

**RISPERIDONE FOR DISRUPTIVE BEHAVIOUR IN
CHILDREN AND ADOLESCENTS WITH LEARNING DISABILITY**

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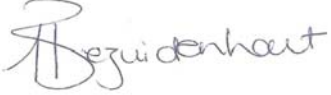
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A research report submitted to the Faculty of Health Sciences, University of the
Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree
of Master of Science in Medicine (Child Health Neurodevelopment).

Cape Town, September 2009

DECLARATION

I, HEIDRE BEZUIDENHOUT declare that this research report is my own work. It is submitted for the degree of Master of Science in Medicine (Child Health Neurodevelopment) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

SIGNED:  _____

DATE: 13th September 2009

NOTE ABOUT COCHRANE SYSTEMATIC REVIEW FORMAT

The research contained in this thesis has been registered as a systematic review of the same title with the Cochrane Collaboration, Developmental Psychosocial and Learning Problems Group. The structure and format of this thesis therefore follows the strict guidelines of the Cochrane Collaboration.

ABSTRACT

Background

Disruptive behaviour is the most commonly reported mental health problem in individuals with learning disability. Pharmacotherapy is part of a multidisciplinary approach to the treatment of disruptive behaviour. Risperidone, an atypical antipsychotic drug, is the most commonly used treatment for symptom improvement. It is therefore important to establish the efficacy and safety of risperidone therapy in this dependent, vulnerable and young population, given the well documented adverse effects and the potential for long term treatment.

Objectives

To assess the effects of risperidone for disruptive behaviour in children and adolescents with learning disability.

Search strategy

The following electronic databases were searched: CENTRAL (Cochrane Central Register of Controlled Trials); MEDLINE; PsycINFO; CINAHL; Clinicaltrials.gov; National Research Register (NRR). In addition, reference lists of relevant publications and narrative reviews were checked; handsearches were done; authors of published trials and pharmaceutical manufacturer of risperidone (Risperdal) were contacted.

Selection criteria

All randomised or quasi-randomised controlled trials of risperidone versus placebo (or no treatment) for children and adolescents (age less than 18 years) with a diagnosis of learning disability and disruptive behaviour were considered.

Data collection and analysis

Trial eligibility and data quality were evaluated and analysed by the author and independently verified by an additional reviewer. Unpublished data were considered for inclusion and relevant authors were contacted in the case of incomplete data.

Results

Four randomised controlled trials involving 279 children and adolescents were identified. The majority of the children were living at home and not institutionalised. Meta-analyses of the primary outcome scales (Nisonger Child Behaviour Rating Form, Aberrant Behaviour Checklist, Behaviour Problem Inventory) measuring several core symptoms of disruptive behaviour, namely conduct problems, self-injury, irritability, aggressive / destructive behaviours and stereotypy suggest statistically significant improvement in disruptive type behaviours in children treated with risperidone compared to placebo. Adverse event data showed that the prevalence of adverse effects viz. weight gain, sedation / somnolence and raised prolactin levels were significantly higher in the children receiving risperidone.

Conclusions

In the studies included in this review, risperidone treatment for disruptive behaviour in learning disabled children and adolescents appears to have a beneficial effect on certain symptoms of disruptive behaviour. However, the applicability of these findings to wider clinical practice remains unclear, due to poor methodological quality, inadequate study sample size and short duration of treatment of the included studies. Long term safety has not been established and serious adverse effects, affecting growth, are of concern. Further research is required to establish the efficacy and safety of risperidone for disruptive behaviour in learning disabled children and adolescents in clinical practice.

PLAIN LANGUAGE SUMMARY

Risperidone is a medication, usually used for the treatment of psychotic disorders in adults, which has also been used to treat disruptive behavioural problems, such as aggression, in people with learning disability (below normal intellect). This review showed that four studies found risperidone beneficial for improving certain symptoms of disruptive behaviour, however, the studies were small and had some technical issues that could affect their validity and applicability. In addition, potentially harmful side effects affecting growth, were identified. Further research is necessary to determine if the benefits of risperidone outweigh the potential risks.

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ABBREVIATIONS

AAMR	American Association on Mental Retardation
AAIDD	American Association on Intellectual and Developmental Disabilities
ABC	Aberrant Behaviour Checklist
APA	American Psychiatric Association
BPI	Behaviour Problem Inventory
CGI	Clinical Global Impressions Scale
CI	Confidence Interval
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Text Revision
ESRS	Extrapyramidal Symptom Rating Scale
FDA	Food and Drug Administration
ICD-10	International Classification of Diseases, 10 th edition
IQ	Intellectual Quotient
LD	Learning Disability
NCBRF	Nisonger Child Behaviour Rating Form
RCT	Randomised Controlled Trial
RevMan 5	Review Manager 5
SAMF	South African Medicines Formulary
SD	Standard Deviation
USA	United States of America
VAS	Visual Analogue Scale
WHO	World Health Organization

1. BACKGROUND

1.1. DESCRIPTION OF THE CONDITION

1.1.1. Learning Disability

Terminology

The definition and classification of individuals with impairment of intellectual functioning is the subject of an ongoing global debate in the field of mental health. Various terms and criteria are used in different countries throughout the world, leading to confusion and complexity in both clinical and academic settings. The term "learning disability" in this review is consistent with the definition used in the United Kingdom which refers to individuals with a lower than normal intellectual functioning. In the United States of America (USA) and Canada, the term "learning disability" refers to individuals with specific problems with learning academic skills, for example impairments of speaking, listening, reading, writing, spelling and doing mathematics. In the USA and Canada, impaired intellectual functioning is referred to as "intellectual disability" or "mental retardation".

There is no global consensus on the terminology referring to individuals with impaired intellectual functioning, however there is a move towards removing the stigma of the labels these individuals have been given in the past - terms like imbecile, cretin and moron have fallen out of favour. The latest development in the USA is to change the current term "mental retardation" to "intellectual disability". The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (APA 1994) and the International Classification of Diseases (ICD-10) (WHO 1992) still refer to this condition as "mental retardation", but this is likely to change in future editions as the

American Association on Mental Retardation (AAMR) have formally changed their name to the American Association on Intellectual and Developmental Disabilities (AAIDD).

Definition

The definition of learning disability comprises the impairment of both cognitive and adaptive functioning, with onset during the first 18 years of life, during childhood or adolescence (APA 2000; WHO 1992).

Cognitive functioning is normally measured by the Intelligence Quotient (IQ) using standardised psychometric tests, which are valid and reliable for the individual's circumstances (sensitive to culture, language or other disabilities).

Adaptive functioning refers to an individual's ability to function well on a personal and social level in different circumstances, adapting and adopting specific behaviours to suit the different settings of daily life (work, play and home). The child's social environment demands certain behaviours that display social maturity. These behaviours change as a child matures into adulthood and accomplishes social maturity. Adaptive skills are dependant on the community and culture the individual grows up and lives in. Instruments to measure adaptive functioning are often in the form of questionnaires or interviews with the carers of the individual to assess everyday performance. Individuals with learning disability may have the ability to display certain behaviour, but do not routinely display such behaviour when the setting requires it. Impaired adaptive functioning is often the most notable presenting feature of an individual with learning disability and is also the area in which the most improvement is seen with remedial therapy.

Synonyms for learning disability in medical literature are "mental retardation", "intellectual disability", "subaverage intelligence", "subnormal intelligence", "cognitive disability", "mental handicap" and "oligophrenia".

Aetiology

There are multiple aetiologies of learning disability: genetic disorders, congenital malformations, metabolic, ante- and perinatal causes such as infection and toxin exposure, birth asphyxia, postnatal infections, trauma, nutritional, metabolic and psychosocial problems. In 30-50% of cases the aetiology is unknown despite intensive investigation (Sadock 2005). The more severe forms of learning disability are more likely to have an identifiable organic cause. Learning disabilities are 1.5 times more common amongst males than females (APA 2000) and individuals with learning disability have a greater risk to have a concomitant mental illness. Neurological conditions, for example seizures and behavioural problems, are also more prevalent in this population (APA 2000).

Prevalence

The prevalence of learning disability in the USA is estimated at approximately 1% of the general population (APA 2000), and approximately 2% in the United Kingdom (Emerson 2004). South African data is sparse, however the "CASE Disability survey" for the Department of Health undertaken in 1997, estimated the prevalence of learning disability in South Africa to be 1.1% (CASE 2002). A later study showed the prevalence to be as high as 35.6 per 1000 (3.56%) in rural settings (Christianson 2002).

Classifications

The classifications most frequently used in clinical practice and research to diagnose an individual with learning disability are the DSM IV-TR (the latest 2000 text revision of the 1994 publication) (APA 2000) and the ICD-10 (WHO 1992); both of these classifications use the term "mental retardation" when referring to "learning disability".

DSM IV-TR: Mental Retardation

The DSM IV-TR classification consists of 5 Axes on which diagnoses could be made. Mental retardation is an Axis II diagnosis, code 317. Table 1 presents the criteria to diagnose mental retardation using the DSM IV-TR classification. The diagnosis of mental retardation is further refined as levels of impaired intellectual functioning, as displayed in Table 2.

Table 1. DSM IV-TR Criteria to diagnose Mental Retardation

- | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>A. Significantly subaverage intellectual functioning: an IQ of approximately 70 or below on an individually administered intelligence test (for infants, a clinical judgement of significantly subaverage intellectual functioning).</p> <p>B. Concurrent deficits or impairments in adaptive functioning (i.e. the person's effectiveness in meeting the standards expected for his or her age by his or her cultural group) in at least two of the following skill areas: communication, self-care, home living, social or interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health, and safety.</p> <p>C. Onset before 18 years of age.</p> |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Table from: American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM IV. 4th edition. Text revision. Washington, DC: American Psychiatric Association, 2000.

Table 2. DSM IV-TR Levels of Mental Retardation

Mild mental retardation (IQ of 55 to 70)

Individuals with mild mental retardation are usually only identified on entering formal schooling; may achieve sixth grade academic skills or some may even graduate from high school; able to acquire some vocational skills; usually able to live independently and self-support as adults, but may need support and guidance when stressed.

Moderate mental retardation (IQ 40 to 55)

Individuals with moderate mental retardation are usually identified before entering school; most will need special education services; at school most will progress to second or third grade level; able to acquire some basic vocational skills and perform unskilled or semi-skilled work under sheltered conditions; most will require supportive services throughout their lifetime.

Severe mental retardation (IQ of 25 to 40)

Individuals with severe mental retardation often have an identifiable organic cause to explain their developmental delays, that often includes motor and other neurological dysfunction as well; most will not benefit from education services except in pre-academic subjects, but may be taught some simple routines; most not able to acquire even basic vocational skills; most will require specialized supportive services throughout their lifetime.

Profound mental retardation (IQ of 25 and below)

Individuals with profound mental retardation often have an identifiable organic cause to explain their early and prominent developmental delays across all areas (motor, communication, cognitive); most will require nursing care and constant supervision throughout their lifetime, many will even need intensive training to attend to basic self-care routines like eating and toilet-habits.

Borderline intellectual functioning usually refers to individuals with an IQ range of 71 to 84. But as there is a measurement error of 5 points on an IQ score, some clinicians or researchers may diagnose mental retardation in an individual with an IQ score above 70, if they have impairment of adaptive functioning.

Table from: American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM IV. 4th edition. Text revision. Washington, DC: American Psychiatric Association, 2000.

ICD-10: Mental retardation

The ICD-10 definition of mental retardation is presented in Table 3. The classification includes levels of severity as well as levels of associated behavioural impairments, as presented in Table 4.

Table 3. ICD-10 Definition of Mental Retardation

A condition of arrested or incomplete development of the mind, which is especially characterized by impairment of skills manifested during the developmental period, which contribute to the overall level of intelligence, i.e. cognitive and language, motor and social abilities. Adaptive behaviour is always impaired, but in a protected social environment where support is available this impairment may not be at all obvious in subjects with mild mental retardation. Reduced level of intellectual functioning resulting in diminished ability to adapt to the daily demands of the normal social environment.

From: World Health Organization. International Classification of Disease and related disorders (ICD-10). Geneva: World Health Organisation, 1992.

Table 4. ICD-10 Levels of Mental Retardation

ICD-10 Levels of Mental Retardation

F70 Mild mental retardation (IQ of 50 to 69)

F71 Moderate mental retardation (IQ of 35 to 49)

F72 Severe mental retardation (IQ of 20 to 34)

F73 Profound mental retardation (IQ of less than 20)

F78 Other mental retardation - Sensory, physical and behavioural impairments preclude IQ testing

F79 Unspecified mental retardation - Evidence of mental retardation, but insufficient information is available to assign the individual to categories F70-F78.

ICD-10 Code to specify concurrent behavioural impairment

F7x.0 No, or minimal, impairment of behaviour

F7x.1 Significant impairment of behaviour requiring attention or treatment

F7x.8 Other impairments of behaviour

F7x.9 Without mention of impairment of behaviour

From: World Health Organization. International Classification of Disease and related disorders (ICD-10). Geneva: World Health Organisation, 1992.

1.1.2. Disruptive Behaviour

Definition and classification

For the purposes of this review, the term "disruptive behaviour" is used to describe the following:

- persistent patterns of socially unacceptable behaviour that is either aggressive behaviour towards others and/or self;
- stereotypic, repetitive self-harm behaviours; or
- violent and destructive actions and defiance.

Disruptive behaviour corresponds to the term "challenging behaviour" that is more often used in adult research literature and publications to describe the aforementioned patterns of behaviours (Emerson 1995). Classification systems like the DSM IV-TR and ICD-10 do have formal codes to describe disruptive type disorders (Tables 5 and 6 respectively), although studies describing disruptive behaviour in children seldom use them. Disruptive behaviours in the DSM IV-TR classification system are categorised as either oppositional defiant disorders or conduct disorders (APA 2000). The previous edition, the DSM IV, included a category - Disruptive behaviour disorders not otherwise specified (NOS) - which has been used in some publications

(APA 1994). Disruptive behaviours in the ICD-10 classification system are categorised as either conduct disorder confined to the family context, oppositional defiant disorders, other conduct disorders, conduct disorder, unspecified, conduct or oppositional defiant disorders.

Aetiology and prevalence

Disruptive behaviour is the most common psychiatric diagnosis in children with a prevalence of 4-9% (Scott 1998). There are currently no specific known causes and it is unclear whether disruptive behaviour is in fact a mental illness with a biological basis, or a symptom complex resulting from an interplay between the environment, biology and psychology of an individual, emerging during development. The latter seems the most plausible explanation. There is a higher incidence of disruptive behaviour in males and those with a family history, suggesting a genetic component (Sadock 2005). There is some evidence to suggest that disruptive types of behaviour may be a serotonergic effect, and that is why the serotonin-antagonistic type drugs may improve such symptoms (Eichelman 1992).

The population of children with learning disability has a high prevalence of disruptive behaviour disorders, contributing to the challenges these children's caregivers have to contend with (Benson 1999; Campbell 1991; Scott 1998). Children with learning disability potentially have three to four times the risk of developing behavioural problems compared to other children. (Campbell 1991). Some syndromes associated with learning disability have well defined aggressive behavioural phenotypes, such as self-biting in Lesch-Nyhan syndrome and nail pulling and head banging in Smith-Magenis syndrome.

Table 5. DSM IV-TR - Disruptive Behaviour Disorders

312. Oppositional defiant disorders

Individual displays a persistent pattern of negativistic, hostile, disobedient and defiant behaviour and results in significant impairment of functioning. Usually the behaviour does not violate the rights of others or any social norms. Behaviour pattern has to be present for more than 6 months.

312. Conduct Disorders

Individual displays a persistent pattern of behaviour that violates the basic rights of others or major age-appropriate societal norms.

From: American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders:DSM IV. 4th edition. Text revision. Washington, DC: American Psychiatric Association, 2000.

Table 6. ICD 10 - Conduct Disorders

The ICD-10 defines conduct disorders as: "repetitive and persistent pattern of dissocial, aggressive or defiant conduct. Such behaviour, when at its most extreme for the individual, should amount to major violations of age-appropriate social expectations, and is therefore more severe than ordinary childish mischief or adolescent rebelliousness". The pattern of behaviour must be enduring and could be symptomatic of other psychiatric conditions.

F 91.0 Conduct disorder confined to the family context

F 91.3 Oppositional defiant disorders

F 91.8 Other conduct disorders

F 91.9 Conduct disorder, unspecified

From: World Health Organization. International Classification of Disease and related disorders (ICD-10). Geneva: World Health Organisation, 1992.

1.2. DESCRIPTION OF THE INTERVENTION

1.2.1. Atypical Antipsychotics

Atypical antipsychotics or second-generation antipsychotics refer to a group of serotonin-dopamine antagonistic drugs. They have comparable efficacy and an improved side-effect profile compared to first-generation antipsychotics, which work as dopamine receptor antagonist. This has led to a much wider use of these drugs in psychiatry, beyond treating schizophrenia, than the first-generation antipsychotics. The improved side-effect profile could be explained by the atypical antipsychotics blocking more serotonin type 2 receptors compared to dopamine type 2 (D2) receptors, and by having greater affinity for the mesolimbic system compared to the striatal dopamine system (Sadock 2005). The serious adverse effects of the first generation antipsychotics, i.e. extrapyramidal symptoms, especially tardive dyskinesia (a potentially irreversible neurological syndrome characterised by involuntary, repetitive, purposeless movements), dystonia, involuntary movements; and neuroleptic malignant syndrome (a symptom complex consisting of hyperthermia, muscle rigidity, altered mental status and instability of the autonomic system and carries a mortality risk) has led to the less frequent use of these agents.

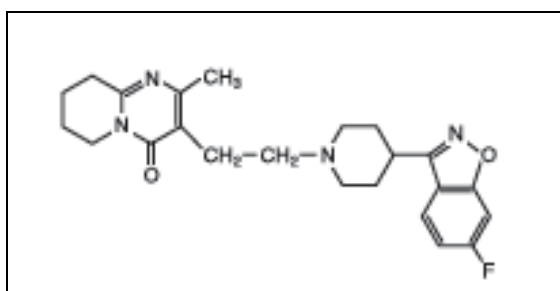
1.2.2. Risperidone preparations and pharmacodynamics

Risperidone is an atypical antipsychotic initially patented and marketed as Risperdal by Janssen-Silag, now called Ortho-McNeil-Janssen Pharmaceuticals Inc., a subsidiary of Johnson & Johnson. Preparations include tablet formulation (0.5 mg, 1mg, 2 mg, 3 mg, 4 mg), orodispersible tablets, *Quicklet* (0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg), oral solution (1 mg/ml) and long-acting injectable formulation (Risperdal Consta) (25 mg, 37.5 mg, 50 mg) (SAMF 2008) .

Risperidone is a benzisoxazole derivative (Figure 1) that is metabolized in the liver to 9-hydroxy risperidone, which has the same pharmacological action as the parent compound. Peak plasma levels are reached within 1-2 hours of ingestion. The mechanism of action is via central serotonin (especially 5-HT_{2A}) and dopamine (D₂) receptor antagonism. Risperidone also has high affinity for α_1 and α_2 -receptors and lower affinity for β -adrenergic and muscarinic receptors.

Ortho-McNeil-Janssen's patent for risperidone expired in December 2007 and the Food and Drug Administration (FDA) approved a generic version of risperidone in July 2008, manufactured by TEVA pharmaceuticals. Currently a generic version of risperidone is available and manufactured by several other pharmaceutical companies (TEVA Pharmaceuticals, Apotex Corporation, Mylan Pharmaceuticals, Patriot Pharmaceuticals) in tablet and oral solution, but not in an injectable formulation.

Figure 1. Molecular structure of risperidone



1.2.3. Indications for use

The South African Medicines Formulary 2008 (SAMF) states the indications for risperidone as: Adults - Schizophrenia, acute or chronic psychoses. Behavioural symptoms (aggression, wandering, agitation) and psychosis associated with dementia. Paediatrics - Disruptive behaviour disorders in children older than 5 years with sub-average intellectual functioning or mental retardation. Contraindicated in children

under 5 years. Efficacy and safety not established in schizophrenia in children under 15 years old. Paediatric dose: Oral, 5-12 years under 50 kg, initially 0.01 mg/kg once daily, increased if necessary by 0.01 mg/kg/day not more frequently than every other day. Maintenance 0.02-0.04 mg/kg daily (SAMF 2008).

In the United States risperidone was approved in October 2006 by the Food and Drug Administration (FDA) for treatment of irritability in autistic children (5 -16 years) (FDA 2006) and in August 2007 approved for treatment of schizophrenia in children (age 13 to 17) as well as treatment of bipolar disorder in children age 10 to 17 years (FDA 2007). Risperidone is not currently registered in the United States to be used to treat disruptive behaviour in children and adolescents with learning disability/ mental retardation, but is used off-label in practice regardless (FDA 2009).

1.2.4. Adverse effects

The South African Medicines Formulary 2008 (SAMF) lists the adverse effects of risperidone as: Common - insomnia, agitation, extrapyramidal effects, anxiety, headache, sedation (more frequent in children/ adolescents than adults). Uncommon - somnolence, fatigue, dizziness, impaired concentration, constipation, dyspepsia, nausea, vomiting, abdominal pain, weight gain, blurred vision, priapism, erectile dysfunction, urinary incontinence, rhinitis, rash and other allergic reactions. Tardive dyskinesia, seizures, orthostatic hypotension, cerebrovascular events, hyperprolactinaemia (galactorrhoea, gynaecomastia, menstrual disturbances), hyponatraemia due to polydipsia or syndrome of inappropriate anti-diuretic hormone (SIADH), and temperature dysregulation have been reported. Rare complications include neuroleptic malignant syndrome, hyperglycaemia following intramuscular

injection, and in some extreme cases keto-acidosis or hyperosmolar coma or death (SAMF 2008).

A boxed warning has been issued by the manufacturers of risperidone for its use in the treatment in the elderly patient with dementia-related psychosis after trials showed an increased mortality in this population group. Risperidone is currently not approved to be used for the treatment of individuals with dementia-related psychosis in the United States (FDA 2009).

Weight gain and its resulting metabolic sequelae (insulin insensitivity or diabetes mellitus, hyperlipidaemia) is a commonly reported adverse event of risperidone use, possibly explained by the H₁ and 5-HT_{2c} receptor blockage. Raised plasma prolactin levels may be a consequence of dopamine (D₂) receptor activity.

1.3. HOW THE INTERVENTION MIGHT WORK

1.3.1. Management of Disruptive Behaviour in Individuals with Learning Disability

Disruptive type behaviour or "aggressive, antisocial and self-injurious behaviour" (Aman 1991) is the most commonly reported mental health problem in individuals with learning disability. A multidisciplinary approach to the treatment of disruptive behaviours includes cognitive therapy, behaviour treatment, psychotherapy, social learning therapy, enhancement of parental skills and pharmacotherapy. The cognitive and behavioural modification therapies are an essential part of the holistic management plan for an individual with learning disability, though quite costly and labour intensive, with a long latency before any positive effects may be observed. Individuals with a severe level of learning disability may also have limited benefit

from cognitive therapies. A Cochrane review done on the efficacy of behavioural and cognitive-behavioural interventions for aggressive behaviour in learning disabled people found little evidence to support the efficacy of these interventions (Hassiotis 2004). Pharmacotherapy for disruptive behaviour is often used in conjunction with the other treatment modalities. The first antipsychotic agent to be used to treat behavioural problems was chlorpromazine in the 1950's (Schaal 1994). The introduction of the newer atypical antipsychotic agents has sparked a renewed interest in the use of antipsychotics for the pharmacotherapy of behavioural problems, especially in children, as these agents have fewer reported adverse effects. Risperidone, in particular, has been the agent used in numerous studies to establish the pharmacological efficacy in improving disruptive types of behaviour.

1.3.2. Literature reviews

A number of published randomised controlled studies and reviews have assessed antipsychotics, in particular risperidone, for symptoms of aggression and irritability both in adults and children. These publications are presented below as an overview of relevant evidence in the field, with a more detailed discussion of the publications concerning risperidone use in children with learning disability in section 4 of this review.

Normal or near normal intelligence

A small randomised controlled study found that risperidone use in children with normal intelligence and a diagnosis of conduct disorder resulted in an improvement of aggression symptoms and was not associated with extra-pyramidal side-effects (Findling 2000). Nevertheless the authors did stress that the findings of this pilot

study should not be applied to all children with conduct disorders. A large randomised, placebo-controlled study on risperidone maintenance for disruptive behaviour disorders in children and adolescents with a wide range of intellectual disability (IQ > 84) concluded that risperidone was of benefit in children who initially responded to the drug and then prescribed for an additional 6 months (Reyes 2006b). Risperidone at low-doses improved a wide range of behavioural and social symptoms in children enrolled in the study.

Learning disability

Several published randomised controlled studies assessing the use of risperidone in children with learning disability, found risperidone to be well tolerated and effective in treating severely disruptive behaviours (such as aggression and destructiveness) (Aman 2002, Buitelaar 2001, Snyder 2002). Risperidone was also found to be significantly more effective than placebo in controlling behavioural disturbances (Van Bellinghen 2001). Cross-over studies that included both children and adults with learning disability showed risperidone to be effective in treating behavioural disturbances (Hellings 2006; Vanden 1993; Zarcone 2001). Hellings et al observed risperidone to have significant adverse effects in the form of increased appetite, weight gain and sedation. A recent randomised controlled study undertaken in adults with learning disability assessing risperidone, haloperidol and placebo concluded that the use of antipsychotics to treat behavioural problems in learning disabled individuals should not be recommended as a first line treatment, even at low doses, as treatment with risperidone or haloperidol were not found to be superior to placebo (Tyrrer 2008). The authors supported alternative forms of management i.e. psychological interventions.

Predominantly positive reviews

A literature review done on the use of antipsychotics in individuals with intellectual disability by La Malfa concluded that risperidone was the most efficacious and safest drug to use in this population group for behavioural problems. However, the review authors did comment extensively on the inadequate methodological quality of the majority of the included studies (La Malfa 2006). The review referred to two consensus conferences that promoted the efficacy and safety of atypical antipsychotics to treat behavioural problems in learning disability (AAMR 2000; SIRM 2002).

A literature review done by Dr G Pandina, Director of Clinical Development at Janssen Pharmaceutica Inc., on risperidone for disruptive behaviour in paediatric patients concluded that there was enough evidence to show the efficacy of risperidone to treat disruptive behaviour disorders in children (Pandina 2006). A recommendation arising from the review was the need to anticipate possible adverse effects resulting from the use of risperidone such as excessive weight gain, premature sexual maturation and metabolic derangements.

Another review that recommended the use of psychotropic medication such as risperidone, for behavioural problems in learning disability also highlighted the possible adverse effects of the drug (Deb 2007). The reviewers were concerned about the poor methodological quality of the current literature on this topic and emphasized the need for further research in this area.

Predominantly negative reviews

A recent review of evidence-based treatments for individuals with learning disability concluded that current evidence does not support the use of risperidone for the management of behavioural problems in patients with learning disorders (Ulzen 2008). The review commented on the small sample sizes, poor methodological quality, the lack of emphasis on important issues such as polypharmacy, and the use of depot preparations. The reviewers proposed that future literature include important issues such as management of acute onset agitation and the prevalence of underlying organic aetiology as cause for disruptive behaviour.

A systematic review by South African authors reviewing pharmacotherapy of disruptive behaviour disorders in children and adolescents highlighted the fact that there are currently no registered medications to treat disruptive behaviour disorders (Ipser 2007). They concluded that the results of two randomised controlled trials (Aman 2002; Snyder 2002) showing significant benefit for risperidone, should be interpreted with caution as many of the study participants were receiving psychotropic medication at the same time. The reviewers concluded that there was not sufficient evidence at the time to advocate the use of risperidone to treat disruptive behaviour in children, and that further research was needed to further explore the high prevalence of adverse events and establish its long term safety. This review did not explore disruptive behaviour in children or adolescents with learning disability.

A review done by Singh et al on the use of risperidone among learning disabled individuals found that its general use was not evidence-based (Singh 2005). These authors also commented on the poor methodological quality of studies reported in the

current literature and suggested recommendations for improving the design for future studies.

Another comprehensive review done by Matson et al on psychopharmacology in patients with learning disability found no evidence to support the use of antipsychotics to treat aggression in individuals with learning disability (Matson 2000). The authors raised the important question of ethics in this vulnerable population and included criticism for the poor methodological quality of studies that have been published. In their conclusion the authors issued the following statement: "given the overall paucity of evidence, the continued, inappropriate use of psychotropic medications in persons with mental retardation extends beyond a question of ethics and becomes an urgent moral dilemma" (Matson 2000).

A Cochrane systematic review done on the use of antipsychotic agents for disruptive behaviour in adults with learning disability concluded that caregivers of people with learning disability should be informed of the "paucity of evidence for the efficacy of this treatment" (Brylewski 2004).

There is no published systematic review or meta-analysis on the use of risperidone for disruptive behaviour in children with learning disability. Most of the published reviews on risperidone for treatment of disruptive behaviour are focused specifically on adult patients.

Safety

The long term safety of risperidone therapy in children with disruptive behaviour was

explored by a publication containing pooled data from 5 studies, (n=350 for growth data, n=222 for sexual maturation data), in children aged 5 – 15 years, treated with risperidone of up to 1 year. They concluded that there was no clinical or statistical evidence to indicate growth failure or sexual maturation failure or progression (Dunbar 2004). This publication did not evaluate long-term weight gain as a safety outcome. A few open label studies have reported on the adverse effects experienced by patients treated with risperidone and found somnolence, weight gain, headaches and raised prolactin levels to be the most common adverse effects (Croonenberghs 2005; Findling 2004; Turgay 2002). Adverse events that lead to the discontinuation of a study using risperidone by Croonenburghs et al (n=504), was weight gain in nine patients, increased appetite in four patients, gynaecomastia in three patients, somnolence in three patients, headache in three patients and extrapyramidal symptoms in six patients (two cases of tardive dyskinesia). Extrapyramidal adverse effects resulted in five patients (1%) needing additional anti-parkinsonism medications during the study. The incidence of important reported adverse effects in the study were as follows: any adverse event 462 (91.7%), somnolence 149 (29.6%), weight gain 87 (17.3%), and hyperprolactinaemia 56 (11.1%).

Autism

A Cochrane systematic review on the use of risperidone for autism spectrum disorders concluded that risperidone is beneficial in some of these patients with behavioural disturbances. A small number of randomised controlled trials were suitable for inclusion and because the majority had small sample sizes, the author concluded that "carers and clinicians should be aware of the paucity of evidence in administering this drug in such a vulnerable group of people" (Jesner 2007).

WHY IT IS IMPORTANT TO DO THIS REVIEW

The effective management of behavioural problems in children with learning disability is of great importance and can improve the quality of life for the learning disabled individual. Disruptive behaviour is also very challenging for the caregivers of children with learning disability who have to act in their best interest and provide a treatment that has proven to be safe. In an attempt to address the need and strive for evidence-based care, the American Journal on Intellectual and Developmental Disabilities are calling for papers to be included in a "Special Section on Evidence-Based Practices for Persons with Intellectual and Developmental Disabilities" to be published in the journal over the next 3 years.

The diagnosis of problem behaviours in learning disabled children, especially in those with poor communication abilities, as a specific disruptive behaviour disorder is very difficult, because the behaviour could also be a symptom of another organic illness or other psychosocial problem (Rush 2000). Their abnormal behaviour may be the only way of communicating their needs, and clinicians should be mindful of this when assessing an individual before implementing treatment. Tyrer et al emphasized the importance of accurately diagnosing the underlying cause of behavioural problems in individuals with learning disability (Tyrer 2008).

Just as disruptive behaviour may be challenging to diagnose in a learning disabled individual, it is just as challenging to manage and treat the symptom complex. It is very important to manage it effectively, as the implications are serious for both the individual and their caregivers. Disruptive behaviour may result in institutional placement of children who have become unmanageable. Physical traumas to patients,

caregivers and others are a serious reality and have even led to litigation cases. The cost of caring for learning disabled individuals with severe disruptive behaviour on the health, education and social services can be excessive (Scott 1998). A costing analysis of the care of these individuals was done in the USA in 1989 and estimated to be \$3 billion dollars for one year (Campbell 1991).

Some authors have postulated that individuals with learning disability have a specific vulnerability to antipsychotics and are therefore more likely to develop adverse effects (La Malfa 2006). The use of risperidone in children may be hazardous and needs proper evidence-based scrutiny before recommending widespread use particularly because of its known adverse effect profile, such as affects on growth and sexual maturation parameters (weight and prolactin).

Polypharmacy and a high prevalence of prescribed antipsychotic drugs has been a concern in the learning disability population. As many as 22-45% of learning disabled people in the hospital setting and 20% in the community setting are taking antipsychotic medication (Branford 1994). There have been concerns expressed in the literature about the dangers of using medications such as risperidone as a first line treatment option for disruptive behaviour and stressing the importance of re-evaluating behaviour and attempting withdrawal of drug treatment in these patients (Ahmed 2000; Gainotti 2008; Tyrer 2008). Under resourced facilities have been guilty of using risperidone more frequently and earlier than clinically indicated (Turk 2008). In countries such as South Africa, which is poorly resourced and where support systems for patients with learning disability are underdeveloped, there may be pressure to over use pharmacotherapy in the management of behaviour disorders in

learning disabled children. The availability and affordability of the various generic formulations of risperidone could certainly allow and encourage the wider use of risperidone.

All health interventions should be critically appraised to ensure safety and effectiveness of treatments. To confidently conclude that risperidone is an evidence-based treatment for disruptive behaviour in children with learning disability, a systematic review of the literature using meta-analysis could be done. A meta-analysis is a statistical procedure used to assess individual studies with similar research hypothesis and design, in order to combine all of the studies' results to produce an accurate and objective overall estimate of effect (Balair 1997; Borenstein 1999; Elwood 1998). This statistical procedure improves accuracy of data analysis, as studies are weighed according to their statistical power which is dependant on the sample size and research design rigour, before their contribution to the overall effect size is calculated. It is a transparent logical process, with which all the details of the data can be evaluated, from the research design and methodology to the final results and conclusions (Balair 1997; Elwood 1998). It enables the exploration of the heterogeneity of the different studies and allows for the results to be generalized to specific populations. A disadvantage of this procedure is that even though published and unpublished studies can and should be included in the analysis, in reality publication bias can distort the overall estimate of effect, as studies showing a positive effect are published more readily (Borenstein 1998). Nonetheless, a systematic review with meta-analysis is still the gold standard of data collation and analysis. The Cochrane collaboration is an international network of health care professionals and epidemiologists based in the United Kingdom dedicated to organise and circulate

systematic reviews of health care interventions in order to promote evidence-based health care. The collaboration composes systematic reviews of randomised controlled trials, using meta-analysis to appraise current health care evidence to propose recommendations regarding current treatment practices and future research.

A systematic approach using Cochrane methodology to assess the current available evidence in the use of risperidone for disruptive behaviour in learning disabled children and adolescents would therefore have important clinical and financial implications.

2. OBJECTIVES

The objective of this review is to assess the effects of risperidone for disruptive behaviour in children and adolescents with learning disabilities.

3. METHODS

3.1. CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

3.1.1. Types of studies

All randomised controlled trials and quasi-randomised trials that included at least one standardised measure of outcome, such as a behaviour checklist, used for both the intervention and the control group.

3.1.2. Types of participants

Participants under the age of 18 years who have been diagnosed with learning disability were considered for inclusion. The diagnosis must have been made using established diagnostic criteria - either the ICD-10 or DSM IV / IV-TR classifications. No restrictions were made on the setting of the participants i.e. community-based, institutionalized or hospitalised. Disruptive behaviour had to be diagnosed using established specified criteria. Studies that included both adults and children were excluded from this review if the data for the children could not be extracted.

3.1.3. Types of interventions

Risperidone by any means of delivery, dose and duration. The control group had to be either a placebo group, a wait-list control group or no treatment group.

3.1.4. Types of outcome measures

Primary outcomes

Disruptive behaviour (aggression to others, non-aggressive challenging behaviour, aggression to self)

Secondary outcomes

Adverse effects

Types of measurement instruments

Standardised diagnostic assessment instruments for primary outcomes:

Nisonger Child Behaviour Rating Form (NCBRF)

Aberrant Behaviour Checklist (ABC)

Behaviour Problem Inventory (BPI)

Clinical Global Impressions Scale (CGI)

Standardised diagnostic assessment instrument for secondary outcomes:

Extrapyramidal Symptom Rating Scale (ESRS)

Other measurement instruments

Measurement of primary outcomes:

Visual Analogue scale (VAS)

Measurement of secondary outcomes:

Prolactin level

Weight gain

3.2. SEARCH METHODS FOR IDENTIFICATION OF STUDIES

3.2.1. Electronic searches

Relevant trials were identified by searching the following databases. No language restrictions were applied:

CENTRAL (Cochrane Central Register of Controlled Trials) 2009

MEDLINE, with OVID online (1966 to June 2009)

PsycINFO, with OVID (1887 to June 2009)

CINAHL, with EBSCO online (1982 to June 2009)

Clinicaltrials.gov (USA) (June 2009)

National Research Register (NRR) (UK) 2009

Search strategies

The search strategies were designed to be both sensitive and specific. The specific search strategy to identify randomised controlled trials, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions in Box 6.4.a, was used in conjunction with medical subject headings and text words specific for learning disability and risperidone (Higgins 2008). When searching different databases, the search terms and strategies were changed to the appropriate syntax to search the appropriate fields. No language restrictions were applied.

Search terms for CENTRAL were as follows:

(mental-retardation*: ME or mentally-disabled-persons*:ME or (learning or mental* or intellect* or cognitiv*) near (difficult* or handicap* or retard* or disable* or disabilit* or deficien* or incapacit* or impair*) or (subnormal* next cognit*) or

(subnormal* near intel*) or (subnormal* near mental*) or (education* near subnormal*)) and (antipsycho* or anti-psycho* or ANTIPSYCHOTIC AGENT or atypical anti-psycho* or atypical antipsycho* or risperidone or risper*)

Search terms for MEDLINE were as follows:

- 1 randomized controlled trial.pt.
- 2 controlled clinical trial.pt.
- 3 randomized.ab.
- 4 placebo.ab.
- 5 drug therapy.fs.
- 6 randomly.ab.
- 7 trial.ab.
- 8 groups.ab.
- 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
- 10 humans.sh.
- 11 9 and 10
- 12 risperidone.mp.
- 13 risper\$.mp.
- 14 106266-06-2.rn.
- 15 or/12-14
- 16 exp mental retardation/
- 17 exp Learning Disorders/
- 18 mentally disabled persons/
- 19 ((learn\$ or mental\$ or intellect\$ or cognitive\$) adj3 (difficult\$ or disable\$ or disabilit\$ or disorder\$ or deficien\$ or incapacit\$ or retard\$ or handicap\$

or impair\$)).tw.

20 ((subnormal\$ or subaverage) adj3 (intel\$ or cognit\$ or mental\$)).tw.

21 (education\$ adj3 subnormal\$).tw.

22 or/16-21

23 11 and 15 and 22

24 limit 23 to animal

25 23 not 24

Search terms for PsychINFO were as follows:

1 randomized

2 controlled clinical trial

3 randomized.ab.

4 placebo.ab.

5 drug therapy.ab.

6 randomly.ab.

7 trial.ab.

8 groups.ab.

9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10 (((mental* or learning or intell* or cognitive*) AND (handicap* or retard* or disab* or difficult* or impair* or subnormal*)) or oligophren* or (mental* or learning or intell* or cognitive*) AND (handicap* or retard* or disab* or difficult* or impair* or subnormal*))

11 explode 'Mental-Retardation' in DE

12 explode 'Learning-Disorders' in DE

13 (antipsycho* or anti-psycho* or neuroleptic* or risperidone*)

14 explode 'Neuroleptic-Drugs' in DE

15 or/10-12

16 13 or 14

17 9 and 15 and 16

Search terms for CINAHL were as follows:

(mental-retardation* OR mentally-disabled-persons* OR cognitiv* impair* OR subnormal* intel* OR (learning OR mental* OR intellect* OR cognitiv*) AND (difficult* OR handicap* OR retard* OR disable* OR disabilit* OR deficien* OR incapacit* OR impair*))

AND (antipsycho* OR anti-psycho* OR ANTIPSYCHOTIC AGENT* OR atypical anti-psycho* OR atypical antipsycho* OR risperidone OR risper*)

3.2.2. Searching other resources

The papers identified through the above search strategy were screened for additional relevant references and their eligibility assessed for inclusion in this review. The references of narrative reviews on this topic were also searched for relevant studies. Handsearches were done on the journals American Journal on Intellectual and Developmental Disabilities (1993 - 2009) (previously known as the American Journal of Mental Retardation) and the Journal of Intellectual Disability Research (1993 - 2009), as risperidone was first approved for use in 1993 by the FDA and it is highly improbable that studies would have used the drug before then. No language restrictions were applied. Ortho-McNeil-Janssen Pharmaceuticals, Inc. the pharmaceutical manufacturers of Risperdal, was contacted to obtain data regarding unpublished and ongoing trials.

3.3. DATA COLLECTION AND ANALYSIS

3.3.1. Selection of studies

Studies eligible for inclusion in this review were all published and unpublished randomised controlled trials and quasi-randomised controlled trials that included information on children and adolescents with learning disability who received risperidone as treatment for disruptive behaviour, identified by the previously described search strategies. The identified titles and available study abstracts were screened by the author and checked independently by the supervisor (AC) to create a pool of eligible studies. Full-text articles were obtained for all titles and abstracts considered relevant and an eligibility form was completed for each of the relevant studies. Any disagreements on the eligibility of any study were resolved by discussion. A study that did not fulfil the inclusion criteria were excluded from this review. Additional information from trial authors were requested where published results did not allow accurate assessment of eligibility.

3.3.2. Data extraction and management

The author extracted the data on study design, participants, and outcome measures using a pre-designed data collection form, and was then checked by the supervisor (AC) for accuracy. At data extraction the study's eligibility was reassessed. All data was entered and organised using Review Manager 5 (RevMan 2008). All data was double-checked for accuracy at data entry. If two or more homogenous studies met the inclusion criteria and reported the same outcome measures using the same scale, a meta-analysis was performed. The statistical analysis was performed by using RevMan 5.

3.3.3. Assessment of risk of bias in included studies

The methodological quality of the selected studies was assessed using standard quality assessment criteria according to the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). Individual study quality was assessed by reviewing the generation of allocation sequence, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other bias. Where inadequate details of randomization and other characteristics of trials were reported, the authors were contacted in order to obtain further information.

Adequate sequence generation was assessed as "Yes", "No" and "Unclear".

- Criteria to be judged as "Yes", indicating low risk of bias:

Random number table, computer generated random numbers, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots, minimization.

- Criteria to be judged as "No", indicating high risk of bias:

Sequences generated by a non-random process like dates of birth, admission date, hospital record number or clinician discretion.

- Criteria to be judged as "Unclear", indicating uncertain risk of bias:

Not enough information available to be judged as "yes" or "no".

Adequate allocation concealment was assessed as "Yes", "No" and "Unclear".

- Criteria to be judged as "Yes", indicating low risk of bias:

Neither investigators nor enrolling participants could predict assignment to groups. Using methods such as central allocation, sequentially numbered identical drug containers, sequentially numbered opaque sealed envelopes.

- Criteria to be judged as "No", indicating high risk of bias:

Either investigators or enrolling participants could possibly predict assignment to groups, introducing selection bias. Using methods such as an open random allocation list, non-opaque and unsealed envelopes, allocation on alternation or rotation, allocation on date of birth, allocation on hospital record number.

- Criteria to be judged as "Unclear", indicating uncertain risk of bias:

Not enough information available to be judged as "yes" or "no".

Adequate blinding (participants, personnel and outcome assessors) was assessed as "Yes", "No" and "Unclear".

- Criteria to be judged as "Yes", indicating low risk of bias:

Certain blinding of participants and their caregivers, as well as key study personnel.

- Criteria to be judged as "No", indicating high risk of bias:

No blinding or incomplete blinding of participants or their caregivers, or the outcome assessors of the study.

- Criteria to be judged as "Unclear", indicating uncertain risk of bias:

Not enough information available to be judged as "yes" or "no".

Incomplete outcome data (addressed) was assessed as "Yes", "No" and "Unclear".

- Criteria to be judged as "Yes", indicating low risk of bias:

No missing outcome data, missing outcome data balanced between groups, missing outcome data unrelated to key outcomes, missing data appropriately and correctly imputed.

- Criteria to be judged as "No", indicating high risk of bias:

Missing data crucial to key outcomes, overall attrition >20%, missing data cause a mismatch of participant numbers between intervention and comparison groups

(attrition difference >10% between groups), missing data inappropriately and incorrectly imputed.

- Criteria to be judged as "Unclear", indicating uncertain risk of bias:

Not enough information available to be judged as "yes" or "no".

Selective outcome reporting (addressed) was assessed as "Yes", "No" and "Unclear".

- Criteria to be judged as "Yes", indicating low risk of bias:

All predefined and expected primary and secondary outcome data reported.

- Criteria to be judged as "No", indicating high risk of bias:

Not all of the predefined and expected primary and secondary outcome data reported, some primary outcomes reported using measurements and scales not predefined, reporting outcomes not pre-specified, one or more key outcome data incompletely reported.

- Criteria to be judged as "Unclear", indicating uncertain risk of bias:

Not enough information available to be judged as "yes" or "no".

Free of other bias was assessed as "Yes", "No" and "Unclear".

- Criteria to be judged as "Yes", indicating low risk of bias:

Study seems free of other sources of bias that could have compromised the validity of the study.

- Criteria to be judged as "No", indicating high risk of bias:

Study has at least one important risk of bias that could have compromised the validity of the study - such as crucial study design flaw, extreme baseline inequality between intervention groups, fraudulent claims.

- Criteria to be judged as "Unclear", indicating uncertain risk of bias:

Not enough information available to be judged as "yes" or "no".

3.3.4. Measures of treatment effect

Binary data - where the outcomes from either standardised instrument scales or diagnostic evaluations were expressed as proportions, results were expressed as relative risks (RR), at a conventional significance level of 5 % ($\alpha=0.05$, 95% confidence interval).

Continuous data - where a score was the outcome measure of a standardised assessment tool, comparisons were made between the means of these scores. If outcome measures were on the same scales, a meta-analysis was performed using a 'weighted' mean difference, at a conventional significance level of 5 % ($\alpha=0.05$, 95% confidence interval).

3.3.5. Unit of analysis issues

The studies included in this systematic review had a standard simple parallel group design, no non-standard designed studies i.e. cross-over, cluster-randomised trials, were found eligible to be included. Thus each study represented a unit in the analysis, where the participants were allocated to a placebo control group or to a risperidone intervention group and only compared to the other participants within that study and not with participants from any other trial.

3.3.6. Dealing with missing data

All missing data and trial drop-outs were reported in the review. Missing statistics, such as standard deviations or correlation coefficients, and insufficient data were requested from the relevant trial authors. Where these data were unavailable or unobtainable, the available data were still included in the review if possible; if not

possible the results of these studies were summarized in the text of the review. In the case of unreported standard deviations or if a study reported only standard errors, the standard deviations were calculated from the available study data, as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008).

3.3.7. Assessment of heterogeneity

Heterogeneity in the results of included studies was assessed using the I^2 measure (Higgins 2002) and the Chi squared test of heterogeneity and also by visual assessment of the graphical display of data in the forest plots. In the presence of significant heterogeneity (i.e. $p < 0.1$, $I^2 > 50\%$), the accuracy of the data was checked to exclude a data capturing error. A fixed-effect method of meta-analysis was used for summarizing the results of the included studies as there was no significant heterogeneity between trial results.

3.3.8. Assessment of reporting biases

Every attempt has been made to identify unpublished studies. One such a study (Read 2008) was found. A funnel plot was not considered to be appropriate to assess reporting bias in this review due to the limited number of included studies.

3.3.9. Data synthesis

Meta-analyses could be performed for the primary outcome of the review, disruptive behaviour, using four outcome measures (Nisonger Child Behaviour Rating Form (NCBRF), Aberrant Behaviour Checklist (ABC), Clinical Global Impression Scale - Improvement (CGI-I), Behaviour Problem Inventory (BPI)) and for three of the secondary outcomes of this review (Adverse effects - Extrapyramidal symptom -

Parkinsonism; Weight gain; Prolactin level). A fixed-effects model was used.

3.3.10. Subgroup analysis and investigation of heterogeneity

Sub-group analyses were planned a priori:

1. Level of learning disability
2. Risperidone therapy in conjunction with behavioural therapies compared to risperidone treatment alone

No subgroup analyses could be performed in this review as data were not reported in such a manner that allowed further analysis.

3.3.11. Sensitivity analysis

The robustness of the review conclusions was intended to undergo further sensitivity analyses i.e. comparing studies with high risk of bias to studies with low risk of bias, and also comparing industry sponsored studies to non-industry sponsored studies. However, insufficient data were available to perform these sensitivity analyses to assess how the study quality would affect the meta-analysis.

4. RESULTS

4.1. DESCRIPTION OF STUDIES

4.1.1. Results of the search

The search strategies were performed in June 2009. The following citations were identified: 203 in MEDLINE, 109 in CENTRAL, 181 in CINAHL, 78 in PsycINFO. Only 63 citations qualified for further inspection. The references of the identified publications were also screened for other publications that might have been relevant to this review. Two authors (Tyrer P, Pandina G) responded to a request for information on other and unpublished studies.

4.1.2. Included studies

Four studies were eligible to be included in this review (Aman 2002; Buitelaar 2001; Snyder 2002; Van Bellinghen 2001). The studies were described as randomised and double-blind. Participants were children and adolescents between 5 and 14 years of both sexes, with a diagnosis of learning disability and reports of disruptive behaviour. A summary of the details of the included studies can be viewed in Table A1 in Appendix A (Characteristics of Included Studies).

Participants

A total of 279 participants received treatment (133 risperidone and 146 placebo) in the four studies combined. The number of participants in the studies were relatively small, ranging from 13 (Van Bellinghen 2001); 38 (Buitelaar 2001); 110 (Snyder 2002); to 118 (Aman 2002). Notably 228 (81.7%) participants in this review are drawn from the two larger studies (Aman 2002; Snyder 2002). All the trials stated the

age range of the participants to be between 5 to 14 years. In addition, all studies stated the gender distribution of participants (218 male, 61 female) and all four trials had well defined inclusion and exclusion criteria. All the participants in the Buitelaar 2001 study were hospitalised, most of the participants in the Snyder 2002 study were living at home with parents, and while the Aman 2002 and Van Bellinghen 2001 studies did not describe the exact location of their study participants, it is highly improbable that they were either hospitalised or institutionalised. The participants in the study by Buitelaar 2001 were institutionalized for very severe aggressive behaviour that was refractory to treatment. The average period of institutionalization was two years.

Intervention

Risperidone was the sole intervention with placebo being used as the comparison in all the included studies. The dosing and duration of the risperidone treatment varied between the studies, with a range of 0.01 mg/kg/day to 0.09 mg/kg/day. Three trials administered the risperidone/ placebo for 6 weeks (Aman 2002; Buitelaar 2001; Snyder 2002), and one study for 4 weeks (Van Bellinghen 2001). All studies used the oral form of risperidone.

Outcomes

All four included studies used the improvement of disruptive behaviour or aggression in children with learning disability as a primary outcome. These behaviours were also the major inclusion criteria for this review. The studies used both validated and unvalidated scales as outcome measures. These are listed in Table 7 and described in more detail below.

Table 7. Scales & measures used in the studies

Scale / measure	Aman 2002	Buitelaar 2001	Snyder 2002	Van Bellinghen 2001
Aberrant Behaviour Checklist (ABC)	Yes	Yes	Yes	Yes
Behaviour Problems Inventory (BPI)	Yes	-	Yes	-
Clinical Global Impression (CGI)	Yes	Yes	Yes	Yes
Extrapyramidal Symptom Rating Scale for Children (ESRS)	Yes	Yes	Yes	Yes
Nisonger Child Behaviour Rating Form	Yes	-	Yes	-
Overt Aggression Scale – Modified OAS-M	-	Yes	-	-
Personal Assessment Checklist (PAC)	-	-	-	Yes
Visual Analogue Scale – Parent rated (most troublesome symptoms)	Yes	-	Yes	-

Validated ScalesNisonger Child Behaviour Rating Form (NCBRF) (Aman 1996)

This instrument is used to assess behaviour severity and change in children with developmental disabilities. A Parent and Teacher version are available. The Parent NCBRF consists of 2 positive social subscales and 6 problem behaviour subscales. The positive/social subscales are as follows: 1) Compliant/Calm, and 2) Adaptive Social. The categories are presented in a question format and allow awarding of high scores to good behaviour. The score for each subscale item ranges from 0 (indicating "not true") to 3 ("always true"). A high score indicates less severe symptoms.

The Problem Behaviour subscales are: 1) Conduct problems, 2) Insecure/Anxious, 3) Hyperactive, 4) Self-injury/ Stereotypic, 5) Self-isolating/ Ritualistic, 6) Overly sensitive. There are 66 question items, with a score for each item ranging from 0 (indicating "no problem") to 3 ("severe problem"). Unlike the social subscales, a high score achieved on the Problem Behaviour subscale indicate severe symptoms.

Aberrant Behaviour Checklist (Aman 1986)

This behaviour assessment instrument assesses the efficacy of behaviour management in individuals with developmental disabilities. It is comprised of 5 subscales, with 58 subcategories in total viz. 1) Irritability (15 items), 2) Lethargy/Social withdrawal (16 items), 3) Stereotypic Behaviour (7 items), 4) Hyperactivity/ Non-compliance (16 items), and 5) Inappropriate speech (4 items). The score for each item begins at 0 indicating "no problem" with the highest score indicating a "severe problem". A high score on the ABC denotes severe symptoms.

Clinical Global Impression Scale (Guy 1976)

This scale is used to assess the severity of illness and the response to treatment in individuals with mental illness. It is made up of three categories viz. 1) Severity of Illness, 2) Global Improvement, 3) Efficacy Index. The first item is rated on a seven-point scale (1=normal to, 7=extremely ill); Item 2 has a seven-point scale (1=very much improved, to 7=very much worse); and Item 3 is comprised of a four-point scale (from "none" to "outweighs therapeutic effect"). The scales are often used individually. The utility of the scale is in the clinical setting to assess by how much the patient's symptoms have improved or worsened compared to a baseline state. Low scores indicate a decrease in the severity of symptoms.

Behaviour Problem Inventory (Rojahn 2001)

This instrument is used to assess aggression, self-injury and stereotypic behaviour in individuals with developmental disabilities.

Extrapyramidal Symptom Rating Scale (Chouinard 1980)

The extrapyramidal symptom rating scale is used to assess the presence and severity of extrapyramidal symptoms in an individual. It consists of 5 sections each comprised of subsections viz. 1) Open-ended questions addressed to the individual or carer regarding extrapyramidal symptoms (12 items), 2) Parkinsonism section (8 items), 3) Dystonia section (2 items), 4) Dyskinesia section (7 items), 5) Global impression of overall severity of parkinsonism and dyskinesia.

Unvalidated Scales

Overt Aggression Scale (OAS-M) (Yudofsky 1986)

This scale is used to assess aggression and violence in an individual. Four types of aggression are scored on a 4-point scale viz. 1) Verbal aggression, 2) Destruction of property, 3) Aggression to self, 4) Physical violence. The total score ranges from 0 to 16, with a high score indicating severity of symptoms.

Visual Analogue Scale (VAS)

The VAS / Symptom tool is used to measure the rating of the severity of the most troublesome symptom in a participant. Observations by the carer or parent are recorded and rated. The VAS/ Sedation tool is used to measure the rating of the severity of sedation in a participant. Observations by the carer or parent are recorded and rated.

Personal Assessment Checklist (PAC)

Unvalidated scale not used often in clinical practice or research (Ettinger 2006).

4.1.3. Excluded studies

Twenty six studies did not meet the inclusion criteria for this review and were therefore excluded from this review. The full list of excluded studies and their reason for exclusion are reported in Table A2 in Appendix A (Characteristics of Excluded Studies). The most common reason for exclusion was because they were open label trials and not randomised controlled trials.

4.2. RISK OF BIAS IN INCLUDED STUDIES

Only one study reported adequate sequence generation (Snyder 2002), but did not report sufficient details to assess allocation concealment. None of the included studies reported sufficient information to assess adequate allocation concealment. Two studies described blinding briefly but adequately (Aman 2002; Snyder 2002).

All studies reported attrition rates and causes of attrition; and used an intention-to-treat analysis. Two studies were reviewed to have a low risk of bias as assessed by their reporting of incomplete outcome data (Buitelaar 2001; Van Bellinghen 2001).

All participants completed the Van Bellinghen 2001 study, 2 participants receiving placebo withdrew from the Buitelaar 2001 study early (before the end of the double-blind period) and 1 participant on risperidone withdrew during the washout period.

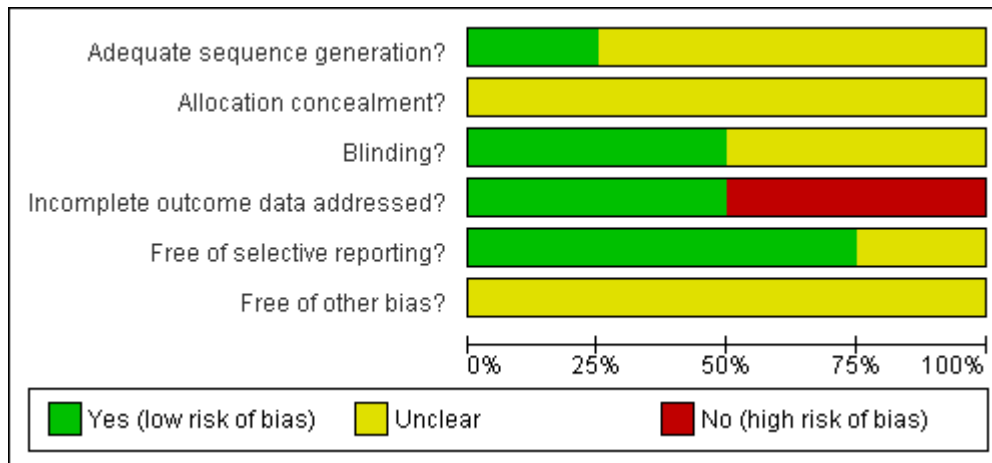
Two studies were reviewed to have a high risk of bias when assessing their attrition

rates (Aman 2002; Snyder 2002). Thirty one of the 118 participants did not complete the study with an overall attrition rate of 26% in the Aman 2002 study. There was a noticeable difference between the attrition numbers in the risperidone (12/55 (21 %)) and placebo (19/63 (30 %)) groups. The reasons for early withdrawal differed between the risperidone and placebo groups. In the risperidone group the reasons for attrition were reported as; 4 (7.3%) insufficient response; 3 (5.5%) non-compliance; 2 (3.6%) adverse events; 1 (1.8%) lost to follow up (LTFU); 1 (1.8%) consent withdrawn; 1 (1.8%) medication lost. In the placebo group the reasons for attrition were reported as; 15 (23.8%) insufficient response; 3 (4.8%) lost to follow up; 1 (1.6%) consent withdrawn. The study excluded three risperidone participants on whom no outcome data were collected from the efficacy analysis. However, these participants appeared not to have been included in the study's attrition report. A recalculation shows that the total risperidone attrition rate could be slightly higher with figures of 15/55 (27%). In the Snyder 2002 study, 25 out of the 110 participants did not complete the study, with an overall attrition rate of 22.7%. There was a noticeable difference between the attrition numbers in the risperidone (6/53 (11.3 %)) and placebo (19/57 (33.3 %)) groups. The reasons for early withdrawal in the risperidone group were reported as; 2 (3.8%) insufficient response; 1 (1.9%) lost to follow up; 3 (5.7%) loss of consent. In the placebo group the reason was; 19 (33.3%) insufficient response.

Three studies reported all outcomes (Aman 2002; Buitelaar 2001; Snyder 2002). It was unclear if any of the included studies were free of other bias, and all of the four studies were industry sponsored (Ortho-McNeil-Janssen Pharmaceuticals, Inc.). The risk of bias table for each included study is presented at the bottom of Table A1 in

Appendix A (Table of Characteristics of Included Studies). The summary of the risk of bias in all included studies is presented in Figure 2, Methodological quality summary.

Figure 2. Methodological quality summary



4.3. EFFECTS OF INTERVENTIONS

Four studies involving 279 participants were included in this systematic review. However, because of the variation in the presentation of results and data, all four studies were not able to be used simultaneously in the meta-analyses of each outcome measure. Limited analyses was possible using two to three of the studies for each of the five different measurement scales for the primary outcome and the secondary outcomes or adverse events which included weight gain, prolactin levels and an extrapyramidal symptom (parkinsonism) using the Extrapyramidal Symptom Rating Scale (ESRS). Primary and secondary outcome measurements and results are presented narratively, all the data tables are presented in Appendix B and all the forrest plots in Appendix C.

4.3.1. Primary Outcome (disruptive behaviour)

Disruptive behaviour as the primary outcome denominator was principally measured on the Nisonger Child Behaviour Rating Scale and then comparing the participants behaviour at baseline to their behaviour at study endpoint. The symptoms listed on the Nisonger conduct problem subscale correspond well with the diagnostic criteria of the DSM IV Disruptive behaviour disorders. Other behaviour assessment tools used were the Aberrant Behaviour Checklist (ABC); the Behaviour Problem Inventory (BPI); and the investigator's rating on the Clinical Global Impression Improvement scale (CGI-I). Additionally, a change in the Visual Analogue Scale (VAS) rating of an individual target symptom reported by parents for each patient was assessed. The unvalidated Personal Assessment checklist (PAC) was only used by one study Van Bellinghen 2001, as was the Overt Aggression scale (OAS-M) (Buitelaar 2001) and their results reported narratively. Please refer to section 4.1.2 for the scales of measurement for the different measurement tools to interpret the size of differences in the mean scores.

Nisonger Child Behaviour Rating form - NCBRF (Tassé 1996)

For the Nisonger scale, meta-analysis was carried out on two studies (Aman 2002 and Snyder 2002) in which the parent version of the social competence and problem behaviours subscales was used. Snyder 2002 reported the means at baseline and endpoint, while Aman 2002 reported the change in means at endpoint. A fixed-effects model meta-analysis was used and a low degree of heterogeneity was found on most subscales as both studies were similarly designed and had similar sample populations. The results of the meta-analysis are as follows:

Nisonger: Social Competence Subscale 01: Compliant/calm

The analysis of the compliant/calm subscale yielded a mean positive score of 1.89 higher on risperidone than on placebo [95% CI = 0.94, 2.84 ($p < 0.0001$)]. The Chi² test for Heterogeneity was 0.09 on 1 degree of freedom ($p = 0.77$) and the I² was 0% for this outcome.

Nisonger: Social Competence Subscale 02: Adaptive/social

The analysis of the adaptive/social subscale yielded a mean positive score 1.54 higher on risperidone than on placebo [95% CI = 0.88, 2.20 ($p < 0.00001$)]. Chi² test for Heterogeneity = 0.02, $df = 1$ ($p = 0.88$); I² = 0%.

Nisonger: Problem Behaviours Subscale 01: Conduct problem

The analysis of the conduct problem subscale, the principle measure of the primary outcome in this review, yielded a mean positive score -8.67 lower on risperidone than on placebo [95% CI = -11.72, -5.62 ($p < 0.00001$)]. Chi² test for Heterogeneity = 0.06, $df = 1$ ($p = 0.80$); I² = 0%.

Nisonger: Problem Behaviours Subscale 02: Insecure/anxious

The analysis of the insecure/anxious subscale yielded a mean positive score -4.24 lower on risperidone than on placebo [95% CI = -6.13, -2.35 ($p < 0.0001$)]. Chi² test for Heterogeneity = 1.54, $df = 1$ ($p = 0.21$); I² = 35%.

Nisonger: Problem Behaviours Subscale 03: Hyperactive

The analysis of the hyperactive subscale yielded a mean positive score -2.84 lower on risperidone than on placebo [95% CI = -4.39, -1.30 ($p = 0.0003$)]. Chi² test for Heterogeneity = 1.40, $df = 1$ ($p = 0.24$); I² = 28%.

Nisonger: Problem Behaviours Subscale 04: Self-injury/stereotypic

The analysis of the self-injury/stereotypic subscale yielded a mean positive score -0.83 lower on risperidone than on placebo [95% CI = -1.71, 0.05 ($p = 0.06$)]. Chi² test

for Heterogeneity = 0.31, df = 1 (p = 0.58); I² = 0%.

Nisonger: Problem Behaviours Subscale 05: Self-isolated/ritualistic

The analysis of the self-isolated/ritualistic subscale yielded a mean positive score -1.47 lower on risperidone than on placebo [95% CI = -2.45, -0.48 (p = 0.004)]. Chi² test for Heterogeneity = 0.09, df = 1 (p = 0.77); I² = 0%.

Nisonger: Problem Behaviours Subscale 06: Overly sensitive

The analysis of the overly sensitive subscale yielded a mean positive score -0.95 lower on risperidone than on placebo [95% CI = -1.87, -0.04 (p = 0.04)]. Chi² test for Heterogeneity = 7.07, df = 1 (p = 0.008); I² = 86%.

Both Aman 2002 and Snyder 2002 reported benefit in the two positive/social subscales that assigned higher scores to improved behaviour, with a similar statistically significant overall summary effect of benefit. The summary effect also showed benefit in all the problem behaviour subscales that assigned lower scores to improved behaviour. All meta-analyses of problem behaviour subscales were statistically significant at a level of 95% confidence interval except for the self-injury/stereotypic subscale which was marginally statistically insignificant (p=0.06).

Aberrant Behaviour Checklist- ABC (Aman 1986)

For this validated scale, meta-analysis was possible as Aman 2002, Buitelaar 2001 and Snyder 2002 all used the measurement throughout its five subscales. Van Bellinghen 2001 used this scale, but did not report any standard deviations or enough data to calculate standard deviations. Two of the ABC subscales (irritability and stereotypy) are measures of disruptive behaviour which is the primary outcome. Although Buitelaar 2001 and Snyder 2002 reported the means at baseline and

endpoint, and Aman 2002 reported the change in means at endpoint, the data could still be combined in a fixed-effects model meta-analysis with the results below. A numerical error was found in the irritability subscale data point of ABC in Snyder 2002, however the correct figure was obtained from the text.

ABC Subscale 01: Irritability

The analysis of the ABC subscale of irritability yielded a mean score on risperidone of -4.00 lower than on placebo [95% CI = -6.07, -1.92 (p = 0.0002)]. Chi² test for Heterogeneity = 2.40, df = 2 (p = 0.30) and the I² was 17% for this outcome.

ABC Subscale 02: Social withdrawal/ Lethargy

The analysis of the ABC subscale of social withdrawal/lethargy yielded a mean score on risperidone of -2.55 lower than on placebo [95% CI = -4.07, -1.02 (p = 0.001)]. Chi² test for Heterogeneity = 0.63, df = 2 (p = 0.73); I² = 0%.

ABC: Subscale 03: Hyperactivity

The analysis of the ABC subscale of hyperactivity yielded a mean score on risperidone of -0.77 lower than on placebo [95% CI = -1.68, 0.13 (p = 0.09)]. Chi² test for Heterogeneity = 0.03, df = 2 (p = 0.98); I² = 0%.

ABC: Subscale 04: Stereotypy

The analysis of the ABC subscale of stereotypy yielded a mean score on risperidone of -6.65 lower than on placebo [95% CI = -9.24, -4.05 (p < 0.00001)]. Chi² test for Heterogeneity = 3.88, df = 2 (p = 0.14); I² = 48%.

ABC: Subscale 05: Inappropriate speech

The analysis of the ABC subscale of inappropriate speech yielded a mean score on risperidone of 0.77 higher than on placebo [95% CI = 0.15, 1.40 (p = 0.02)]. Chi² test for Heterogeneity = 30.58, df = 2 (p < 0.00001); I² = 93%.

The results of the ABC irritability and stereotypy subscales appear to significantly favour risperidone compared to placebo, at a level of 95% confidence interval. The results of the social withdrawal / lethargy subscale were also significantly in favour of risperidone, but the changes in the hyperactivity and inappropriate speech subscales were not significant. The markedly high heterogeneity ($I^2 = 93\%$) in the analysis of the inappropriate speech subscale was an unexpected finding compared to the other subscales and the cause remains unclear. A change in the effects model of analysis does not change the heterogeneity of this subscale significantly. The result of the inappropriate subscale should thus be interpreted with caution, although the very low heterogeneity on all the other subscales is reassuring to validate the results of each subscale, as well as those of the primary outcome.

Behaviour Problems Inventory Subscale (BPI) (Rojahn 2001)

Aman 2002 and Snyder 2002 were the only two studies to report data using the BPI scale, allowing a meta-analysis to be performed across its three subscales. The first two subscales (“aggressive / destructive” and “self-injurious”) recognize the key features of disruptive behaviour which is the primary outcome in this study review:

BPI Subscale 01: Aggressive/ destructive

The analysis of the aggressive/ destructive subscale yielded a mean score of -4.96 lower on risperidone than on placebo [95% CI = -7.31, -2.61 ($p < 0.0001$)]. The Chi² test for Heterogeneity was 0.25 on 1 degree of freedom ($p = 0.62$) and the I^2 was 0% for this outcome.

BPI Subscale 02: Self-injurious

The analysis of the self-injurious subscale yielded a mean score -0.41 lower on

risperidone than on placebo [95% CI = -2.12, 1.29 (p = 0.63)]. Chi² test for Heterogeneity = 0.03, df = 1 (p = 0.87); I² = 0%.

BPI Subscale 03: Stereotyped

The analysis of the stereotyped subscale yielded a mean score -0.38 lower on risperidone than on placebo [95% CI = -1.46, 0.69 (p = 0.48)]. Chi² test for Heterogeneity = 0.53, df = 1 (p = 0.47); I² = 0%.

The result of the BPI aggressive / destructive subscale appears to significantly favour risperidone compared to placebo, at a level of 95% confidence interval. The changes in the self-injurious and stereotyped subscales were not significant.

Clinical Global Impression Scale -CGI scale (Guy 1976)

Although the CGI scale was used by all four studies, (Buitelaar 2001) was the only study to report on the Severity scale without the Improvement scale. The data collected in the seven point Improvement scale in Aman 2002, Snyder 2002 and Van Bellinghen 2001 was reported on different ways in each study. Van Bellinghen 2001 combined the seven points into two categories, but no standard deviations were reported, so it could not be included in a meta-analysis. The data from Aman 2002 and Snyder 2002 was converted into two categories comparing "much worse / worse / unchanged" to "minimally improved/ moderately improved / much improved / very much improved". With the data in binary form, the relative risk (Mantel-Haenszel Risk Ratio) of improvement in the CGI-I was shown to be 2.69 [95% CI = 2.00, 3.62 (p < 0.00001)], indicating a significant difference between the use of risperidone and placebo, favouring risperidone. Heterogeneity did not appear sizeable (Chi² = 1.19, df = 1 (p = 0.28); I² = 16%).

Visual Analogue Scale for most severe symptoms (caregiver)

The VAS is an unvalidated and relatively inaccurate test for assessing change in behaviour by caregivers, however it was used as a secondary efficacy measure of the primary outcome in Aman 2002 and Snyder 2002. Meta-analysis was possible and showed a significant difference between groups, favouring risperidone, with a mean score of -22.56 mm lower on the 100 mm scale at endpoint [95% CI = -24.09, -21.02 ($p < 0.00001$)], however there was moderate to substantial Heterogeneity ($\text{Chi}^2 = 1.90$, $\text{df} = 1$ ($p = 0.17$); $I^2 = 47\%$)

Study results not included in meta-analyses

Results from Buitelaar 2001 for the OAS-M showed that risperidone treatment was associated with a significant reduction of the overall score ($p < 0.01$), as well as in the physical aggression subscale ($p < 0.001$) and aggression to property subscale ($p < 0.01$). Results from Van Bellinghen 2001 for the PAC showed that risperidone was significantly superior than placebo in the social relationship subscale ($p < 0.05$) and occupational attitudes ($p < 0.05$). Neither of these two subscales are core diagnostic features of disruptive types of behaviours.

4.3.2. Secondary Outcomes

Adverse events

Adverse events were reported in 117 participants (88.0%) in the risperidone groups and 103 (70.5%) in the placebo groups in total in the four studies. The numbers of adverse events in each study are presented in Table 8 below; however the authors included mild, moderate and severe adverse effects together in this data. Two participants discontinued treatment and withdrew from one study (Aman 2002)

because of adverse events (significant somnolence in both cases). No other participants withdrew due to adverse effects in the other three studies. Adverse effects of importance or clinical significance such as extrapyramidal symptoms, weight gain, sedation/ somnolence and prolactin levels are presented in detail below.

Table 8. Number of adverse events (%) in risperidone and placebo groups

Study	Risperidone	Placebo
Aman 2002	54 / 55 (98%)	44 / 63 (70%)
Buitelaar 2001	17 / 19 (89%)	11 / 19 (58%)
Snyder 2002	42 / 53 (79%)	46 / 57 (81%)
Van Bellinghen 2001	4 / 6 (67%)	2 / 7 (29%)
Total	117 / 133 (88%)	103 / 146 (71%)

Extrapyramidal Symptom Rating Scale for Children (ESRS)

All four studies used the ESRS to assess extrapyramidal symptoms in the risperidone and placebo groups. All four studies reported no significant between-group differences in extrapyramidal symptoms on any indicator of the ESRS scale, however only Aman 2002 presented complete data. Buitelaar 2001 reported data for the parkinsonism subscale of the ESRS, and thus meta-analysis was possible only for this indicator, showing no significant difference between the groups ($p = 0.85$). Only one participant in Snyder 2002 and one participant in Buitelaar 2001 were rated as developing tardive dyskinesia and orofacial dyskinesia respectively, however these participants were both receiving placebo. No participants in any of the studies required medication to treat extrapyramidal symptoms.

Weight

Aman 2002, Buitelaar 2001 and Snyder 2002 each showed significant increases in mean difference in weight in participants on risperidone compared to placebo (1.30 kg, 1.70 kg and 2.00 kg respectively), while Van Bellinghen 2001 showed no statistical significant difference at endpoint. All four studies reported extractable data for weight of participants at endpoint, allowing meta-analysis using all participant data, resulting in a significant increase of 1.46 kg in mean difference in weight for participants on risperidone compared to placebo [95% CI =0.96, 1.97 ($p < 0.00001$)]. Heterogeneity was negligible ($\text{Chi}^2 = 1.23$, $\text{df} = 3$ ($p = 0.75$); $I^2 = 0\%$).

Sedation / somnolence

Aman 2002, Buitelaar 2001 and Snyder 2002 reported the number of adverse events of sedation or somnolence, with 52 (40.9%) participants in the three studies experiencing sedation in the risperidone groups versus 14 (10.1%) in the placebo groups in total. A fixed-effects meta-analysis showed a significant effect of sedation in those on risperidone versus placebo with a Mantel-Haenszel Risk Ratio of 4.00 [95% CI =2.37, 6.76 ($p < 0.00001$)] with no substantial evidence of heterogeneity ($\text{Chi}^2 = 1.20$, $\text{df} = 2$ ($p = 0.55$); $I^2 = 0\%$).

Aman 2002 also used an unvalidated visual analogue scale for sedation (where higher scores are indicative of sedation), reporting mean scores of 5.90 for risperidone compared to -2.02 for placebo ($F=7.43$, $\text{df}=1$, 99 , $p= 0.008$, ANCOVA with factors for site, baseline, and disorder). Aman 2002 reported that most cases of somnolence were mild, with only two cases reported as severe, but the authors did not specify in which group the severe cases were found. Van Bellinghen 2001 did not report

separate data for adverse events occurring in six participants in the study, but commented that all adverse events were mild except for somnolence, which was moderate.

Prolactin

Aman 2002 and Snyder 2002 both measured and reported prolactin levels separately for male and female participants, which were combined in a fixed-effects meta-analysis. The mean difference in prolactin was 14.56 ng/mL higher at endpoint in female participants on risperidone versus placebo [95% CI =7.35, 21.76 ($p < 0.0001$)], however with substantial heterogeneity ($\text{Chi}^2 = 2.87$, $\text{df} = 1$ ($P = 0.09$); $I^2 = 65\%$). In males, this difference was even higher, with those on risperidone having a mean difference in prolactin of 20.70 ng/mL higher at endpoint compared to placebo [95% CI =15.73, 25.68 ($p < 0.00001$)], with no evidence of heterogeneity ($\text{Chi}^2 = 0.00$, $\text{df} = 1$ ($P = 0.98$); $I^2 = 0\%$). Gynaecomastia, amenorrhoea, or other prolactin-related adverse events were not reported in any of the studies, although Snyder 2002 reported one case of dysmenorrhoea.

Other adverse effects measures

After the adverse effects reported above, the most common symptoms reported by the studies were headache, vomiting, dyspepsia, increased appetite and rhinitis. Data from two studies, Aman 2002 and Snyder 2002, have been collated and presented in Table 9 below. The combined placebo group seems to have a markedly high prevalence of non-specific adverse effects, notably headaches (23.1% in placebo group versus 10.8% in risperidone group).

Vital signs were measured in all studies. A temporary increase in heart rate of 11bpm was found in the first 2 weeks of treatment but not at endpoint in one study (Aman 2002), while a smaller study of 13 participants found a 9.3 bpm increase at endpoint (p=0.05, Van Bellinghen 2001). No significant differences in diastolic blood pressure were found in any of the four studies.

No abnormalities were detected on electrocardiography (ECG). ECG analyses specifically included the calculation of the QTc interval in two studies (Aman 2002, Snyder 2002).

There were no clinically relevant mean changes in haematology, clinical chemistry (including electrolytes, liver function and thyroid tests), or urinalysis parameters in either of the groups reported in any of the studies.

Snyder 2002 detected no significant cognitive changes due to drug condition on any of variables of the California Verbal Learning Test for Children (CVLT).

Table 9. Prevalence of other reported adverse events for risperidone and placebo in two studies (Aman 2002, Snyder 2002)

Adverse events	Placebo (n = 108)		Risperidone (n = 120)	
	N	(%)	n	(%)
Headache	25	23.1%	13	10.8%
Vomiting	17	15.7%	8	6.7%
Dyspepsia	16	14.8%	8	6.7%
Increased appetite	14	13.0%	6	5.0%
Rhinitis	13	12.0%	8	6.7%

5. DISCUSSION

5.1. SUMMARY OF MAIN RESULTS

5.1.1. Clinical therapeutic effects/ efficacy

This systematic study review has shown that risperidone may be of some benefit for the management of certain types of disruptive behaviours in children and adolescents with learning disability, though the findings should be interpreted with caution.

The meta-analyses of the primary outcome scales (Nisonger Child Behaviour Rating Form, Aberrant Behaviour Checklist, Behaviour Problem Inventory) measuring some core symptoms of disruptive behaviour, namely conduct problems, self-injury, irritability, aggressive/ destructive behaviours, stereotypy suggest statistically significant improvement in disruptive type behaviours in children treated with risperidone compared to placebo. Positive behaviours as measured on the Nisonger outcome measurement scale also showed a statistically significant improvement in the children treated with risperidone versus placebo.

5.1.2. Adverse events

As all the randomised controlled trials were of short duration, this review lacked adequate data to confidently comment on the magnitude of adverse effects and the long term safety profile of risperidone. The analysis of the adverse event data from the included studies showed that the prevalence of adverse effects viz. weight gain, sedation/ somnolence and raised prolactin level was significantly higher in the children receiving risperidone.

5.2. OVERALL COMPLETENESS AND APPLICABILITY OF EVIDENCE

5.2.1. Age

The age range of children in the four included studies was between 5 to 14 years, although those over 12 years old were not well represented overall. Therefore caution should be taken when considering the application of this review to younger children below 5 years or older children over the age of 12 years.

5.2.2. Gender

The gender distribution of participants was predominantly male, with 218 male participants and 60 female participants. This ratio approximates the 3:1 ratio of boys to girls diagnosed with conduct disorder (Sadock 2005), providing sufficient confidence of the relevance of the review.

5.2.3. Geographic location

The two larger studies from which 81.7% of participants were drawn for this review were carried out in North America (Aman 2002 in the USA and Snyder 2002 in Canada). The two studies in Central Europe only represented 18.3% of the participants in the review (Buitelaar 2001 in the Netherlands and Van Bellinghen 2001 in Belgium). No details were provided on the ethnicity of the children recruited in the baseline characteristics of the studies. The applicability of this review to most regions outside of North America and in low resource healthcare settings may be limited.

5.2.4. Diagnostic criteria and measurements

Study participants were categorised by classification of severity of IQ score using the DSM-IV classification system (APA 1994), not the most recent DSM-IV TR system (APA 2000). The majority of participants were categorised as borderline severity (IQ 70 – 85). Severe and profound learning disability (IQ < 35) were not represented in any of the studies, and thus the applicability of this review is limited to higher functioning children with borderline, mild and moderate learning disability.

Three of the studies (Aman 2002; Buitelaar 2001; Snyder 2002), representing 95.3% of the participants in the review, used the DSM-IV system to classify disruptive behaviours, categorizing the children into three groups: (i) oppositional defiant, (ii) conduct disorder, (iii) disruptive behaviour disorder not otherwise specified (APA 1994). Van Bellinghen 2001 used a list of persistent behavioural disturbances, some of which correspond to the symptom criteria used in the DSM-IV system. Although the DSM-IV classification system was used in these studies, its use in clinical practice is often limited in children with learning disabilities (Rush 2000; Tyrer 2008). The evidence for the use of risperidone in this review is therefore limited to children with learning disabilities who have met sufficient criteria for the DSM-IV classification of oppositional defiant, conduct disorder or disruptive behaviour disorder not otherwise specified. Its use in children with learning disabilities who have only isolated symptoms such as aggression, or in children who have not been assessed with the DSM-IV classification system for disruptive behaviour disorders is therefore uncertain.

5.2.5. Therapeutic dose

All studies used the oral form of risperidone, while the intramuscular depot preparation was not used, therefore no conclusions can be drawn about the injectable form of the medication. Dosages ranged from 0.01 mg/kg/day to 0.09 mg/kg/day, although doses below 0.03mg/kg/day were not well represented overall. There was no direct comparison of different dosages, therefore no dose-response outcomes could be ascertained. The duration of risperidone treatment was short term, either 4 or 6 weeks, with a significant number of participants not reaching the 6 week endpoint due to high attrition rates. The effects of using risperidone beyond 6 weeks could also not be assessed.

5.3. QUALITY OF THE EVIDENCE

This study review included four studies involving 279 children with learning disability. The overall methodological quality of the studies was insufficient to provide robust evidence in this review. The studies had relatively small sample sizes, with two studies lacking sufficient statistical power (Buitelaar 2001; Van Bellinghen 2001). An overall assessment showed a moderately high risk of bias in the studies (see Figure 2), raising the possibility of artificially influencing the treatment effect estimates in the results. Attrition, in particular, was assessed as high in the two largest studies (Aman 2002; Snyder 2002), and even though the authors reported methods to account for missing data (intent-to-treat analysis), bias could still have affected the study outcomes. The fact that all studies were funded by Ortho-McNeil-Janssen, the manufacturer of the original Risperdal patented drug, raises further questions about the independence of the results.

5.4. POTENTIAL BIASES IN THE REVIEW PROCESS

All attempts were made to minimize the introduction of bias in the review process itself, by extensive and rigorous screening and selection of potentially eligible studies from major electronic databases and the systematic and methodical assessment of the quality of the included studies. This thorough process did result in the finding of an unpublished study. However, despite all these efforts it is possible that selection bias could have been introduced as the databases EMBASE and LILACS were not available to conduct a search. The conference proceedings of the annual American Psychiatric Association (APA) conference were also not available to be handsearched as originally planned.

5.5. AGREEMENTS / DISAGREEMENTS WITH OTHER STUDIES OR REVIEWS

Cochrane systematic reviews have been published on the use of antipsychotic agents (including risperidone) for challenging and disruptive behaviours in adults with learning disability and on the use of risperidone for aggression and self injury in autism spectrum disorders. This study review is in agreement with systematic and other literature reviews that some evidence exists to suggest that risperidone is helpful for the treatment of disruptive types of behaviour (such as aggression), although the methodological quality and inadequate statistical power of the currently available studies limits its widespread application.

6. AUTHOR'S CONCLUSIONS

6.1. IMPLICATIONS FOR PRACTICE

(i). The evidence for risperidone management of disruptive behaviour in children and adolescents with learning disability is not conclusive; there is some evidence to show that risperidone may improve behaviour in certain cases of disruptive behaviour in children with learning disability, however the current evidence is weakened by poor methodological quality. The known potential risk of risperidone to cause serious adverse effects and the unknown long term safety profile should caution clinicians in its use.

ii). If risperidone is used in children with learning disability, it should only be used to treat disruptive type behaviours on a short term basis for symptomatic care as part of a multidisciplinary approach. It should never be used as a first line treatment for the management of disruptive type behaviours, and pharmacological treatment should always be considered second line to non-pharmacological methods of management. Risperidone should preferably only be prescribed by a specialist in the field. The patient should be followed-up on a regular basis with regular monitoring of potential adverse effects (especially weight gain, sedation and prolactin levels). After symptoms have been managed, a trial of withdrawal from the drug should be implemented. No child should received risperidone therapy routinely on a long term basis. Attempts to withdraw the medication should be carried out as a matter of course.

(iii). The optimum duration of treatment is not yet established.

(iv). It is very important to exclude other causes (organic, psychological, social) of disruptive behaviour and due consideration should be given to the differential diagnoses of disruptive behaviour, before considering pharmacotherapy such as risperidone as a treatment option.

(v). Before risperidone is prescribed to a child with learning disability and disruptive behaviour both the caregiver and patient must be made aware of the paucity of available evidence to support the efficacy and safety of its use for this purpose. It is essential that caregivers in the USA know that risperidone is being used off-label as it is not registered or indicated for use in children with learning disability and disruptive behaviour.

(vi). South African clinicians need to be aware of the available evidence on the efficacy of risperidone as well as the discrepancy between the South African and USA approval of risperidone for use in disruptive behaviours in children with learning disability.

(vii). Risperidone should not replace other management modalities of disruptive behaviour as first line treatment in poorly resourced communities that have suboptimal facilities for managing patients with learning disability and disruptive behaviour.

6.2. IMPLICATIONS FOR RESEARCH

- (i). Further research is needed to add to the current body of evidence.

- (ii). The methodological quality of future research designs should be improved to reflect the true effect of risperidone in this population. Adequate study sample sizes, the reporting of standard deviations, the publication of negative trials and trials not sponsored by the drug manufacturer would decrease some of the bias existing in the current literature and increase the statistical power for analyses.

- (iii). Studies need to use standardised diagnostic criteria to diagnose behavioural problems in children with learning disability. The ICD-10 Mental retardation classification should be considered as such a standard, as it contains a descriptive behavioural component.

- (iv). Studies should use the same standardised rating scales to assess disruptive behaviours, to enable comparison of studies.

- (v). Future studies need to be of longer duration to assess the long term effects and safety profile of risperidone, especially on growth and sexual maturation.

- (vi). Studies should report the levels of severity of learning disability in the participants in more detail.

- (vii). Studies need to compare risperidone to other treatment modalities viz. other drugs and non-pharmacological treatments.

(viii). Studies undertaken in locations outside the USA and Canada would enhance the applicability and validity of the evidence.

(ix). More research is needed on the efficacy of other treatment modalities of disruptive behaviours in learning disabled children.

7. REFERENCES

7.1. REFERENCES TO STUDIES

7.1.1. Included studies

Aman 2002

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8. DECLARATION OF INTEREST / SOURCES OF SUPPORT

No known conflict of interest.

No external sources of support.

APPENDIX A: CHARACTERISTICS OF STUDIES

Table A1. Characteristics of Included Studies

Aman 2002 Characteristics table

Methods	<p>Allocation: Randomised, stratified by diagnosis (conduct disorder versus other diagnoses (oppositional defiant disorder or disruptive behaviour disorder not otherwise specified)). No further details on method of randomization.</p> <p>Blindness: Double-blind, risperidone and placebo identical in appearance, taste and smell. No further details.</p> <p>Duration: 1 week single blind treatment with placebo to exclude placebo responders, remaining patients entered 6 weeks double blind phase.</p>
Participants	<p><u>Inclusion criteria:</u> Children with total rating ≥ 24 on the conduct problem subscale of the Nisonger Child Behaviour Rating Form DSM-IV axis I diagnosis of conduct disorder, oppositional defiant disorder, or disruptive behaviour disorder not otherwise specified DSM-IV axis II diagnosis of subaverage IQ (IQ ≥ 36 and ≤ 84) Vineland Adaptive Behaviour Scale score ≤ 84 Sufficiently severe symptoms that investigator determined need for antipsychotic treatment Responsible accompanying parent or caretaker for study visits, to provide reliable assessments, and to dispense study medication.</p> <p><u>Exclusion criteria:</u> Previous use of risperidone Diagnosis of pervasive developmental disorder, schizophrenia, or other psychotic disorder Head injury as a cause of intellectual disability Seizure disorder requiring medication Known hypersensitivity to risperidone or neuroleptics History of tardive dyskinesia or neuroleptic malignant syndrome Serious or progressive illness Human Immunodeficiency Virus (HIV) infection Use of an investigational drug within previous 30 days Laboratory values of standard blood screening outside the normal range (unless investigator determined that deviations not clinically relevant) Sexually active female subjects of childbearing age not using a medically validated birth control method Total study N = 118 subjects Recruited and screened = 142 subjects Randomised = 119 subjects</p>

	<p>Age: 5 - 12 years Age mean in risperidone group = 8.7 years Age mean in placebo group = 8.1 years Sex: 97 male, 21 female Risperidone group = 47 boys, 8 girls Placebo group = 50 boys, 13 girls <u>Location:</u> Multi-centre study with 11 study sites (only USA mentioned, but locations of all 11 study sites not detailed) Participants recruited at centres for developmental disabilities</p>
Interventions	<p>1. Risperidone: N=55 2. Placebo: N=63 <u>Dosage and administration:</u> Commenced on day 1 at a dose of 0.01 mg/kg per day and increased to 0.02 mg/kg per day on day 3 Dose adjusted at weekly intervals as necessary only until 28 days, then dose remained constant Maximum dose of 0.06mg/kg per day Administered once daily in the morning unless subject experienced breakthrough symptoms in evening, then administered twice daily Risperidone and placebo identical in appearance, taste and smell</p>
Outcomes	<p><u>Primary efficacy measures:</u> 1. Conduct problem subscale of Nisonger Child Behaviour Rating Form Secondary efficacy measures: 2. Other subscales in problem behaviour section and social competence section of Nisonger Child Behaviour Rating Form 3. Aberrant Behaviour Checklist subscale 4. Clinical Global Impression (CGI) severity scale and CGI improvement scale 5. Visual Analogue Scale for target symptom</p> <p>Other outcome measures: 6. Adverse events 7. Prolactin 8. Growth Hormone 9. Continuous Performance Test 10. California Verbal Learning Test, Childrens' version 11. Extrapyrmidal Symptom Rating Scale 12. Vital signs 13. Weight</p>
Notes	<p>Concomitant use of other antipsychotics, anticonvulsants, antidepressants, lithium, carbamazepine, valproic acid, or cholinesterase inhibitors not permitted. Psychostimulants (e.g., methylphenidate, pemoline, dextroamphetamine) permitted if dose stable for 30 days. Behavioural therapy permitted if initiated at least 30 days before the start of study.</p>

	<p>No medications for sleep or anxiety to be initiated during trial. Subjects receiving antihistamines, chloral hydrate, or melatonin for sleep before the screening visit could continue this medication unchanged during the trial.</p> <p>Medications commonly used to treat extrapyramidal symptoms (e.g., diphenhydramine, benztropine, trihexyphenidyl) were discontinued at study entry. If extrapyramidal symptoms arose during study, the dose of study medication was decreased. If this resulted in deterioration of conduct disorder symptoms or failed to improve the extrapyramidal symptoms, anti-extrapyramidal symptom medication could be considered.</p>
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Aman 2002 Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	"randomized" "were randomly assigned to treatment groups" "randomization was stratified according by diagnosis". Insufficient information to determine.
Allocation concealment?	Unclear	No information.
Blinding?	Yes	"double-blind" "two study solutions were identical in appearance, taste and smell"
Incomplete outcome data addressed?	No	<p>Attrition rates and reasons reported Intention-to-treat-analysis done Overall attrition 26 % Unbalanced in numbers across risperidone and placebo group (Risperidone 12/55 (21 %), Placebo 19/63 (30 %) Unbalanced in reason for attrition across risperidone and placebo group Risperidone 4 (7.3%) insufficient response 3 (5.5%) non-compliance 2 (3.6%) adverse events 1 (1.8%) LTFU 1 (1.8%) consent withdrawn 1 (1.8%) medication lost</p> <p>The three risperidone participants on whom no outcome data was collected and then excluded from efficacy analysis do not seem to be included in the study's attrition report. The total risperidone attrition could thus be 15/55 (27%) Placebo 15 (23.8%) insufficient response 3 (4.8%) LTFU 1 (1.6%) consent withdrawn</p>
Free of selective reporting?	Yes	All outcomes and standard deviations reported.
Free of other bias?	Unclear	Manufacturer sponsored.

Buitelaar 2001 Characteristics table

Methods	<p>Allocation: Randomised, randomization code was generated by computer in blocks of 4 numbers.</p> <p>Blindness: Double-blind, psychiatrist outcome assessors blinded to treatment.</p> <p>Duration: 2 week baseline period, 6 weeks double-blind treatment period, and then a 2 week washout period.</p>
Participants	<p><u>Inclusion criteria:</u> Children aged between 12 and 18 years of age Full scale IQ between 60 and 90 on the Wechsler Intelligence Scale for Children, Revised DSM-IV axis I diagnosis of conduct disorder, oppositional defiant disorder, or attention-deficit/hyperactivity Aggressive behaviour persisted in ward (at least score of 1 on Overt Aggression Scale (OAS-M)) Clinical indication for drug treatment Aggressive behaviour failed to respond to behaviour treatment approach</p> <p><u>Exclusion criteria:</u> Neurologic, pulmonary, cardiac or hepatic disease Diagnosis of primary mood disorder, schizophrenia, or other active psychosis, or suicidality Comorbid DSM IV diagnosis of substance abuse disorder Major change in treatment regime anticipated in near future Female subjects, who were pregnant or using inadequate contraception Considered inappropriate to discontinue current psychotropic medication</p> <p>Total study N = 38 subjects Recruited and screened = 145 subjects Eligible and invited to partake in study = 45 Randomised = 38 subjects Age: 12-18 years Age mean in risperidone group = 14 years Age mean in placebo group = 13.7 years Sex: 33 male, 5 female Risperidone group = 17 boys, 2 girls Placebo group = 16 boys, 3 girls</p> <p><u>Location:</u> Tertiary referral centres in the Beele (Voorts) and Groot Emaus (Ermelo), in the Netherlands, for adolescents with severe aggressive behaviour and borderline intelligence or mild learning disability.</p>
Interventions	<p>1. Risperidone: N = 19 2. Placebo: N = 19</p>

	<p><u>Dosage and administration:</u> Commenced on day 1 at a dose of 1mg per day 6 week double blind phase consisted of 2 week dose-rising phase and 4 week fixed-dose phase Titration started with 0.5 mg twice daily (8 am and 6 pm) Maximum dose of 5 mg twice per day</p>
Outcomes	<p><u>Primary efficacy measures:</u> 1. Clinical Global Impression (CGI) severity scale</p> <p><u>Secondary efficacy measures:</u> 2. Overt Aggrion Scale (OAS-M) 3. Aberrant Behaviour Checklist subscale</p> <p><u>Other outcome measures:</u> 4. Extrapyramidal Symptom Rating Scale (ESRS) 5. Vital signs 6. Weight 7. Adverse events</p>
Notes	No concomitant psychotropic medication allowed during double blind period, except for biperiden and oxazepam for extrapyramidal symptoms and sedation.

Buitelaar 2001 Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Yes	"randomization code had been generated by computer in blocks of 4 numbers"
Allocation concealment?	Unclear	No information on allocation concealment.
Blinding?	Yes	"double-blind conditions" "dosage was adjusted....responsible psychiatrist (JKB or RJ vd G) who was blind to the treatment"
Incomplete outcome data addressed?	Yes	Attrition adequately reported and described Attrition: Placebo 2 Risperidone 1 (during washout period) Endpoint analysis, last observation carried forward
Free of selective reporting?	Yes	All outcomes reported.
Free of other bias?	Unclear	Manufacturer sponsored.

Snyder 2002 Characteristics table

Methods	<p>Allocation: Randomized, placebo-controlled parallel-group. Stratified by diagnosis (conduct disorder vs oppositional defiant disorder or disruptive behaviour disorder not otherwise specified). No further details on method of randomization.</p> <p>Blindness: Double-blind. No further details.</p> <p>Duration: 1 week single blind treatment with placebo to exclude placebo responders, remaining patients entered 6 weeks double blind phase.</p>
Participants	<p><u>Inclusion criteria:</u> DSM-IV diagnosis of CD, ODD, or DBD-NOS Parent/caregiver rating of <24 or higher on the Conduct Problem subscale of the Nisonger Child Behaviour Rating Form IQ between 36 and 84 inclusive Vineland Adaptive Behaviour Scale score <84 Healthy on the basis of a pre-trial physical examination, medical history, and ECG Consent by parent/caregiver</p> <p><u>Exclusion criteria:</u> Diagnosis of pervasive developmental disorder, schizophrenia, or other psychotic disorders Head injury as a cause of impaired IQ Seizure condition requiring medication Females who were sexually active without a reliable form of birth control Serious or progressive illness or clinically abnormal laboratory values History of tardive dyskinesia, neuroleptic malignant syndrome, or hypersensitivity to any antipsychotic drug Known presence of Human Immunodeficiency Virus (HIV) Previous treatment with risperidone</p> <p>Total study N = 110 subjects Recruited and screened = 133 subjects Placebo responders excluded: 23 subjects (17.3%) Randomised to treatment/control = 110 subjects Did not complete full 6 week study = 25 subjects (22.7%) Age: 5 - 12 years Age mean in risperidone group = 8.6 years Age mean in placebo group = 8.8 years Sex: 83 male, 27 female Risperidone group = 41 boys, 12 girls Placebo group = 42 boys, 15 girls</p> <p><u>Location:</u> Multi-centre study with 16 clinical sites (10 in Canada, 4 in the United States, and 2 in South Africa)</p>

	Participants were recruited from clinical practices of the investigators and colleagues, local school districts, self-referrals via newsletter stories, and newspaper and radio advertising
Interventions	<p>1.Risperidone: N=53 2.Placebo: N=57</p> <p><u>Dosage and administration:</u> Medication (risperidone or placebo) was given as an oral solution in the morning Dose began at 0.01 mg/kg for the first 2 days and at 0.02 mg/kg for the next 5 days The physician could increase the dosage weekly by 0.02 mg/kg per day to a maximum of 0.06 mg/kg per day, or decrease the dose by any amount for the remainder of the trial</p>
Outcomes	<p><u>Primary efficacy measures:</u> 1.Conduct problem subscale of Nisonger Child Behaviour Rating Form 2.Other subscales in problem behaviour section and social competence section of Nisonger Child Behaviour Rating Form</p> <p><u>Secondary efficacy measures:</u> 3.Aberrant Behaviour Checklist subscale 4.Behaviour Problems Inventory 5.Visual Analogue Scale for target symptom 6.Clinical Global Impression (CGI) severity scale and CGI improvement scale</p> <p><u>Other outcome measures:</u> 7.Reported adverse events 8.Extrapyramidal Symptom Rating Scale 9.Prolactin 10.Vital signs 11.Weight 12.Cognitive tests (Continuous Performance Test and modified children's version of California Verbal Learning Test)</p>
Notes	<p>Subjects taking previously prescribed stable dosages of concomitant medication for 30 days prior to trial entry were included provided the concomitant medication was expected to remain stable for the duration of the trial. Examples of allowed concomitant medications included medication for pre-existing medical conditions, psychostimulants (for co-morbid attention-deficit/hyperactivity disorder [ADHD]), and sleep medication (antihistamines, chloral hydrate, and melatonin). No other medication was allowed with the exception of anticholinergic medication to treat EPS, if it occurred during the trial.</p>

Snyder 2002 Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	"randomized" "stratified by diagnosis (conduct disorder versus oppositional defiant disorder or disruptive behaviour disorder not otherwise specified)" "Janssen Research Foundation prepared the randomization list, and subjects were assigned a medication kit upon randomization"
Allocation concealment?	Unclear	No information on allocation concealment
Blinding?	Unclear	"double-blind"
Incomplete outcome data addressed?	No	Attrition rates and reasons reported Intention-to-treat-analysis done Overall attrition 22.7% Unbalanced in numbers across risperidone and placebo group (Risperidone 6/53 (11.3%), Placebo 19/57 (33.3%)) Unbalanced in reason for attrition across risperidone and placebo group Risperidone 2 (3.8%) insufficient response 1 (1.9%) LTFU 3 (5.7%) loss of consent Placebo 19 (33.3%) insufficient response
Free of selective reporting?	Yes	All outcomes reported.
Free of other bias?	Unclear	Manufacturer sponsored.

Van Bellinghen 2001 Characteristics table

Methods	<p>Allocation: Randomised, No details on method of randomization.</p> <p>Blindness: Double-blind, No further details.</p> <p>Duration: 4 weeks double blind period</p>
Participants	<p><u>Inclusion criteria:</u> Children between the ages of 6 and 18 years IQ between 45 and 85 Persistent behavioural disturbances (hostility, aggressiveness, irritability, agitation or hyperactivity)</p> <p><u>Exclusion criteria:</u> Diagnosis of clinical relevant non-neurologic disease Laboratory values of standard blood screening outside the normal range Epileptic crisis in the previous 3 months Remoxipride treatment in the previous 4 weeks Oral neuroleptics or psychotropics in the previous week Previous Remoxipride treatment with abnormal haematological values Depot neuroleptic injection within one treatment cycle of the time of selection Use of an investigational drug within previous 4 weeks Female subjects of childbearing age not using a medically validated birth control method, or pregnant or lactating</p> <p>Total study N = 13 subjects Age: 6 - 14 years Age mean in risperidone group = 10.5 years Age mean in placebo group = 11 years Sex: 5 male, 8 female Risperidone group = 2 boys, 4 girls Placebo group = 3 boys, 4 girls Location: Institutionalised, Belgium</p>
Interventions	<p>1. Risperidone: N = 6 2. Placebo: N = 7</p> <p><u>Dosage and administration:</u> Dose once daily in the evenings During the first week dose was titrated from 0.01 to 0.04 mg/kg/day Followed by 3 week flexible dosing period From day 7, dose increase to 0.05 mg/kg/day if the CGI score remained unchanged or worsened From day 14, dose increased by 0.02 mg/kg/week if the CGI score worsened Maximum dose of 0.09 mg/kg/day</p>

Outcomes	<u>Efficacy measures:</u> 1. Clinical Global Impression (CGI) severity scale 2. Personal Assessment Checklist (PAC) 3. Aberrant Behaviour Checklist 4. Extrapyramidal Symptom Rating Scale (ESRS) 5. Visual Analogue Scale 6. Vital signs 7. Weight
Notes	Nil lost to follow up Mean IQ 75.6 Anti – epileptic treatment permitted in 1 patient (Sodium Valproate) and Ritalin in 1 patient.

Van Bellinghen 2001 Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	"patients were randomized to "
Allocation concealment?	Unclear	No information on allocation concealment.
Blinding?	Unclear	"double-blind"
Incomplete outcome data addressed?	Yes	"all patients completed the study" Intent-to-treat analysis
Free of selective reporting?	Unclear	No standard deviations reported with data.
Free of other bias?	Unclear	Manufacturer sponsored.

Table A2. Characteristics of Excluded Studies**Ad-Dab'bagh 2000**

Reason for exclusion	Retrospective chart review
----------------------	----------------------------

Biederman 2006

Reason for exclusion	Discussion of Aman 2002 data
----------------------	------------------------------

Brylewski 2004

Reason for exclusion	Cochrane systematic review on adults
----------------------	--------------------------------------

Buitelaar 2000

Reason for exclusion	Open label trial, mixed diagnoses
----------------------	-----------------------------------

Croonenberghs 2005

Reason for exclusion	Open label trial
----------------------	------------------

Findling 2000

Reason for exclusion	Randomised Controlled Trial (RCT), children with conduct disorder, no learning disability
----------------------	-------------------------------------------------------------------------------------------

Findling 2004

Reason for exclusion	Open label extension trial
----------------------	----------------------------

Friedlander 2001

Reason for exclusion	Chart review
----------------------	--------------

Gagiano 2005

Reason for exclusion	RCT, adults
----------------------	-------------

Haas 2008

Reason for exclusion	Open label extension trial, no learning disability
----------------------	----------------------------------------------------

Hellings 2006

Reason for exclusion	Cross-over design, children and adults
----------------------	----------------------------------------

La Malfa 2006

Reason for exclusion	Literature review
----------------------	-------------------

LeBlanc 2005

Reason for exclusion	Discussion of Aman 2002 and Snyder 2002 data
----------------------	----------------------------------------------

Matson 2000

Reason for exclusion	Literature review
----------------------	-------------------

Pandina 2006

Reason for exclusion	Literature review
----------------------	-------------------

Pandina 2007

Reason for exclusion	Not RCT, pooled data from Aman 2002; Croonenberghs 2005; Findling 2004; Snyder 2002; Turgay 2002
----------------------	--------------------------------------------------------------------------------------------------

Read 2008

Reason for exclusion	Open label, no control group
----------------------	------------------------------

Reyes 2006

Reason for exclusion	Open label extension
----------------------	----------------------

Reyes 2006a

Reason for exclusion	Open label extension
----------------------	----------------------

Reyes 2006b

Reason for exclusion	RCT, range of intellect
----------------------	-------------------------

Turgay 2002

Reason for exclusion	Open label extension trial
----------------------	----------------------------

Tyrer 2008

Reason for exclusion	RCT in adults, Risperidone and Haloperidol
----------------------	--------------------------------------------

Valdovinos 2002

Reason for exclusion	Case studies, adults
----------------------	----------------------

Valdovinos 2004

Reason for exclusion	Cross-over design, adults and children
----------------------	----------------------------------------

Vanden 1993

Reason for exclusion	Cross-over design, children and adults
----------------------	----------------------------------------

Zarcone 2001

Reason for exclusion	Cross-over design, children and adults
----------------------	----------------------------------------

APPENDIX B: DATA AND ANALYSES

Table B1. Nisonger Child Behaviour Rating Scale

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1. Compliant/ calm	2	225	Mean Difference (IV, Fixed, 95% CI)	1.89 [0.94, 2.84]
2. Adaptive/ social	2	225	Mean Difference (IV, Fixed, 95% CI)	1.54 [0.88, 2.20]
3. Conduct problems	2	225	Mean Difference (IV, Fixed, 95% CI)	-8.67 [-11.72, -5.62]
4. Insecure/ anxious	2	225	Mean Difference (IV, Fixed, 95% CI)	-4.24 [-6.13, -2.35]
5. Hyperactive	2	225	Mean Difference (IV, Fixed, 95% CI)	-2.84 [-4.39, -1.30]
6. Self-injury/ stereotypic	2	225	Mean Difference (IV, Fixed, 95% CI)	-0.83 [-1.71, 0.05]
7. Self-isolated/ ritualistic	2	225	Mean Difference (IV, Fixed, 95% CI)	-1.47 [-2.45, -0.48]
8. Overly sensitive	2	225	Mean Difference (IV, Fixed, 95% CI)	-0.95 [-1.87, -0.04]

Table B2. ABC (Aberrant Behaviour Checklist)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1. Irritability	3	263	Mean Difference (IV, Fixed, 95% CI)	-4.00 [-6.07, -1.92]
2. Social withdrawal/ lethargy	3	263	Mean Difference (IV, Fixed, 95% CI)	-2.55 [-4.07, -1.03]
3. Hyperactivity	3	263	Mean Difference (IV, Fixed, 95% CI)	-0.77 [-1.68, 0.13]
4. Stereotypy	3	263	Mean Difference (IV, Fixed, 95% CI)	-6.65 [-9.24, -4.05]
5. Inappropriate speech	3	263	Mean Difference (IV, Fixed, 95% CI)	0.77 [0.15, 1.40]

Table B3. CGI-I (Clinical Global Impression - Global Improvement) (RR)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
Participants improved / very much improved	2	225	Risk Ratio (M-H, Fixed, 95% CI)	2.69 [2.00, 3.62]

Table B4. BPI (Behaviour Problems Inventory Subscale)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1. Aggressive / destructive	2	225	Mean Difference (IV, Fixed, 95% CI)	-4.96 [-7.31, -2.61]
2. Self-injurious	2	225	Mean Difference (IV, Fixed, 95% CI)	-0.41 [-2.12, 1.29]
3. Stereotyped	2	225	Mean Difference (IV, Fixed, 95% CI)	-0.38 [-1.46, 0.69]

Table B5. VAS (Visual Analogue Scale) [mm]

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
Severity of most troublesome symptom	2	225	Mean Difference (IV, Fixed, 95% CI)	-22.56 [-24.09, -21.02]

Table B6. ESRS (Extrapyramidal Symptom Rating Scale for Children)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
Parkinsonism	2	151	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.72, 0.60]

Table B7. Weight [kg]

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
Weight	4	276	Mean Difference (IV, Fixed, 95% CI)	1.46 [0.96, 1.97]

Table B8. Sedation / somnolence (RR)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
Sedation / somnolence	3	266	Risk Ratio (M-H, Fixed, 95% CI)	4.00 [2.37, 6.76]

Table B9. Prolactin [ng/mL]

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1. Female Prolactin levels	2	38	Mean Difference (IV, Fixed, 95% CI)	14.56 [7.35, 21.76]
2. Male Prolactin levels	2	125	Mean Difference (IV, Fixed, 95% CI)	20.70 [15.73, 25.68]

APPENDIX C: FIGURES

C1 Nisonger Child Behaviour Rating Scale

Figure C1.1 Compliant / calm

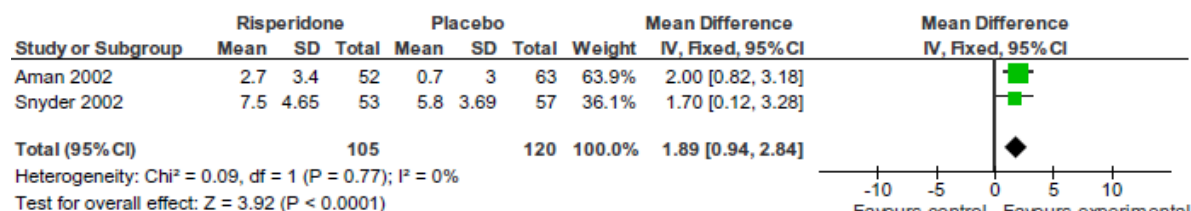


Figure C1.2 Adaptive / social

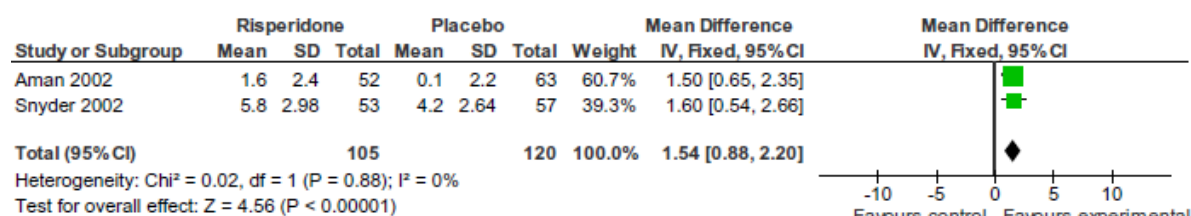


Figure C1.3 Conduct problems

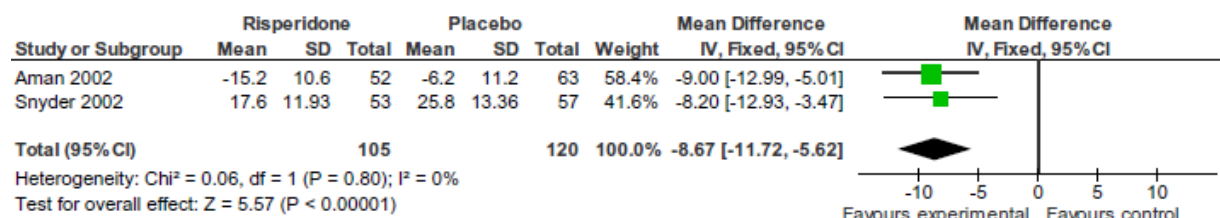


Figure C1.4 Insecure / anxious

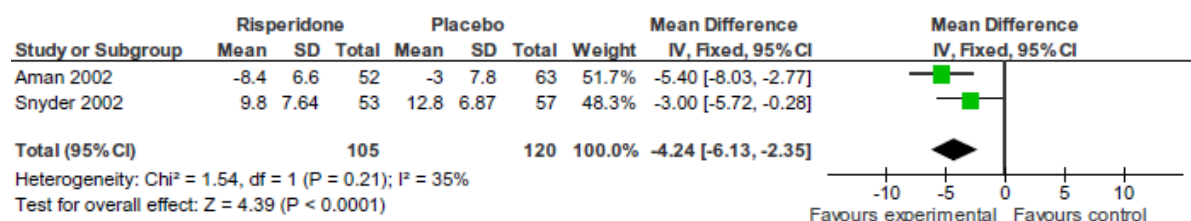


Figure C1.5 Hyperactive

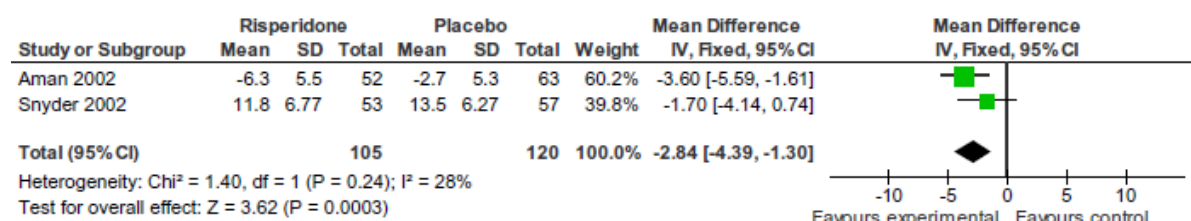


Figure C1.6 Self-injury / stereotypic

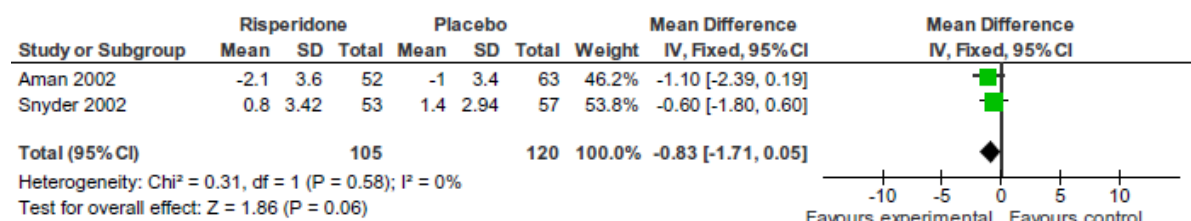


Figure C1.7 Self-isolated / ritualistic

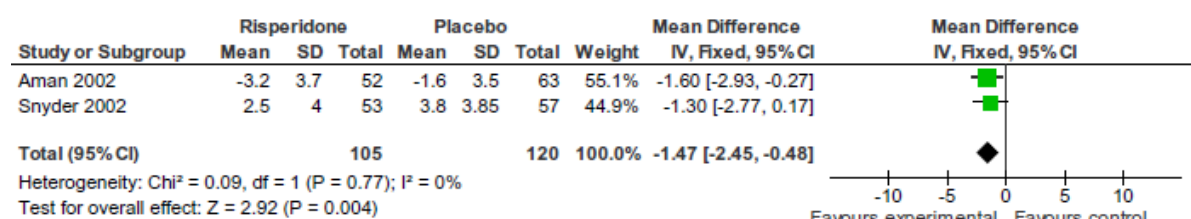
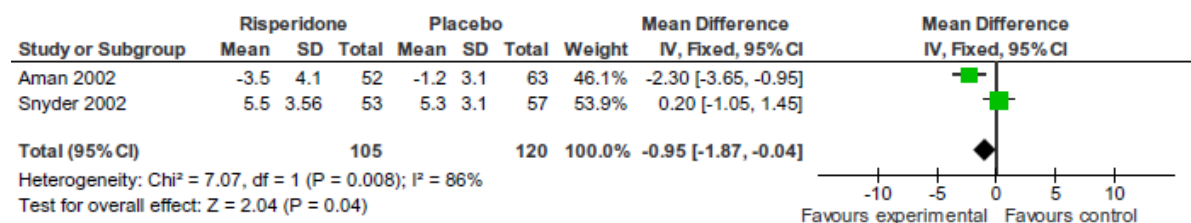


Figure C1.8 Overly sensitive



C2 ABC (Aberrant Behaviour Checklist)

Figure C2.1 Irritability

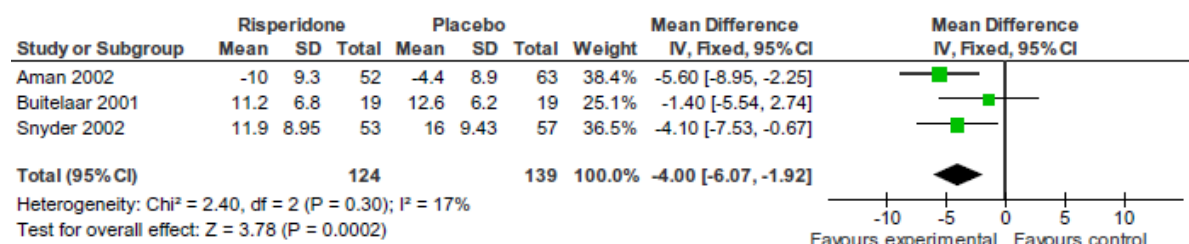


Figure C2.2 Social withdrawal / lethargy

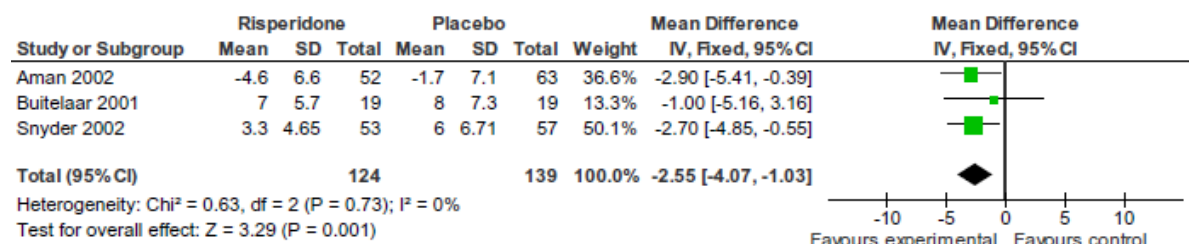


Figure C2.3 Hyperactivity

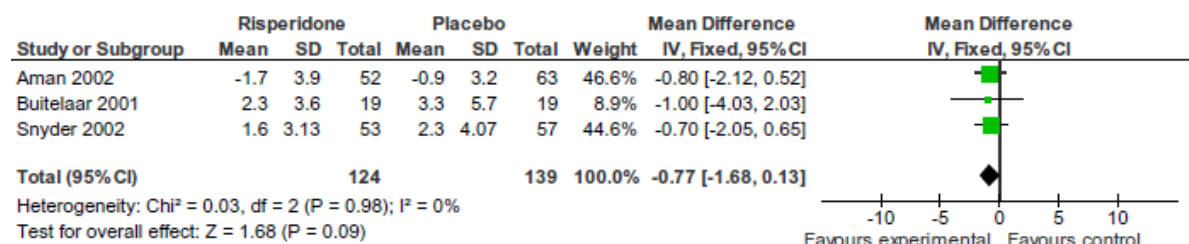


Figure C2.4 Stereotypy

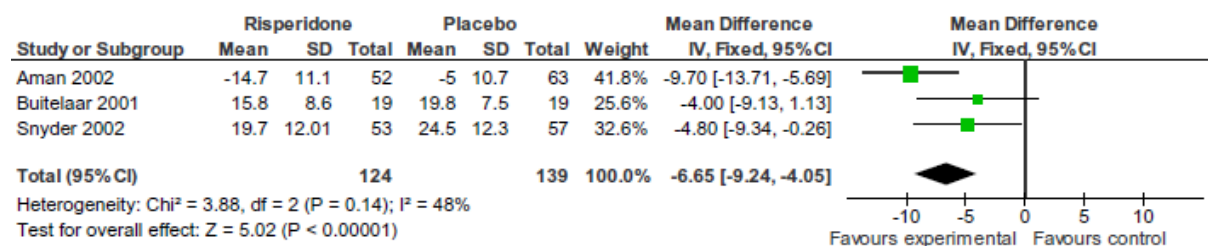
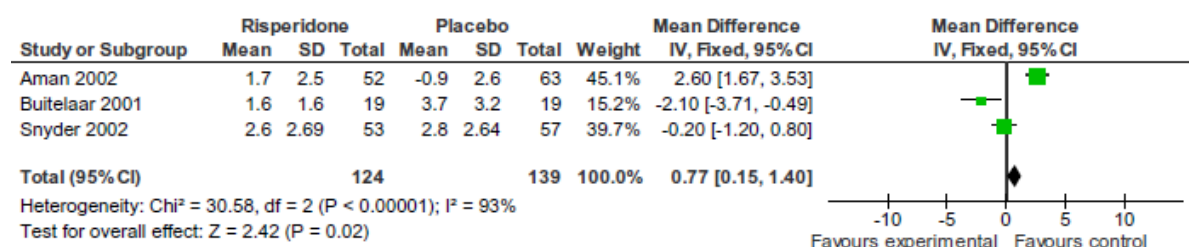
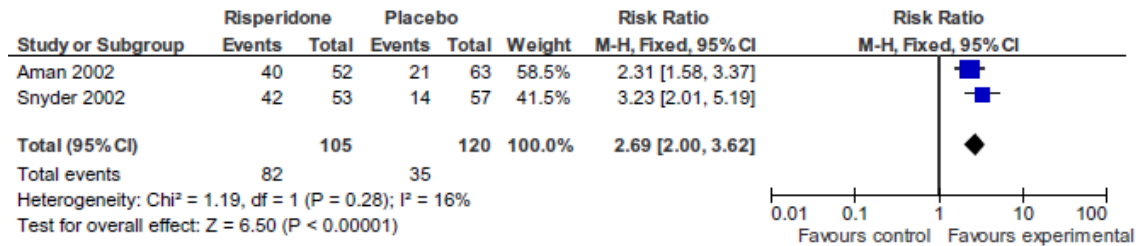


Figure C2.5 Inappropriate speech



C3 CGI-I (Clinical Global Impression - Global Improvement) (RR)

Figure C3.1 CGI-I Participants improved/ very much improved



C4 BPI (Behavior Problems Inventory Subscale)

Figure C4.1 Aggressive/ destructive

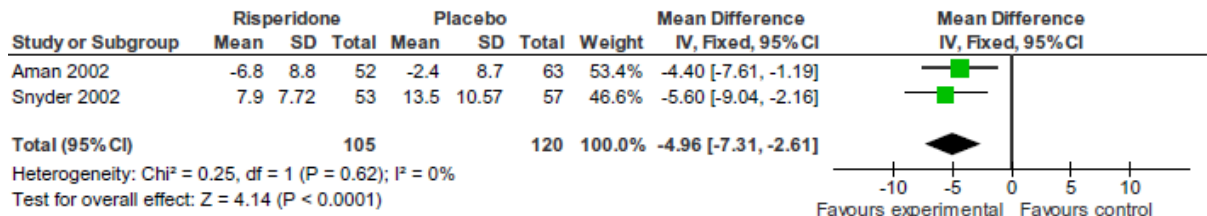


Figure C4.2 Self-injurious

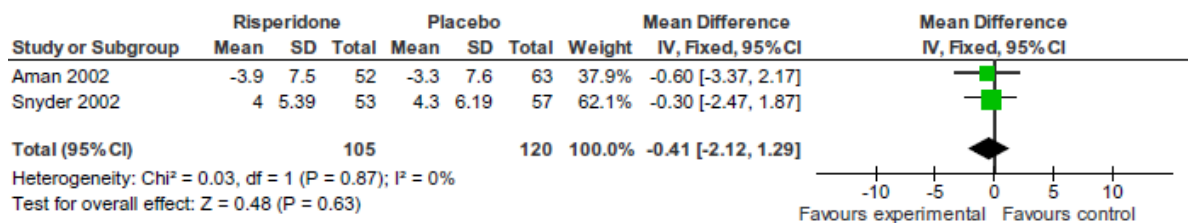
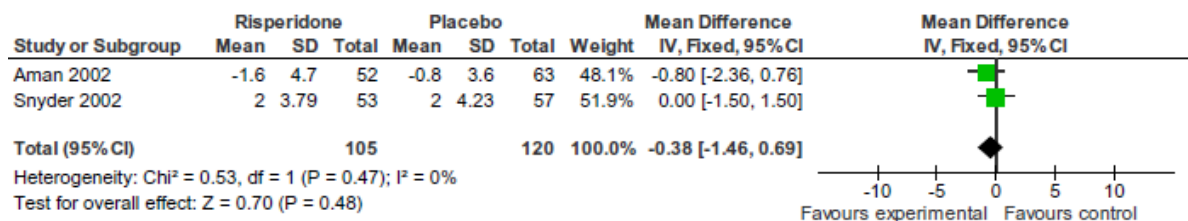
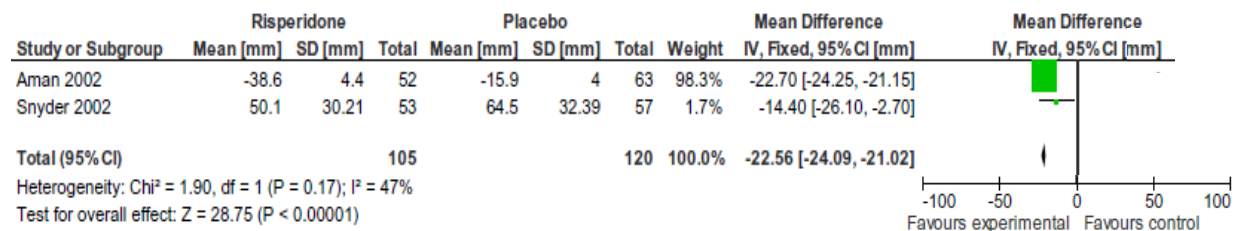


Figure C4.3 Stereotyped



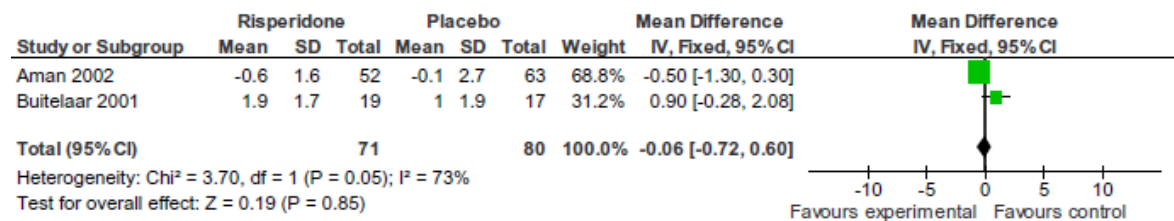
C5 VAS (Visual Analogue Scale) [mm]

Figure C5.1 Severity of most troublesome symptom [mm]



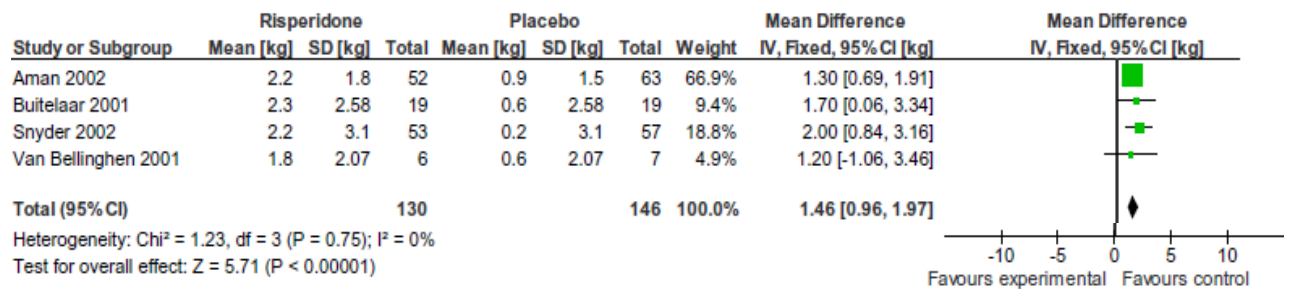
C6 ESRS (Extrapyramidal Symptom Rating Scale for Children)

Figure C6.1 Parkinsonism



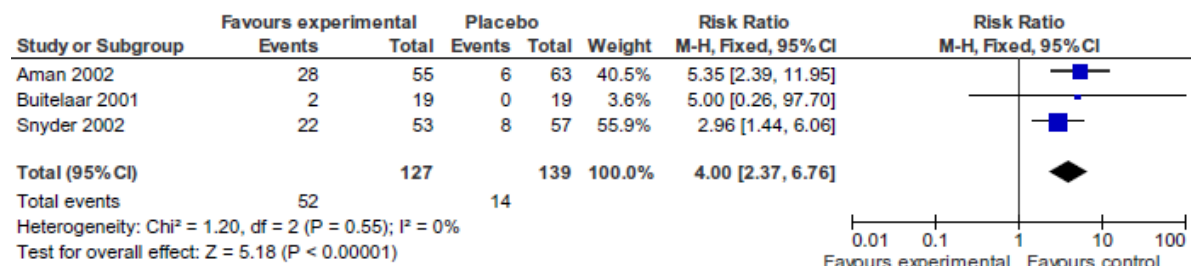
C7 Weight [kg]

Figure C7.1 Weight [kg]



C8 Sedation / somnolence

Figure C8.1 Sedation / somnolence



C9 Prolactin [ng/mL]

Figure C9.1 Female Prolactin levels [ng/mL]

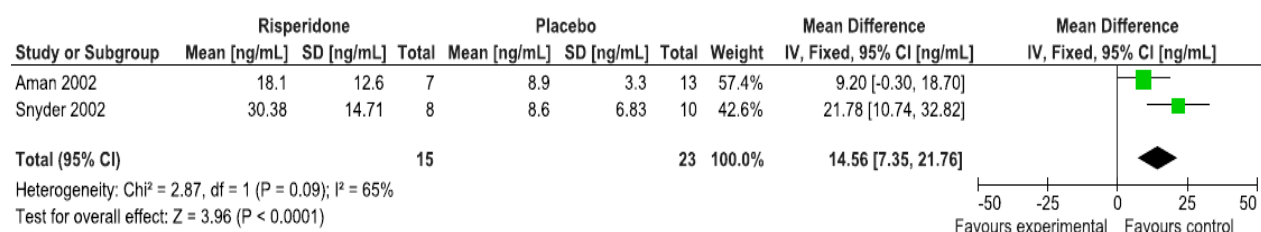
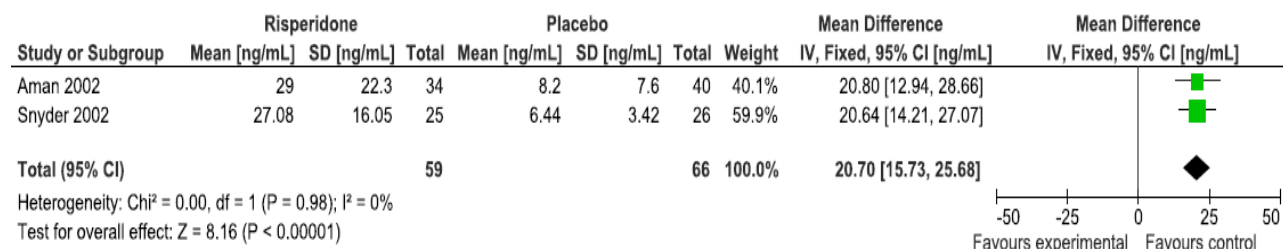


Figure C9.2 Male Prolactin levels [ng/mL]



APPENDIX D: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

R14/49 Bezuidenhout

CLEARANCE CERTIFICATE

PROTOCOL NUMBER M070606

PROJECT

Risperidone for Disruptive Behaviour in Children and Adolescents with Learning Disability

INVESTIGATORS

Dr H Bezuidenhout

DEPARTMENT

Department of Paediatrics

DATE CONSIDERED

07.06.29

DECISION OF THE COMMITTEE*

APPROVED UNCONDITIONALLY

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 07.07.02

CHAIRPERSON

(Professors PE Cleaton-Jones, A Dhali, M Vorster, C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr A Cilliers

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.

I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX E: ELIGIBILITY FORM

STUDY ELIGIBILITY FORM _____ (Reference ID)										
<p>Type of study Is study randomised or quasi-randomised controlled trial?</p>	<table border="0"> <tr> <td>YES</td> <td>UNCLEAR</td> <td>NO</td> </tr> <tr> <td style="text-align: center;">↓</td> <td style="text-align: center;">↓</td> <td style="text-align: center;">↓</td> </tr> <tr> <td style="text-align: center;">Go to next question</td> <td></td> <td style="text-align: center;">Exclude Study type: _____</td> </tr> </table>	YES	UNCLEAR	NO	↓	↓	↓	Go to next question		Exclude Study type: _____
YES	UNCLEAR	NO								
↓	↓	↓								
Go to next question		Exclude Study type: _____								
<p>Trial intervention Was the intervention risperidone?</p>	<table border="0"> <tr> <td>YES</td> <td>UNCLEAR</td> <td>NO</td> </tr> <tr> <td style="text-align: center;">↓</td> <td style="text-align: center;">↓</td> <td style="text-align: center;">↓</td> </tr> <tr> <td style="text-align: center;">Go to next question</td> <td></td> <td style="text-align: center;">Exclude</td> </tr> </table>	YES	UNCLEAR	NO	↓	↓	↓	Go to next question		Exclude
YES	UNCLEAR	NO								
↓	↓	↓								
Go to next question		Exclude								
<p>Trial participants Were trial participants children under 18 years, with intellectual disability and behavioural problems?</p>	<table border="0"> <tr> <td>YES</td> <td>UNCLEAR</td> <td>NO</td> </tr> <tr> <td style="text-align: center;">↓</td> <td style="text-align: center;">↓</td> <td style="text-align: center;">↓</td> </tr> <tr> <td style="text-align: center;">Go to next question</td> <td></td> <td style="text-align: center;">Exclude</td> </tr> </table>	YES	UNCLEAR	NO	↓	↓	↓	Go to next question		Exclude
YES	UNCLEAR	NO								
↓	↓	↓								
Go to next question		Exclude								
<p>Any other reason for excluding study? Specify</p>	<table border="0"> <tr> <td>NO</td> <td>YES</td> </tr> <tr> <td style="text-align: center;">↓</td> <td style="text-align: center;">↓</td> </tr> <tr> <td style="text-align: center;">Include, subject to clarification of unclear points</td> <td style="text-align: center;">Exclude</td> </tr> </table>	NO	YES	↓	↓	Include , subject to clarification of unclear points	Exclude			
NO	YES									
↓	↓									
Include , subject to clarification of unclear points	Exclude									
<p>Final decision</p>	<p>INCLUDE UNCLEAR EXCLUDE</p>									

APPENDIX F: DATA COLLECTION FORM

Data Collection Form "Risperidone for Disruptive Behaviour/ Aggression in Children and Adolescents with Learning Disability"				
Date:				
Reviewer ID:				
Study ID:				
Authors:				
Journal:(yr/vol/iss/pg)		published	unpublished	
Title:				
Location of trial:				
Setting:				
Date of trial:	Recruitment and enrollment:		Duration:	
Methodological quality:				
Trial type:				
Generation of Allocation sequence:		UNCLEAR	YES	NO
Allocation concealment:				
Adequate:			YES	NO
Inadequate:			YES	NO
Unclear:			YES	NO
Not reported:			YES	NO
Blindness:		UNCLEAR	YES	NO
If YES, who was blind?				
Follow-up:				
Type:				
Frequency:				

Duration:			
Loss to follow-up:			
Ethics and consent:			
Study and Participants characteristics:			
Inclusion criteria:			Unclear
Exclusion criteria:			Unclear
Diagnostic criteria of Learning Disability:			
Range of Learning Disability:			
Diagnostic criteria of Disruptive Behaviour:			
Number recruited			
Number randomised			
Total study N =	Intervention N =		Placebo N =
Mean study AGE =	Intervention Age =		Placebo Age =
Study SEX - male	Intervention Male =		Placebo Male =
Study SEX - female	Intervention Female =		Placebo Female =
Study Excluded:	Intervention Excluded =		Placebo Excluded =
Number loss to follow-up:	Intervention Loss to follow-up =		Placebo Loss to follow up =
Interventions:			
Intervention drug -	Risperidone	Dose =	
		Frequency =	
		Duration =	
Placebo -		Dose =	
		Frequency =	
		Duration =	
Co-treatments			

Outcomes:						
Primary outcomes						
Secondary outcomes						
Primary outcomes:	Main study outcome measure:	Change in Mean	Size of effect	p-value	Confidence Interval	
Outcome assessed after _____						
Source _____						
Outcome measurement tools :						
	CGI-S Intervention Group	CGI-S Control Group	Nisonger Intervention Group	Nisonger Control Group	ABC Intervention Group	ABC Control Group
Score Unchanged						
Score improved						
Score worsen						
Adverse effects:	Intervention group:					
	Control group:					
Outcomes unable to use:						
Leaving study early: Loss to follow-up, withdrawals						
Notes:						
Details form other relevant papers cited:						
Additional information required from authors:						

APPENDIX G: AUTHOR DATA REQUEST FORM

Author Data Collection Form: Author, Journal Year

Title of article

For Systematic Review: Risperidone for Disruptive Behaviour / Aggression in Children with Learning Disabilities

Welcome: Thank you for taking the time to participate and provide further information for the Systematic Review on "Risperidone for Disruptive Behavior / Aggression in Children with Learning Disabilities". This review is being conducted by Dr Heide Bezuidenhout at the University of the Witwatersrand in South Africa as part of a Masters thesis and this title is also registered with Cochrane Collaboration

Instructions: (i) Please complete the tables below, providing all the missing data you may have available that was not included in the publication. Please fill in red boxes.
 (ii) If only the Standard Error (SE) is available and not the Standard Deviation (SD) is available, please indicate that you are using the SE.

Aberrant Behavior Checklist subscale scores

Measure	Subjects Receiving Placebo N =				Subjects Receiving Risperidone N =			
	Baseline		Endpoint		Baseline		Endpoint	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Irritability								
Lethargy/social withdrawal								
Stereotypic behavior								
Hyperactivity/noncompliance								
Inappropriate speech								

Data sufficient for meta-analysis

Nisonger Child Behavior Rating Form

Measure	Subjects Receiving Placebo N =				Subjects Receiving Risperidone N =			
	Baseline		Endpoint		Baseline		Endpoint	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Social competence subscale score								
Compliant/calm								
Adaptive/social								
Problem behaviors subscale score								
Conduct problem								
Insecure/anxious								
Hyperactive								
Self-injury/stereotypic								
Self-isolated/ritualistic								
Overly sensitive								

Data sufficient for meta-analysis

Clinical Global Impression Improvement Score (CGI-I)

(please note this is the CGI Improvement scale, not Severity or Efficacy scales)

Measure	@ 6 weeks				@ Endpoint			
	Placebo		Risperidone		Placebo		Risperidone	
	n	%	n	%	n	%	n	%
CGI - Improvement (3 categories)								
Improved (all improved categories)								
Unchanged (no change)								
Worsened (all worsened categories)								
Total (N)								

Please fill in either (A) the 3 point scale above or (B) the 7 point scale below of CGI-I

CGI - Improvement (7 point scale)	Placebo		Risperidone		Placebo		Risperidone	
	n	%	n	%	n	%	n	%
	1 - Very much improved							
2 - Much improved								
3 - Minimally improved								
4 - No change								
5 - Minimally worse								
6 - Much worse								
7 - Very much worse								
Total (N)								

Data sufficient for binary analysis, but insufficient for full meta-analysis

Data insufficient for meta-analysis

Behavior Problems Inventory Subscale score

Measure	Subjects Receiving Placebo N =				Subjects Receiving Risperidone N =			
	Baseline		Endpoint		Baseline		Endpoint	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Aggressive/destructive								
Self-injurious								
Stereotyped								

Data sufficient for meta-analysis

Visual analogue scale score measuring severity of most troublesome symptom

Measure	Subjects Receiving Placebo N =				Subjects Receiving Risperidone N =			
	Baseline		Endpoint		Baseline		Endpoint	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Visual analogue scale score (symptom)								

Data sufficient for meta-analysis

Weight Gain (kgs)

Measure	Subjects Receiving Placebo N =				Subjects Receiving Risperidone N =			
	Baseline		Change by Endpoint		Baseline		Change by Endpoint	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Weight (kgs)								

Data insufficient for meta-analysis

Extrapyramidal Symptom Rating Scale for Children

Measure	Subjects Receiving Placebo N =				Subjects Receiving Risperidone N =			
	Baseline		Endpoint		Baseline		Endpoint	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total score on interview questionnaire								
Score on neurologic examination								
Total								
Parkinsonism								
Dystonia								
Dyskinesia								
Buccolingual/masticatory								
Chorea/athetoid movements								

Data insufficient for meta-analysis

Prolactin levels (ng/ml)

Subject gender and Time Point	Placebo				Risperidone			
	Baseline		Endpoint		Baseline		Endpoint	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Female	Subjects Receiving Placebo N =				Subjects Receiving Risperidone N =			
Male	Subjects Receiving Placebo N =				Subjects Receiving Risperidone N =			

Data sufficient for meta-analysis

Thank you for your time and effort to provide further data for this Systematic Review. Please email this form to heidrob@sun.co.za
 Dr Heide Bezuidenhout