Pharmacological intervention for irritability, aggression, and self-injury in Autism Spectrum Disorders (ASD) (Protocol)


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Pharmacological intervention for irritability, aggression, and self-injury in Autism Spectrum Disorders (ASD)

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

1. To assess the effectiveness of pharmacological interventions for assisting with the management of challenging behaviours (i.e. irritability, aggression, and self-injury) in autism spectrum disorder (ASD).

2. To generate a clinically useful ranking of available pharmacological interventions for challenging behaviours in ASD according to their safety, efficacy, and tolerability.

BACKGROUND

Description of the condition

Autism spectrum disorder (ASD) is characterised by persistent deficits in social communication and social interaction across multiple contexts, as well as restricted repetitive patterns of behaviour, interests, or activities (APA 2013).

There are currently five diagnostic criteria used by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) for the diagnosis of ASD, including 1) persistent deficits in social communication and social interaction across multiple contexts; 2) restricted, repetitive patterns of behaviour, interests, or activities; 3) presentation of symptoms in the early developmental period; 4) symptoms cause clinically significant impairment in important areas of current functioning; and 5) these disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay (APA 2013).

Thirty years ago research suggested that ASD was a rare categorical disorder with a prevalence of just 4 in 10,000; more recent prevalence studies show it to be a common spectrum condition with a prevalence of close to 1 to 2 in 1000 (Baron-Cohen 2008).
Prevalence rates vary across continents. Recent prevalence rate estimates range from 2.64% in South Korea (Kim 2011), 1.9 per 10,000 to 72.6 per 10,000 in Europe, 2.8 per 10,000 to 94 per 10 000 in Western Pacific, South East Asia, and the Eastern Mediterranean, and 11 per 10,000 to 50.5 per 10,000 in America (Elsabbagh 2012).

The prevalence rate also varies across different ethnic groups. Recent prevalence rate estimates from the Centers for Disease Control and Prevention (CDC) show that non-Hispanic white children were approximately 30% more likely to be identified with ASD than non-Hispanic black children and were almost 50% more likely to be identified with ASD than Hispanic children (Wingate 2014). Some have attributed this rise to a true increase in the problems seen in ASD. Others have disputed this, attributing the rise to factors such as earlier diagnosis or broadening of diagnostic criteria (Tantam 2012). The prevalence of ASD in males appears to exceed that of females, and although the exact ratio may be impossible to specify, a recent review suggested an overall male to female ratio of 4.62 (Watkins 2014).

In addition to the previously cited core symptoms, people with ASD may often exhibit challenging behaviours. These most commonly include irritability, aggression, and self-injury (Lecavalier 2006). Prevalence rates indicate that as many as one in four children with ASD are known to present with aggressive behaviour in the clinical range as measured by the Child Behaviour Checklist (CBC) (Kim 2011). This same study found that the presence of aggressive behaviour was significantly associated with increased use of psychotropic drugs, lower cognitive functioning, lower ASD severity, and greater comorbid sleep, internalising, and attention problems (Kim 2011). Furthermore, there is a high comorbidity of ASD with other neurodevelopmental disorders, such as attention deficit hyperactivity disorder (ADHD), to the extent that both ASD and ADHD can now be diagnosed together (APA 2013). People with comorbid ASD and ADHD may be at even greater risk of demonstrating challenging behaviours, considering this is a common overlapping feature of the two disorders (Craig 2015).

Overall, the difficulties faced by this population can place a lifetime and often significant burden on both the people with ASD, and their families and carers. Not only can they lead families and carers to experience high levels of stress, but they can also create barriers for adult independence and community involvement (Smith 2014).

**Description of the intervention**

Although there is no cure for ASD, educational and behavioural interventions can be associated with positive outcomes for children with ASD in treating both core ASD symptoms as well as associated behaviours and skill deficits. These include improvements in cognitive functioning, language skills, and social behaviours (Weitlauf 2014).

For individuals with ASD, non-pharmacological interventions (such as educational interventions and behavioural and psychological therapies) and pharmacological interventions can help treat some of the more challenging behaviours such as irritability, aggression and self-injury (Posey 2001).

This review will focus solely on medications that are used to target irritability and aggression in people with autism. These medications include antidepressants, antipsychotics, cholinesterase inhibitors, mood stabilisers, and N-methyl-D-aspartate (NMDA) receptor antagonists.

**Antidepressants**, such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), are medications that treat symptoms of depression, anxiety, and obsessiveness. The use of antidepressants in children and young people with ASD has been associated with reductions in irritability and hyperactivity (Hurwitz 2012).

**Antiepileptic medications**, such as gabapentin and guanfacine, may also be efficacious in managing these behaviours. Both were originally developed for the treatment of hypertension, but they have been reported to reduce symptoms of irritability and aggression in people with autism (Handen 2008; Ming 2008).

**Antiparkinsonian medication**, such as amantadine, has been studied for the treatment of people with autism to address symptoms of irritability and aggression. A double-blind, placebo-controlled trial of children with autism aged 5 to 19 years found that symptoms of irritability and aggression were reduced in those receiving amantadine as the active medication. [King 2001].

**Antipsychotics**, such as risperidone, are medications that treat the symptoms of disorganised thinking and poor awareness of reality. The use of antipsychotic drugs has also been associated with reduced irritability, social withdrawal, hyperactivity, and stereotypical behaviours in young people with ASD (Jesner 2007).

**Cholinesterase Inhibitors**, such as donepezil, are primarily used to treat individuals with Alzheimer's dementia. Previous studies have shown that the use of this drug has been associated with changes in expressive and receptive speech and aberrant behaviours of children with ASD (Chez 2003).

**Mood stabilisers**, such as divalproex sodium, are primarily used in bipolar illness. Use of these drugs has also been associated with improvement in affective instability, impulsivity, and aggression in autism (Hollander 2001).

**NMDA receptor antagonists**, such as memantine, are primarily used to treat individuals suffering from Alzheimer's dementia. Some research indicates that they may improve language function,
social behaviour, and self-stimulatory behaviours of some people with ASD (Chez 2004). A smaller improvement in irritability symptoms has also been indicated [Erickson 2007]. All of the above drugs have their own unique spectrum of side effects and adverse reactions.

**How the intervention might work**

While each of the previously listed drugs are believed to affect one of the five categories of aberrant behaviours listed by the Aberrant Behaviour Checklist (ABC), each medication works in a different way. In addition, many of the mechanisms of action are yet to be universally agreed, and a number of the following descriptions are currently theoretical rather than conclusive.

**Antidepressants and antipsychotics**

Autism has been associated with abnormalities in both the dopaminergic system and serotonergic systems. Specifically, studies examining changes in the binding of serotonin and dopamine transporters, which are highly selective markers for their respective neuronal systems, have found dopamine transporter binding to be significantly higher in the orbitofrontal cortex of adults with autism, and serotonin transporter binding to be significantly lower throughout the brain in people with ASD compared with controls (Nakamura 2010). Altered serotonin levels have been found to lead to changes in several psychological processes, which are also altered in individuals with autism, including mood, irritability, and aggression (Young 2002). Dopamine over-activation has also been linked with excessive motor activity and stereotyped behaviours, which are also traits often observed in individuals with autism (Previc 2007). Antidepressant drugs and some antipsychotic drugs increase the availability of serotonin, typically by slowing its reuptake from synapses, and can block uptake of other neurotransmitters, including norepinephrine or dopamine. Antipsychotic drugs block dopamine receptors, and may act via other receptor systems, including the serotonin-2 receptor. It is plausible that antidepressant drugs ameliorate some of the symptoms of autism through enhancement of serotonin, while antipsychotics work on both serotonin and dopamine. In addition, antidepressants target some of the common comorbidities of ASD such as anxiety, depression, and obsessive compulsive disorder.

**Antiepileptic medications**

The mechanism by which antiepileptic drugs, such as gabapentin, work on irritability and aggression remains unclear. What is known is that gabapentin is an amino acid derivative of p-aminobutyric acid, which binds to the subunit protein of voltage-gated calcium channels. Therefore, some researchers have speculated that 2-C subunit protein plays a significant role in this condition (Guglielmo 2013).

**Alpha adrenergic agonists**

Both clonidine and guanfacine are centrally acting α2-adrenergic agonists that have been administered to children with autism for the treatment of hyperactivity and impulsivity. Because guanfacine has a longer half-life than clonidine, it can be administered in less frequent doses, thus lowering the risk of rebound hypertension (Strange 2008).

**Antiparkinsonian medication**

Amanatadine is a glutamatergic antagonist that works by inhibiting the NMDA receptor. By binding to the NMDA receptor, it can avoid its excessive excitation by the glutamate neurotransmitter (Hosenbocus 2013).

**Cholinesterase inhibitors**

According to recent studies, acetylcholine and nicotinic receptor activity may appear to be lower in brain samples of people with autism. It has been suggested, therefore, that acetylcholinergic enhancement through the use of donepezil hydrochloride-an acetylcholinesterase inhibitor-may improve some behaviours associated with ASD (Chez 2003).

**Mood stabilisers**

It has been suggested that mood stabilisers, such as divalproex sodium, may work by enhancing GABA; inhibiting glutamate; acting on serotonin and norepinephrine systems; and via limbic kindling (Hollander 2001).

**NMDA receptor antagonists**

Like many of the drugs in this review, the precise mechanisms by which they affect people is not well known. However, one suggestion is that memantine may act through a stimulatory effect on dendritic spine maturation and excitatory synapse formation, as well as promoting adhesion of cultured cerebellar granule cells (Chez 2004).

**Why it is important to do this review**

To date, there have been four previously published Cochrane systematic reviews focusing on the use of pharmacological interventions in ASD. The first review focused on risperidone and found some evidence that the medication may lead to significant improvements in irritability (Jesner 2007). The second review focused on aripiprazole and also found some evidence that it too...
could lead to improvements in irritability (Ching 2012). The third review focused on tricyclic antidepressants (TCA), which were found to show small positive effects in children and adolescents with ASD, particularly with regards to reducing irritability, although results remain conflicting (Hurwitz 2012). Finally, the fourth review focused on selective serotonin reuptake inhibitors (SSRI) and found some evidence that they may lead to improvement in an adult’s aggression, yet evidence consistently came from studies with high risk of bias (Williams 2013). To date, no Cochrane review has focused on any of the remaining pharmacological interventions that can be used to address challenging behaviours in ASD.

The extent to which the age of the person receiving the treatment will affect the intervention’s efficacy remains unclear. Autism spectrum disorder is a lifelong condition and therefore it is important to understand the effect of interventions, including medication, across the lifespan (Tantam 2012).

The previously conducted single drug intervention reviews have already provided useful high quality information regarding each individual drug’s effectiveness and safety relative to placebo or no treatment. However, no systematic network meta-analysis (NMA) has yet been conducted to systematically explore the effectiveness and safety of each drug relative to one another. When making decisions about medication, clinicians are faced with problems of a certain type and severity that have failed to respond to other interventions and they need to be able to compare the risks and benefits of different medications for the particular problems they are trying to resolve. Current evidence is provided in such a way that they would have to find multiple systematic reviews to answer the questions they need answered and there would be no opportunity for direct comparison.

By using a NMA, and conducting both direct and indirect comparisons and then combining them, we hope to create mixed estimates of the relative effects of different types of pharmacological interventions. The results of such a review may be of greater use to clinicians and policy makers, by presenting all of the relevant information together in one review and looking at the different options in relation to one another.

Finally, a clinically useful ranking of available pharmacological treatments will be helpful for deciding second and third line treatments, and for guiding treatment choice when first line treatment is unavailable (Salanti 2011).

OBJECTIVES

1. To assess the effectiveness of pharmacological interventions for assisting with the management of challenging behaviours (i.e. irritability, aggression, and self-injury) in autism spectrum disorder (ASD).

2. To generate a clinically useful ranking of available pharmacological interventions for challenging behaviours in ASD according to their safety, efficacy, and tolerability.

METHODS

Criteria for considering studies for this review

Types of interventions

Any pharmacological intervention used with the intention-to-treat or manage unwanted challenging behaviours in ASD, specifically irritability, aggression, or self-injury. Interventions may be given at any dosage, for any duration, and regardless of frequency of administration. Relevant pharmacological interventions include selective serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), first generation antipsychotics such as haloperidol, second generation antipsychotics such as risperidone and aripiprazole, antiepileptic medications, antihypertensive medications, antiparkinsonian medication, cholinesterase inhibitors, mood stabilisers, and N-methyl-D-aspartate (NMDA) receptor antagonists.

We are primarily interested in primary studies that make direct comparisons of any two or more of these relevant interventions (e.g. TCA versus SSRI, SSRI versus haloperidol, or risperidone versus aripiprazole etc.).
Where appropriate, and after assessing plausibility of transitivity, we will also seek to make indirect comparisons by including primary studies that compare relevant interventions to either placebo treatment, wait-list or no treatment conditions, or an active common comparator. Transitivity requires the assumption that any patient that meets the inclusion criteria could reasonably be randomised among any selection of eligible interventions. It is possible that additional eligible interventions that review authors are not aware of may be identified in the course of the review. If we identify any pharmacological interventions that were not initially included, we will consider them as eligible and we will include them in the network after assessing their comparability with those named above. Because pharmacological interventions are more commonly used as supplements to non-pharmacological treatment, we will include any papers that make reference to populations receiving concurrent non-pharmacological treatments, provided that they are identical across intervention arms.

Types of outcome measures

Primary outcomes

1) Unwanted challenging behaviours in ASD*, specifically:
   • irritability;
   • aggression; and
   • self-injury.

These outcomes will be measured by standardised instruments such as the ‘irritability, agitation’ subscale of the Aberrant Behaviour Checklist (ABC). Where possible, preference will be given to analysing each of these three specific challenging behaviours separately. Where this is not possible, we will combine measures across studies to create a composite ‘challenging behaviour’ outcome. In the event that study authors report several similar scales, we will establish a hierarchy of preferred scales/instruments. This hierarchy will be established through discussion with the full review group.

2) Adverse effects* (including sedation and weight gain).

Secondary outcomes

3) Quality of life for both the child and the parents or carers or family* (as measured by standardised instruments such as the Pediatric Quality of Life Inventory (PedsQL), or through quality of life questionnaires).

4) Tolerability and acceptability of the intervention (as measured by self-reported or clinician-reported adherence to treatment). We will use outcomes indicated by an asterisk (*) to populate the ‘Summary of findings’ table for the main comparison, where data permit. Where data are insufficient, we will provide a narrative account of the outcomes.

Where feasible, we will make comparisons at the following specific follow-up periods:
   • short term (less than six months);
   • medium term (6 to 12 months); and
   • long term (over 12 months).

Search methods for identification of studies

Electronic searches

We will search all available years of the following databases for all possible comparisons formed by the interventions of interest.

1. Cochrane Central Register of Controlled Trials (CENTRAL), part of the Cochrane Library, current issue.
2. Ovid MEDLINE, 1946 to current.
3. Ovid MEDLINE In-Process and other non-indexed Citations, current issue.
4. Embase (Ovid), 1980 to current.
5. CINAHL: Cumulative Index to Nursing and Allied Health Literature (EBSCOhost), 1937 to current.
6. PsycINFO (Ovid), 1806 to current, 1806 to current.
7. ERIC (EBSCOhost), 1966 to current.
8. Science Citation Index (SCI; Web of Science), 1970 to current.
10. Conference Proceedings Citation Index - Science (CPCI-S) (Web of Science), 1990 to current.
11. Conference Proceedings Citation Index - Social Sciences & Humanities (CPCI-SS&H) (Web of Science), 1990 to current.
12. Cochrane Database of Systematic Reviews (CDSR), part of the Cochrane Library, current issue.
14. LILACS (lilacs.bvsalud.org/en/).
16. ClinicalTrials.gov (clinicaltrials.gov/).
17. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (isrctn.com/).

We will use the strategy for Ovid MEDLINE, shown in Appendix 1, and modify it appropriately for other databases. We will use search filters for RCTs where appropriate. We will not apply any language or date restrictions. We will not restrict by publication status, and we will seek translation of documents where necessary.

Searching other resources

We will scan bibliographies of included and excluded studies for possible additional references of interest. We will contact relevant pharmaceutical companies, authors, and key scholars to identify any additional ongoing or missed studies.

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Data collection and analysis

Selection of studies
Two authors (NL, LB) will independently select and assess studies to determine whether they meet the inclusion criteria for this review. Any disagreements between the authors will be resolved through discussion with the full review group.

Data extraction and management
Two authors (NL, LB) will extract data independently and enter data into a piloted data extraction form. Any disagreements between the authors will be resolved through discussion with the full review group. We will extract the following data.

Outcome data
From each included study, we will extract relevant details on all primary and secondary outcome measures used, as defined by the review authors; and length of follow-up and summary data, including means, standard deviations, confidence intervals and significance levels for continuous data, and proportions for dichotomous data. We will extract arm-level data.

Data on potential effect modifiers
From each included study, we will extract data on the following study, participant, intervention, and comparison characteristics that may act as effect modifiers:
- study characteristics (study design, study duration, details of attrition, and risk of bias concerns);
- participant characteristics (number randomised, age of participants, specific diagnosis, comorbidities, gender distribution, geographical location of study);
- intervention characteristics (type of antidepressant or antipsychotic, dose, duration, frequency, age medication began, concurrent interventions); and
- comparison characteristics (form, frequency, and duration of ‘standard care’).

Other data
From each included study, we will extract data on the following additional information:
- study author(s), year of publication, citation, and contact details; and
- sources of funding and other potential commercial interests.

Assessment of risk of bias in included studies
Using the data extraction form, two authors (NL, LB) will independently assess each study for risk of bias and assign each included study to one of the following categories as outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011):
- high risk of bias;
- low risk of bias; or
- unclear or unknown risk of bias.

Assessments of risk of bias for each study will be based on the following criteria as outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011):
- sequence generation (was the allocation sequence adequately generated?);
- allocation concealment (was allocation adequately concealed?);
- blinding of participants and personnel (was knowledge of the allocated intervention adequately prevented during the study?);
- blinding of outcome assessors (was knowledge of the allocated intervention adequately prevented during the study?);
- incomplete outcome data (were incomplete outcome data adequately addressed?);
- selective outcome reporting (are reports of the study free of suggestion of selective outcome reporting?); and
- other sources of bias (was the study apparently free of other problems that could put it at a high risk of bias?).

Measures of treatment effect

Relative treatment effects
We will estimate the pairwise relative treatment effects of the competing interventions by calculating effect sizes as odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous outcome data (e.g. adherence), and by calculating standardised mean differences (SMDs) with 95% CIs for continuous outcome data (e.g. scores on standardised measures). We will present results from the network meta-analysis (NMA) as summary relative effect sizes (SMD or OR) for each possible pair of treatments.

Relative treatment ranking
We will also estimate the ranking probabilities for each treatment. This is the probability that each treatment is the first, second, third etc. best in the network. We will obtain a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA) (Chaimani 2013), and mean ranks. SUCRA can also be expressed as a percentage and interpreted as the percentage of efficacy or safety of treatment that would be ranked first without uncertainty.
Unit of analysis issues

Cluster-randomised trials, in which allocation to the intervention group has occurred by school, hospital or by community as opposed to by individual, are not anticipated in this research area. However, in the event that we identify relevant cluster-randomised trials, it is likely that investigators will have controlled for a clustering effect when presenting their results. When this information is unclear, we will contact authors for further information. If the clustering effect was not controlled for, we will request individual participant data to calculate an estimate of the intraclass correlation coefficient (ICC). If individual participant data are not available, we will search for external estimates of the ICC from similar studies or available resources. If an appropriate ICC cannot be found from any available resources, we will seek statistical advice to obtain an estimate of the ICC and use this to reassess the trial data to obtain approximate correct analyses. We will then enter these data into Review Manager (RevMan) software (Review Manager 2014) to analyse effect sizes and CIs using the generic inverse variance method (Higgins 2011).

Cross-over trials, in which all participants receive both the control and intervention treatment but in a different order, are possible in this research area. In the event that we identify one or more eligible randomised cross-over studies, we will include them in the review but will only use data during the first period of the study, up to the point of the first cross-over, to avoid any problems associated with any carry-over effect from the first phase to the second phase of the study.

Studies with multiple intervention groups are anticipated in this area. If NMA is performed, data from any relevant multi-arm trial can be retained in its original form and entered into the model accordingly.

If NMA is not feasible, a direct pairwise analysis may be performed. In this event, if two or more eligible interventions groups are compared to a single eligible control group, we will split the sample size for the shared comparator group to prevent the same comparator participants being included twice. We will clearly document decisions made during this process in the review. Some studies may also include more than one control group, each undergoing different yet equally eligible forms of ‘management as usual’. In this situation, we will combine the control groups to create a single pair-wise comparison. If this strategy poses a problem for the investigation of heterogeneity, we will compare each group separately as part of the subgroup analyses.

Data that are not missing at random are likely to be missing for reasons related to the outcomes of the missing data. For example, if a participant agrees to take part in a trial but is unhappy with the outcome of allocation, fails to adhere to the medication or experiences adverse effects as a result of the medication, then they may be unwilling to complete any follow-up assessments. In such a situation, where dichotomous data are missing, we will impute data on the assumption that the participants experienced the less favourable outcome (e.g. ‘participant did not adhere to the treatment’).

If insufficient information is given regarding the exact number missing from each group, data imputation may not be possible, in which case we will analyse only the available data. Where continuous data are missing, we will impute data using a ‘last observation carried forward’ (LOCF) approach. Where cases are missing from the first outcome measure, we will analyse only the available data.

We will conduct a Sensitivity analysis to examine the impact of changes in the assumptions made about missing data on the results. For example, where dichotomous data cases are missing, we will explore the possibility that those missing experienced the positive outcome (e.g. ‘participant did adhere to the treatment’) and impute data based on this assumption.

Where studies have missing summary data, such as missing standard deviations, we will derive these where possible using calculations provided in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will specify the methods used to address any missing data in the ‘Characteristics of included studies’ tables. If imputation is not possible, we will outline the reasons for this in the text.

Assessment of heterogeneity

We will examine clinical heterogeneity within each pairwise comparison by inspecting each included study for variability in the participants, interventions or outcomes described. We will examine methodological heterogeneity within each pairwise comparison by inspecting each included study for variability in the study design and risk of bias. Any unexpected variability that may arise will be discussed in full.

We will visually assess the assumption of transitivity by examining the distribution of potential effect modifiers extracted as above; for example, whether antidepressants are administered the same way in studies comparing antidepressants to placebo and in those comparing antidepressants to antipsychotics.

Dealing with missing data

We will contact the original investigators to request missing data. If we cannot obtain the data, we will make assumptions as to whether the data appears to be ‘missing at random’ or ‘not missing at random’ and follow the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).
Data synthesis

Methods for direct treatment comparisons
We will first perform standard pairwise meta-analyses on the results when data from at least two included studies are available for any treatment comparison. Due to expected heterogeneity among included studies, we will perform a random-effects meta-analysis using an inverse variance weighting method using RevMan software (Review Manager 2014). When meta-analysis is inappropriate, we will provide a narrative description of the individual study results. We will perform both fixed-effect and random-effects analyses as part of our Sensitivity analysis.

Methods for indirect and mixed comparisons
If the direct and indirect comparisons appear to be in agreement, and if the assessment of transitivity seems reasonable, we will combine direct and indirect evidence to create mixed estimates of the relative effects of the different types of pharmacological interventions. We will perform NMA in STATA (StataCorp 2013), using the ‘mvmeta’ command (White 2012), and self-programmed STATA routines (Chaimani 2013).

Assessment of statistical heterogeneity

Assumptions when estimating the heterogeneity
In a standard pairwise meta-analysis, we estimate separate heterogeneity variances for each pairwise comparison. In NMA, we assume a common estimate for heterogeneity variance across different comparisons.

Measures and tests for heterogeneity
In pairwise analyses, we will assess statistically the presence of heterogeneity within each pairwise comparison using the Chi² statistic and its P value, and the I² statistic and its 95% CI. The assessment of statistical heterogeneity in the NMA will be based on the magnitude of the heterogeneity variance parameter (τ²) estimated from the NMA models. For dichotomous outcomes, the magnitude of the heterogeneity variance can then be compared with the empirical distribution described by meta-epidemiological studies (Savović 2012; Turner 2012).

Assessment of statistical inconsistency

Local approaches for evaluating inconsistency
We will use the loop-specific approach to evaluate the presence of inconsistency locally. This method separately evaluates consistency in each closed loop of the network, where consistency is defined as the difference between direct and indirect estimates for a specific comparison in that loop (inconsistency factor). Then, the magnitude of the inconsistency factors and their 95% CIs can be used to infer the presence of inconsistency in each loop. We will assume a common heterogeneity estimate and will present the results of this approach graphically in a forest plot using the ‘ifplot’ command in STATA (Chaimani 2013).

Global approaches for evaluating inconsistency
To check the assumption of consistency in the entire network, we will use the ‘design-by-treatment’ model as described by Higgins and colleagues (Higgins 2012). This method assesses different sources of inconsistency that can occur when studies with different designs (e.g. two-arm trials versus three-arm trials) give different results as well as disagreement between direct and indirect evidence. Using this approach we will infer about the presence of inconsistency from any source in the entire network based on a Chi² test. We will perform the design-by-treatment model in STATA using the ‘mvmeta’ command.

Summary of findings
We will create ‘Summary of findings’ tables using the system developed by the Grades of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group. We will use outcomes indicated by an asterisk (*) in the Types of outcome measures section to populate the ‘Summary of findings’ table for the main comparison, where data permit. We will use GRADE profiler (GRADEpro 2008) to import data from RevMan (Review Manager 2014) to create ‘Summary of findings’ tables for the main comparisons and outcomes indicated under ‘Types of outcome measures’. For information regarding the GRADE approach, and factors that influence the assessment, see Table 1, Table 2, Table 3, and Table 4.

Subgroup analysis and investigation of heterogeneity
Providing that there are a sufficient number of studies, we will perform the following subgroup analyses.
1. The differential effects of interventions by the age at which the drug was first administered; for example, infant/toddler (birth to six years of age) versus school age (6 to 12 years of age) versus adolescent (12 to 18 years of age), versus adult (18 years of age and over).
2. The differential effects of interventions by communication ability; for example, low communication ability versus high communication ability.
3. The differential effects of interventions by cognitive ability; for example, low cognitive ability versus high cognitive ability.
4. The differential effects of interventions by the gender of the participant; for example, male versus female.

**Sensitivity analysis**

We will perform sensitivity analyses to assess whether the findings of this review are robust to the decisions made in the process of obtaining them. We will perform sensitivity analyses by conducting the following.

1. Reanalysis excluding studies according to study quality issues, including those with low sample size, high risk of bias, or high attrition and dropout rate.
2. Reanalysis without imputing data for the missing participants.
3. Reanalysis using a fixed-effect model.

**ACKNOWLEDGEMENTS**

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**Handen 2008**


**Higgins 2011**


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Pharmacological intervention for irritability, aggression, and self-injury in Autism Spectrum Disorders (ASD) (Protocol)

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Posey 2001

Previc 2007

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Review Manager 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration.

Salanti 2011

StataCorp 2013 [Computer program]
StataCorp. Stata statistical software: release 13. College Station, TX: StataCorp LP, 2013.

Strange 2008

Tantam 2012

Turner 2012

Watkins 2014

Weitlauf 2014
**Additional Tables**

Table 1. Levels of quality of a body of evidence in the GRADE approach

<table>
<thead>
<tr>
<th>Underlying methodology</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trials; or double-upgraded observational studies</td>
<td>High</td>
</tr>
<tr>
<td>Downgraded randomized trials; or upgraded observational studies</td>
<td>Moderate</td>
</tr>
<tr>
<td>Double downgraded randomized trials; or observational studies</td>
<td>Low</td>
</tr>
<tr>
<td>Triple downgraded randomized trials; or downgraded observational studies, or case series/case reports</td>
<td>Very low</td>
</tr>
</tbody>
</table>

Copy of Table 12.2.a from Schünemann 2011.

GRADE: Grades of Recommendations, Assessment, Development, and Evaluation.

Table 2. Factors that may decrease the quality level of a body of evidence

1. Limitations in the design and implementation of available studies suggesting high likelihood of bias
2. Indirectness of evidence (indirect population, intervention, control, outcomes)
3. Unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses)
4. Imprecision of results (wide confidence intervals)
5. High probability of publication bias

Copy of Table 12.2.b from Schünemann 2011.
Table 3. Factors that may increase the quality level of a body of evidence

| 1. Large magnitude of effect |
| 2. All plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results show no effect |
| 3. Dose-response grade |

Copy of Table 12.2.c from Schünemann 2011.

Table 4. GRADE Working Group grades of evidence

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Further research is very unlikely to change our confidence in the estimate of effect</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate</td>
</tr>
<tr>
<td>Low</td>
<td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate</td>
</tr>
<tr>
<td>Very low</td>
<td>We are very uncertain about the estimate</td>
</tr>
</tbody>
</table>

GRADE: Grades of Recommendations, Assessment, Development, and Evaluation.

APPENDICES

Appendix 1. Ovid MEDLINE search strategy

1 exp child development disorders, pervasive/
2 Developmental Disabilities/
3 pervasive development$ disorder$.tw.
4 (pervasive adj3 child$).tw.
5 (PDD or PDDs or PDD-NOS or ASD or ASDs).tw.
6 autis$.tw.
7 asperger$.tw.
8 kanner$.tw.
9 childhood schizophrenia.tw.
10 Rett$.tw.
11 or/1-10
12 Drug Therapy/
13 ((pharma$ or drug) adj1 (intervention$ or therap$ or treat$)).tw.
CONTRIBUTIONS OF AUTHORS

All six authors contributed to the development of this review. Livingstone will conduct the literature searches in collaboration with the Trials Search Co-ordinator of the Cochrane Developmental, Psychosocial and Learning Problems Group. Livingstone and Baker will screen the results for eligibility, extract data independently, enter data into a piloted data extraction form, and assess each study for risk of bias. All six authors will contribute in the event of any disagreements. Livingstone and Caldwell will conduct the meta-analyses. All six authors will contribute to the write-up of the review.

DECLARATIONS OF INTEREST

Nuala Livingstone - is an Editor with the Cochrane Developmental, Psychosocial and Learning Problems Group and the Cochrane Editorial Unit.

Geraldine Macdonald - is the Co-ordinating Editor for the Cochrane Developmental, Psychosocial and Learning Problems Group.

Katrina Williams - gave a talk about treatments for autism at a symposium organised by Janssen-Cilag Pty Ltd. Janssen-Cilag had no control over the contents of the talk and the speaker's fee was paid to the University that employs her. She has no ongoing relationship with Janssen-Cilag. Katrina is an Editor with the Cochrane Developmental, Psychosocial and Learning Problems Group.

Deborah M Caldwell - is funded by an UK Medical Research Council, Population Health Scientist Fellowship award (G0902118).

Louise Brigid Baker - none known.
Philip Hazell - has worked as a consultant for Eli Lilly and Janssen and has had research contracts with Eli Lilly and Celltech. He is a member of the advisory board of Eli Lilly, Australia; Janssen, Australia; Novartis, Australia; and Shire, International. Professor Hazell has given presentations for Eli Lilly, Pfizer, Janssen, and Sanofi. He is an investigator on a non-industry funded trial of fluoxetine for autism spectrum disorders (ASD). In the past 36 months, Philip Hazell’s institution has received payment from Lilly and Shire for his participation in advisory boards; Lilly, Janssen, Pfizer, and Shire lectures, and service for speakers bureaus. Professor Hazell’s institution has received payment from Lilly for his work on developing educational presentations. In all cases, these activities related to the assessment and management of attention deficit hyperactivity disorder (ADHD), but in some patients there is comorbidity between ADHD and ASD. Professor Hazell is an Editor with the Cochrane Developmental, Psychosocial and Learning Problems Group. Owing to a potential conflict of interest, Philip Hazell will not be directly involved in data extraction and decisions about data management. Philip is an investigator on a study in progress that addresses related issues “ACTRN12608000173392: Fluoxetine for the treatment of rigid, repetitive and stereotyped behaviours in children and adolescents with autism: a randomised double-blind placebo-controlled trial.”

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**Internal sources**
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  Salary (Katrina Williams)
- University of Bristol, UK.
  Salary (Deborah M Caldwell)
- Royal Children’s Hospital, Australia.
  Salary (Louise Baker)

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  Cochrane Fellowship (Nuala Livingstone)
- UK Medical Research Council, Other.
  Population Health Scientist Fellowship award (G0902118) (Deborah M Caldwell)