevated lipid and prolactin levels and development of type 2 diabetes.[1] The use of antipsychotics for treating the pediatric population with mental health disorders has increased significantly during the past 20 years.[1,3] For children, antipsychotic drug recommendations by all specialists increased by 114% from 2005 to 2009 in Canada and the majority of recommendations were for SGAs.[4] In the USA, the frequency of prescribing antipsychotic drugs increased from 8.6 per 1000 children to 39.4 per 1000 in 2002.[5] The majority of antipsychotic drugs approved in the USA for pediatric patients were restricted mainly for schizophrenia and bipolar disease.[1] However the drugs are being used for off-label indications. The increased use of antipsychotic medications in the pediatric population has raised concerns and controversies.[6]

The purpose of this report is to provide evidence on the clinical benefits and harms of treatments with antipsychotic medications in the pediatric population and to summarize evidence-based guidelines on the use of antipsychotics in these patients. This report is an update of a previous report [7] on this topic, produced by the Canadian Agency for Drugs and Technologies in Health (CADTH).

RESEARCH QUESTIONS

1. What are the clinical benefits and harms of using anti-psychotics in the pediatric population?

2. What are the guidelines regarding use of anti-psychotics in the pediatric population?

KEY MESSAGE

Overall, treatments with second generation antipsychotics resulted in improvements in a variety of disorders in pediatric patients, but they are associated with adverse effects, such as weight gain, extrapyramidal side effects, increased prolactin levels and dyslipidemia.

METHODS:

Literature Search Strategy

A limited literature search was conducted on key resources including Ovid MEDLINE, Ovid PsycINFO, PubMed, The Cochrane Library (2012, Issue 11), University of York Centre for Reviews and Dissemination (CRD), Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, guidelines, and safety data. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and November 19, 2012.

Selection Criteria and Methods

Table 1: Selection Criteria

Population	Pediatric population (<18 years old)
Intervention	Antipsychotics (any type, any generation)
Comparator	NA
Outcomes	Efficacy, Safety, Guidelines
Study Designs	Health technology assessments, systematic reviews and meta-analyses, randomized controlled trials (RCT), non-randomized studies and guidelines

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria in Table 1, if they were published prior to 2008, duplicate publications of the same study and did not provide additional relevant information. Studies which were on a mixed population (pediatric and adult) and did not report data separately for the groups relevant for this report were excluded. Systematic reviews which included studies reported in recent systematic reviews were excluded. Articles were restricted to English language articles.

Critical Appraisal of Individual Studies

Critical appraisal of a study was conducted based on a quality assessment (QA) tool appropriate for the particular study design. The AMSTAR checklist[8] was used for systematic reviews and the AGREE checklist[9] for guidelines.

For the critical appraisal, a numeric score was not calculated. Instead, the strength and limitations were described.

SUMMARY OF EVIDENCE:

Quantity of Research Available

Due to the large volume of literature available a decision was made to restrict the final selection of articles to health technology assessments, systematic reviews and meta-analyses and not consider individual RCTs and non-randomized studies.

The literature search yielded 577 citations. Upon screening titles and abstracts, 541 articles were excluded and 36 potentially relevant articles were selected for full-text review. One potentially relevant article was identified from the grey literature. One article was identified from the website provided in an included article and contained some additional details. Of these 38 articles, 23 did not satisfy the inclusion criteria and were excluded. The 15 included articles comprised of 13 systematic reviews[1,3,5,6,10-19] and one evidence-based guideline.[20] Of the 13 systematic reviews, one systematic review was described in two articles.[1,5] No relevant health technology assessment was identified. Details of the study selection process are outlined in Appendix 1.

Summary of Study Characteristics

Characteristics of the included systematic reviews and guideline are summarized below and details are provided in Appendix 2 and 3 respectively.

Systematic reviews

Autistic spectrum disorder (ASD)

Four systematic reviews[10-13] on ASD were included. Two systematic reviews[10,11] were published in 2012 from Canada, and two[12,13] were published from USA in 2011 and 2008. Of the four systematic reviews, two[10,11] included only RCTs and two[12,13] included both RCTs and non-randomized studies. The duration of studies in the systematic reviews varied from up to eight weeks to up to one year. The total number of patients in these systematic reviews ranged between 270 and 608 and the age range was three to 18 years. The antipsychotics considered were risperidpone in one[11] systematic review, aripiprazole in one,[10] risperidone, aripiprazole or haloperidol in one[12] and risperidone, olanzapine or quetiapine in one.[13] Efficacy using various rating scales were reported in all four systematic reviews and adverse effects were reported in three[10,12,13] systematic reviews. Commonly reported adverse effects were weight gain and sedation.

Bipolar disease

One systematic review [14] on bipolar disease was included. It was published from USA in 2011. It included double blind RCTs and open-label studies. The duration of the studies varied between three and 48 weeks. The total number of patients was 1,491 and mean age was ≤ 18 years. The antipsychotics considered were aripiprazole, risperidone, quetiapine and ziprasidone. Effectiveness was reported using the Young mania rating scale (YMRS). Commonly reported adverse effects were weight gain and sedation.

Disruptive behavior disorder

One systematic review [15] on disruptive behavior was included. It was published from New Zealand in 2012. It included RCTs of duration four to 10 weeks. The antipsychotics considered were risperidone, and quetiapine. The total number of patients was 678 and patient ages varied from five to 18 years. Efficacy using different rating scales was reported. Commonly reported adverse effect was weight gain.

Schizophrenia

Two systematic reviews [16,19] on patients with schizophrenia were included. One systematic review[19] was published from Italy in 2010 and one[16] from USA in 2008. Both systematic reviews include only RCTs. The duration of studies in the systematic reviews varied from 8.9 to 16.2 weeks in one[16] systematic review and from six to eight weeks in the other.[19] The total number of patients in these systematic reviews was 666 in one[19] and 816 in the other.[16] and the age range was 8.9 to 16.2 years in one[16] and 13 to 17 years in the other.[19] The drugs considered were haloperidol, loxapine, thiothixene, thioridazine, risperidone, clozapine, olanzapine, aripiprazole. Effectiveness using different rating scales was reported. Commonly reported adverse effects were weight gain and EPS.

Several conditions

Five systematic reviews[3,5,6,17,18] included patients with several different conditions such as autism, attention deficit hyperactive disorder (ADHD), bipolar disorder, Tourette syndrome, and schizophrenia. Three systematic reviews[3,5,18] were published from Canada in 2012, 2011 and 2010, one[17] from France in 2012, and one[6] from Belgium in 2011. Two systematic reviews[3,6] included only RCTs and three[5,17,18] included both RCTs and non-randomized studies. The duration of studies in the systematic reviews varied from one to 151 weeks. The total number of patients in these systematic reviews varied between 3463 and 6483. Mean age was ≤18 years. All four systematic reviews included SGAs and one[5] included in addition FGAs. Effectiveness using different rating scales was reported. Commonly reported adverse effects were weight gain, increased prolactin levels, and EPS

Summary of Critical Appraisal

Critical appraisal of the included systematic reviews and guideline are summarized below and details are provided in Appendix 4.

Systematic reviews

Autistic spectrum disorder (ASD)

Of the four systematic reviews[10-13] on pediatric patients with ASD, one[10] satisfied most items of the quality assessment tool, two[12,13] satisfied a fair number of items and one[11] satisfied few items.

Bipolar disease

The one systematic review[14] identified on pediatric patients with bipolar disease satisfied a fair number of items of the QA tool.

Disruptive behavior disorder

The one systematic review[15] identified on pediatric patients with disruptive behavior disorder, satisfied most items of the QA tool.

Schizophrenia

Of the two systematic reviews[16,19] on pediatric patients with schizophrenia, one[19] satisfied most items on the QA tool and one[16] satisfied a fair number of items

Several conditions

Of the five systematic reviews[3,5,6,17,18] on pediatric patients with a variety of conditions, three[3,5,17] satisfied most items of the QA tool and two[6,18] satisfied few items.

Of the 13 systematic reviews, all provided characteristics of the included studies[3,5,6,10-19],12 included a comprehensive literature search[3,5,6,10-17,19], 12 described the inclusion and exclusion criteria[3,5,6,10,12-19], eight described the study selection[3,5,6,10,12,15,17,19] and seven included quality assessment of the included studies[3,5,10,12,13,15,19].
Of the 13 systematic reviews, 12 did not explore publication bias[3,5,6,10-13,15-19] and eight did not include a excluded study list [3,6,11-14,16,18].

Guidelines

One relevant evidence based guideline[20] published from the United Kingdom in 2011 was identified. This guidance was prepared by the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom using the single technology appraisal process. The appraisal committee comprised of experts from relevant areas and also included one lay member. The appraisal committee considered evidence from the manufacturer's submission and the review of the submission by the Evidence Review Group. The recommendations developed were explicit.

Summary of Findings

The overall findings are summarized below and findings from the individual systematic reviews and the evidence based guideline are provided in Appendix 5 and 6 respectively.

What are the clinical benefits and harms of using anti-psychotics in the pediatric population?

Systematic reviews

Autistic spectrum disorder (ASD)

All four systematic reviews[10-13] on pediatric patients with ASD, reported on efficacy using various rating scales Improvements were demonstrated with aripiprazole in two systematic reviews,[10,12] with olanzapine in one,[13] and with risperidone in three.[11-13] One systematic review[13] showed no significant improvements with quetiapine. One systematic review[12] indicated improvement with haloperidol but mentioned that strength of evidence was insufficient. Of the four systematic reviews, three[10,12,13] reported on adverse effects (AEs). Two systematic reviews.[10,12] showed that aripiprazole was associated with weight gain, sedation and EPS. One systematic review[13] showed that olanzapine was associated with weight gain and sedation but no abnormal movements, EPS or dyskinesias. Two systematic reviews[12,13] showed that risperidone was associated with weight gain and sedation, one[12] showed association with EPS and one[13] showed increased prolactin levels.

Bipolar disease

One systematic review[14] was identified on pediatric patients with bipolar disease. It demonstrated improvements (based on young mania rating scale [YMRS] score) with aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone. Adverse effects commonly associated with arpiprazole, olanzapine, quetipine, and risperidone were headache, sedation and gastrointestinal (GI) problems and with ziprasidone, sedation.

Disruptive behavior disorder

One systematic review[15] was identified on pediatric patients with disruptive behavior disorder. It demonstrated improvements with risperidone based on a variety of assessment scales. However, risperidone was associated with weight gain.

Schizophrenia

Two systematic reviews[16,19] were identified on pediatric patients with schizophrenia. Both systematic reviews evaluated aripiprazole, olanzapine and risperidone and one[16] in addition evaluated clozapine and a number of first generation antipsychotics (haloperidol, loxapine, thioxene, and thioridazine). Treatment of pediatric patients with antipsychotics resulted in improvement based on assessment using a variety of rating scales but the treatments were associated with adverse effects. Both systematic reviews demonstrated weight gain and incidences of EPS. One systematic review[16] also reported incidences of sedation, dyslipidemia, and prediabetes.

Several conditions

Five systematic reviews[3,5,6,17,18] on pediatric patients considered a variety of conditions such as ASD, attention deficit hyperactive disorder (ADHD), bipolar disease, disruptive behavioral disorder, pervasive developmental disorder (PPD), schizophrenia, and Tourette syndrome. All five systematic reviews evaluated SGAs and one[5] in addition considered studies with FGAs but there were few studies with FGAs. Outcomes related to efficacy were reported in two systematic reviews[5,18] and outcomes related to adverse effects were reported in all five systematic reviews.[3,5,6,17,18] Treatment of pediatric patients with antipsychotics resulted in improvement based on assessment using a variety of scales but treatments were associated with adverse

effects, such as EPS, weight gain, dyslipidemia, increased levels of prolactin, increase glucose levels.

What are the guidelines regarding use of anti-psychotics in the pediatric population?

One relevant evidence based guideline[20] was identified. It provided guidance on the use of aripiprazole in pediatric patients. Aripiprazole was recommended as a treatment option for patients with schizophrenia, in the age range 15 to 17 years and for whom risperidone was not suitable. Further details are provided in Appendix 6.

Limitations

There was some overlap in the studies included in the systematic reviews. Not all outcomes, however, were reported in all the systematic reviews. Nevertheless, it should be noted that the total number of unique studies contributing to the results were less than what may appear to be, based on the number of studies reported for each systematic review.

In one study[5] on several conditions, the inclusion criteria was ≤24 years however the mean age of patients for the different conditions ranged between 8.1 and 15.8 years and hence was included here. It is possible there could be a few patients of age greater than 18 years but is unlikely to affect the overall results.

All 13 systematic reviews assessed SGAs and two[5,16] of the 13 also assessed FGAs, so there is insufficient evidence on the efficacy and safety of FGAs in the pediatric population.

In a number of systematic reviews and meta-analyses which considered several conditions, data for different conditions were pooled together. Hence, it would be difficult to know the extent of effect of the intervention for a specific condition. Furthermore, not all studies reported all outcomes. Various scales for efficacy assessment were used in the different individual studies. There appears to be little consensus on the scales to use for evaluating outcomes. The findings may be considered generalizable to some extent, considering that antipsychotic treatments in a variety of conditions in the pediatric population were assessed.

The systematic reviews, which are described in this report, included mainly studies on second generation antipsychotics. There is little information here with respect to first generation antipsychotics.

Information on the use of antipsychotics in patients less than five years old is scarce. Studies were mostly short term (3 weeks to 12 weeks). The few studies that were relatively long (48 weeks to 151 weeks) were non-randomized studies.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

This report, which is a follow up to a previous CADTH report[7] on the effects of antipsychotics in pediatric patients, contains information that was available since publication of the previous report in 2008. This report includes four systematic reviews specifically on ASD, one systematic review each specifically for bipolar disease and disruptive behavior disorder, two systematic reviews specifically for schizophrenia and five systematic reviews for a variety of conditions.

Overall, treatments with second generation antipsychotics result in improvements in a variety of disorders in pediatric patients but they are associated with adverse effects such as weight gain, extrapyramidal side effects, increased prolactin levels and dyslipidemia. Most of the evidence is from short term studies. Several authors mentioned the need for further studies that examine long term efficacy and in particular safety of antipsychotics for the pediatric population. There is need for head-to-head drug comparisons to determine the relative benefits and harms of specific drugs.

One evidence based guideline recommended aripiprazole as a treatment option for patients with schizophrenia, in the age range 15 to 17 years and for whom risperidone was not suitable. There appears to be a dearth of evidence based guidelines on the use of antipsychotics for treating the pediatric population

It is possible that different antipsychotics may be more effective in targeting certain symptoms compared to others and therefore it is important to keep in mind that different treatments may be appropriate for different individuals.[11]

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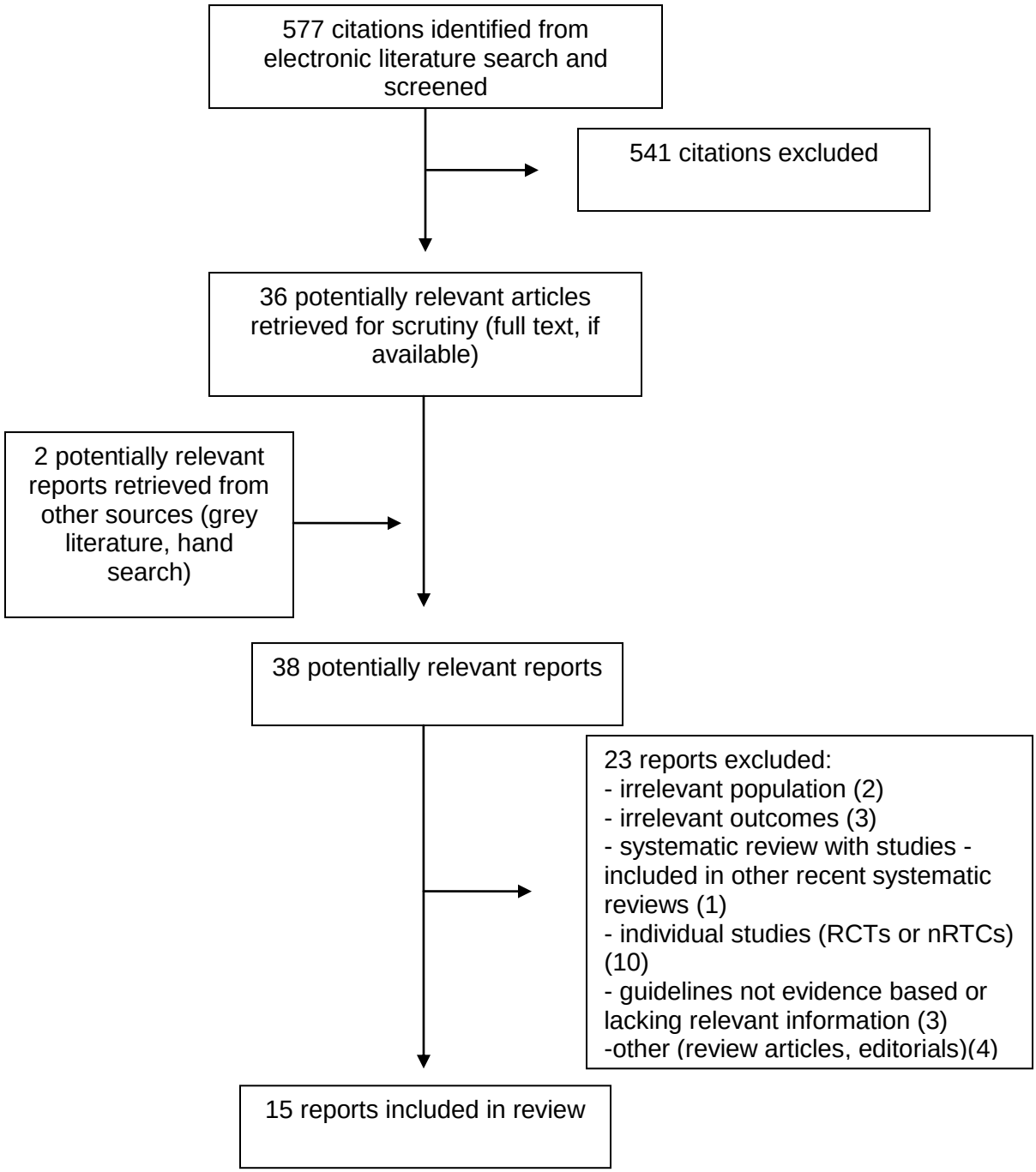
ABBREVIATIONS

AAP	Atypical antipsychotic
ABC	Aberrant behavior checklist
ABC-C	Aberrant behavior checklist community version
ABC-C-H	ABC-C hyperactivity/noncompliance subscale
ABC-C-I	ABC-C irritability/agitation/crying subscale
ABC-C-S	ABC-C stereotypy subscale
ADHD	attention deficit hyperactive syndrome
AE	adverse events
ASD	autism spectrum disorder or autistic spectrum disorder
BMI	body mass index
BPI	behavior problems inventory
BPRS	Brief psychiatry rating scale
BPRS-C	Brief psychiatry rating scale for children
CARS	Checklist for autism rating scale
CGAS	Children's global assessment scale
CGI	Clinical Global Impression scale
CGI-I	Clinical Global Impression –improvement scale
CGI-S	Clinical Global Impression – severity of illness
CI	confidence interval
CPRS	comprehensive psychopathological rating scale
CY-BOCS	Children's Yale-Brown Obsessive Compulsive Scale
DBD	disruptive behavior disorder
EPS	extrapyramidal side effects
FGA	first generation antipsychotic
MD	mean difference
N	number of patients or number of studies as indicated
NCBR	Nisonger child behavior rating
NR	not reported
NS	not significant
nRCT	non-randomized study
OAS-M	Modified overt aggression scale
OC	obsessive compulsive
OR	odds ratio

PANSS	positive and negative syndrome scale
PDD	pervasive developmental disorder
QA	quality assessment
RCT	randomized controlled trial
RF-RLRS	Ritvo-Freeman real life rating scale
RR	relative risk
SANS	scale for assessment of negative syndrome
SAPS	scale for assessment of positive syndrome
SMD	standardized mean difference
SGA	second generation antipsychotic
SR	systematic review
SR-MA	systematic review and meta-analysis
VABS	Vineland adaptive behavior scale
VAS	Visual analog scale
vs	versus
YAPA-SIBS	Yale-Paris self-injurious behavior scale
YMRS	young mania rating scale

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Studies

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size (n)	Intervention	Comparators	Outcomes Measured
Systematic reviews (SR) and meta-analyses (MA)					
Autistic spectrum disorder (ASD)					
Ching,[10] 2012, USA and Canada	SR-MA (2 RCTs), 8 weeks	ASD (6-17 years), N= 316	Aripiprazole	placebo	ABC scores, CY-BOCS scores, CGI scores; AE: body weight and BMI
Sharma,[11] 2012, Canada	SR-MA (21 RCTs), 6 weeks to 1 year	ASD (3-17 years), N= 608	Risperidone	placebo	ABC, RF-RLRS, YAPA-SIBS,CARS, VABS, CPRS, CGI, CGAS
McPheeters,[12] 2011, USA	SR (7 RCTs & 2 prospective case series), 8 weeks to 6 months	ASD (<13 years), N>496 (patient number not reported for some studies)	Antipsychotics (risperidone, aripiprazole, haloperidol)	Placebo, haloperidol	ABC-C, ABC-C-I, ABC-C-S, ABC-C-H, AE
West,[13] 2008, USA	SR (1 uncontrolled pilot, 4 open label, 4 RCTs), 7 to 16 weeks	Autism, PDD. Age 5 to 18 years. N= 270	Antipsychotics (risperidone, olanzapine, quetiapine) (Also assessed other pharmacologic treatments not of interest for this review so not included here)	Placebo	Efficacy (CGI, CY-BOCS, CARS, VABS) AE (weight gain, sedation)
Bipolar					
Liu,[14] 2011, USA	SR-MA(8 double-blind RCTs, 11 open label), 3 to 48 weeks	Bipolar disorder, Mean age ≤18 years in all studies (min age was 4 years and one study included age range of 13 -20 years), N = 1491 (ranged between 10 to 296)	Anti psychotics (SGA: aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) (Also assessed other pharmacologic treatments not of interest for this review so not	Placebo	Efficacy (YMRS, CGI, other)

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size (n)	Intervention	Comparators	Outcomes Measured
			included here)		
Disruptive behavior disorder					
Loy,[15] 2012, Australia, New Zealand	SR-MA (8 RCTs), 4 to 10 weeks	Disruptive behavior disorder, age 5 to 18 years, N = 678	Atypical antipsychotics (risperidone, quetiapine)	Placebo	Efficacy (NCBR, ABC, CGI-S, CGI-C, visual analog scale, aggression scales); AE (weight gain, change in metabolic parameters)
Schizophrenia					
Ardizzone,[19] 2010, Italy	SR-MA (3 RCTs). Duration= 6 to 8 weeks	Early onset schizophrenia. Age: 13 -17 years. N= 666	Antisychotics (aripiprazole, risperidone, olanzapine)	Placebo or active control	Efficacy (CGI, PANSS) AE (weight gain, EPS)
Kumra[16] 2008, USA	SR (10 RCTs), Duration= 4 to 12 weeks	Schizophrenia, Mean age= 8.9 to 16.2 years N= 816	Antipsychotics (FGA, SGA)	Placebo or active control	Efficacy (BPRS, BPRS-C CGI-I, CGI-S, SANS, SAPS, PANSS); AE (EPS)
Several conditions					
Cohen,[17] 2012, France	SR- MA (Bayesian) (41 controlled studies), Duration= 3 to 12 weeks	Several conditions (schizophrenia, bipolar disorder, behavioral impairments comorbid to autism or intellectual disability, Tourette syndrome, and conduct disorder). Mean age: 5 to 17.2 years. N= 4015 (range 9 to 302)	Antipsychotics (SGA [risperidone, clozapine, ziprasidone, aripiprazole, olanzapine, quetiapine])	Placebo or SGA	AE (weight gain; changes in glucose, triglycerides, cholesterol, prolactin; somnolence/sedation; EPS)
Seida,[5] 2012, Canada	SR-MA (62 RCTs, 1 nRCT, 17 cohort studies); Duration: 4 to 11.2 weeks	Several conditions (PDD, DBD, bipolar, schizophrenia Tourette syndrome, behavioral symptoms and multiple conditions); Age ≤ 24 years (however the mean age for the different conditions ranged between 8.1 years	Antipsychotics (FGA [chlorpromazine, droperidol, fluphenazine, haloperidol, loxapine, perphenazine, pimozide, prochlorpera	Placebo, antipsychotics (FGA, SGA)	Disorder-specific and non-specific symptoms, HRQL, medication adherence, patient-, parent-, or careprovider-related outcomes, and suicide-related behaviors;

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size (n)	Intervention	Comparators	Outcomes Measured
		and 15.8 years; N = 6483 (185 to 2544 for the different conditions)	zine, thiothixene, thioridazine or tri fluoperazine] , SGA [aripiprazole, asenapine, clozapine, iloperidone, olanzapine, palperidone, quetiapine, risperidone, or ziprasidone])		AE (dyslipidemia, extrapyramidal symptoms, insulin resistance, prolactin-related and sexual side effects, sedation, and weight and body composition)
De Hert,[6] 2011, Europe, USA	SR-MA (31 RCTs), FU= 3 to 24 weeks	Several conditions (bipolar, schizophrenia, autism, ADHD, pervasive developmental disorder, conduct disorder), age< 18 years, N= 3595	Antipsychotics (arpiprazole, olanzapine, quetiapine, risperidone, ziprasidone)	Placebo (except antipsychotic in 2 RCTs which were not used in the analyses)	AE (Weight gain, metabolic changes)
Pringsheim,[3] 2011, Canada, USA	SR-MA (35 RCTs), 3 weeks to 6 months	Mental health disorders (Autism, ADHD, disruptive behavior , subaverage intelligence, Tourette syndrome, tic, bipolar, schizophrenia, PDD, mania), Age <18 years, N= 3463 (range: 11 to 335 for individual studies)	Antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole, clozapine, ziprasidone,)	Placebo or active comparator	Metabolic and neurological adverse effects as measures using physical examination, maneuvers, rating scales or laboratory tests.
Panagiotopolos,[18] 2010, Canada	SR (42 RCTs for efficacy and 24 studies for metabolic outcomes [24 includes1	Several conditions (bipolar, schizophrenia, autism, ADHD, developmental disorder, Tourette), age< 18 years, N= NR (efficacy studies)	Aripiprazole, clozapine, haloperidol, olanzapine, quetiapine, risperidone, ziprasidone		Efficacy, metabolic outcomes (such as weight, BMI, prolactin, glucose, lipids)

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size (n)	Intervention	Comparators	Outcomes Measured
	RCT, 8 prospective open-label, 1 open label or double blind, 2 cross-sectional, 1 longitudinal, 7 retrospective chart review, 1 retrospective cohort, 1 case series, 2 letters to editor]), 1 to 150 weeks,	N= 6308 (metabolic outcome studies)			

ABC= Aberrant behavior checklist, ABC-C= Aberrant behavior checklist community version, ABC-C-H= ABC-C hyperactivity/noncompliance subscale, ABC-C-I= ABC-C irritability/agitation/crying subscale, ABC-C-S= ABC-C stereotypy subscale, ADHD= attention deficit hyperactive syndrome, AE= adverse effects, ASD= autism spectrum disorder or autistic spectrum disorder, BMI= body mass index, BPI= behavior problems inventory, BPRS= Brief psychiatry rating scale, BPRS-C= Brief psychiatry rating scale for children, CARS= Checklist for autism rating scale, CGAS= Children's global assessment scale, CGI= Clinical Global Impression scale, CGI-I= Clinical Global Impression – improvement scale, CGI-S= Clinical Global Impression – severity of illness, CPRS= comprehensive psychopathological rating scale, CY-BOCS= Children's Yale-Brown Obsessive Compulsive Scale, DBD= disruptive behavior disorder, EPS= extrapyramidal side effects, FGA= first generation antipsychotic, , NCBR= Nisonger child behavior rating, nRCT= non-randomized study, OAS-M= Modified overt aggression scale, PANSS= positive and negative syndrome scale, PDD= pervasive developmental disorder, RCT= randomized controlled trial, RF-RLRS= Ritvo-Freeman real life rating scale, SANS- scale for assessment of negative syndrome, SAPS- scale for assessment of positive syndrome SGA= second generation antipsychotic, SR= systematic review, SR-MA= systematic review and meta-analysis, VABS= Vineland adaptive behavior scale, VAS= Visual analog scale, YAPA-SIBS= Yale-Paris self-injurious behavior scale.

APPENDIX 3: Grading of Recommendations and Levels of Evidence

Guideline Society or Institute, Year	Recommendation	Level of Evidence
NHS - NICE technology appraisal guidance,[20] 2011	Level of strength of recommendation - NR	NR
NHS= National Health Service, NICE= National Institute of Health and Clinical Excellence, NR = not reported		

APPENDIX 4: Summary of Study Strengths and Limitations

First Author, Publication Year, Country	Strengths	Limitations
Systematic reviews and meta-analyses		
Autistic spectrum disorder (ASD)		
Ching,[10] 2012, USA and Canada	• The objective was stated. • The inclusion and exclusion criteria were stated. • Comprehensive literature search • Study selection described and flow chart presented • List of included and excluded studies provided • Article selection and data extraction were done in duplicate • Characteristics of the individual studies were provided • Quality assessments of studies were conducted • Methods used to combine the findings of studies were appropriate • Conflict of interest was stated - supported by University of Calgary; no external support	• Publication bias was not explored
Sharma,[11] 2012, Canada	• The objective was stated. • Comprehensive literature search, • List of included studies provided • Characteristics of the individual studies were provided	• Details of inclusion and exclusion criteria were not provided. • Study selection sparsely described and flow chart not presented • List of excluded studies not provided • Unclear if article selection and data extraction were done in duplicate • Unclear if quality assessments of studies were conducted • Sufficient information lacking to determine if methods used to combine the findings of studies were appropriate • Publication bias was not explored • Conflict of interest was not stated

First Author, Publication Year, Country	Strengths	Limitations
McPheeters,[12] 2011, USA	• The objective was stated. • The inclusion criteria were stated. • Comprehensive literature search • Study selection described and flow chart presented • List of included studies provided • Data extraction was done in duplicate • Characteristics of the individual studies were provided • Quality assessments of studies were conducted • Meta-analysis was not conducted as there was considerable heterogeneity. • Conflict of interest was stated	• The exclusion criteria were not explicitly stated probably as they were embedded in the inclusion criteria. • List of excluded studies not provided • Not clear if article selection was done in duplicate • Publication bias was not explored
West,[13] 2008, USA	• The objective was stated. • The inclusion and exclusion criteria were stated. • Comprehensive literature search. • List of included studies provided • Characteristics of the individual studies were provided • Quality assessments of studies were conducted • Publication bias was explored • Conflict of interest was stated	• Study selection was not described or presented in a flow chart • List of excluded studies not provided • Not mentioned as to how article selection and data extraction were performed • Publication bias was not explored • Conflict of interest was not stated
Bipolar		
Liu,[14] 2011, USA	• The objective was stated. • The inclusion and exclusion criteria were stated. • Comprehensive literature search (Single database – PubMed, but additional hand searching). • List of included studies provided • Data extraction were done in duplicate • Characteristics of the individual studies were provided • Methods used to combine the findings of studies were appropriate • Publication bias was explored (Egger test) and it appeared there was none • Conflict of interest was stated	• Study selection not described and flow chart not presented • List of excluded studies not provided • Unclear if article selection was done in duplicate • Quality assessments of studies were not conducted • Forest plots presented but numerical values were not presented

First Author, Publication Year, Country	Strengths	Limitations
Disruptive behavior disorder		
Loy,[15] 2012, Australia, New Zealand	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Comprehensive literature search. • Study selection described and flow chart presented • List of included and excluded studies provided • Article selection and data extraction were done in duplicate • Characteristics of the individual studies were provided • Quality assessments of studies were conducted • Methods used to combine the findings of studies were appropriate • Conflict of interest was stated	• Publication bias was not explored due to limited number of studies
Schizophrenia		
Ardizzone,[19] 2010, Italy	• The objective was stated. • The inclusion and exclusion criteria were stated. • Comprehensive literature search. • Study selection described • List of included and excluded studies provided • Article selection was done in duplicate • Characteristics of the individual studies were provided • Quality assessments of studies were conducted • Methods used to combine the findings of studies were appropriate	• Unclear if data extraction were done in duplicate • Publication bias was not explored (of note there were only 3 included studies) • Conflict of interest was not stated
Kumra[16] 2008, USA	• The objective was stated. • The inclusion and exclusion criteria were stated. • Comprehensive literature search (single database: Medline but explored additional sources (investigators, manufacturers). • List of included studies provided • Characteristics of the individual studies were provided • Conflict of interest was stated	• Study selection not described and flow chart not presented • List of excluded studies not provided • Nothing mentioned as to how article selection and data extraction were done • Quality assessments of studies were not conducted • Publication bias was not explored

First Author, Publication Year, Country	Strengths	Limitations
Several conditions		
Cohen,[17] 2012, France	• The objective was stated. • The inclusion and exclusion criteria were stated. • Comprehensive literature search. • Study selection described and flow chart presented • List of included and excluded studies provided • Data extraction were done in duplicate • Characteristics of the individual studies were provided • Methods used to combine the findings of studies were appropriate • Conflict of interest was stated	• Not mentioned if article selection and was done in duplicate • Not mentioned if quality assessments of studies were conducted • Not mentioned if publication bias was explored
Seida,[5] 2012, Canada	• The objective was stated. • The inclusion and exclusion criteria were stated. • Comprehensive literature search. • Study selection described and flow chart presented • List of included and excluded studies provided • Article selection and data extraction were done in duplicate • Characteristics of the individual studies were provided • Quality assessments of studies were conducted • Methods used to combine the findings of studies were appropriate • Conflict of interest was stated	• Publication bias was not explored
De Hert,[6] 2011, Europe, USA	• The objective was stated. • The inclusion and exclusion criteria were stated but not in detail. • Comprehensive literature search • Flow chart of study selection presented • List of included studies provided • Characteristics of the individual studies were provided • Random effects model was used because of heterogeneity	• List of excluded studies not provided • Not mentioned if article selection and data extraction were done in duplicate • Not mentioned if quality assessments of studies were conducted • Not mentioned if publication bias was explored • In the analyses the placebo group was counted multiple times

First Author, Publication Year, Country	Strengths	Limitations
	• Conflict of interest was stated	in case of subgroups of different doses for a drug
Pringsheim,[3] 2011, Canada, USA	• The objective was stated. • The inclusion and exclusion criteria were stated. • Comprehensive literature search. • Study selection described and flow chart presented • List of included studies provided • Article selection and data extraction were done in duplicate • Characteristics of the individual studies were provided • Quality assessments of studies were conducted • Methods used to combine the findings of studies were appropriate • Conflict of interest was stated	• List of excluded studies not provided • Publication bias was not explored
Panagiotopolos,[18] 2010, Canada	• The objective was stated. • The inclusion and exclusion criteria were stated. • Single database (PubMed) searched • Study selection described and flow chart presented • List of included studies provided • Characteristics of the individual studies were provided • Conflict of interest was stated	• Study selection not described and flow chart not presented • List of excluded studies not provided • Not mentioned if article selection and data extraction were done in duplicate • Not mentioned if quality assessments of studies were conducted • Few details of study characteristics • Not mentioned if publication bias was explored
Guidelines		
NHS - NICE technology appraisal guidance,[20] 2011	• The scope and purpose were implicitly stated. • The appraisal committee comprised of individuals from relevant areas. • The appraisal committee considered evidence from the manufacturer's submission and a review of the submission by the Evidence Review Group. • Cost implications were considered. • Recommendations were clear • Declaration of interest of the appraisal committee members were posted the NICE website	• Unclear if patient input was sought but the appraisal committee included one lay member.

APPENDIX 5: Main Study Findings and Authors' Conclusions

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td colspan="2">Systematic reviews and meta-analyses</td></tr>
<tr><td colspan="2">Autistic spectrum disorder (ASD)</td></tr>
<tr><td>Ching,[10] 2012, USA and Canada</td><td>Main findings:
Findings with aripiprazole
<table>
<tr><th>Outcome</th><th>Effect (95% CI) relative to placebo</th></tr>
<tr><td>ABC irritability subscale mean score change</td><td>MD (95% CI)= -6.17 (-9.07, -3.26)</td></tr>
<tr><td>ABC hyperactivity subscale mean score change</td><td>MD (95% CI)= -7.93 (-10.98, -4.68)</td></tr>
<tr><td>ABC stereotypy subscale mean score change</td><td>MD (95% CI)= -2.66 (-3.55, -1.77)</td></tr>
<tr><td>Weight gain</td><td>MD (95% CI)= 1.13 (0.71, 1.54)</td></tr>
<tr><td>Sedation</td><td>RR (95% CI)= 4.28 (1.58, 11.60)</td></tr>
<tr><td>Tremor</td><td>RR (95% CI)= 10.26 (1.37, 76.63)</td></tr>
<tr><td colspan="2">ABC= = Aberrant behavior checklist, CI= confidence interval, MD= mean difference, RR= relative risk</td></tr>
</table>
Authors' Conclusion:
"Evidence from 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 stereotypes (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." p. 2</td></tr>
<tr><td>Sharma,[11] 2012, Canada</td><td>Main findings:
Findings with risperidone
<table>
<tr><th>Outcome</th><th>Study type/number</th><th>Weighted mean effect size*, variance</th></tr>
<tr><td>Behavioral</td><td>All (N= 21)</td><td>1.131, 0.161</td></tr>
<tr><td>Behavioral</td><td>Open-label (N=15)</td><td>1.135, 0.225</td></tr>
<tr><td>Behavioral</td><td>Placebo-controlled (N=6)</td><td>1.121, 0.021</td></tr>
<tr><td>Maladaptive behaviors (irritability and aggression)</td><td>NR (N=11)</td><td>1.102, 0.171</td></tr>
<tr><td colspan="3">ASD= autistic spectrum disorder, N= number of studies, NR= not reported
*Effect size is within the large effect size range based on Cohen's classification. Therefore risperidone significantly improves symptoms associated with ASD</td></tr>
</table>
Authors' Conclusion:
"Outcome measures demonstrated mean improvement in problematic behaviors equating one standard deviation, and thus current evidence supports the effectiveness of risperidone in managing behavioral problems and symptoms for children with ASD. Although Risperdal has several adverse</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>effects, most are manageable or extremely rare. An exception is rapid weight gain, which is common and can create significant health problems. Overall, for most children with autism and irritable and aggressive behavior, risperidone is an effective psychopharmacological treatment." p. 291</td></tr>
<tr><td>McPheeters,[12] 2011, USA</td><td>Main findings:
Findings with arpiprazole, risperidone or haloperidol
<table>
<tr><th>Treatment</th><th>Study type/quality</th><th>Findings</th></tr>
<tr><td>Risperidone vs placebo</td><td>4 RCTs (1 good quality & 3 fair quality) and 2 prospective case-series</td><td>"Improvements in challenging and repetitive behaviors; strength of evidence for reducing challenging and repetitive behaviors is moderate. Strength of evidence for adverse events is high on the basis of results of RCTs and case series; common adverse effects include weight gain, sedation, and extrapyramidal effects" p. e1317</td></tr>
<tr><td>Aripiprazole vs placebo</td><td>2 RCTs of good quality</td><td>"Improvements in challenging and repetitive behaviors; strength of evidence for reducing challenging and repetitive behaviors is high; strength of evidence for adverse events is high; common adverse effects include weight gain, sedation, and extrapyramidal effects" p. e1317</td></tr>
<tr><td>(Cyproheptadine + haloperidol) vs Halperidol + placebo)</td><td>1 RCT of fair quality</td><td>"Behavioral improvement reported but without indicating specific domains….; strength of evidence is insufficient" p. e1317</td></tr>
</table>
Authors' Conclusion:
"Although many children with ASDs are currently treated with medical interventions, strikingly little evidence exists to support benefit for most treatments. Risperidone and aripiprazole have shown benefit for challenging and repetitive behaviors, but associated adverse effects limit their use to patients with severe impairment or risk of injury" p. e1312</td></tr>
<tr><td>West,[13] 2008, USA</td><td>Main findings:
Findings with risperidone, olanzapine or quetiapine
<table>
<tr><th>Treatment</th><th>Finding</th></tr>
<tr><td>Risperidone</td><td>Efficacy:
Significant improvement in CGI-I, CARS, CY-BOCS, VABS and Ritvo Freeman real life rating scale ratings

AE:
Weight gain in 67% to 83% of patients, sedation in 33% to 66% of patients and increased prolactin levels by as much as 57%</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td></td></tr>
<tr><td>Olanzapine</td><td>Efficacy:
Significant improvement for all items in the autism factor of the Child Psychiatric Rating Scale except underproductive speech.

AE;
No reports of abnormal movements, EPS, or dyskinesias. Weight gain and sedation were notable adverse effects.</td></tr>
<tr><td>Quetiapine</td><td>No significant improvements and adverse effects caused many patients to drop out.</td></tr>
</table>

Authors' Conclusion:
"Preliminary evidence demonstrates possible uses for atypical antipsychotic agents…..in decreasing the core behaviors and associated symptoms of autism. More studies and longer follow-up are needed before definitive guidelines can be suggested." p. 75</td></tr>
<tr><td>Bipolar</td><td></td></tr>
<tr><td>Liu,[14] 2011, USA</td><td>Main findings:
Findings with aripiprazole, olanzapine, quetiapine, risperidone or ziprasidone
<table>
<tr><th>Treatment</th><th>Study type</th><th>No. of studies (No. of patients)</th><th>Finding</th></tr>
<tr><td>Aripiprazole</td><td>Open-label</td><td>2 (29)</td><td>Mean change in YMRS score: -18.1 in one and -14.9 in the second study
No significant changes in weight, metabolic or cardiovascular parameters in one study.
Most common AE: sedation, GI complaints, cold symptoms, headache, tiredness, confusion, depressive symptoms.</td></tr>
<tr><td>Aripiprazole vs placebo</td><td>Double-blind</td><td>2 (339)</td><td>Mean change in YMRS score-
One study: -27.22 vs -19.52 (p= 0.02),
Second study: -14.2 vs -8.2 (p<0.05);
Change in weight not significantly different between groups</td></tr>
<tr><td>Olanzapine</td><td>Open-label</td><td>3 (55)</td><td>Mean change in YMRS score: --19.5 in one, -12.1 in the second and -10.6 in the third study.
Weight gain
Most common AE: appetite change, somnolence, sedation, headache, common cold</td></tr>
</table></td></tr>
</table>

First Author, Publication Year, Country	Main Findings and Authors' Conclusion

			symptoms, GI problems
Olanzapine vs placebo	Double-blind	1 (161)	Mean change in YMRS score: -17.65 vs -9.99 (p= 0.001), Weight gain, increase in fasting glucose, cholesterol and prolactin
Quetiapine	Open-label	2 (70)	Mean change in YMRS score: -- NR in one, -14.5 (for 176 mg/d) and -13.2 (for 249 mg/d) in the second study
Quetiapine vs placebo	Double-blind	3 (364)	Mean change in YMRS score: One study: -24 vs -15 (p= 0.01), Second study: -23 vs 19 (NS), Third study: -14 vs -9, p<0.001 (for 400 mg/d) and -15 vs -9, p<0.001 (for 600 mg/d). Most common AE: sedation, nausea, headache, GI problems
Risperidone	Open-label	2 (46)	Mean change in YMRS score: -18.3 in one and -14.4 in the second study. Weight gain, increase in prolactin. Most common AE: appetite change, cold symptoms, headache, sedation, GI problems
Risperidone vs placebo	Double-blind	1 (169)	Mean change in YMRS score: -18.5 vs -9.1 (p< 0.001), Weight gain Most common AE: somnolence, headache, fatigue
Ziprasidone	Open-label	1 (21)	Mean change in YMRS score: -10.8, No significant weight gain
Ziprasidone vs placebo	Double-blind	1 (237)	Mean change in YMRS score: -14 vs -10 (p< 0.001), No significant weight gain, Most common AE: sedation,, dizziness, somnolence

Authors' Conclusion:
"A substantial body of scientific literature has evaluated the safety and efficacy of various medicines and drug classes in the treatment of mania in pediatric bipolar disorder. More work is needed to assess the safety and efficacy of psychotropic compounds, and to further evaluate the effects of naturopathic compounds, and to further evaluate the effects of antimanic treatments for the management of depression and attention-deficit/hyperactivity disorder." p. 749

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td colspan="2">Disruptive behavior disorder</td></tr>
<tr><td>Loy,[15] 2012, Australia, New Zealand</td><td>
Main findings:
Findings with quetiapine or risperidone
<table>
<tr><th>Outcome</th><th>No. of studies</th><th>No. of participants</th><th>MD* (95% CI)</th></tr>
<tr><td>Aggression: Change scores (ABC irritability)</td><td>3</td><td>238</td><td>-6.49 (-8.79, -4.19)</td></tr>
<tr><td>Aggression: Final scores (OAS-M and OAS)</td><td>2</td><td>57</td><td>SMD (95% CI) -0.18 (-0.70, 0.34)</td></tr>
<tr><td>Weight gain</td><td>2</td><td>138</td><td>2.37 (0.26, 4.49)</td></tr>
<tr><td>Conduct problems (NCBRF-CP)</td><td>2</td><td>225</td><td>-8.61 (-11.49, -5.74)</td></tr>
<tr><td>Conduct problems (CPRS-CP)</td><td>2</td><td>36</td><td>-12.67 (-37.45, 12.11)</td></tr>
<tr><td colspan="4">*If not otherwise stated</td></tr>
</table>
Authors' Conclusion:
"There is some limited evidence of efficacy of risperidone reducing aggression and conduct problems in children aged 5 to 18 with disruptive behavior disorders in the short term.....Use of medication, however, was associated with significant weight gain. The findings need to be considered with caution because of the limitations of the evidence……We recommend that more research is carried out in this field to find out the long-term efficacy and safety of these medications in treating disruptive behaviour disorders in children and youth." p. 2, 3
</td></tr>
<tr><td colspan="2">Schizophrenia</td></tr>
<tr><td>Ardizzone,[19] 2010, Italy</td><td>
Main findings:
Findings with aripiprazole, olanzapine or risperidone
<table>
<tr><th>Outcome</th><th>Finding</th></tr>
<tr><td colspan="2">Efficacy – SMD as Hedges's g (95% CI)</td></tr>
<tr><td>PANSS total score</td><td>-0.415 (-0.560, -0.270)</td></tr>
<tr><td>PANSS positive subscale</td><td>-0.433 (-0.578, -0.286)</td></tr>
<tr><td>PANSS positive subscale</td><td>-0.254 (-0.398, -0.110)</td></tr>
<tr><td>CGI</td><td>-0.418 (-0.563, -0.273)</td></tr>
<tr><td colspan="2">AE – OR (95% CI)</td></tr>
<tr><td>EPS - akathesia</td><td>2.297 (1.112, 4.744)</td></tr>
<tr><td>EPS - diskinesia</td><td>3.866 (1.068, 14.139)</td></tr>
<tr><td>EPS - Parkinson</td><td>4.025 (2.150, 7.536)</td></tr>
<tr><td>EPS – dystonia events</td><td>3.841 (1.751, 8.426)</td></tr>
<tr><td>EPS - tremor</td><td>3.486 (1.516, 8.014)</td></tr>
<tr><td>Weight gain</td><td>Proportion of patients who reported a significant weight gain with olanzapine, risperidone and two different doses (30 mg, 10 mg) of aripiprazole were respectively, 45%, 8%, 22% and 0%.</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td></td></tr>
<tr><td></td><td>Authors' Conclusion:
"Results demonstrated that antipsychotic treatment with Risperidone, Olanzapine and Aripiprazole in adolescents affected by Schizophrenia led to significant improvements in symptomatology. A pharmacological treatment for adolescents suffering from Schizophrenia must fulfill several prerequisites, to grant the most favourable outcomes, avoiding acute and long term side-effects. Treatment with a 10 mg daily dose of Aripiprazole was associated with the lowest incidence of extrapyramidal symptoms and showed no significant weight gain. If a treatment with antipsychotic drugs associated with significant weight gain as Olanzapine or Risperidone is needed, compensative measures should be soon considered." p. 45</td></tr>
<tr><td>Kumra[16] 2008, USA</td><td>Main findings:
Findings with first or second generation antipsychotics (FGA, SGA)*
<table><tr><th>Outcome</th><th>Findings for treatment with antipsychotics (No. of studies)</th></tr><tr><td rowspan="4">Efficacy</td><td>Improvement in BPRS or BPRS-C ratings (4)</td></tr><tr><td>Improvement in CGI-I or CGI-S ratings (3)</td></tr><tr><td>Improvement in SAPS or SANS ratings (3)</td></tr><tr><td>Improvement in PANSS ratings (3)</td></tr><tr><td rowspan="5">Adverse effects</td><td>Weight gain (5)</td></tr><tr><td>Incidence of EPS (4)</td></tr><tr><td>Sedation (3)</td></tr><tr><td>Incidence of dyslipidemia (2)</td></tr><tr><td>Incidence of prediabetes (1)</td></tr></table>*FGA includes haloperidol, loxapine, thiothixene, or thioridazine and SGA includes aripiprazole, clozapine, olanzapine, or risperidone</td></tr>
<tr><td></td><td>Authors' Conclusion:
"The available data from short-term studies suggest that youth might be more sensitive than adults to anti-psychotic-related adverse side effects (eg, extrapyramidal side effects, sedation, prolactin elevation, weight gain). In addition, preliminary data suggest that SGA use can lead to the development of diabetes in some youth a disease which itself carries with it significant morbidity and mortality. Such a substantial risk points to the urgent need to develop therapeutic strategies to prevent and/or mitigate weight gain and diabetes early in the course of treatment in this population." p. 60</td></tr>
<tr><td colspan="2">Several conditions</td></tr>
<tr><td>Cohen,[17] 2012, France</td><td>Main findings:
Findings with aripiprazole, clozapine, olanzapine, quetiapine, risperidone, or ziprasidone
<table><tr><th>Outcome</th><th>No. of studies (no. of patients)</th><th>Finding</th></tr><tr><td>% of patients who had weight gain</td><td>25 (3041)</td><td>O> C> Q. R> A> Z> P</td></tr><tr><td>Weight ↑</td><td>30 (3221)</td><td>O> C> Q. R> A> P</td></tr><tr><td>Glucose↑</td><td>10 (1784)</td><td>R> A> O> Q> Z> P</td></tr><tr><td>Cholesterol↑</td><td>10 (1784)</td><td>Q> O> A> R> Z> P</td></tr></table></td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>
<table>
<tr><td>Triglycerides↑</td><td>10 (1655)</td><td>O> Q> R> A> Z> P</td></tr>
<tr><td>Prolactin↑</td><td>12 (1180)</td><td>R> O> Z> Q> P</td></tr>
<tr><td>% of patients complaining of sedation/ somnolence</td><td>29 (3348)</td><td>Z> O> R> A> Q> P</td></tr>
<tr><td>% of patients showing EPS</td><td>28 (3258)</td><td>Z> O> A> R> Q> P</td></tr>
<tr><td colspan="3">A= aripiprazole, C= clozapine, O= olanzapine, P= placebo, Q= quetiapine, R= risperidone, Z= ziprasidone
↑= increase</td></tr>
</table>
Authors' Conclusion:
"This meta-analysis supports the view that SGAs as a class have substantial adverse effects and that each compound has a specific secondary-effect profile that should be taken into account in treatment decision making." p. 314
</td></tr>
<tr><td>Seida,[5] 2012, Canada</td><td>
Main findings:
Findings with various first and second generation antipsychotics (FGA, SGA)
<table>
<tr><th>Outcome</th><th>Comparison (no. of studies)</th><th>Strength of evidence</th><th>Finding MD* (95% CI)</th></tr>
<tr><td colspan="4">Pervasive developmental disorder</td></tr>
<tr><td rowspan="2">Autistic symptoms</td><td>FGA vs SGA (2 RCTs)</td><td>low</td><td>NS</td></tr>
<tr><td>SGA vs placebo (7 RCTs)</td><td>low</td><td>Favors SGA for
ABC: -18.3 (-27.1, -9.5);
CARS: -4.9 (-8.5, -1.4)</td></tr>
<tr><td>CGI</td><td>SGA vs placebo (3 RCTs)</td><td>low</td><td>NS</td></tr>
<tr><td>OC symptoms</td><td>SGA vs placebo (3 RCTs)</td><td>low</td><td>Favors SGA
-1.7 (-3.2, -0.3)</td></tr>
<tr><td>Medication adherence</td><td>SGA vs placebo (2 RCTs)</td><td>low</td><td>NS</td></tr>
<tr><td colspan="4">Disruptive behavior disorder</td></tr>
<tr><td>Aggression</td><td>SGA vs placebo (5 RCTs)</td><td>low</td><td>NS</td></tr>
<tr><td>Anxiety</td><td>SGA vs placebo (4 RCTs)</td><td>low</td><td>No evidence of difference</td></tr>
<tr><td>Behavior symptoms</td><td>SGA vs placebo (7RCTs)</td><td>moderate</td><td>Favors SGA for
ABC:-21.0 (-31.1, -10.8)
BPI: -3.8 (-6.2, -1.4)
NCBRF: -6.9 (-10.4, -3.5)</td></tr>
<tr><td>CGI</td><td>SGA vs placebo (7RCTs)</td><td>moderate</td><td>Favors SGA for
CGI-I: -1.0 (-1.7, -0.3);
CGI-S: -1.3 (-2.2, -0.5)</td></tr>
<tr><td>Medication adherence</td><td>SGA vs placebo (5 RCTs)</td><td>low</td><td>NS</td></tr>
</table>
</td></tr>
</table>

First Author, Publication Year, Country	Main Findings and Authors' Conclusion			
	Bipolar disorder			
	CGI	SGA vs placebo (6 RCTs)	moderate	Favors SGA -0.7 (-0.8, -0.5)
	Depression	SGA vs placebo (4 RCTs)	low	NS
	Manic symptoms	SGA vs placebo (8 RCTs)	low	All except one study favor SGA (results were not pooled due to high heterogeneity)
	Medication adherence	SGA vs placebo (2 RCTs)	low	Favors placebo RR (95% CI)= 2.0 (1.0, 4.0)
	Suicide related behaviors	SGA vs placebo (7 RCTs)	moderate	NS
	Schizophrenia			
	CGI	FGA vs SGA (3 RCTs)	low	Favors SGA -0.8 (-1.3, -0.3)
		Clozapine vs olanzapine (2 RCTs)	low	NS
		Olanzapine vs risperidone (3 RCTs)	low	NS
		SGA vs placebo (6 RCTs)	moderate	Favors SGA -0.5 (-0.7, -0.3)
	Positive and negative symptoms	FGA vs SGA (3 RCTs, 1 PCS)	low	NS
		Clozapine vs olanzapine (2 RCTs, 1 PCS)	low	NS
		Olanzapine vs risperidone (3 RCTs, 1 PCS)	low	NS
		SGA vs placebo (6 RCTs)	moderate	Favors SGA -8.7 (-11.8, -5.6)
	Medication adherence	FGA vs SGA (2 RCTs, 1 PCS)	low	NS
		Olanzapine vs quetiadine (2	low	NS

First Author, Publication Year, Country	Main Findings and Authors' Conclusion

	RCTs)		
	Olanzapine vs risperidone (4 RCTs, 1 PCS)	low	NS
	SGA vs placebo (2 RCTs)	low	NS
Suicide related behaviors	SGA vs placebo (5 RCTs)	low	NS
Tourette syndrome			
Tics	SGA vs placebo (2 RCTs)	moderate	Favors SGA -7.0 (-10.3, -3.6)
Behavior symptoms			
Autistic symptoms	Risperidone vs placebo (2 RCTs)	low	Favors risperidone in one study; NR in second study
*If not otherwise stated			

Summary of adverse effects

Outcome	FGA vs SGA	SGA vs SGA	Placebo controlled studies
Dyslipidemia	Insufficient evidence	Moderate strength evidence R<O, Low strength evidence A<O, A<Q. No significant difference for C vs O, O vs Q, or Q vs R	Low strength evidence Higher with A, O, or Q compared to P
EPS	Low strength evidence O<H, R<H	Low strength evidence No significant difference for C vs O, C vs R, O vs Q, O vs R, or Q vs R	Moderate strength evidence Higher with A, or R, compared to P. Low strength evidence No significant difference for P vs O, or P vs Q
Insulin	Insufficient	Low strength	Low strength

First Author, Publication Year, Country	Main Findings and Authors' Conclusion

resistance	evidence	evidence No significant difference for O vs Q, O vs R, Q vs R	evidence No significant difference for A vs P, or O vs P
Prolactin related and sexual AE	Low strength evidence No significant difference for H vs O or H vs R	Moderate strength evidence O<R, Low strength evidence C<O, No significant difference for Q vs R	Moderate strength evidence A<P, P<O, Low strength evidence P<R, No significant difference for Q vs P
Sedation	Low strength evidence No significant difference for H vs O or H vs R	Low strength evidence No significant difference for C vs O, O vs Q, O vs R, Q vs R.	Moderate strength evidence P<R, P<Z, Low strength evidence P<A. No significant difference for P vs O, P vs Q
Weight gain	Low strength evidence H<O, No significant difference for H vs R	Moderate strength evidence Q<O, R<O, Low strength evidence A<O, A<Q, A<R. No significant difference for C vs O, C vs R, Q vs R	Moderate strength evidence Higher with A, O, Q or R compared to P. Low strength evidence No significant difference for Z vs P
A= aripiprazole, C= clozapine, H= haloperidol, O= olanzapine, P= placebo, Q= quetiapine, R= risperidone, Z= ziprasidone			

Authors' Conclusion:
"This is the first comprehensive review comparing the effectiveness and safety across the range of antipsychotics for children and young adults. The evidence on the comparative benefits and harms of antipsychotics is limited. Some

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>SGAs have a better side effect profile than other SGAs. Additional studies using head-to-head comparisons are needed." p. e771</td></tr>
<tr><td>De Hert,[6] 2011, Europe, USA</td><td>Main findings:
Findings with aripiprazole, olanzapine, quetipine, risperidone, ziprasidone

Weight gain
<table>
<tr><th>Treatment</th><th>No. of studies or subgroups</th><th>Mean difference* (95% CI)</th><th>Heterogeneity (I^2)</th></tr>
<tr><td>Aripiprazole</td><td>9</td><td>0.79 (0.54, 1.04)</td><td>0</td></tr>
<tr><td>Olanzapine</td><td>3</td><td>3.45 (2.93, 3.97)</td><td>0</td></tr>
<tr><td>Quetiapine</td><td>5</td><td>1.43 (1.17, 1.69)</td><td>0</td></tr>
<tr><td>Risperidone</td><td>12</td><td>1.76 (1.27, 2.25)</td><td>76%</td></tr>
<tr><td>Ziprasidone</td><td>3</td><td>-0.04 (-0.38, 0.30)</td><td>0</td></tr>
<tr><td colspan="4">CI= confidence interval
*In the analysis, the placebo group was counted multiple times in case of studies with multiple doses for a drug</td></tr>
</table>
Changes in prolactin, glucose and lipids
<table>
<tr><th rowspan="2">Treatment</th><th colspan="3">Change in</th></tr>
<tr><th>Prolactin</th><th>Glucose</th><th>Lipids</th></tr>
<tr><td>Aripiprazole</td><td>Decrease (4)</td><td>No change (4)</td><td>No change (4)</td></tr>
<tr><td>Olanzapine</td><td>Increase (2)</td><td>Increase (1), no change (1)</td><td>Increase (2)</td></tr>
<tr><td>Quetiapine</td><td>Decrease (1), no change (3)</td><td>No change (4)</td><td>Increase (3), no change (1)</td></tr>
<tr><td>Risperidone</td><td>Increase (7)</td><td>No change (3)</td><td>No change (3)</td></tr>
<tr><td>Ziprasidone</td><td>Increase (1), no change (2)</td><td>No change (3)</td><td>Decrease (2), no change (1)</td></tr>
<tr><td colspan="4">Number in brackets indicate the number of studies</td></tr>
</table>
Authors' Conclusion:
"…children and adolescents have a high liability to experience antipsychotic induced hyperprolactinaemia, weight gain and associated metabolic disturbances" p. 144
"Evidence of efficacy and safety of the use of atypical antipsychotics in children and adolescent is growing, but still limited, especially regarding the cardiometabolic safety of the available treatment alternatives." p. 155</td></tr>
<tr><td>Pringsheim,[3] 2011, Canada, USA</td><td>Main findings:
Findings with aripiprazole, clozapine, olanzapine, quetiapine, risperidone or ziprasidone</td></tr>
</table>

First Author, Publication Year, Country	Main Findings and Authors' Conclusion

Outcome	No. of studies	No. of patients	Effect measure	Finding	Hetero-geneity I^2 (%)
Risperidone vs placebo (< 12 weeks)					
Weight gain (kg)	10	833	MD (95% CI)	1.72 (1.17, 2.26)	74
Prolactin at end-pt (ng/mL)	3	196	MD (95% CI)	20.70 (16.78, 24.62)	0
Extrapyramidal disorder	7	773	OR (95% CI)	3.35 (2.04, 5.48)	0
Risperidone vs placebo (> 12 weeks)					
Weight gain (kg)	3	397	MD (95% CI)	1.95 (1.14, 2.75)	49
Olanzapine vs placebo (< 12 weeks)					
Weight gain (kg)	3	278	MD (95% CI)	3.47 (2.94, 3.98)	7
Change in BMI (kg/m^2)	2	267	MD (95% CI)	1.28 (0.96, 1.59)	45
Triglyceride*	2	268	OR (95% CI)	5.13 (2.78, 9.45)	0
Change in cholesterol	2	241	MD (95% CI)	3.67 (1.43, 5.92)	1
Prolactin†	2	255	OR (95% CI)	30.52 (10.66, 87.38)	0
ALT‡	2	265	OR (95% CI)	18.74 (3.64, 96.45)	0
Quetiapine vs placebo (< 12 weeks)					
Weight gain (kg)	3	81	MD (95% CI)	1.14 (1.01, 1.81)	0
Aripiprazole vs placebo (< 12 weeks)					
Weight gain (kg)	5	861	MD (95% CI)	0.85 (0.57, 1.13)	17
Change in BMI (kg/m^2)	3	720	MD (95% CI)	0.27 (0.11, 0.42)	0
Change in prolactin (ng/mL)	4	796	MD (95% CI)	-5.03 (-7.80, -2.26)	47
Extrapyramidal disorder	5	952	OR (95% CI)	3.70 (2.37, 5.77)	0

*high triglyceride at any time during treatment
†elevated prolactin at any time during treatment
‡clinically significant elevation in ALT

First Author, Publication Year, Country	Main Findings and Authors' Conclusion
	Clozapine Children treated with clozapine for <3 months experienced weight gain, increase in BMI, elevated triglycerides and a decrease in absolute neutrophil counts **Ziprasidone** Data on the treatment of children with ziprasidone is scarce. One 8-week RCT showed that weight gain and prolactin levels were similar with ziprasidone and placebo
	Authors' Conclusion: "There good evidence to support the existence of both metabolic and neurological adverse effects in children treated with these medications. Proper attention and vigilance to potential metabolic and neurological adverse effects is necessary and should be considered part of the standard of care." p. 652 (Medications reviewed in this study: risperidone, olanzapine, quetiapine, aripiprazole, clozapine, ziprasidone)
Panagiotopolos,[18] 2010, Canada	**Main findings:** **Findings with aripiprazole, clozapine, olanzapine, quetipine, risperidone, ziprasidone** Of the 42 RCTs investigating efficacy of AAPs, 41 showed a positive outcome and one RCT showed no improvement. Metabolic effects were investigated in 24 studies of various types. Weight gain: The magnitude of weight gain varied between AAPs, with olanzapine producing the greatest weight gain. One study showed significant weight gain within 4 weeks of AAP initiation (average weight gain was 4.52 kg for olanzapine, , 2.87 kg for for quetiapine, 2.72 kg for risperidone and 1.61 kg for aripiprazole). Two studies showed that extreme weight gain (defined as an increase of 7% from baseline weight) was observed in 84% of olanzapine treated, 56% of quetiapine treated, 64% risperidone treated and 58% of aripiprazole treated. Waist circumference: One study showed significant mean increases inwaist circumference after 12 weeks of treatment with olanzapine (8.6 cm), aripprazole (5.4 cm), quetiapine (5.3 cm), and risperidone (5.1 cm) compared to untreated controls. Glucose and Insulin Case series studies have shown that occurrence of diabetes and diabetic ketoacidosis in children and adolescents following treatmentwith clozapine, olanzapine, risperidone and quetiapine. Lipids: Two studies showed a significant increase in total cholesterol following olanzapine, quetiapine, and risperidone treatment. One study showed increase in triglycerides with olanzapine, quetiapine and risperidone and increase in LDL-cholesterol with aripiprazole and olanzapine.

First Author, Publication Year, Country	Main Findings and Authors' Conclusion
	Prolactin: One study showed increase in prolactin levels with risperidone. Olanzapine and clozapine also showed increase in prolactin levels (four studies). Aripiprazole was found to decrease prolactin levels (one study).
	Authors' Conclusion: "A wide range of metabolic effects including weight gain, increased waist circumference, dysglycemia, dyslipidemia, hypertension, elevated hepatic transaminases and prolactin levels have been reported….. There is urgent need for national clinical practice guidelines that provide, not only appropriate treatment algorithms for AAP-use based on evidence, but also address metabolic monitoring and subsequent management of complications in these vulnerable population." p. 124

AAP= atypical antipsychotic, ABC= Aberrant behavior checklist, ABC-C= Aberrant behavior checklist community version, ABC-C-H= ABC-C hyperactivity/noncompliance subscale, ABC-C-I= ABC-C irritability/agitation/crying subscale, ABC-C-S= ABC-C stereotypy subscale, ADHD= attention deficit hyperactive syndrome, AE= adverse effects, ASD= autism spectrum disorder or autistic spectrum disorder, BMI= body mass index, BPI= behavior problems inventory, BPRS= Brief psychiatry rating scale, BPRS-C= Brief psychiatry rating scale for children, CARS= Checklist for autism rating scale, CGAS= Children's global assessment scale, CGI= Clinical Global Impression scale, CGI-I= Clinical Global Impression –improvement scale, CGI-S= Clinical Global Impression – severity of illness, CPRS= comprehensive psychopathological rating scale, CY-BOCS= Children's Yale-Brown Obsessive Compulsive Scale, DBD= disruptive behavior disorder, EPS= extrapyramidal side effects, FGA= first generation antipsychotic, , NCBR= Nisonger child behavior rating, nRCT= non-randomized study, OAS-M= Modified overt aggression scale, PANSS= positive and negative syndrome scale, PDD= pervasive developmental disorder, RCT= randomized controlled trial, RF-RLRS= Ritvo-Freeman real life rating scale, SANS- scale for assessment of negative syndrome, SAPS- scale for assessment of positive syndrome SGA= second generation antipsychotic, SMD= standardized mean difference, SR= systematic review, SR-MA= systematic review and meta-analysis, VABS= Vineland adaptive behavior scale, VAS= Visual analog scale, YAPA-SIBS= Yale-Paris self-injurious behavior scale, YMRS= Young mania rating scale.

APPENDIX 6: Guidelines and Recommendations

Guideline Society, Country, Author, Year	Recommendations
NHS - NICE technology appraisal guidance,[20] 2011	Guidance: "1.1 Aripiprazole is recommended as an option for the treatment of schizophrenia in people aged 15 to 17 years who are intolerant of risperidone, or to whom risperidone is contraindicated, or whose schizophrenia has not been adequately controlled with risperidone. 1.2 People aged 15 to 17 years currently receiving aripiprazole for the treatment of schizophrenia who do not meet the criteria specified in 1.1 should have the option to continue treatment until it is considered appropriate to stop. This decision should be made jointly by the clinician and the person with schizophrenia, and if appropriate, with their parents or carers" p. 4