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[Intervention Review]

Memantine for dementia in people with Down syndrome

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ABSTRACT

Background

Alzheimer's dementia (AD) is the most common form of dementia in people with Down Syndrome (DS). There is an understanding that an increase in L-glutamate contributes to the pathogenesis of cerebral ischemias and AD. Memantine acts as an antagonist of N-methyl-D-aspartate (NMDA) type receptors, which is thought to reduce abnormal activation of glutamate neurotransmission. It binds with a low affinity to the NMDA receptor and so should not prevent learning and the formation of memory. Memantine can improve cognitive function and slow the decline of AD in the general population over time, and is the subject of this review. It is important to note that people with DS tend to present with AD at a much younger age than the normal population as well as having subtle differences in physiology (e.g. metabolism and heart rate) and may therefore have different requirements from the general population. This review was superseded by a new review titled '*Pharmacological interventions for cognitive decline in people with Down syndrome*' in the *Cochrane Database of Systematic Reviews (CDSR)* in 2015.

Objectives

To determine the effectiveness and safety of memantine for people with DS who develop AD.

Search methods

CENTRAL, MEDLINE, EMBASE, CINAHL, PsycINFO, BIOSIS, SCI, SSCI and the NRR were searched up to October 2008. We contacted the manufacturers of memantine, as well as experts in the field, to ask about reports of unpublished or ongoing trials.

Selection criteria

Randomised controlled trials of participants with DS and AD in which treatment with memantine was administered compared with a placebo group.

Data collection and analysis

No study was identified which met the inclusion criteria for this review.

Main results

No study was identified which met inclusion criteria for this review, however there is an on-going randomised controlled study being conducted in the UK and data are expected in 2009.

Authors' conclusions

As there are no included trials, recommendations cannot be made about memantine for AD in DS. Well-designed, adequately powered studies are required.

PLAIN LANGUAGE SUMMARY

Memantine for dementia in people with Down syndrome

Memantine is thought to improve cognitive function and slow the decline of AD over time. The effects of memantine on AD are reported to be beneficial for people with moderate to severe AD in the general population. However, people with DS tend to present with AD at a much younger age than the general population as well as being physically different in terms of size, metabolism and heart rate, and may therefore have different requirements. Results from the one randomised controlled trial for the treatment of dementia in DS are not yet available (expected 2009).

This review was superseded by a new review titled '*Pharmacological interventions for cognitive decline in people with Down syndrome*' in the CDSR in 2015.

BACKGROUND

Description of the condition

Dementia in Down syndrome

The most common genetic disorder recognised at birth is Down syndrome (DS) (Bishop 1997). This is caused by the presence of all or part of an extra copy of chromosome 21, which can lead to deficits in areas of assimilation and adaption along with cognitive impairment. Alzheimer's disease (AD) is a degenerative disease, clinically manifesting as a progressive dementia with a loss of global functioning and cognitive abilities. It is characterized by an increase in amyloid plaques and neurofibrillary tangles in the brain, and reduced levels of cerebral cortical levels of acetylcholine (Prasher 1999). There are well established and recognised neuropathological and neurochemical links between DS and AD with both associated with chromosome 21 (Wisniewski 1995; Teller 1996). In Down Syndrome this additional chromosome can lead to fewer neurons and lower levels of acetylcholine as compared to the general population. Research suggests that cholinergic deficits have been linked to the loss of neurons in the nucleus basalis of Meynert in patients with AD and also with people who have DS. (Casanova 1985; Zigman 1996; Prasher 1999).

People with DS have the risk of getting dementia of the Alzheimers type earlier by about 30 years than the general population (Prasher 1995; Holland 2000). Alzheimer's disease is diagnosed in about 22-25% of people with DS who are 40 or more years old (Janicki 2000; Holland 2000), compared to about 2-3% of people with other developmental disabilities (Janicki 1995; Janicki 2000). For those aged 40-49, the percentages of people with DS who were diagnosed with Alzheimer's disease have been reported to range between 9% and 22% (Prasher 1995; Visser 1997; Holland 1998; Sekijima 1998; Janicki 2000). For those aged 50-59, the reported percentages who were diagnosed with Alzheimer's disease are higher, 36%-66% (Prasher 1995; Visser 1997; Sekijima 1998; Holland 2000).

Alzheimer's disease in the general population usually presents initially as global cognitive decline. Within the learning disabilities population, there may be differences in presentation such as features indicative of frontal lobe dysfunction. These features include language and speech difficulties, and emotional and behavioural changes and may present in DS adults in the 30-49 years age group as well as in individuals whose AD begins at age 30 or younger (Holland 2000; Deb 2007).

Assessing and monitoring dementia in people with Down syndrome

Dementia is a state of cognitive decline, and those with DS are starting from a lower but unpredictable baseline than others in the population, so it is especially important to try to establish premorbid level of functioning to assess if, and at what rate, the dementia is progressing. History should be collected from a carer/informant who has observed the patient in different settings, in order to acquire full psychiatric, personal, past medical and family histories, as well as an examination of current mental state. Mental status examinations that are commonly used to assess dementia in the general population (e.g. the Mini-Mental Scale, Folstein 1975) are usually inappropriate for individuals with DS because they were designed for individuals whose previous level of cognitive function was assumed to be normal; however the CAMDEX-DS (Ball 2004) includes a cognitive mental state examination for adults with DS. It

is important that tests used in this population can be administered and repeated at intervals, when evaluating the progression of the dementia and a possible response to treatment. Such tests need to take into account the relatively low IQ range for people with DS.

A report by the American Association on Mental Retardation - International Association for the Scientific Study of Intellectual Disability (AAMR-IASSID) (Aylward 1997) suggested a battery of tests for the diagnosis of dementia applied to people with learning disabilities. An extensive, detailed list is available (Burt 2000). A more recent discussion of the issues around diagnosing dementia and its progression can be found in UK guidance (NICE 2006).

To mention a few which are administered to the informant/carers:

- the Dementia Scale for Downs Syndrome [DSDS] (Gedye 1995) can assess short and long term memory, orientation, speech, language, praxis, fine motor skills, practical skills, mood, activity/interest, behavioural disturbances, seizure onset and is designed to measure dementia in its early, middle and late stages;
- the Dementia Questionnaire for Persons with Mental Retardation [DMR] (Evenhuis 1996) (revised edition: the Dementia Questionnaire for People with Learning Disabilities (Evenhuis 2006)) has questions to assess sum of cognitive scores (SCS which includes short and long term memory, spatial and temporal orientation) and sum of social scores (SOS which include speech, practical skills, mood, activity/interest and behavioural disturbance) and is used in this population to help with diagnosis and prognosis;
- the Adaptive Behaviour Scale [ABS] (Nihira 1974) is a semi structured interview assessing ten domains of adaptation and eight domains of maladaptive behaviour;
- the Adaptive Behaviour Dementia Questionnaire [ABDQ] is a 15 item questionnaire to detect changes in adaptive behaviour, which can be used as a screening tool (Prasher 2004b).

Of those tests administered to people who have little or no speech, the Test for Severe Impairment (Modified) assesses short and long term memory, motor skills, language, conceptualisation, general knowledge (Albert 1992) and the Spatial Recognition Span assesses immediate spatial recognition (Moss 1986). It is important to rule out treatable causes of dementia such as depression, thyroid problems etc., in addition to motor slowness, sensory deficits and general physical ill-health, as these can all present with symptoms similar to dementia (Aylward 1997).

Although we have various tests available, at this present time there is no definitive mental status examination or neuropsychological instrument that can diagnose dementia in people with DS. There is a need for attention to issues around ease of use and interpretation by those administering such tests (NICE 2006). For example, neuroimaging results for people with DS may appear to give results which are 'false positives' for AD from an early age, if the standards for the general population are used.

Description of the intervention

The amino acid L-glutamate is recognised to be the main excitatory neurotransmitter. As such it is involved in learning and memory, as well as maintaining the ability of the neuronal system to adapt to change (Doraiswamy 2003; Sucher 1996). There is an

understanding that an increase in L-glutamate contributes to the pathogenesis of cerebral ischemias and AD.

Memantine hydrochloride acts as an antagonist of N-methyl-D-aspartate (NMDA) type receptors. It binds with a low affinity to the NMDA receptor and so should not prevent learning and the formation of memory but as its affinity is higher than magnesium ions it is able to inhibit the prolonged influx of calcium ions, which is triggered by magnesium and causes cell damage (i.e. it is an uncompetitive open channel NMDA receptor antagonist; it blocks the open channel quickly but reverses if a barrage of glutamate comes along). This action on the NMDA site is felt to be the basis of the effects of memantine on AD (Parsons 2007; Stahl 2008).

Memantine also acts as an uncompetitive antagonist at 5HT₃ receptors and nicotinic neuronal receptors. The significance of this for the treatment of AD is unknown, but generally nicotinic receptors are reduced in AD (Rammes 2001; Gotti 2004). It also acts on the dopaminergic system (Seeman 2008).

The most common side effects reported are fatigue, increased blood pressure, dizziness, headache, constipation, nausea, vomiting, confusion, somnolence, and difficulty in breathing. Caution is warranted with a prior history of epilepsy and renal impairment. In general it is thought that the side effects are well tolerated.

How the intervention might work

A Cochrane review by McShane 2006 summarized the possible mode of action and evidence available for the effectiveness of this medication in people with Alzheimer's Disease. The results of the review stated that memantine "has a small beneficial effect at six months in moderate to severe AD". In patients with mild to moderate dementia, there were small positive effects in cognition for participants who had AD, Memantine was well tolerated in the studies reported in this review and the review authors reported that "drug is well tolerated in general and the incidence of adverse effects is low".

The rationale for using memantine is to reduce abnormal activation of glutamate and thus interfere with the pathophysiology of AD, improve cognitive function and slow the rate of decline over time. Although memantine is reported to be generally well tolerated in the general population, it is not clear as to how it affects the learning disabled population.

Why it is important to do this review

Whilst Down syndrome has a high incidence of AD, relatively little research has been done on its treatment. In the United Kingdom, the psychiatry of learning disability is a specialty in its own right, but people with learning disabilities outside the UK may be under the care of the general psychiatric services (Fan 2001) and this may contribute to the lack of published work on therapies for dementia in Down syndrome. National and international guidelines are lacking; in their place are 'fact sheets' only (Alzheimer's Australia 2005; American AIDD 2008). The use of medication for AD in people with DS is therefore more controversial than in the general population (Stanton 2004).

In the UK, where guidance seems clearest, the National Institute for Health and Clinical Excellence (NICE) has amended and reissued guidance following the outcome of a judicial review, and only

donepezil, galantamine and rivastigmine were recommended for the treatment of Alzheimer's disease (NICE 2007). The document also emphasized that clinicians should be mindful of the need to secure equality of access to treatment. As people with Down syndrome would virtually never meet the cognitive levels (for example, those needed for assessment by the MMSE) to qualify for the use of such medication, the revised guidance recommended that healthcare professionals should not rely entirely on the MMSE test to assess whether someone with learning disabilities has moderate Alzheimer's disease, or when making decisions about starting or stopping treatment. Therefore other assessment tools can be used (please see [Description of the condition](#) for examples of such tests) and treatment may be given on the basis of the results of these assessments. However, despite the recommendations that people with learning disabilities and Alzheimers should have equality of access to treatment, there is little research evidence which assesses if any of the available treatments are effective in this population (Prasher 2004a).

Given that memantine has the potential to improve symptoms of dementia in individuals in the general population (McShane 2006), and particularly because its side effect profile may be more favourable for this population than other drugs, up-to-date systematic reviews of the effects of this and similar medications in this population are required. Other drugs that are reviewed in a series of linked reviews include: donepezil, a reversible inhibitor of acetylcholinesterase (ACH) (Mohan 2009a); galantamine (Mohan 2009b), a reversible inhibitor of acetylcholinesterase that also has nicotinic receptor agonist properties; and rivastigmine (Mohan 2009c) a reversible non-competitive inhibitor of acetylcholinesterases.

The protocol for the donepezil review served as the template for the whole suite of reviews.

OBJECTIVES

To determine the effectiveness and safety of memantine for people with DS who develop mild, moderate or severe dementia.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (including cross-over studies) of participants with Alzheimer's disease in DS in which treatment with memantine was administered for more than a day and compared with a placebo group.

Types of participants

People with DS of any age, diagnosed with dementia using standardised instruments, see 'Assessing and monitoring dementia in people with Down syndrome in '[Description of the condition](#)').

Types of interventions

Any oral dose of memantine compared against placebo.

Types of outcome measures

Primary outcomes

1. Improvement of:

- global functioning and cognitive abilities (as measured by validated scales including, for example, the Dementia Scale for Mentally Retarded Persons (DMR) ([Evenhuis 1996](#));
 - behavioural problems (as measured by validated scales including, for example, the Adaptive Behavior Scale [ABS] ([Nihira 1974](#)) or the Neuropsychiatric Inventory [NPI] ([Cummings 1994](#)));
 - day to day skills (as measured by carer report).
2. Adverse events.
 3. Institutionalisation.
 4. Death.

Secondary outcomes

- reduction in carers' stress;
- economic outcomes if available.

Search methods for identification of studies

This review is part of a linked series in this area ([Mohan 2009a](#); [Mohan 2009b](#); [Mohan 2009c](#)).

Electronic searches

A single search strategy to identify all interventions was employed. We searched the following databases:

MEDLINE searched 1966 to October 2008 ([Appendix 1](#))

EMBASE searched 1980 to 2008 week 43 ([Appendix 2](#))

The Cochrane Library (CENTRAL) searched 2008 (Issue 4) ([Appendix 3](#))

CINAHL searched 1982 to October 2008 ([Appendix 4](#))

BIOSIS (Biological Abstracts) searched 1985 to October 2008 ([Appendix 5](#))

metaRegister of Controlled Trials (mRCT) (replacing National Research Register) searched Oct 2008 ([Appendix 6](#))

PsycINFO searched 1872 to 2008 October week 4 ([Appendix 7](#))

Science Citation Index searched 1900 to October 2008 and Social Science Citation Index searched 1956 to October 2008 ([Appendix 8](#))

The search strategies for the databases searched are reproduced in the Appendices. No language or date restrictions were used when searching. Due to the small numbers of records found no search filters were used.

Searching other resources

We also contacted the manufacturers of memantine as well as experts in the field, to ask about reports of unpublished or ongoing trials. Please see [Appendix 9](#).

Data collection and analysis

Selection of studies

Two authors (MM and CB) independently reviewed titles and abstracts of references retrieved from the searches and selected all potentially relevant studies. Copies of these articles were obtained, and reviewed independently by the same authors against the inclusion criteria of the study.

Authors were not blinded to the names of the trial authors, institutions or journal of publication. There was no disagreement between the authors and they did not approach or appeal to the editorial base of the Cochrane Developmental, Psychosocial and Learning Problems Group (CDPLPG) for consensus. No relevant reports of studies of memantine were obtained. If updated searches retrieve any reports of studies which meet the inclusion criteria for this review, they will be analysed using the methods detailed in [Appendix 10](#).

RESULTS

Description of studies

These reviews are part of a linked series in this area ([Mohan 2009a](#); [Mohan 2009b](#); [Mohan 2009c](#)).

Results of the search

One hundred and fifty two potential reports of randomised controlled trials were identified by electronic database searches (please see [Figure 1](#)).

Figure 1. Quorum flowchart

Included studies

No study was identified which met the inclusion criteria for this review. We found duplicate reports (Prasher 2008) of one study (Margallo-Lana 2005; Margallo-Lana 2008) which is a randomised controlled study being conducted in the UK and data are expected in 2009 (Margallo-Lana 2005). If studies are found by searches for updates of this review in the future, they will be analysed using the methods described in Appendix 10.

Excluded studies

There were no reports of memantine as a therapy for dementia in people with Down syndrome.

Risk of bias in included studies

No studies met the inclusion criteria for this review.

Effects of interventions

No studies met the inclusion criteria for this review.

DISCUSSION

After extensive searches, no study was identified as being eligible for inclusion for this review.

The mechanism of excitatory neuro-toxicity remains active throughout the disease process in AD. The rationale for using memantine is to reduce abnormal activation of glutamate and thus interfere with pathophysiology of AD, improve cognitive function and slow the rate of decline over time. Its action via the glutamate system in AD is different from ACE inhibitors which boost acetylcholine, and so it can be given concomitantly with acetylcholinesterase inhibitors. Because of cardiac problems in the DS

population (Greenwood 1976; Carpenter 1995), ACE inhibitors may not be recommended if a reduced heart rate is already present. Memantine may therefore be preferable and trials are urgently called for to test this hypothesis. Results from the one randomised controlled trial for the treatment of dementia in DS are not yet available (expected 2009) (Margallo-Lana 2005). The side effect profile of memantine also differs from the ACE inhibitors and it can therefore be used with some people who cannot use ACE inhibitors.

Summary of main results

No completed trials were identified; however, one UK-based study is ongoing (Margallo-Lana 2005).

It may be the case that treatment of AD in DS remains in the infancy stage because of the difficulties encountered while conducting research in the learning disability population in general, which have been noted elsewhere (Fraser 1999). These include ethical committee approval, consent (opt in/opt out process) and difficulties in diagnosis (Stanton 2004; Cooke 2006; Hewison 2006). In addition, a lack of appropriate and validated scales for measurement of progress or side effects for participants who have learning disabilities, and hardships regarding recruitment of both participants and their families, remain problematic.

Overall completeness and applicability of evidence

No trials were identified; one UK-based study is ongoing (Margallo-Lana 2005).

Potential biases in the review process

None known.

Agreements and disagreements with other studies or reviews

For reasons described in the Background, research in this area is predominantly UK-based.

In the UK, the National Institute for Health and Clinical Excellence (NICE) has amended and reissued guidance following the outcome of a judicial review, and memantine is not recommended as an option for people with moderately severe to severe Alzheimer's disease unless it is being used as part of a clinical trial (NICE 2007). As mentioned in related reviews, research evidence in learning disability is limited (Prasher 2004a). Despite extensive searches of

the international literature we were only able to locate one ongoing clinical trial, which is being conducted in the UK and results are expected in 2009 (Margallo-Lana 2005). The results of this trial may lead to revised guidance for use of this medication by people who have DS and dementia.

AUTHORS' CONCLUSIONS

Implications for practice

No data were available when considering the impact of memantine for people with DS who develop mild, moderate or severe dementia.

Current use of memantine in clinical practice remains a matter for the prescribing physician and should ideally be based on consultation with the multi-disciplinary team involved in individual care.

Implications for research

More studies are needed before firm conclusions can be drawn. Collaborative work between patients, carers and clinicians/researchers in order to produce large clinically relevant data is paramount, to ensure outcomes are relevant and participation is maximised. Future randomised controlled trials comparing donepezil and placebo are required. Attention should be paid to:

- clear inclusion and exclusion criteria with details of the reasons for exclusion of potential participants and the numbers excluded; good internal validity (i.e., collection of detailed demographic / baseline data);
- close attention to best available knowledge concerning dosage, particularly concerning tolerability and adverse effects (researchers should also collect and report reasons for dropout);
- adequate power (employing perhaps a multicentre design);
- long term follow-up which takes account of the differing rates of progression of AD in DS;
- clinically meaningful outcomes (including what levels of lack of deterioration are clinically significant);
- economic analyses.

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dementia in Alzheimer's disease in adults with Down syndrome. *Research in Developmental Disabilities* 2004;**25**(4):385-97.

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Rammes G, Rupprecht R, Ferrari U, Zielgansberger W, Parsons CG. The N-methyl-D-aspartate receptor channel blockers Memantine, MRZ 2/579 and other amino-alkyl-cyclohexanes antagonise 5-HT(3) receptor currents in cultured HEK-293 and N1E-115 cell systems in a non-competitive manner. *Neuroscience Letters* 2001;**306**(1-2):81-4.

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Visser FE, Aldenkamp AP, van Huffelen AC, Kuilman M, Overweg J, & van Wijk J Visser FE, et al. Prospective study of the prevalence of Alzheimer-type dementia in institutionalized individuals with Downs syndrome. *American Journal of Mental Retardation* 1997;**101**:400-12.

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Wisniewski KE, Wisniewski HM, Wen GY. Occurrence of neuropathological changes and dementia of Alzheimer's disease in Down's syndrome. *Annals of Neurology* 1995;**17**:278-82.

Zigman 1996

Zigman W, Silverman W, Wisniewski H. Aging and Alzheimer's disease in Down Syndrome: Clinical and pathological changes in Down Syndrome: Clinical and pathological changes. *Mental Retardation & Developmental Disability Research Reviews* 1996;**2**(2):73-9.

CHARACTERISTICS OF STUDIES

Characteristics of ongoing studies [ordered by study ID]

Margallo-Lana 2005

Study name	Efficacy and safety of meantime hydrochloride, a low affinity antagonist to n-methyl-d-aspartate (NMDA) type receptors, in the prevention of cognitive decline and disease progression in older people with Down's syndrome, with and without dementia.
Methods	Comparing memantine to placebo.
Participants	Older people with Down's syndrome, with and without dementia.
Interventions	Memantine and placebo.
Outcomes	Details not known
Starting date	Jan 7 2005
Contact information	Margallo-Lana, Dr Maria Luisa (Northgate and Prudhoe NHS Trust and King's College London, Northgate Hospital, Morpeth, Northumberland, NE61 3BP, United Kingdom) and Wolverhampton City Primary Care Trust

Margallo-Lana 2005 (Continued)

Notes

ISSN: N0281175554

Margallo-Lana 2008

Study name	Efficacy and Safety of Memantine Hydrochloride, a Low Affinity Antagonist to N-Methyl-D-Aspartate (NMDA) Type Receptors, in the Prevention of Cognitive Decline and Disease Progression in Down's Syndrome. Clinical Trials.Gov Identifier NCT 00240760.
Methods	Randomized controlled trial
Participants	Participants with learning disabilities due to Down's syndrome aged 18 and older with a diagnosis of dementia; must be able to understand and answer simple requests; not receiving memantine currently or within previous 4 weeks. Carer must have capacity to assist.
Interventions	Memantine and placebo
Outcomes	<p>Primary outcome measures (as specified by study protocol):</p> <ul style="list-style-type: none"> Down's Attention Memory and Executive Function Scale Part 1 of the Adaptive Behaviour Scale <p>Secondary outcome measures:</p> <ul style="list-style-type: none"> The Quality of Life in Alzheimer's disease Clinician's Global Impression of Change
Starting date	October 2005
Contact information	Maria Luisa Margallo-Lana, PhD; Verinder Prasher, PhD.
Notes	ClinicalTrials.gov identifier: NCT00240760

APPENDICES

Appendix 1. MEDLINE search strategy

MEDLINE was searched via OVID 1966 to October 2008

- 1 donepezil.tw.
- 2 aricept.tw.
- 3 galantamin\$.tw.
- 4 galanthamin\$.tw.
- 5 reminyl.tw.
- 6 rivastigmine.tw.
- 7 exelon.tw.
- 8 memantine.tw.
- 9 ebixa.tw.
- 10 E2020.tw.
- 11 ENA 713.tw.
- 12 ENA-713.tw.
- 13 GALANTAMINE/
- 14 MEMANTINE/
- 15 TACRINE/
- 16 tacrine.tw.

17 cognex.tw.
18 Cholinesterase Inhibitors/
19 Down Syndrome/
20 mongol.tw.
21 Trisomy 21/
22 trisomy.tw.
23 ((downs adj syndrome) or (down adj syndrome) or down disease).tw.
24 (or/1-18)
25 or/19-23
26 24 and 25

Appendix 2. EMBASE search strategy

EMBASE, searched via OVID, 1980 to 2008 week 43

1 exp Cholinesterase Inhibitor/
2 donepezil.tw.
3 aricept.tw.
4 galantamin\$.tw.
5 galanthamin\$.tw.
6 reminyl.tw.
7 rivastigmine.tw.
8 exelon.tw.
9 memantine.tw.
10 ebixa.tw.
11 E2020.tw.
12 ENA 713.tw.
13 ENA-713.tw.
14 Donepezil/
15 GALANTAMINE/
16 RIVASTIGMINE/
17 MEMANTINE/
18 TACRINE/
19 tacrine.tw.
20 cognex.tw.
21 or/1-20
22 Down Syndrome/
23 (down syndrome or downs syndrome or down disease).tw.
24 mongol\$.tw.
25 Trisomy 21/
26 trisomy.tw.
27 or/22-26
28 21 and 27

Appendix 3. Cochrane Library (CENTRAL) search strategy

CENTRAL, searched via the Cochrane Library, 2008 (Issue 4)

#1 (donepezil) or (aricept) or (galanthamin*) or (galantamin*) or (reminyl)
#2 (rivastigmine) or (exelon) or (memantine) or (ebixa) or (E2020)
#3 (ENA 713) or (ENA-713) or (tacrine) or (cognex)
#4 MeSH descriptor Galantamine explode all trees
#5 MeSH descriptor Memantine explode all trees
#6 MeSH descriptor Tacrine explode all trees
#7 MeSH descriptor Cholinesterase Inhibitors, this term only
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9 MeSH descriptor Down Syndrome explode all trees
#10 (mongol*) or (trisomy) or (down syndrome) or (downs syndrome) or (down disease)
#11 (#9 OR #10) 2054
#12 (#8 AND #11)

Appendix 4. CINAHL search strategy

CINAHL, searched via OVID, 1982 to October week 2 2008

Memantine for dementia in people with Down syndrome (Review)

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1 exp Cholinesterase Inhibitor/
 2 donepezil.tw.
 3 aricept.tw.
 4 galantamin\$.tw.
 5 galanthamin\$.tw.
 6 reminyl.tw.
 7 rivastigmine.tw.
 8 exelon.tw.
 9 memantine.tw.
 10 ebixa.tw.
 11 E2020.tw.
 12 ENA 713.tw.
 13 ENA-713.tw.
 14 Donepezil/
 15 GALANTAMINE/
 16 RIVASTIGMINE/
 17 MEMANTINE/
 18 TACRINE/
 19 tacrine.tw.
 20 cognex.tw.
 21 or/1-20
 22 Down Syndrome/
 23 (down syndrome or downs syndrome or down disease).tw.
 24 mongol\$.tw.
 25 trisomy.tw.
 26 or/22-25
 27 21 and 26

Appendix 5. BIOSIS search strategy

BIOSIS Previews, searched via ISI Web of Knowledge, 1985 to October 2008

#16 #15 AND #9
 DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;
 #15 #14 OR #13 OR #12 OR #11 OR #10
 DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;
 #14 TS=(cholinesterase SAME inhibitor*)
 DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;
 #13 TS=(trisomy)
 DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;
 #12 TS=(mongol*)
 DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;
 #11 TS=(down* SAME disease)
 DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;
 #10 TS=(down* SAME syndrome)
 DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;
 #9 #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
 DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;
 #8 TS=(cholinesterase SAME inhibitors)
 DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;
 #7 TS=(tacrine OR cognex)
 DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;
 #6 TS=(ENA 713 OR ENA-713)
 DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;
 #5 TS=(ebixa OR E2020)
 DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;
 #4 TS=(exelon OR memantine)
 DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;
 #3 TS=(reminyl OR rivastigmine)
 DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;
 #2 TS=(galantamin* OR galanthamin*)
 DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;

#1 TS=(donepezil OR aricept)
DocType=All document types

Appendix 6. metaRegister of Controlled Trials (replacing NRR) search strategy

Searched October 2008

- #1. donepezil
- #2. aricept
- #3. galantamin*
- #4. galanthamin*
- #5. reminyl
- #6. rivastigmine
- #7. exelon
- #8. memantine
- #9. ebixa
- #10. e2020
- #11. (ena next 713)
- #12. ena-713
- #13. tacrine
- #14. cognex
- #15. GALANTAMINE single term (MeSH)
- #16. MEMANTINE single term (MeSH)
- #17. TACRINE single term (MeSH)
- #18. CHOLINESTERASE INHIBITORS single term (MeSH)
- #19. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18)
- #20. DOWN SYNDROME single term (MeSH)
- #21. mongol*
- #22. trisomy
- #23. (down next syndrome)
- #24. (downs next syndrome)
- #25. (down next disease)
- #26. (#20 or #21 or #22 or #23 or #24 or #25)
- #27. (#19 and #26)

Appendix 7. PsycINFO search strategy

PsycINFO, searched via SilverPlatter, 1872 to 2008 October

- #10 ((mongol* or trisomy or (down syndrome) or (downs syndrome) or (down disease)) or ("Downs-Syndrome" in MJ,MN)) and ((("Cholinesterase-Inhibitors" in MJ,MN) or (ENA-713 or tacrine or cognex) or (rivastigmine or exelon or memantine or ebixa or E2020 or ENA 713) or (donepezil or aricept or galantamin* or galanthamin* or reminyl) or ("Galanthamine-" in MJ,MN))
- #9 (mongol* or trisomy or (down syndrome) or (downs syndrome) or (down disease)) or ("Downs-Syndrome" in MJ,MN)
- #8 mongol* or trisomy or (down syndrome) or (downs syndrome) or (down disease)
- #7 "Downs-Syndrome" in MJ,MN
- #6 ("Cholinesterase-Inhibitors" in MJ,MN) or (ENA-713 or tacrine or cognex) or (rivastigmine or exelon or memantine or ebixa or E2020 or ENA 713) or (donepezil or aricept or galantamin* or galanthamin* or reminyl) or ("Galanthamine-" in MJ,MN)
- #5 "Galanthamine-" in MJ,MN
- #4 "Cholinesterase-Inhibitors" in MJ,MN
- #3 ENA-713 or tacrine or cognex
- #2 rivastigmine or exelon or memantine or ebixa or E2020 or ENA 713
- #1 donepezil or aricept or galantamin* or galanthamin* or reminyl

Appendix 8. Science and Social Science Citation Indexes search strategy

Science Citation Index (SCI) and Social Science Citation Index (SSCI) searched via ISI Web of Knowledge. SCI searched 1900 to Oct 2008. SSCI searched 1956 to Oct 2008

- #16 #15 AND #9
- DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;
- #15 #14 OR #13 OR #12 OR #11 OR #10
- DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;
- #14 TS=(cholinesterase SAME inhibitor*)
- DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;

#13 TS=(trisomy)

DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;

#12 TS=(mongol*)

DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;

#11 TS=(down* SAME disease)

DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;

#10 TS=(down* SAME syndrome)

DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;

#9 #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;

#8 TS=(cholinesterase SAME inhibitors)

DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;

#7 TS=(tacrine OR cognex)

DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;

#6 TS=(ENA 713 OR ENA-713)

DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;

#5 TS=(ebixa OR E2020)

DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;

#4 TS=(exelon OR memantine)

DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;

#3 TS=(remintyl OR rivastigmine)

DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;

#2 TS=(galantamin* OR galanthamin*)

DocType=All document types; LitType=All literature types; Language=All languages; Taxa Notes=All Taxa Notes;

#1 TS=(donepezil OR aricept)

DocType=All document types

Appendix 9. Correspondence with pharmaceutical manufacturers

Lundbeck, the manufacturer for memantine was contacted to request information on unpublished trial data on 22 April 2008. No further data was obtained.

Appendix 10. Methods to be used in future updates of this review

No relevant reports of studies of memantine were obtained. If updated searches retrieve any reports of studies which meet the inclusion criteria for review, they will be analysed using the methods detailed in this appendix.

Selection of studies

Authors will independently review titles and abstracts of references retrieved from the searches and select all potentially relevant studies. Copies of these articles will be obtained, and reviewed independently by the same authors against the inclusion criteria of the study. Authors will not be blinded to the names of the trial authors, institutions or journal of publication.

The authors will extract data from included trials and assess trial quality independently.

Data extraction and management

The following data will be extracted and entered into a pre-designed form:

Study procedures including recruitment, diagnosis, dosage, duration and setting

1. Study design (e.g. randomised or quasi-randomised).
2. Randomisation method (including list generation)
3. Method of allocation concealment
4. Blinding participants
5. Blinding of investigators
6. Blinding of outcome assessors

Participants

1. Inclusion/exclusion criteria
2. Number (total/per group)
3. Age distribution
4. Gender

Follow-up data

1. Duration of follow-up
2. Loss to follow-up

Analysis data

1. Methods of analysis (intention-to-treat/ per-protocol analysis)
2. Comparability of groups at baseline (yes/no)

Additionally, data will be sought for:

- adverse events, particularly sudden death;
- economics issues;
- quality of life of individuals receiving treatment and/or their parents/carers.

Data will be entered into Review Manager (RevMan 5) by one author (MM) and then checked by the second author (PC).

Assessment of risk of bias in included studies

We will evaluate the validity of the trials by the following criteria:

Methodological quality will be assessed independently by two review authors according to the Cochrane Collaboration Handbook. Review authors will independently assess the risk of bias within each included study based on the following six domains with ratings of 'Yes' (low risk of bias); 'No' (high risk of bias) and 'Unclear' (uncertain risk of bias):

Sequence generation

Description: the method used to generate the allocation sequence will be described in detail so as to assess whether it should have produced comparable groups; review authors' judgment: was the allocation concealment sequence adequately generated?

Ratings: 'Yes' (low risk of bias); 'No' (high risk of bias) and 'Unclear' (uncertain risk of bias)

Allocation concealment

Description: the method used to conceal allocation sequence will be described in sufficient detail to assess whether intervention schedules could have been foreseen in advance of, or during, recruitment; review authors' judgment: was allocation adequately concealed?

Ratings: 'Yes' (low risk of bias); 'No' (high risk of bias) and 'Unclear' (uncertain risk of bias)

Blinding

Description: any measures used to blind participants, personnel and outcome assessors will be described so as to assess knowledge of any group as to which intervention a given participant might have received; review authors' judgment: was knowledge of the allocated intervention adequately prevented during the study?

Ratings: 'Yes' (low risk of bias); 'No' (high risk of bias) and 'Unclear' (uncertain risk of bias)

Incomplete outcome data

Description: If studies do not report intention-to-treat analyses, attempts will be made to obtain missing data by contacting the study authors. Data on attrition and exclusions will be extracted and reported as well the numbers involved (compared with total randomized), reasons for attrition/exclusion where reported or obtained from investigators, and any re-inclusions in analyses performed by review authors; review authors' judgment: were incomplete data dealt with adequately by the reviewers? (See also 'Handling missing data', below).

Ratings: 'Yes' (low risk of bias); 'No' (high risk of bias) and 'Unclear' (uncertain risk of bias)

Selective outcome reporting

Description: attempts will be made to assess the possibility of selective outcome reporting by investigators; review authors' judgment: are reports of the study free of suggestion of selective outcome reporting?

Ratings: 'Yes' (low risk of bias); 'No' (high risk of bias) and 'Unclear' (uncertain risk of bias)

Other sources of bias

We will assess if the study was apparently free of other problems that could put it at a high risk of bias.

Measures of treatment effect

Relative risk (RR) estimations with 95% confidence intervals (CI) will be used for binary outcomes. Data on continuous outcomes will be analysed using either mean differences or standardised mean differences if continuous outcomes are measured with similar, but not

identical, instruments across studies. All analyses will include all participants in the treatment groups to which they were allocated, whenever possible

Unit of analysis issues

Crossover trials

In the absence of the concern for a serious carryover effect, where cross-over trials are reported we will approximate, if necessary, a paired analysis by imputing standard deviations (MD analyses) or correlation coefficients (SMD analyses) 'borrowed' from one trial to another. If there is a concern over a serious carryover effect, then data from the first period only will be used and treated as for a parallel group trial.

Dealing with missing data

In the first instance, authors will be contacted to supply data missing from included studies. Missing data and drop-outs/attrition will be assessed for each included study, and the extent to which the results/conclusions of the review could be altered by the missing data will be assessed and discussed. Studies from which there is more than 20% differential dropout between intervention and control will be reported on in the text and analyzed in sensitivity analysis.

Assessment of heterogeneity

Clinical heterogeneity will be assessed by comparing the distribution of important participant factors between trials (e.g. age), and trial factors (randomisation concealment, blinding of outcome assessment, losses to follow-up, treatment type, co-interventions). Statistical heterogeneity will be assessed by examining I^2 (Higgins 2002), a quantity which describes approximately the proportion of variation in point estimates that is due to heterogeneity rather than sampling error. In addition, a chi-squared test of homogeneity will be employed to determine the strength of evidence that heterogeneity is genuine.

Assessment of reporting biases

Funnel plots (estimated differences in treatment effects against their standard error) will be drawn if sufficient studies are found. Asymmetry could be due to publication bias, but can also be due to a relationship between trial size and effect size. In the event that a relationship is found, clinical diversity of the studies will be examined (Egger 1997).

Data synthesis

Where the interventions are the same or similar enough, we plan to synthesize results in a meta-analysis if there is no important clinical heterogeneity. Both a random effects and a fixed-effect model will be employed.

Subgroup analysis and investigation of heterogeneity

If data permit, we will conduct sub-group analyses by stage of dementia (mild, moderate or severe).

Sensitivity analysis

Sensitivity analyses will be conducted to assess the impact of study quality.

WHAT'S NEW

Date	Event	Description
20 May 2021	Review declared as stable	This review is no longer being updated. It was superseded by a new review titled ' <i>Pharmacological interventions for cognitive decline in people with Down syndrome</i> ', in the CDSR in 2015, see www.cochranelibrary.com/cd-sr/doi/10.1002/14651858.CD011546.pub2/full . See Published notes .
20 May 2021	Amended	Abstract, Plain Language Summary and Notes amended to explain that this review was superseded by a new review published in the <i>Cochrane Database of Systematic Reviews</i> (CDSR) in 2015.

HISTORY

Review first published: Issue 1, 2009

CONTRIBUTIONS OF AUTHORS

All authors contributed to the writing of the protocol. The search strategy was devised by Joanne Abbott, TSC of the Cochrane Developmental, Psychosocial and Learning Problems Group.

CB carried out eligibility assessments, extracted data, wrote to study investigators and drug companies for further information, drafted the text, and corrected and edited the text.

MM contributed to the text, carried out the eligibility assessments, and wrote the first draft of the results.

PC mentored MM throughout the review process and checked and revised successive drafts of the review.

DECLARATIONS OF INTEREST

MM: none known, pharmaceutical company sponsored academic programme attended.

PC: none known, pharmaceutical company sponsored academic programme attended.
(Both attend multi-professional academic meetings for which the hospitality is sponsored by pharmaceutical companies, occasionally one of them is a manufacturer of donepezil).

CB: independent researcher and the proprietor of Systematic Research Ltd., received payment for her contribution to the review.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- DOH Cochrane Incentive Scheme, UK

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the wording of outcomes for clarity (subsuming global functioning and cognitive abilities into one category) and moved adverse events to 'Primary outcomes' in accordance with recent Cochrane guidance.

NOTES

This review is no longer being updated because it was superseded by a new review in 2015. See www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011546.pub2/full.

INDEX TERMS

Medical Subject Headings (MeSH)

Alzheimer Disease [*drug therapy] [etiology]; Down Syndrome [*complications]; Memantine [*therapeutic use]; Receptors, N-Methyl-D-Aspartate [*antagonists & inhibitors]

MeSH check words

Humans