Atypical antipsychotics for disruptive behaviour disorders in children and youths (Review)

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[Intervention Review]

Atypical antipsychotics for disruptive behaviour disorders in children and youths

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ABSTRACT

Background

Disruptive behaviour disorders include conduct disorder, oppositional defiant disorder and disruptive behaviour not otherwise specified. Attention deficit hyperactivity disorder (ADHD) is frequently associated with disruptive behaviour disorders. The difficulties associated with disruptive behaviour disorders are demonstrated through aggression and severe behavioural problems. These often result in presentation to psychiatric services and may be treated with medications such as atypical antipsychotics. There is increasing evidence of a significant rise in the use of atypical antipsychotics for treating disruptive behaviour disorders in child and adolescent populations.

Objectives

To evaluate the effect and safety of atypical antipsychotics, compared to placebo, for treating disruptive behaviour disorders in children and youths.

Search methods

We searched the following databases in August 2011: CENTRAL (2011, Issue 3), MEDLINE (1948 to August Week 1), EMBASE (1980 to 2011 Week 32), PsycINFO (1806 to August Week 2 2011), CINAHL (1937 to current), ClinicalTrials.gov (searched 15 August 2011), Australian New Zealand Clinical Trials Registry (ANZCTR) (searched 15 August 2011), CenterWatch (searched 15 August 2011) and ICTRP (searched 15 August 2011).

Selection criteria

We included randomised controlled trials with children and youths up to and including the age of 18, in any setting, with a diagnosis of a disruptive behaviour disorder. We included trials where participants had a comorbid diagnosis of attention deficit hyperactivity disorder, major depression or an anxiety disorder.

Data collection and analysis

Two review authors independently selected the studies and disagreements were resolved by discussion. Two review authors extracted data independently. One review author entered data into Review Manager software and another checked it. We contacted trial authors for information about adverse effects and to provide missing data.

Main results

We included eight randomised controlled trials, spanning 2000 to 2008. Seven assessed risperidone and one assessed quetiapine. Three of the studies were multicentre. Seven trials assessed acute efficacy and one assessed time to symptom recurrence over a six-month maintenance period.

We performed meta-analyses for the primary outcomes of aggression, conduct problems and weight changes but these were limited by the available data as different trials reported either mean change scores (average difference) or final/post-intervention raw scores and used different outcome measures. We also evaluated each individual trial's treatment effect size where possible, using Hedges' *g*.

For aggression, we conducted two meta-analyses. The first included three trials (combined *n* = 238) using mean difference (MD) on the Aberrant Behaviour Checklist (ABC) Irritability subscale. Results yielded a final mean score with treatment that was 6.49 points lower than the post-intervention mean score with placebo (95% confidence interval (CI) -8.79 to -4.19). The second meta-analysis on aggression included two trials (combined *n* = 57) that employed two different outcome measures (Overt Aggression Scale (modified) (OAS-M) and OAS, respectively) and thus we used a standardised mean difference. Results yielded an effect estimate of -0.18 (95% CI -0.70 to 0.34), which was statistically non-significant.

We also performed two meta-analyses for conduct problems. The first included two trials (combined *n* = 225), both of which employed the Nisonger Child Behaviour Rating Form - Conduct Problem subscale (NCBRF-CP). The results yielded a final mean score with treatment that was 8.61 points lower than that with placebo (95% CI -11.49 to -5.74). The second meta-analysis on conduct problems included two trials (combined *n* = 36), which used the Conners' Parent Rating Scale - Conduct Problem subscale (CPRS-CP). Results yielded a mean score with treatment of 12.67 lower than with placebo (95% CI -37.45 to 12.11), which was a statistically non-significant result.

With respect to the side effect of weight gain, a meta-analysis of two studies (combined *n* = 138) showed that participants on risperidone gained on average 2.37 kilograms more than those in the placebo group over the treatment period (MD 2.37; 95% CI 0.26 to 4.49).

For individual trials, there was a range of effect sizes (ranging from small to large) for risperidone reducing aggression and conduct problems. The precision of the estimate of the effect size varied between trials.

Authors' conclusions

There is some limited evidence of efficacy of risperidone reducing aggression and conduct problems in children aged 5 to 18 with disruptive behaviour disorders in the short term.

For aggression, the difference in scores of 6.49 points on the ABC Irritability subscale (range 0 to 45) may be clinically significant. For conduct problems, the difference in scores of 8.61 points on the NCBRF-CP (range 0 to 48) is likely to be clinically significant.

Caution is required due to the limitations of the evidence and the small number of relevant high-quality studies. The findings from the one study assessing impact in the longer term suggest that the effects are maintained to some extent (small effect size) for up to six months. Inadequately powered studies produced non-significant results. The evidence is restricted by heterogeneity of the population (including below average and borderline IQ), and methodological issues in some studies, such as use of enriched designs and risk of selection bias. No study addressed the issue of pre-existing/concurrent psychosocial interventions, and comorbid stimulant medication and its dosage was only partially addressed. There is currently no evidence to support the use of quetiapine for disruptive behaviour disorders in children and adolescents.

It is uncertain to what degree the efficacy found in clinical trials will translate into real life clinical practice. Participants in the studies were recruited from clinical services but those who agree to take part in the clinical trials are a subset of the overall population presenting for care. There are no research data for children under five years of age. Further high-quality research is required with large samples of clinically representative youths and long-term follow-up to replicate current findings.

PLAIN LANGUAGE SUMMARY

Atypical antipsychotic drugs for disruptive behaviour disorders in children and youths

Children and young people with disruptive behaviour disorders often present with aggression and severe behaviour problems. These can result in families seeking psychiatric services, where a number of medications, including atypical antipsychotics, may be used to reduce these symptoms. There is evidence that the use of atypical antipsychotics for disruptive behaviour disorders in youths is on the

increase. We searched for clinical studies of atypical antipsychotics used for disruptive behaviour disorders in children and young people to evaluate whether these medications are effective and safe. We found eight studies. Seven of these studies investigated the efficacy of risperidone and one study used quetiapine. The analysis suggested that risperidone led to a reduction of aggression and conduct problems to some extent after six weeks of treatment and that the medication appeared safe during the study period. Use of medication, however, was associated with significant weight gain. The findings need to be considered with caution because of the limitations of the evidence. For example, the studies measured and reported different outcome measures, which limited our ability to combine the findings, and there were no studies with children under the age of five years. We recommend that more research is carried out in this field to find out the long-term efficacy and safety of these medications in treating disruptive behaviour disorders in children and youths.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Atypical antipsychotics for disruptive behaviour disorders						
Population: children and adolescents with disruptive behaviour disorders Setting: inpatient and outpatient Intervention: atypical antipsychotics						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Atypical antipsychotics				
Aggression Aberrant Behaviour Checklist Irritability subscale Follow-up: 4 to 6 weeks	The mean aggression score ranged across control groups from -4.4 to 0.1 ¹	The mean aggression score in the intervention groups was 6.49 points lower than in the control groups (8.79 to 4.19 lower)		238 (3 studies)	⊕⊕⊕○ low ²	
Aggression Overt Aggression Scale Modified and Overt Aggression Scale Follow-up: 6 weeks	The mean aggression score ranged across control groups from 8.1 to 49.4 ⁴	The mean aggression score in the intervention groups was 0.18 standard deviations lower (0.7 lower to 0.34 higher)		57 (2 studies)	⊕⊕○○ low ^{3,5}	SMD -0.18 (-0.7 to 0.34)
Weight gain Follow-up: 6 to 10 weeks	The mean weight gain ranged across control groups from 2.2 to 4.2 kg	The mean weight gain in the intervention groups was 2.37 kg higher (0.26 to 4.49 higher)		138 (2 studies)	⊕⊕⊕○ low ⁶	

Conduct problems Nisonger Child Rating Form - Conduct Problem subscale Follow-up: 6 weeks	The mean conduct problems score ranged across control groups from 15.2 to 17.6 ¹	The mean conduct problems score in the intervention groups was 8.61 points lower (11.49 to 5.74 lower)	225 (2 studies)	low ⁷
Conduct problems Conners' Parent Rating Scale - Conduct Problem subscale Follow-up: 6 to 10 weeks	The mean conduct problems score ranged across control groups from 11.3 to 28 ¹	The mean conduct problems score in the intervention groups was 12.67 points lower (37.45 lower to 12.11 higher)	36 (2 studies)	low ^{3,8}

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval

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.

¹ Expressed as mean change scores.

² 1-week placebo run-in used in two studies potentially inflating the therapeutic effect; unclear risk of bias due to lack of information on selection bias and detection bias in 2 studies. Unclear risk of bias due to lack information and poor reporting standards in one study

³ Non-significant result of the meta-analysis, imprecise CI including the null value. One study was a pilot of quetiapine while the other study was a small trial of risperidone.

⁴ Expressed as final values.

⁵ Small sample size, low power to detect significant differences, high attrition rate. One study was a pilot trial of quetiapine while the second study was a trial of risperidone in an inpatient setting.

⁶ One study had 1-week placebo run-in potentially inflating therapeutic effect; one study with small sample size, low power and high attrition rate.

⁷ 1-week placebo run-in used in both studies potentially inflating the therapeutic effect; unclear risk of bias due to lack of information on selection bias and detection bias in both studies.

⁸ Small sample sizes and low power to detect statistically significant differences; high attrition rate in both studies.

BACKGROUND

Description of the condition

Disruptive behaviour disorders form a group of psychological problems that include conduct disorder, oppositional defiant disorder and disruptive behaviour disorder not otherwise specified (Findling 2008). Subclinical presentations of ODD or conduct disorder are diagnosed as disruptive behaviour disorder not otherwise specified. Disruptive behaviour disorders are frequently comorbid with attention deficit hyperactivity disorder (ADHD) (Findling 2008).

According to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition revised (DSM IV-TR), conduct disorder is defined as a repetitive and persistent pattern of behaviour that violates the basic rights of others or violates major age appropriate societal rules or norms (American Psychiatric Association 2000). In the preceding 12 months at least three of the following criteria must be present, with at least one criterion present in the last six months: aggression towards people or animals, destruction of property, deceitfulness or theft, or serious violation of rules. The behaviour disturbances must also cause clinically significant impairment in social, academic or occupational functioning. Conduct disorder can be classed as mild, moderate and severe (American Psychiatric Association 2000). It is also categorised into childhood onset and adolescent onset subgroups (American Psychiatric Association 2000). The early onset group is believed to have a poorer prognosis with a more persistent course and more pervasive disturbances (Steiner 1997).

Oppositional defiant disorder (ODD) (American Psychiatric Association 2000) is diagnosed when a child has a minimum of four of the following behaviours for at least six months: often loses temper, often argues with adults, often actively defies or refuses to comply with adults' requests or rules, often deliberately annoys people, often blames others for his or her mistakes or misbehaviour, is often touchy and easily annoyed by others, is often angry and resentful and is often spiteful and vindictive. ODD is conceptualised as a potential precursor of conduct disorder if no interventions occur.

Reported community prevalence rates of ODD range from 2% (Loeber 1998) to 16% (Cohen 1993), depending on the criteria and assessment methods used, the time period considered and the number of informants. Prevalence of conduct disorder in the general population is estimated to be between 1.5% and 4% of children and adolescents using clinical interviewing as a method of detection (Steiner 1997). The ratio of boys to girls is between 5:1 and 3.2:1 depending on the age range (Steiner 1997).

Comorbidity

ODD or conduct disorder may be comorbid in more than 50% of ADHD cases (Barkley 2006; Connor 2010). From psychology

literature, there is evidence that children with comorbid attention-deficit/hyperactivity, oppositional defiant disorder and conduct disorder experience multiple childhood and psychosocial risk factors that begin during infancy (Shaw 2001). According to Steiner 2007, 14% of child patients have comorbid anxiety disorders and 9% have comorbid depressive disorder. Greene 2002 reported comorbidity of disruptive behaviour disorders with paediatric bipolar affective disorder of up to 40% to 50% (Greene 2002). However, there is a lack of clarity in the diagnosis of paediatric bipolar affective disorder and controversy in the literature, especially with emotionally dysregulated children and youths (Parens 2010).

Impact

A significant proportion of children (about 30%) with early onset of ODD go on to develop conduct disorder (Waschbusch 2002). ODD significantly predicts compromised psychiatric, family and social functioning independently of the presence of conduct disorder (Biederman 1996; Greene 2002). In Biederman's study of ODD in boys, ODD was found to be associated with major depression in the interval between the four-year and 10-year follow-up (Biederman 2008).

Conduct disorder leads to multiple negative outcomes in adulthood (Moffitt 2002). From the Christchurch longitudinal study, Fergusson and Horwood (Fergusson 1998) demonstrated that children scoring in the top 5% for conduct problems at age eight were at 4.8 times higher risk of leaving school without qualifications than children in the least disturbed 50%, and their rates of unemployment at age 18 were 2.9 times higher. This study also indicated that conduct problems at age seven to nine were statistically significantly associated with a wide range of adverse psychosocial outcomes in adulthood including crime, substance dependence, mental health problems and relationship difficulties, even after controlling for confounding factors (Fergusson 2004). Clinically, a significant proportion of children and youths with severe disruptive behaviour disorders may not be seen in psychiatric clinics, but are seen and dealt with by general practitioners, pediatricians, schools, welfare agencies, police and/or courts.

Psychosocial treatments

For young children up to early adolescence, there are a variety of parent training programmes (Kazdin 1997; Weisz 2004; Kaminski 2008). The programmes that do best are those that increase positive parent-child interactions and emotional communication skills, teach parents to use time out and the importance of consistency, and those that require parents to practise new skills with their children (Kaminski 2008).

For youths, the main focus of interventions for conduct disorder is at the family or systemic level. They include functional family therapy and multi-systemic therapy (Scott 2008). Functional family therapy is a treatment combining a family approach with cognitive and behavioural modification to improve family communication

patterns and support functions (Scott 2008). A Cochrane review of functional family therapy is currently underway (Littell 2007). Multisystemic therapy (MST) is a family-based treatment involving multiple systems (family, school, community). There were previous reports of effectiveness in some studies (Karnik 2007). However, a Cochrane review has reported that there is inconclusive evidence of the effectiveness of MST compared with other interventions in youths (Littell 2005).

Pharmacological treatments

The difficulties associated with disruptive behaviour disorders include problematic aggression and severe behavioural problems. These often result in presentation to psychiatric services, where a number of medications are used for disruptive behaviours, including off-label use of some medications designed for other disorders, for example stimulant medications, mood stabilisers and antipsychotics (Tcheremissine 2006). None of these were originally developed for the treatment of disruptive behaviours.

Stimulant medications for the treatment of ADHD have been widely studied. There is convincing evidence that when ADHD co-occurs with disruptive behaviour disorders and is treated with stimulant medications, improvements can be observed in disruptive behaviour disorder and aggression (Pappadopulos 2006; Ipser 2007).

The mood stabiliser lithium has been studied in inpatient settings for young people with conduct disorders. The evidence about its efficacy showed significant variability (Pappadopulos 2006; Ipser 2007). Two studies did not meet the inclusion criteria used in the systematic review by Pappadopulos 2006. One was a study of 20 youths with explosive temper and mood lability, in which sodium valproate was superior to placebo in reducing aggressive symptoms (Donovon 2000). Another was a seven-week cross-over RCT of 71 youths with CD, in which participants receiving higher doses (500-1500mg/day) of sodium valproate experienced greater global improvement scores and self-reported impulse control than those randomized to low doses (250 mg/day) (Steiner 2003). Only one RCT of 22 inpatient youths with CD indicated that carbamazepine was no different than placebo in reducing aggression and explosiveness (Cueva 1996). Preliminary studies of alpha-2 agonists (clonidine, guanfacine) suggest some effect on aggressive behaviour in patients with diagnoses of autism and ADHD with comorbid tics (Pappadopulos 2006).

Antipsychotic agents are used to control disruptive behaviour in clinical practice, particularly when aggression is a core feature. In the 1980s typical antipsychotics were studied (Findling 2008). However, interest has since shifted to atypical antipsychotics (Findling 2008). Of the atypical antipsychotics, risperidone is the most widely studied in the disruptive behaviour disorder population (Pappadopulos 2006). Currently, aripiprazole, olanzapine, quetiapine and risperidone have FDA-approved paediatric indications for bipolar mania (age 10 to 17 years except for olanzapine, 13 to 17 years) and for schizophrenia (age 13 to 17

years) (FDA 2009; Correll 2010). In addition, aripiprazole and risperidone are also indicated for irritability and aggression associated with autistic disorder (age 6 to 17 years) (Correll 2010; Ching 2012). Any usage for disruptive behaviour disorder is considered off-label except in Europe (European Medicines Agency 2011) and the individual clinician is medico-legally responsible for the usage.

Description of the intervention

This review focuses on atypical antipsychotics because of the clinical interest and usage in disruptive behaviour disorders (Doey 2007; Harrison-Woolrych 2007). The atypical antipsychotics include risperidone, olanzapine, quetiapine, aripiprazole, amisulpiride, sertindole, ziprasidone, zotepine, clozapine, paliperidone, asenapine and iloperidone.

How the intervention might work

A potential focus of the use of atypical antipsychotics is to target aggression in disruptive behaviour disorders (Findling 2008). Reviewing the neurotransmitters of aggression, Swann 2003 postulates that the increased risk of impulsive behaviour may be associated with elevated dopaminergic or noradrenergic function. Results of animal studies suggest that trait impulsivity may result from an imbalance between dopamine and serotonin, where animals with serotonin depletions are impulsive due to release of a dopaminergic activation systems from serotonin depletion (Harrison 1997). Atypical antipsychotics block dopamine and serotonin receptor systems and some investigators have proposed that their anti-aggressive action comes from this effect (Schur 2003). However, the pharmacological mechanism of action through which atypical antipsychotics may inhibit aggression is not yet fully established and further research is needed (Schur 2003).

Why it is important to do this review

There are several studies showing increasing, widespread use of atypical antipsychotics amongst children and youths. In Canada, Doey 2007 conducted a survey of atypical antipsychotic use among 349 child and adolescent psychiatrists and 97 developmental paediatricians, with an overall return rate of 46.3%. In all, 59.4% respondents reported prescribing this class of medication for conduct disorder and 51.2% for oppositional defiant disorder. In Brisbane, Australia, Dean 2006 carried out a retrospective review of 122 inpatient and 126 outpatient charts. The most common indication for atypical antipsychotic usage, especially risperidone, was aggression or behavioural/conduct disturbances unrelated to diagnoses. This occurred in 23% of inpatients and 3.2% of outpatients. Harrison-Woolrych 2007 conducted a nationwide prospec-

tive cohort study in New Zealand looking at atypical antipsychotic usage in children. The cohort included 420 children aged two to 15 years. Ninety-four per cent of the drug exposure was to risperidone. The most common diagnoses were disruptive behaviour disorders. The symptoms most frequently targeted were aggression and difficult behaviour. In the United Kingdom, from a cross-sectional study looking at children and youths up to 18 years of age registered on the General Practice Research Database (GPRD), [Rani 2008](#) found that the prescription of all antipsychotic drugs increased between 1993 to 2005 (from 0.39 to 0.77 users per 1000 patient years; $P < 0.01$). This was driven by the increase in atypical antipsychotic medications between 1994 and 2005. Conduct and behavioural disorders were the most common diagnoses in the under 12 years age bracket while affective disorders were most common in 13- to 18-year olds. The caution here is that the GPRD does not directly associate diagnoses with drug prescription. In the USA, [Olson 2010](#) carried out a trend analysis in antipsychotic treatment of privately insured children aged two to five years. They compared two time points: 1999 to 2001 ($n = 400,196$) and 2007 ($n = 755,793$). The annualised rate of any antipsychotic use per 1000 children increased from 0.78 to 1.59, with the adjusted rate ratio of 1.76. In the 2007 sample, the common clinical diagnoses were pervasive developmental disorder or mental retardation (28.2%), attention deficit hyperactivity disorder (23.7%) and disruptive behaviour disorder (12.9%). Of concern was that only 40.8% had a mental health assessment during the year.

These studies show a significant increase in the use of atypical antipsychotics in vulnerable child and adolescent populations. However, as Greenhill points out, there is a lack of a corresponding increase in the clinical research evaluating efficacy or safety in this population ([Greenhill 2003](#)). This review seeks to address this important gap.

OBJECTIVES

To evaluate the effect and safety of atypical antipsychotics compared to placebo in disruptive behaviour disorders in children and youths. The aim was to evaluate each drug separately rather than the class effect, on the grounds that this is clinically more useful.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled double-blind trials.

Types of participants

Children and adolescents up to and including the age of 18, in any setting, with a diagnosis of a disruptive behaviour disorder including oppositional defiant disorder, conduct disorder and disruptive behaviour disorder not otherwise specified (NOS).

We included studies in which participants had comorbid diagnoses of attention deficit hyperactivity disorder, major depression or anxiety disorders.

We excluded studies in which participants had a comorbid diagnosis of pervasive developmental disorder/autistic spectrum disorder, a comorbid psychotic disorder or bipolar affective disorder. This was to exclude those conditions in which antipsychotic agents may be treating symptoms other than disruptive behaviour as in those cases clinical improvement may be related to improvement in the underlying psychopathology.

Types of interventions

Any atypical antipsychotic, whether the mode of delivery was oral or intramuscular, compared with placebo.

Types of outcome measures

Primary outcomes

1. Aggression: reduction in aggressive behaviour, measured through changes in scores of validated rating scales.
2. Conduct problems: reduction in conduct problems or disruptive behaviour problems, measured through reduction in relevant validated rating scales or subscales.
3. Adverse events: weight gain (absolute weight gain or changes in body mass index (BMI)) and metabolic parameters (specifically glucose and lipid profiles).

The hierarchy of preferred time points was: i) six-week time point for initial efficacy and ii) six-month time point after six months maintenance treatment for long-term efficacy ([Jensen 2007](#)).

Validated rating scales indicated that scales accurately assessed what they were designed to assess, were reliable and had normative data if possible ([Myers 2002](#)). [Collett 2003](#), [Jensen 2007](#) and [Steiner 2007](#) had listed scales that were suitable and outlined the psychometric properties for the majority of them:

- *Scales for aggression (observer rated)*: Children's Aggression Scale - Parent's version (CAS-P), Children's Aggression Scale - Teacher's version (CAS-T), Overt Aggression Scale (OAS), Modified Overt Aggression scale (MOAS), Overt Aggression Scale Modified, Proactive and Reactive Aggression Scale (PRA), Revised Teacher Rating Scale for Reactive and Proactive Aggression (R-TRPA), Vitiello Aggression Questionnaire (VAQ), Children's Social Behaviour Scale (CSBS), General Behavior Inventory (Parent Version) (P-GBI) and Life History of Aggression (LHA).

- *Scale for aggression (self report)*: Buss-Durkee Hostility Inventory (BDHI), Aberrant Behaviour checklist - irritability subscale, Child Behaviour Checklist - aggression subscale, Barratt Aggressive Acts Questionnaire (AAQ), Spielberger Anger and Expression of Anger Inventory (STAXI), Anger Irritability and Aggression Questionnaire (AAIQ), Buss-Perry Aggression Questionnaire (B-PAQ), Aggression Questionnaire (AQ).

- *Scales for disruptive behaviour disorders or conduct disorder*: Nisonger Child Behaviour Rating Scale - conduct problem subscale, Connor Parent and Teacher Rating scale revised, SNAP IV - subscale, Vanderbilt Teacher and Parents - subscale, Achenbach Child Behavior Checklist (CBCL), Eyberg Child Behaviour Inventory (ECBI), New York Teacher Rating Scale for Disruptive and Antisocial Behaviour (NYTRS), Home and School Questionnaire (HSQ/SSQ), Antisocial Process Screening Device (APSD), Sutter-Eyberg Student Behavior Inventory Revised (SESBI-R), Youth Self Report (YSR), Conners/Wells' Adolescent Self Report of Symptoms (CASS) - conduct problem and anger control problem subscales, Parent Daily report (PDA), Interview for Antisocial Behaviour (IAB).

Steiner 2007 ranked some of the above scales in three categories:

- *Excellent psychometric properties*: cohesion, convergent, discriminant and predictive validity had all been tested in representative samples.
- *Good psychometric properties*: as above but studies had one or two criteria missing.
- *Adequate psychometric properties*: more than two of the criteria listed above were not met but the scale *was* conceptually interesting or particularly suitable for clinical practice.

Where there were several rating scales for a particular outcome, we selected the one with known better psychometric properties. We explored whether or not the population assessed in the trial was different from that used in the validation studies for the measures used whenever possible.

Secondary outcomes

1. General functioning, measured by the Children's Global Assessment Scale (CGAS).
2. Non-compliance, measured as the proportion of participants discontinuing treatment.
3. Adverse events, measured as the incidence of overall adverse events and breakdown by types of adverse events, taking into consideration frequency, severity and clinical importance, and including extrapyramidal side effects measured by standardised side effect scales, sedation and hyperprolactinaemia.
4. Social functioning.
5. Family functioning.
6. Parent satisfaction.
7. Functioning at school.

The outcomes deemed important for inclusion in the 'Summary of findings' table included aggression, conduct problems, adverse

events (specifically weight gain and metabolic parameters) and general functioning.

Search methods for identification of studies

We ran database searches in June 2010 and updated them in August 2011. We first searched trials registers in August 2010 and updated these in August 2011. We used no date or language limits.

Electronic searches

We searched the following databases.

- CENTRAL, 2011 (Issue 3), last searched 15 August 2011
- MEDLINE, 1948 to August Week 1 2011, last searched 15 August 2011
- EMBASE, 1980 to 2011 Week 2, last searched 15 August 2011
- PsycINFO, 1806 to August Week 2 2011, last searched 15 August 2011
- CINAHL, 1937 to current, last searched 15 August 2011
- ClinicalTrials.gov, last searched 15 August 2011
- CenterWatch, last searched 15 August 2011
- Australian New Zealand Clinical Trials Registry (ANZCTR), last searched 15 August 2011
- ICTRP, last searched 15 August 2011
- metaRegister of Controlled Trials, last searched 17 August 2010. mRCT was experiencing downtime at the time of the updated search so was not searched in August 2011
- National Research Register Archive, last searched 17 August 2010 and not updated in 2011 because the archive is closed
- UK Clinical Research Network (UKCRN), last searched 15 August 2011

Searching other resources

We examined reference lists of included studies and other review articles to identify relevant studies. We contacted authors of the identified randomised controlled trials to request further information. We also contacted pharmaceutical companies to request information about any published/unpublished trials using atypical antipsychotics for disruptive behaviour disorders in children and youths.

Data collection and analysis

Selection of studies

Two review authors (JL and KS) independently examined the titles and abstracts of all studies obtained through the search strategy. The same two authors obtained and independently assessed the full articles of relevant articles appearing to meet the inclusion

criteria. Any conflicts of opinion were discussed and arbitrated by another review author (SM) until consensus was reached.

Data extraction and management

The two authors (JH and KS) carried out data extraction independently. Any disagreements were discussed with review author SM.

We extracted the following data:

(1) Study methods

- a) Randomisation method/sequence generation.
- b) Method of allocation concealment.
- c) Blinding method (for those giving the treatment, participants, outcome assessors).
- d) Stratification factors (if relevant).

(2) Participants

- a) Inclusion/exclusion criteria.
- b) Number (total/per group).
- c) Age distribution.
- d) Gender.
- e) Ethnicity.
- f) Comorbidity.
- g) Setting.

(3) Intervention

- a) Type of medication.
- b) Dosage.
- c) Length of prescription.
- d) Mode of delivery.

(4) Outcome data

- a) Reduction of aggression; scale used.
- b) Reduction of conduct problems; scale used.
- c) Social functioning; scale used.
- d) General functioning; scale used.
- e) Family functioning; measurement method.
- f) Parent satisfaction; measurement method.
- g) School functioning; measurement method.
- h) Duration of follow-up.
- i) Loss to follow-up and any reasons given by investigators for same.
- j) Non-compliance: proportion of participants discontinuing treatment.

(5) Analysis data

- a) Methods of analysis (intention-to-treat/per-protocol analysis).
- b) Comparability of groups at baseline (yes/no).
- c) Any other statistical techniques used by the investigators.

(6) Safety data

- a) Adverse events (overall incidence).
- b) Weight gain; lipid and glucose profile if available.
- c) Breakdown by type of adverse events, taking into consideration frequency, severity and clinical importance.

JL and KS individually entered data into Review Manager 5 software ([RevMan 2008](#)). We compared extracted data to ensure accuracy. We resolved any discrepancies by consensus.

Assessment of risk of bias in included studies

For each included study, two review authors (JH and KS) independently assessed risk of bias using the six domains set out below from the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2009](#)), with ratings of 'low risk', 'high risk' and 'unclear risk'.

1. Sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessors.
5. Incomplete outcome data.
6. Selective outcome reporting.

We did not exclude studies from meta-analysis on the basis of the 'Risk of bias' assessment. In future updates, we would consider conducting a sensitivity analysis for the primary outcome excluding trials with 'no' or 'unclear' ratings for allocation concealment if appropriate. We reported the remainder of the risk of bias assessments for the trials and include discussion of the assessment in the Results and Discussion sections.

Measures of treatment effect

For continuous outcomes, where studies used the same outcome measure for comparisons, we pooled data by calculating the mean difference (MD). Where different measures were used to assess the same outcome, we considered whether to pool data by calculating the standardised mean difference (SMD), with 95% confidence intervals (CI).

Unit of analysis issues

For cross-over trials, we planned to do paired analysis if data were presented. Otherwise, we planned to take all measurements from intervention periods and all measurements from control periods and analyse these as if the trial was a parallel-group trial, acknowledging that there might be unit of analysis errors that could underestimate the precision of the estimate of the treatment effect ([Higgins 2011](#)). However, no cross-over trials were identified.

There were no cluster-randomised controlled trials so we did not have to take this into account in our analyses.

Dealing with missing data

1. Missing statistics

In the first instance, we made attempts to contact the original researchers for any missing data. If only standard error (SE) or P values were reported, we calculated standard deviations (SD) and have documented this in the review.

2. Missing participants

For continuous data, if available, we used intention-to-treat data with a note of the methods used by authors for imputing missing data, such as last observation carried forward.

Our intention for dichotomous data was to analyse data on the intention-to-treat principle with drop-outs included in the analysis. We intended to calculate the best and worst-case scenarios for the clinical response outcome if possible. For example, the best-case scenario assumed that drop-outs in the intervention group had positive outcomes and those in the control group had negative outcomes. In the worst-case scenario, drop-outs in the intervention group had negative outcomes and those in the control group had positive outcomes.

Assessment of heterogeneity

We assessed clinical heterogeneity by comparing the differences in the distribution of important participant factors between trials (for example, age, gender, specific diagnosis, duration and severity of disorder, associated comorbidities). We assessed methodological heterogeneity by comparing trial factors (randomisation, concealment, blinding of outcome assessment, losses to follow-up). We assessed statistical heterogeneity by performing the χ^2 test of heterogeneity, where a significance level of less than 0.10 was interpreted as evidence of heterogeneity, and by using the I^2 statistic, which calculated the percentage of variability due to heterogeneity rather than sampling error. The *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) recommended using a range for I^2 and a guide to interpretation. For this review, if either moderate heterogeneity (I^2 in the range of 30% to 60%) or substantial heterogeneity (I^2 in the range of 50% to 90%) was found, we planned to examine it using specified subgroup and sensitivity analyses. We planned sensitivity analyses regardless of heterogeneity to assess the robustness of results to methods used. We planned to give careful thought to the clinical importance of the observed degree of inconsistency across studies, its potential impact on the conclusions of the meta-analysis and the appropriateness of carrying out a meta-analysis. In the event, there were too few studies in any of the analyses for us to carry out any subgroup or sensitivity analyses.

Assessment of reporting biases

In order to assess outcome reporting bias, we compared between what the authors said they would report and what they actually reported for the main clinical outcomes. We assessed whether authors provided actual data for each outcome or just reported statistical significance without actual data, as missing data could indicate reporting bias.

Data synthesis

We performed meta-analysis only where studies were considered to have sufficiently similar participants, interventions, comparators and outcome measures. We used a random-effects model.

According to the Cochrane handbook, where different outcomes measures are used the standardised mean difference (SMD) should be used to pool results and where the outcome measure is the same the mean difference (MD) should be used. The statistical advice we had was that while we can pool outcomes based on different measures using the SMD, this can only be done using final scores and not on mean change scores. This is because using the SMD makes the assumption that there is an equal correlation between the baseline and final scores in each trial/for each measure and information is seldom provided to confirm this. If some studies have a small correlation between baseline and final scores and others have a large correlation then pooling these makes the result meaningless. This is also the reason that change and final scores cannot be combined using SDM. We therefore undertook separate meta-analyses of those studies reporting outcomes as change scores and those reporting them as final scores.

Subgroup analysis and investigation of heterogeneity

There was inadequate information to perform subgroup analyses.

Sensitivity analysis

Sensitivity analyses to assess the impact of study risk of bias on the results of meta-analysis were inappropriate, as there were a limited number of studies.

Any methods stipulated in the protocol but not used in this version of the review were summarised in additional Table 1.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

Results of the search

We found 2556 citations using the search strategy run in June 2010, of which there were 106 abstracts of potential interest. After retrieving the articles and excluding duplications, 19 were relevant for further assessment of which eight were included and 11 were excluded. We re-executed the searches in August 2011 to cover the period from June 2010 and an additional 436 citations were found. None of them qualified for this review. See [Figure 1](#).

Figure 1. Study flow diagram

Included studies

Location of studies

Three trials (Aman 2002; Snyder 2002; Reyes 2006) were multi-centre and included data from several countries (Belgium, Canada, Germany, Great Britain, Israel, Netherlands, Poland, South Africa, Spain and United States). The other trials were conducted in the United States of America (Findling 2000; Armenteros 2007; Connor 2008), Belgium (Van Bellinghen 2001) and the Netherlands (Buitelaar 2001).

Study designs

The eight included studies were all randomised controlled trials. They spanned the period 2000 to 2008. Seven assessed risperidone (Findling 2000; Buitelaar 2001; Van Bellinghen 2001; Aman 2002; Snyder 2002; Reyes 2006; Armenteros 2007) and one assessed quetiapine (Connor 2008).

Sample sizes ranged from 13 to 335. In five of the trials, the total number of participants was 25 or fewer (Findling 2000; Buitelaar 2001; Van Bellinghen 2001; Armenteros 2007; Connor 2008), four of which were pilot trials (Findling 2000; Van Bellinghen 2001; Armenteros 2007; Connor 2008). Two trials (Aman 2002; Snyder 2002) had 115 and 110 participants respectively and one had 335 participants (Reyes 2006).

All trials used inactive placebo as control.

One trial (Reyes 2006) was a three-stage trial that included a six-week open-label phase, followed by a six-week single-blind phase of risperidone and then a six-month maintenance double-blind RCT. It is important to note that randomisation occurred not at the acute phase but only after participants responded to active treatment. The objective of the study was to evaluate long-term maintenance treatment. Participants were excluded from the trial once they had symptom recurrence.

The remainder of the studies were between four weeks and 10 weeks in duration, with follow-up from four weeks in two trials (Van Bellinghen 2001; Armenteros 2007) to six weeks in four trials (Buitelaar 2001; Aman 2002; Snyder 2002; Connor 2008) and 10 weeks in another (Findling 2000).

Three trials (Aman 2002; Snyder 2002; Connor 2008) used a one-week placebo run-in or 'single-blind placebo phase' (Connor 2008), after which placebo responders were excluded from further participation in the trial.

Participants

Participants were between 5 and 18 years of age. In seven of the trials, there were significantly more males than females (Findling

2000; Buitelaar 2001; Aman 2002; Snyder 2002; Reyes 2006; Armenteros 2007; Connor 2008). Six trials included outpatients while Van Bellinghen 2001 included children from residential care and Buitelaar 2001 included inpatients.

Six studies included a significant number of participants with sub-average to borderline IQ (IQ 36 to IQ 84) (not Armenteros 2007 or Connor 2008).

Studies varied in their inclusion criteria for participants. Aman 2002, Snyder 2002 and Reyes 2006 included participants with DSM IV criteria for conduct disorder (CD), oppositional defiant disorder (ODD) and disruptive behaviour disorder not otherwise specified (DBDNOS) and included participants with comorbid ADHD. Buitelaar 2001 included participants with DSM IV criteria for CD, ODD and ADHD. Findling 2000 and Connor 2008 included participants with CD only. Armenteros 2007 specifically looked at participants with DSM IV criteria for ADHD and a specific aggression criterion as it was an ADHD augmentation trial, while Van Bellinghen 2001 included participants with symptoms of "persistent behavioural disturbances including hostility, aggression, irritability, agitation and hyperactivity" rather than DSM IV diagnoses.

Thus, five trials included ADHD comorbidity, and in one of these (Armenteros 2007) ADHD was the main diagnosis. In Van Bellinghen 2001, ADHD comorbidity was not stated other than one participant in placebo group was on Ritalin which was discontinued during the trial. In Findling 2000 there was no information on ADHD comorbidity. Doses of concomitant stimulant medications were not mentioned in any of the primary trials.

Interventions

For risperidone, the mean doses at endpoint ranged from 0.98 mg/day to 1.5 mg/day. For quetiapine (one study only), the mean dose at endpoint was 294 ± 78 mg/day, with a range of 200 to 600 mg/day (Connor 2008). All trials used the oral method of administration, four of them using risperidone solution (Van Bellinghen 2001; Aman 2002; Snyder 2002; Reyes 2006). The duration of intervention was four weeks in two trials (Van Bellinghen 2001; Armenteros 2007); six weeks in four trials (Buitelaar 2001; Aman 2002; Snyder 2002; Connor 2008) and 10 weeks in one trial (Findling 2000). There was one trial (Reyes 2006) with a markedly different design. In this trial, after two six-week phases (open-label followed by single-blind risperidone treatment), all responders were randomised to six months maintenance of risperidone or placebo. The primary efficacy measure was time to symptom recurrence.

In one trial (Buitelaar 2001), it was specified that participants had to have failed psychosocial treatment (contingency management and social skills training) before starting medication. Aman

2002 permitted behavioural therapy started 30 days before the trial. [Armenteros 2007](#) and [Connor 2008](#) allowed “pre-existing or current psychosocial interventions”. There was no information in the rest of the trials as to how many participants actually had concomitant psychosocial treatments and further details of those treatments.

Outcomes

Primary outcomes

1. Aggression (endpoints fall between 4 to 10 weeks)

Aggression was assessed in the trials using the following rating scales:

- Aberrant Behaviour Checklist (ABC) - Irritability subscale ([Aman 1985a](#); [Aman 1985b](#))
- Child Behaviour Checklist (CBCL) - Aggression subscale ([Achenbach 1991](#))
- Overt Aggression Scale (OAS) ([Yudofsky 1986](#))
- Overt Aggression Scale - Modified (OAS-M) ([Kay 1988](#))
- Rating of aggression against people and/or property scale (RAAP) ([Kemph 1993](#))
- Children's Aggression Scale - Parent (CAS-P) and Teacher (CAS-T) ([Halperin 2002](#); [Halperin 2003](#))

[Aman 2002](#), [Snyder 2002](#) and [Van Bellinghen 2001](#) used the ABC - Irritability subscale. [Buitelaar 2001](#) used OAS-M and [Connor 2008](#) used OAS. [Findling 2000](#) used both CBCL - Aggression subscale and RAAP. [Armenteros 2007](#) used CAS-P and CAS-T. For [Reyes 2006](#), aggression was not a specific outcome.

2. Conduct problems (endpoints fall between six weeks to six months)

Conduct problems were assessed using the following rating scales:

- Nisonger Child Behaviour Rating Form - Conduct Problem subscale (NCBRF-CP) ([Aman 1996](#); [Tasse 1996](#))
- Conners' Parent Rating Scale - Conduct Problem subscale (CPRS-CP) ([Conners 1989](#))

[Findling 2000](#), [Aman 2002](#), [Snyder 2002](#) and [Reyes 2006](#) used NCBRF-CP. [Connor 2008](#) used CPRS-CP. [Van Bellinghen 2001](#), [Buitelaar 2001](#) and [Armenteros 2007](#) did not measure conduct problems.

Details of the standardised scales used to assess aggression and conduct problems are presented in additional [Table 2](#) and additional [Table 3](#).

3. Adverse events: weight gain in kilograms; metabolic parameters (lipid and glucose profile)

All trials assessed weight gain in kilograms. [Findling 2000](#), [Aman 2002](#) and [Reyes 2006](#) had presented mean weight gain and standard deviations.

Metabolic parameters were not available in the trials except for [Reyes 2006](#).

Secondary outcomes

1. General functioning, measured by the Children's Global Assessment Scale (CGAS)

Only one trial ([Reyes 2006](#)) used the Children's Global Assessment Scale (CGAS).

2. Non-compliance

Data on non-compliance and attrition rate were available from all the trials.

3. Other adverse events

Data on other adverse events were available from all the trials.

4. Social functioning

One trial ([Van Bellinghen 2001](#)) used Personal Assessment Checklist (PAC), part of which rated social relationships.

5. Family functioning

No trial set out to examine this as an outcome.

6. Parent satisfaction

No trial set out to examine this as an outcome.

7. Functioning at school

No trial set out to examine this as an outcome.

Excluded studies

For full details see [Characteristics of excluded studies](#).

Eleven studies were excluded from this review as they did not meet all our inclusion criteria. [Tyrer 2008](#) was a randomised controlled trial of risperidone, haloperidol and placebo in the treatment of aggressive challenging behaviour in adults with intellectual disability. Three studies were on olanzapine. One was a clinical case series of six aggressive youths ([Soderstrom 2002](#)); one was a retrospective chart review of olanzapine treatment in adolescents with

conduct disorder (Masi 2006), and one was an open-label prospective trial of olanzapine in youths with disruptive behaviour disorder and below average intelligence (Handen 2006). One study was an open-label trial of quetiapine in aggressive children with conduct disorder (Findling 2006). There was one open-label study of risperidone in inpatient children and youths with psychiatric disorders associated with aggressive behaviour (Buitelaar 2000). There were five studies that were long-term, open-label studies of risperidone in children with disruptive behaviour disorders, four of which were up to a year's duration (Turgay 2002; Croonenberghs 2005; Findling 2004; Haas 2008) and one of which was up to three year's duration (Reyes 2006a).

Risk of bias in included studies

Allocation

Random sequence generation

We judged sequence generation to be at low risk of bias for five of the eight trials (Findling 2000; Buitelaar 2001; Snyder 2002; Reyes 2006; Armenteros 2007). For one trial (Aman 2002) there was insufficient information available and in two it was not described and therefore we judged the risk of bias in these three trials to be unclear.

Allocation concealment

We judged allocation concealment to be at low risk of bias for two trials (Findling 2000; Reyes 2006). Findling 2000 used a random number list. The list was kept in the Center for Drug Research and was not accessible to either the primary investigator or other study raters. Reyes 2006 used treatment numbers allocated at each investigative centre in chronological order. In the other six trials the method of concealment was not described (Buitelaar 2001; Van Bellinghen 2001; Aman 2002; Snyder 2002; Armenteros 2007; Connor 2008) and we judged the risk of bias to be unclear.

Blinding

Blinding of participants and personnel

We judged blinding of participants and personnel to be at low risk of bias for six trials (Findling 2000; Aman 2002; Snyder 2002; Reyes 2006; Armenteros 2007; Connor 2008). For one trial (Van Bellinghen 2001) details of blinding were not described and for another trial (Buitelaar 2001) we judged details of blinding to be inadequate, therefore we rated both studies as unclear risks.

Blinding of outcome assessors

None of the studies included sufficient details on the blinding of outcome assessors, therefore we deemed the risk of bias to be unclear for all.

Incomplete outcome data

Out of the eight trials in this review, one trial did not have any drop outs (Van Bellinghen 2001) in both the treatment and placebo arms. For the other seven trials the attrition rate ranges from 0-40% in the treatment arm and 8-70% in the placebo arm. The reasons for discontinuation/missing outcome data were all clearly described in all trials except for Reyes 2006, where the reasons were only partially described (treatment arm discontinued n=24, four due to side effects, 20 others not described; placebo arm discontinued n=25, four due to side effects, 21 others not described). Patient flow chart were available in three studies (Reyes 2006, Armenteros 2007, Connor 2008).

There was imbalance in the proportion missing between the treatment and placebo arms in three studies in particular (Findling 2000, Snyder 2002, Connor 2008). In Findling 2000, three out of 10 youths assigned to risperidone were withdrawn by their guardian because of lack of effect, and one youth who received risperidone was withdrawn from the study during week 4 due to the development of a rash (side effect). Four out of 10 patients assigned to placebo were withdrawn by their guardians because of lack of benefit, two more were withdrawn from the study by the principal investigator because of non-compliance with study procedures, and one youth randomly assigned to placebo was lost to follow-up. For Connor 2008, one out of nine participants withdrew from the medication (quetiapine) group due to side effect. Out of 10 participants in the placebo group, five withdrew due to lack of efficacy and two withdrew due to protocol violation. In Snyder 2002, six out of 53 participants dropped out of the risperidone group and 19 out of 57 participants dropped out from the placebo group. Reasons for discontinuation included (i) insufficient response (two from risperidone group and 19 from placebo group); (ii) loss to follow-up (one from risperidone group); and (iii) loss of parental consent (three from risperidone group). Thus in two of the studies (Connor 2008, Snyder 2002), the imbalance between the treatment and placebo arms was attributable to the lack of effect from the placebo.

In the of reporting of missing data, no study did a comparison between key baseline characteristics between individuals with missing and observed outcomes.

In the analysis of missing data, five studies used the last observation carried forward (LOCF) as an imputation method to address incomplete data (Buitelaar 2001; Aman 2002; Snyder 2002; Reyes 2006; Armenteros 2007). Criticisms against this method is the underlying assumption that an individual's missing value has not changed from the previously measured value and that it fails to account for the uncertainty about missing values (Wood 2004,

Sterne 2009) and risk resulting in standard errors to be too small (Sterne 2009) or confidence interval that are too narrow (Higgins 2011). One study used mixed-effect longitudinal analysis (Connor 2008) and one study was not explicit in the method used (Findling 2000).

The assumptions made in the main analysis were not made explicit in the studies except for Connor 2008. No formal sensitivity analyses were performed by any study to explore the effect of departures from the assumptions made in the main analysis. All authors of the eight trials stated that intention-to-treat analyses (ITT) had been undertaken.

Selective reporting

No protocol was available for any of the eight trials. Therefore, we judged all studies to be of unclear risk of bias. There may be a possible reporting bias in Armenteros 2007 as dichotomous results were presented while no differences in mean scores were detected.

Other potential sources of bias

All authors stated that intention-to-treat analyses (ITT) had been undertaken. However, a full application of the intention-to-treat principle is only possible when complete outcome data are available for all randomised participants (Hollis 1999). As noted above, no efficacy data were recorded for three participants in the treatment arm of Aman 2002 and subsequently the Aman 2002 study presented the data for 52 out of the 55 participants randomised to the active arm.

None of the studies reported any conflict of interest with regard to the funding of the studies.

Effects of interventions

See: [Summary of findings for the main comparison Atypical antipsychotics for disruptive behaviour disorders](#)

Our initial aim was to have two meta-analyses overall, one for aggression and one for conduct problems. The studies identified for inclusion reported results in two ways, some reported pre-intervention and post-intervention means, while others presented mean change scores. Despite our best efforts we were unable to get data from the authors to allow us to get the data in a consistent format. In addition some studies used the same measures while others used different measures.

According to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), where different outcomes measures are used the SMD should be used to pool results and where the outcome measure is the same the MD should be used. However it is more complex when the results are presented differently as outlined above.

The statistical advice we had was that while we can pool outcomes based on different measures using the SMD, this can only be

done using final scores and not on mean change scores. This is because using the SMD makes the assumption that there is an equal correlation between the baseline and final scores in each trial/ for each measure and information is seldom provided to confirm this. If some studies have a small correlation between baseline and final scores and others have a large correlation then pooling these makes the result meaningless. This is also the reason that change and final scores cannot be combined using SMD.

Therefore, we undertook separate analyses. For aggression, the first uses the mean difference method of meta-analysing data as we had several studies that used the same outcome measure. The second uses the SMD to combine outcome data from two different measures (but both reported final scores). We used a similar approach for the outcome 'conduct problems'.

The results are also presented for each study individually in Table 4 and Table 5 and discussed in the text. We specifically excluded Reyes 2006 from the meta-analysis because the design and objective of the trial was markedly different from the other studies. However, the results are summarised in Table 5 and in the text.

We performed meta-analyses for the primary outcomes of aggression, conduct problems and weight change. We also evaluated the treatment effect size of each individual trial where possible, using Hedges' *g*, and presented a summary in Table 4 and Table 5. We used rules of thumb for interpreting effect sizes. For example, less than 0.40 is considered small, 0.40 to 0.70 is moderate and more than 0.70 signifies a large effect size.

Primary outcomes

I. Aggression

For aggression, the effect sizes in six trials that measured it ($n = 314$) ranged from small (-0.13) to large (-1.26) (see Table 4). We noted that the confidence interval (CI) overlapped zero in three studies (Findling 2000; Buitelaar 2001; Connor 2008), which meant that they included the null value (Higgins 2011). Aman 2002 reported findings with a moderate effect size of -0.61 (95% CI -0.99 to -0.24) and Snyder 2002 found a large effect size of -0.72 (95% CI -1.11 to -0.34). In Van Bellinghen 2001, our estimate of the effect size (ES) was large but also imprecise (ES -1.26; 95% CI -2.49 to -0.02). For Armenteros 2007, the results were presented as dichotomous variables and no change scores or final scores were available.

We were able to perform two sets of meta-analyses. The first meta-analysis included three trials (Van Bellinghen 2001; Aman 2002; Snyder 2002) ($n = 238$), which employed the ABC Irritability subscale. Results for the ABC Irritability subscale yielded a final mean score on treatment that was 6.49 points lower on this subscale than with placebo (95% CI -8.79 to -4.19). The I^2 statistic for this outcome was 0%. The second meta-analysis included two trials (Buitelaar 2001; Connor 2008) ($n = 57$), which employed two

different outcome measures (Overt Aggression Scale (modified) (OAS-M) and OAS, respectively) and thus we used the standardised mean difference (SMD). Results yielded an effect estimate of -0.18 (95% CI -0.70 to 0.34), which was non-significant. The I^2 for this outcome was 0%.

2. Conduct problems

Five out of the eight trials ($n = 596$) reported on conduct problems. Overall, for conduct problems, the effect size ranged from small (-0.14) to large (-1.63) (see Table 5). Both Aman 2002 and Snyder 2002 showed a large effect size, with Aman 2002 showing an effect size of -0.82, (95% CI -1.20 to -0.44) and Snyder 2002 showing an effect size of -0.73 (95% CI -1.17 to -0.29). Both trials had a treatment period of six weeks. Reyes 2006 (which was a six-month maintenance trial) had a small effect size of ES -0.37 (95% CI -0.58 to -0.15). The confidence interval of Findling 2000 was wide, making the estimate of effect size imprecise and the confidence interval in Connor 2008 overlapped the null value.

We conducted two sets of meta-analyses. The first meta-analysis included two trials (Aman 2002; Snyder 2002) ($n = 225$), both of which employed the Nisonger Child Behaviour Rating Form - Conduct Problem subscale (NCBRF-CP). The results yielded a mean score at the end of the intervention period that was 8.61 points lower than that on placebo (95% CI -11.49 to -5.74). The I^2 for this outcome was 0%.

The second meta-analysis included two trials (Findling 2000; Connor 2008) ($n = 36$) that used the Conners' Parent Rating Scale - Conduct Problem subscale (CPRS-CP). Results yielded a mean score on treatment of 12.67 lower than on placebo (95% CI -37.45 to 12.11). This was a non-significant result. The I^2 for this outcome was 90%.

We excluded Reyes 2006 from the meta-analysis as the study's objectives and methodology were significantly different from the other trials (investigation of symptom recurrence up to six months, rather than six weeks acute efficacy).

3. Adverse events

i) Weight gain

We were able to pool data from two trials (Findling 2000; Aman 2002) (combined $n = 138$) for a meta-analysis. We used the mean difference (MD). The results revealed that participants on risperidone on average gained 2.37 kilograms (kg) more than those in the placebo group over the treatment period of six to 10 weeks (mean difference (MD) 2.37; 95% CI 0.26 to 4.49).

We excluded Reyes 2006 from the analysis for the same reason as noted above. The authors reported that over the six-month maintenance phase, the mean weight increase was 2.1 kg (standard deviation (SD) = 2.7) for risperidone-treated patients while partici-

pants receiving placebo had a decrease in mean weight of -0.2 kg (SD = 2.2) (Reyes 2006).

ii) Metabolic parameters

Only one trial (Reyes 2006) reported data for this outcome. The authors of the trial reported "no clinically significant changes in mean fasting glucose levels during treatment" but no specific data was provided in the published study. There was no information reported on glucose or lipid profiles from other trials.

We wrote to all eight authors and had replies from four of them. They were from Professor Connor and Dr Coppola, from Johnson and Johnson, responding on behalf of 3 authors: Aman, Synder and Reyes. The response for Reyes for glucose was: 'No statistical testing was performed on laboratory analyses for this study. The statement is based on clinical assessment of mean changes. Note that the protocol specified that blood samples for clinical laboratory evaluations were to be obtained after an overnight fast. Although the majority ($n = 368$) of subjects were considered fasting, 138 subjects were identified as not fasting in regard to glucose changes from screening. The results described here (in the raw data) are for all data regardless of the fasting conditions.' We were unable to interpret the raw data given which had a mixture of fasting and non-fasting glucose values.

Secondary outcomes

1. General functioning

Only one trial reported on general functioning (Reyes 2006), using the Children's Global Assessment Scale (CGAS). Participants treated with risperidone improved significantly more on CGAS than those on placebo.

2. Non-compliance

The number of participants who withdrew due to adverse events was small ($n = 12$) (Findling 2000 = 1, Aman 2002 = 2, Reyes 2006 = 8, Connor 2008 = 1). Overall, very few participants ($n = 9$) withdrew due to non-compliance with treatment protocol (Armenteros 2007 = 2, Aman 2002 = 3, Findling 2000 = 2, Connor 2008 = 2). Details of non-compliance were not defined in the studies. The other causes of attrition/incomplete outcome data had been discussed in full in the Incomplete outcome data (attrition bias) section.

3. Other adverse events

Table 6 summarises other adverse events besides weight gain and metabolic parameters, which are reported above. We grouped them into general, neurological, gastrointestinal, respiratory and cardiovascular side effects and 'other'. Two trials (Snyder 2002; Reyes

2006) reported serious adverse events unspecified but provided no details on what they were. There were no data on adverse events provided by Van Bellinghen 2001.

4. Social functioning

One trial, Van Bellinghen 2001, reported that Personal Assessment Checklist scores significantly favoured risperidone over placebo in terms of social relationships (mean change at endpoint = 1.3 for risperidone-treated group compared with mean change at endpoint = 0.1 for placebo-treated group) but no SD were provided by the authors and the number of participants was low in this study ($n = 13$).

5. Other secondary outcomes: family functioning; parent satisfaction; functioning at school

There was no information available on family functioning, parent satisfaction and functioning at school.

Subgroup analysis

The systematic review became essentially focused on risperidone as there was only one pilot study on quetiapine. There was no clinically significant diversity in doses of risperidone between studies. The mean doses at endpoint ranged from 0.98 mg/day to 1.5 mg/day. There was inadequate information to do subgroup analyses by presence or absence of ADHD and intellectual disability from the original papers. We note that two of the studies (Aman 2002; Snyder 2002) had post hoc analysis assessing risperidone effects in the presence/absence of psychostimulant medicine in participants with ADHD and disruptive behaviour disorders (Aman 2004) and showed significant reductions in both disruptive behaviour and hyperactivity, compared to placebo, regardless of concomitant stimulant use.

With regard to the duration of treatment, two pilot risperidone studies were 10 weeks (Findling 2000) and four weeks (Van Bellinghen 2001) respectively. Subsequent studies were mainly six weeks in duration (Buitelaar 2001; Aman 2002; Snyder 2002) and four weeks for Armenteros 2007. The pilot study on quetiapine was six weeks (Connor 2008). There was only one study looking at six months risperidone maintenance treatment and time to symptom recurrence (Reyes 2006). Trial authors reported that time to symptom recurrence was significantly longer in patients who continued risperidone than in those switched to placebo. The data for meta-analysis for primary outcomes of aggression and conduct problems were from the short-term studies (Findling 2000; Buitelaar 2001; Van Bellinghen 2001; Aman 2002; Snyder 2002; Connor 2008).

DISCUSSION

Summary of main results

Overall, there was some evidence of limited efficacy of risperidone in reducing aggression and conduct problems in children and youths (aged 5 to 18 years) with disruptive behaviour disorders in the short term (four to 10 weeks) from a small number of studies in which there was some risk of bias of overestimating the true intervention effect. There were significant limitations to this evidence, due to methodological shortcomings, which are discussed below. The study on quetiapine (Connor 2008), which had a small sample size and was inadequately powered, produced a non-significant result for aggression.

Eight randomised trials assessed the efficacy of atypical antipsychotics (seven for risperidone and one for quetiapine) in disruptive behaviour disorders in children and youths. Of the seven risperidone studies, three were pilot studies. One was a pilot trial of risperidone augmentation for treatment-resistant aggression in attention deficit hyperactivity disorder (ADHD) (Armenteros 2007); one was the study of risperidone in the treatment of conduct disorder (Findling 2000), and one was a pilot trial of risperidone in the treatment of behavioural disturbances in children and youths in residential care with borderline intellectual functioning (Van Bellinghen 2001). The quetiapine trial was a pilot study of quetiapine in the treatment of conduct disorder (Connor 2008). Aman 2002 and Snyder 2002 were larger outpatient multicenter randomised double-blind controlled trials of risperidone and placebo of children and youths with disruptive behaviour disorders and subaverage IQ. Buitelaar 2001 was a randomised double blind controlled trial of risperidone and placebo of inpatient youths with disruptive behaviour disorders and IQ 60-90.

Seven trials focused on acute efficacy (Findling 2000; Van Bellinghen 2001; Buitelaar 2001; Aman 2002; Snyder 2002; Armenteros 2007; Connor 2008), with the duration of intervention at four, six and 10 weeks and the eighth study was a six-month maintenance trial looking at time to symptom recurrence (Reyes 2006). The duration of a randomised trial (RCT) is an important consideration, given the episodic nature of aggression, the natural waxing and waning of conduct problems, and the stability and the chronicity of the diagnosis of disruptive behaviour disorder and in particular of conduct disorder (Steiner 1997; Steiner 2007; Connor 2008).

There were small numbers of participants in five trials (38 participants or fewer) (Findling 2000; Buitelaar 2001; Van Bellinghen 2001; Armenteros 2007; Connor 2008). This had a significant impact on the power of the studies and the precision of the estimate of the effect. Two trials (Aman 2002; Snyder 2002) had over 100 participants each and only one had over 300 participants (Reyes 2006). Participants in the trials were between 5 and 18 years of age. There were no data for children under five.

For aggression, the first meta-analysis of three trials (Van Bellinghen 2001; Aman 2002; Snyder 2002) (combined $n = 238$), which employed the ABC Irritability subscale, yielded a mean score on treatment of 6.49 lower than on placebo (95% confidence

interval (CI) -8.79 to -4.19). The second meta-analysis included two trials (Buitelaar 2001; Connor 2008) (n = 57), which employed two different outcome measures (Overt Aggression Scale (modified) (OAS-M) and OAS, respectively). Results yielded an effect estimate of -0.18 (95% CI -0.70 to 0.34), which was non-significant.

For conduct problems, the first meta-analysis of two studies (Aman 2002; Snyder 2002) (n = 225) yielded a mean Nisonger Child Behaviour Rating Form - Conduct Problem subscale (NCBRF-CF) score on treatment of 8.61 lower than on placebo (95% CI -11.49 to -5.74). The second meta-analysis included two trials (Findling 2000; Connor 2008) (n = 36) that used Conners' Parent Rating Scale - Conduct Problem subscale (CPRS-CP). Results yielded a mean score on treatment of 12.67 lower than on placebo (95% CI -37.45 to 12.11). This was a non-significant result.

For aggression, the difference in scores of 6.49 points on the ABC Irritability subscale (range 0 to 45) may be clinically significant. Owen 2009 used a difference of seven points on the ABC Irritability subscale as a measure of a clinically significant difference between treatment and placebo for children and adolescents with autistic disorder. Hassiotis 2009 used a difference of eight points on the ABC Irritability subscale between the treatment and control group to detect a clinically significant difference for challenging behaviour in adults with intellectual disabilities. For conduct problems, the difference in scores of 8.61 points on the NCBRF-CP (range 0 to 48) is likely to be clinically significant. A difference of seven or more points on NCBRF-CP by Reyes 2006 and a difference of at least eight points on NCBRF-CP by Tasse 1996 were considered to be clinically relevant differences between treatment and placebo in children and adolescents with disruptive behaviour disorders.

For individual risperidone trials, the effect sizes ranged from small to large for reducing aggression and conduct problems. The precision of the estimate of effect size varied between studies. There were significant differences in the quality and power of the studies. Studies that were inadequately powered showed non-significant results. Meta-analyses based on inadequately powered studies demonstrated non-significant results. There was only one study that investigated the effect over a six-month period (Reyes 2006), which demonstrated a small effect size of ES -0.37 (95% CI -0.58 to -0.15) for the reduction of conduct problems.

For weight gain, data pooled from two trials (Findling 2000; Aman 2002) (combined n = 138) revealed that participants on risperidone gained 2.37 kilograms (kg) on average more than those in the placebo group over the treatment period of six to 10 weeks (MD 2.37; 95% CI 0.26 to 4.49).

Overall completeness and applicability of evidence

Six trials focused on DSM IV diagnosis of a disruptive behaviour disorder with comorbid ADHD (Findling 2000; Buitelaar 2001;

Aman 2002; Snyder 2002; Reyes 2006; Connor 2008); one trial focused on treatment-resistant aggression in ADHD (Armenteros 2007), and one trial measured behavioural symptoms instead of diagnoses (Van Bellinghen 2001). Trials that used DSM IV diagnoses would be more applicable clinically. The majority of the trials included participants with moderate to severe symptom severity and of clinical concern. This reflected clinical practice and circumstances where medication was warranted.

Six trials included significant number of participants with subaverage to borderline range IQ (IQ 36 to IQ 84) (Findling 2000; Buitelaar 2001; Van Bellinghen 2001; Aman 2002; Snyder 2002; Reyes 2006) though only Reyes 2006 provided information on numbers, with approximately two-thirds of the participants having an IQ of greater than 84. Armenteros 2007 and Connor 2008 specifically excluded participants with subaverage IQ. Thus, this was a mixed sample, and it was unclear whether the evidence was generalisable to children and youths within normal IQ.

With regards to the setting, six studies were conducted with the outpatient population, while one study looked at children in residential care (Van Bellinghen 2001) and one was carried out with inpatients (Buitelaar 2001). Outpatient management would be the most common in clinical practice and some children and youths with intellectual disability/mental retardation may be in residential care.

An important limitation in the evidence base was that it did not address the issue of pre-existing or concurrent use of psychosocial treatments for disruptive behaviour disorders with medications, which is applicable in clinical practice. In one trial (Buitelaar 2001), it was specified that the participants had previously failed psychosocial treatment (contingency management and social skills training) before starting intervention antipsychotic medication. Aman 2002 permitted behavioural therapy if it had started 30 days before the trial. Armenteros 2007 and Connor 2008 allowed "pre-existing or current psychosocial interventions". The remaining trials did not comment on psychosocial interventions. There was no information in any of the trials about how many participants actually had concomitant psychosocial treatments and no further details of those treatments were described.

Another limitation of the evidence was the comorbid treatment of ADHD with stimulant medication. There was no information available in the original papers on the doses of stimulant medications used by participants.

The overall attrition rate was relatively high, varying between 0% and 40% in the intervention group and 0% and 70% in the control group. This group of participants is difficult to study as by definition; children and youths with disruptive behaviour disorders may not adhere to the rules of the treatment and research protocol; they may be oppositional and may not come for follow-up appointments, and they may be itinerant. Therefore, high drop-out rates may be expected. Six trials utilised last observation carried forward (LOCF) as an imputation method to address incomplete data (Buitelaar 2001; Van Bellinghen 2001; Aman 2002; Snyder

2002; Reyes 2006; Armenteros 2007), one trial used mixed-effect longitudinal analysis (Connor 2008) and one trial used restricted maximum likelihood (Findling 2000). The trials all reported using intention-to-treat analysis to deal with the missing data.

Due to the short duration of treatment in most trials there was a focus on short-term adverse events. Earlier trials focused on weight gain, extrapyramidal side effects and prolactin levels. Metabolic side effects were poorly addressed. Some trials continued as open-label studies looking at safety, tolerability and continuation of effects of risperidone but they were outside the parameters of this review. The long-term open-label studies of risperidone in children with disruptive behaviour disorders were Turgay 2002; Croonenberghs 2005; Findling 2006 and Haas 2008, with up to a year's follow-up, and one study of up to three year's follow-up was Reyes 2006a.

Quality of the evidence

Important methodological limitations were present in the trials included in this review. Some of the trials were carried out pre-CONSORT (Consolidated Standards of Reporting Trials) statement of 2001 (Moher 2001), thus the level of reporting currently expected was not available in the papers describing these studies, particularly with regard to the allocation concealment, randomisation and blinding processes. Reyes 2006 reported that they were unable to exclude the possibility of selection bias as only patients who responded to the initial acute treatment were subsequently randomised. No protocol was available for any of the trials. Three out of the eight trials (Aman 2002; Snyder 2002; Connor 2008) implemented a one-week placebo run-in to exclude placebo responders. One critique of this design was that placebo washout caused artificial inflation of the numbers apparently responding to the active drug and reduction of the numbers apparently responding to placebo (Jackson 2005, cited in Timimi 2008). There were shortcomings in dealing with incomplete outcome data, in particular the use of the last observation carried forward (LOCF) as an imputation method to address incomplete data (Buitelaar 2001; Aman 2002; Snyder 2002; Reyes 2006; Armenteros 2007). Criticisms against this method is the underlying assumption that an individual's missing value has not changed from the previously measured value and that it fails to account for the uncertainty about missing values (Wood 2004, Sterne 2009) and risk resulting in standard errors to be too small (Sterne 2009) or confidence interval that are too narrow (Higgins 2011).

All trials had some degrees of pharmaceutical support or sponsorship. One trial specifically stated that the authors analysed all the data and completed all the writing (Connor 2008). There was no information available regarding this for the rest of the trials.

For each study in the review, there were some areas of unclear bias and these are listed in the risk of bias tables under characteristics of included studies. The overall quality of three studies (Aman 2002, Snyder 2002, Reyes 2006) were better than others, due to these

studies being adequately powered. Overall we have also graded the quality of evidence as low (which means that 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) given all the study limitations as well as methodological shortcomings. These are also listed in our summary of findings table below.

Potential biases in the review process

We did not identify any potential biases in the review process.

Agreements and disagreements with other studies or reviews

Pappadopulos 2006 reported a mean effect size (ES) of 0.9 for aggression for risperidone in treating disruptive behaviour disorders in children and adolescents. The studies that required ES calculations for multiple raters were averaged to determine the overall ES. There were two duplications in this review as both Aman 2004 and LeBlanc 2005 were not stand-alone studies but described post hoc analyses of the combination of Aman 2002 and Snyder 2002 data. The review also included some studies with children and youths with autistic spectrum disorder (ASD) and with disruptive behaviour disorders in the same analysis while ASD was not in our inclusion criteria. The analysis by Jensen 2007a was similar to our review. There were six studies in the review with the exception of Armenteros 2007 and Connor 2008. An issue was that the two reviews did not present confidence intervals alongside the effect sizes. Since 2009, the sixth edition of the APA Publication Manual states that "estimates of appropriate effect sizes and confidence intervals are the minimum expectations" (American Psychological Association 2009, p. 33).

The weight gain reported in our review is of concern. It is unclear if the effect will attenuate over time. Correll 2009 suggests that interpretation of data may be hampered by variable prior antipsychotic medication exposure which can obscure cardiometabolic effects. In his prospective cohort study of weight and metabolic changes in pediatric patients naive to antipsychotic medication, 22.1% (n=60) of the sample (N=272) had disruptive or aggressive behaviour disorders. The rest had mood or schizophrenia spectrum disorders. After a median of 10.8 weeks of treatment, weight increased by 5.3 kg (95% CI, 4.8 to 5.9 kg) in those treated with risperidone (n=135). However, other authors of open label studies of risperidone for disruptive behaviour disorders in children and youth suggest that weight gain was greatest early on and levelled off between 6 to 12 months (Croonenberghs 2005, n=504; Turgay 2002, n=77) and 2 years (Reyes 2006a, n=35). About half of the mean weight gain of participants on risperidone at one year was attributable to developmentally expected growth (Turgay 2002; Findling 2004; Croonenberghs 2005).

AUTHORS' CONCLUSIONS

Implications for practice

There is some limited evidence that risperidone reduces aggression and conduct problems in the short term in children and youths (aged 5 to 18) with disruptive behaviour disorders. This evidence comes from a small number of studies conducted in clinical sites in which there was some risk of bias of overestimating the true intervention effect due to methodological shortcomings. The children and adolescents in the trials were recruited from inpatient and outpatient populations so that findings are potentially generalisable. The size of the effect reported in these studies is likely to be clinically meaningful. However, the limitations of the evidence and the very limited number of high-quality studies conducted requires caution in the interpretation of findings. There are methodological issues in some studies including a lack of detail in the reporting of the implementation of the trials, usage of enriched designs, the risk of selection bias and the risk of attrition bias. Studies that are inadequately powered had non-significant results. There is large heterogeneity of the population including subaverage and borderline IQ. The trials do not address the issue of pre-existing/comorbid psychosocial interventions. Comorbid stimulant medication and its dosage is only partially addressed.

The participants of risperidone trials on average gained over 2.3 kg over the treatment period of six to 10 weeks. It is unclear if the effect will attenuate over time. There is a paucity of data regarding metabolic side effects in these trials. There is only one controlled study (Reyes 2006) suggesting that the therapeutic effects of risperidone are maintained to some extent (with a small effect size) for six months.

There is currently no evidence to support the use of quetiapine for disruptive behaviour disorders in children and adolescents. There are no research data for children under five years of age. The use of risperidone ultimately needs to be contextualised and be regarded as one of the potential, carefully considered, targeted and time-limited interventions in the whole continuum of care available for children and youths with disruptive behaviour disorders.

Implications for research

This review highlights the limited evidence base regarding the use of atypical antipsychotics for disruptive behaviour disorders in children and youths. There is a need for more adequately pow-

ered and high-quality trials in this area. In particular, randomised controlled trials need to examine the longer-term effects and safety of atypical antipsychotics in children and youths with disruptive behaviour disorders. There is some evidence that clinical practice does not match research with regard to the duration of administration of atypical antipsychotics. A study on pharmacoepidemiology of antipsychotic medications for Canadian children and adolescents 2005-2009 (Pringsheim 2011) showed that atypical antipsychotics were prescribed for ADHD (17%), mood disorder (16%), conduct disorder (14%) and psychotic disorder (13%). Drug recommendations for atypical antipsychotics were 285,070 in 2005 and 631,980 in 2009. Risperidone was the most commonly recommended drug. For risperidone, the median duration of use was 90 days in children aged 1-6, 180 days in children aged 7-12 and 200 days in adolescents aged 13-18. In contrast, the duration of trials in our review ranges from 28 to 70 days for disruptive behaviour disorders (which includes ADHD and conduct disorders) and there is only one trial of 180 days duration for maintenance treatment.

There are issues in the construct and measurement of aggression including significant overlap between aggression subscales and conduct problem subscales (Jensen 2007; Calles 2011). Rating scales for aggression may measure traits of impulsive aggression or aggressive acts and Jensen 2007 has recommended that both should be measured in clinical trials.

From an ethical perspective, in the future, add-on medication studies may be the preferred clinical design. This is to ensure that participants are being optimally treated for comorbid ADHD and/or have previously received or are receiving concurrent psychosocial intervention (Jensen 2007). It would be useful to have details of these interventions made explicit in future trials.

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REFERENCES

References to studies included in this review

Aman 2002 {published data only}

Aman MG, Binder C, Turgay A. Risperidone effects in the presence/absence of psychostimulant medicine in children in ADHD, other disruptive disorders and subaverage IQ. *Journal of Child and Adolescent Psychopharmacology* 2004;**14**(2):243–54.

* Aman MG, De Smedt G, Derivan A, Lyons B, Findling RL, Risperidone Disruptive Behavior Study Group. Double-blind, placebo-controlled study of risperidone for the treatment of disruptive behaviors in children with subaverage intelligence. *American Journal of Psychiatry* 2002;**159**:1337–46.

Armenteros 2007 {published data only}

Armenteros JL, Lewis JE, Davalos M. Risperidone augmentation for treatment-resistant aggression in attention-deficit/hyperactivity disorder: a placebo-controlled pilot study. *Journal of American Academy of Child and Adolescent Psychiatry* 2007;**46**(5):558–65.

Buitelaar 2001 {published data only}

Buitelaar JK, van der Gaag RJ, Cohen-Kettenis P, Melman CT. A randomized controlled trial of risperidone in the treatment of aggression in hospitalized adolescents with subaverage cognitive abilities. *Journal of Clinical Psychiatry* 2001;**62**(4):239–48.

Connor 2008 {published data only}

Connor DF, McLaughlin TJ, Jeffers-Terry M. Randomized controlled pilot study of quetiapine in the treatment of adolescent conduct disorder. *Journal of Child and Adolescent Psychopharmacology* 2008;**18**(2):140–56.

Findling 2000 {published data only}

Findling RL, McNamara NK, Branicky LA, Schluchter MD, Lemon E, Blumer JL. A double-blind pilot study of risperidone in the treatment of conduct disorder. *Journal of American Academy of Child and Adolescent Psychiatry* 2000;**39**(4):509–16.

Reyes 2006 {published data only}

Reyes M, Buitelaar J, Toren P, Augustyns I, Eerdekens M. A randomized, double-blind, placebo-controlled study of risperidone maintenance treatment in children and adolescents With disruptive behavior disorders. *American Journal of Psychiatry* 2006;**163**:402–10.

Snyder 2002 {published data only}

Aman MG, Binder C, Turgay A. Risperidone effects in the presence/absence of psychostimulant medicine in children in ADHD, other disruptive disorders and subaverage IQ. *Journal of Child and Adolescent Psychopharmacology* 2004;**14**(2):243–54.

LeBlanc JC, Binder CE, Armenteros JL, Aman MG, Wang JS, Hew H, et al. Risperidone reduces aggression in boys with disruptive behaviour disorder and below average intelligence quotient: analysis of two placebo-controlled

randomized trials. *International Clinical Psychopharmacology* 2005;**20**:275–83.

* Snyder R, Turgay A, Aman M, Binder C, Fisman S, Carroll A, et al. Effects of risperidone on conduct and disruptive behavior disorders in children with subaverage IQs. *Journal of American Academy of Child and Adolescent Psychiatry* 2002;**41**(9):1026–36.

Van Bellinghen 2001 {published data only}

Van Bellinghen M, De Troch C. Risperidone in the treatment of behavioral disturbances in children and adolescents with borderline intellectual functioning: a double-blind, placebo-controlled pilot trial. *Journal of Child and Adolescent Psychopharmacology* 2001;**11**(1):5–13.

References to studies excluded from this review

Buitelaar 2000 {published data only}

Buitelaar JK. Open-label treatment with risperidone of 26 psychiatrically hospitalized children and adolescents with mixed diagnoses and aggressive behavior. *Journal of Child and Adolescent Psychopharmacology* 2000;**10**:19–26.

Croonenberghs 2005 {published data only}

Croonenberghs J, Fegert JM, Findling RL. Risperidone in children with disruptive behavior disorders and subaverage intelligence: a 1 year open label of 504 patients. *Journal of American Academy of Child and Adolescent Psychiatry* 2005;**44**:64–72.

Findling 2004 {published data only}

Findling RL, Aman MG, Eerdekens M, Derivan A, Lyons B, Risperidone Disruptive Behavior Study Group. Long term open label study of risperidone in children with severe disruptive behavior disorders and below average IQ. *American Journal of Psychiatry* 2004;**161**(4):677–84.

Findling 2006 {published data only}

Findling RL, Reed MD, O'Riordan MA, Demeter CA, Stansbrey RJ, McNamara NK. Effectiveness, safety and pharmacokinetics of quetiapine in aggressive children with conduct disorder. *Journal of American Academy of Child and Adolescent Psychiatry* 2006;**45**(7):792–800.

Haas 2008 {published data only}

Haas M, Karcher K, Pandina GJ. Treating disruptive behavior disorders with risperidone: a 1-year, open-label safety study in children and adolescents. *Journal of Child and Adolescent Psychopharmacology* 2008;**18**(4):337–45.

Handen 2006 {published data only}

Handen BL, Hardon AY. Open-label prospective trial of olanzapine in adolescents with subaverage intelligence and disruptive behavior disorders. *Journal of American Academy of Child and Adolescent Psychiatry* 2006;**45**(8):928–35.

Masi 2006 {published data only}

Masi G, Milone A, Canepa G, Millepiedi S, Mucci M, Muratori F. Olanzapine treatment in adolescents with severe conduct disorder. *European Psychiatry* 2006;**21**(1):51–7.

Reyes 2006a {published data only}

Reyes M, Olah R, Csaba K, Augustyns I, Eerdeken M. Long term safety and efficacy of risperidone in children with disruptive behaviour disorder: results of a 2-year extensive study. *European Child and Adolescent Psychiatry* 2006;**15**: 97–104.

Soderstrom 2002 {published data only}

Soderstrom H, Rastam M, Gillberg C. A clinical case series of six extremely aggressive youths treated with olanzapine. *European Child and Adolescent Psychiatry* 2002;**11**:138–41.

Turgay 2002 {published data only}

Turgay A, Binder C, Snyder R, Fisman S. Long term safety and efficacy of risperidone for the treatment of disruptive behavior disorders in children with subaverage IQs. *Pediatrics* 2002;**110**:e34.

Tyrer 2008 {published data only}

Tyrer P, Oliver-Africano PC, Ahmed Z, Bouras N, Cooray S, Deb S, et al. Risperidone, haloperidol and placebo in the treatment of aggressive challenging behaviour in patients with intellectual disability: a randomised controlled trial. *Lancet* 2008;**371**:57–63.

References to ongoing studies**NCT00676429 {unpublished data only}**

NCT00676429. Ziprasidone for severe conduct and other disruptive behavior disorders. <http://clinicaltrials.gov/ct2/show/NCT00676429?term=severe+conduct&rank=1> (accessed 15 August 2011).

NCT00796302 {unpublished data only}

NCT00796302. Treatment of Severe Childhood Aggression (the TOSCA Study). <http://clinicaltrials.gov/ct2/show/NCT00796302?term=severe+childhood+aggression&rank=1> (accessed 15 August 2011).

Additional references**Achenbach 1991**

Achenbach TM. *Manual for the Child Behavior Checklist 4-18 and 1991 Profile*. Burlington, VT: University of Vermont, Department of Psychiatry, 1991.

Aman 1985a

Aman MG, Singh NN, Stewart AW, Field CJ. The aberrant behavior checklist: a behavior rating scale for the assessment of treatment effects. *American Journal of Mental Deficiency* 1985;**89**(5):485–91.

Aman 1985b

Aman MG, Singh NN, Stewart AW, Field CJ. Psychometric characteristics of the aberrant behavior checklist. *American Journal of Mental Deficiency* 1985;**89**(5):492–502.

Aman 1996

Aman MG, Tasse MJ, Rojahn J, Hammer D. The Nisonger CBRF: a child behavior rating form for children with developmental disabilities. *Research in Developmental Disabilities* 1996;**17**(1):41–57.

Aman 2004

Aman MG, Binder C, Turgay A. Risperidone effects in the presence/absence of psychostimulant medicine in children in ADHD, other disruptive disorders and subaverage IQ. *Journal of Child and Adolescent Psychopharmacology* 2004;**14**(2):243–54.

American Psychiatric Association 2000

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)*. Washington DC: American Psychiatric Association, 2000.

American Psychological Association 2009

American Psychological Association. *Publication Manual of the American Psychological Association*. 6th Edition. Washington DC: American Psychological Association, 2009.

Barkley 2006

Barkley RA. *Attention-deficit Hyperactivity Disorder: a Handbook for Diagnosis and Treatment*. 3rd Edition. New York: Guilford Press, 2006.

Biederman 1996

Biederman J, Faraone SV, Milberger S, Jetton JG, Chen L, Mick E, et al. Is childhood oppositional defiant disorder a precursor to adolescent conduct disorder? Findings from a four year follow up study of children with ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry* 1996;**35**(9):1193–204.

Biederman 2008

Biederman J, Petty CR, Dolan C, Hughes S, Mick E, Monuteaux MC, et al. The long-term longitudinal course of oppositional defiant disorder and conduct disorder in ADHD boys: findings from a controlled 10 year prospective longitudinal follow-up study. *Psychological Medicine* 2008;**38**(7):1027–36.

Calles 2011

Calles JL. Psychopharmacologic control of aggression and violence in children and adolescents. *Pediatric Clinics of North America* 2011;**58**(1):73–84.

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]

Cohen 1993

Cohen P, Cohen J, Kasen S, Velez CN, Hartmark C, Johnson J, et al. An epidemiological study of disorders in late childhood and adolescence: age and gender-specific prevalence. *Journal of Child Psychology and Psychiatry and Allied Disciplines* 1993;**34**(6):851–67.

Collett 2003

Collett BR, Ohan JL, Myers KM. Ten year review of rating scales VI: scales assessing externalising behaviors. *Journal of the American Academy of Child and Adolescent Psychiatry* 2003;**42**(10):1143–70.

Conners 1989

Conners CK. *Manual for Conners' Rating Scales*. North Tonawanda, NY: Multi-Health Systems, 1989.

Connor 2010

Connor DF, Steeber J, McBurnett K. A review of attention-deficit/hyperactivity disorder complicated by symptoms of oppositional defiant disorder or conduct disorder. *Journal of Developmental & Behavioral Pediatrics* 2010;**31**(5):427–40.

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. *Journal of American Medical Association* 2009;**302**(16):1765–1773.

Correll 2010

Correll CU. Antipsychotic use in youth. <http://www.medscape.com/viewarticle/718519?src=mp&spon=12&uac=123108CX> (accessed 26 March 2010).

Cueva 1996

Cueva JE, Overall JE, Small AM, Armenteros JL, Perry R, Campbell M. Carbamazepine in aggressive children with conduct disorder: a double-blind and placebo-controlled study. *Journal of American Academy of Child and Adolescent Psychiatry* 1996;**35**(4):480–490.

Dean 2006

Dean AJ, McDermott BM, Marshall RT. Psychotropic medication utilization in a child and adolescent mental health service. *Journal of the American Academy of Child and Adolescent Psychiatry* 2006;**16**(3):273–85.

Doey 2007

Doey T, Handelman K, Seabrook JA, Steele M. Survey of atypical antipsychotic prescribing by Canadian child psychiatrists and developmental paediatricians for patients aged 18 years. *Canadian Journal of Psychiatry* 2007;**52**:363–8.

Donovan 2000

Donovan SJ, Stewart JW, Nunes EV, Quitkin FM, Parides M, Daniel W, Susser E, Klein DF. Divalproex treatment for youth with explosive temper and mood lability: a double-blind, placebo-controlled crossover design. *American Journal of Psychiatry* 2000;**157**(5):818–820.

Egger 1997

Egger M, Davey-Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphic test. *BMJ* 1997;**315**(7):629–34.

European Medicines Agency 2011

European Medicines Agency. European Medicines Agency decision P/167/2011. http://www.ema.europa.eu/docs/en_GB/document_library/PIP_decision/WC500110116.pdf 2011.

FDA 2009

FDA US Food and Drug Administration. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM193200.pdf> (accessed 8 June 2010).

Fergusson 1998

Fergusson DM, Horwood LJ. Early conduct problems and later life opportunities. *Journal of Child Psychology and Psychiatry and Allied Disciplines* 1998;**39**:1097–108.

Fergusson 2004

Fergusson DM, Horwood LJ, Ridder E. Show me the child at seven: the consequences of conduct problems in childhood for psychosocial functioning in adulthood. *Journal of Child Psychology and Psychiatry and Allied Disciplines* 2004;**46**:837–49.

Findling 2008

Findling RL. Atypical antipsychotic treatment of disruptive behavior disorders in children and adolescents. *Journal of Clinical Psychiatry* 2008;**69**(Suppl 4):9–14.

Greene 2002

Greene RW, Biederman J, Zerwas S, Monuteaux MC, Goring JC, Faraone SV. Psychiatric comorbidity, family dysfunction and social impairment on referred youth with oppositional defiant disorder. *American Journal of Psychiatry* 2002;**159**:1214–24.

Greenhill 2003

Greenhill LL, Vitiello B, Riddle MA, Fisher P, Shockey E, March JS, et al. Review of safety assessment methods used in pediatric psychopharmacology. *Journal of the American Academy of Child and Adolescent Psychiatry* 2003;**42**:627–33.

Halperin 2002

Halperin J, McKay K, Newcorn J. Development, reliability, and validity of the Children's Aggression Scale - Parent Version. *Journal of American Academy of Child and Adolescent Psychiatry* 2002;**41**:245–52.

Halperin 2003

Halperin J, McKay K, Grayson R, Newcorn J. Reliability, validity, and preliminary normative data for the Children's Aggression Scale - Teacher Version. *Journal of American Academy of Child and Adolescent Psychiatry* 2003;**42**:965–71.

Harrison 1997

Harrison AA, Everitt BJ, Robbins TW. Central 5-HT depletion enhances impulsive responding without affecting the accuracy of attentional performance: interactions with dopaminergic mechanisms. *Psychopharmacology* 1997;**133**(4):329–42.

Harrison-Woolrych 2007

Harrison-Woolrych M, Garcia-Quiroga J, Ashton J, Herbison P. Safety and usage of atypical antipsychotic medicines in children, a nationwide prospective cohort study. *Drug Safety* 2007;**30**:569–79.

Hassiotis 2009

Hassiotis A, Robotham D, Canagasabay A, Romeo R, Langridge D, Blizard R, et al. Randomized, single-blind, controlled trial of a specialist behavior therapy team for challenging behavior in adults with intellectual disabilities. *American Journal of Psychiatry* 2009;**166**(11):1278–85.

Higgins 2009

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.2 [updated

- September 2009]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.
- Higgins 2011**
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. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
- Hollis 1999**
Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ* 1999;**319**:670–4.
- Ipser 2007**
Ipser J, Stein DJ. Systematic review of pharmacotherapy of disruptive behaviour disorders in children and adolescents. *Psychopharmacology* 2007;**191**:127–40.
- Jensen 2007**
Jensen PS, Youngstrom EA, Steiner H, Findling RL, Meyer RE, Malone RP, et al. Consensus report on impulsive aggression as a symptom across diagnostic categories in child psychiatry: implications for medication studies. *Journal of the American Academy of Child and Adolescent Psychiatry* 2007;**46**(3):309–22.
- Jensen 2007a**
Jensen PS, Buitelaar J, Pandina GJ, Binder C, Haas M. Management of psychiatric disorders in children and adolescents with atypical antipsychotics, a systematic review of published clinical trials. *European Child and Adolescent Psychiatry* 2007;**16**(2):104–20.
- Kaminski 2008**
Kaminski JW, Valle LA, Filene JH, Boyle CL. A meta-analytic review of components associated with parent training program effectiveness. *Journal of Abnormal Child Psychology* 2008;**36**:567–89.
- Karnik 2007**
Karnik NS, Steiner H. Evidence for interventions for young offenders. *Child and Adolescent Mental Health* 2007;**12**:154–9.
- Kay 1988**
Kay SR, Wolkenfeld F, Murrill LM. Profiles of aggression among psychiatric patients: I. nature and prevalence. *Journal of Nervous and Mental Disease* 1988;**176**:539–46.
- Kazdin 1997**
Kazdin AE. Parent management training: evidence, outcomes and issues. *Journal of the American Academy of Child and Adolescent Psychiatry* 1997;**36**(10):1349–56.
- Kemph 1993**
Kemph JP, de Vane CL, Levin GM, Jarecke R, Miller RL. Treatment of aggressive children with clonidine: results of an open pilot study. *Journal of American Academy of Child and Adolescent Psychiatry* 1993;**32**:577–81.
- Littell 2005**
Littell JH, Popa M, Forsythe B. Multisystemic therapy for social, emotional, and behavioral problems in youth aged 10–17. *Cochrane Database of Systematic Reviews* 2005, Issue 4. [DOI: 10.1002/14651858.CD004797.pub4]
- Littell 2007**
Littell JH, Winsvold A, Bjørndal A, Hammerstrøm KT. Functional Family Therapy for families of youth (age 11–18) with behaviour problems (Protocol). *Cochrane Database of Systematic Reviews* 2007, Issue 2. [DOI: 10.1002/14651858.CD006561]
- Loeber 1998**
Loeber R, Farrington DP, Stouthamer-Loeber M, Van Kammen WB (editors). *Antisocial Behavior and Mental Health Problems: Explanatory Factors in Childhood and Adolescence*. Mahwah, NJ: Erlbaum, 1998.
- Moffitt 2002**
Moffitt TE, Caspi A, Harrington H, Milne BJ. Males on the life-course persistent and adolescence-limited antisocial pathway: follow up at age 26. *Development and Psychopathology* 2002;**14**:179–206.
- Moher 2001**
Moher D, Schulz KF, Altman DG, Lepage L. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Lancet* 2001;**357**:1191–94.
- Myers 2002**
Myers K, Winters NC. Ten year review of rating scales I: overview of scale functioning, psychometric properties and selection. *Journal of the American Academy of Child and Adolescent Psychiatry* 2002;**41**(2):114–22.
- Olfson 2010**
Olfson M, Crystal S, Huanf C, Gerhard G. Trends in antipsychotic drug use by very young privately insured children. *Journal of the American Academy of Child and Adolescent Psychiatry* 2010;**49**(1):13–23.
- Owen 2009**
Owen R, Sikich L, Marcus R, 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.
- Pappadopulos 2006**
Pappadopulos E, Woolston S, Chait B, Perkins M, Connor DE, Jensen P. Pharmacotherapy of aggression in children and adolescents: efficacy and effect size. *Journal of the American Academy of Child and Adolescent Psychiatry* 2006;**15**(1):27–39.
- Parrens 2010**
Parrens E, Johnston J. Controversies concerning the diagnosis and treatment of bipolar disorder in children. *Child and Adolescent Psychiatry and Mental Health* 2010;**4**:9. [DOI: 10.1186/1753-2000-4-9]
- Pringsheim 2011**
Pringsheim T, Lam D, Patten SB. The pharmacoepidemiology of antipsychotic medications for canadian children and adolescents: 2005–2009. *Journal of Child and Adolescent Psychopharmacology* 2011;**21**(6):537–543.

Rani 2008

Rani F, Murray ML, Byrne PJ, Wong ICK. Epidemiologic feature of antipsychotic prescribing to children and adolescents in primary care in the United Kingdom. *Pediatrics* 2008;**121**:1002–9.

RevMan 2008

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

Schur 2003

Schur SB, Sikich L, Findling RL, Malone RP, Crismon ML, Derivan A, et al. Treatment recommendations for the use of antipsychotics for aggressive youth (TRAAY). Part 1: A review. *Journal of the American Academy of Child and Adolescent Psychiatry* 2003;**42**(2):132–44.

Scott 2008

Scott S. An update on interventions for conduct disorder. *Advances in Psychiatric Treatment* 2008;**14**:61–70.

Shaw 2001

Shaw DS, Owens EB, Giovannelli J, Winslow EB. Infant and toddler pathways leading to early externalizing disorders. *Journal of American Academy of Child and Adolescent Psychiatry* 2001;**40**(1):36–43.

Steiner 1997

Steiner H, Matthews Z, Pitts T, Benton-Hardy L, Williams S, Feldman S, et al. Practice parameters for the assessment and treatment of children and adolescents with conduct disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 1997;**36**(Suppl 10):122S–39S.

Steiner 2003

Steiner H, Saxena K, Chang K. Psychopharmacologic strategies for the treatment of aggression in juveniles. *CNS Spectrums* 2003;**8**(4):298–308.

Steiner 2007

Steiner H, Remsing L, Work Group on Quality Issues. Practice parameters for the assessment and treatment of children and adolescents with oppositional defiant disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 2007;**46**(1):126–41.

Sterne 2009

Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward M, Wood AM, Carpenter JR. Multiple imputation

for missing data in epidemiological and clinical research: potential and pitfalls. *British Medical Journal* 2009;**339**:157–160.

Swann 2003

Swann AC. Neuroreceptor mechanisms of aggression and its treatment. *Journal of Clinical Psychiatry* 2003;**64**(Suppl 4):26–35.

Tasse 1996

Tasse MJ, Aman MG, Hammer D, Rojahn J. The Nisonger child behavior rating form: age and gender effect and norms. *Research in Developmental Disabilities* 1996;**17**:59–75.

Tcheremissine 2006

Tcheremissine OV, Lieving LM. Pharmacological aspects of the treatment of conduct disorder in children and adolescents. *CNS Drugs* 2006;**20**:549–65.

Timimi 2008

Timimi S. Child psychiatry and its relationship with the pharmaceutical industry: theoretical and practical issues. *Advances in Psychiatric Treatment* 2008;**14**:3–9.

Waschbusch 2002

Waschbusch DA, Pelham WE Jr, Jennings JR, Greiner AR, Tarter RE, Moss HB. Reactive aggression in boys with disruptive behaviour disorders: behaviour, physiology and affect. *Journal of Abnormal Child Psychology* 2002;**30**:641–56.

Weisz 2004

Weisz JR. *Psychotherapy for Children and Adolescents, Evidence-Based Treatments and Case Examples*. New York: Cambridge University Press, 2004:251–443.

Wood 2004

Wood AM, White IR, Thompson SG. Are missing outcome data adequately handled? A review of published randomized controlled trials in major medical journals. *Clinical Trials* 2004;**1**:368–376.

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.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Aman 2002

Methods	Double-blind randomised controlled trial of risperidone solution and placebo	
Participants	Outpatients, multicentre Aged 5 to 12 years (mean age in the active arm: 8.7 years, SD = 2.1; placebo arm: 8.1, SD = 2.3) N = 118 55 in active treatment (reported for 52 participants), 63 in the placebo arm 97 male, 21 female IQ range 36 to 84 Inclusion criteria: NCBRF > = 24 (70th percentile) on the Conduct Problem Subscale DSM IV diagnosis of Conduct Disorder, Oppositional Defiant Disorder, or Disruptive Behaviour Disorder Not Otherwise Specified 70 with comorbid ADHD (33 in the active arm and 37 in placebo arm) 31 withdrawn (12 from the active treatment arm, 19 from the placebo arm) Use of consistent doses of psychostimulants was permitted if the dose had been stable for at least 30 days before the start of the study Behavioural therapy was permitted if it was initiated at least 30 days before the start of the study No changes to psychostimulant use or behavioural therapy were allowed during the trial	
Interventions	Intended dose: risperidone solution 0.01 mg/kg increasing to 0.02 mg/kg on day 3 Mean dose at endpoint: 1.16 mg/day (mean 0.037 mg/kg per day)	
Outcomes	Primary: conduct problem subscale on Nisonger Child Behaviour Rating Form Secondary: Aberrant Behaviour Checklist, Behaviour Problem Inventory, Clinical Global Impression - Severity Rating Scale (CGI-S), Clinical Global Impression - Change Scores (CGI-C), Visual Analogue Scale of the target symptoms Follow-up interval: 6 weeks	
Notes	1-week placebo run-in “to rule out placebo responders” (p. 1338) Imputation method for incomplete data: last observation carried forward (LOCF) (page 1339) “Supported by Janssen Research Foundation” (p. 1344) “Study medication was provided by Janssen Research Foundation” (p. 1338)	
Risk of bias		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“Randomly assigned” (p. 1338) - insufficient information
Allocation concealment (selection bias)	Unclear risk	Not stated

Aman 2002 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Appearance and taste of solutions were identical. All trial medications were labelled with the protocol number, medication number, lot number and strata. A tear-off label was provided on each box of study medication which contained the medication code. The label was placed in the Case Report Form on the appropriate page. The code should only be broken in case of an emergency (email correspondence)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	12 (22%) participants in the risperidone and 19 (30%) in the placebo group withdrew. Four in the risperidone and 15 in the placebo group due to insufficient response, two in the risperidone because of adverse events, three in the risperidone due to non-compliance, one in risperidone and three in placebo lost to follow-up, one in risperidone and one placebo withdrew consent and one in risperidone lost medication No efficacy data were recorded for three patients in the risperidone group and hence they were not included in any efficacy analyses (but the authors stated to have used an intention-to-treat analysis)
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable

Armenteros 2007

Methods	Double-blind randomised controlled trial of risperidone and placebo added to pre-existing stimulants
Participants	Outpatients Aged 7 to 12 (mean age in the active arm: 7.3 year, SD = 3.7; placebo arm: 8.8 year, SD = 3.1) N = 25 12 in the active treatment, 13 in placebo arm 22 males and 3 females IQ greater or equal to 75 Inclusion criteria: DSM IV criteria for ADHD, aggression criteria documented by the presence of 3 acts of aggression in the past week, 2 of which had to be acts of physical aggression against other people, objects or self. Patients had an Aggression Questionnaire

	<p>Predatory - Affective index score of 0 or below indicating primarily an affective or impulsive type of aggression, CGI-S > = 4 (moderately ill)</p> <p>All with comorbid ADHD</p> <p>2 withdrawn (one from active treatment, one from the placebo arm)</p> <p>Patients were required to have been treated with a constant dose of stimulant medication during the 3 weeks before entering the study and still meet the aggression criteria</p> <p>Type and dose of concomitant stimulant not controlled for (p. 564)</p> <p>Patients were allowed to continue receiving any psychosocial treatment that was in place before entering the study. Patients were not allowed to seek psychosocial interventions during the study</p>
Interventions	<p>Intended dose: 0.5 mg/day at bedtime individually regulated until optimum efficacy.</p> <p>Max 2 mg a day</p> <p>Mean end dose: 1.08 mg/day</p>
Outcomes	<p>Primary: Children's Aggression Scale - Parents, Children's Aggression Scale - Teachers</p> <p>Secondary: Conners' Parent Rating Scale, Conners' Teacher Rating Scale, Clinical Global Impression - Improvement, Clinical Global Impression - Severity</p> <p>Follow-up interval: 28 days</p>
Notes	<p>Small number of participants therefore a limited power to detect differences</p> <p>Imputation method for incomplete data: "data from last known prior session were used for subsequent missing time points" (LOCF)</p> <p>Dr. Armenteros has received research support and is on the speakers' panel of Janssen Pharmaceuticals. The other authors have no financial relationships to disclose. (p. 564)</p> <p>"This study was supported by Janssen Pharmaceuticals" (p. 558)</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Assignment of subjects to treatment groups was carried out by following a table of random permutations, which balanced the number of subjects in each group. The research staff was not informed of the length of the permutations." (p. 560)
Allocation concealment (selection bias)	Unclear risk	No stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All of the subjects and clinical and research staff were blind to treatment condition" (p. 560)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated

Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant [8%] in the risperidone group dropped out of the study after one week of treatment and one subject [8%] in the placebo group also dropped out of the study after two weeks of treatment. In both cases, subjects failed to comply with treatment regulations. The rest of the sample completed the 28 days of treatment as per protocol (P. 561)
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable. Possible reporting bias as dichotomous results were presented while no differences in mean scores were detected

Buitelaar 2001

Methods	Double-blind randomised controlled trial of risperidone and placebo
Participants	<p>Inpatients (2 centres)</p> <p>Aged 12 to 18 (mean age in the active arm: 14 years, SD = 1.5; in placebo 13.7 years, SD = 2.0)</p> <p>N = 38</p> <p>33 male, 5 female</p> <p>19 in the active treatment, 19 in the placebo arm</p> <p>IQ range 60 to 90</p> <p>Inclusion criteria: DSM IV criteria for Conduct Disorder, Oppositional Defiant Disorder, ADHD; persistent overt aggressive behaviour as evidenced by ≥ 1 on OAS-M; failure of behavioural treatment</p> <p>ADHD comorbidity: 14 in the active group and 12 in placebo arm</p> <p>2 withdrawals (2 from placebo)</p> <p>Participants were included if "their aggressive behavior failed to respond to behavioral treatment approaches (typically, these behavioral treatments involve contingency management and social skills training delivered on an individual basis for at least 2 months)." (p. 240)</p>
Interventions	<p>Intended dose: from 0.5 mg twice daily increased by 1 mg up to 5 mg. As fixed as possible, could be adjusted down if adverse event present</p> <p>Mean end dose: 63% on 3 mg a day, mean 2.9 mg (1.5 to 4 mg)</p>
Outcomes	<p>Primary: Clinical Global Impression - Severity</p> <p>Secondary: Overt Aggression Scale - Modified, Aberrant Behaviour Checklist (all scales nurse and teacher rated)</p> <p>Follow-up interval: 6 weeks</p>
Notes	<p>No reasons given why 145 approached and 49 found to be eligible</p> <p>Imputation method for incomplete data: LOCF (p. 242)</p> <p>"Greater severity of psychosocial stressors in the risperidone group" (p. 242)</p>

	“Supported by Janssen-Cilag, BV, Tilburg, the Netherlands” (p. 239)	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“Randomization code had been generated by computer in block of four numbers.” (p. 241)
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	“Dosage was adjusted by the responsible psychiatrist who was blind to the treatment.” (p. 241)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two subjects [11%] in the placebo group stopped treatment during the double-blind period because of lack of therapeutic effects and uncontrollable aggressive behavior (p. 242)
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable

Connor 2008

Methods	Double-blind randomised controlled trial of oral quetiapine and placebo
Participants	<p>Single site, outpatients aged 12 to 17, mean age 14.1 (1.6)</p> <p>Male 74%</p> <p>N = 19</p> <p>9 in the active treatment, 10 in the placebo arm</p> <p>8 withdrawals (1 active treatment, 7 placebo)</p> <p>Primary psychiatric diagnosis of conduct disorder</p> <p>Moderate to severe aggressive behaviour as evidenced by OAS ≥ 25</p> <p>CGI-S ≥ 4</p> <p>Excluded significantly subaverage IQ assessed by the clinician based on school history</p> <p>ADHD in active 8 and control 7</p> <p>Current psychosocial therapies were allowed in the protocol as long as therapy was not changed during the study</p>
Interventions	<p>Intended: 25 mg twice daily, by day 14 at least 200 mg, after day 14 up to 800 mg at the discretion of a clinician</p> <p>Mean dose at endpoint: 294 $\pm$ 78 mg/day, range 200 to 600 mg/day, average weight</p>

	adjusted 4.5 ± 2.5 mg/kg per day	
Outcomes	Primary: Clinical Global Impression - Severity, Clinical Global Impression - Improvement Secondary: Overt Aggression Scale - parent-rated, Conners' Parent Rating Scale - conduct problem subscale, Quality of Life Enjoyment and Satisfaction Questionnaire Follow-up interval: 6 weeks	
Notes	1-week single-blind placebo to start with Small sample size and therefore limited power to detect differences Imputation method for incomplete data: used mixed-effect longitudinal analysis (p. 146) First author is a consultant for Shire Pharmaceuticals. This study was supported by an Investigator Initiated Grant to Dr Connor from Astra Zeneca Pharmaceuticals (p. 153) . Dr Connor and McLaughlin analysed all the data and completed all the of the writing of this submission (p.153)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study medication was blinded and encapsulated by placing whole tablets into identical looking tablets by institutional research pharmacist (p.144)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	One (11%) participant withdrew from the medication (quetiapine) group due to side effects. Five participants withdrew from the placebo group due to lack off efficacy and two withdrew due to protocol violation (70%)
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable

Findling 2000

Methods	Randomised double-blind control trial of risperidone and placebo
Participants	<p>Outpatients aged 5 to 15 (mean 9.2 (2.9) range 6 to 14)</p> <p>N = 20</p> <p>19 male, 1 female</p> <p>10 in the active treatment, 10 in the placebo arm</p> <p>Inner city academic outpatient medical centre</p> <p>DSM IV of conduct disorder</p> <p>CGI-S moderate severity</p> <p>CBCL aggression subscale T-score 2 SD or more above mean for age and gender-matched peers</p> <p>IQ more than 70</p> <p>11 withdrawal (4 active treatment, 7 placebo)</p> <p>Moderate to severe ADHD excluded</p> <p>Psychosocial interventions not mentioned</p>
Interventions	<p>Intended dose: for under 50 kg 0.25 mg increasing to 1.5 mg and for over 50 kg 0.5 mg increasing to 3 mg</p> <p>Mean dose at endpoint: 0.028 ± 0.004 mg/kg per day (range 0.75 to 1.50 mg/day)</p>
Outcomes	<p>Primary: Rating of Aggression Against People and Property Scale</p> <p>Secondary: Conners' Parent Rating Scale - conduct problem subscale, Child Behaviour Checklist, Clinical Global Impression - Severity, Clinical Global Impression - Improvement</p> <p>Follow-up interval: 10 weeks</p>
Notes	<p>Small sample size and therefore limited power to detect differences</p> <p>Imputation method for incomplete data: unclear from the published study</p> <p>This work was supported in part by Janssen Research Foundation (The Stanley Foundation) (p.1)</p> <p>Medication and placebo were supplied by Janssen (p.3)</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random number list. The list was kept in the Center for Drug Research and not was not accessible to either PI or other study raters (p.3)
Allocation concealment (selection bias)	Low risk	A random number list. The list was kept in the Center for Drug Research and not was not accessible to either PI or other study raters (p.3)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Risperidone and placebo matched in appearance (3rd page). The blind was not broken during the course of the trial (3rd page)

Findling 2000 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 10 youths assigned to risperidone, six completed the entire study [40% attrition]. Three youths who were assigned to receive risperidone were withdrawn by their guardian because of lack of effect, and one youth who received risperidone was withdrawn from the study during week 4 of the development of a rash. Only three youth who received placebo finished the trial [70% attrition]. Four patients assigned to placebo were withdrawn from the protocol by their guardians because of lack of benefit, two more were withdrawn from the study by the principal investigator because of non-compliance with study procedures, and one youth randomly assigned to placebo was lost to follow-up (4th page)
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable

Reyes 2006

Methods	Randomised double-blind controlled trial of risperidone and placebo
Participants	International, multicentre, 3-stage: acute 6 weeks open label (N=527), continuation 6 weeks single blind risperidone (N=436), maintenance 6 months double-blind RCT (N=335) Outpatients Aged 5 to 17 (mean 1.1 (2.95)) N = 335 (for the 6 month double blind, maintenance treatment) 290 male, 45 female 172 in the active treatment, 163 in the placebo arm DSM IV for conduct disorder, oppositional defiant disorder or disruptive behaviour disorder not otherwise specified NCBRF parent version >= 24 227 with comorbid ADHD (overall, 24% treated with concomitant stimulant p. 409) 216 with IQ > 84 119 with IQ < 84 Completed treatment = 162; experienced symptom recurrence = 124; discontinued = 49 (out of these 8 experienced an adverse event)
Interventions	Oral risperidone solution Intended: 1 mg/ml oral solution once or twice daily, same dose as in continuation phase max < 50 kg 0.75 mg or > 50 kg 1.5 mg

	Mean dose at endpoint: < 50 kg 0.81 (0.34), > 50 kg 1.22 (0.36)	
Outcomes	Primary: time to symptom recurrence, deterioration of >= 2 points on CGI-I or 7 points on conduct problem subscale Secondary: rate of discontinuation, Nisonger Children’s Behaviour Rating Form, Clinical Global Impression - Severity, visual analogue scale of the most troublesome symptoms, Children’s Global Assessment Scale Follow-up interval: 6 months Pre-existing or comorbid psychosocial interventions not mentioned	
Notes	(P.409) Only patients who responded to initial treatment were randomised potentially introducing a selection bias. This was in part addressed by including a single-blind phase Imputation method for incomplete data: LOCF (page 405) This study was supported by Johnson & Johnson R&D (p. 410) The first author’s correspondence address is at J & J Pharmaceuticals	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation code was generated by study sponsor (p. 403)
Allocation concealment (selection bias)	Unclear risk	Treatment numbers allocated at each investigative centre in chronological order (p. 404)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo and risperidone oral solution were identical in flavour (p. 404)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In the risperidone group 24 discontinued treatment and that included 4 participants who experienced an adverse event. In the placebo group 25 discontinued and that included 4 participants who had experienced an adverse event. The reasons for discontinuations (besides those stopping due to adverse events) were not reported
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable

Snyder 2002

Methods	Randomised double-blind controlled trial of risperidone and placebo
Participants	<p>Outpatients</p> <p>Multicentre (10 sites in Canada, 4 in USA and 2 in South Africa)</p> <p>Aged 5 to 12</p> <p>N = 110</p> <p>83 male, 27 female</p> <p>53 active treatment, 57 placebo</p> <p>DSM IV for conduct disorder, oppositional defiant disorder, or disruptive behaviour disorder not otherwise specified</p> <p>NCBRF parent version ≥ 24</p> <p>Comorbid ADHD 80% n = 84, 45 were treated</p> <p>IQ 36 to 84 (n = 53 borderline, n = 42 mild, n = 15 moderate ID)</p> <p>25 withdrawals (6 risperidone, 19 placebo)</p> <p>Psychosocial interventions was not mentioned but its design was stated to be identical to Aman 2002: behavioural therapy was permitted if it was initiated at least 30 days before the start of the study. No changes to behavioural therapy were allowed during the trial</p>
Interventions	<p>Intended dose: max 0.06 mg/kg in the morning</p> <p>Mean dose at endpoint: 0.98 mg/day (SE = 0.06), which equalled 0.033 mg/kg (SE = 0.001) range 0.40 to 3.80 mg/day</p>
Outcomes	<p>Primary: Nisonger Childrens Behaviour Rating Form - Conduct Disorder subscale</p> <p>Secondary: Aberrant Behaviour Checklist, Behaviour Problem Inventory, Clinician Global Impression - Improvement, visual analogue scale symptom (parent-rated)</p> <p>Follow-up interval: 6 weeks</p>
Notes	<p>1 week placebo run-in</p> <p>Discrepancy in drop-outs (6) between the table data and the narrative and graph</p> <p>Imputation method for incomplete data: "last post randomization assessments were used in endpoint analysis" (LOCF)</p> <p>2 sites in South Africa - unclear if followed the same protocol</p> <p>Sponsorship: Janssen Research Foundation provided randomisation and training, company central co-ordination</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	5th page - Janssen Research Foundation prepared randomisation list
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Appearance and taste of solutions were identical. All trial medications were labelled with the protocol number, medication number, lot number and strata. A tear-off label was provided on each box of study

Snyder 2002 (Continued)

		medication which contained the medication code. The label was placed in the Case Report Form on the appropriate page. The code should only be broken in case of an emergency (email correspondence)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Six (11.3%) participants dropped out of the risperidone group and 19 (33%) dropped out from the placebo group. Reasons for discontinuance included (1) insufficient response (two from risperidone group and 19 from placebo group); (2) loss to follow-up (one from risperidone group); and (3) loss of parental consent (three from risperidone group)
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable

Van Bellinghen 2001

Methods	Double-blind randomised controlled trial of risperidone and placebo
Participants	Residential care Aged 6 to 18 (mean age in the active arm 10.5 years, range: 6 to 14; placebo arm 11 years, range 7 to 14) N = 13 5 male and 8 female 6 in the active treatment, 7 placebo arm IQ range 45 to 85 Inclusion criteria: symptoms: "Persistent behavioural disturbance" (hostility, aggressive behaviour, irritability, agitation, hyperactivity). Primary psychiatric diagnoses were not specified ADHD comorbidity not reported other than one patient in placebo group was on ritalin but this was discontinued during the trial and one (in the active group) received concurrent antiepileptic (valproate) No withdrawals No description of pre-existing or comorbid psychosocial interventions
Interventions	Once daily, evenings, week 1 0.01 to 0.04 mg/kg/day, week 2 to 4 flexible dosing Mean dose at endpoint: 0.05 mg/kg (range 0.03 to 0.06 mg/kg or 1.2 mg/day)
Outcomes	Primary: no pre-specified primary endpoint (from email correspondence) Secondary: Aberrant Behaviour Checklist, Personal Assessment Checklist, Clinical Global Impression, visual analogue scale for the most disturbing symptom

	Follow-up interval: 4 weeks	
Notes	Pilot study, limited by a small sample size and thus limited power to detect differences No SDs or SEs reported Imputation method for incomplete data: LOCF (page 7) “Support for this work was received from Janssen Pharmaceutica, Berchem, Belgium” (p. 5)	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study (p. 7).
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable

ADHD: attention deficit hyperactivity disorder; CBCL: Child Behaviour Checklist; CGI-C: Clinical Global Impression - Change; CGI-I: Clinical Global Impression - Improvement; CGI-S: Clinical Global Impression - Severity; DSM IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; LOCF: last observation carried forward; NCBRF: Nisonger Child Behaviour Rating Form; OAS: Overt Aggression Scale; PI: principal investigator; RCT: randomised controlled trial; SD: standard deviation; SE: standard error

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Buitelaar 2000	Open-label study of risperidone treatment in 26 hospitalised children and youths with borderline or sub-average IQ with mixed diagnoses and aggressive behaviour
Croonenberghs 2005	1-year, multi-site, open-label study looking at safety and effectiveness of risperidone in 504 children and youths aged 5 to 14 with DBD and below average intelligence. 73% of participants completed the study

(Continued)

Findling 2004	48-week, open-label study of risperidone in 107 children aged 5 to 12 with severe disruptive behaviour disorders and below average IQ
Findling 2006	8-week, pilot, open-label outpatient trial of quetiapine in 17 aggressive children with conduct disorder aged 6 to 12 years old
Haas 2008	1-year open-label safety extension study in 232 children with DBD treated with risperidone. 73% of participants completed the study
Handen 2006	Open-label trial of olanzapine in 16 youths with subaverage intelligence and disruptive behaviour disorders
Masi 2006	A retrospective chart review of olanzapine treatment in adolescents with conduct disorder
Reyes 2006a	Open-label study over a cumulative period of 3 years, looking at safety and tolerability of risperidone in 35 children with DBD and borderline and subaverage IQ
Soderstrom 2002	A clinical case series of 6 extremely aggressive youths treated with olanzapine
Turgay 2002	48-weeks, open-label study of risperidone for the treatment of disruptive behaviour disorders in 77 children with subaverage IQs
Tyrer 2008	A randomised controlled trial in adults of risperidone, haloperidol and placebo in the treatment of aggressive challenging behaviour in adult patients with intellectual disability

DBD: disruptive behaviour disorders

Characteristics of ongoing studies [ordered by study ID]

NCT00676429

Trial name or title	Ziprasidone for severe conduct and other disruptive behavior disorders
Methods	Double-blind randomised controlled trial
Participants	Children aged 7 to 17 years
Interventions	Ziprasidone hydrochloride oral solution versus placebo
Outcomes	Primary: Nisonger Child Behavior Rating Form: typical IQ - combined subscales 'conduct problem' and 'oppositional behavior'
Starting date	July 2006
Contact information	Principal investigator: Eberhard Schulz

NCT00676429 *(Continued)*

Notes	Based in Germany
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NCT00796302

Trial name or title	Treatment of severe childhood aggression (the TOSCA study)
Methods	Double-blind randomised controlled trial
Participants	Children aged 6 to 12 years with ADHD
Interventions	Methylphenidate HCl, risperidone, parent management training, placebo
Outcomes	Primary: parent ratings of aggression measured on the Nisonger Child Behavior Rating Form: typical IQ - disruptive total score
Starting date	August 2008
Contact information	Principal investigators: Michael G. Aman, Oscar G. Bukstein, Kenneth Gadow, Robert L. Findling
Notes	Study based in US. Phase 2. Sponsored by National Institute of Mental Health and Ortho-McNeil Janssen Scientific Affairs

DATA AND ANALYSES

Comparison 1. Medication vs. placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Aggression	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Mean change scores (ABC irritability)	3	238	Mean Difference (IV, Random, 95% CI)	-6.49 [-8.79, -4.19]
2 Final scores (OAS-M and OAS)	2	57	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.70, 0.34]
3 Weight gain	2	138	Mean Difference (IV, Random, 95% CI)	2.37 [0.26, 4.49]
3.1 Mean change scores	2	138	Mean Difference (IV, Random, 95% CI)	2.37 [0.26, 4.49]
4 Conduct problems	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 NCBRE-CP	2	225	Mean Difference (IV, Random, 95% CI)	-8.61 [-11.49, -5.74]
4.2 CPRS-CP	2	36	Mean Difference (IV, Random, 95% CI)	-12.67 [-37.45, 12.11]

Analysis 1.1. Comparison 1 Medication vs. placebo, Outcome 1 Aggression.

Review: Atypical antipsychotics for disruptive behaviour disorders in children and youths

Comparison: 1 Medication vs. placebo

Outcome: 1 Aggression

Analysis 1.2. Comparison 1 Medication vs. placebo, Outcome 2 Final scores (OAS-M and OAS).

Review: Atypical antipsychotics for disruptive behaviour disorders in children and youths

Comparison: 1 Medication vs. placebo

Outcome: 2 Final scores (OAS-M and OAS)

Analysis 1.3. Comparison 1 Medication vs. placebo, Outcome 3 Weight gain.

Review: Atypical antipsychotics for disruptive behaviour disorders in children and youths

Comparison: 1 Medication vs. placebo

Outcome: 3 Weight gain

Analysis 1.4. Comparison 1 Medication vs. placebo, Outcome 4 Conduct problems.

Review: Atypical antipsychotics for disruptive behaviour disorders in children and youths

Comparison: 1 Medication vs. placebo

Outcome: 4 Conduct problems

ADDITIONAL TABLES

Table 1. Methods specified in protocol and not used in this review

Method	Protocol	Review
Assessment of reporting bias	We intended to draw funnel plots (effect size versus standard error) to assess publication bias if sufficient studies were found. Asymmetry of the plots may indicate publication bias, although they may also represent a true relationship between trial size	Due to limited studies, funnel plots were not considered relevant

Table 1. Methods specified in protocol and not used in this review (Continued)

	and effect size. If such a relationship were identified, we planned to examine the clinical diversity of the studies as a possible explanation (Egger 1997). However we did not do funnel plots because of the limited number of studies	
Subgroup analysis	It was our intention to conduct separate analyses on the following subgroups, where possible: <ol style="list-style-type: none"> 1. Each separate drug 2. Diversity in doses of the same drug 3. Presence or absence of comorbid ADHD 4. Duration of treatment: 6 weeks or less compared to more than 6 weeks 5. Participants with intellectual disability versus participants without intellectual disability 	There was inadequate information to do subgroup analyses
Sensitivity analysis	We intended to perform sensitivity analyses to explore whether the results of the review were robust in relation to certain study characteristics. We intended to exclude trials with 'No' or 'Unclear' ratings for allocation concealment and use the fixed-effect model for our primary outcome	We identified a limited number of trials and we did not exclude any of them based on the ratings of allocation concealment. We were not able to carry out a sensitivity analysis due to a small number of trials

ADHD: attention deficit hyperactivity disorder

Table 2. Rating scales used in the reviewed trials to assess aggression

Name of rating scale	Description	Construction	Study	Source of Information used in the study
Aberrant Behaviour Checklist (ABC) (Aman 1985a; Aman 1985b)	Symptom checklist for assessing problem behaviours of children and adults with mental retardation. It is also used for classifying problem behaviours of children and adolescents with mental retardation	58 items, 5 scales: <ol style="list-style-type: none"> 1) Irritability and agitation 2) Lethargy and social withdrawal 3) Stereotypic behaviour 4) Hyperactivity and non-compliance 5) Inappropriate speech 	Aman 2002; Van Bellinghen 2001; Snyder 2002	Parent/caregiver
Child Behaviour Checklist (CBCL) (Achenbach 1991)	Checklist for evaluating maladaptive behavioural and emotional problems	113 items, 8 subscales: <ol style="list-style-type: none"> 1) Withdrawn 2) Somatic complaints 3) Anxious/depressed 4) Social problems 5) Thought problems 6) Attention problems 7) Delinquent problems 	Findling 2000	Parent

Table 2. Rating scales used in the reviewed trials to assess aggression (Continued)

		8) Aggressive behaviour		
Overt Aggression Scale (OAS) (Yudofsky 1986)	Assesses the severity and frequency of overt aggression	25 items 1) Verbal aggression 2) Physical aggression against self 3) Physical aggression against objects 4) Physical aggression towards other people Within each category, aggressive behaviour is rated according to its severity	Connor 2008	Parent
Overt Aggression Scale - Modified (OAS-M) (Kay 1988)	Assesses the severity and frequency of over aggression	20 items, 4 scales 1) Verbal aggression 2) Destruction of property 3) Aggression to self 4) Physical violence 5-point interval scale that represents increasing level of aggression. The total aggression score is obtained by multiplying the 4 individual scales by weights of 1, 2, 3 or 4 and then summing the 4 weighted scores	Buitelaar 2001	Nurse or teacher
Rating of aggression against people and/or property scale (RAAP) (Kemph 1993)		Global rating scale, 1 item Scored from 1 (no aggression reported) to 5 (intolerable behaviour)	Findling 2000	Clinician
Children's Aggression Scale - Parent and Teacher (CAS-P; CAS-T) (Halperin 2002, 2003)	Retrospectively measures the frequency and severity of 4 categories of aggression: verbal aggression, aggression against objects and animals, provoked physical aggression and initiated physical aggression	Respondents (parents/guardians and teachers) complete a Likert scale to evaluate the frequency of an act. The frequency of aggressive events is multiplied by its designated severity weight factor and then summed to yield a total score	Armenteros 2007	Parents and teacher

Table 3. Rating scales used in the reviewed trials to assess conduct problems

Name of rating scale	Description	Construction	Study	Source of Information used in the study
Conners' Parent Rating Scale (CPRS) (Conners 1989)	Checklist for assessing behavioural and emotional difficulties	48 items, 6 subscales 1) Conduct problem 2) Learning problem 3) Psychosomatic 4) Impulsive-hyperactive 5) Anxiety 6) Hyperactivity index	Findling 2000 Connor 2008	Parent
Nisonger Child Behaviour Rating Form (NCBRF) (Aman 1996; Tasse 1996)	Assesses behaviour of children and adolescents with intellectual disability and/or autism spectrum disorders	76 items, 8 subscales 1) Compliant/calm 2) Adaptive/social 3) Conduct problem 4) Insecure/anxious 5) Hyperactive 6) Self injury/stereotypic 7) Self isolated/ritualistic 8) Overly sensitive	Aman 2002; Snyder 2002; Reyes 2006; Findling 2000	Parent

Table 4. Aggression

Study	Measure	Antipsychotic			Placebo			Effect Size	95% CI
		Mean	SD	Total	Mean	SD	Total		
Mean change scores									
Aman 2002	ABC Irritability	-10	9.3	52	-4.4	8.9	63	-0.61	-0.99 to -0.24
Snyder 2002	ABC Irritability	-10.9	8.5	53	-4.2	9.8	57	-0.72	-1.11 to -0.34
Findling 2000	CBCL Aggression	-24.2	17.1	9	-11.5	14.23	10	-0.78	-1.72 to 0.17
Van Bellinghen 2001 ¹	ABC Irritability	-10.8	6.05	6	0.1	9.4	7	-1.26	-2.49 to -0.02
Final scores									

Table 4. Aggression (Continued)

Buitelaar 2001	OAS-M (ward)	6.7	6.3	19	8.1	6.9	19	-0.21	-0.85 to 0.43
Connor 2008 (pilot study of quetiapine)	OAS	43.3	55.6	9	49.4	27.8	10	-0.13	-1.04 to 0.77

ABC: Aberrant Behaviour Checklist; CBCL: Child Behaviour Checklist; CI: confidence interval; OAS: Overt Aggression Scale; OAS-M: Overt Aggression Scale - modified; SD: standard deviation

Table 5. Conduct problems

Study	Measure	Antipsychotic			Placebo			Effect size	95% CI
		Mean	SD	Total	Mean	SD	Total		
Mean change scores									
Aman 2002	NCBRF-CP	-15.2	10.6	52	-6.2	11.2	63	-0.82	-1.20 to -0.44
Findling 2000	CPRS-CP	-28	13.86	8	-1.75	16.5	9	-1.63	-2.76 to -0.49
Reyes 2006	NCBRF-CP	5	9.5	172	8.8	11.2	163	-0.37	-0.58 to -0.15
Final scores									
Connor 2008 (pilot study of quetiapine)	CPRS-CP	11.3	7.7	9	12.2	4.4	10	-0.14	-1.04 to 0.76
Snyder 2002	NCBRF-CP	17.6	11.24	53	25.8	10.91	57	-0.73	-1.17 to -0.29

CI: confidence interval; CPRS-CP: Conners' Parent Rating Scale - Conduct Problem subscale; NCBRF-CP: Nisonger Child Behaviour Rating Form - Conduct Problem subscale; SD: standard deviation

Table 6. Other adverse events

		Aman 2002		Armenteros 2007		Buitelaar 2001		Connor 2008		Findling 2000		Reyes 2006		Snyder 2002		Van Bellinghen 2001	
		Risperidone (n = 55)	Placebo (n = 63)	Risperidone (n = 12)	Placebo (n = 13)	Risperidone (n = 19)	Placebo (n = 19)	Quetiapine (n = 9)	Placebo (n = 10)	Risperidone (n = 10)	Placebo (n = 10)	Risperidone (n = 172)	Placebo (n = 163)	Medication (n = 53)	Placebo (n = 57)	Risperidone (n = 6)	Placebo (n = 7)
Sys-tems	Spe-cific AE																
Gen-eral	Se-da-tion	28	6	1	2	2	0	6	9	3	2	3	2	22	8		
	Head-ache	16	9			4	2			1	1	8	11	9	4		
	Dizzi-ness					2	1										
	De-crease in en-ergy/ fa-tigue					2	0	3	5			3	0	4	0		
	Tired-ness					2	5										
Neu-ro-logi-cal	Pro-lac-ti-naemia	7	1									5	0	6	0		
	Akathi					3	5	1 (dis-con-tin-ued)	0								
	Aggi-ta-tion			1	0			6	9								

Table 6. Other adverse events (Continued)

tion																
	EPSE (un-specified)	2	0									3	1	7	3	
	Tremor					4	2									
	Muscle stiffness					3	2	1	2							
	Decrease facial expression							1	6							
	Difficulty swallowing/talking					4	0									
	Tardive dyskinesia					0	1							0	1	
Gastro-intestinal	Abdominal pain/dyspepsia	8	4	3	1							6	3	8	4	

Table 6. Other adverse events (Continued)

	Vom- iting	11	4	2	3								6	4		
	Nau- sea					3	0			1	1					
	In- crease ap- petite	6	4	1	0					3	0	4	0	8	2	
	Anore													4	2	
	Sial- or- rhea					4	0							6	1	
Res- pira- tory	Pharyn- gitis											10	4	5	3	
	URTI											13	9			
	Nose bleeds													5	0	
	Rhini- tis	6	3			11	1							7	5	
Seri- ous AE (un- spec- i- fied)												6	5	5	10	
Car- dio- vas- cular	No QTc ab- nor- mal- ities.			Not re- ported		Not re- ported		No dif- fer- ences across groups		No clin- i- cally sig- nifi-		No sig- nifi- cant change in		No ab- nor- mal QTc in-		

Table 6. Other adverse events (Continued)

		Tempo- po- rary 11 bpm in- crease in heart rate dur- ing first 2 weeks						found on ECG QRS or QTc in- ter- vals		cant chang in ECG		QTc in- ter- vals		ter- vals			
Other	Rash													4	1		
	Ab- nor- mal cry- ing													4	0		
	Enure- sis/ uri- nary in- con- ti- nence									0	1			7	3		
	Rest- less- ness									1	0						
	Irri- tabil- ity									1	0						
	Sleep- ing prob- lems									1	0						

AE: adverse event; bpm: beats per minute; ECG: electrocardiogram; URTI: upper respiratory tract infection

APPENDICES

Appendix I. Search strategies

CENTRAL

- #1 MeSH descriptor Child Behavior Disorders, this term only
- #2 MeSH descriptor Attention Deficit and Disruptive Behavior Disorders, this term only
- #3 MeSH descriptor Attention Deficit Disorder with Hyperactivity, this term only
- #4 MeSH descriptor Conduct Disorder, this term only
- #5 conduct NEAR/5 (disorder* or disturb*)
- #6 oppositional*
- #7 MeSH descriptor Antisocial Personality Disorder, this term only
- #8 (antisocial or anti NEXT social) NEAR/5 (behav* or histor* or conduct*)
- #9 attention NEAR/5 deficit*
- #10 ad/hd
- #11 adhd or “ad/hd” or adhkd or addh or adhs
- #12 hyperactiv*
- #13 MeSH descriptor Hyperkinesis, this term only
- #14 hyperkine*
- #15 MeSH descriptor Aggression, this term only
- #16 aggress*
- #17 MeSH descriptor Agonistic Behavior, this term only
- #18 agonistic*
- #19 MeSH descriptor Anger, this term only
- #20 MeSH descriptor Rage, this term only
- #21 anger or angry
- #22 malic*
- #23 hostil*
- #24 deceit*
- #25 cruel*
- #26 MeSH descriptor Juvenile Delinquency, this term only
- #27 threaten*
- #28 (dangerous* or disrupt*) NEAR/5 (behav* or histor* or conduct*)
- #29 MeSH descriptor Impulsive Behavior, this term only
- #30 impulse* or impulsiv*
- #31 MeSH descriptor Crime explode all trees
- #32 criminal* or violen* or unlawful* or delinquen*
- #33 MeSH descriptor Violence, this term only
- #34 offend* or offence* or offense*
- #35 correctional* or penal*
- #36 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35)
- #37 MeSH descriptor Clozapine, this term only
- #38 MeSH descriptor Risperidone, this term only
- #39 risperidon*
- #40 clozapin*
- #41 amisulprid*
- #42 amisulpirid*
- #43 aripiprazol*
- #44 olanzapin*
- #45 quetiapin*

#46 sertindol*
 #47 ziprasidon*
 #48 zotepin*
 #49 atypical NEAR/3 (anti next psychotic* or antipsychotic*)
 #50 (#37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49)
 #51 MeSH descriptor Infant, this term only
 #52 MeSH descriptor Child explode all trees
 #53 MeSH descriptor Adolescent, this term only
 #54 MeSH descriptor Minors, this term only
 #55 (child* or boy* or girl* or baby or babies or toddler* or infant* or teen* or adolescen* or juvenile* or preschool* or pre next school* or schoolchild*)
 #56 youth* or young* people
 #57 young* people
 #58 (#51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57)
 #59 (#36 AND #50 AND #58)

OVID MEDLINE(R)

1 Child Behavior Disorders/ (16334)
 2 Attention Deficit Disorder with Hyperactivity/ (14813)
 3 "Attention Deficit and Disruptive Behavior Disorders"/ (1421)
 4 Conduct Disorder/ (1528)
 5 (conduct adj5 (disorder\$ or disturb\$)).mp. (3679)
 6 oppositional\$.mp. (1494)
 7 ((antisocial\$ or anti-social\$) adj5 (behav\$ or histor\$ or conduct)).mp. (2560)
 8 Antisocial Personality Disorder/ (6542)
 9 (attention adj5 deficit\$).mp. (19209)
 10 (adhd or "ad/hd" or adhkd or addh or adhs).tw. (8897)
 11 hyperactiv\$.mp. (31912)
 12 Hyperkinesis/ (3286)
 13 hyperkine\$.mp. (6027)
 14 Aggression/ (22599)
 15 Agonistic behavior/ (1470)
 16 aggress\$.mp. (107506)
 17 agonistic\$.mp. (7182)
 18 Anger/ (4788)
 19 Rage/ (451)
 20 (anger or angry).mp. (10241)
 21 malic\$.mp. (4654)
 22 hostile\$.mp. (8787)
 23 ((dangerous\$ or disrupt\$ or defiant\$) adj3 (behav\$ or histor\$ or conduct\$)).mp. (7069)
 24 deceit\$.mp. (248)
 25 cruel\$.mp. (708)
 26 juvenile delinquency/ (6355)
 27 delinquen\$.mp. (8024)
 28 threaten\$.mp. (56635)
 29 Impulsive Behavior/ (3204)
 30 impulsiv\$.mp. (8200)
 31 impulse\$.mp. (20212)
 32 unlawful\$.mp. (334)
 33 Violence/ (19675)
 34 violen\$.mp. (34905)
 35 exp Crime/ (87490)

36 criminal\$.mp. (16699)
 37 penal\$.mp. (5700)
 38 (offend\$ or offenc\$ or offens\$).mp. (14883)
 39 correctional.mp. (1631)
 40 or/1-39 (375592)
 41 amisulprid\$.mp. (537)
 42 amisulpirid\$.mp. (20)
 43 aripiprazol\$.mp. (1262)
 44 Clozapine/ (5843)
 45 clozapin\$.mp. (8076)
 46 olanzapin\$.mp. (4845)
 47 quetiapin\$.mp. (2184)
 48 Risperidone/ (3992)
 49 risperidon\$.mp. (5464)
 50 sertindol\$.mp. (318)
 51 ziprasidon\$.mp. (1066)
 52 zotepin\$.mp. (215)
 53 (atypical\$ adj3 (antipsychotic\$ or anti-psychotic)).mp. (5606)
 54 or/41-53 (18538)
 55 (child\$ or boy\$ or girl\$ or baby or babies or toddler\$ or infant\$ or teen\$ or adolescen\$ or juvenile\$ or preschool\$ or pre-school\$ or schoolchild\$).mp. (2669408)
 56 (youth\$ or young\$ people).mp. (36481)
 57 Child/ or Child, preschool/ (1332516)
 58 Infant/
 59 Adolescent/
 60 Minors/
 61 or/55-60
 62 40 and 54 and 61

EMBASE

1 behavior disorder/ or attention deficit disorder/ or disruptive behavior/ or impulse control disorder/ or oppositional defiant disorder/
 2 (conduct adj5 (disorder\$ or disturb\$)).mp.
 3 oppositional\$.mp.
 4 antisocial behavior/
 5 ((antisocial\$ or anti-social\$) adj5 (behav\$ or histor\$ or conduct)).mp.
 6 ((antisocial\$ or anti-social\$) adj personality adj disorder\$).mp.
 7 (attention adj5 deficit\$).mp.
 8 (adhd or "ad/hd" or adhkd or addh or adhs).tw.
 9 hyperactiv\$.mp.
 10 hyperkinesia/
 11 hyperkine\$.mp.
 12 exp aggression/
 13 aggress\$.mp.
 14 agonistic\$.mp.
 15 (anger or angry).mp.
 16 malic\$.mp.
 17 hostil\$.mp.
 18 ((dangerous\$ or disrupt\$) adj3 (behav\$ or histor\$ or conduct\$)).mp.
 19 deceit\$.mp.
 20 cruel\$.mp.
 21 delinquen\$.mp.
 22 threaten\$.mp.

23 impulsiveness/
 24 impulse control disorder/
 26 unlawful\$.mp.
 27 exp violence/
 28 violen\$.mp.
 29 exp crime/
 30 criminal\$.mp.
 31 penal\$.mp.
 32 (offend\$ or offenc\$ or offens\$).mp.
 33 correctional.mp.
 34 or/1-33
 35 exp atypical antipsychotic agent/
 36 amisulprid\$.mp.
 37 amisulpirid\$.mp.
 38 aripiprazol\$.mp.
 39 clozapin\$.mp.
 40 olanzapin\$.mp.
 41 quetiapin\$.mp.
 42 risperidon\$.mp.
 43 sertindol\$.mp.
 44 ziprasidon\$.mp.
 45 zotepin\$.mp.
 46 (atypical\$ adj3 (antipsychotic\$ or anti-psychotic\$)).mp.
 47 or/35-46
 48 (baby or babies or infant\$ or toddler\$ or child\$ or boy\$ or girl\$ or preschool\$ or pre school\$ or teen\$ or adolescen\$ or juvenile\$ or minor\$ or youth\$ or young people).tw.
 49 infant/
 50 child/
 51 school child/
 52 preschool child/
 53 adolescent/
 54 or/49-53
 55 34 and 47 and 54

CINAHL (EBSCO host)

S53 S33 and S47 and S52
 S52 (S48 or S49 or S50 or S51)
 S51 AG preschool
 S50 AG adolescent
 S49 AG child
 S48 baby or babies or infant* or toddler* or child* or boy* or girl* or
 preschool* or pre school* or schoolchild* or juvenile* or minor* or teen*
 or adolescen* or youth* or young* people
 S47 S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or
 S44 or S45 or S46
 S46 atypical* N3 anti psychotic*
 S45 atypical* N3 antipsychotic*
 S44 zotepin*
 S43 ziprasidon*
 S42 sertindol*
 S41 risperidon*
 S40 quetiapin*

S39 olanzapin*
 S38 clozapin*
 S37 aripiprazol*
 S36 amisulpirid*
 S35 amisulpirid*
 S34 (MH "Aripiprazole") or (MH "Clozapine") or (MH "Olanzapine") or (MH "Quetiapine") or (MH "Risperidone")
 S33 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32
 S32 impulse* or impulsiv*
 S31 (MH "Impulse Control Disorders")
 S30 (MH "Violence") or (MH "School Violence") or (MH "Sibling Violence")
 S29 (MH "Juvenile Delinquency") or (MH "Juvenile Offenders+")
 S28 (MH "Crime")
 S27 (MH "Public Offenders")
 S26 offend* or offenc* or offens*
 S25 violen* or criminal* or penal* or correctional* or unlawful* or threaten*
 S24 delinquen*
 S23 (disrupt* N3 behav*) or (disrupt* N3 histor*) or (disrupt* N3 conduct*)
 S22 (dangerous* N3 behav*) or (dangerous* N3 histor*) or (dangerous* N3 conduct*)
 S21 cruel*
 S20 deceit*
 S19 hostil*
 S18 malic*
 S17 anger or angry or rage*
 S16 aggress* or agonistic*
 S15 hyperkine*
 S14 hyperactiv*
 S13 adhd or "ad/hd" or adhkd or addh or adhs
 S12 attention N5 deficit*
 S11 (anti social* N5 behav*) or (anti social* N5 histor*) or (anti social* N5 conduct*)
 S10 (antisocial* N5 behav*) or (antisocial* N5 histor*) or (antisocial* N5 conduct*)
 S9 oppositional*
 S8 (conduct N5 disorder*) OR (conduct N5 disturb*)
 S7 (MH "Anger")
 S6 (MH "Aggression")
 S5 (MH "Hyperkinesis")
 S4 (MH "Disruptive Behavior")
 S3 (MH "Antisocial Personality Disorder")
 S2 (MH "Attention Deficit Hyperactivity Disorder")
 S1 (MH "Child Behavior Disorders")

PsycINFO strategies

During the course of this review the supplier for PsycINFO changed and search was adapted in 2011 for the OVID platform.

PsycINFO (EBSCO host) searched 2010

S52 S47 and S48 and S51
 S51 S49 or S50
 S50 baby or babies or infant* or toddler* or child* or boy* or girl* or preschool* or pre school* or schoolchild* or juvenile* or minor* or teen* or adolescen* or youth* or young* people
 S49 (ZG “adolescence (13-17 yrs)”) or (ZG “childhood (birth-12 yrs)”) or (ZG “infancy (2-23 mo)”) or (ZG “preschool age (2-5 yrs)”) or (ZG “schoolage (6-12 yrs)”)

S48 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33
 S47 S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46
 S46 atypical* N3 anti psychotic*
 S45 atypical* N3 antipsychotic*
 S44 zotepin*
 S43 ziprasidon*
 S42 sertindol*
 S41 risperidon*
 S40 quetiapin*
 S39 olanzapin*
 S38 clozapin*
 S37 aripiprazol*
 S36 amisulpirid*
 S35 amisulprid*
 S34 DE “Aripiprazole” or DE “Clozapine” or DE “Olanzapine” or DE “Quetiapine” or DE “Risperidone”
 S33 impulsiv* or impulse*
 S32 DE “Impulsiveness”
 S31 (DE “Violent Crime”) or (DE “Violence”)
 S30 DE “Crime”
 S29 DE “Criminal Behavior” OR DE “Juvenile Delinquency”
 S28 offend* or offenc* or offens*
 S27 violen* or criminal* or penal* or correctional*
 S26 unlawful*
 S25 threaten*
 S24 delinquen*
 S23 (disrupt* N3 behav*) or (disrupt* N3 histor*) or (disrupt* N3 conduct*)
 S22 (dangerous* N3 behav*) or (dangerous* N3 histor*) or (dangerous* N3 conduct*)
 S21 cruel*
 S20 deceit*
 S19 hostile*
 S18 malic*
 S17 anger or angry or rage*
 S16 aggress* or agonistic*
 S15 hyperkine*
 S14 hyperactiv*
 S13 adhd or “ad/hd” or adhkd or addh or adhs
 S12 attention N5 deficit*
 S11 (anti social* N5 behav*) or (anti social* N5 histor*) or (anti social* N5 conduct*)
 S10 (antisocial* N5 behav*) or (antisocial* N5 histor*) or (antisocial* N5 conduct*)
 S9 oppositional*
 S8 (conduct N5 disturb*)
 S7 (conduct N5 disorder*)
 S6 DE “Anger” OR DE “Hostility”
 S5 (DE “Attention Deficit Disorder with Hyperactivity” or DE “Attention Deficit Disorder” or DE “Hyperkinesis” or DE “Impulsiveness” or DE “Oppositional Defiant Disorder”)
 S4 DE “Aggressive Behavior” or DE “Aggressiveness”

S3 DE "Conduct Disorder"
S2 DE "Behavior Disorders"
S1 (DE "Antisocial Personality Disorder")

PsycINFO (OVID) searched August 2011

1 antisocial behavior/
2 Antisocial Personality Disorder/
3 Behavior Disorders/
4 Conduct Disorder/
5 Aggressive Behavior/
6 Aggressiveness/
7 Impulsiveness/
8 Oppositional Defiant Disorder/
9 exp attention deficit disorder/
10 Hyperkinesis/
11 Anger/
12 Hostility/
13 (conduct adj5 (disorder\$ or disturb\$)).mp.
14 oppositional\$.mp.
15 ((antisocial\$ or anti-social\$) adj5 (behav\$ or histor\$ or conduct)).mp.
16 (attention adj5 deficit\$).mp.
17 (adhd or "ad/hd" or adhkd or addh or adhs).tw.
18 hyperactiv\$.mp.
19 hyperkine\$.mp.
20 aggress\$.mp.
21 agonistic\$.mp.
22 (anger or angry).mp.
23 malic\$.mp.
24 hostil\$.mp.
25 ((dangerous\$ or disrupt\$ or defiant\$) adj3 (behav\$ or histor\$ or conduct\$)).mp.
26 deceit\$.mp.
27 cruel\$.mp.
28 Juvenile Delinquency/
29 delinquen\$.mp.
30 threaten\$.mp.
31 impulsiv\$.mp.
32 impulse\$.mp.
33 unlawful\$.mp.
34 Violence/
35 violen\$.mp.
36 exp Crime/
37 criminal\$.mp.
38 penal\$.mp.
39 (offend\$ or offenc\$ or offens\$).mp.
40 correctional.mp.
41 or/1-40
42 Clozapine/
43 clozapin\$.mp.
44 exp Olanzapine/
45 olanzapin\$.mp.
46 Quetiapine/
47 quetiapin\$.mp.

48 Risperidone/
 49 risperidon\$.mp.
 50 sertindol\$.mp.
 51 ziprasidon\$.mp.
 52 zotepin\$.mp.
 53 amisulprid\$.mp.
 54 amisulpirid\$.mp.
 55 aripiprazole/
 56 aripiprazol\$.mp.
 57 (atypical\$ adj3 (antipsychotic\$ or anti-psychotic\$)).mp.
 58 or/42-57
 59 (child\$ or boy\$ or girl\$ or baby or babies or toddler\$ or infant\$ or teen\$ or adolescen\$ or juvenile\$ or preschool\$ or pre-school\$ or schoolchild\$).mp.
 60 (youth\$ or young\$ people).mp.
 61 ("100" or "120" or "140" or "160" or "180" or "200" or "320").ag.
 62 59 or 60 or 61
 63 41 and 58 and 62

Trials registers

ANZCTR

atypical antipsychotic or amisulpride or amisulpiride or aripiprazol or clozapine or olanzapine or quetiapine or risperidone or sertindole or ziprasidone or zotepine

ClinicalTrials.gov

(adhd OR disruptive OR oppositional OR conduct OR impulsive OR anger OR rage OR antisocial) AND (aripiprazole OR olanzapine OR quetiapine OR sertindole OR ziprasidone OR zotepine OR clozapine OR risperidone OR amisulpride OR amisulpirid) AND Child, Adult

ICTRP

Interventional aripiprazole OR olanzapine OR quetiapine OR sertindole OR ziprasidone OR zotepine OR clozapine OR risperidone OR amisulpride OR amisulpiride

CenterWatch

Advanced search: (amisulpride or amisulpiride or aripiprazole or clozapine or olanzapine or quetiapine or risperidone or sertindole or ziprasidone or zotepine) AND (adhd or disruptive or

oppositional or "conduct disorder" or impulsive or anger or rage or antisocial

metaRegister of Controlled Trials

antipsychotic* AND child* AND behav*

UK Clinical Research Network (UKCRN)

atypical antipsychotics

HISTORY

Protocol first published: Issue 6, 2010

Review first published: Issue 9, 2012

CONTRIBUTIONS OF AUTHORS

Jik Loy, Sally Merry and Sarah Hetrick prepared the protocol.

Jik Loy, Sally Merry, Chohye Park and Sarah Hetrick revised the protocol.

Jik Loy and Karolina Stasiak did the data collection and extraction.

Jik Loy, Sally Merry, Sarah Hetrick and Karolina Stasiak contributed to the data analysis.

Jik Loy, Sally Merry, Sarah Hetrick and Karolina Stasiak contributed to the writing.

DECLARATIONS OF INTEREST

Jik Loy - none known.

Sally N Merry - none known.

Chohye Park - none known.

Sarah E Hetrick - none known.

Karolina Stasiak - none known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For secondary outcomes, general functioning, we had used CGI-S as a very indirect approximation of functioning as no data were available for CGAS. Under sensitivity analysis, we had stated that we would exclude trials with 'no' or 'unclear' ratings for allocation concealment. However, we judged allocation concealment to be unclear in seven out of eight trials.

INDEX TERMS

Medical Subject Headings (MeSH)

Aggression; Antipsychotic Agents [adverse effects; *therapeutic use]; Anxiety Disorders [drug therapy]; Attention Deficit Disorder with Hyperactivity [drug therapy]; Attention Deficit and Disruptive Behavior Disorders [*drug therapy]; Conduct Disorder [drug therapy]; Depressive Disorder, Major [drug therapy]; Dibenzothiazepines [adverse effects; *therapeutic use]; Randomized Controlled Trials as Topic; Risperidone [adverse effects; *therapeutic use]; Weight Gain

MeSH check words

Adolescent; Humans

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Author/s:

Loy, JH;Merry, SN;Hetrick, SE;Stasiak, K

Title:

Atypical antipsychotics for disruptive behaviour disorders in children and youths.

Date:

2012-09-12

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