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[Intervention Protocol]

Memantine for autism spectrum disorder

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effects of memantine on the core features of ASD, including, but not limited to, social functioning, communication skills and stereotypical behaviours.

BACKGROUND

Description of the condition

Autism spectrum disorder (ASD) is a pervasive neurodevelopmental condition that is characterised by difficulties in social interaction and communication, and the presence of restricted, repetitive behaviours (i.e. stereotypies) (APA 2013; WHO 2018). The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) uses five criteria for the diagnosis of ASD: (1) persistent deficits in social communication and social interaction across multiple contexts; (2) restricted, repetitive patterns of behaviour, interests or activities; (3) symptoms are present in the early developmental period; (4) symptoms cause clinically significant impairment; and (5) these disturbances are not better explained by intellectual disability or global developmental delay (APA 2013). The *International Classification of Diseases, 11th edition* (ICD-11) is also used to diagnose ASD and mirrors the DSM-5 criteria in most key aspects (WHO 2018). The *International Classification of Diseases, 10th Edition* (ICD-10), and the previous *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) grouped diagnoses under 'pervasive developmental disorders', including diagnoses of autistic disorder, childhood autism, Asperger's disorder/syndrome, Rett syndrome, childhood disintegrative disorder, atypical autism, pervasive developmental disorder, unspecified and pervasive developmental disorder not otherwise specified (PDD-NOS) (APA 2000; WHO 1992; Wing 1997). There was no diagnosis of ASD in the ICD-10 and DSM-IV, but it was generally accepted that ASD included all of the diagnoses listed above, with the exception of Rett syndrome and childhood disintegrative disorder. With the publication of the DSM-5, the term ASD replaced previous historical terms used to describe the condition, including Kanner's syndrome, infantile autism, and autistic disorder (Volkmar 2014).

There is wide variability in the severity and manifestation of symptoms in individuals with ASD (Shattuck 2007; Van Wijngaarden-Cremers 2014). However, individuals with ASD generally have core symptoms characterised by persistent deficits in social interaction, social communication, forming and maintaining relationships, and understanding social cues from other people (APA 2013; Shattuck 2007). Other core symptoms include restricted, repetitive patterns of interests and behaviours such as preoccupations or special interests, rigid adherence to routines, hypo- or hyper-reactivity to or interest in sensory stimuli, and stereotypical behaviours (APA 2013). Comorbid symptoms commonly seen in individuals with ASD include anxiety, language difficulties, attention deficit hyperactivity disorder (ADHD), intellectual disability, irritability and aggression, but these features do not occur in all individuals with ASD and are not required to make a diagnosis (Lai 2014). Individuals with ASD also commonly have sleep difficulties (ranging from half to two thirds of individuals); about a third have epilepsy and up to 70% of those with low intellectual functioning have movement abnormalities (Maski 2011). Comorbid psychiatric disturbances are prevalent and contribute significantly to functional outcomes in individuals with ASD. Studies in adults with ASD indicate that up to 18% have associated psychoses and about one in two individuals have at least one anxiety disorder (Vannucchi 2014).

The prevalence of ASD has been estimated at around one in 54 children aged eight years old in the USA (Maenner 2020). Some studies report increasing incidence and prevalence of ASD, although this appears to be due to better case ascertainment, milder symptoms, earlier diagnosis and increased awareness and diagnostic substitution, rather than a true increase in ASD (Elsabbagh 2012; Fisch 2012; Fombonne 2011; May 2020). ASD is three times more common in males than in females (Loomes 2017). There is no one cause of ASD, but increasing genetic findings support what has been suspected: that rather than a true increase in ASD, there are different genetic pathways to ASD, with a wide range of single genes reported, known genetic problems with increased risk of autism, and early reports that multiple common variant genes play a role. The possibility of gene-environment interactions are also being explored (Bayou 2008; Hallmayer 2011; Lai 2014).

ASD is a diagnostically stable condition. Children who are diagnosed with ASD continue to manifest symptoms as adults (Woolfenden 2012). However, the severity of symptoms may vary over the lifetime trajectories of people with ASD (Vannucchi 2014). Adults with ASD have variable outcomes in areas such as educational attainment, employment, relationships and functional independence. Generally, individuals with associated low intelligence or comorbid psychiatric diagnoses, such as depression or anxiety disorder, have poorer lifetime outcomes (Gotham 2015).

Description of the intervention

Therapies for ASD

There are no interventions that result in the complete resolution of ASD symptoms. This is due to the wide variability in the manifestations and severity of core and non-core symptoms in individuals with ASD. Most interventions for ASD target behaviour and development, and often employ a combination of behavioural and developmental, educational, medical-related or allied-health therapies. No pharmacological interventions have been shown to target the core symptoms of ASD effectively. Most pharmacologic interventions are used as adjunctive therapy to target specific unwanted behaviours (typically non-core symptoms of ASD, such as restricted and repetitive behaviours, hyperactivity, inattention, irritability and aggression (Farmer 2013)), or to assist with the management of anxiety.

More recently, there has been an interest in the potential effectiveness of pharmacological interventions that might target atypical neuropathological pathways. These include: acetylcholinesterase inhibitors (for example, donezepil, galantamine); anti-depressant selective serotonin reuptake inhibitors (SSRIs; such as fluoxetine, citalopram); anti-psychotic drugs (for example, risperidone, aripiprazole); mood stabilisers or anti-epileptic agents (for example, lamotrigine, sodium valproate); psychostimulants (for example, methylphenidate); and glutamate receptor-related medications (for example, memantine) (Doyle 2012; Farmer 2013; Rossignol 2014; Siegel 2012). This study will look at the current available evidence for the use of memantine in ASD.

Memantine

Memantine is a pharmacological agent, which acts as a non-competitive antagonist of glutamatergic N-methyl-D-aspartate (NMDA) type receptors. It works by inhibiting pathological overactivation and subsequent neuroexcitation and cell death of NMDA receptor cells by glutamate - an amino acid normally found in the brain. Individuals with ASD have been reported to have

pathologically increased activity levels of glutamate and NMDA receptors, hence the aim to modulate this biochemical effect, and potentially ameliorate the clinical symptoms of ASD. This property of memantine has been employed in the treatment of Alzheimer's disease and is the basis for trials in the treatment of individuals with ASD (e.g. Aman 2017a; Hardan 2019; Hosenbocus 2013; Kavirajan 2009; Wei 2012). The American Psychiatric Association currently endorses the use of memantine in the treatment of moderate to severe Alzheimer's dementia, and it is used off-label in mild to moderate vascular dementia (Rabins 2007).

Research trials have also been carried out on the use of memantine as a pharmacologic treatment for some psychiatric conditions that often occur as comorbidities in individuals with ASD, such as obsessive-compulsive disorder (OCD) (Haghighi 2013; Stewart 2010), ADHD (Biederman 2017; Findling 2007; Mohammadi 2015; Surman 2013), anxiety (Feusner 2009; Rapp 2013; Schwartz 2012) and depression (Caddy 2015; McCloud 2015; Smith 2013; Strzelecki 2013; Zarate 2006). These studies have found memantine to have variable effectiveness as either single or adjuvant therapy. Hence, further research on its use is warranted.

Memantine has been used in clinical trials for the treatment of individuals with ASD, yet the dosage used across studies has varied. One small, open-label, retrospective study of individuals with ASD aged six to 19 years, used memantine to a maximum dose of 20 mg/day. This small study of 18 individuals reported significant beneficial effects on social withdrawal and inattention (Erickson 2007). A larger prospective trial reported improvements in language and social interaction in children with autism who were treated with open-label memantine doses between 2.5 and 30 mg/day in addition to their pre-existing medications (Chez 2007).

Memantine has been described as relatively safe, well tolerated, and with an adverse effect profile between 0% to 2% higher than placebo treatment, from trials carried out in elderly patients who have Alzheimer's dementia (Farlow 2008; Thomas 2009; Van Dyck 2007). Reported adverse effects associated with memantine treatment include falls, injuries, pain, arthralgia, agitation, anxiety, depression, confusion, headaches, hypertension, peripheral oedema, dizziness, fatigue, somnolence, insomnia, flu-like symptoms, cough, dyspnoea, upper respiratory tract infections, nausea, diarrhoea, constipation, vomiting, anorexia, increase in blood urea nitrogen, urinary incontinence and urinary tract infections (Ott 2007; Thomas 2009). There are limited study data on adverse effects in children and adults with ASD.

Following oral administration, memantine is rapidly and completely absorbed through the gastrointestinal tract, with bioavailability close to 100% (Kornhuber 2007). The elimination half-life of memantine has been described as 60 to 80 hours, and the time to reach maximum plasma concentration (Tmax) is about three to eight hours (Kavirajan 2009; Kornhuber 2007). It follows a linear pharmacokinetic pattern at a single dose of up to 40 mg (or a twice daily dose of 20 mg), which implies that the half-life will remain constant, no matter how high the concentration (Kavirajan 2009). Memantine undergoes minimal hepatic metabolism and is not strongly bound to plasma proteins, hence its minimal drug-to-drug interaction through these mechanisms (Kavirajan 2009; Kornhuber 2007). Over 80% of memantine undergoes renal excretion. Patients with significant renal impairment are recommended to have the dose of memantine limited to 5 mg twice daily (Kornhuber 2007). All data are from studies in adults, and the pharmacokinetic and pharmacodynamic properties of memantine may well vary in children and adolescents.

How the intervention might work

Glutamate and the glutamatergic pathway

Glutamate, an amino acid, is the main excitatory neurotransmitter in the nervous system. It is released from vesicles in pre-synaptic neural cells in response to transmission of a neuronal impulse, from where it goes into the extra-cellular space, and then into post-synaptic neuronal cells. Glutamate binds to and activates glutamate receptors in the post-synaptic cell, namely NMDA and α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Glutamate is found in many parts of the brain, such as the hippocampus and parts of the cerebral cortex (Rojas 2014), and it is involved in learning and memory functions in the brain through synaptic plasticity - the modification of synaptic activity over time. Specifically, it enhances persistent synaptic activity through long-lasting increases in neuronal transmission, known as long-term potentiation (LTP). These actions contribute to the neuroexcitatory effects of glutamate.

Glutamate transporters are responsible for the removal of excess glutamate from the extra-cellular space, as increased glutamate release or reduced uptake results in accumulation of excess glutamate outside synaptic cells. The resulting accumulation of glutamate within the extra-cellular space causes an influx of calcium ions into the synaptic receptor cells through NMDA receptors, which leads to overactivation of the NMDA receptors, neurotoxicity and eventually neuronal cell death. This process has been implicated in some conditions, including ASD and Alzheimer's disease (Rojas 2014; Uzunova 2014).

Memantine acts as a non-competitive antagonist of glutamatergic NMDA type receptors, and it works by modulating NMDA receptor activity, thereby mediating the potential neurotoxic effects of glutamate. This property of memantine has been employed in the treatment of Alzheimer's disease and has been used in trials for individuals with ASD (Aman 2017a; Hardan 2019; Rossignol 2014; Wei 2012). Some studies have described memantine as helpful for reducing the core symptoms of ASD, such as social withdrawal and language difficulties, as well as non-core symptoms such as irritability, hyperactivity and inattention (Chez 2007; Erickson 2007; Ghaleiha 2013; Hardan 2019; Niederhofer 2007; Owley 2006).

Memantine has other mechanisms of action besides non-competitive NMDA receptor blockage (Sani 2012), including non-competitive, voltage-dependent antagonism of type 3 serotonin 5-HT(3) receptors (Rammes 2001; Reiser 1988). 5-HT(3) receptors are ligand-gated ion channels which help to mediate neuronal depolarisation and excitation, including release of neurotransmitters such as glutamate. They can be found in the gut and throughout the central and peripheral nervous systems (Nichols 2008). Serotonin, the neurotransmitter which binds to 5-HT(3) receptors, is involved in some neurocognitive functions such as memory, learning and mood. The exact mechanism of action is still unclear, but it is thought that inhibition of 5-HT(3) receptors by memantine might improve cognition and learning and reduce anxiety, either by increasing circulating serotonin levels or preventing receptor activation and glutamate release (Rammes 2001; Reiser 1988). Memantine also acts as a non-competitive antagonist of nicotinic acetylcholine receptors

(nACHRs) in the hippocampus and has been implicated in learning and cognitive functioning (Becker 2013). Another mechanism of action of memantine is as an agonist of dopaminergic D2 receptors, which helps to enhance neurocognitive functioning (Sani 2012; Seeman 2008). Further research is required to establish the exact mechanisms of memantine in the treatment of core symptoms and associated symptoms seen in ASD.

Why it is important to do this review

The lifelong and limiting symptoms of ASD often mean that many individuals with the condition undergo various combinations of interventions and therapies, several of which have limited evidence of effectiveness in treating the primary symptoms or behaviours of ASD (Cheuk 2011; James 2011; Millward 2008; Nye 2005; Sinha 2011; Williams 2012; Williams 2013). These interventions often incur a financial cost to the individual, their families and sometimes communities. In addition, most medications have side effects, and it is important to consider these when they are prescribed. This review will contribute to informed decision-making for therapy and provide data for policy and guideline development for individuals with ASD.

We will describe the response to memantine treatment by assessing core outcome measures such as: difficulties with social cognition and interaction and social communication; restrictive, repetitive and rigid behaviours; and secondary comorbidities such as hyperactivity, inattention, irritability, aggression and anxiety. We will also assess important functional outcomes such as improvement in cognition, memory, quality of life of individuals and their families, general health and daily function, as these outcomes are of particular importance to individuals with ASD and their families. We will also include an assessment of whether any side effects from memantine treatment are to be considered with its use in individuals with ASD.

In addition to assessing the postulated efficacy of memantine, it is also important to investigate whether memantine has an impact on, and correlates with: the severity of symptoms (for instance, individuals with verbal abilities versus those with no verbal skills; individuals with an associated low intelligence quotient (IQ)); the age of participants (children versus adults); different dosage and frequency of memantine administration (once a day versus multiple daily dosing); and duration of treatment.

OBJECTIVES

To assess the effects of memantine on the core features of ASD, including, but not limited to, social functioning, communication skills and stereotypical behaviours.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs). This includes cross-over RCTs, which are trials where participants are randomly allocated to study arms where each arm consists of a sequence of two or more treatments given consecutively. We will not include quasi-randomised controlled trials.

Types of participants

Children and adults with a diagnosis of ASD and who meet the diagnostic criteria for DSM-IV-TR, DSM-5 and ICD-10 or ICD-11 classifications of ASD. Diagnoses may be made with or without supporting standardised clinical instruments, including the Childhood Autism Rating Scale (CARS; Schopler 1986), Autism Diagnostic Observation Schedule (ADOS; Lord 2012), Autism Diagnostic Interview - Revised (ADI-R; Lord 1994), and Diagnostic Interview for Social and Communication Disorders (DISCO; Wing 2002). Children can be with or without additional medical or developmental diagnoses, although children and adults with a diagnosis of childhood disintegrative disorder (CDD) or Rett syndrome will be excluded. Rett syndrome and CDD are no longer included under DSM-5 criteria for ASD and the autism characteristics seen in these two conditions are only present for a narrow window of time in the life of a child.

Types of interventions

Memantine given at any dose, frequency and duration, and administered in any setting, compared with placebo or no treatment.

We will include studies in which memantine is taken in addition to other pharmacological agents as long as all participants recruited to the trial were already in receipt of the same or comparable medications, and these continue to be provided to participants in both arms of the trial. We will also include trials that give memantine as an adjunct to behavioural interventions if the behavioural interventions were provided equally to both arms.

Types of outcome measures

Outcomes will be measured using standardised assessments, parent or teacher questionnaires and rating scales, and behavioural observation. We will consider quantitative and qualitative data from all measures. Where both parent and teacher measures are used, we will prioritise parent-reported measures. Where studies present two or more measures for one outcome, we will prioritise standardised measures over non-standardised measures (e.g. rating scales). We will analyse observed, parent-reported, teacher-reported and self-reported data separately.

Primary outcomes

- Core symptoms of ASD, assessed using any measure for:
  - social communication, measured by diagnostic instruments such as the Childhood Autism Rating Scale (CARS; Schopler 1986), Autism Diagnostic Observation Schedule (ADOS; Lord 2012), Autism Diagnostic Interview - Revised (ADI-R; Lord 1994) and Diagnostic Instrument for Social Communication Disorders (DISCO; Wing 2002); and
  - repetitive and rigid behaviour, including stereotypy, measured by diagnostic instruments such as the CARS (Schopler 1986), ADOS (Lord 2012), ADI-R (Lord 1994) and DISCO (Wing 2002).

- Adverse effects, including the risk or presence of side effects directly attributable to the use of memantine, such as:
  * gastrointestinal (for example, constipation, nausea);
  * neurological (for example, headache, irritability, somnolence); and
  * cardiovascular (for example, hypertension).

Secondary outcomes

- Improvement in any commonly associated non-core symptoms associated with ASD, including hyperactivity, irritability and aggression. Examples of measures used to assess these symptoms include the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; McKay 2003), which is used to measure obsessive compulsive behaviours, and Connors' Abbreviated Parent-Teacher Questionnaire (APTQ; Conners 1997) for hyperactivity and aggression.
- Improvement in cognition in individuals with ASD, specifically in attention and memory, measured by a cognitive or IQ test (e.g. Wechsler 2014).
- Improved quality of life for individuals with ASD and their carers, measured by scales such as the Family Quality of Life Scale (FQOLS; Beach Center on Disabilities 2006).
- General health and function at home and school, measured by tools such as the Clinical Global Impression-Improvement scale (CGI-I; Guy 1976).

Estimates suggest that 33% to 75% of people with ASD are reported to have an intellectual disability associated with ASD (Bourke 2016; Maenner 2020). Given these figures, we will highlight the properties of the psychometric tests used to assess outcomes in individuals treated with memantine, and discuss, in particular, how these properties influence the measurement of outcomes in individuals with comorbid intellectual disabilities versus those without intellectual disabilities. We will indicate the evidence supporting the validity of each tool in the following categories: individuals with comorbid intellectual disability versus those without an intellectual disability; adults versus children; and assessment of social communication and social interaction versus repetitive and restrictive behaviours (Anagnostou 2015; McConachie 2015; Scahill 2015). For instance, in individuals with ASD without comorbid intellectual disability, we will examine studies using the Social Responsiveness Scale (SRS; Constantino 2011), which measures various aspects of social cognition such as social awareness, social information processing, capacity for reciprocal social communication, social anxiety and avoidance, and preoccupations, as it has been described as a useful tool in measuring response to intervention (Payakachat 2012). On the other hand, the use of the Aberrrant Behaviour Checklist (ABC; Aman 2017b) has been validated as a tool to assess treatment in individuals with an intellectual disability, and there is limited evidence at present for its use in assessing change in social function in individuals with ASD without comorbid intellectual disability (Payakachat 2012).

Search methods for identification of studies

Electronic searches

We will search the following databases and trials registers.

- Cochrane Central Register of Controlled Trials (CENTRAL; current issue), in the Cochrane Library, which includes the Cochrane Developmental, Psychosocial and Learning Problems Group specialised register.
- MEDLINE Ovid (1946 onwards).
- MEDLINE Ovid In-Process & Other Non-indexed Citations (1946 onwards).
- MEDLINE Ovid Epub Ahead of Print (current issue).
- Embase Ovid (1974 onwards).
- *Cochrane Database of Systematic Reviews* (CDSR; current issue), part of the Cochrane Library.
- Epistemonikos (limited to systematic reviews; www.epistemonikos.org).
- CINAHL Plus EBSCOhost (Cumulative Index to Nursing and Allied Health Literature; 1937 onwards).
- APA PsycINFO Ovid (1806 onwards).
- ERIC EBSCOhost (Education Resources Information Center; 1966 onwards).
- Science Citation Index Web of Science, Clarivate (SCI; 1970 onwards).
- Social Sciences Citation Index Web of Science, Clarivate (SSCI; 1970 onwards).
- LILACS (Latin American Caribbean Health Sciences Literature; search.bvsalud.org/portal/advanced/?lang=en).
- SciELO Citation Index Web of Science (2002 onwards).
- TOXLINE subset in PubMed (pubmed.ncbi.nlm.nih.gov).
- Conference Proceedings Citation Index-Science Web of Science, Clarivate (CPCI-S; 1990 onwards).
- Conference Proceedings Citation Index-Social Sciences & Humanities Web of Science, Clarivate (CPCI-SSH; 1990 onwards).
- ClinicalTrials.gov (clinicaltrials.gov).
- World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP, apps.who.int/trialsearch).
- EU Clinical Trials Register (www.clinicaltrialsregister.eu).
- ProQuest Dissertations & Theses A&I (current issue).

We will use the Cochrane Highly Sensitive Search Strategy to identify RCTs in Ovid MEDLINE, as described in the Technical Supplement of Chapter 4 in the *Cochrane Handbook for Systematic Reviews of Interventions* (hereafter referred to as the *Cochrane Handbook*; Lefebvre 2020). We will search Ovid MEDLINE using the search terms shown in Appendix 1. We will modify these search terms, as appropriate, for the other databases and trial registers listed above.

We will not limit the searches by publication date, language, or publication status. Before publication, we will conduct a search to ensure none of our included studies have been corrected or retracted.

Searching other resources

We will contact the first author of each included study and known experts in the field of developmental paediatrics and child psychiatry to ask if they can provide details of any additional relevant studies not already identified by the electronic searches. We will also search the reference lists of relevant studies and reviews for RCTs that meet our inclusion criteria.

Data collection and analysis

Selection of studies

Two review authors (AB, TM) will independently assess for eligibility the titles and abstracts identified through the searches. We will then retrieve and examine full-text reports for those studies deemed potentially relevant or for which more information is needed to determine relevance. We will group multiple publications of the same study. We will exclude studies that do not meet inclusion criteria. We will attempt to resolve any disagreements about eligibility by discussion between the two review authors. If necessary, a third review author (KW) will act as arbiter. We will report the calculated Kappa statistic, which is a measure of the overall reported agreement between authors determining the eligibility of studies for inclusion, as described in Chapter 5 of the *Cochrane Handbook* (Lefebvre 2020; Li 2019). We will present the results of our selection process in a PRISMA diagram (Moher 2009). Covidence (Covidence) will be used for screening the reports.

We will list any excluded studies that seem relevant in the 'Characteristics of Excluded studies' tables.

Data extraction and management

We will use Covidence (Covidence) and Excel for data organisation and management. Two review authors (AB and TM) will independently extract data from each included study. Data will be extracted on the following.

- Study methods and setting: study type (type of RCT), study site, country of publication, language of publication, publication type and study duration.
- Participant details: age, sex, diagnosis and diagnosis tool.
- Intervention details: intervention type, including dosage, mode of delivery, frequency and duration; placebo type, including dosage, mode of delivery, frequency and duration.
- Outcomes: all primary and secondary outcomes.

We will also extract data that will allow risk of bias ratings to be made. In case of a disagreement, a third review author (KW) will check the extracted data and act as arbiter. One review author (AB) will enter the extracted data into RevMan 5 software (Review Manager 2020) and a second author (TM) will check the data entry. See Appendix 1 and Appendix 2 for further details on data to be extracted and risk of bias criteria.

Assessment of risk of bias in included studies

We will use a data extraction form to collect information when assessing risk of bias. This form will include the criteria described in the Cochrane 'Risk of bias' assessment tool for assessing risk of bias in randomised controlled trials, in Chapter 8 of the Cochrane Handbook (Higgins 2011). We will pilot the data collection form and modify the form as required. Two review authors (AB and TM) will independently assess the risk of bias of the included studies and, in case of any disagreements, a third review author (KW) will act as arbiter. The following five potential sources of bias will be assessed: sequence generation; allocation concealment; blinding of participants and personnel and blinding of outcome assessment; incomplete outcome data; and selective reporting. The risk of bias for each study will be rated as high, low or unclear and presented in a table, with justifications to support the decisions. We will judge each study's overall validity and rate studies as: high risk of bias overall if one or more domain(s) have been rated at high risk of bias; low risk of bias overall if all five domains have been rated at low risk of bias; and unclear risk of bias overall if all five domains have been rated at varying risks of unclear and low risks of bias. These judgements will then be used to guide overall assessments of quality of the evidence (GRADE ratings). See Data synthesis. For example, if the body of evidence for a particular outcome comes from one or more study at high risk of bias, the overall quality of the evidence will be downgraded. If most evidence comes from studies that met criteria for low risk of bias, the quality of the evidence will not be downgraded.

Measures of treatment effect

We will enter data into RevMan 5 software (Review Manager 2020), and present it using Cochrane 'Characteristics of included studies' tables. We will record data on effect size for each individual study.

Dichotomous data

We will analyse dichotomous outcomes by calculating the odds ratio (OR), and corresponding 95% confidence intervals (CIs), as the OR is associated with the best mathematical properties and is more easily computed from other measures of effect size. We will calculate the OR using RevMan 5 (Review Manager 2020), as described in Chapter 10 of the *Cochrane Handbook* (Deeks 2020). If other forms of effect measures (e.g. standardised mean difference (SMD)) are provided in studies reviewed, we will use the available information to compute the OR using the formulae given in Chapter 10 of the *Cochrane Handbook* (Deeks 2020). If outcomes are not reported within a 2 x 2 table, we will contact the study authors for this information. There may be zero counts for the outcome in one or both arms of the intervention. In this case, we will use meta-analysis software (including RevMan (Review Manager 2020) that manages zero counts by adding a fixed value (e.g. 0.5) to all cells of the relevant study.

Continuous Data

If studies use the same scales to measure continuous outcomes (for example, scores or standardised measures of improved behaviour), we will estimate the effect size by computing the pooled mean difference (MD) and 95% CI using the means and standard deviations we have extracted from the studies. If the scales used in studies are different but the outcomes they measure are conceptually similar, we will calculate the standardised mean difference (SMD), as recommended in Chapter 10 of the *Cochrane Handbook* (Deeks 2020).

We will focus on final values unless change scores are used in the studies. We will combine in the same meta-analysis studies that report final values with studies that report only change scores, provided that the studies use the same rating scale. A potential problem of including change scores is that the standard deviation of the changes may not be reported in the included study (Higgins 2020a). If data are not reported or unable to be extracted, we will contact trial authors. If we are unable to contact authors or they do not provide the required data, we will attempt to estimate the standard deviation of changes (Dealing with missing data). We will collect data from studies that have provided logarithmic values due to skewed data. These data may be included in meta-analyses or (if statistically appropriate) will be transformed back to the raw scale.

Multiple outcomes

If different studies provide multiple, interchangeable measures of the same construct at the same point in time, we will calculate the average SMD across the outcomes and the average estimated variances, as recommended in Chapter 6 of the *Cochrane Handbook* (Higgins 2020b). All eligible outcomes or measures will be documented in the 'Characteristics of included studies' table where we will specify which outcome measure was selected and why. If a study reported data for a particular outcome using two or more assessment instruments (e.g. a questionnaire and a direct assessment), we will choose the one that has been used most frequently by the pooled included studies for effect size calculation. This is to minimise the heterogeneity of study outcomes. We will use standardised tests (as compared to non-standardised) if a study has not presented the commonly used measure.

Unit of analysis issues

We will assess all included trials to determine the unit of randomisation and whether or not this unit of randomisation is consistent with the unit of analysis. We do not intend to use individual patient data (IPD), as we do not consider that an IPD review is warranted until a non-IPD systematic review is completed, and more is known about whether or not IPD would add value to findings for this particular review. We will use available published or aggregate data as our units of analysis, as described under Measures of treatment effect.

Cluster-RCTs

We do not anticipate including any cluster-RCTs in our review given the nature of the intervention. However, if we come across eligible studies that have used cluster-RCT methods, we expect that the cluster effects will have been appropriately controlled for. If it is unclear whether appropriate controls for cluster effects have been carried out, we will aim to contact the study authors to obtain necessary information. If appropriate controls have not been applied, we will request the IPD and re-analyse the data using the generic inverse variance method in order to adjust for correlation, as outlined in Chapter 10 of the *Cochrane Handbook* (Deeks 2020). We will analyse the effect size and standard error using RevMan 5 (Review Manager 2020). Where this is not possible due to insufficient available data to control for clustering, we will use individuals as the unit of analysis, and then assess the impact of insufficient control of clustering on the effect estimate by using sensitivity analysis (Sensitivity analysis).

Cross-over trials

We will clearly identify eligible randomised trials in which participants receive both placebo and memantine but in a different order (phase). We will analyse the data according to recommendations in the *Cochrane Handbook* for cross-over trials (Higgins 2020a). We will include data up until the point of the first cross-over. We will not include data from any subsequent periods due to the likelihood of carry-over effects from the prior intervention to the second phase of the study. We will use the effect estimate and standard deviation based on a paired t-test. If we are able to conduct a meta-analysis combining the results of cross-over trials, we will use the generic inverse variance method (Deeks 2020). We will seek statistical advice for the analysis of cross-over trials.

Trials with repeated measurements

In studies with repeated measurements for the same patient over different time points, we will prioritise analysis of the most meaningful time points (for example, outcome measures at the first point where memantine is expected to show clinical improvement or side effects). If this is not possible, then we will report the most frequently reported time points (Higgins 2020a). We will conduct separate analyses for data from different points of measurement (i.e. immediately post-treatment, follow-up data between 0 and 3 months, 3 and 12 months, and more than 12 months). If there are multiple measurements within the one interval (e.g. the 6- to 12-month interval), we will use the latest time point.

Trials with multiple treatment arms

For studies with multiple treatment arms, we will create a single pair-wise comparison, where appropriate (for example, where memantine is given in different formulations such as immediate- and extended-release formulations of memantine). If this is not feasible, we will use all treatment arms but divide the comparison arms (control arms) equally across the intervention arms (Higgins 2020a). We will determine the relevance of the treatment arms for each comparison by assessing clinical relevance (for example, if the clinical effects of memantine are comparable or not). If two formulations are used in a trial and one formulation of memantine is more readily available than another, we may chose to exclude the less commonly available formulation. If a treatment arm is not found to be relevant to our study outcomes, we will exclude the group from our analysis. We will clearly document all decisions made in the 'Characteristics of included studies' tables.

Dealing with missing data

We will assess missing data and dropouts for each included study. Two review authors (AB, TM) will attempt to contact the primary study authors for any relevant missing data (such as participant age, intellectual ability, memantine dose and regimen used, tools used to measure change in outcomes) or attrition (such as reasons for dropout). If study authors provide the missing data, we will include these data according to intention-to-treat (ITT) principles, and use all of the data. We will keep participants in the treatment group to which they were originally randomised, regardless of the treatment they received, as recommended in the *Cochrane Handbook* (Higgins 2020a).

If we are unsuccessful in obtaining a response from study authors after two attempts, no further contact will be made. We will analyse only the available data. We will state our assumptions as to whether the data are 'not missing at random' (such as due to unfavourable outcomes or non-adherence to treatment) or 'missing at random', and we will analyse only the available data, as recommended in Chapter 10 of the *Cochrane Handbook* (Deeks 2020).

If there are missing summary data (such as the standard deviation or mean of the outcomes), we will aim to derive calculated values, as recommended in Chapter 10 of the *Cochrane Handbook* (Deeks 2020). If there is concern about a large amount of missing data and we deem it inappropriate to include the data in a meta-analysis, we will provide a qualitative summary in the text. We will perform a Sensitivity analysis to explore the validity of the imputations made by carrying out an analysis without the imputed values, and assess for any differences between the result obtained and the calculated assumed mean. We will discuss the impact the method for analysis

of missing data may have on the interpretation of our results in the Discussion section of the review.

Assessment of heterogeneity

We will assess clinical heterogeneity by comparing the populations included in the studies (for example, children versus adults), the settings, the treatment modalities (for example, types of dosing regimens), and the outcomes. Additionally, we will assess methodological heterogeneity within our included studies by examining key trial characteristics (for example, risk of bias in allocation concealment, blinding, outcome measurements, losses to follow-up). We will report any significant sources of heterogeneity in the 'Risk of bias' tables and discuss it in the review.

We will assess statistical heterogeneity by performing a Chi^2 test, with statistical significance set at P value less than 0.10, and calculating the I^2 value - a quantity which describes the approximate proportion of variation in point estimates that can be attributed to heterogeneity rather than sampling error - as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity; and
- 75% to 100%: considerable heterogeneity (Higgins 2020a).

To estimate the between-study variance, we will use the Tau^2 in a random-effects meta-analysis (Deeks 2020; DerSimonian 1986), which we will perform in RevMan 5 (Review Manager 2020). We will incorporate the refinements to the standard approach for meta-analysis recommended by DerSimonian 2015, using a robust variance estimator for testing the overall effect.

Assessment of reporting biases

If we find 10 or more studies that meet our inclusion criteria (Criteria for considering studies for this review), we will draw a funnel plot to explore the relationship between the intervention effect estimate and standard error of the intervention effect estimate. If there appears to be asymmetry, we will also use Begg's test (Begg 1994), and Egger's test (Egger 1997), to explore the reason for asymmetry, such as publication bias or low methodological quality. Begg's test ranks correlation between a standardised intervention effect and its standard error; and Egger's test analyses the linear regression of an intervention effect estimate against its standard error, weighted by the inverse of the variance of the intervention effect estimate (see Chapter 10 of the *Cochrane Handbook*; Deeks 2020). For each outcome of interest, we will explore if there is selective reporting of outcome data, which could bias the direction of results. If selective reporting of outcomes is suspected, we will contact the study authors where possible, in order to collect this missing outcome data**.** We will explore the impact on results of published versus any unpublished data by means of a Sensitivity analysis (Higgins 2020a).

Data synthesis

We will conduct standard pair-wise meta-analysis if at least two relevant studies have available data and they do not have substantial clinical or methodological heterogeneity (e.g. differences in study design or comparison group) (see Assessment of heterogeneity). We anticipate that there will be a mixture of change-from-baseline values and final values. If this is the case, we will extract both change-from-baseline and final values provided the data are available. If change-from-baseline data are reported but standard deviations (SD) are not, we will contact the study authors to obtain the necessary data. If we cannot obtain the SD from the study authors, we will calculate the SD from the standard error or CI of the mean (Higgins 2020a). If we find a mixture of change scores and absolute scores in different studies using the same measurement tool, we will pool the data using the (non-standardised) mean difference with inverse-variance weighting in RevMan 5 (Review Manager 2020), as recommended in Chapter 10 of the *Cochrane Handbook* (Higgins 2020a).

We will synthesise the results in a meta-analysis using a random-effects model with inverse-variance weighting (Deeks 2020; DerSimonian 1986). This approach minimises the imprecision of the pooled effect estimate (Higgins 2020a). We will use a fixed-effect model when studies are similar regarding the intervention, population and methods. When combining results from cross-over trials for meta-analysis, we will use inverse variance methods (Higgins 2020a). The results will be displayed in a forest plot. If it is not possible to conduct a meta-analysis (e.g. data are too heterogeneous, there is high statistical heterogeneity or there are too few studies), we will provide a narrative description of the results. Our primary analysis will include all eligible studies but we will conduct sensitivity analysis (by excluding studies at unclear or high risk of bias for lack of blinding) to test the robustness of the results to decisions made throughout the review process (see Sensitivity analysis).

For data synthesis, we will investigate funnel plot asymmetry. If we find there is none, we will perform a random-effects meta-analysis, which assumes that there is true heterogeneity between each of the included studies. However, if we find there is asymmetry, we will perform both random-effects and fixed-effect analyses, of which the latter assumes that the true effect of an intervention is the same in each study and the observed differences are due to chance. We will then compare the results of these to determine if there is agreement on the effect or lack of effect. If the findings of these investigations are different, we will report this in the Results section of the review.

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analyses to explore differential effects of the following, providing there is sufficient data (i.e. at least 10 observations for each characteristic being analysed).

- Drug dosage (for example, small-dose (likely less than 5 mg/kg/day) versus medium-dose (likely 5 mg/kg/day to 9 mg/kg/day) versus high-dose (likely more than 10 mg/kg/day) memantine).
- Frequency of administration (for example, once daily dose versus divided daily doses).
- Duration of administration (less than 6 months versus 6 to 12 months versus more than 12 months).
- Ages of participants: preschoolers (2 to 6 years of age) versus primary school-aged children (6 to 12 years of age) versus teenagers (13 to 18 years of age); and children versus adults (18 years and older).
- Severity of ASD symptoms (for example, minimal communication skills versus well-developed communication skills).
- IQ of study participants: cognition of participants will be classified as those with an IQ less than 70 (intellectual disability)

versus participants with an IQ above 70 (no intellectual disability).

Sensitivity analysis

We will conduct a sensitivity analysis to assess the impact of risk of bias on the overall result. We will do this by adding or removing studies at high or unclear risk of bias in the following assessment areas from the meta-analysis.

- Blinding participants or personnel or outcome assessments: we will re-analyse data by excluding studies at high (or unclear) risk of bias for blinding participants or personnel or outcome assessments.
- Attrition bias: we will re-analyse data by excluding studies that have more than 30% attrition or where there is a difference in attrition between each group.

We will perform a sensitivity analysis to explore the impact of missing data on the overall outcome by comparing the analyses with available outcome data with those following the ITT principle (see Dealing with missing data).

Summary of findings and assessment of the certainty of the evidence

We will export data from RevMan 5 (Review Manager 2020) to GRADEpro (GRADEpro), to create our 'Summary of findings' tables for the comparisons between memantine versus placebo or memantine versus no treatment. We will include all primary outcomes (core symptoms of ASD; adverse effects) and secondary outcomes (improvement in any commonly associated non-core symptoms associated with ASD; improvement in cognition; improved quality of life (for individuals and carers); and general health and function at home and school) in the 'Summary of findings' table. We will choose one measurement for each outcome. We will collect data for immediate, short- and long-term time points but will use only the immediate time point for inclusion in the table.

Using the GRADE system (Schünemann 2020), two review authors (AB, TM) will independently assess the certainty of the evidence for all primary and secondary outcomes (Types of outcome measures). The GRADE system takes into account directness, risk of bias, precision, consistency and publication bias. 'Directness' assesses how well included studies address the review question; 'risk of bias' assesses the overall risk of bias of included studies that provided data for each outcome; 'precision' assesses the statistical precision of the results; 'consistency' assesses how well unexplained heterogeneity has been accounted for in the study results; and 'publication bias' assesses transparency of publication and risk of publication bias among the studies that contribute to the outcome (Schünemann 2020). We will rate the certainty of the evidence as high, moderate, low or very low. We will treat RCTs as high-certainty evidence initially, and downgrade the certainty ratings up to a maximum of three levels depending on the presence of the aforementioned criteria (Schünemann 2020). We will indicate our reasons for downgrading the certainty of the evidence for each outcome in the footnotes to the 'Summary of findings' table (Schünemann 2020). We will resolve any disagreements by discussion or in consultation with a third author (KW).

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APPENDICES

Appendix 1. Criteria for assigning risk of bias

Random sequence generation

1. Low risk of bias: the investigators describe a random component in the sequence generation (e.g. referring to a random number table, using an electronic random number generator)

2. High risk of bias: the investigators describe a component in the sequence generation process that is not strictly random or is nonrandom (e.g. by date of birth, by judgement of the clinician or by preference of the participant)

3. Unclear risk of bias: there is insufficient information available regarding the sequence generation process to make a judgement of high or low risk of bias

Allocation concealment

1. Low risk of bias: both participants and investigators could not foresee assignment (e.g. due to central allocation or sealed envelopes)

2. High risk of bias: participants or investigators could possibly foresee the assignments (e.g. using an open random allocation schedule, alternation on rotation)

3. Unclear risk of bias: there is insufficient information available regarding allocation concealment to make a judgement of high or low risk of bias

Blinding of participants and personnel

1. Low risk of bias: blinding of participants and key study personnel is ensured; or the outcomes are not likely to be influenced by the lack of blinding

2. High risk of bias: the lack of blinding is likely to have influenced the outcome; or the blinding could have been broken

3. Unclear risk of bias: there is insufficient information available regarding this issue to make a judgement of high or low risk of bias

Blinding of outcome assessment

1. Low risk of bias: blinding of outcome assessment is ensured; or it is judged unlikely that outcome measurement could have been influenced by the lack of blinding

2. High risk of bias: a lack of blinding is likely to have influenced the outcome measurement; or the blinding could have been broken

3. Unclear risk of bias: insufficient information is available to make a judgement of high or low risk of bias

Incomplete outcome data

1. Low risk of bias: there are no missing outcome data; it is unlikely that missing outcome data are related to the true outcomes; and/or missing data are imputed using appropriate methods

2. High risk of bias: it is likely that missing outcome data are related to the true outcome because of, for example, imbalance in numbers, when an 'as-treated' analysis is done with substantial differences between the intervention received and the intervention assigned in the randomisation, or when there is a potentially inappropriate application of imputation

3. Unclear risk of bias: there is insufficient information reported to make a judgement of high or low risk of bias

Selective reporting

1. Low risk of bias: the study protocol is available and all of the pre-specified outcomes have been reported in the pre-specified way; or the study protocol is not available but the published reports include all expected or pre-specified outcomes

2. High risk of bias: there are discrepancies between reporting of outcomes that were pre-specified and the actual reported outcomes; or outcomes are reported incompletely

3. Unclear risk of bias: there is insufficient information available to make a judgement of high or low risk of bias

Other sources of bias

1. Low risk of bias: no additional sources of bias can be identified

2. High risk of bias: a potential source of bias is identified (e.g. related to study design)

3. Unclear risk of bias: there is insufficient information available or there is insufficient rationale or evidence that an identified problem will introduce bias

Taken from Chapter 8 of the *Cochrane Handbook* (Higgins 2011)

Appendix 2. Data to be extracted from studies

1. Study methods and setting: study ID, study type, study site, country of publication, language of publication, publication type and study duration.

2. Participant details: sample size, age, sex, diagnosis (includes subtypes), diagnostic tool, intelligence and/or adaptive behaviour level

3. Intervention details: number of participants in each group, missing participants, intervention type, including dosage, mode of delivery, frequency and duration; placebo type, including dosage, mode of delivery, frequency and duration.

4. Outcomes: all primary and secondary outcomes (see Primary outcomes; Secondary outcomes) and time points these were collected (2x2 table for dichotomous data and mean; SD for continuous data)

5. Risk of bias and the rating for each criteria: Randomisation process, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, other sources of bias

Appendix 3. Ovid MEDLINE search strategy

1 exp child development disorders, pervasive/
2 Developmental Disabilities/
3 Neurodevelopmental Disorders/
4 pervasive development$ disorder$.tw,kf.
5 (pervasive adj3 child$).tw,kf.
6 (PDD or PDDs or PDD-NOS or ASD or ASDs).tw,kf.
7 autis$.tw,kf.

8 asperger$.tw,kf.
9 kanner$.tw,kf.
10 childhood schizophrenia.tw,kf.
11 or/1-10
12 memantine/
13 Amantadine/
14 (Abixa or Adaxor or Admed or Akatinol or Alceba or Alios or Almenta or Alois or Alzant or Alzer or Alzia or Alzinex or Alzixa or Alzmenda or Alzmex or Apo-Memantine or Axura or Biomentin or Carrier or Cogito or Cognomem or Conexine or Cordure or Dantex or Demantin or Demax or Dementa or Dementexa or Ebixa or Ebitex or Emantin or Emaxin or Esmirtal or Eutebrol or Evy or Ezemantis or Fentina or Korint or Lemix or Lindex or Lucidex or Manotin or Mantine or Mantomed or Marbodin or Mardewel or Marixino or Maruxa or Maxiram or Melanda or Memabix or Memamed or Memando or Memantin or Memantina or Memantine or Memantinol or Memantyn or Memanvitae or Memanxa or Memanzaks or Memary or Memax or Memexa or Memigmin or Memikare or Memogen or Memolan or Memorel or Memorix or Memotec or Memox or Memxa or Mentadem or Mentikline or Mentium or Mentixa or Merandex or Merital or Mexia or Mimetix or Mirvedol or Modualz or Morysa or Nemdaa or Namenda or Namzaric or Nemdatine or Neumantine or Neuro-K or Neuroplus$ or Noojerone or PMS-Memantine or Polmatine or Prilben or Pronervon or Ratio-Memantine or Ravemantine or Sandoz-Memantine or Talentum or Timantil or Tingreks or Tonibral$ or Tormoro or Valcoxia or Vilimen or Vivimex or Witgen or Xapimant or Ymana or Zalatine or Zarlyn or Zeimer or Zemertinex or Zenmem or Zenmen or Zimer).mp.
15 or/12-14
16 11 and 15
17 randomized controlled trial.pt.
18 controlled clinical trial.pt.
19 randomi#ed.ab.
20 placebo$.ab.
21 drug therapy.fs.
22 randomly.ab.
23 trial.ab.
24 groups.ab.
25 or/17-24
26 exp animals/ not humans.sh.
27 25 not 26
28 16 and 27

HISTORY

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CONTRIBUTIONS OF AUTHORS

AB wrote, updated and modified all sections of the protocol. All co-authors (CM, KW, CP, TM) provided comments on drafts and approved the final protocol. Biola Araba, Katherine Wilkins and Kristine Egberts (acknowledged above) contributed to writing the first draft of the protocol. AB is the guarantor for the review.

DECLARATIONS OF INTEREST

Amanda Brignell (AB) is an Associate Editor with Cochrane Developmental, Psychosocial and Learning Problems (CDPLP). AB is involved in autism research and declares that she does not receive funding from any commercial or for-profit organisation for her autism research, drug-related or otherwise.

Tamara May (TM) is involved in clinical care and research with non-pharmacological interventions for individuals with autism spectrum disorder. TM has received no funding from commercial or for-profit organisations for her autism research or clinical care.

Chidambaram Prakash (CP) is involved in the clinical care of young people between the ages of five and 18 years with ASD, using both pharmacological and non-pharmacological means of interventions. CP is involved in research into demographics and other aspects of autism, receives no funding and carries out the research during clinical time.

Catherine Marraffa (CM) is involved in both clinical care and research with pharmacological and non-pharmacological interventions for individuals with autism spectrum disorder. CM has received no funding from commercial organisations for research or clinical care.

Katrina Williams (KW) declares that she is an Editor with CDPLP and has funding or paid roles linked to interventions for autism but not directly for memantine or other similar medications. KW has provided advice for a fee to the Therapeutic Goods Administration in Australia about the effectiveness of melatonin for improving sleep in children with a rare condition or autism. This advice was provided once to a committee as a presentation to assist their deliberations and decision-making. KW receives royalties for a book called *Understanding autism. The essential guide for parents*, which she co-authored with Professor J Roberts. The book provides broad advice for parents

about autism. KW declares that a competitive grant-funded trial from the Australian Medical Research Futures Fund, for assessing the effectiveness of cannabidiol for severe behaviour disorder in young people with intellectual disability or autism (or both), will commence in 2021. KW is a Chief Investigator for a completed behavioural sleep intervention trial for autism funded by the National Health and Medical Research Council. KW has not received funding from any commercial or for-profit organisation for these trials. KW was also on the data monitoring committee for one pharmacological trial of SSRIs (selective serotonin reuptake inhibitors) for repetitive behaviours in children with ASD, which was funded by the National Health and Medical Research Council and from donations from the Royal Children's Hospital Foundation. KW has not received funding from any commercial or for-profit organisation for this trial.

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External sources

- None, Other

  N/A