Cochrane Library

Cochrane Database of Systematic Reviews

Aripiprazole for autism spectrum disorders (ASD) (Review)

Hirsch LE, Pringsheim T

Hirsch LE, Pringsheim T.
Aripiprazole for autism spectrum disorders (ASD).
Cochrane Database of Systematic Reviews 2016, Issue 6. Art. No.: CD009043.
DOI: 10.1002/14651858.CD009043.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Aripiprazole for autism spectrum disorders (ASD)

Lauren E Hirsch[1], Tamara Pringsheim[2]

[1]Department of Clinical Neurosciences, University of Calgary, Calgary, Canada. [2]Department of Clinical Neurosciences, Psychiatry, Pediatrics and Community Health Sciences, University of Calgary, Calgary, Canada

Contact address: Tamara Pringsheim, Department of Clinical Neurosciences, Psychiatry, Pediatrics and Community Health Sciences, University of Calgary, Mathison Centre for Mental Health Reseach and Education, 4th floor, TRW Building, 4D72, 3280 Hospital Drive NW, Calgary, AB, T2N 4Z6, Canada. tmprings@ucalgary.ca.

Editorial group: Cochrane Developmental, Psychosocial and Learning Problems Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 6, 2016.

Citation: Hirsch LE, Pringsheim T. Aripiprazole for autism spectrum disorders (ASD). *Cochrane Database of Systematic Reviews* 2016, Issue 6. Art. No.: CD009043. DOI: 10.1002/14651858.CD009043.pub3.

ABSTRACT

Background

Autism spectrum disorders (ASD) include autistic disorder, Asperger's disorder and pervasive developmental disorder - not otherwise specified (PDD-NOS). Antipsychotics have been used as a medication intervention for irritability related to ASD. Aripiprazole, a third-generation, atypical antipsychotic, is a relatively new drug that has a unique mechanism of action different from that of other antipsychotics. This review updates a previous Cochrane review on the safety and efficacy of aripiprazole for individuals with ASD, published in 2011 (Ching 2011).

Objectives

To assess the safety and efficacy of aripiprazole as medication treatment for individuals with ASD.

Search methods

In October 2015, we searched the Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and seven other databases as well as two trial registers. We searched for records published in 1990 or later, as this was the year aripiprazole became available.

Selection criteria

Randomised controlled trials (RCTs) of aripiprazole (administered orally and at any dosage) versus placebo for treatment of individuals with a diagnosis of ASD.

Data collection and analysis

Two review authors independently collected, evaluated and analysed data. We performed meta-analysis for primary and secondary outcomes, when possible. We used the GRADE (**G**rades of **R**ecommendation, **A**ssessment, **D**evelopment and **E**valuation) approach to rate the overall quality of the evidence.

Main results

We included three trials in this review. Two were included in the previous published review, and the results of one, placebo-controlled discontinuation study were added to this review. Although we searched for studies across age groups, we found only studies conducted in children and youth. Included trials had low risk of bias across most domains. High risk of bias was seen in only one trial with incomplete outcome data. We judged the overall quality of the evidence for most outcomes to be moderate.

Two RCTs with similar methods evaluated use of aripiprazole for a duration of eight weeks in 316 children/adolescents with ASD. Meta-analysis of study results revealed a mean improvement of -6.17 points on the Aberrant Behavior Checklist (ABC) - Irritability subscale (95% confidence intervals (CIs) -9.07 to -3.26, two studies, 308 children/adolescents, moderate-quality evidence), -7.93 points on the ABC - Hyperactivity subscale (95% CI -10.98 to -4.88, two studies, 308 children/adolescents, moderate-quality evidence) and -2.66 points on the ABC - Stereotypy subscale (95% CI -3.55 to -1.77, two studies, 308 children/adolescents, moderate-quality evidence) in children/adolescents taking aripiprazole relative to children/adolescents taking placebo. In terms of side effects, children/adolescents taking aripiprazole had a greater increase in weight, with a mean increase of 1.13 kg relative to placebo (95% CI 0.71 to 1.54, two studies, 308 children/adolescents, moderate-quality evidence), and had a higher risk ratio (RR) for sedation (RR 4.28, 95% CI 1.58 to 11.60, two studies, 313 children/adolescents, moderate-quality evidence) and tremor (RR 10.26, 95% CI 1.37 to 76.63, two studies, 313 children/adolescents, moderate-quality evidence). A randomised, placebo-controlled discontinuation study found that 35% of children/adolescents randomised to continue intervention with aripiprazole relapsed with respect to their symptoms of irritability, compared with 52% of children/adolescents randomised to placebo, for a hazard ratio of 0.57 (95% CI 0.28 to 1.12, 85 children/adolescents, low-quality evidence).

All three included trials were supported by Bristol-Myers Squibb (Princeton, NJ) and Otsuka Pharmaceutical Company, Ltd. (Tokyo, Japan), with editorial support provided by Ogilvy Healthworld Medical Education and Bristol-Myers Squibb.

Authors' conclusions

Evidence from two RCTs suggests that aripiprazole can be effective as a short-term medication intervention for some behavioural aspects of ASD in children/adolescents. After a short-term medication intervention with aripiprazole, children/adolescents showed less irritability and hyperactivity and fewer stereotypies (repetitive, purposeless actions). However, notable side effects, such as weight gain, sedation, drooling and tremor, must be considered. One long-term, placebo discontinuation study found that relapse rates did not differ between children/adolescents randomised to continue aripiprazole versus children/adolescents randomised to receive placebo, suggesting that re-evaluation of aripiprazole use after a period of stabilisation in irritability symptoms is warranted. Studies included in this review used criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) (APA 2000) for ASD diagnosis; however, the diagnostic criteria for ASD changed significantly with release of the fifth edition of the DSM (DSM-5) in 2013 (APA 2013).

PLAIN LANGUAGE SUMMARY

Aripiprazole for autism spectrum disorders (ASD)

Background

Aripirazole is an antipsychotic drug - a type of medication used to treat serious mental disorders such as paranoia. It has also been used to treat behavioural problems (e.g. aggression, severe temper tantrums) in people with autism spectrum disorders (ASD). Aripiprazole has been shown to be well tolerated and to improve behavioural problems in other disorders such as schizophrenia and bipolar disorder. As aripiprazole is a relatively new drug, it is important to understand both the benefits and side effects of this drug in patients with ASD.

Review question

Do children and adults with ASD benefit from treatment with aripiprazole, compared with other children and adults with ASD who receive a drug with no active ingredient (placebo)?

Study characteristics

In this review, we included three studies that investigated effects of aripiprazole. Two were short-term (eight weeks) studies that evaluated whether aripiprazole improved behavioural problems in a total of 316 children/adolescents. The third was a longer-term (up to 16 weeks) study in which 85 children/adolescents whose symptoms initially improved on aripiprazole discontinued the medication to evaluate whether their behavioural problems recurred. All participants were between six and 17 years of age. All studies used multiple behavioural checklists to assess symptoms of ASD.

Key results and quality of evidence

Short-term studies found improved irritability, hyperactivity and stereotypy (i.e. repetitive behaviours) and inappropriate speech in children/adolescents with ASD taking aripiprazole as compared with placebo. Researchers found no improvement in lethargy/withdrawal (i.e. lack of energy and reduced alertness). White children/adolescents were less likely to relapse (return to older, problematic behaviours) when taking aripiprazole, but this finding was not reported in children/adolescents of other races. Rates of movement disorder side effects such as tremor, muscle rigidity and involuntary movement were higher in children/adolescents taking aripiprazole in all trials. Results of this review suggest that short-term use of aripiprazole may improve irritability, hyperactivity and repetitive movements in children/adolescents with ASD, although both weight gain and neurological side effects (e.g. involuntary movements of the face and jaw) can occur. Children and adolescents taking aripiprazole should be re-evaluated periodically to monitor improvements in ASD symptoms and side effects. Overall, the quality of this evidence is moderate. Since the time these studies were conducted, an updated version of the manual for diagnosing ASD and other conditions has been published. Additional studies evaluating safety and benefits of long-term use of aripiprazole would be helpful.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Aripiprazole compared with placebo for autism spectrum disorders (ASD)*

Patient or population: children/youth with ASD

Settings: ambulatory care

Intervention: aripiprazole

Comparison: placebo

Outcomes	Effect (95% confidence interval)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
ABC - Irritability subscale Mean score changes 8 weeks of treatment	MD -6.17 (-9.07 to -3.26) points relative to placebo, in favour of aripiprazole	308 (2)	⊕⊕⊕⊖ **Moderate**[a]	-
ABC - Hyperactivity subscale Mean score changes 8 weeks of treatment	MD -7.93 (-10.98 to -4.88) points relative to placebo, in favour of aripiprazole	308 (2)	⊕⊕⊕⊖ **Moderate**[a]	-
ABC - Stereotypy subscale Mean score changes 8 weeks of treatment	MD -2.66 (-3.55 to -1.77) points relative to placebo, in favour of aripiprazole	308 (2)	⊕⊕⊕⊖ **Moderate**[a]	-
Weight gain 8 weeks of treatment	MD 1.13 (0.71 to 1.54) points relative to placebo	308 (2)	⊕⊕⊕⊖ **Moderate**[a]	-
Sedation 8 weeks of treatment	RR 4.28 (1.58 to 11.60)	313 (2)	⊕⊕⊕⊖ **Moderate**[a]	-
Tremor 8 weeks of treatment	RR 10.26 (1.37 to 76.63)	313 (2)	⊕⊕⊕⊖ **Moderate**[a]	-
Relapse rate 16 weeks of treatment	HR 0.57 (0.28 to 1.12)	85 (1)	**Low**[b]	-

ABC: Aberrant Behavior Checklist; **GRADE:** Grades of Recommendation, Assessment, Development and Evaluation; **HR:** hazard ratio;**MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]Quality was rated as moderate because of unclear risk of bias for some domains in Marcus 2009 and Owen 2009, and because of the overall small number of studies conducted using aripiprazole in ASD.
[b]Quality of evidence for long-term trials was rated as low because of high risk of attrition bias for incomplete outcome data in Findling 2014. Further research may have an important impact on our confidence in the estimate of effect and may change the estimate.
*A small number of studies have evaluated the use of aripiprazole for ASD. Only one study examined aripiprazole at a duration longer than eight weeks. Future trials of aripiprazole in children/adolescents with ASD are likely to impact the estimates found in this review.

BACKGROUND

Description of the condition

Before 2013, autism spectrum disorders (ASD) represented pervasive developmental disorders of variable severity, defined as autistic disorder, Asperger's disorder and pervasive developmental disorder - not otherwise specified (PDD-NOS) in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition - Text Revision* (DSM-IV-TR) (APA 2000), and as childhood autism, atypical autism, Rett's syndrome, other childhood disintegrative disorder, Asperger's syndrome, other pervasive developmental disorder and pervasive developmental disorder unspecified in the *International Statistical Classification of Diseases and Related Health Problems, Tenth Edition* (ICD-10) (WHO 1994). The three characteristic manifestations of ASD are (1) impaired social interaction, (2) impaired communication and (3) restricted repetitive and stereotyped patterns of behaviour. Diagnostic criteria for ASD changed significantly with the release of the fifth edition of the DSM (DSM-5) in 2013 (APA 2013). Autistic disorder, Asperger's disorder and PDD-NOS were collapsed into a single diagnosis of ASD - a single diagnosis with considerable diagnostic variability. The social and communication domains of ASD were combined, leaving two key symptom domains: (1) social communication and (2) restricted and repetitive behaviours.

As a result of symptom variability, clinicians are encouraged to describe diagnostic specifics in detail, in particular, intelligence and speech and language level. Kanner first described autism in 1943 through his observations of several afflicted children, noting their affinity for extreme aloneness and sameness, and their inability to form purposeful relationships with other people (Kanner 1943). Secondary characteristics, such as emotional and behavioural problems, are extremely common; examples of these include irritability, aggression, poor temper, self injury and injury to others (Lecavalier 2006). As no biomarkers have been established, the diagnosis of ASD is based on behavioural features.

Autism spectrum disorder is a lifelong condition. Individuals with ASD are frequently affected by other neuropsychiatric conditions as well, the most common of which are attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD) and anxiety disorders (Simonoff 2008). Autism spectrum disorder is a neurodevelopmental disorder, but the exact genetic and environmental factors contributing to its cause are unknown. Boys are three to four times more likely to have ASD than girls, again suggesting the importance of genetics in the disorder.

Estimates of the prevalence of ASD vary. A systematic review of prevalence studies of ASD from 1966 to 2004 identified an overall estimate of prevalence of 7.1 per 10,000 for autism (95% confidence interval (CI) 1.6 to 30.6) and 20 per 10,000 (95% CI 4.9 to 82.1) for all ASD (Williams 2006). Variation in the prevalence estimate of typical autism has been significantly affected by the diagnostic criteria used, the age of children screened and study location. More recent prevalence studies have yielded higher estimates. The 2007 National Survey of Children's Health (N (sample size) = 78,037) found the weighted ASD point prevalence to be 110 per 10,000 in the United States (Kogan 2009). In a UK school-based population study in the Special Educational Needs register, the prevalence estimate for ASD was 94 per 10,000 (Baron-Cohen 2009). Most recently, a 2014 report by the Centers for Disease Control and Prevention (CDC) found the point prevalence of ASD to be 14.7 per 1000 eight-year-olds (CDC 2014). A systematic review found that the median worldwide prevalence of autistic disorder was 17 per 100,000, with a range of 2.8 to 94 per 100,000; the median worldwide prevalence of pervasive developmental disorder was 62 per 100,000, with a range of 1 to 189 per 100,00 (Elsabbagh 2012).

Both pharmacological and non-pharmacological interventions are available for children and adults with ASD. Non-pharmacological interventions include educational, behavioural and social communication strategies that are used alone or in combination as part of an individual plan to enhance learning and community participation. These interventions strive to improve communication, social skills, daily living skills, play and leisure skills, academic achievement and maladaptive behaviours (Meyers 2007).

Description of the intervention

Aripiprazole is a novel, atypical, antipsychotic drug with distinct mechanisms of action through its receptor binding profile. Typical antipsychotic medications, such as haloperidol, are potent antagonists at D_2-dopamine receptors. Second-generation antipsychotics, such as risperidone, are high-affinity antagonists at D_2-dopamine receptors and serotonin 5-HT_{2A} receptors. Aripiprazole has functionally significant interactions at D_2, D_3 and D_4 dopamine receptors, and at 5-HT_1A, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_6 and 5-HT_7 serotonin receptors. Aripiprazole is postulated to work by being a dopamine-serotonin partial agonist, or by working through the mechanism of functional selectivity, whereby D_2 functional effects are dependent on the cellular location of the D_2 receptor (Shapiro 2003). The functional selectivity hypothesis proposes that depending upon the cellular milieu, a mixture of agonist, partial agonist and antagonist actions is likely. Thus, the unique and robust mechanism of aripiprazole lies in its ability to be a dopamine agonist when levels are too low, and a dopamine antagonist when levels are too high (Goodnick 2002).

What is known about other antipsychotic medications in ASD?

Both typical (first-generation) and atypical (second-generation) antipsychotics have been evaluated for the treatment of behavioural symptoms in individuals with ASD. Although short-term randomised controlled trials (RCTs) suggest efficacy for improving some symptoms of ASD, important side effects limit their use. Typical antipsychotics have been associated with drug-induced movement disorders. Haloperidol, for example, has been evaluated for the treatment of ASD in several trials and has been associated with improvements in withdrawal and stereotypies (Anderson 1989), as well as positive effects on learning (Campbell 1982); however, it has also been associated with extrapyramidal side effects such as acute dystonic reactions, withdrawal dyskinesias and tardive dyskinesia in this population (Campbell 1997). A systematic review of risperidone for ASD demonstrated efficacy of this medication in treating symptoms of aggression, irritability and repetitive behaviour; notable side effects included weight gain, increased appetite and sedation (Jesner 2009) .

How the intervention might work

Alterations in dopaminergic and serotonergic neurotransmission have been implicated in ASD, and abnormalities in these systems have been demonstrated through neuroimaging and metabolic

studies (Posey 2008). As aripiprazole has affinity for both dopamine and serotonin receptors, it is likely to exert its action through mechanisms similar to those of other antipsychotic medications. When compared, the 5-HT_2 antagonism of aripiprazole is higher than most atypical antipsychotics but lower than ziprasidone or risperidone; however its degree of antagonist activity, along with partial D_2 agonist activity, is at an optimal level, reducing the risk of extrapyramidal signs such as tardive dyskinesia (Goodnick 2002). Aripiprazole has moderate H_1 receptor affinity, which results in decreased sedation and risk of weight gain, compared with clozapine and olanzapine, which have high affinities at this receptor (Goodnick 2002).

Aripiprazole use in other disorders

Aripiprazole has been shown in a placebo-controlled trial to be an effective intervention for positive and negative symptoms of schizophrenia, with a lower propensity to induce certain movement disorders, weight gain or sedation, or to increase cholesterol and prolactin levels, compared with drugs such as olanzapine or risperidone (Komossa 2009). Studies have shown that antipsychotic medications can cause increased weight gain and increased risk of type 2 diabetes in children and adolescents (Bobo 2013; Correll 2009). Aripiprazole was well tolerated in a placebo-controlled trial of adolescents with schizophrenia, causing few side effects (Findling 2008). Another placebo-controlled trial has shown its efficacy and tolerability in treating adolescents with bipolar I disorder or mixed episodes, with no significant weight changes compared with placebo (Findling 2009). The half-life of aripiprazole of 72 hours allows once-daily dosing and increased assurance of full absorption (Goodnick 2002).

Why it is important to do this review

This review updates a previous Cochrane review on the safety and efficacy of aripiprazole for individuals with ASD published in 2011 (Ching 2011). Aripiprazole currently has United States (US) Food and Drug Administration (FDA)-labelled indications for the treatment of schizophrenia, bipolar disorder, major depressive disorder and autistic disorder (FDA 2010). Although several antipsychotics have demonstrated benefit in the treatment of behavioural symptoms of ASD, all currently available medication interventions have side effects that limit their use. As aripiprazole is a relatively new drug, it is important to understand both the efficacy and the side effects of this intervention in individuals with ASD. It is also important to determine whether intervention effects are dependent on factors such as age, length of intervention or medication dosage. A synthesis of available data on aripiprazole in ASD will be useful for clinicians considering use of this agent for people with ASD.

OBJECTIVES

To assess the safety and efficacy of aripiprazole as medication treatment for individuals with ASD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), including both parallel-group and cross-over designs, of any duration.

Types of participants

Children and adults with a clinical diagnosis of ASD made by an established classification system. Diagnosis of ASD includes individuals with autistic disorder, Asperger's disorder and pervasive developmental disorder - not otherwise specified (PDD-NOS).

Diagnosis of ASD in trial participants was corroborated by administration of a standardised instrument such as the Autism Diagnostic Interview - Revised (ADI-R) (Lord 1994).

Given the high rate of co-morbidity between ASD and other neuropsychiatric disorders, we did not exclude individuals with co-morbid disorders. However, we did exclude participants receiving co-interventions such as other antipsychotics, psychostimulants, antidepressants or mood stabilisers. We did not exclude participants receiving non-pharmacological therapy (i.e. behaviour therapy) provided it was equally accessible to all study participants, stable before trial entry and consistent throughout the study.

Types of interventions

Aripiprazole administered orally for ASD at any dosage compared with placebo.

Types of outcome measures

Primary outcomes

- Emotional and behavioural symptoms, as measured by validated clinician- or parent-reported scales.
  - Irritability (e.g. Aberrant Behaviour Checklist (ABC) - Irritability subscale (Aman 1986)).
  - Hyperactivity (e.g. ABC - Hyperactivity subscale (Aman 1986)).
  - Stereotypy (e.g. ABC - Stereotypy subscale (Aman 1986)).
  - Inappropriate speech (e.g. ABC - Inappropriate Speech subscale (Aman 1986)).
  - Lethargy/withdrawal (e.g. ABC - Lethargy/Withdrawal subscale (Aman 1986)).
  - Aggression (e.g. Overt Aggression Scale (OAS) (Yudofsky 1986)).
  - Clinical Improvement (e.g. Clinical Global Impression (CGI) - Improvement scale (Guy 1976)).
- Extrapyramidal side effects*, as measured by scales such as the modified Webster Scale (mWS) (Webster 1968), the Abnormal Involuntary Movements Scale (AIMS) (Guy 1976) or the Barnes Akathisia Scale (BARS) (Barnes 1989).

Secondary outcomes

- Obsessive-compulsive behaviours as rated by, for example, the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (Goodman 1989).
- Weight gain and metabolic side effects*.
- Other side effects*, for example, somnolence, insomnia, headache and constipation.

We planned to synthesise results for the following time points: less than three months, three to six months and over six months. We were able to synthesise two trials that were eight weeks in duration and to describe, in detail, a discontinuation study of 16 weeks' duration.

*Please note, we use the term 'side effects' to describe any harms, adverse effects or adverse drug reactions associated with aripiprazole.

Search methods for identification of studies

Electronic searches

Searches for the original review were run in May 2011. We limited the search to 1990 onwards, as this is the year in which aripiprazole first became available. We applied no language restrictions. We ran searches for this update in November 2014 and again in October 2015, using the search strategies presented in Appendix 1. We have reported in Appendix 2 additional details about the searches, including exact search dates for each database. We searched the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 9; part of *The Cochrane Library*), which also contains the Cochrane Developmental, Psychosocial and Learning Problems Group Specialised Register.
- Ovid MEDLINE (1946 to October Week 1 2015).
- Embase (1980 to Week 41 2015; Ovid).
- CINAHL Plus (1937 to current; EBSCOhost).
- PsycINFO (1806 to October Week 1 2015; Ovid).
- Cochrane Database of Systematic Reviews (CDSR; 2015, Issue 10; *The Cochrane Library*).
- Database of Abstracts of Reviews of Effects (DARE; 2015, Issue 2; *The Cochrane Library*).
- Conference Proceedings Citation Index - Science (CPCI-S; 1990 to current; Web of Science).
- Autism Data (all available years).
- ZETOC (limited to conference proceedings; all available years).
- WorldCat (limited to theses and dissertations; all available years).
- ClinicalTrials.gov (all available years).
- World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP; all available years).

Searching other resources

We contacted the drug company that makes aripiprazole to determine whether any trials were ongoing or results unpublished in this area.

Data collection and analysis

Selection of studies

For the initial review, two review authors (TP, HC) independently reviewed titles and abstracts obtained from the searches and selected potentially relevant studies. Two review authors (TP, LH) followed the same procedure for this update. We obtained full-text articles and read them in detail to determine whether they fulfilled inclusion criteria. In the event of any dispute as to whether a study met the inclusion criteria, a discussion between review authors took place. We did not need to refer any disagreement to an independent arbiter.

Data extraction and management

Both review authors (TP and HC original; TP and LH update) independently extracted data from included studies and entered them onto a pre-designed data extraction form. We extracted and entered the following data.

- Study procedures, including recruitment, diagnosis, medication, dosage, duration and clinical setting.
- Study design.
- Method of randomisation.
- Method of allocation concealment.
- Blinding of participants, personnel and outcome assessors.
- Inclusion and exclusion criteria for participants.
- Number of participants.
- Age distribution.
- Gender.
- Loss to follow-up.
- Premature discontinuation and reasons for such.
- Outcomes.
- Incomplete outcome data and selective outcome reporting.
- Method of analysis.
- Comparability of groups at baseline.

We compared extracted data to ensure accuracy, and we resolved discrepancies through discussion between review authors. One review author (TP) entered data into Review Manager (RevMan 2014), and the other (LH) checked the data for accuracy.

Assessment of risk of bias in included studies

Two review authors (original review: TP and HC; this update: TP and LH) independently assessed the risk of bias of each included study according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Review authors assessed each included study against the seven domains described below and assigned a rating of low risk of bias, high risk of bias or unclear risk of bias (uncertain risk of bias). When risk of bias was unclear, we sought additional information from the study authors. When the two review authors disagreed, we consulted the original paper until we were able to make a decision.

Random sequence generation

Description: The method by which participants were randomly allocated to different intervention groups is described in sufficient detail as to determine whether comparable groups were produced.

Review authors' judgement: Was the allocation sequence adequately generated?

Allocation concealment

Description: The method by which participants were notified of intervention schedules is described in sufficient detail to assess whether such schedules could be foreseen in advance of, or during, recruitment.

Review authors' judgement: Was allocation adequately concealed?

Blinding of participants and personnel

Description: Any measures taken to blind participants and personnel were described in sufficient detail to determine whether knowledge of intervention type was revealed at any point during the study.

Review authors' judgement: Was blinding adequate during the study?

Blinding of outcome assessment

Description: Any measures taken to blind outcome assessors were described in sufficient detail to determine whether knowledge of intervention type was revealed at any point during the study.

Review authors' judgement: Was blinding adequate during the study?

Incomplete outcome data

Description: Intention-to-treat analysis (analysis comparing participants in the groups to which they were originally randomly assigned versus complete outcome data available for all randomised participants) was included in each study. Review authors extracted and reported data on the distribution across intervention groups, on attrition and exclusion, on reasons for missed outcomes and on re-inclusion in analyses.

Review authors' judgement: Were incomplete study data dealt with adequately by study authors?

Selective outcome reporting

Description: We attempted to assess the possibility of selective outcome reporting by study authors. We checked study protocols through trial registries and compared outcomes listed in the protocol versus the published report. We then compared outcomes listed in the methods section of the manuscript versus those those listed in the results section. We also assessed and reported which studies collected data on a small number of key outcomes that are routinely measured.

Review authors' judgement: Are included studies free of any possibility of selective outcome reporting?

Other sources of bias

Description: We investigated any possibility of potential threats to validity in the included studies. Possible sources included:

- design-specific risk of bias;
- early stopping;
- baseline imbalance;
- inappropriate administration of a co-intervention; and
- use of an insensitive instrument to measure outcomes.

Review authors' judgement: Are included studies free of other problems that could put the investigation at high risk of bias?

Measures of treatment effect

Binary data

We used risk ratio (RR) estimations with 95% CIs for binary outcomes.

Continuous data

For continuous outcomes, we used the mean difference (MD) to pool outcomes measured on the same scale across studies. We also performed an intention-to-treat analysis and included all randomised participants in the analysis, retained in the groups to which they were allocated. For additional methods to be used in future updates of this review, please see our protocol (Ching 2011) and Appendix 3.

Time-to-event data

We used hazard ratio (HR) estimations with 95% CIs for time-to-event outcomes.

Unit of analysis issues

We did not encounter any unit of analysis issues. Please see our protocol (Ching 2011) and Appendix 3 for methods that we will use to deal with these issues when we update this review.

Dealing with missing data

When data were missing, we first attempted to contact the study authors. Neither of the included studies reported standard deviations for data on the Aberrant Behavior Checklist (ABC) (Aman 1986), the Clinical Global Impression - Severity (CGI-S) scale (Guy 1976) and the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (Goodman 1989). Furthermore, although study authors responded to our requests for further information, they were not able to provide us with the standard deviations that we requested. Correspondence with study authors and a statistician allowed us to use statistical methods, when necessary, to back-calculate missing data. Therefore, for Marcus 2009, we back-calculated standard deviations from given standard errors. For Owen 2009, we back-calculated standard deviations from given 95% CIs. We performed back-calculations using the methods specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We described missing data and dropouts for each study included in the review in the 'Risk of bias' tables (beneath the Characteristics of included studies tables).

Assessment of heterogeneity

We assessed methodological heterogeneity by comparing trial designs, and clinical heterogeneity by comparing the distribution of important participant factors such as age. We estimated heterogeneity through the DerSimonian and Laird method. We then assessed statistical heterogeneity by examining the I^2 statistic, an approximate quantity that describes the proportion of variation in point estimates that is due to heterogeneity of studies rather than to sampling error. In addition, we performed a Chi^2 test of homogeneity to determine the strength of evidence that heterogeneity is genuine. We examined I^2 and Chi^2 statistics in conjunction with one another because of the limitations of each statistic independently, especially considering the small number of studies included in this review. We used a significance level of 0.10 for the Chi^2 test. We also described tau^2, an estimate of between-study variability, when presenting results of the random-effects model.

Assessment of reporting biases

As we found only three studies, we did not assess reporting bias. See our protocol (Ching 2011) and Appendix 3 for methods to be used for future updates of this review.

Data synthesis

We performed a meta-analysis of the data, using both fixed-effect and random-effects models, which we compared to assess statistical heterogeneity. We used Mantel-Haenszel methods for RRs because of the rarity of these events, as the Mantel-

Haenszel weighting scheme is preferable with sparse data (Higgins 2011c). We analysed time-to-event data and MDs using inverse variance methods. We did not plan to combine trials with important differences in methods, inclusion criteria, participants and administration of medication (e.g. trials with only adult participants would not be combined with trials of only children; trials lasting two weeks would not be combined with trials lasting one year). When we were unable to perform a meta-analysis, we described trial data with respect to the review's primary and secondary outcomes. When significant heterogeneity was present in the fixed-effect model, we presented results from the random-effects model.

Summary of findings

We created a 'Summary of findings' table, which includes the effect estimate, 95% CIs, number of participants and quality of evidence for major outcomes included in the review (ABC - Irritability subscale, ABC - Hyperactivity subscale, ABC - Stereotypy subscale, weight gain, sedation, tremor, relapse rate). We used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) method to assess the quality of the body of evidence for each outcome (Guyatt 2011). Although we considered RCTs to provide high-quality evidence, we downgraded the level of evidence to moderate for all outcomes because of the presence of limitations in the design of available studies, and the overall small number of studies in this area. It is thus likely that further research could have an important impact on our confidence in the estimate of effect and may change the estimate.

Subgroup analysis and investigation of heterogeneity

As we found only two studies, we did not perform a subgroup analysis. See our protocol (Ching 2011) and Appendix 3 for methods to be used for future updates of this review.

Sensitivity analysis

As we found only two studies, we did not perform a sensitivity analysis. See our protocol (Ching 2011) and Appendix 3 for methods to be used for future updates of this review.

RESULTS

Description of studies

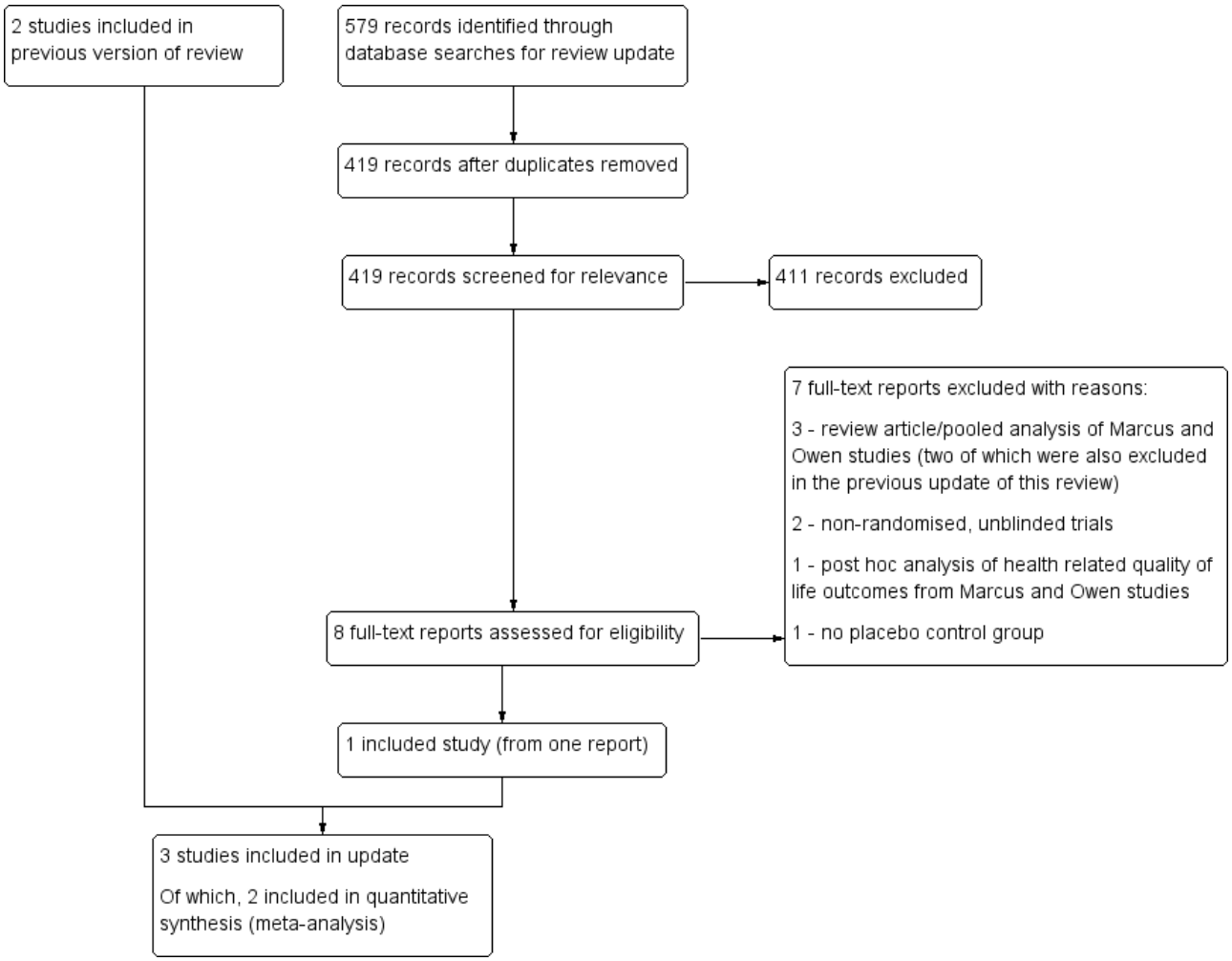
See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

In 2011, we found 1569 records, discarded the duplicates and screened 1323 titles and abstracts. We obtained and reviewed 14 full-text reports. Two studies fitted our inclusion criteria of being randomised, placebo-controlled, and double-blinded trials (Marcus 2009; Owen 2009). We excluded the remaining 12 studies because they were review articles, pooled analyses, open-label retrospective studies or case series studies (Ching 2012).

For this update, we ran searches in November 2014 and found 468 records. From these, we reviewed eight full-text reports. We excluded seven of the eight studies (see Excluded studies) and included data from one new study in the update of this review (see Figure 1). The included study was an RCT investigating the safety and efficacy of long-term maintenance treatment with aripiprazole in ASD (Findling 2014). We updated the searches again in October 2015. Among the 111 records found, we identified no eligible studies.

Figure 1. Study flow diagram.



We found no cluster-randomised or cross-over trials. Also, no studies conducted repeated observations on participants.

Included studies

See Characteristics of included studies tables.

Two studies included within this review were described as randomised, placebo-controlled, double-blinded trials; each lasted eight weeks (Marcus 2009; Owen 2009). The third study was a randomised, placebo-controlled, double-blinded relapse prevention trial, which included two phases (Findling 2014). Phase one - the stabilisation phase - consisted of 13 to 26 weeks of single-blind aripiprazole, and phase two - the randomisation phase - consisted of up to 16 weeks of double-blinded treatment with aripiprazole or placebo. Participants whose symptoms of irritability demonstrated a stable response to aripiprazole therapy for 12 consecutive weeks in phase one were eligible for randomisation into phase two.

Study location

All three studies were multi-centre studies conducted in the United States (Findling 2014; Marcus 2009; Owen 2009).

Study participants

All participants in the studies were individuals (children or young people) younger than 18 years of age (age range six to 17 years) (Findling 2014; Marcus 2009; Owen 2009). Although the search was not restricted to children/adolescents, results of the search yielded appropriate studies involving only children/adolescents. Every child/adolescent had been diagnosed with autistic disorder. Both boys and girls were included and the number of children/adolescents ranged from 85 (Findling 2014) to 218 (Marcus 2009).

Study interventions and dosage

The intervention used was aripiprazole in several doses, ranging from 2 mg to 15 mg per day. In the Findling 2014 study, during phase one - the stabilisation phase - aripiprazole was flexibly dosed between 2 mg and 15 mg per day. During phase two - the randomisation phase - children/adolescents randomised to aripiprazole continued at the dose prescribed at the end of phase one.

Study outcomes

Primary outcomes

Emotional and behavioural symptoms

All three studies used the Aberrant Behaviour Checklist (ABC) to assess five categories of emotional and behavioural symptoms of ASD, notably, irritability, hyperactivity, stereotypy, inappropriate speech and lethargy/withdrawal. The ABC, developed by Aman 1986, consists of 58 items, organised within five subscales: irritability, hyperactivity, stereotypy, inappropriate speech and withdrawal/lethargy. Each item is scored on a scale from zero (not a problem) to three (severe). In interpreting results of this scale, a decreased score correlates with an improvement in the category, and an increased score correlates with a decline in that category. For example, the highest possible number of points for the irritability subscale is 45 (15 items × three points) and would depict the most severe case.

Studies by Marcus 2009 and Owen 2009 used the illness severity and global improvement subscales of the Clinical Global Impression (CGI) scale (Guy 1976) to measure clinical improvement. Illness severity is rated from one through seven, with one indicating normal, four moderately ill and seven most severely ill. Thus, a decrease in score for CGI-S (severity) marks an improvement in disease state. Global improvement (illness change) is also rated from one through seven, with one meaning very much improved, four meaning no change and seven meaning very much worse. Thus, a decrease in score for CGI-C (change) also marks an improvement in disease state.

The Findling 2014 relapse prevention trial evaluated time from randomisation to relapse of behavioural symptoms. Relapse was defined in one of the following ways.

- Aberrant Behavior Checklist - irritability (ABC-I) score increase > 25% compared with end-of-phase one score, and Clinical Global Impressions - Improvement (CGI-I) rating of “much worse” or “very much worse” relative to the end of phase one, for two consecutive visits.
- ABC-I and CGI-I scores as per definition above at one visit, plus “lost-to-follow-up” at the next visit.
- ABC-I and CGI-I scores as per definition above at one visit, plus initiation of a prohibited drug to treat worsening symptoms of irritability associated with autistic disorder at the next visit.
- Child discontinued because of hospitalisation for worsening symptoms of irritability associated with autistic disorder or because of lack of efficacy based on the investigator's assessment.

Extrapyramidal side effects

All three studies used the Simpson Angus Scale (SAS) (Simpson 1970), the Abnormal Involuntary Movement Scale (AIMS) (Guy 1976) and the Barnes Akathisia Scale (BARS) (Barnes 1989) to measure extrapyramidal symptoms.

Secondary outcomes

Obsessive-compulsive behaviours

Both Marcus 2009 and Owen 2009 used the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (Scahill 1997) to assess obsessive-compulsive behaviours. The CY-BOCS is an adapted version of the Yale-Brown Obsessive Compulsive Scale (Goodman 1989). It requires two informants - child and parent - to rate 10 items on a scale of zero to four. In general, a score of zero on each item shows no symptoms, and a score of four shows extreme symptoms (Scahill 1997); the total maximum score is 40. Therefore, as a higher number corresponds with greater severity of illness, a decrease in mean score on this particular scale shows improvement in symptoms. Both trials looked at the MD in scores between aripiprazole and placebo on these outcome scales.

Findling 2014 did not provide data related to this outcome.

Weight gain and metabolic side effects

The three studies also reported data on weight gain. As weight gain is a common occurrence for patients taking antipsychotic medications, more than one way of looking at this outcome was presented. Absolute weight gain in kilograms (kg) was presented in all studies, in addition to change in body mass index (BMI). Clinically relevant weight gain was defined in studies as an increase in weight of 7% or more of baseline body weight.

Other side effects

All three studies measured cholesterol, triglycerides and blood sugar. Studies also measured other side effects, including sedation, drooling and tremor.

Excluded studies

Overall, we excluded 19 out of 22 studies.

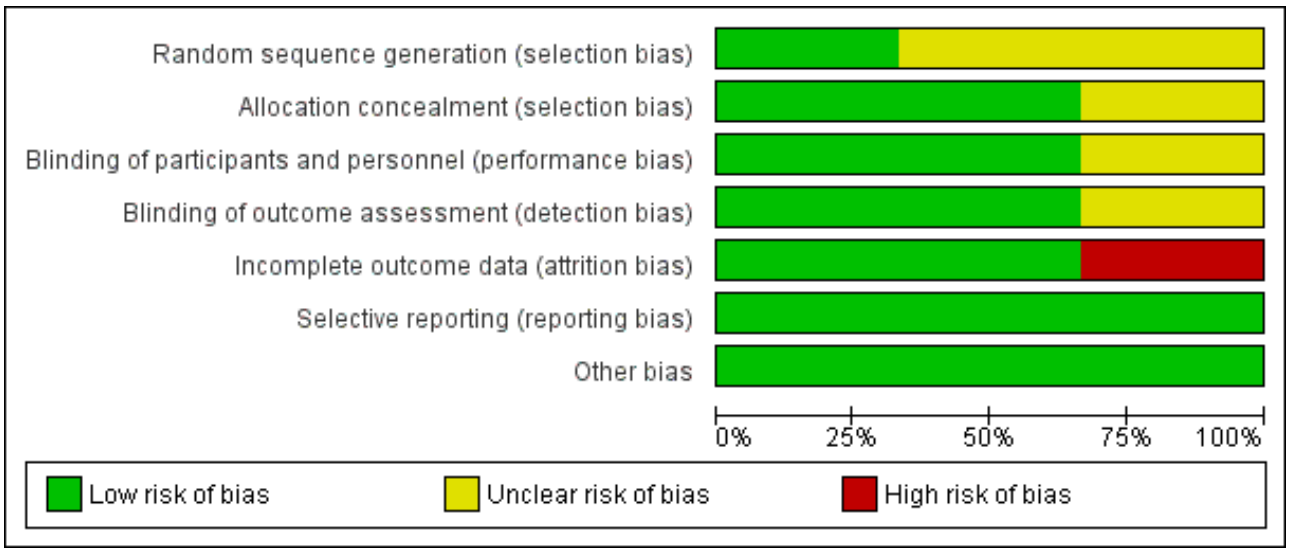
In the original review, we excluded 12 of 14 studies because they were review articles, pooled analyses, open-label retrospective studies or case series studies (Ching 2011).

In this updated review, we excluded seven of eight studies: two because they used unblinded, non-randomised, controlled study designs (D'Alessandro 2012, Maloney 2014), three because they were review articles or pooled analyses of the Marcus 2009 and Owen 2009 studies (Benton 2011; Douglas-Hall 2011; Robb 2011), one randomised trial because it did not include a placebo control (Ghanizadeh 2014) and one study because it provided quality of life data (Varni 2012) from the two original studies included in our review (Marcus 2009; Owen 2009); however, this was not an outcome of interest in our review. Two of these studies were also excluded from the previous version of this review (Benton 2011; Robb 2011).

Risk of bias in included studies

See Figure 2 and 'Risk of bias' tables beneath the Characteristics of included studies tables.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation

In Findling 2014, eligible children/adolescents were randomly assigned (1:1) to placebo or aripiprazole (continued at the dose prescribed), but the randomisation sequence generation was not described in the manuscript. In Marcus 2009, children/adolescents were randomised to receive placebo or aripiprazole (5, 10 or 15 mg/d) in a 1:1:1:1 ratio, but the randomisation sequence generation was not described in the manuscript. We emailed each of the study authors for clarification but received no response. Consequently, we rated both of these studies as having unclear risk of selection bias. In Owen 2009, eligible children/adolescents were randomly assigned (1:1) to flexibly dosed aripiprazole or placebo according to a computer-generated randomisation schedule prepared by Bristol-Myers Squibb, using a permuted block design. We rated this study as having low risk of bias.

Allocation concealment

In Findling 2014, investigational sites accessed a centralised, call-in system for randomisation. In Owen 2009, investigational sites accessed a call-in, interactive voice response system when children/adolescents were ready to be randomly assigned. This system assigned a medication bottle number to each child/adolescent. We rated both of these studies as having low risk of bias in this domain. However, in Marcus 2009, allocation concealment was not described; thus it is unclear whether knowledge of assignment was adequately prevented.

Blinding

Performance bias

In all studies, children/adolescents were reported to be blinded to intervention type. We rated both Findling 2014 and Owen 2009 as having low risk of bias. For Marcus 2009, a double-blind trial was described, but the study did not describe assurance of blinding, and so we rated this study as having unclear risk of bias.

Detection bias

In all studies, outcome assessors were reported to be blinded to intervention type. We rated both Findling 2014 and Owen 2009 as having low risk of bias. For Marcus 2009, a double-blind trial was described, but the study did not describe assurance of blinding, and so we rated this study as having unclear risk of bias.

Incomplete outcome data

All studies gave details of attrition. Intention-to-treat analyses were performed in all three studies. Below, we describe missing data and dropouts for each study included in the review.

In Findling 2014, 19 out of 44 children/adolescents completed the placebo arm of the trial. Twenty-five discontinued - 23 because of lack of efficacy. Out of 41 children/adolescents, 22 completed the aripiprazole arm of the trial. Nineteen discontinued, 13 because of lack of efficacy, five withdrew consent and one was lost to follow-up. We rated this study as having high risk of attrition bias. All study participants were included in the analysis of effect. If a participant dropped out of the study, investigators used the last observation carried forward (LOCF) method.

In Marcus 2009, 38 out of 52 children/adolescents completed the placebo arm of the trial. Fourteen discontinued for various reasons: lack of efficacy (n = 3), side effects (n = 4), withdrawal of consent (n = 2), loss to follow-up (n = 3), non-compliance (n = 1) and no longer meeting study criteria (n = 1). Out of 164, 140 children/adolescents completed the aripiprazole arm of the trial, whether 5 mg, 10 mg or 15 mg/d. In total, 26 discontinued for various reasons: side effects (n = 17), withdrawal of consent (n = 3), loss to follow-up (n = 2), non-compliance (n = 3) and other (n = 1). None discontinued because of lack of efficacy. The safety sample included all children/adolescents who took at least one dose of study medication, whereas the efficacy sample included all children/adolescents who had at least one post-randomisation efficacy evaluation performed and compared with baseline values. Study authors performed a LOCF analysis for any child who discontinued. Despite the slightly higher percentage of dropouts in the aripiprazole arm, we rated

this study as having low risk of attrition bias, as discontinuations due to side effects were generally higher in active treatment groups compared with placebo groups.

In Owen 2009, 36 out of 51 children/adolescents completed the placebo arm of the trial. Fifteen discontinued for various reasons: lack of efficacy (n = 6), side effects (n = 3), withdrawal of consent (n = 2) and loss to follow-up (n = 4). Thirty-nine out of 47 children/adolescents finished the aripiprazole arm of the trial. Eight discontinued for various reasons: lack of efficacy (n = 1), side effects (n = 5), withdrawal of consent (n = 1) and loss to follow-up (n = 1). The safety sample included all but one child who was lost to follow-up before entering the intervention phase. In the efficacy sample, two children were excluded (withdrawal of consent and side effects), as they did not complete a post-baseline efficacy evaluation. We rated this study as having low risk of attrition bias.

Selective reporting

All three studies pre-specified primary and secondary outcomes and reported expected measures of outcomes. Study protocols are available online at clinicaltrials.gov (NCT00332241, NCT00337571, NCT01227668); thus, we judged these studies to be at low risk of selective reporting bias.

Please see our protocol (Ching 2011) and Appendix 3 for additional methods that we would have used to assess small-study effects had we identified 10 or more studies.

Other potential sources of bias

Although all three studies received funding from pharmaceutical companies, we did not judge this to be a matter of concern and thus rated all three studies as having low risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison**

We were able to perform a meta-analysis of data from Marcus 2009 and Owen 2009, as no important clinical heterogeneity was found. Furthermore, because both trials used the same measures and reported changes in scores and endpoint data in the same way, we were able to perform meta-analyses for most of the outcomes listed below. The Findling 2014 trial had important differences in methods; therefore, we have described the results of this trial separately. For the study by Findling 2014, if a participant dropped out of the study, investigators used the LOCF method for their analysis.

We used both fixed-effect and random-effects models, which we then compared to assess statistical heterogeneity. Random-effects and fixed-effect models yielded nearly identical results in all analyses performed, with no difference greater than 0.1 point for any measure. Below, we present results from random-effects models.

Minimal clinically important differences are not listed, as they are difficult to define because they vary depending on who is making the judgement and how severe underlying symptoms are determined to be. Thus, when combined with variation in our estimates (95% CIs), these differences will not lead to an accurate interpretation of study results. Instead, we have given information about the rating scales used, including maximum number of points possible, so that clinicians can make their own judgement as to whether the amount of change seen is clinically important.

Primary outcomes

Emotional and behavioral symptoms

Irritability

All three studies (Findling 2014; Marcus 2009; Owen 2009) assessed irritability using the ABC - Irritability subscale (15 items yielding a maximum of 45 points) (Aman 1986).

A meta-analysis of two studies (Marcus 2009; Owen 2009) yielded an MD of -6.17 points (change from baseline) between aripiprazole and placebo, in favour of aripiprazole (95% CI -9.07 to -3.26, $tau^2 = 1.47$, $I^2 = 33\%$, P value < 0.00001, 308 children/adolescents, moderate-quality evidence; Analysis 1.1).

Findling 2014 found no differences in scores between children/adolescents treated with aripiprazole and those treated with placebo from the end of phase one to week 16 of phase two.

Hyperactivity

All three studies (Findling 2014; Marcus 2009; Owen 2009) assessed hyperactivity using the ABC - Hyperactivity subscale (16 items yielding a maximum of 48 points) (Aman 1986).

A meta-analysis of two studies (Marcus 2009; Owen 2009) yielded an MD of -7.93 points (change from baseline) between aripiprazole and placebo, in favour of aripiprazole (95% CI -10.98 to -4.88, $tau^2 = 2.27$, $I^2 = 44\%$, P value < 0.00001, 308 children/adolescents, moderate-quality evidence; Analysis 1.2).

Findling 2014 reported differences in scores between children/adolescents treated with aripiprazole and those treated with placebo (MD -5.2, 95% CI -10.2 to -0.2, P value = 0.041, 85 children/adolescents).

Stereotypy

All three studies (Findling 2014; Marcus 2009; Owen 2009) assessed stereotypy using the ABC - Stereotypy subscale (seven items yielding a maximum 21 points) (Aman 1986).

A meta-analysis of two studies (Marcus 2009; Owen 2009) yielded an MD of -2.66 points (change from baseline) between aripiprazole and placebo, in favour of aripiprazole (95% CI -3.55 to -1.77, $tau^2 = 0.00$, $I^2 = 0\%$, P value < 0.00001, 308 children/adolescents, moderate-quality evidence; Analysis 1.3).

Findling 2014 reported differences in scores between children/adolescents treated with aripiprazole and those treated with placebo (MD -2.0, 95% CI -3.70 to -0.40, P value = 0.018, 85 children/adolescents).

Inappropriate speech

All three studies (Findling 2014; Marcus 2009; Owen 2009) assessed inappropriate speech using the ABC - Inappropriate Speech subscale (four items yielding a maximum 12 points) (Aman 1986).

A meta-analysis of two studies yielded an MD of -1.43 points (change from baseline) between aripiprazole and placebo, in favour of aripiprazole (95% CI -2.60 to -0.27, $tau^2 = 0.51$, $I^2 = 71\%$, P value = 0.02, 308 children/adolescents; Analysis 1.4).

Findling 2014 reported differences in scores between children/adolescents treated with aripiprazole and those treated with placebo (MD -1.5, 95% CI -2.6, -0.3, P value = 0.013).

Lethargy/withdrawal

Marcus 2009 and Owen 2009 assessed lethargy/withdrawal using the lethargy/withdrawal subscale of the ABC (16 items yielding a maximum of 48 points) (Aman 1986). We combined these studies in a meta-analysis. Results yielded an MD of -1.19 points (change from baseline) between aripiprazole and placebo, in favour of aripiprazole (95% CI -2.77 to 0.40, $tau^2 = 0.00$, $I^2 = 0\%$, P value = 0.14, 308 children/adolescents; Analysis 1.5).

Aggression

No studies provided data on this outcome.

Clinical improvement

All three studies (Findling 2014; Marcus 2009; Owen 2009) assessed severity using the CGI-S subscale (Guy 1976). A meta-analysis of two studies (Marcus 2009; Owen 2009) found an MD of -0.57 point (mean change from baseline) between aripiprazole and placebo, in favour of aripiprazole (95% CI -0.96 to -0.18, $tau^2 = 0.05$, $I^2 = 63\%$, P value = 0.004, 308 children/adolescents; Analysis 1.6). Findling 2014 found no differences in scores between children treated with aripiprazole and those treated with placebo from the end of phase one to week 16 of phase two.

Two studies (Marcus 2009; Owen 2009) assessed clinical improvement using the CGI-I subscale (Guy 1976). A meta-analysis of these studies yielded an MD of -1.33 points between aripiprazole and placebo, which approximates a one-point change on the scale (of one to seven), in favour of aripiprazole (95% CI -1.75 to -0.92, $tau^2 = 0.00$, $I^2 = 0\%$, P value < 0.00001, 308 children/adolescents; Analysis 1.7).

Findling 2014 reported no differences between aripiprazole and placebo for the primary endpoint - time from randomisation to relapse (P value = 0.097). Kaplan-Meier relapse rates at week 16 were 35% for aripiprazole and 52% for placebo, for a hazard ratio (aripiprazole/placebo) of 0.57 (95% CI 0.28 to 1.12, low-quality evidence). A treatment-by-race interaction was explored and was found (P value = 0.034). Among white children/adolescents (n = 59), aripiprazole treatment resulted in a lower relapse rate (25.8%) than placebo (60.7%), with a hazard ratio of 0.33 (95% CI 0.14 to 0.78, P value = 0.011), whereas among non-white children/adolescents (n = 26), the two treatment arms did not differ. An age-interaction test found no evidence of an age interaction.

Extrapyramidal side effects

Extrapyramidal side effects are adverse, movement-related symptoms, which include drug-induced parkinsonism, dystonia, akathisia and tardive dyskinesia.

A meta-analysis of two studies (Marcus 2009; Owen 2009) found no difference in rates of extrapyramidal symptom events among children/adolescents treated with aripiprazole compared with placebo (RR 1.89, 95% CI 0.98 to 3.66, $tau^2 = 0.00$, $I^2 = 0\%$, P value = 0.06, 313 children/adolescents; Analysis 1.8). The result may not have reached statistical significance because the analysis lacked power with only two included studies. We were not able to perform a meta-analysis on extrapyramidal side effects, as neither study provided standard deviations, standard errors or CIs for data from SAS (Simpson 1970), AIMS (Guy 1976) and BARS (Barnes 1989). Owen 2009 did not find differences between intervention groups with respect to mean change from baseline on these three measures. Marcus 2009 reported no differences between placebo- and aripiprazole-treated children/adolescents in the mean change from baseline on BARS. On SAS, children/adolescents treated with a 10 mg dose of aripiprazole had significantly greater change from baseline (+ 0.7) compared with placebo-treated children/adolescents (-0.4) (P value = 0.006). Marcus 2009 also reported a significant change from baseline on the AIMS in all aripiprazole-treated children/adolescents compared with placebo-treated children/adolescents. Children/adolescents taking aripiprazole showed a decrease in scores (-0.1 to -0.2 points) compared with placebo-treated children/adolescents, who had an increase in score of 0.2 points (P value < 0.05).

Findling 2014, in phase one (the single-blind phase), reported that 27 children/adolescents (17.4%) had treatment-emergent extrapyramidal symptom-related side effects. Extrapyramidal symptom-related side effects occurred in 7.7% of children/adolescents treated with aripiprazole and in 7% of children/adolescents treated with placebo. Investigators reported no differences between groups on SAS, AIMS and BARS. Movement disorders were also common in phase two (5.1% for aripiprazole versus 0% for placebo).

Secondary outcomes

Obsessive-compulsive behaviours

Two studies (Marcus 2009; Owen 2009) used the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (Scahill 1997) to assess obsessive-compulsive behaviours in 308 children/adolescents. We combined these studies in a meta-analysis (Analysis 1.9). Results yielded an MD of -1.93 points (mean change from baseline) between aripiprazole and placebo, in favour of aripiprazole (95% CI -3.86 to 0.00, $tau^2 = 1.65$, $I^2 = 84\%$, P value = 0.05).

Weight gain and metabolic side effects

In a meta-analysis of two studies (Marcus 2009; Owen 2009), the RR of clinically relevant weight gain while taking aripiprazole was approximately 3.78 kg compared with placebo (95% CI 1.78 to 8.02, $tau^2 = 0.00$, $I^2 = 0\%$, P value = 0.0005, 308 children/adolescents; Analysis 1.10). The MD in weight gain between the aripiprazole group and the placebo group was 1.13 kg (95% CI 0.71 to 1.54, $tau^2 = 0.00$, $I^2 = 0\%$, P value < 0.00001, two studies, 308 children/adolescents, moderate-quality evidence; Analysis 1.11). We noted no difference between study groups as regards change in body mass index (BMI) (MD 0.44, 95% CI -0.27 to 1.16, $tau^2 = 0.00$, $I^2 = 0\%$, P value = 0.22, two studies, 313 children/adolescents; Analysis 1.12). Both Marcus 2009 and Owen 2009 (313 children/adolescents) reported no differences in rates of abnormal triglycerides between children/adolescents treated with placebo and those treated with aripiprazole (Analysis 1.13), nor in low-density lipoprotein (Analysis 1.14), high-density lipoprotein (Analysis 1.15) or blood sugar (Analysis 1.16).

Findling 2014 reported an increase of 25.2% in weight in phase one (all children/adolescents took aripiprazole during phase one). At week 16 of phase two, children/adolescents treated with aripiprazole gained a mean of 2.2 kg and placebo recipients gained

0.6 kg. Investigators reported no changes on metabolic laboratory tests (cholesterol, triglycerides and glucose) from baseline to week 16, during phase two, between children/adolescents treated with aripiprazole and those treated with placebo.

Other side effects

For the two studies included in the meta-analysis (Marcus 2009; Owen 2009), we chose clinically relevant effects of concern, such as sedation, drooling and tremor. Such side effects were common in the aripiprazole group. In comparison with the control group, the RR of experiencing sedation was 4.28 times more likely if taking aripiprazole (95% CI 1.58 to 11.60, tau^2 = 0.00, I^2 = 0%, P value = 0.004, two studies, 313 children/adolescents, moderate-quality evidence; Analysis 1.17). A person was 9.64 times more likely to experience drooling if taking aripiprazole (95% CI 1.29 to 72.10, tau^2 = 0.000, I^2 = 0%, P value = 0.03, two studies, 313 children/adolescents; Analysis 1.18) and was 10.26 times more likely to experience tremor (95% CI 1.37 to 76.63, tau^2 = 0.00, I^2 = 0%, P value = 0.02, two studies, 313 children/adolescents, moderate-quality evidence; Analysis 1.19) compared with placebo.

Findling 2014 reported that somnolence (14.8%) and vomiting (14.2%) were common side effects in phase one (all children/adolescents treated with aripiprazole during phase one), and in phase two, the most common side effects with aripiprazole were upper respiratory tract infection (10.3% for aripiprazole versus 2.3% for placebo) and constipation (5.1% for aripiprazole versus 0% for placebo).

DISCUSSION

Summary of main results

Both short-term studies showed that aripiprazole can improve some symptoms of autism spectrum disorders (ASD). From these results, we can suggest that aripiprazole appears effective for the short-term medication intervention of children/adolescents with ASD. Several significant results point towards efficacy of aripiprazole as a short-term medication intervention for children/adolescents with ASD. Most of the primary outcomes specified were significantly better with aripiprazole as compared with placebo intervention. These primary outcomes, as stated earlier in the Types of outcome measures section, include score changes on the Aberrant Behaviour Checklist (ABC) (Aman 1986) and Clinical Global Impression (CGI) scales (Guy 1976).

Meta-analysis of mean changes in scores on the ABC - Irritability subscale and the CGI - Improvement scale from both Marcus 2009 and Owen 2009 shows efficacy of aripiprazole in treating this behavioural symptom (see Analysis 1.1 and Analysis 1.7). Significant improvements also occurred in the hyperactivity and stereotypy subscales of the ABC. Changes on remaining ABC subscales pertaining to social withdrawal and inappropriate speech were not expected, as no evidence suggests that antipsychotic therapy is helpful in treating the core social and communication impairments of ASD. The magnitude of change on the ABC - Irritability subscale was 6.17 points with aripiprazole relative to placebo. With mean baseline scores in the study group ranging from 25 to 30 out of a total of 45 points on this scale, a six-point reduction in symptoms may be considered clinically meaningful by caregivers. Similarly, for the ABC - Hyperactivity subscale, the magnitude of change was 7.93 points with aripiprazole relative to placebo, with baseline scores in the study group on this subscale ranging from 30 to 35 out of a total of 48 points. This change in hyperactivity score may be clinically meaningful for caregivers. Changes in stereotypy scores were more modest, with a decrease of 2.66 points with aripiprazole relative to placebo. Stereotypy subscale baseline scores ranged from 10 to 12 among study groups at baseline, out of a total of 21 points.

Secondary outcomes included results from the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (Scahill 1997), metabolic side effects such as weight gain, extrapyramidal symptoms and other side effects such as sedation, drooling and tremor. We noted no improvement in obsessive-compulsive behaviours. Multiple children/adolescents in the aripiprazole group experienced side effects compared with those in the placebo group. Evidence was consistent for both an increase and a decrease in extrapyramidal symptoms. Risk of experiencing side effects of sedation, drooling and tremor was higher if treated with aripiprazole. Individuals treated with aripiprazole gained more weight relative to placebo, and clinically significant weight gain was more likely to occur if treated with aripiprazole than placebo.

The Findling 2014 relapse prevention trial found no difference between aripiprazole and placebo during maintenance treatment (P value = 0.097). However, evidence showed a treatment-by-race relationship (P value = 0.034), wherein white children/adolescents demonstrated lower relapse rates on aripiprazole than placebo, although no difference was noted between non-white children/adolescents. These results suggest that some children/adolescents may benefit from continued use of aripiprazole, and others may not. For secondary endpoints, the most clinically important effect observed was a deterioration in scores on the ABC - Hyperactivity subscale, among children/adolescents treated with placebo compared with aripiprazole. Greater weight gain and increased movement disorders were associated with continued aripiprazole. In combination with results from Marcus 2009 and Owen 2009, it is suggested that children/adolescents taking aripiprazole should be re-evaluated periodically to determine whether aripiprazole remains appropriate for treatment of ASD symptoms.

Overall completeness and applicability of evidence

Although the two short-term use studies are complete in their reporting, and provide highly applicable findings, world literature on the use of aripiprazole for ASD is small. Only one long-term use study has been conducted and is at high risk of bias due to attrition. Short-term use studies found clinically important moderate improvements in irritability and hyperactivity, and small improvements in stereotypies, with aripiprazole compared with placebo. This review aimed to determine the safety and efficacy of aripiprazole for any ASD, but data were available only on children/adolescents with a diagnosis of autistic disorder, and failed to include those with Asperger's syndrome or pervasive developmental disorders - not otherwise specified (PDD-NOS), or adults with ASD. Although classification of these disorders changed in 2013, studies included only those at the most severe end of the spectrum. Data from a 14-week open-label study of aripiprazole, which was not eligible for inclusion (Stigler 2009), provided information on participants with Asperger's syndrome and PDD-NOS and found similar trends of efficacy as the studies included in this review. Furthermore, all included studies were performed

in the United States and were sponsored by pharmaceutical companies.

No trials examined the specific link between medication and behavioural interventions. Trials that include behavioural interventions and the addition of medication for families in crisis, or with behavioural interventions that are not sufficient, would provide the most applicable evidence related to current guidelines for treatment of ASD.

One study, which did not meet our inclusion criteria for the review, provided information on comparative efficacy of aripiprazole. Ghanizadeh 2014 randomised 59 children/adolescents with ASD to risperidone or aripiprazole twice daily. Investigators assessed outcomes using the ABC (Aman 1986), the CGI - Improvement scale (Guy 1976) and systematic examination for extrapyramidal symptoms and other side effects. Both aripiprazole and risperidone decreased all ABC subscale scores significantly (P value < 0.05), but no significant difference between intervention groups was evident. Researchers also reported no difference between intervention groups on the CGI-I subscale scores at endpoint. Both interventions were well tolerated, and the most common side effects were increased appetite, drooling and drowsiness. One child from each intervention arm withdrew because of side effects. Therefore, this study found that aripiprazole and risperidone show similar efficacy and side effects for treatment of ASD symptoms in children/adolescents.

Another study that did not meet our inclusion criteria for the review provided information on the impact of aripiprazole on quality of life. In a post hoc analysis of data from Marcus 2009 and Owen 2009, Varni 2012 evaluated the effects of use of aripiprazole in children/adolescents with ASD on health-related quality of life (HRQoL). A total of 316 children/adolescents were randomised to aripiprazole or placebo and were evaluated at baseline and at eight weeks by means of three Pediatric Quality of Life Inventory (PedsQL) scales (Varni 1999). Aripiprazole was associated with greater improvement in the PedsQL combined scale total score (MD 7.8, 95% CI 3.8 to 11.8, P value < 0.001), and in all three PedsQL scales (emotional functioning: MD 7.8, 95% CI 3.4 to 12.2, P value < 0.05; social functioning: MD 6.2, 95% CI 0.7 to 11.8, P value < 0.05; and cognitive functioning: MD 9.3, 95% CI 3.8 to 14.9; P value < 0.05). These findings suggest that short-term treatment with aripiprazole is associated with increased HRQoL in children/adolescents with ASD.

Quality of the evidence

The quality of studies performed on the use of aripiprazole in ASD was moderate. We rated quality as moderate because of unclear risk of bias for some domains in Marcus 2009 and Owen 2009, and because of the overall small number of studies conducted on the use of aripiprazole in ASD. We rated quality of evidence for long-term trials as low because risk of attrition bias for incomplete outcome data was high in Findling 2014. Further research may have an important impact on our confidence in the estimate of effect and may change the estimate.

Potential biases in the review process

We have no other potential biases to report in the review process. Although we have synthesised all existing RCTs of aripiprazole for the treatment of behavioural symptoms in ASD, it must be recognised that available evidence is limited.

Agreements and disagreements with other studies or reviews

No other formal systematic reviews on use of aripiprazole for the treatment of ASD have been published to our knowledge. A pooled analysis of data on side effects from Marcus 2009 and Owen 2009 has been published (Robb 2011). Results and conclusions of our study with respect to side effects of aripiprazole are similar to those provided by Robb and colleagues.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence from this review shows that use of aripiprazole for the short-term treatment of irritability in children/adolescents with ASD may be worth considering. If the decision is made to use aripiprazole, clinicians should follow established best practice and provide information about side effects such as weight gain, tremor, drooling and sedation to children/adolescents and their families, so they can consider the benefits and risks of treatment before commencing a medication trial. Children/adolescents undergoing a trial of therapy with aripiprazole should be monitored for clinical effectiveness of the medication, as well as for side effects. In the absence of high-quality evidence, and given that similar relapse rates are observed for both aripiprazole and placebo, evidence suggests that the use of aripiprazole should be re-evaluated periodically for continued efficacy, and that it might be appropriate to consider discontinuation of aripiprazole after successful treatment for 12 weeks.

Implications for research

Additional trials should be conducted to investigate use of aripiprazole versus placebo for longer than three months. Only one trial compared aripiprazole head-to-head with another medication, risperidone. Future trials comparing aripiprazole versus other medications should be conducted to improve our understanding of the efficacy and safety of aripiprazole relative to other pharmacological interventions. Trials of these medications in older individuals with continuing symptoms should also be performed. Furthermore, trials that use behavioural interventions as a first-line approach and medication interventions as an adjunct should be performed. Future reviews should include health-related quality of life as an outcome measure.

ACKNOWLEDGEMENTS

The review authors wish to acknowledge the Departments of Clinical Neurosciences and Pediatrics, at the University of Calgary, and the Cochrane Developmental, Psychosocial and Learning Problems Group.

REFERENCES

References to studies included in this review

Findling 2014 *{published data only}*

Findling RL, Mankosi R, Timko K, Lears K, McCartney T, McQuade RD, et al. Randomized controlled trial investigating the safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric patients with irritability associated with autistic disorder. *Journal of Clinical Psychiatry* 2014;**75**(1):22-30. [PUBMED: 24502859]

Marcus 2009 *{published data only}*

Marcus RN, Owen R, Kame L, Manos G, McQuade RD, Carson WH, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 2009;**48**(11):1110-9. [PUBMED: 19797985]

Owen 2009 *{published data only}*

Owen R, Sikich L, Marcus RN, Corey-Lisle P, Manos G, McQuade RD, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics* 2009;**124**(6):1533-40. [PUBMED: 19948625]

References to studies excluded from this review

Aman 2010 *{published data only}*

Aman M, Kasper W. Line-item analysis of the Aberrant Behaviour Checklist: results from two studies of aripiprazole in the treatment of irritability associated with autistic disorder. *Journal of Child and Adolescent Psychopharmacology* 2010;**20**(5):415-22. [PUBMED: 20973712]

Benton 2011 *{published data only}*

Benton T. Aripiprazole to treat irritability associated with autism: a placebo-controlled, fixed-dose trial. *Current Psychiatry Reports* 2011;**13**(2):77-9. [DOI: 10.1007/s11920-010-0172-0]

Blankenship 2010 *{published data only}*

Blankenship K, Erickson C, Stigler KA, Posey DJ, McDougle CJ. Aripiprazole for irritability associated with autistic disorder in children and adolescents aged 6-17 years. *Pediatric Health* 2010;**4**(4):375-81.

D'Alessandro 2012 *{published data only}*

D'Alessandro TMM. Low-dose Abilify and the Treatment of Disruptive Behaviours in Children with Autism Spectrum Disorders [PhD thesis]. Florida: University of Florida, 2012.

Douglas-Hall 2011 *{published data only}*

Douglas-Hall P, Curran S, Bird V, Taylor D. Aripiprazole: a review of its use in the treatment of irritability associated with autistic disorder patients aged 6-17. *Journal of Central Nervous System Disease* 2011;**3**:143-53. [DOI: 10.4137/JCNSD.S4140]

Erickson 2010 *{published data only}*

Erickson C, Stigler K, Posey DJ, McDougle CJ. Aripiprazole in autism spectrum disorders and fragile X syndrome. *Neurotherapeutics* 2010;**7**(3):258-63. [DOI: 10.1016/j.nurt.2010.04.001]

Farmer 2011 *{published data only}*

Farmer CA, Aman MG. Aripiprazole for the treatment of irritability associated with autism. *Expert Opinion on Pharmacotherapy* 2011;**12**(4):635-40.

Ghanizadeh 2014 *{published data only}*

Ghanizadeh A, Sahraeizadeh A, Berk M. A head-to-head comparison of aripiprazole and risperidone for safety and treating autistic disorders, a randomized double blind clinical trial. *Child Psychiatry and Human Development* 2014;**45**(2):185-92. [PUBMED: 23801256]

Huang 2010 *{published data only}*

Huang SC, Tsai SJ, Yang HJ. Aripiprazole improves social interaction in Taiwanese children with pervasive developmental disorder. *Chang Gung Medical Journal* 2010;**33**(2):211-5.

Lewis 2009 *{published data only}*

Lewis D, Owen R. Efficacy and safety of aripiprazole for the treatment of irritability associated with autistic disorder in children and adolescents (6-17 years): results from two 8-week, randomized, double-blind, placebo controlled trials. *Neurology* 2009;**72**(11 Suppl 3):A428.

Maloney 2014 *{published data only}*

Maloney A, Mick EO, Frazier J. Aripiprazole decreases irritability in 12 out of 14 youth with autism spectrum disorder. *Journal of Child and Adolescent Psychopharmacology* 2014;**24**(6):357-9.

Masi 2009 *{published data only}*

Masi G, Cosenza A, Millepiedi S, Muratori F, Pari C, Salvadori F. Aripiprazole monotherapy in children and young adolescents with pervasive developmental disorders: a retrospective study. *CNS Drugs* 2009;**23**(6):511-21.

Narasimhan 2006 *{published data only}*

Narasimhan T, Bruce T, BallardJF, Patkar A, Masand P, Rech R. Poster session III: an open label trial of aripiprazole in the treatment of autism and its correlation to whole blood serotonin levels and serotonin transporter (5HTTPLR) function. Neuropsychopharmacology. Proceedings of the American College of Neuropsychopharmacology 45th Annual Meeting; 2006 December 3-7; Hollywood, Florida. 2006; Vol. 31 (Suppl 1s):S259-60.

Robb 2011 *{published data only}*

Robb A, Andersson C, Bellocchio EE, Manos G, Rojas-Fernandez C, Mathew S, et al. Safety and tolerability of aripiprazole in the treatment of irritability associated with autistic disorder in pediatric subjects (6-17 years): results from a pooled analysis of 2 studies. *Primary Care Companion for CNS Disorders* 2011;**13**(1):e1-9. [PUBMED: 21731831]

Stigler 2004 *{published data only}*

Stigler K, Posey D, McDougle CJ. Aripiprazole for maladaptive behaviour in pervasive developmental disorders. *Journal of*

Child and Adolescent Psychopharmacology 2004;**14**(3):455-63. [PUBMED: 15650503]

Stigler 2006 *{published data only}*

Stigler KA, Diener JT, Kohn AE, Erickson CA, Posey DJ. McDougle CJ. Poster session II: a prospective open-label study of aripiprazole in youth with Asperger's disorder and pervasive developmental disorder not otherwise specified. Neuropsychopharmacology. Proceedings of the American College of Neuropsychopharmacology 45th Annual Meeting; 2006 December 3-7; Hollywood, Florida. 2006; Vol. 31 (Suppl 1s):S194.

Varni 2012 *{published data only}*

Varni, JW, Handen, BL, Corey-Lisle P, Guo Z, Manos G, Ammerman DK, et al. Effect of aripiprazole 2 to 15 mg/d on health-related quality of life in the treatment of irritability associated with autistic disorder in children: a post hoc analysis of two randomized controlled trials. *Clinical Therapeutics* 2012;**34**(4):982-92. [PUBMED: 22444782]

Additional references

Aman 1986

Aman M, Singh N. Aberrant Behaviour Checklist: Manual. New York: Slosson Educational Publications, 1986.

Anderson 1989

Anderson LT, Campbell M, Adams P, Small AM, Perry R, Shell J. The effects of haloperidol on discrimination learning and behavioural symptoms in autistic children. *Journal of Autism and Developmental Disorders* 1989;**19**(2):227-39.

APA 2000

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th Edition. Washington, DC: American Psychiatric Association, 2000.

APA 2013

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th Edition. Arlington, VA: American Psyciatric Publishing, 2013.

Barnes 1989

Barnes TR. A rating scale for drug-induced akathisia. *British Journal of Psychiatry* 1989;**154**:672-6. [PUBMED: 2574607]

Baron-Cohen 2009

Baron-Cohen S, Scott FJ, Allison C, Williams J, Bolton P, Matthews FE, et al. Prevalence of autism spectrum conditions: UK school based population study. *British Journal of Psychiatry* 2009;**194**(6):500-9.

Bobo 2013

Bobo WV, Cooper WO, Stein CM, Olfson M, Graham D, Daugherty J, et al. Antipsychotics and the risk of type 2 diabetes mellitus in children and youth. *JAMA Psychiatry* 2013;**70**(10):1067-75. [PUBMED: 23965896]

Campbell 1982

Campbell M, Anderson LT, Small AM, Perry R, Green WH, Caplan R. The effects of haloperidol on learning and behaviour in autistic children. *Journal of Autism and Developmental Disorders* 1982;**12**(2):167-75. [PUBMED: 7174605]

Campbell 1997

Campbell M, Armenteros JL, Malone RP, Adams PB, Eisenberg ZW, Overall JE. Neuroleptic-related dyskinesias in autistic children: a prospective, longitudinal study. *Journal of the American Academy of Child and Adolescent Psychiatry* 1997;**36**(6):835-43. [PUBMED: 9183140]

CDC 2014

Centers for Disease Control and Prevention. Community Report from the Autism and Developmental Disabilities Monitoring (ADDM) Network: a snapshot of autism spectrum disorder among 8-year-old children in multiple communities across the United States in 2010. http://www.cdc.gov/ncbddd/autism/documents/community_report_autism.pdf (accessed 4 September 2015).

Correll 2009

Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA* 2009;**302**(16):1765-73. [PUBMED: 19861668]

Elbourne 2002

Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analysis involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140-9. [PUBMED: 11914310]

Elsabbagh 2012

Elsabbagh M, Divan G, Koh Y, Kim YS, Kauchali S, Marcin C, et al. Global prevalence of autism and other pervasive developmental disorders. *Autism Research* 2012;**5**(3):160-79. [PUBMED: 22495912]

FDA 2010

Food, Drug Administration. Label and approval history: ability. www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseraction=Search.Label_ApprovalHistory#apphist (accessed 28 February 2010).

Findling 2008

Findling RL, Robb A, Nyilas M, Forbes RA, Jin N, Ivanova S, et al. A multiple-center, randomized, double-blind, placebo-controlled study of oral aripiprazole for treatment of adolescents with schizophrenia. *American Journal of Psychiatry* 2008;**165**(11):1432-41. [PUBMED: 18765484]

Findling 2009

Findling RL, Nyilas M, Forbes RA, McQuade RD, Jin N, Iwamoto T, et al. Acute treatment of pediatric bipolar I disorder, manic or mixed episode, with aripiprazole: a randomized, double-blind, placebo-controlled study. *Journal of Clinical Psychiatry* 2009;**70**(10):1441-51. [PUBMED: 19906348]

Goodman 1989

Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Archives of General Psychiatry* 1989;**46**(11):1006-11. [PUBMED: 2684084]

Goodnick 2002

Goodnick PJ, Jerry JM. Aripiprazole: profile on efficacy and safety. *Expert Opinion on Pharmacotherapy* 2002;**3**(12):1773-81. [PUBMED: 12472374]

Guy 1976

Guy W. Early Clinical Drug Evaluation Unit (ECDEU) Assessment Manual for Psychopharmacology. National Institute Mental Health. Bethesda, MD: National Institute of Mental Health, 1976.

Guyatt 2011

Guyatt G, Oxman AD, Aki EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383-94.

Higgins 2011a

Higgins JPT, Altman DG, Sterne J on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Intervention Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org.

Higgins 2011b

Higgins JPT, Deeks JJ, Altman DG on behalf of the Cochrane Statistical Methods Group. Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org.

Higgins 2011c

Deeks JJ, Higgins JPT, Altman DG on behalf of the Cochrane Statistical Methods Group. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Jesner 2009

Jesner OS, Aref-Adib M, Coren E. Risperidone for autism spectrum disorder. *Cochrane Database of Systematic Reviews* 2007, Issue 1. [DOI: 10.1002/14651858.CD005040.pub2]

Kanner 1943

Kanner L. Autistic disturbances of affective contact. *Nervous Child* 1943;**2**:217-50.

Kogan 2009

Kogan MD, Blumberg SJ, Schieve LA, Boyle CA, Perrin JM, Ghandour RM, et al. Prevalence of parent-reported diagnosis of autism spectrum disorders among children in the US, 2007. *Pediatrics* 2009;**124**(5):1395-403.

Komossa 2009

Komossa K, Rummel-Kluge C, Schmid F, Hunger H, Schwarz S, El-Sayeh HGG, et al. Aripiprazole versus other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD006569.pub3]

Lecavalier 2006

Lecavalier L. Behavioral and emotional problems in young people with pervasive developmental disorders: relative prevalence, effects of subject characteristics, and empirical classification. *Journal of Autism and Developmental Disorders* 2006;**36**(8):1101-14. [PUBMED: 16897387]

Lord 1994

Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview - Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders* 1994;**24**(5):659-85.

Meyers 2007

Myers S, Johnson C, Council on Children with Disabilities. Management of children with autism spectrum disorders. *Pediatrics* 2007;**120**(5):1162-82.

Posey 2008

Posey DJ, Stigler SKA, Erickson CA, McDougle CJ. Antipsychotics in the treatment of autism. *Journal of Clinical Investigation* 2008;**118**(1):6-14.

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Scahill 1997

Scahill L, Riddle M, McSwiggin-Hardin M, Ort SI, King RA, Goodman WK, et al. Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity. *Journal of the American Academy of Child and Adolescent Psychiatry* 1997;**36**(6):844-52. [PUBMED: 9183141]

Shapiro 2003

Shapiro DA, Renock S, Arrington E, Chiodo LA, Liu LX, Sibley DR, et al. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. *Neuropsychopharmacology* 2003;**28**(8):1400-11. [PUBMED: 12784105]

Simonoff 2008

Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G. Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity and associated factors in a population derived sample. *Journal of the American Academy of Child and Adolescent Psychiatry* 2008;**47**(8):921-9. [PUBMED: 18645422]

Simpson 1970

Simpson GM, Agnus JWS. A ratings scale for extrapyramidal side effects. *Acta Psychiatrica Scandinavica* 1970;**45**(S212):11-9.

Stigler 2009

Stigler KA, Diener, JT, Kohn AE, Li L, Erickson CA, Posey DJ, et al. Aripiprazole in pervasive development disorder not otherwise specified and Asperger's disorder: a 14-week, prospective, open-label study. *Journal of Child and Adolescent Psychopharmacology* 2009;**19**(3):265-74. [PUBMED: 19519261]

Varni 1999

Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. *Medical Care* 1999;**37**(2):126-39. [PUBMED: 10024117]

Webster 1968

Webster DD. Critical analysis of the disability in Parkinson's disease. *Modern Treatment* 1968;**5**(2):279-81. [PUBMED: 5655944]

WHO 1994

World Health Organization. International Statistical Classification of Diseases and Related Health Problems, 10th Revision. Vol. **1-3**, Geneva: World Health Organization, 1994.

Williams 2006

Williams JG, Higgins JP, Brayne CE. Systematic review of prevalence studies of autism spectrum disorders. *Archives of Diseases in Childhood* 2006;**91**(1):8-15. [PUBMED: 15863467]

Yudofsky 1986

Yudofsky SC, Silver JM, Jackson W, Endicott J, Williams D. The Overt Aggression Scale for the objective rating of verbal and physical aggression. *American Journal of Psychiatry* 1986;**143**(1):35-9. [PUBMED: 3942284]

References to other published versions of this review

Ching 2011

Ching H, Pringsheim T. Aripiprazole for Autism Spectrum Disorders (ASD). *Cochrane Database of Systematic Reviews* 2011, Issue 3. [DOI: 10.1002/14651858.CD009043]

Ching 2012

Ching H, Pringsheim T. Aripiprazole for autism spectrum disorders (ASD). *Cochrane Database of Systematic Reviews* 2012, Issue 5. [DOI: 10.1002/14651858.CD009043.pub2]

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Findling 2014

Methods	**Phase 1:** single-blind, aripiprazole, flexibly dosed, to aripiprazole (2 to 15 mg/d) for 13 to 26 weeks. Chldren and adolescents with a stable response (> 25% decrease in ABC-I subscale score and rating of "much improved" or "very much improved" on CGI-I subscale score for 12 weeks randomised into phase 2) **Phase 2:** 1:1 randomisation to titrated dose of aripiprazole (2 to 15 mg/d) or placebo for 16 weeks in this double-blind, randomised, placebo-controlled, parallel-group study
Participants	**Sample size:** 85 children/adolescents entered phase 2 (double-blind randomisation), from 157 in phase 1 (single-blind stabilisation) **Particpants randomised in phase 2** **Sample size:** 85 (intervention 41, placebo 44) **Sex:** 17 girls (intervention 11, placebo 6), 68 boys (intervention 30, placebo 38) **Mean age:** overall 10.4 (SD 2.8); intervention 10.1 (SD 2.80); placebo 10.8 (SD 2.77) **Race:** 59 white (intervention 31, placebo 28), 19 black/African American (intervention 8, placebo 11), 3 Asian (0 intervention, 3 placebo), 1 American Indian/Alaskan Native (0 intervention, 1 placebo), 3 other (2 intervention, 1 placebo) **Inclusion criteria (both phases)** • Boys or girls • Aged 6 to 17 years inclusive with current DSM-IV-TR diagnosis of autistic disorder and displays behaviours such as tantrums, aggression, self injurious behavior or a combination of these problems. Diagnosis of autistic disorder will be confirmed by ADI-R

Findling 2014 *(Continued)*

- Children/adolescent or designated guardian/caregiver is able to comprehend and satisfactorily comply with protocol requirements, in the opinion of the investigator
- Demonstrates behaviours such as tantrums, aggression or self injury or a combination of these problems
- ABC-I subscale score ≥ 18 AND CGI-S subscale score ≥ 4 at screening and baseline visits
- Mental age ≥ 24 months

Inclusion criteria (phase 2)

- Patients whose symptoms of irritability demonstrated a stable response to aripiprazole therapy for 12 consecutive weeks in phase 1. Response was defined as ≥ 25% decrease from baseline in caregiver-rated ABC-I and rating of 1 or 2 (“very much improved” or “much improved”) on the clinician-rated CGI-I

Interventions	Aripiprazole 2, 5, 10 or 15 mg/d or placebo

Outcomes	**Primary outcome**
	• Percentage of children and adolescents relapsing by week 16, defined by 1 of 4 criteria:
	  * ABC-I score increase > 25% compared with end of phase 1 score and CGI-I rating of "much worse" or "very much worse" relative to end of phase 1 for 2 consecutive visits
	  * ABC-I and CGI-I scores as per above definition at 1 visit plus 'lost to follow-up' at next visit
	  * ABC-I and CGI-I scores as per above definition at 1 visit plus initiation of a prohibited drug to treat worsening symptoms of irritability associated with autistic disorder at the next visit
	  * Child or adolescent discontinued because of hospitalisation for worsening symptoms of irritability associated with autistic disorder or because of lack of efficacy based on investigator assessment
	Secondary outcomes
	• Adjusted mean change from baseline to week 16 on ABC-I subscale score (LOCF)
	• Change from baseline in mean CGI-I scale score at week 16
	• Number of children and adolescents with death as outcome, serious adverse events and adverse events leading to discontinuation during phase 1

Notes	**Study dates:** March 2011 to June 2012 **Study location:** United States **Funding:** Bristol-Myers Squibb **Conflicts of interest** • Dr. Findling receives or has received research support from, acted as a consultant to, received royalties from and/or served on a speaker’s bureau for Abbott, Addrenex, Alexza, American Psychiatric Press, AstraZeneca, Biovail, Bracket, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Forest, GlaxoSmithKline, Guilford Press, Johns Hopkins University Press, Johnson & Johnson, KemPharm, Lilly, Lundbeck, Merck, National Institutes of Health, Neuropharm, Novartis, Noven, Organon, Otsuka, Pfizer, Physicians Postgraduate Press, Rhodes Pharmaceuticals, Roche, Sage, Sanofi-Aventis, Schering-Plough, Seaside Therapeutics, Sepracore, Shionogi, Shire, Solvay, Stanley Medical Research Institute, Sunovion, Supernus, Transcept, Validus, WebMD and Wyeth • Dr. Mankoski was an employee of Bristol-Myers Squibb at the time the research was conducted and currently is a stock shareholder in Bristol-Myers Squibb • Dr. McQuade is an employee of Otsuka and holds stock in Bristol-Myers Squibb • Dr. Amatniek is an employee of and stock shareholder in Bristol- Myers Squibb and is a stock shareholder in Johnson & Johnson and Forest • Drs. Marcus, Sheehan and McCartney and Mr. Eudicone are employees of Bristol-Myers Squibb • Mss. Timko and Lears are employees of and stock shareholders in Bristol-Myers Squibb
Risk of bias	

Findling 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation was not described in the manuscript
Allocation concealment (selection bias)	Low risk	Randomisation was performed via a centralised call-in system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded aripiprazole or matching placebo was taken once daily
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded aripiprazole or matching placebo was taken once daily
Incomplete outcome data (attrition bias) All outcomes	High risk	Not all raw data were provided
Selective reporting (reporting bias)	Low risk	All outcomes in protocol were reported in the study
Other bias	Low risk	From the report, it does not appear that any other sources of bias are present

Marcus 2009

Methods	Randomised 1:1:1:1 to aripiprazole (5, 10 or 15 mg/d) or placebo in this 8-week double-blind, randomised, placebo-controlled, parallel-group study
Participants	**Sample size:** 218 children and adolescents (intervention 166 (54 = 15 mg, 59 = 10 mg, 53 = 5 mg), placebo 52) **Sex:** 23 girls (intervention 19 (4 = 15 mg, 9 = 10 mg, 6 = 5 mg), placebo 4), 195 boys (intervention 147 (50 = 15 mg, 50 = 10 mg, 47 = 5 mg), placebo 48) **Age:** 166 between 6 and 12 years of age (intervention 131 (42 = 15 mg, 45 = 10 mg, 44 = 5 mg), placebo 35), 52 between 13 and 17 years of age (intervention 35 (12 = 15 mg, 14 = 10 mg, 9 = 5 mg), placebo 17) **Race:** 155 white (intervention = 120 (42 = 15 mg, 41 = 10 mg, 37 = 5 mg), placebo = 35), 50 black (intervention = 37 (9 = 15 mg, 13 = 10 mg, 15 = 5 mg), placebo = 13), 46 Asian (intervention = 43 (0 = 15 mg, 42 = 10 mg, 1 = 5 mg), placebo = 3), 7 other (intervention = 6 (3 = 15 mg, 1 = 10 mg, 2 = 5 mg), placebo = 1) **Inclusion criteria** • Boys or girls • Aged 6 to 17 years inclusive at the time of randomisation • Meets current DSM-IV-TR diagnostic criteria for ASD and demonstrates serious behavioural problems; diagnosis confirmed by ADI-R • CGI scale score > 4 AND ABC-I subscale score > 18 at screening and baseline • Mental age ≥ 18 months
Interventions	Aripiprazole (5, 10 or 15 mg/day) versus placebo
Outcomes	**Primary outcome**

Marcus 2009 *(Continued)*

- Mean change (week 8 to baseline) in ABC-I subscale score

Secondary outcomes

- Mean CGI-I score
- Number of children and adolescents with response at week 8 (response defined as ≥ 25% reduction from baseline to endpoint in ABC-I subscale score and CGI-I score of 1 or 2 at endpoint)
- Mean change (week 8 to baseline) in CY-BOCS (compulsion scale only)
- Mean change (week 8 to baseline) in other ABC subscale scores
- Mean change (week 8 to baseline) in CGI-S
- Summary of safety, deaths, adverse events, serious adverse events, treatment-emergent adverse events and adverse events leading to discontinuation
- Change from baseline in body weight

Notes

Study dates: June 2006 to June 2008

Study location: United States

Funding: Bristol-Myers Squibb and Otsuka Pharmaceutical

Conflicts of interest

- Dr. Aman has received research support from and served as a consultant to Bristol-Myers Squibb, Johnson & Johnson and Forest
- Dr. Marcus is an employee of Bristol-Myers Squibb
- Dr. Owen is an employee of Bristol-Myers Squibb
- Dr. Kamen is an employee of Bristol- Myers Squibb
- Dr. Manos is an employee of Bristol-Myers Squibb
- Dr. McQuade is an employee of Otsuka Pharmaceutical Development and Commercializaion
- Dr. Carson is an employee of Otsuka Pharmaceutical Development and Commercializaion

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although a double-blind placebo-controlled trial was described, the study did not describe how randomisation occurred
Allocation concealment (selection bias)	Unclear risk	Although a double-blind placebo-controlled trial was described, the study did not describe the method of concealment of allocation of intervention type
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although a double-blind trial was described, the study did not describe assurance of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Although a double-blind trial was described, the study did not describe assurance of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Sufficient information was provided to address incomplete outcome data and how LOCF analysis of such data was performed. Excluded children and adolescents and reasons for exclusion were reported fully
Selective reporting (reporting bias)	Low risk	Study protocol is available; its pre-specified, primary outcomes have been reported online to reduce the likelihood of selective reporting
Other bias	Low risk	From the report, it seems clear that no other risks of bias are present

Owen 2009

Methods	Randomised 1:1 to flexibly dosed aripiprazole (target dose 5, 10 or 15 mg/d) or placebo in this 8-week, double-blind, randomised, placebo-controlled, parallel-group study
Participants	**Sample size:** 98 children/adolescents (intervention 47, placebo 51) **Sex:** 12 girls (intervention 7, placebo 5), 86 boys (intervention 40, placebo 46) **Age:** 83 between 6 and 12 years of age (intervention 46, placebo 37), 15 between 13 and 17 years of age (intervention 10, placebo 5) **Race:** 73 white (intervention 41, placebo 32), 18 black (intervention 11, placebo 7), 2 Asian (2 intervention, 0 placebo), 5 other (intervention 2, placebo 3) **Inclusion criteria** • Boys or girls • Aged 6 to 17 years inclusive at the time of randomisation • Meets current DSM-IV-TR diagnostic criteria for ASD and demonstrates serious behavioural problems; diagnosis confirmed by ADI-R. CGI score > 4 AND ABC-I subscale score > 18 at screening and baseline • Mental age ≥ 18 months
Interventions	Aripiprazole (5, 10 or 15 mg/d) versus placebo
Outcomes	**Primary outcome** • Mean change (week 8 to baseline) in ABC-I subscale score **Secondary outcomes** • Mean CGI-I score • Number of children/adolescents with response at week 8 (response defined as ≥ 25% reduction from baseline to endpoint in ABC-I subscale score and CGI-I score of 1 or 2 at endpoint) • Mean change (week 8 to baseline) in CY-BOCS (compulsion scale only) • Mean change (week 8 to baseline) in other ABC subscale scores • Mean change (week 8 to baseline) in CGI-S (CGI-S) • Summary of safety, deaths, adverse events, serious adverse events, treatment-emergent adverse events and adverse events leading to discontinuation • Change from baseline in body weight
Notes	**Study dates:** June 2006 to April 2008 **Study location:** United States **Funding:** Bristol-Myers Squibb and Otsuka Pharmaceutical **Conflicts of interest** • Dr. Sikich receives or has received research support from Bristol-Myers Squibb, Curemark, Neuropharm, Seaside Pharmaceuticals, Janssen, Lilly, Pfizer and Otsuka, and has also given continuing medical education lectures supported by Bristol-Myers Squibb • Drs. McQuade and Carson are employees of Otsuka Pharmaceutical Development and Commercialization, Inc • Dr. Findling receives or has received research support from or acted as a consultant and/or served on a speaker's bureau for Abbott, Addrenex, AstraZeneca, Bristol- Myers Squibb, Forest, GlaxoSmithKline, Johnson & Johnson, KemPharm, Lilly, Lundbeck, Neuropharm, Novartis, Organon, Otsuka, Pfizer, Sanofi-Aventis, Sepracore, Shire, Solvay, Supernus Pharmaceuticals, Validus and Wyeth • Drs. Owen, Corey-Lisle, Manos and Marcus are employees of Bristol-Myers Squibb

Owen 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation schedule using permuted block design was used for randomisation
Allocation concealment (selection bias)	Low risk	A call-in interactive voice response system was readily available for participating intervention sites when children and adolescents were ready to be randomly assigned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Medication bottle numbers were assigned to children and adolescents, thus reducing the risk that blinding could have been broken
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators and caregivers were blinded to the intervention; dosage increases were made incrementally
Incomplete outcome data (attrition bias) All outcomes	Low risk	Sufficient information was provided to address incomplete outcome data and the way LOCF analysis of such data was performed. Excluded children and adolescents and reasons for exclusion were reported fully. 3 randomised children were excluded from the analysis - 1 child randomised to placebo was lost to follow-up before entering the double-blind intervention phase, 1 child randomised to placebo withdrew consent and 1 child randomised to aripiprazole discontinued on day 2 of the study before completing a post-baseline efficacy evaluation. We do not think exclusion of these 3 children would alter study results, even if extreme results were obtained in all 3 cases
Selective reporting (reporting bias)	Low risk	Study protocol is available; its pre-specified primary outcomes have been reported online to reduce the likelihood of selective reporting
Other bias	Low risk	From the report, it seems clear that no other risks of bias are present

ABC: Aberrant Behavior Checklist.
ABC-I: Aberrant Behavior Checklist - Irritability.
ADI-R: Autism Diagnostic Interview - Revised.
ASD: autism spectrum disorders.
BMI: body mass index.
CGI: Clinical Global Impressions scale.
CGI-I: Clinical Global Impressions - Improvement scale.
CGI-S: Clinical Global Impressions - Severity scale.
CY-BOCS: Children's Yale-Brown Obsessive Compulsive Scale.
DSM-IV-TR: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*
LOCF: last observation carried forward.
SD: standard deviation.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aman 2010	Post hoc analysis of pooled results of Marcus 2009 and Owen 2009
Benton 2011	Review article

Study	Reason for exclusion
Blankenship 2010	Review article
D'Alessandro 2012	Non-randomised controlled trial
Douglas-Hall 2011	Review article
Erickson 2010	Review article
Farmer 2011	Review article
Ghanizadeh 2014	No placebo control group
Huang 2010	Case series
Lewis 2009	Pooled analysis of results of Marcus 2009 and Owen 2009
Maloney 2014	Non-randomised controlled trial
Masi 2009	Retrospective naturalistic study
Narasimhan 2006	Open-label study
Robb 2011	Pooled analysis of results of Marcus 2009 and Owen 2009
Stigler 2004	Open-label study
Stigler 2006	Open-label study
Varni 2012	Post hoc HRQoL analysis of results of Marcus 2009 and Owen 2009

HRQoL: health-related quality of life.

WHAT'S NEW

Date	Event	Description
15 May 2015	New citation required but conclusions have not changed	We found a new study that evaluates risk of relapse after discontinuation of aripiprazole once symptoms have improved during treatment
20 November 2014	New search has been performed	We updated the review following a new search in November 2014 and a top-up search in October 2015

CONTRIBUTIONS OF AUTHORS

For the original Cochrane review, Heidi Ching drafted the protocol, selected trials for inclusion, extracted data from trials, entered data into RevMan, drafted the final review and carried out the analysis. For this version only, Lauren Hirsch selected trials for inclusion, extracted data from trials, entered data into RevMan and drafted and edited the final review. For both the original Cochrane review (Ching 2012) and this version, Tamara Pringsheim edited the protocol, selected trials for inclusion, extracted data from trials, interpreted the analysis and drafted the final review. Tamara has overall responsibility for the review and will keep the review up-to-date.

DECLARATIONS OF INTEREST

Lauren Hirsch has no conflicts of interest to declare.

Tamara Pringsheim (TP) has received direct financial gain from:

- Teva Canada Innovation, on one occasion in 2014, for consulting. TP declares that Teva does not make or market any products relevant to this review.

TP has received indirect financial gain from:

- Shire Canada, in 2015. TP received an unrestricted educational grant to create an educational curriculum on assessment and treatment of aggression in youth. TP declares that Shire does not make or market any products relevant to this review.

TP declares that the entities listed below are funding agencies that do not make treatments for ASD or any other disease.

- Canadian Institutes of Health Research, for research funding to create a patient decision aid in 2014 and 2015.
- Alberta Mental Health Strategic Clinical Network, for research funding on off-label prescribing of antipsychotics in 2015.
- Mathison Centre for Mental Health Research and Education, for research funding for the Canadian Schizophrenia Guidelines in 2015.

SOURCES OF SUPPORT

Internal sources

- University of Calgary, Department of Clinical Neurosciences, Canada.

  Salary support for Dr. Pringsheim

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We choose not to exclude participants receiving non-pharmacological therapy (i.e. behaviour therapy), provided it was equally accessible to all study participants, stable before trial entry and consistent throughout the study. This was not specified in the protocol (Ching 2011) and therefore reflects a post hoc decision.
- We have specified in the Types of outcome measures section that we use the term 'side effects' to describe any harms, adverse effects or adverse drug reactions associated with aripiprazole.
- We added Conference Proceedings Citation Index - Science and WorldCat to the electronic sources listed in our protocol (Ching 2011) to increase the chance of finding conference papers and theses. We also added Autism Data to search the holdings of the National Autistic Society Information Centre Library. For this update, we also searched the Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts of Reviews of Effects (DARE) to check the reference lists of previous reviews related to our topic.
- In the Assessment of risk of bias in included studies, we reported separately methods for assessing the risk of performance bias due to inadequate blinding of participants and personnel, and methods for assessing the risk of detection bias due to inadequate blinding of outcome assessment.
- We analysed time-to-event data using hazard ratios and their associated 95% CIs. This type of data analysis was not listed in the protocol (Ching 2011) and therefore reflects a post hoc decision.
- We reported tau^2 - an estimate of between-study variance - when reporting results from the random-effects model. This was not specified in the protocol (Ching 2011) and therefore reflects a post hoc decision.
- We added a section on 'Summary of findings', beneath the section on 'Data synthesis'.

INDEX TERMS

Medical Subject Headings (MeSH)

Antipsychotic Agents [*therapeutic use]; Aripiprazole [*therapeutic use]; Child Development Disorders, Pervasive [*drug therapy]; Hyperkinesis [drug therapy]; Irritable Mood [drug effects]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Child; Female; Humans; Male