Rivastigmine for dementia in people with Down syndrome (Review)

Mohan M, Bennett C, Carpenter PK

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2013, Issue 6

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Rivastigmine for dementia in people with Down syndrome

Monica Mohan[1], Cathy Bennett[2], Peter K Carpenter[3]

[1]Department of Neuropsychiatry, Neuropsychology and Epileptology, The Burden Centre, Bristol, UK. [2]Plymouth University Peninsula Schools of Medicine and Dentistry, Plymouth, UK. [3]Litfield House Medical Centre, Bristol, UK

Contact address: Monica Mohan, Department of Neuropsychiatry, Neuropsychology and Epileptology, The Burden Centre, The North Bristol Trust, Frenchay Hospital, Bristol, Avon, BS16 1JB, UK. drmonicamohan@yahoo.co.uk.

Editorial group: Cochrane Developmental, Psychosocial and Learning Problems Group.
Publication status and date: Edited (no change to conclusions), published in Issue 6, 2013.
Review content assessed as up-to-date: 30 October 2008.

Citation: Mohan M, Bennett C, Carpenter PK. Rivastigmine for dementia in people with Down syndrome. *Cochrane Database of Systematic Reviews* 2009, Issue 1. Art. No.: CD007658. DOI: 10.1002/14651858.CD007658.

ABSTRACT

Background

Alzheimer's dementia (AD) is the most common form of dementia in people with Down Syndrome (DS). Acetylcholine is a chemical found in the brain that has an important role in memory, attention, reason and language. Rivastigmine is a "pseudo-irreversible" inhibitor of acetylcholinesterase, which is thought to maintain levels of acetylcholine. Rivastigmine can improve cognitive function and slow the decline of AD in the general population over time. 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.

Objectives

To determine the effectiveness and safety of rivastigmine 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 We contacted the manufacturers of rivastigmine as well as experts in the field, to ask about reports of unpublished or ongoing trials.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 rivastigmine was administered compared with a placebo group.

Data collection and analysis

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

Main results

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

Authors' conclusions

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

PLAIN LANGUAGE SUMMARY

Rivastigmine for dementia in people with Down syndrome

The drug rivastigmine has been reported to have benefits for people with mild to moderate Alzheimer's disease who do not have Down syndrome. 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. This review identified no randomised controlled trials of rivastigmine in people with Down syndrome. Further research is needed.

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/carer:

- 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 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

Acetylcholine is a chemical found in the brain that has an important role in memory, attention, reason, and language. Although there is no cure for dementia, a number of anti-dementia drugs have been developed which may slow the rate of decline and improve symptoms.
Rivastigmine is a molecule with a phenylcarbamate structure which inhibits cholinesterase enzymes that are involved in the breakdown of acetylcholine in the brain. Rivastigmine is both lipophilic (soluble in fats), hydrophilic (soluble in water) and independent of the hepatic cytochrome P450.

How the intervention might work

Unlike donepezil, rivastigmine acts on both acetylcholinesterase and butyryl-cholinesterase, but its effects are shorter-lived (i.e., it occupies the receptors temporarily) and it reverses itself over time (therefore it is called 'pseudo-irreversible') (Kennedy 1999; Birks 2000; Camps 2002, Stahl 2008). It appears to affect enzymes within the central nervous system more than peripherally. It has the potential advantage of absorption trans-dermally and can be dispensed as a trans-dermal patch. As it is metabolised unaltered it can be used in patients with renal or hepatic impairment, and its lack of interaction with other medications makes it potentially useful is those with other co-morbidities (Grossberg 2000).
In a Cochrane review, of rivastigmine for AD in people who did not have Down syndrome, rivastigmine was found to be of benefit for people with mild to moderate Alzheimer's disease. The side effects can be reduced by gradually increasing the dosage, although more research is need on dosage and side effects. In general, rivastigmine appears to be well tolerated with side effects similar to those observed with other acetyl cholinesterase inhibitors (Birks 2000).

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 diabilities 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 2004b).

Given that rivastigmine has the potential to improve symptoms of dementia in individuals in the general population (Birks 2000), 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); memantine (Mohan 2009b) an antagonist of N-methyl-D-aspartate (NMDA) type receptors, and galantamine (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 rivastigmine 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 rivastigmine 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 rivastigmine 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 careers 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 rivastigmine 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 rivastigmine 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

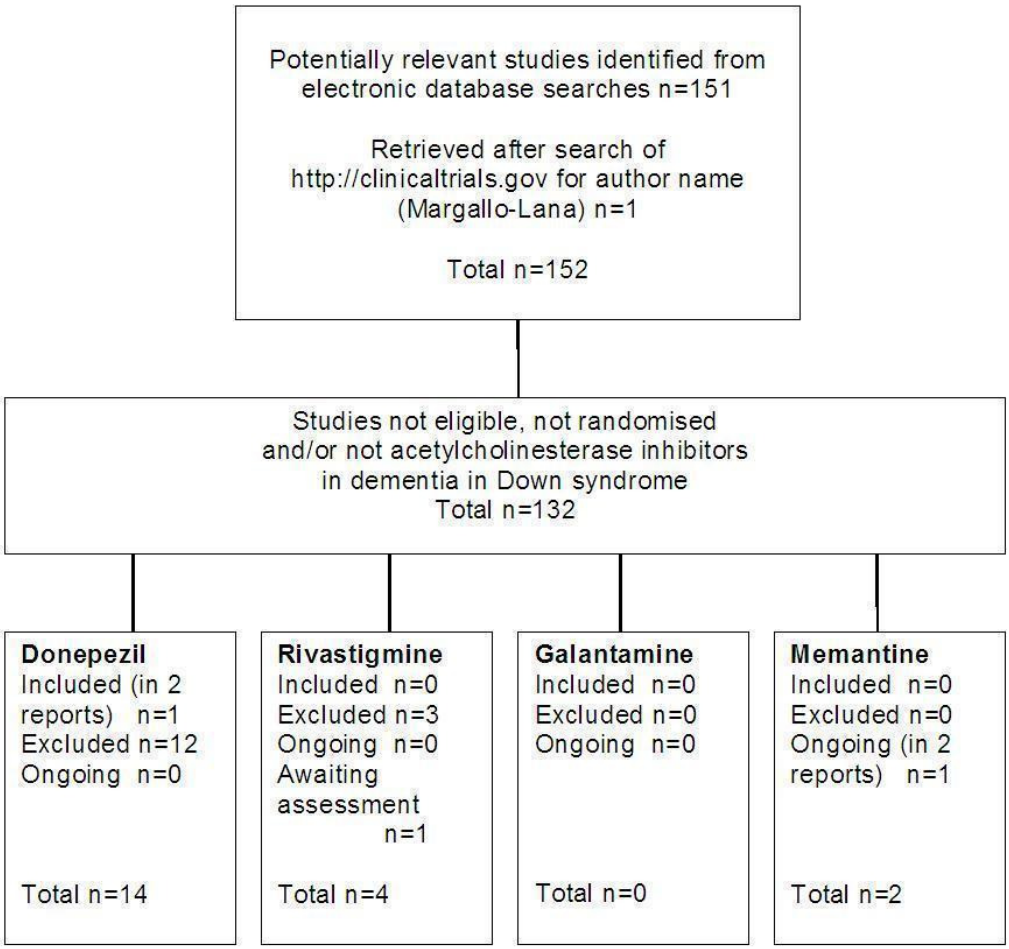
Description of studies

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. Quorom flowchart



Included studies

No studies met the inclusion criteria.

Excluded studies

One study of rivastigmine was excluded from this review. This was an open label study of an unspecified number of adults with Down syndrome and dementia conducted in the UK between 2002 and 2003 (Prasher 2005). Please see Characteristics of excluded studies.

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.

One study of rivastigmine was excluded as it was conducted on a small (unspecified) number of adults with Down syndrome and dementia. The study investigator reported that there was less of decline over 24 weeks in global functioning and adaptive behaviour

compared with the untreated group but these differences were not statistically significant. This is the only report of rivastigmine being used to treat AD in DS and although the lack of effect may have been due to the small sample size, it is difficult to draw conclusions from data obtained from a non randomised controlled trial such as this, as selection bias will always be present. The most commonly reported side effects were "diarrhoea, fatigue, insomnia, nausea and vomiting" (page 497; Prasher 2005). Evidence from randomised controlled trials would help to determine if rivastigmine is safe and effective in the treatment of AD in Down syndrome.

There are other considerations when considering the treatment of AD in DS. 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. Some have recommended that the optimum dose in patients with DS may be lower than the recommended regular dose given the pharmacodynamic and pharmacokinetic presentation of this population. For these reasons it may be beneficial to have smaller dosage formulated than that which is currently available. This is consistent with suggestions from clinical practice that lower dosage is required in people with learning disabilities than the general population in most disorders (Stanton 2004).

Summary of main results

There is therefore no evidence for the effectiveness of rivastigmine in people with DS and AD.
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.

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 donepezil, galantamine and rivastigmine have been recommended as an option for the treatment of moderately severe Alzheimer's disease only (NICE 2007). However, research evidence in learning disability is limited (Prasher 2004a). The use of such medication in people with Down Syndrome is therefore more controversial (Stanton 2004), particularly as current NICE guidelines (NICE 2007) appear to recommend such medication in people with learning disability.

AUTHORS' CONCLUSIONS

Implications for practice

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

Current use of rivastigmine 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 rivastigmine 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.

ACKNOWLEDGEMENTS

We would like to thank Prof. Verinder Prasher for helpful information.

REFERENCES

References to studies excluded from this review

Prasher 2005 ***{published data only}***
Prasher VP, Fung N, Adams C. Rivastigmine in the treatment of dementia in Alzheimer's disease in adults with Down syndrome. *International Journal of Geriatric Psychiatry* 2005;**20**(5):496–7.

Additional references

Albert 1992
Albert M, Cohen C. The test for severe impairment: an instrument for the assessment of patients with severe cognitive dysfunction. *Journal of the American Geriatric Society* 1992;**40**:449–53.

Alzheimer's Australia 2005
Alzheimer's Australia (in collaboration with the Down syndrome Association of Victoria). *Down syndrome and Alzeimer's disease (available online at: http://www.alzheimers.org.au/upload/HS1.18.pdf; accessed November 2008)*. Vol. **Sheet 1.18**, Hawker, ACT: Alzheimer's Australia, 2005 (July).

American AIDD 2008
American Association on Intellectual and Developmental Disabilities. *Fact Sheet: AGING Older Adults and Their Aging Caregivers (available online: http://www.aaidd.org/Policies/faq˙aging.shtml; accessed November 2008)*. Washington, DC: AAIDD, 2008 (6 August, date of last update).

Aylward 1997
Aylward EH, Burt DB, Thorpe LU, et al.Diagnosis of dementia in individuals with intellectual disability. *Journal of Intellectual Disability Research* 1997;**41**:152–64.

Ball 2004
Ball SL, Holland AJ, Huppert FA, Treppner P, Watson P, Hon J. The modified CAMDEX informant interview is a valid and reliable tool for use in the diagnosis of dementia in adults with Down's syndrome. *Journal of Intellectual Disability Research* 2004;**48**(6):611–20.

Birks 2000
Birks J, Grimley Evans J, Iakovidou V, Tsolaki M. Rivastigmine for Alzheimer's disease. *Cochrane Database of Systematic Reviews* 2000, Issue Issue 4. Art. No.: CD001191.

Bishop 1997
Bishop J, Huether CA, Torfs C, Lorey F, Deddens J. Epidemiologic study of Down Syndrome in a racially diverse California population, 1989 - 1991. *American Journal of Epidemiology* 1997;**145**:134–47.

Burt 2000
Burt DB, Aylward EH. Test battery for the diagnosis of dementia in individuals with intellectual disability. *Journal of Intellectual Disability Research* 2000;**44**:175–80.

Camps 2002
Camps P, Munoz-Torrero D. Cholinergic drugs in pharmacotherapy of Alzheimer's disease. *Mini Reviews in Medicinal Chemistry* 2002 Feb;**2**(1):11–25.

Carpenter 1995
Carpenter PK. Cardiovascular and autonomic function in Down syndrome - Prescribing implications. *British Journal of Psychiatry* 1995;**167**:118b–119b.

Casanova 1985
Casanova M, Walker I, Whitehouse P, Price D. Abnormalities of the nucleus basalis of Meynert in Down Syndrome. *Annals of Neurology* 1985;**18**:310–3.

Cooke 2006
Cooke L, Mohan M. Difficulties in Conducting Research in Vulnerable Groups (Rapid Response to Hewison 2006, BMJ, also cited in this review). *BMJ* 2006 (16 August);**E-publication**:Available http://www.bmj.com/cgi/eletters/333/7562/300#139733.

Cummings 1994
Cummings JL. The Neuropsychiatric Inventory. *Neurology* 1994;**44**:2308–2314.

Deb 2007
Deb S, Hare M, Prior L. Symptoms of dementia among adults with Down's syndrome: a qualitative study. *Journal of Intellectual Disability Research* 2007;**51**:726–39.

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

Evenhuis 1996
Evenhuis H M. Further evaluation of the Dementia Questionnaire for Persons with Mental Retardation (DMR). *Journal of Intellectual Disability Research* 1996;**40**:369–73.

Evenhuis 2006
Evenhuis HM, Kengen MMF, Eurlings HAL. *Dementia Questionnaire for People with Intellectual Disabilities (DLD)*. Sydney: Pearson Psychocorp, 2006.

Fan 2001
Fan WT. Psychiatry of learning disability - a time to sow, a time to grow. *Hong Kong Journal of Psychiatry* 2001;**11**(1): 1–3.

Folstein 1975
Folstein MF, Foltein SE, McHugh PR. "Mini-mental state" A practical method for grading the cognitive state of patients for the clinicians. *Journal of Psychiatric Research* 1975;**12**: 185–98.

Fraser 1999
Fraser B. Psychopharmacology and people with learning disability. *Advances in Psychiatric Treatment* 1999;**5**:471–7.

Gedye 1995
Gedye A. *Dementia Scale for Down's Syndrome. Manual*. Vancouver, BC: Gedye Research and Consulting, 1995.

Greenwood 1976
Greenwood RD, Nadas AS. The clinical course of cardiac disease in Down's syndrome. *Pediatrics* 1976;**58**:893.

Grossberg 2000
Grossberg GT, Stahelin HB, Messina JC, Anand R, Veach J. Lack of adverse pharmacodynamic drug interactions with rivastigmine and twenty-two classes of medications. *International Journal of Geriatric Psychiatry* 2000;**15**:242–7.

Hewison 2006
Hewison J, Haines A. Overcoming barriers to recruitment in health research. *BMJ* 2006;**333**:300–2.

Higgins 2002
Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**:1539–58.

Holland 1998
Holland A J, Hon J, Huppert FA, et al.Population-based study of the prevalence and presentation of dementia in adults with Down's syndrome. *British Journal of Psychiatry* 1998;**172**:493–8.

Holland 2000
Holland A J, Hon J, Huppert A, et al.Incidence and course of dementia in people with Down's syndrome: findings from a population-based study. *Journal of Intellectual Disability Research* 2000;**44**:138–46.

Janicki 1995
Janicki MP. *Developmental disabilities and Alzheimer's disease*. Arlington, TX: The Arc of the United States, 1995.

Janicki 2000
Janicki MP, Dalton A. Prevalence of dementia and impact on intellectual disability services. *Mental Retardation* 2000; **38**:277–89.

Kennedy 1999
Kennedy JS, Polinsky RJ, Johnson B, Loosen P, Enz A, Laplanche R, Schmidt D, Mancione LC, Parris WC, Ebert MH. Preferential cerebrospinal fluid acetylcholinesterase inhibition by rivastigmine in humans. *Journal of Clinical Psychopharmacology* 1999;**19**:513–21.

Mohan 2009a
Mohan M, Bennett C, Carpenter P. Donepezil for dementia in people with Down syndrome. *Cochrane Database of Systematic Reviews* 2008, Issue Art. No.: CD007178.

Mohan 2009b
Mohan M, Bennett C, Carpenter P. Memantine for dementia in people with Down syndrome. *Cochrane Database of Systematic Reviews* 2008, Issue Art. No.: CD007178.

Mohan 2009c
Mohan M, Bennett C, Carpenter P. Galantamine for dementia in people with Down syndrome. *Cochrane Database of Systematic Reviews* 2008, Issue Art. No.: CD007178.

Moss 1986
Moss MB, Albert MS, Butters N, et al.Differential patterns of memory loss among patients with Alzheimer's disease, Huntington's disease, and alcoholic Korsakoff's syndrome. *Archives of Neurology* 1986;**43**:239–46.

NICE 2006
National Collaborating Centre for Mental Health. *Dementia: A NICE-SCIE Guideline on Supporting People with Dementia and Their Carers in Health and Social Care (available online: http://www.scie.org.uk/publications/misc/dementia/dementia-fullguideline.pdf, accessed November 2008)*. Leicester, UK: The British Psychological Society and Gaskell, 2006.

NICE 2007
National Institute Health and Clinical Excellence. *Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease: Guidance type: Technology appraisal. Accessible online: http://www.nice.org.uk/guidance/index.jsp?action=download&o=36557 (last accessed May 2008)*. Vol. **TA111**, London: NICE, Date issued: September 2007.

Nihira 1974
Nihira K, Foster R, Shallhaas M, Leland H. AAMD Adabtive behaviour Scale. *American Assocation on Mental Deficiency*. 1974 Revision. Washington, DC: American Association on Mental Deficiency, 1974.

Prasher 1995
Prasher VP. Age-specific prevalence, thyroid dysfunction and depressive symptomatology in adults with Down syndrome and dementia. *International Journal of Geriatric Psychiatry* 1995;**10**:25–31.

Prasher 1999
Prasher VP, Percy M. *Developmental disabilities in Ontario*. Ohio: Front Porch Publishing, 1999.

Prasher 2004a

Prasher V, Farooq A, Holder R. The Adaptive Behaviour Dementia Questionnaire (ABDQ): screening questionnaire for dementia in Alzheimer's disease in adults with Down syndrome. *Research in Developmental Disabilities* 2004;**25** (4):385–97.

Prasher 2004b

Prasher V. Review of donepezil, rivastigmine, galantamine and memantine for the treatment of dementia in Alzheimer's disease in adults with Downs syndrome: implications for the intellectual disability population. *International Journal of Geriatrics Psychiatry* 2004;**19**:509–15.

Sekijima 1998

Sekijima Y, Ikeda S, Tokuda T, Satoh S, Hidaka H, Hidaka E, et al.Prevalence of dementia of Alzheimer type and apolipoprotein E phenotypes in aged patients with Down's syndrome. *European Neurology* 1998;**39**:331–5.

Stahl 2008

Stahl SM, Muntner N. *Essential Psychopharmacology, Neuroscientific Basis and Practical Applications*. ISBN 9780521857024. Cambridge University Press, 2008:924.

Stanton 2004

Stanton LR, Coetzee RH. Down's syndrome and dementia. *Advances in Psychiatic Treatment* 2004;**10**:50–8.

Teller 1996

Teller JK, Russo C, DeBusk LM, Angelini G, Zaccheo D, Dagna-Bricarelli F, et al.Presence of soluble amyloid B - Peptide precedes amyloid plaque formation in Down's syndrome. *Nature Medicine* 1996;**2**:93–5.

Visser 1997

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.

Wisniewski 1995

Wisniewski KE, Wisniewski HM, Wen GY. Occurence 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, Wisniewsi 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.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Prasher 2005	Not an RCT. Open label study of rivastigmine in Down syndrome and dementia

DATA AND ANALYSES

This review has no analyses.

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
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 Knowledege, 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 (mRCT)

metaRegister (mRCT) (replacing National Research Register) 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 week 4
#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=(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 9. Correspondence with pharmaceutical manufacturers

Novartis, the manufacturer for rivastigmine 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 a future update of this review

No relevant reports of studies of rivastigmine 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

Last assessed as up-to-date: 30 October 2008.

Date	Event	Description
13 June 2013	Amended	Typo corrected

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 the 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 supplied

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.

INDEX TERMS

Medical Subject Headings (MeSH)

Alzheimer Disease [*drug therapy; etiology]; Cholinesterase Inhibitors [*therapeutic use]; Down Syndrome [*complications]; Phenylcarbamates [*therapeutic use]

MeSH check words

Humans